PROCESS OF CARE FAILURES IN WOMEN WITH CERVICAL CANCER

Andrea Rose Spence

Department of Epidemiology and Biostatistics
McGill University, Montréal

June 2012

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Doctor of Philosophy

ABSTRACT

Background: In the year 2010, approximately 1,300 incident cases of cervical cancer are predicted to have been diagnosed in Canada, making it the 3rd most common cancer among Canadian women between the ages of 20-49 years. There are reliable screening tools, diagnostic tests and effective treatments for pre-invasive lesions and early stage cancers. Thus, theoretically, invasive cervical cancer is a preventable disease.

Objective: To assess the quality of health care that women with invasive cervical cancer received within 5 years prior to their diagnosis. The goal was to determine deficiencies in Pap screening and diagnostic and treatment care of pre-invasive lesions of study subjects.

Methodology: A case-control study was conducted. Study subjects were long-term residents of Montreal or Laval who were diagnosed with histologically-confirmed primary cervical cancer between January 1, 1998 and December 31, 2004. The identification of cases was done by the Quebec tumour registry and by hospital medical records departments. Cervical screening, diagnostic, and pre-invasive lesion treatment histories were obtained from hospital medical charts, hospital cytology laboratories, subject (or proxy) interviews, and physician questionnaires. The main time window of observation was the interval 5 years before diagnosis but lifetime screening histories were also considered. Processes of care were assessed as per explicit medical review criteria, which were based on clinical practice guidelines and based on consensus by clinical co-investigators. The respondents of the Canadian Community Health Survey (cycle 2.1) and a matched sample of non-cervical cancer cases obtained from the Régie de l'assurance maladie du Québec were used as a comparison group for many analyses. Descriptive statistics and regression modelling techniques were performed to assess associations.

Results: A total of 568 women were diagnosed with cervical cancer and met all inclusion criteria. Immigrants (OR 1.40, 95% CI 1.08-1.82), women in common-law relationships (OR 1.62, 95% CI 1.12-2.33), and women who spoke neither French nor English (OR 4.53, 95% CI 2.26-9.07) were at greatest risk of cervical cancer. The majority of cervical cancer cases (whose screening histories could be classified) were screened at least once during their lifetime (90.4%,

95% CI 87.5-93.3) and 9.6% (95% CI 6.7-12.5%) were never screened. Of those women screened in the past, 43.1% (95% CI 38.0-48.2%) were not screened within 5 years of diagnosis. It was found that the greater the time interval since the last Pap, the greater was the risk of cervical cancer. The greatest risk was found for women screened 5 or more years before diagnosis (OR 14.4, 95% CI 9.94-20.91). Cervical cytological abnormalities found by Pap testing were more likely to be appropriately managed in terms of follow-up procedures and timing compared to the follow-up of diagnosed precancerous cervical lesions. Specifically, 12.5% (95% CI 8.7-16.3) of subjects with an abnormal Pap smear and 19.4% (95% CI 13.9-24.9) of subjects with a diagnosed cervical lesion were not followed-up appropriately according to medical criteria. Similarly, 36.7% (95% CI 31.2-42.3) of subjects with an abnormal Pap smear and 52.5% (95% CI 45.5-59.4) of subjects with a cervical lesion were not managed in a timely manner.

Conclusion: Most women who were diagnosed with cervical cancer were screened at least once in their lifetimes. However, many women with cervical cancer were not screened within 5 years of diagnosis. If an abnormal Pap test occurred or a precancerous lesion was diagnosed, the processes of care were found to be acceptable in most instances; however, delays in the implementation of these processes were more common. Poor follow-up of diagnosed cervical lesions was found to be more common than poor follow-up of abnormal Pap tests.

RÉSUMÉ

Durant l'année 2010, environ 1300 cas incidents de cancer du col de l'utérus sont estimés avoir été diagnostiqués au Canada, ce qui en fait la 3e cause la plus importante de cancer chez les femmes canadiennes âgées entre 20 et 49 ans. Il existe des outils de dépistage fiables, des tests de diagnostique et des traitements efficaces pour les lésions pré-invasives et les cancers au stade précoce. Ainsi, théoriquement, le cancer invasif du col de l'utérus est une maladie évitable.

Objectifs: Évaluer la qualité des soins de santé que les femmes atteintes de cancer invasif du col de l'utérus ont reçus dans les 5 années qui ont précédé leur diagnostic. Le but est de déterminer les faiblesses au niveau du dépistage avec le test Pap, des diagnostics et des traitements des lésions pré-invasives chez les participantes de l'étude.

Méthodes: Une étude cas-témoins a été réalisée. Les participantes de l'étude étaient résidantes depuis longtemps à Montréal ou Laval et avaient reçu un diagnostic de cancer primaire du col de l'utérus (confirmé par histologie) entre le 1er janvier 1998 et le 31 décembre 2004. L'identification des cas a été faite par le registre des tumeurs du Québec et par les départements d'archives médicales d'hôpitaux. L'historique du dépistage Pap, du diagnostic et des traitements des lésions pré-invasives a été obtenu à partir de la revue des dossiers médicaux, des laboratoires de cytologie des hôpitaux, des entrevues des participantes (ou proxy) et des questionnaires relatifs aux médecins. La durée d'observation considérée à été principalement la période de 0-5 ans précédant le diagnostic, par contre, tout l'historique de dépistage à vie de la participante a aussi été considéré. Le processus des soins a été évalué selon des critères médicaux définis à partir des guides de pratiques cliniques et de consensus des co-chercheurs cliniciens. Les répondantes à l'*Enquête sur la santé de la communauté canadienne (cycle 2.1)* et un échantillon apparié de sujets sans cancer du col de l'utérus obtenu de la Régie de l'assurance maladie du Québec ont été utilisées comme groupe de comparaison pour plusieurs analyses. Des statistiques descriptives et des techniques de modélisation de régression ont été effectuées pour évaluer les mesures d'association.

Résultats: Un total de 568 femmes ont reçu un diagnostic de cancer du col de l'utérus et respectaient les critères d'inclusion. Les immigrantes (OR 1.40, IC 95% : 1.08-1.82), les femmes

vivant en union de fait (OR 1.62, IC 95% : 1.12-2.33) et les femmes ne parlant ni français ni anglais (OR 4.53, IC 95% : 2.26-9.07) avaient un plus grand risque de cancer du col de l'utérus. La majorité des cas de cancer du col de l'utérus (celles dont l'historique de dépistage pouvaient être classifié) avait eu au moins un test de dépistage au cours de leur vie (90.4%, IC 95% : 87.5-93.3) et 9.6% (IC 95% : 6.7-12.5) n'avaient jamais eu de test de dépistage. De ces femmes qui ont eu un test de dépistage au cours de leur vie, 43,1% (IC 95% : 38.0-48.2%) n'ont pas eu de dépistage au cours des 5 années précédant leur diagnostic. Il a été montré que plus l'intervalle depuis le dernier test Pap était grand, plus le risque de cancer du col de l'utérus était grand. Le plus haut risque a été trouvé chez des femmes ayant eu un test de dépistage 5 ans et plus avant leur diagnostic (OR 14.4, IC 95% : 9.94-20.91). Les cytologies cervicales anormales trouvées par les tests Pap étaient susceptibles d'être mieux gérées en termes de procédures de suivi et en temps comparé au suivi de lésions précancéreuses diagnostiquées. Spécifiquement, 12.5% (IC 95% : 8.7-16.3) des participantes avec un test Pap anormal et 19.4% (IC 95% : 13.9-24.9) des participantes diagnostiquées avec des lésions cervicales, n'avaient pas eu de suivi approprié selon les critères médicaux définis. De même, 36.7% (IC 95% : 31.2-42.3) des participantes avec un test Pap anormal et 52.5% (IC 95% : 45.5-59.4) des participantes avec des lésions cervicales n'ont pas été gérées de façon appropriée.

Conclusion: La plupart des femmes qui ont reçu un diagnostic de cancer du col utérin ont eu au moins un test de dépistage au cours de leur vie. Cependant, plusieurs femmes avec un cancer du col de l'utérus n'ont pas eu de test de dépistage dans les 5 ans précédant leur diagnostic. Si un test Pap anormal survenait ou si des lésions précancéreuses étaient diagnostiquées, le processus des soins a été reconnu comme acceptable dans la plupart des cas; cependant, des délais dans la mise en œuvre de ces processus ont été fréquents. Un mauvais suivi du diagnostic des lésions cervicales a été plus fréquent que le mauvais suivi pour des tests Pap anormaux.

PREFACE

This thesis is presented in the traditional style, with a sequence of chapters. The chapters include a general introduction, a statement of the study objectives and rationale, a comprehensive literature review of the current knowledge surrounding this topic, a detailed description of the methodology and the statistical analyses used, and a presentation of the study results, both in tabular and descriptive form. I conclude with a discussion of the most cogent findings, a final study conclusion, and a brief discussion of the relevance of the study results in the evolving realm of cervical cancer prevention.

As part of the literature review for this study, I conducted a thorough review and meta-analysis of the previous studies that attempted to assess the quality of care that women with invasive cervical cancer received prior to diagnosis. This study was entitled "*Process of care failures in invasive cervical cancer: systematic review and meta-analysis"* and was published in the Journal Preventive Medicine (Spence AR, Goggin P, Franco EL. Process of care failures in invasive cervical cancer: systematic review and meta-analysis. Prev Med 2007; 45: 93-106). An abridged version of the manuscript is included in this thesis as Chapter 3. This manuscript was co-authored with Dr. Eduardo Franco, who is my PhD supervisor, a professor in the Department of Epidemiology and Biostatistics, and the chair of the Division of Cancer Epidemiology at McGill University. Another co-author was Dr. Patricia Goggin, who is a médecin conseil with the Institut National de Santé Publique du Québec in Montreal. I designed the study, reviewed the literature, conducted the statistical analyses, and wrote the manuscript. Dr. Franco contributed to the design of the study and the writing of the manuscript. Dr. Goggin contributed to the writing and the editing of the final manuscript.

STATEMENT OF ORIGINALITY

The study presented in this thesis represents original research and its results have advanced current knowledge in this research domain. This study examined the processes of care that women with invasive cervical cancer received prior to their diagnosis, with the objective of identifying and enumerating the failures in care that occurred at different points along the cancer care continuum. I first conducted a comprehensive review and meta-analysis of studies that had a similar objective. These studies were limited in their scope as most only examined failures in screening. The few studies that ventured beyond the examination of screening examined the follow-up of abnormal Pap smears. These examinations did not involve a separate assessment of the procedural follow-up and the timing of that follow-up. No studies examined the management of defined cervical lesions. This study went beyond the boundaries of these previous studies to assess how and when cervical pre-invasive lesions were managed. This study sought to address its objectives using a well-defined population base with two different control groups, an in-depth search for data using several different sources, and using a priori defined explicit medical criteria to assess the quality of care that women received prior to diagnosis.

In conjunction with Dr. Franco I designed the study and subsequently, I wrote the protocol for the study, which was funded by the Canadian Institutes for Health Research. With the input of my supervisor and study co-investigators, I was responsible for the coordination of this study and was directly involved in all aspects of this study including data collection, the development of all data collection tools, data management, and the quality assessment of the processes of care for each individual study subject.

Hopefully, the results of this study will lead to an enhanced awareness of the importance of the appropriate management of abnormal Pap smears and cervical precursor lesions. In addition, the results may provide further impetus for the creation of a population-based Pap screening program in Montreal or the whole province of Quebec. This system should ideally have the means to identify women in need of screening and to recall women with abnormal cervical cytology or pathology results in order to ensure their timely management. Further, it should

have a more centralized and cohesive cytology lab system. Perhaps, the failures in care noted within this study will lend further credence to the importance of cervical cancer prevention via HPV vaccination.

STATEMENT OF SUPPORT

Financial support to conduct this study was received from the Canadian Institutes of Health Research (MOP-64454 and IHS-61108).

I received personal funding during my PhD studies from a graduate scholarship awarded by the Cancer Research Society Division of Epidemiology at McGill University.

ACKNOWLEDGMENTS

This thesis is dedicated to all women who have received a diagnosis of invasive cervical cancer. It is all the more tragic as cervical cancer is considered preventable if women are appropriately screened and treated at the precursor stage before invasion has occurred. I would specifically like to thank all the study subjects and their next of kin who opened their hearts and perhaps, opened old wounds, to answer our questions and to provide us with consent to contact their physicians in order to obtain further data.

I wish to express my sincere gratitude to Dr. Eduardo Franco, my PhD supervisor, for guiding me along my journey to becoming an epidemiologist. Thank you for giving me the opportunity to conduct this study. You provided me with your research expertise, direction, and support while respecting my ideas and knowledge. I also learnt a great deal from your professionalism and how you conduct yourself as a researcher.

I would like to thank Dr. Pierre Tousignant, Dr. James Hanley, Dr. Ramana-Kumar Agnihotram, and Dr. Helen Trottier for their epidemiologic and statistical advice regarding my study and for their feedback on my thesis.

Thank you to all my study co-investigators and collaborators for always being available to provide me with your clinical expertise and with any practical assistance I needed with conducting this study: Dr. Pierre Drouin, Dr. Alex Ferenczy, Dr. Patricia Goggin, Dr. Diane Provencher, Dr. Lucy Gilbert, Dr. Martin Dawes, Dr. Abdulaziz Alobaid, Dr. Gerald Stanimir, Dr. Parviz Ghadirian, and Dr. Francois Lehmann. I would especially like to thank Dr. Drouin, Dr. Ferenczy, and Dr. Goggin for their in-depth involvement with the study and always willing to help, give advice, and answer my questions regarding cervical cancer.

To Claude Richard, the study nurse: Thank you for your hard work and dedication to this study. You were instrumental to the successful completion of the study. It was a joy working with you.

I am also grateful to the following people whose work was crucial to the completion of this study: Dr. Flavia Da Silva for aiding with the quality assessment; Solange Piché for helping with the subject interviews; Mario Matus for designing the electronic database for the study data; and Jonathan Assayag and Saoussen Salhi for reviewing entered data for quality control purposes.

Thank you to the many hospital medical records technicians who searched their databases for medical charts. I am also grateful to the lab pathologists and technicians who provided us with lab reports, especially Carmela DiGrappa. Thank you to the many physicians who allowed us to contact their patients, completed the questionnaire, and sent us lab reports. Also, thank you to Michel Beaupré of the Fichier des tumeurs du Québec, for providing us with the names of the women diagnosed with cervical cancer. Thanks also to the Régie de l'assurance maladie du Québec for providing the health services use data for all study subjects.

I will always have very fond memories of my tenure at the Gerald Bronfman Centre, which is the home of the Division of Cancer Epidemiology. It was an absolute pleasure to meet all of the students and staff. Thank you for the friendships, the laughs, the discussions, and the memories. You will forever be in my heart. A big thank you to Candida Pizzolongo for eagerly providing administrative assistance whenever it was needed. I will always remember your warm smile, your hearty laugh, our many conversations, and your very tasty baking.

This thesis is dedicated with love to my dear husband Andrew, my parents Lily and Rudyard, and my brothers Richard and Gordon. Thank you for the immense encouragement you gave me and for the absolutely unwavering belief you had in me and in what I could achieve. The completion of my thesis is as much my accomplishment as it is yours.

To my little boys, James and Matthew: You give me endless joy and I am in awe of both of you. I look forward to watching you grow into adulthood.

TABLE OF CONTENTS

ABSTRACT i
RÉSUMÉ iii
PREFACE v
STATEMENT OF ORIGINALITY vi
STATEMENT OF SUPPORT viii
ACKNOWLEDGMENTS ix
LIST OF TABLES xvi
LIST OF FIGURES xviii
LIST OF APPENDICES xx
LIST OF ABBREVIATIONS xxii

1. INTRODUCTION 1

2. OBJECTIVES 4

3. LITERATURE REVIEW 5

3.1 Descriptive Epidemiology and Etiology of Cervical Cancer 5
3.2 Natural History of Cervical Neoplasia 6
3.3 Papanicolaou Cytology Screening 7
3.4 Cervical Cytopathology Nomenclature 9
3.5 Pap Screening Guidelines 10
3.6 Cancer Care Continuum 10
3.7 Management of Abnormal Pap Smears 11
3.8 Treatment of Pre-Invasive Cervical Lesions 11
3.9 Measuring Quality of Health Care 13
3.10 Process of Care Failures in Cervical Cancer 16

4. PROCESS OF CARE FAILURES IN INVASIVE CERVICAL CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS 17

4.1 Objectives 17
4.2 Methodology 17
4.2.1 Identification of Studies 17
4.2.2 Data Extraction and Statistical Analysis 17
4.3 Results 19
4.3.1 Characteristics of Included Studies and Study Subjects 19
4.3.2 Failure to Screen 20
4.3.3 Failure to Detect an Abnormality 31
4.3.4 Failure to Follow-Up 33
4.4 Discussion 34
4.4.1 Summary of Results 34
4.4.2 Study Limitations and Strengths 37
4.5 Rationale for Current Study 38

5. METHODOLOGY 40

5.1 Study Overview 40
5.2 Method of Quality Assessment 40
5.3 Study Subjects 41
5.3.1 Subject Inclusion Criteria 41
5.3.2 Identification of Study Subjects 42
5.4 Period of Observation 44
5.4.1 Identifying the Trigger Pap Test and Other Pap Tests 46
5.5 Data Collection 47
5.5.1 Hospital Medical Charts 49
5.5.1.1 Development of chart abstraction tool and training of chart abstractors 49
5.5.1.2 Abstraction of data from medical charts 50
5.5.2 Hospital Cytology/Pathology Laboratories 51
5.5.3 Study Subject Questionnaire 52
5.5.3.1 Pilot testing of questionnaire 53
5.5.3.2 Administration of subject questionnaire 56
5.5.4 Physician Questionnaire 59
5.5.5 Administrative Data from the RAMQ 61
5.5.6 Canadian Community Health Survey 64
5.5.7 Canadian Census 64
5.6 Quality of Care Assessment 65
5.6.1 Assessment of Pap Screening History 65
5.6.2 Failures in Detection of Cytological Abnormalities 69
5.6.3 Quality Assessment of Follow-up of Abnormal Pap Smears 72
5.6.4 Quality Assessment of Treatment of Pre-Invasive Cervical Lesions . 74
5.7 Data Quality Control and Security 75
5.8 Ethical Considerations 76
5.9 Statistical Analysis 77
5.9.1 Sources of Study Subjects 77
5.9.2 Reliability of Medical Chart Abstraction 79
5.9.3 Characteristics of Cases 79
5.9.4 Association between Subject Demographics and Incidence of Diagnosis of Cervical Cancer 80
5.9.5 Proportions of Procedural Processes of Care Identified by Each Data Source 82
5.9.6 Screening History and Invasive Cervical Cancer 83
5.9.7 Quality Assessment of Follow-Up of Abnormal Pap Smears and Cervical Lesions 84
5.9.8 Examination of the Time from First Abnormal Pap Smear to the Follow-Up Colposcopy Among Cases 85
5.9.9 Patterns of Health Services Use According to a Matched Case-Control Study 88

6. RESULTS 90

6.1 Identification of Study Subjects by Source 90
6.2 Hospital Medical Charts and Lab Reports 95
6.2.1 Assessment of Reliability of Medical Chart Abstraction 95
6.2.2 Demographic Characteristics of Subjects as Determined by Medical Chart Review 96
6.3 Subject Questionnaire 99
6.3.1 Participation with Subject Questionnaire 99
6.3.2 Characteristics of Subjects According to Participation and Non-Participation with the Questionnaire 103
6.3.3 Demographic Characteristics of Subjects as Determined by Questionnaire 106
6.3.4 Association between Subject Demographics and Cervical Cancer 110
6.3.5 Other Subject Questionnaire Results 115
6.3.5.1 Pap screening knowledge, screening history, physician preferences and cervical cancer symptoms of study subjects 115
6.3.5.2 Health status and physician-use behaviour 115
6.4 Physician Questionnaire 121
6.5 Comparison of Sources of Data 123
6.6 Assessment of Pap Screening Histories 127
6.6.1 Subject Pap Screening Histories 127
6.6.2 Association between Pap Screening History and Cervical Cancer 131
6.7 Failures in Detection of Cytological Abnormalities 135
6.8 Assessment of Follow-Up of Abnormal Pap Smears 136
6.8.1 Quality Assessment of the Follow-Up of Abnormal Pap Smears by Total Number of Events 136
6.8.1.1 Assessment of processes of care and timing of processes of care 136
6.8.1.2 Reasons for unacceptable processes of care 139
6.8.2 Quality Assessment of the Follow-Up of Abnormal Pap Smears Based on Study Subjects 141
6.8.3 The Relationship between Pap Screening History and the Quality of Follow-Up of Abnormal Pap Smears 143
6.8.4 Time between Trigger Pap and Colposcopy 143
6.8.5 Determinants of Time between Trigger Pap and Colposcopy 148
6.9 Assessment of Follow-Up of Cervical Lesions 148
6.9.1 Quality Assessment of the Follow-Up of Cervical Lesions by Total Number of Events 148
6.9.1.1 Assessment of processes of care and the timing of processes of care 148
6.9.1.2 Reasons for unacceptable processes of care 153
6.9.2 Quality Assessment of the Follow-Up of Pre-Invasive Cervical Lesions Based on Study Subjects 153

6.9.3 The Relationship between Pap Screening History and the Quality of Follow-Up of Pre-Invasive Cervical Lesions ……. 154
6.10 Patterns of Health Services Use According to a Matched Case-Control Study. 154

7. DISCUSSION …….. 160
7.1 Summary of Results ……. 160
7.2 More Detailed Results of Study …… 160
7.2.1 Characteristics of Cervical Cancer Cases ……... 160
7.2.2 Assessment of Pap Screening History …… 161
7.2.3 Other Potential Biases ……. 163
7.2.4 Proxy Respondents to Subject Questionnaire ……..... 165
7.2.5 Assessment of the Follow-Up of Abnormal Pap Smears ……... 166
7.2.6 Patient-Level Impediments to the Follow-Up of Abnormal Pap Smears ……. 166
7.2.7 Physician-Level Impediments to the Follow-Up of Abnormal Pap Smears …… 167
7.2.8 Assessment of the Treatment of Pre-Invasive Cervical Lesions …..... 168
7.2.9 Health Services Use in Cervical Cancer Cases ……... 169
7.2.9.1 Visits to gynaecologists …….. 169
7.2.9.2 Visits to family physicians ……..... 170
7.2.9.3 Visits to medical specialists ……... 170
7.2.10 Identification of Cervical Cancer Cases ……. 171
7.3 Limitations of Study …….. 172
7.3.1 Abstraction of Data from Hospital Medical Charts …… 172
7.3.2 Cytology/Pathology Laboratories ……... 173
7.3.3 Subject Questionnaire …… 176
7.3.4 Physician Questionnaire …… 177
7.3.5 Data Obtained from the RAMQ ……..... 179
7.3.6 Canadian Community Health Services ……... 179
7.3.7 Other Study Limitations …… 180
7.4 Strengths of Study ……. 182
7.5 Conclusion ……..... 183

7.6 Recommendations from Study …….. 184

8. THE RELEVANCE OF STUDY RESULTS IN THE CHANGING CERVICAL CANCER PREVENTION ENVIRONMENT …….. 185

References ……. 188

LIST OF TABLES

Table 4.1	Characteristics of studies satisfying the inclusion criteria …….	21
Table 4.2	Review of archived Pap smears by different studies as indicative of false-negative, undercalled or inconsistent results ……..	32
Table 5.1	Hospitals offering cervical cancer diagnostic and treatment services ……	44
Table 5.2	Description of RAMQ medical act codes specific to the cervix ……	63
Table 5.3	Acceptable time intervals between abnormal Pap smear and repeat Pap smear and follow-up colposcopy, based on consensus …….....	74
Table 5.4	Acceptable time intervals between abnormal biopsy and treatment, based on consensus ……...	75
Table 6.1	Number of subjects captured and number of subjects meeting inclusion criteria stratified by source ……	92
Table 6.2	Subject inclusion criteria not met according to source of subject …….	93
Table 6.3	Accuracy of primary invasive cervical cancer subjects identified by the Quebec Tumour Registry and/or hospital medical records departments …..	94
Table 6.4	Characteristics of study subjects as determined by hospital chart review …	97
Table 6.5	Reasons eligible subjects or their next-of-kin were not contacted to administer the questionnaire ……..	102
Table 6.6	Reasons why subjects or next of kin whom researchers attempted to contact did not participate in interview ……...	102
Table 6.7	Comparison of the characteristics of study subjects who were or who were not interviewed ……..	104
Table 6.8	Sociodemographic characteristics of study subjects as determined by questionnaire ……..	107
Table 6.9	Association between subject demographic characteristics and invasive cervical cancer, as measured by odds ratios ……...	111
Table 6.10	Association between subject demographic characteristics and advanced cervical cancer, as measured by odds ratios ……...	113
Table 6.11	Pap screening knowledge, screening history, physician preferences and cervical cancer symptoms as reported during interview ……	116
Table 6.12	Health Status and physician-use behaviour of study subjects as reported during interview …….	119
Table 6.13	Reasons physicians did not complete questionnaire or provide documents ..	123

Table 6.14	Proportion of procedures identified by different data sources ……...	125
Table 6.15	Proportion of procedures exclusively identified by a single source ……...	126
Table 6.16	Subject Pap screening histories stratified by level of uncertainty as to categorization …….....	128
Table 6.17	Characteristics of subjects who could not be defined as being 'ever' or 'never' screened in the past versus those subjects who were defined as 'ever' or 'never' screened ……...	129
Table 6.18	Association between Pap screening history and invasive cervical cancer ….	132
Table 6.19	Association between Pap screening history and cervical cancer stage ……..	134
Table 6.20	Quality assessment of the follow-up of abnormal Pap smears by the total number of events ……	138
Table 6.21	Reasons for quality assessment of abnormal Pap smears deemed "not acceptable" …….	140
Table 6.22	Quality assessment of the procedures used for the follow-up of abnormal Pap smears and the timing analyzed using subjects as the units of analysis ..	142
Table 6.23	Time interval between the first abnormal Pap test (trigger Pap) and the follow-up colposcopy stratified by the result of the trigger Pap ……	146
Table 6.24	Determinants of time between first abnormal Pap smear (trigger Pap) and colposcopy ……..	149
Table 6.25	Quality assessment of the follow-up of pre-invasive cervical lesions by the total number of events ……	151
Table 6.26	Reasons for quality assessment of abnormal cervical lesions deemed "not acceptable" …….	153
Table 6.27	Quality assessment of the procedures used for the follow-up of pre-invasive cervical lesions and the timing analyzed by number of subjects ……	155
Table 6.28	Association between number of physician visits prior to first abnormal Pap test and risk of developing cervical cancer …….	158

LIST OF FIGURES

Figure 3.1	Cancer care continuum …….	11
Figure 3.2	Algorithm for the management of abnormal Pap smears …….	12
Figure 4.1	Percentages and 95% CIs from studies that examined the proportion of subjects with deficient screening histories stratified by type of screening policy ……	26
Figure 4.2	Percentages and 95% CIs from studies that examined the proportion of subjects with deficient screening histories stratified by geographic region..	27
Figure 4.3	Percentages and 95% CIs from studies that examined the proportion of subjects never screened stratified by time period …….....	28
Figure 4.4	Percentages and 95% CIs from studies that examined the proportion of subjects with false-negative Pap smears …….....	29
Figure 4.5	Percentages and 95% CIs from studies that examined the proportion of subjects with poor follow-up care ……	30
Figure 5.1	Periods of observation for the assessment of quality of care ……...	46
Figure 5.2	An example of identifying the trigger Pap test ……	47
Figure 5.3	Sequence of data collection steps from primary data sources ……..	48
Figure 5.4	Definition of ever screened …….....	66
Figure 5.5	Definition of never screened ……	67
Figure 5.6	Procedure used to qualify the reliability of subject screening histories …...	71
Figure 5.7	Sources of cervical cancer case ascertainment …….	78
Figure 6.1	Subject questionnaire participation ……..	101
Figure 6.2	Physician questionnaire participation ……..	122
Figure 6.3	Acceptable procedural follow-up of cytologically abnormal Pap smears by the acceptability of the timing of follow-up based on number of events.	139
Figure 6.4	The relationship between the quality of Pap screening history and the quality of the follow-up of abnormal Pap smears ……	144

Figure 6.5	Distribution of time to colposcopy, separately for those where, according to guidelines, colposcopy is or is not considered mandatory ……...	147
Figure 6.6	Distribution of time to colposcopy, separately by result of trigger Pap test.	147
Figure 6.7	Acceptable procedural follow-up of cervical lesions by the acceptability of the timing of follow-up based on number of events ……	152
Figure 6.8	The relationship between the quality of Pap screening history and the quality of the follow-up of cervical lesions ……..	156
Figure 6.9	Number of visits to gynaecologists versus number of visits to family physicians by cases prior to their first abnormal Pap test ……	159

LIST OF APPENDICES

	Preamble to Appendices ……...	202
Appendix 1	Cervical cytopathology nomenclature ……..	203
Appendix 2	Medical chart abstraction form ……	205
Appendix 3	Results of medical chart abstractor reliability measurements …….	213
Appendix 4	Subject questionnaire ……...	221
Appendix 5	Pilot testing of subject questionnaire: Interview script ……..	237
Appendix 6	Pilot testing of subject questionnaire: Introductory letter ……..	239
Appendix 7	Pilot testing of subject questionnaire: Post-questionnaire administration questions ……...	241
Appendix 8	Subject questionnaire: Physician permission letter and form to contact their patient ……..	243
Appendix 9	Subject questionnaire: Introductory letter sent to subject from our study office ……	246
Appendix 10	Subject questionnaire: Introductory letter sent to subject by her physician or the director of professional services ……	248
Appendix 11	Subject questionnaire: Introductory letter sent to next of kin from our study office ……...	250
Appendix 12	Subject questionnaire: Introductory letter sent to next of kin by physician or the director of professional services ……	252
Appendix 13	Subject questionnaire: Interview script ……...	254
Appendix 14	Subject questionnaire: Consent form ……..	256
Appendix 15	Physician Questionnaire ……...	260
Appendix 16	Physician Questionnaire: Introductory letter for family physicians ……...	267
Appendix 17	Physician Questionnaire: Introductory letter for gynaecologists …….....	270
Appendix 18	Article published in L'actualité médicale …….....	273
Appendix 19	Letter written by Dr. Goggin, medical officer with the Institut National de Santé Publique du Québec ……...	275

Appendix 20 Medical criteria for quality assessment …… 277

Appendix 21 An example of the quality assessment of the processes care for one subject …….. 279

Appendix 22 Listing and description of all variables …… 282

LIST OF ABBREVIATIONS

AD	Adenocarcinoma
AGUS	Atypical glandular cells of undetermined significance
AIS	Adenocarcinoma in-situ
AS	Adenosquamous
ASCUS or ASC-US	Atypical squamous cells of undetermined significance
ASC-H	Atypical squamous cells, cannot exclude HSIL
CAI	Commission d'accès a l'information du Québec
CCHS	Canadian Community Health Survey
CEGEP	Collège d'enseignement général et professionnel
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
CIS	Carcinoma in-situ
DNA	Deoxyribonucleic acid
ECC	Endocervical curettage
HMO	Health maintenance organization
HPV	Human papillomavirus
HSIL	High grade squamous intraepithelial lesion
ICC	Invasive cervical cancer
ICD	International Classification of Diseases
ISQ	Invasive squamous cell
KPCP	Kaiser Permanente Care Program
LEEP	Loop electrosurgical excision procedure
LLETZ	Large loop excision of the transformation zone
LSIL	Low grade squamous intraepithelial lesion
MA	Macroinvasive
MD	Median
ME	Mean
MI	Microinvasive
NA	Not applicable
NOS	Not otherwise specified
OT	Other
Pap	Papanicolaou
Pop	Population
PPV	Positive predictive value
RAMQ	Régie de l'assurance maladie du Québec
Reg	Regional
RG	Range
SC	Small cell
SEER	Surveillance Epidemiology and End Results
SIL	Squamous intraepithelial lesion
SOGC	Society of Obstetricians and Gynecologists of Canada
SQ	Squamous cell
UNK	Unknown
WNL	Within normal limits

1. INTRODUCTION

Invasive cervical cancer is a disease that affects female populations of mostly developing countries, where the majority of the world's cases are concentrated. In contrast, there has been a dramatic decline in the incidence of invasive cervical cancer in Canada, and in other developed countries, over the past several decades. This decline has largely been attributed to the successful implementation of the Papanicolaou (Pap) screening test. Cervical cancer development gradually proceeds through a succession of well-defined precursor stages. The purpose of the Pap test is to detect these precursor lesions prior to their progression to the invasive stage; the former being most amenable to successful treatment and more likely to lead to a better prognosis. Cervical carcinogenesis is estimated to take upwards of one to two decades to develop into invasive cancer. Although a single application of the Pap test has poor test sensitivity, the recommended periodic screening with the Pap test is able to exploit this long latency period in order to improve overall detection.

Successful cancer control consists of not only secondary prevention but also a sequence of many different types of care. These include the following: 1) risk assessment, 2) primary prevention, 3) screening, 4) diagnosis, 5) treatment, 6) recurrence surveillance, and 7) palliative care. Of course, palliative care is the final type of care when all previous opportunities for cancer control have failed. Cervical cancer, besides having a proven screening tool, also has reliable diagnostic tests and effective treatments for pre-invasive lesions and early stage cancers. Thus, theoretically, all cervical cancers should be halted as intra-epithelial lesions and not allowed to progress to the invasive stage. Hence, invasive cervical cancer is considered a preventable disease.

The continued incidence of invasive cervical cancer within populations that have access to screening and effective treatment modalities for precursor lesions leads one to question the pre-diagnostic quality of health care received by women diagnosed with invasive cancer. Studies conducted in the past in various hospitals or populations have attempted to examine the antecedent care that women with cervical cancer received prior to their final diagnosis. A published meta-analysis that summarized the results of these studies (42 in total) found that the

most common failure in care was poor screening histories (Spence et al., 2007). Specifically, a cumulative 53.8% of women with cervical cancer were never screened or not screened within an appropriate time interval. An estimated 29% of women with cervical cancer had a false-negative Pap smear prior to diagnosis and about 12% had a failure in follow-up care of an abnormal Pap smear.

The main limitation of these studies was that their scope was limited as most restricted their attention to failures to receive Pap screening, with very few documenting failures in follow-up of abnormal results. This limitation, along with others, led us to design and carry-out this current study. This study is a case-control study consisting of women diagnosed with invasive cervical cancer between 1998 and 2004 residing in Montreal or Laval and diagnosed at a hospital within one of these regions. There were two control groups: One consisted of female respondents to the 2003 Canadian Community Health Survey. The other control group consisted of women obtained from an administrative database. This latter group was matched by age and region of residence to study cases. This study used medical review criteria, which were based upon clinical guidelines and upon consensus by study clinical co-investigators. These criteria were applied to all processes of care that cases experienced within 5 years prior to diagnosis. The intent was to enumerate failures in terms of Pap screening, failures in the appropriate management of abnormal Pap smears, and failures in the appropriate treatment of cervical pre-invasive lesions.

This thesis begins with an in-depth literature review of the epidemiology of cervical cancer including the natural history of its development, which proceeds gradually through a series of reversible pre-invasive stages. The secondary prevention of cervical cancer is discussed through the use of the Pap smear. The management of abnormal Pap smears and the treatment of pre-invasive lesions are then discussed. The results of the meta-analysis noted above are discussed, including a discussion of the limitations of those studies that were included in the review. The methodology, including the statistical analysis, and the results are presented. The discussion and conclusion sections follow. Finally, recommendations that arise from this study are presented along with a discourse about the how the realm of cervical cancer prevention is changing with the introduction of HPV testing and the HPV vaccine.

This thesis is mostly written in the first person to show ownership of my research work. In some instances I use the pronouns “we” or “us” to indicate when the research team or my assistants were involved in a specific aspect of the study.

2. OBJECTIVES

The primary objective of this study was to assess the quality of health care that women with invasive cervical cancer received within 5 years prior to their diagnosis. The goal was to determine deficiencies in Pap screening and diagnostic and treatment care of pre-invasive lesions of study subjects. Explicit review criteria were used to evaluate the processes of care as they pertain to the cancer care continuum. A secondary objective of this study was to explore some of the methodological issues pertaining to the data collection phase of this study.

3. LITERATURE REVIEW

3.1 Descriptive Epidemiology and Etiology of Cervical Cancer

An estimated 493,000 incident cases of invasive cervical cancer occur annually worldwide, rendering it the most common gynaecologic neoplasm and the most frequent cancer in women, second only to breast cancer (Ferlay et al., 2004). This neoplasm affects mostly the developing world, with about 83% of cervical cancers occurring there. Regions of highest incidence include sub-Saharan Africa, Melanesia, Latin America and the Caribbean, South-Central Asia, and South East Asia.

Cervical cancer is a less common neoplasm in Canada. In the year 2010, approximately 1,300 incident cases of cervical cancer are predicted to have occurred and an estimated 370 women will have died from this cancer (Canadian Cancer Society, 2010). In Quebec, specifically, about 280 women will be diagnosed with cervical cancer and an estimated 70 women will die from it, annually. The Canadian age-standardized incidence rates have declined by more than 50% over the last three decades from an estimated 21.8 per 100,000 to its current rate of 6.9 per 100,000. The age-standardized mortality rates have also declined from 3.7 to 2.0 per 100,000 between 1980 and 2010. Although tremendous progress has been made in the prevention of cervical cancer, it is the third most common malignancy among women ages 20 to 49 years (Health Canada, 2002).

Epidemiologic and molecular evidence have revealed that the Human Papillomavirus (HPV) is not only the cause of cervical cancer but, in fact, its necessary cause (Franco et al., 1999; Walboomers et al., 1999; Bosch et al., 2002). Specifically, a persistent infection with a high-risk type of HPV, particularly, HPV types 16 and 18, is the viral causal agent of this neoplasm (Schlecht et al., 2001; Kjaer et al., 2002). HPV does not act in isolation as it is not a sufficient cause of cervical cancer, rather endogenous and exogenous co-factors impact the carriage of HPV and the evolution of the neoplastic process. These co-factors include tobacco smoking, oral contraceptives, parity, dietary factors and host genetic factors (Castellsagué et al., 2003).

3.2 Natural History of Cervical Neoplasia

The two main histologic types of cervical carcinomas and its precursors are squamous carcinomas and adenocarcinomas (Tiltman, 2005). These carcinomas arise from squamous and glandular epithelium, respectively. The majority of cervical dysplasias are squamous cell carcinomas. In general, the relative proportion of adenocarcinomas increases in populations that have a higher degree of Pap screening and hence, a lower incidence of cervical carcinoma (Parkin et al., 2006). This is the case in Western countries where adenocarcinomas may comprise as much as 25% of cervical cancer cases (Parkin et al., 2002). A less common histologic type of cervical neoplasia is adenosquamous carcinoma, which consists of both squamous and glandular histologic components.

The development of cervical cancer, specifically those originating from squamous epithelium, gradually proceeds through a series of reversible, increasingly dysplastic precursor stages initially confined to the cervical epithelium. Each stage involves steady infiltration of the epithelial layer, which if left untreated, may eventually extend through the full thickness of the epithelium (Franco and Rohan, eds, 2002). These preneoplastic squamous lesions are termed cervical intraepithelial neoplasia (CIN) and are separated into three grades known as CIN 1, CIN 2, and CIN 3 depending on the severity of the lesion. (cervical cytohistopathology terminology is discussed in further detail in section 3.4). CIN 1 involves only the lower one-third of the squamous mucosa, CIN 2 involves two-thirds, and with CIN 3, the normal cervical epithelial tissue is completely replaced with the dysplastic cells (Tiltman, 2005). The earliest lesions are mainly transient in nature as they have a high probability of regression. A study found that 74.0% and 63.1% of women with mild dysplasia and moderate dysplasia regressed to normal within 5 years, respectively (Holowaty et al., 1999). Within this same five year period, 5.5% of mild dysplasia and 25.2% of moderate dysplasia progressed to severe dysplasia or worse. If regression does not take place and the lesion is not destroyed or removed, then it may progress to invasive cancer, which is a slow, gradual process that is estimated to take from 10 to 20 years for the earliest lesions (Sellors et al., 2003; Wright et al., 2007).

Pre-invasive lesions that develop from cervical glandular epithelium are known as adenocarcinoma-in-situ (AIS) and they may eventually progress to invasive adenocarcinoma.

3.3 Papanicolaou Cytology Screening

The secondary prevention of cervical cancer is based on the use of the Pap test, which was first introduced in North America more than 60 years ago. The purpose of the Pap test is the detection of pre-invasive lesions or very early microinvasive cancers that may develop into overt invasive cancer (Koss, 1989). This test involves the collection of cells from the uterine cervix using a specially designed sampling brush or spatula. The sample is then smeared onto a glass slide, fixed, stained, and microscopically examined for cytologic abnormalities. Depending on the severity of the initial Pap test, a cytologic diagnosis of dyplasia can then be followed up by a repeat Pap test or by referral for magnified examination of the cervix using an instrument called a colposcope and a cervical biopsy, and then treatment of the pre-invasive lesion if found.

The Pap test is considered to be the most successful cancer screening tool ever. The basis for its effectiveness is the ease of accessibility of the cervix for cellular sampling, which is not the case for most other organs; hence, making the detection and subsequent treatment of cervical pre-cancerous lesions more feasible. In fact, the utilization of the Pap test has been largely deemed responsible for the decrease in the incidence and mortality from cervical cancer in North America (Franco et al., 2001; Gustafsson et al., 1997). Countries that have implemented the use of the Pap test as part of opportunistic or organized cervical cancer screening programs that included quality assurance, large population coverage, and adequate follow-up experienced a reduction in the incidence and mortality for the disease. Moreover, the extent of this reduction appeared to be proportional to the degree of screening coverage (Franco et al., 2002). Therefore, although Pap cytology was never subjected to the rigours of randomized controlled trials, its effectiveness has been proven through decades of surveillance in populations where screening has been successfully adopted (IARC, 2005).

Despite the success with cervical cancer control that has been attributed to the Pap test, historically it is known that the Pap test has a high false-negative rate. Sensitivity for an LSIL/CIN 1 threshold level is estimated to range from 30% to 87%, with a mean of 47% (Nanda et al., 2000) and for CIN 2 or greater, the sensitivity is estimated to be 53% (Cuzick et al., 2006). Fortunately, it has been established that it may take up to two decades for invasive cervical

cancer to develop (Sellors et al., 2003; Wright, 2007). This allows for the Pap test to be repeated at short regular time intervals in order to allow enhancement of the test sensitivity since subsequent testing will hopefully catch any pre-invasive lesions missed at previous screenings (Nanda et al., 2000; Wright et al., 2007). An estimated two-thirds of false-negative Pap smears are due to non-optimal methods used for specimen collection and slide preparation and one-third to errors in slide interpretation (McCrory et al., 1999; Atkins, 2003). The interpretation of Pap tests involves a great deal of subjectivity on the part of the cytopathologist and cytotechnologist, with poor interobserver agreement (Stoler et al., 2001; Schiffman et al., 2007).

There have been some technologic advances to cervical cytologic screening over recent years. Liquid-based cytology is one such improvement. The cervical cellular specimen, which is collected in the same manner as for the conventional Pap smear, is suspended in a fixative solution rather then being directly smeared on a glass slide. The suspension is agitated in order to separate out blood, mucous and cellular debris, and a thin layer of material is then applied to a glass slide, stained, and reviewed by a cytotechnologist. Liquid-based cytology results in cellular material that is more evenly spread on the slide with less obscuring by unwanted substances. This lends itself to both a more rapid review of slides and to a lower frequency of inconclusive slides. In addition, the remaining liquid can be used to test for HPV DNA without necessitating further cervical cell sampling (Russell et al., 2005; Kitchener et al., 2006). Computer-assisted screening technology has also been developed by various companies in different forms over the last two decades. Older imaging technology was only designed to re-screen slides that were already reviewed manually, they entailed the viewing of digitized pictures of slides on a television screen, and they were based on the review of the conventional Pap test and hence, their introduction did not yield the anticipated increase in disease detection (Lozano, 2007). More recently developed computer-assisted technology is designed to do a preliminary scan of liquid-based Pap smears, highlighting those areas of significance for the cytotechnologist to review.

3.4 Cervical Cytopathology Nomenclature

The microscopic morphology of the cervical cells on Pap smears is classified on a spectrum from normal to invasive cancer. There has been several classification systems for cervical cytology proposed over the years (Appendix 1). The earliest cytology classification system was the Papanicolaou system (Papanicolaou, 1954). This system was composed of a sequence of five numeric classes ranging from class I (benign) to class V (changes consistent with cancer). Each class represented an increasing degree of abnormality of the exfoliated cervical cells. As the progress in research allowed for a better understanding of the linkage between cervical cytologic changes and histology, this system was eventually replaced by the dysplasia terminology in 1956 (Franco et al., 2002a; Reagan et al., 1956). The terms mild, moderate, and severe dysplasia (or dyskaryosis) and carcinoma in situ (CIS) were created to describe the extent of replacement of the cervical epithelium by abnormal cells. This system was replaced by the cervical intraepithelial neoplasia (CIN) terminology system in 1968 (Richart, 1968). The terms CIN 1, 2, and 3 were coined to convey the fact that neoplastic change is a continuum, as discussed above. These terms directly correspond to the three levels of the dysplasia terminology: CIN 1 corresponds to mild dysplasia, CIN 2 to moderate dysplasia and the terms severe dysplasia and CIS were combined into one histologic level, CIN 3. In 1990, the CIN system was modified to include two grades: low-grade CIN comprising koilocytic atypia and CIN 1 and high-grade CIN comprising CIN 2 and 3. Koilocytes were included in this nomenclature as it was recognized that these cells indicated changes due to HPV infection (Richart, 1990). In 1988, the Bethesda system was first introduced in an attempt to standardize the nomenclature for cervical cytology reporting. It was later modified in 1991 and 2001. The term squamous intra-epithelial lesion (SIL) was created and included two grades, LSIL and HSIL (National Cancer Institute Workshop, 1989; National Cancer Institute Workshop, 1993; Solomon et al., 2002) The terms ASCUS (atypical squamous cells of undetermined significance) and AGCUS (also abbreviated as AGUS) (atypical glandular cells of undetermined significance" were introduced in 1989. These terms refer to atypical cells, squamous and glandular, respectively, whose clinical significance is questionable. In the most recent Bethesda System, the category ASCUS has been replaced by ASC-US (atypical squamous cells of undetermined significance) or ASC-H (atypical squamous cells, cannot exclude HSIL) in an attempt to overcome the ambiguity of the former term (Solomon et al., 2002).

3.5 Pap Screening Guidelines

There are no Pap screening guidelines specific to the province of Quebec. However, a national workshop was convened in Ottawa in 1989 with the specific mandate to develop cervical screening guidelines (Miller et al., 1991) and in 1991, the Canadian Task Force on Preventive Health Care also made recommendations based on those of a previous meeting (Morrison, 1994). The recommendations for screening are as follows: Pap screening should be initiated at age 18 or after the start of sexual activity. Screening should continue annually for two years and if both smears are normal, screening frequency can be extended to every 3 years until the age of 69. Screening can be more frequent for high-risk women. The Society of Obstetricians and Gynecologists of Canada (SOGC) recommend that screening should be conducted annually until all parts of an organized program are in place (SOGC, 1998). Pap screening can be terminated for women older than 69 years who have had a minimum of two Pap smears deemed satisfactory and cytologically normal in the previous nine years and who have never had a biopsy-confirmed precursor lesion.

3.6 Cancer Care Continuum

The secondary prevention of cervical cancer is accomplished by halting neoplastic development within the cervical epithelium before it becomes invasive and the prognosis worsens. The Pap test is just one modality used in the fight against cancer and is not sufficient on its own to prevent the development of invasive cancer. Rather, prevention requires not only the adoption of the Pap test, but also the appropriate referral and treatment of cervical intraepithelial lesions before they progress to invasion.

Cancer control activities comprise several types of care, which are all interconnected. The so-called cancer care continuum can be conceptualized as consisting of the following ordered stages of care: risk assessment, primary prevention, secondary prevention, diagnosis, cancer or precursor treatment, recurrence surveillance, and end-of-life care (Zapka et al., 2003) (Figure 3.1). Although the continuum may be displayed as a linear pathway, a patient can enter, exit, and re-enter the continuum.

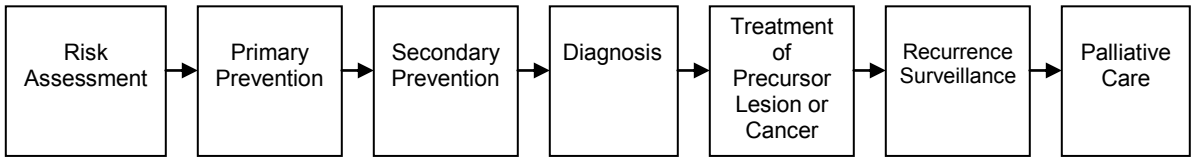

Figure 3.1. Cancer care continuum

3.7 Management of Abnormal Pap Smears

There are no guidelines regarding the management of abnormal Pap results specific to the province of Quebec or the region of Montreal. Several Canadian and American organizations have developed guidelines, some more conservative and others more aggressive in the management algorithms they recommend. The Society of Obstetricians and Gynaecologists of Canada (SOGC) published the following guidelines in 1998 (SOGC, 1998). They are depicted in Figure 3.2. A Pap test deemed to be ASCUS, either unqualified or favouring a reactive process, can be followed by three repeat Pap tests in three to six month intervals. If all of them are found to be "within normal limits" (WNL), then the woman can be returned to annual cytologic screening. If any of them are not WNL, then the woman should be referred for colposcopy and treatment as appropriate. A Pap smear deemed to be ASCUS-favouring neoplasia (ASC-H in the most recent Bethesda review) should be followed-up by immediate colposcopy. Like the ASCUS Pap, a Pap test found to be LSIL can be followed by three repeat Pap tests in three to six month intervals and the woman followed by annual repeat Pap tests if all three Paps are normal. She should be examined by colposcopy if any of the three Paps are not WNL. A woman with an HSIL, AGUS, or AIS Pap smear must be sent for immediate colposcopy.

3.8 Treatment of Pre-Invasive Cervical Lesions

Cervical intraepithelial neoplasia can either be treated by ablative (or destructive) or excisional modalities (Jordan et al., 2006). Ablative techniques involve the destruction of the cervical epithelium and stroma to a specific depth. These techniques include CO_2 laser vaporization, cryotherapy, cold coagulation, and electrodiathermy. Excisional methods, which include CO_2

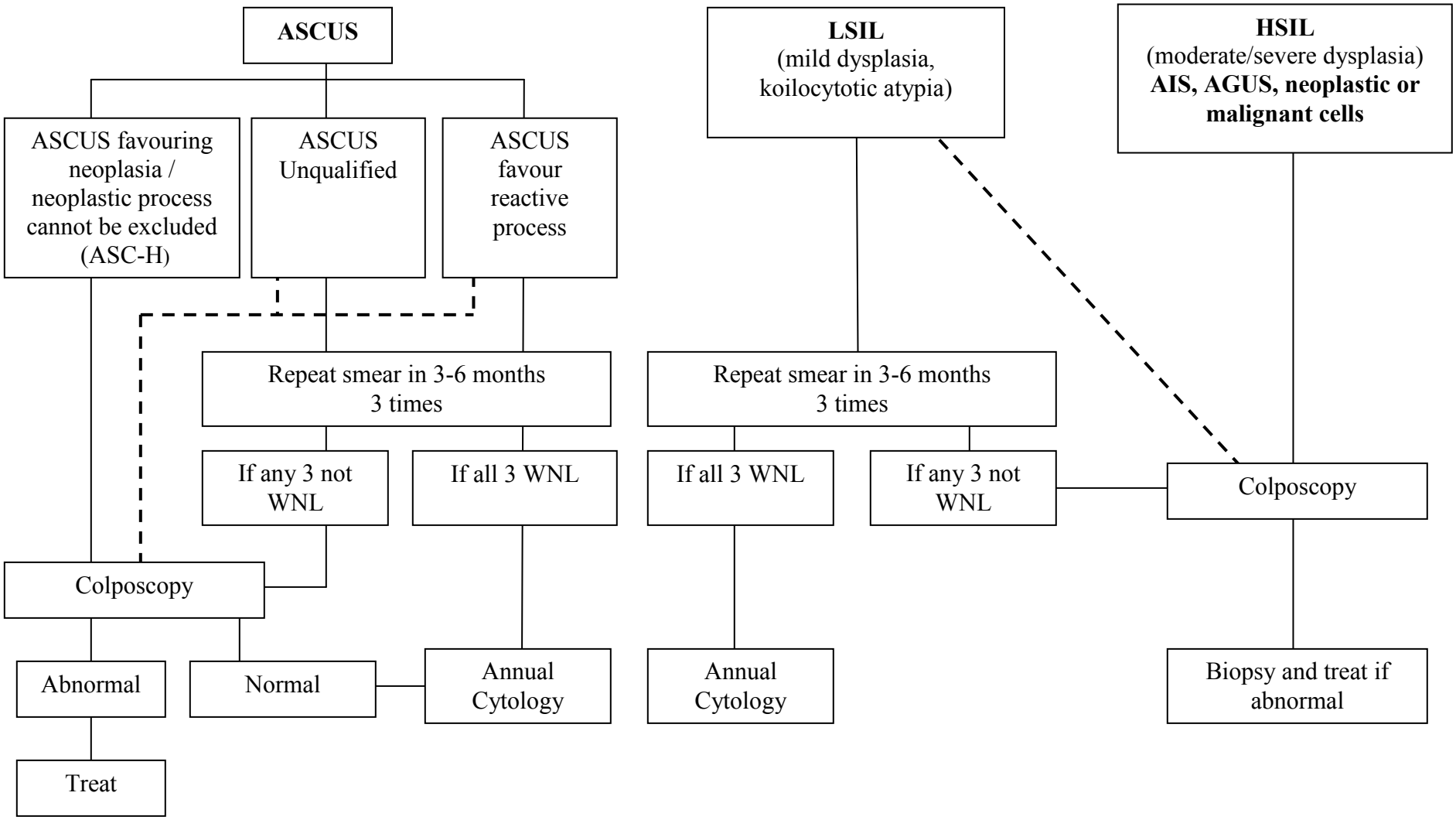

Figure 3.2. Algorithm for the management of abnormal Pap smears (developed from the SOGC guidelines, 1998)
The dashed lines indicate that although colposcopy is not the recommended course of immediate follow-up for these Pap results according to the SOGC guidelines, it is still considered acceptable care by medical professionals.

laser conization, cold knife conization (often simply referred to as a cone), loop electrosurgical excision procedure (LEEP or LLETZ, for large loop electrosurgical excision of the transformation zone), and hysterectomy, involve removal of the abnormal cervical tissue. Excisional treatments have the added benefit of allowing for pathologic examination of the excised tissue. The most common treatment techniques used in Montreal are CO_2 laser vaporization, cryotherapy, conization, LEEPs, and hysterectomy (personal communication, Dr. Alex Ferenczy, Professor, Department of Pathology, McGill University and Pathologist, Jewish General Hospital).

Despite the plethora of treatment techniques available, it has been concluded by many randomized controlled trials comparing various treatment modalities that that there is essentially no difference in outcomes between these techniques (Wright et al., 2003). Prior to conducting an ablative procedure, a technically satisfactory colposcopic examination should be performed (i.e. the entire transformation zone must be visualized). The preferred treatment for women with biopsy-confirmed CIN I, II or III and an unsatisfactory colposcopy is an excisional procedure. Adenocarcinoma in situ that is found upon colposcopy should be treated by an excisional procedure, making sure that the margins are negative for disease (SOGC, 1999). A hysterectomy is considered appropriate if the woman does not wish to maintain her fertility.

3.9 Measuring Quality of Health Care

Quality assessment is one approach to measuring the quality of health care. It involves the comparison of one or more aspects of the care provided to a patient with the accepted norms or standards, such as outlined in clinical practice guidelines (Ashton et al., 1999). Quality assessment essentially involves determining deviations in care between "good" quality care and actual care, with no attempt made to improve the level of care (Buetow et al., 1999). Before proceeding to measure the quality of health care, the concept of quality as it pertains to the provision of health care, must first be defined (Donabedian, 1978). The most widely-used definition in the literature is the one proposed by the Institute of Medicine, who defined quality as the "degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge." (Lohr, 1990).

Inferences about the quality of care involve the evaluation of one or more levels of health care, which include health care structure, process, or outcome. Structure refers to the human, physical, and organizational characteristics of the setting in which health care occurs (Renwick, 1992; Donabedian, 1980). Examples of structure include staffing numbers, qualifications of health care providers, physical space, and equipment (Brien et al., 2009). Process of care refers to the health provider's activities in terms of making a diagnosis and recommending and providing treatment. It may also refer to the patient's role in searching for health care and adhering to recommended follow-up care (Donabedian, 1988). Examples of process measures include the provision of follow-up care or the administration of appropriate medications (Brien et al., 2009). Outcome is defined as a patient's health status after receiving health care services (Garnick et al., 2006) and may include, for instance, quality of life measures, disease-specific mortality rates, length of hospital stay, or readmission to hospital rates (Brien et al., 2009). It is advantageous to use structural measures as they are often concrete measures that are easily obtained (Donabedian, 1966). Like structure, outcome indicators are also rather concrete entities that are amenable to measurement, and they are usually available from routinely collected data. Outcomes are the ultimate measure of quality of medical care (Donabedian, 1966; Mant, 2001). However, process measures, compared to outcome measures, may be considered the more sensitive indicators of quality because a poor outcome does not necessarily consistently result from poor processes of care (Brook et al., 1996). For example, a person suffering a heart attack may receive poor care at the hospital but, despite this, still survives (Mant, 2001). Further, quality of care based on process measures may be considered the most relevant measures as they will be able to determine whether appropriate health care has been provided. In addition, process measures do not simply measure the ability of physical entities to achieve desired outcomes, as do structural measures (Donabedian, 1966).

Once, the concept of quality has been appropriately defined for a specific context and purpose and it has been decided that structural, process, or outcome measures will be the basis of the quality assessment, the next step is to establish the specific attributes that will be measured to achieve the evaluation. These attributes, which are termed medical review criteria or simply, criteria, are definable and measurable characteristics of structure or processes of care (Donabedian, 1981). The underlying basis of quality of care assessment should preferably be

evidence-based best practices, such as clinical practice guidelines (Brien et al., 2009). Criteria are derived from clinical practice guidelines and are defined as "Systematically developed statements that can be used to assess specific health care decisions, services, and outcomes." (Agency for Health Care Policy and Research, 1995). Criteria may be implicit or explicit in nature. Quality assessment based on implicit criteria means that the reviewer(s) does not have a prior set of elucidated standards as to what constitutes good quality care (Brook et al., 1996). Rather, the reviewer(s) judges quality using his/her own clinical knowledge and the criteria used to do so remain concealed in his/her mind (Agency for Health Care Policy and Research, 1995). Unfortunately, implicit review can be highly dependent on the reviewer(s) and it has been found that studies using implicit criteria were more likely to have weak inter-rater reliability (Ashton et al., 1999). Explicit criteria are statements elucidated and written out in advance of quality evaluation to define what constitute good care (Agency for Health Care Policy and Research, 1995). Compared to implicit review, explicit review is stricter, has high inter-rater reliability, and the strength of the assessment of quality is dependent on the criteria themselves and to a much lesser degree on the individuals making the judgments (Ashton et al., 1999). Criteria, explicit or implicit, are then applied to individual cases to determine if each conforms to a specific part of the relevant guidelines and the evaluations of individual cases are then pooled to derive performance rates (Agency for Health Care Policy and Research, 1995).

Besides quality assessment, there are various other approaches to measuring health quality. One such approach is called administrative or normative evaluation. This activity is essentially the same as quality assessment in terms of its overall purpose and approach but it is applied to a specific intervention (Champagne et al., 1986; Contandriopoulos et al., 2000). An intervention is defined as "an organized system of actions applied within a given environment and period of time to correct a problematic situation". Quality assurance is another method of measuring quality of care. Quality assurance begins with an assessment of quality to identify outlying results that may indicate inappropriate care. In contrast with quality assessment, quality assurance then involves the implementation of recommendations to improve care and also continued surveillance of the problem (Steinwachs et al., 1990; Kazandjian, 1996). Another evaluative activity is quality improvement, which on the surface may appear similar to quality assurance but there exists some fundamental differences between them. Quality assurance,

which tends to be a reactive endeavour, usually focuses on the actions of individuals, typically physicians, and attempts to identify poor performers. In contrast, the basic tenet of quality improvement is that individuals work within processes and their functioning cannot be separated from the limitations of these processes. Hence, quality improvement activities focus on determining why processes failed and on how they could be continuously improved in order to minimize systemic variation in clinical practice (Laffel et al., 1989). Audit is another means of measuring quality and it also it is often mistakenly used synonymously with the term quality assurance. Audits are typically locally-driven initiatives performed by health professionals through peer-review, whereas quality assurance activities are the responsibility of managers who purchase health care (Closs et al., 1996).

3.10 Process of Care Failures in Cervical Cancer

Although great strides have been made in reducing the public health burden due to invasive cervical cancer, its continued occurrence in populations with access to screening has prompted many researchers to investigate the reasons why cervical cancer cases were not identified at the pre-malignant stage (studies are listed in Table 4.1). The general goal of all these studies was essentially to identify failures in the process of care aimed at preventing cervical cancer development. Although not explicitly stated by the authors of these studies, to some degree the studies all essentially involved the assessment of the quality of health care these cervical cancer cases received prior to diagnosis with cervical cancer. Typically, these studies enumerated all cervical cancer cases in an individual hospital(s) or region(s) within a given period of time and performed a review with the purpose of identifying deficient screening histories as the primary reason for why such cases were only identified at the invasive stage. A few studies, however, assessed the occurrence of false-negative screening results and determined the timeliness or existence of follow-up care received for any abnormal cytologic smears or cervical pre-invasive lesions found. The following chapter presents a review of these studies and also a meta-analytic summary of the failures in the processes of care (Spence et al., 2007).

4. PROCESS OF CARE FAILURES IN INVASIVE CERVICAL CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS

4.1 Objectives

The objectives of this study were to review and to summarize the findings of studies that examined the antecedent process of care failures of cervical cancer cases. Meta-analyses were performed to determine overall summary statistics for the types of failures. The potential impact that several subject-level variables may have had on each type of failure were explored by stratifying each analysis by these variables and observing the stratified meta-analytic plots.

4.2 Methodology

4.2.1 Identification of Studies

We identified studies through an extensive search of MEDLINE (1950 to the 2nd week of January 2007) based on an exhaustive combination of title and abstract keywords that encompassed the contexts of disease identification via screening, process of care, and evaluation, specifically for cervical cancer. Reference lists of identified articles were also searched for relevant studies. Studies were either case-control or case-only designs that enumerated all cases of invasive cervical cancer (ICC) that occurred within a given population during a defined time period. Included studies were restricted to those that involved determination of the cervical cancer care subjects received prior to diagnosis of ICC and at a minimum, must have collected data about Pap screening histories. Studies that involved controls or subjects diagnosed with cervical carcinoma-in-situ must have provided separate data for these groups and for subjects diagnosed with invasive cancer to be included. Studies involving only microinvasive cancers were excluded, as were studies involving sampling of subjects. Studies were limited to those written in English.

4.2.2 Data Extraction and Statistical Analysis

Data pertaining to the following topics were extracted from each article: year of publication, demographic characteristics, study characteristics, stage and histology, type of local screening

policy, and Pap screening and follow-up history. For those studies that included a comparison group or a group diagnosed with pre-malignant lesions, only the data pertaining to the women diagnosed with cancer were extracted. The ultimate outcomes of interest were the study-specific proportions of total number of subjects who experienced failures of care at each point along the cancer care continuum. If proportions were not explicitly provided within an article or they were not provided in relation to a specific denominator, they were calculated, if possible, using the available data. We present data as percentages with 95% confidence intervals (CI).

The cancer care continuum formed the basis for these meta-analyses (Zapka et al., 2003) (Figure 3.1). Failures in care and hence, the development of invasive cancer, can result from insufficient provision of services during any of the five steps of care. The analyses here focused on the following outcomes: failure to screen, failure in detection (which includes false-negative or under-called Pap smears prior to diagnosis), and failures in follow-up (which includes delays or failures to receive care for an abnormal Pap smear). Failure in detection is a failure of care that occurs between secondary prevention and diagnosis. These three types of failures were hierarchical in nature. Specifically, the 'failure to screen' category was the base level and each enumeration of subsequent failure types was based on women who did not experience a failure in the previous level. This also meant that each failure type was mutually exclusive for subjects in that a woman who had more than one failure in care would only be assigned to the first failure category. In the analysis of failure to screen we examined both the proportion of women who were never screened over their lifetimes and the proportion of women who had deficient screening. The latter outcome considered only studies that determined both the number of women who were never screened and the proportion of previously screened women who were not screened within a specified time interval prior to diagnosis. As this estimate was a composite of these two components, studies that only assessed one factor were omitted since their inclusion would underestimate the proportion of women with deficient screening histories as a function of total cancer cases. In the failure to detect category, Pap smears were deemed to be false negative if normal or benign Pap smears were considered abnormal or "false-negative" upon review. I did not make a judgment as to the categorical level of abnormality when determining the inclusions into this failure category.

DerSimonian and Laird random effect models, which use weights incorporating estimates of between-study variance and within-study variance, were used to calculate overall summary percentages (Deeks et al., 2001). The Q statistic, which assumes a chi-square distribution and k-1 degrees of freedom, was used to assess whether the between-study variance was greater than that expected by chance (Deeks et al., 2001). Meta-analytic plots were done for each type of failure in care and they were each stratified by the following categorical variables: 1) Time period of diagnosis (1985 or earlier and 1986 or later). Studies that included dates of diagnosis that straddled these two time periods were categorized into one of these categories depending on the time period for the majority of cases. 2) Type of screening policy (invitation-based or opportunistic screening). Studies based in health maintenance organizations (HMO) were included in the latter category as were organized screening programs that did not invite women to be screened. This information was either stated in the article or was obtained from the literature (IARC, 2005). 3) Geographic region (Canada, United States, Australia, United Kingdom, Nordic countries, Other European countries). 4) Study base (Population, HMO, Hospital). The last category also included clinic-based studies. 5) Time interval prior to ICC diagnosis during which Pap smears were considered (1 to 2 years, 3 years, 5 to 6 years). This variable was only applied to the "Failure to Detect" analysis. Upon observation of the stratified plots, those variables that appeared to be sources of heterogeneity were then used to characterize subgroups and meta-analyses were conducted in each stratum (Deeks et al., 2001).

All P-values were two-sided and values <0.05 were considered statistically significant. Statistical analyses were performed using Stata version 9.0 (StataCorp, College Station, Texas) and forest plots were generated using the R program version 1.6.2.

4.3 Results

4.3.1 Characteristics of Included Studies and Study Subjects

Overall, 305 articles were identified, of which 42 met our inclusion criteria (Table 4.1). Subject inclusion criteria, which varied amongst studies, included cancer specific variables, such as tumour histologic type and degree of invasion and subject-related characteristics, such as age at diagnosis, ethnicity/race, Pap screening history, treatment received for ICC, and receipt of

invitation to attend for screening.

Among the included studies that provided some demographic information about their study subjects, the greater proportion of subjects were non-immigrants (Fruchter et al., 1980; Anderson et al., 1992), married (Hogenmiller et al., 1994), Caucasian (Hogenmiller et al., 1994; Anderson et al., 1992; Sung et al., 2000; Leyden et al., 2005), had at most a high-school education (Fruchter et al., 1980; Nasca et al., 1991), and had a mean or median age ranging from the late 40s to early 50s. Amongst those studies without histologic exclusions, squamous cell carcinoma was the most common histologic type, encompassing from 66% to 94% of ICCs identified. The relative proportion of squamous cell carcinomas declined over time, with a larger proportion of adenocarcinomas identified in the more recent studies. Similarly, the proportion of women diagnosed with stage I cancer increased and concomitantly, the proportions diagnosed with more advanced cancers declined with time.

4.3.2 Failure to Screen

The results of the meta-analyses for all the failures in care are presented in Figures 4.1 to 4.5. Collectively, 53.8% (95% CI: 43.6-66.3) of women had deficient screening histories, either never screened or not screened within a given number of years before diagnosis. When considered separately, 41.5% (95% CI: 35.4-48.7) of women were never screened. There was evidence of significant heterogeneity among the studies included in both meta-analyses (p=0.000). Studies done in Nordic countries and those done in populations with invitation-based screening programs appeared to account for some of the variation among studies that measured deficiencies in the frequency of screening. On average, 64.8% (95% CI: 56.8-73.9) of women exposed to opportunistic screening had deficient screening compared with 42.2% (95% CI: 29.9-59.6) of women invited to screening (p=0.000) (Figure 4.1). As shown in Figure 4.2, women living in Nordic countries seemed to have a much lower probability of being screening deficient compared with American Women; 31.0% (95% CI: 19.3-49.8) and 68.5% (95% CI: 56.1-83.7), respectively. Among studies that examined the proportion of women never screened, era of diagnosis was the only variable that appeared to be a source of variation. The stratified analysis found that 47.7% (95% CI: 35.0-65.0) of women diagnosed prior to 1986 were never screened compared to 37.3% (95% CI: 30.9-45.2) of women diagnosed after this time period (Figure 4.3).

Table 4.1. Characteristics of studies satisfying the inclusion criteria

First author (publication year; location)	Inclusion Criteria	Diagnosis Date	Setting	# of subjects	Stage (%)	Histology (%)	Age (% or years)
Rylander (1976; Stockholm, Sweden)	Stages I to IV; established Stockholm resident invited to the city cytological screening program	1968-1974	Pop	171	IA (20.3) IB-IV (79.7)		
Berkowitz (1979; Boston, Massachusetts, USA)	ICC; slide review limited to women ≤35 years	Jan 1975-June 1978	Hospital	110	I (61.8) II (28.2) III (8.2) IV (1.8)	SQ (86.4) AD (13.6)	≤35 (24.5) >35 (75.5) Md 29.6 Rg 30.0
Fruchter (1980; Brooklyn, New York, USA)	ICC	July 1976-Dec 1978	Hospital	97			<50 (48.5) ≥50 (51.5)
Dunn (1981; Alameda County, California, USA)	ICC; resident of county between 1971-1975; diagnostic workup besides Pap testing; primary cervical cancer; non-sarcoma histology	1971-1975	Pop	367	CIS-MI (5.4) MI (17.4) MI-MA (11.7) MA (65.4)		20-39 (22.6) 40-59 (41.4) ≥60 (36.0)
Holman (1981; Western Australia)	ISQ	1977-1980	Hospital	100		Limited to SQ	Rg 23-84
Brown (1982; Metropolitan Portland, Oregon, USA)	ICC; enrolled in KPCP for minimum 2 years before diagnosis	1965-1975	HMO (KPCP)	63	IA (31.7) IB (25.4) II (20.6) III (19.4) IV (3.2)		Md 52 Rg 24-84
Bjerre (1983; Malmo, Sweden)	Stages IA-IV; previous Pap smears	1966-1979	Pop	131	IA (35.0) IB (35.0) II (24.0) III (5.0)		
Walker (1983; Cambridge, UK)	ISQ; excluded MI; treated by surgery or radiotherapy in Addenbrooke's Hospital; tumour depth >5mm; pathology reports available	Jan 1978-July 1981[a]	Hospital	93	IB (40.9) IIA (16.1) IIB (19.4) III (20.4) IV (3.2)	Limited to SQ	≤35 (9.7) 36-50 (23.7) >50 (66.7)
Carmichael (1984; Kingston, Ontario, Canada)	ICC	Jan 1973-Oct 1982	Clinic	245	IA (11.4) IB (39.2) II-IV (49.4)	SQ (86.1) AD (11.1) AS (2.4)	

Table 4.1. continued

First author (publication year; location)	Inclusion Criteria	Diagnosis Date	Setting	# of subjects	Stage (%)	Histology (%)	Age (% or years)
Dunn (1984; Memphis and Shelby Counties, Tennessee, USA)	ICC; prior negative cytology	1952-1978	Pop	430			<35 (18.1) 35-50 (41.2)
Paterson (1984; Yorkshire, Yorkshire)	ICC; treated by the 2 co-authors; availability of pap history	1968-1980[a]	Hospital	312	I (54.2) II (30.4) III (14.1) IV (1.3)		≤35 (17.6) 36-45 (19.2) 46-55 (22.8) 56-65 (26.3) >65 (14.1)
Attwood (1985; Birmingham, England)	ICC	1974-1981	Hospital	346			≤50 (34.0) >50 (66.0)
Roberts (1985; Queensland, Australia)	ICC; ≤40 years of age; adequate records available	1972-1981	Clinic	194			Limited to subjects ≤40 years
Olesen (1988; Denmark)	ICC; completed questionnaire; timing and # of slides known; stage known	1983	Pop	420	1 (55.7) 2 (22.9) 3 (14.8) 4 (6.7)		
Choyce (1990; Leicestershire County, England)	ICC	1985	Pop	54		SQ (94.0) AD (6.0)	<40 (31.5) ≥40 (68.5)
Turner (1990; Dublin, Ireland)	Early ICC; received a radical hysterectomy	1980-1989[a]	Hospital	100	I (73.0) II (27.0)	SQ (93.0) AD (7.0)	<30 (11.0) 30-39 (39.0) 40-49 (27.0) >49 (23.0)
Kristensen (1991; Funen County, Denmark)	ICC; screened within 3 years prior to diagnosis	1979-1983	Pop	202			≤35 (27.2) 36-45 (25.7) 46-55 (21.2) 56-65 (14.4) ≥66 (11.4)
Nasca (1991; New York, USA (excluding New York City))	ICC; 20-69 years of age; participated in interview	July 1983-Sept 1985	Pop (Cross-section)	261	Local (61.3) Reg (25.2) Distant (5.0) UNK (8.4)		20-34 (14.9) 35-44 (26.1) 45-54 (26.1) 55-64 (25.7) ≥65 (7.3
Sweet (1991; Prince Edward Island, Canada)	ISQ; primary cervical disease; complete record available	1981-1986	Pop	37		SQ (68.5) AD (18.6) OT (12.9)	20-29 (3.0) 30-39 (29.7) 40-49 (13.5) 50-59 (16.2) 60-69 (16.2) 70-79 (18.9) 80-89 (2.7)

Table 4.1. continued

First author (publication year; location)	Inclusion Criteria	Diagnosis Date	Setting	# of subjects	Stage (%)	Histology (%)	Age (% or years)
Anderson (1992; British Columbia, Canada)	ICC (excluding microinvasive)	1985-1988	Pop	437	IB (51.0) II (26.0) III-IV (23.3)	SQ (74.1) AD (14.2) AS (11.7)	<35 (15.8) 35-49 (28.8) ≥50 (55.4)
Wain (1992; Paddington, New South Wales, Australia)	ICC; referred to gynaecological oncology unit	Nov 1986-July 1990 (referral period)	Hospital	237	≤IIa (75.9) >IIa (24.1)	SQ (74.7) OT (25.3)	Me (49.9) Rg (23-91)
Ciatto (1993; Florence, Italy)	ICC; 25-70 years of age	1988-1989	Pop	69			Me (53.0) Rg (27-70)
Mobius (1993; Schwerin District, Germany)	ICC; histologically diagnosed	1980-1988	Pop	577	IA (17.2) IB (33.7) II (23.2) III (22.4) IV (3.5)		
Ratima (1993; New Zealand)	ICC; Maori Women; Presented at one of 6 treatment centres	May 1, 1989 - April 30, 1991	Pop	46	I (34.8) ≥II (56.5) UNK (8.7)		<40 (34.8) 40-54 (34.8) ≥55 (30.4) Me (48.0) Rg (26-76)
Hogenmiller (1994; Nebraska, USA)	ICC	Jan 1, 1988-Dec 31, 1990	Hospital	101	1 (58.8) 2 (29.4) 3 (9.8) 4 (2.0)	SQ (73.5) AD (22.5) AS (2.9) SC (1.0)	≤35 (30.4) >35 (69.6) Me (45.0) Md (41.0)
Janerich (1995; Connecticut, USA)	ICC; Connecticut resident; participation in interview by subject or by next of kin	Mar 1, 1985 -Feb 23, 1990	Pop	481	I (53.2) II (23.5) III-IV (12.5) UNK (10.8)	SQ (80.0) AD (16.2) AS (3.7)	Me (51.6)
Van Wijngaarden (1995; Dundee and Angus, Scotland)	ICC; stage IB or worse; known histology and/or stage; Pap screening data for women >50 years of age	1982-1991	Pop	195	Ib (51.8) II (28.2) III/IV (19.0)	SQ (88.2) AD (11.8)	<35 (14.9) 35-54 (31.8) >54 (53.3)
Kenter (1996; western part of Netherlands)	ISQ; availability of Pap history 3.5 years prior to diagnosis	Jan 1980-Dec 1989	Hospital	306	I (57.2) II (27.1) III (13.4) IV (2.3)	Limited to SQ	<35 (14.7) 35-55 (40.8) >55 (44.4)
Sasieni (1996; England, Wales, Scotland, United Kingdom)	ICC	1992	Pop	348	IA (25.9) ≥IB (53.4) I NOS (6.9) UNK (13.8)		20-34 (20.4) 35-49 (31.9) 50-64 (22.1) 65-74 (17.2) ≥75 (8.3)

Table 4.1. continued

First author (publication year; location)	Inclusion Criteria	Diagnosis Date	Setting	# of subjects	Stage (%)	Histology (%)	Age (% or years)
Stenkvist (1996; Gävleborg, Sweden)	ISQ	1986-1987	Pop	22		Limited to SQ	
Baldauf (1997; Strasbourg, France)	ICC; last report on last normal smear was available	Jan 1985-Dec 1995	Hospital	86	Ia (17.4) Ib (41.9) II (27.9) III (9.3) IV (3.5)	SQ (93.0) AD (7.0)	Me (51.2)
Stuart (1997; Alberta, Canada)	ICC; residing in Alberta at diagnosis; primary disease of cervix	Jan 1990-Dec 1991	Pop	246	IA (5.0) IB (51.6) II (8.7) III-IV (12.6)	SQ (80.5) AD (14.6) AS (3.7) NOS (1.2)	≤49 (65.0) >49 (35.0)
Jansson (1998; Uppsala, Sweden)	ISQ	1991-1994	Pop	43		Limited to SQ	
Kinney (1998; Northern California, USA)	ICC; member of KPCP in Northern California; diagnosed and treated at KPCP facility	1988-1994	HMO	642			
Womack (1998; Peterborough District, United Kingdom)	ICC excluding MI	1988-1996	Hospital	99		SQ (73.7) AD (23.3) AS (2.0) SC (1.0)	Me (53.0) Rg (25-90)
Andersson-Ellstrom (2000; Varmland, Sweden)	ISQ	1990-1997	Pop	112	I (60.7) II (18.8) III (12.5) IV (8.0)	Limited to SQ	20-29 (6.3) 30-49 (52.7) 50-59 (8.0) 60-79 (32.1) 80-99 (6.3) Rg (24-98)
Kreuger (2000; Rotterdam, Netherlands)	ICC; primary or secondary ICC; living in Rotterdam area	1992-1994	Pop	165		SQ (77.6) AD (21.2) AS (0.6) NOS (0.6)	Me (57) Rg (26-91)
Sung (2000; Greater San Francisco Bay, California, USA)	ICC; member of KPCP in Northern California for minimum 33 months of 36 months prior to diagnosis; Diagnosed and treated at KPCP facility	Jan 1, 1988 - Dec 31, 1994	HMO	455	<IIB (82.2) ≥IIB (17.8)	SQ (67.9) AD (24.4) AS (4.4) Both (0.4) SC (1.5) NOS (1.3)	<40 (25.0) 40-54 (41.8) ≥55 (33.2) Me (49.6) Rg (26-89

Table 4.1. continued

First author (publication year; location)	Inclusion Criteria	Diagnosis Date	Setting	# of subjects	Stage (%)	Histology (%)	Age (% or years)
Brinkmann (2005; London, UK)	ICC	1988-1998	Hospital	66			Md 45 Rg 21-81
Leyden (2005; Seattle, Detroit, Oakland, Pasadena, Portland, Denver, Honolulu, USA)	ICC; member of KPCP for minimum 33 months of 36 months prior to diagnosis; member at diagnosis; complete medical records; definitive evidence of invasion	Jan 1, 1995 - Dec 31, 2000	HMO	833	Localized (65.1) Regional (24.8) Distant metastases (6.5) UNK (3.6)	SQ (66.6) AD (23.9) AS (5.0) OT (4.4)	16-39 (24.1) 40-49 (31.2) 50-64 (27.7) ≥65 (16.9)
Nygard (2005; Norway)	ICC	2000-2002	Pop	777	I (57.0) II (20.7) III (12.6) IV (6.4) UNK (3.2)		
Bos (2006; Netherlands)	ICC	1994-1997	Pop	2074			

ICC, invasive cervical cancer; MI, microinvasive; MA, macroinvasive; CIS, carcinoma in-situ; SQ, squamous cell; AD, adenocarcinoma; AS, adenosquamous; SC, small cell; ISQ, invasive squamous cell; NOS, not otherwise specified; UNK, unknown; Me, mean; Md, median; Rg, range; OT, other; KPCP, Kaiser Permanente Care Program; Pop, population; HMO, health maintenance organization; Reg, regional.

[a] Refers to treatment date.

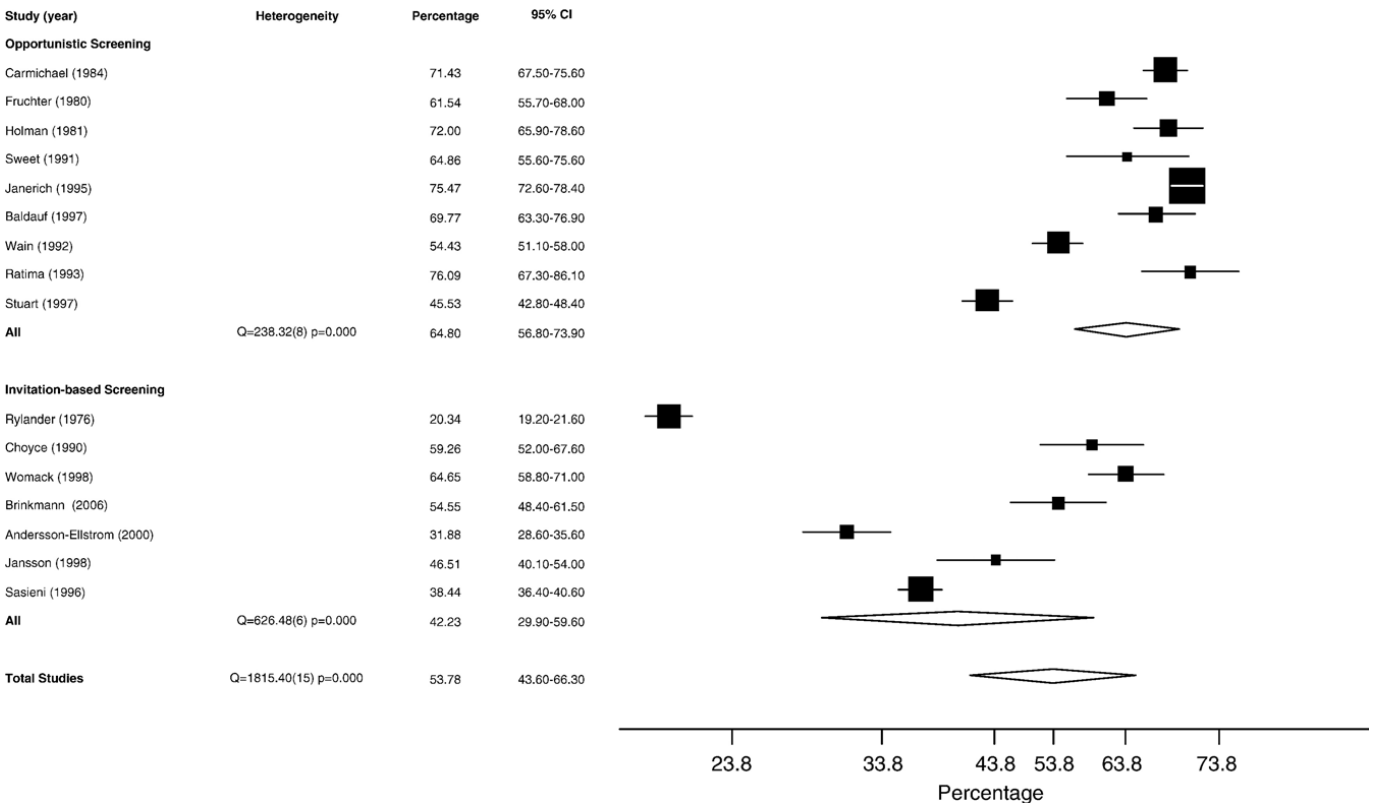

Figure 4.1. Percentages and 95% CIs from studies that examined the proportion of subjects with deficient screening histories stratified by type of screening policy.

Point estimates for individual studies are represented by boxes, the sizes of which are inversely proportional to the variance. The horizontal lines represent confidence intervals. The diamonds represent the summary estimates for multiple studies and their ends indicate the confidence limits.

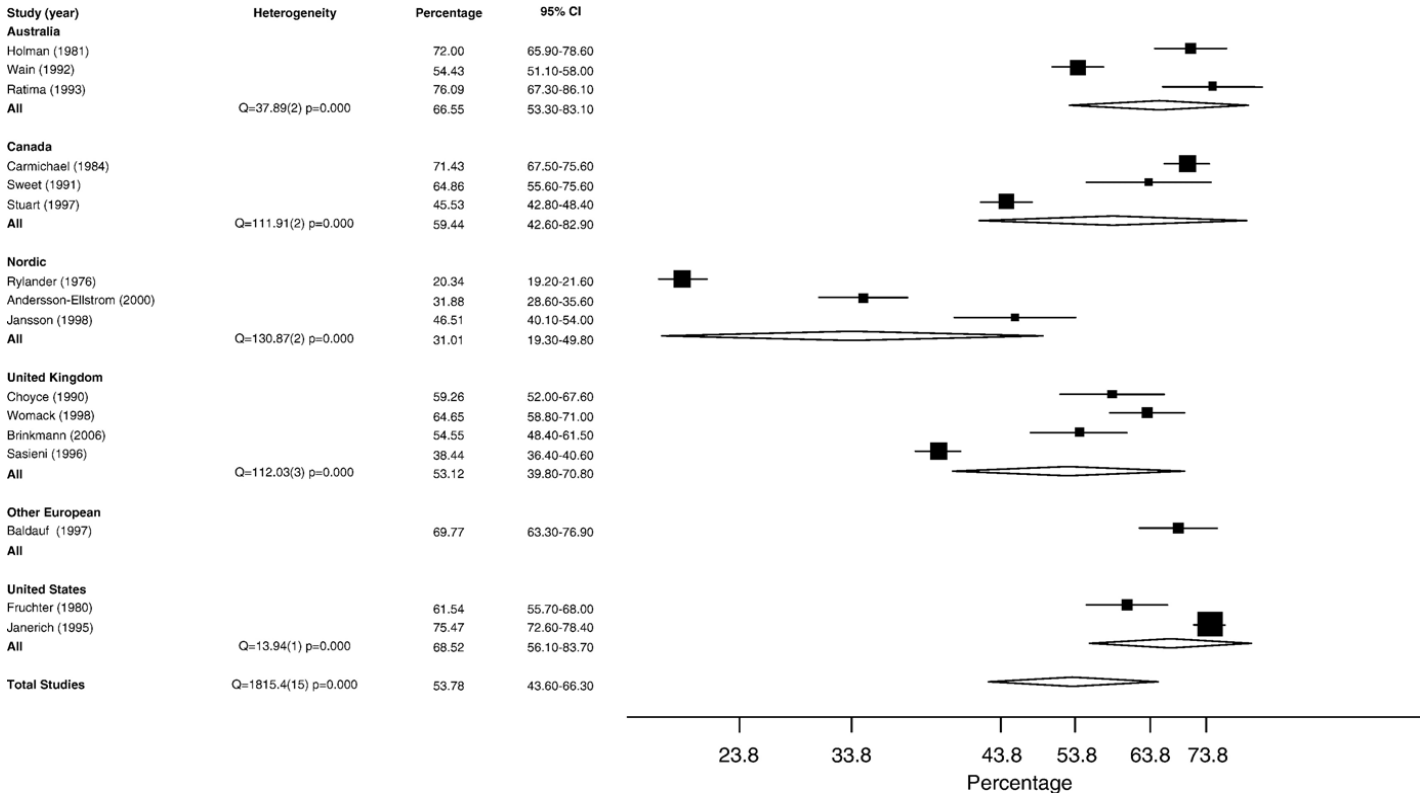

Figure 4.2. Percentages and 95% CIs from studies that examined the proportion of subjects with deficient screening histories stratified by geographic region.

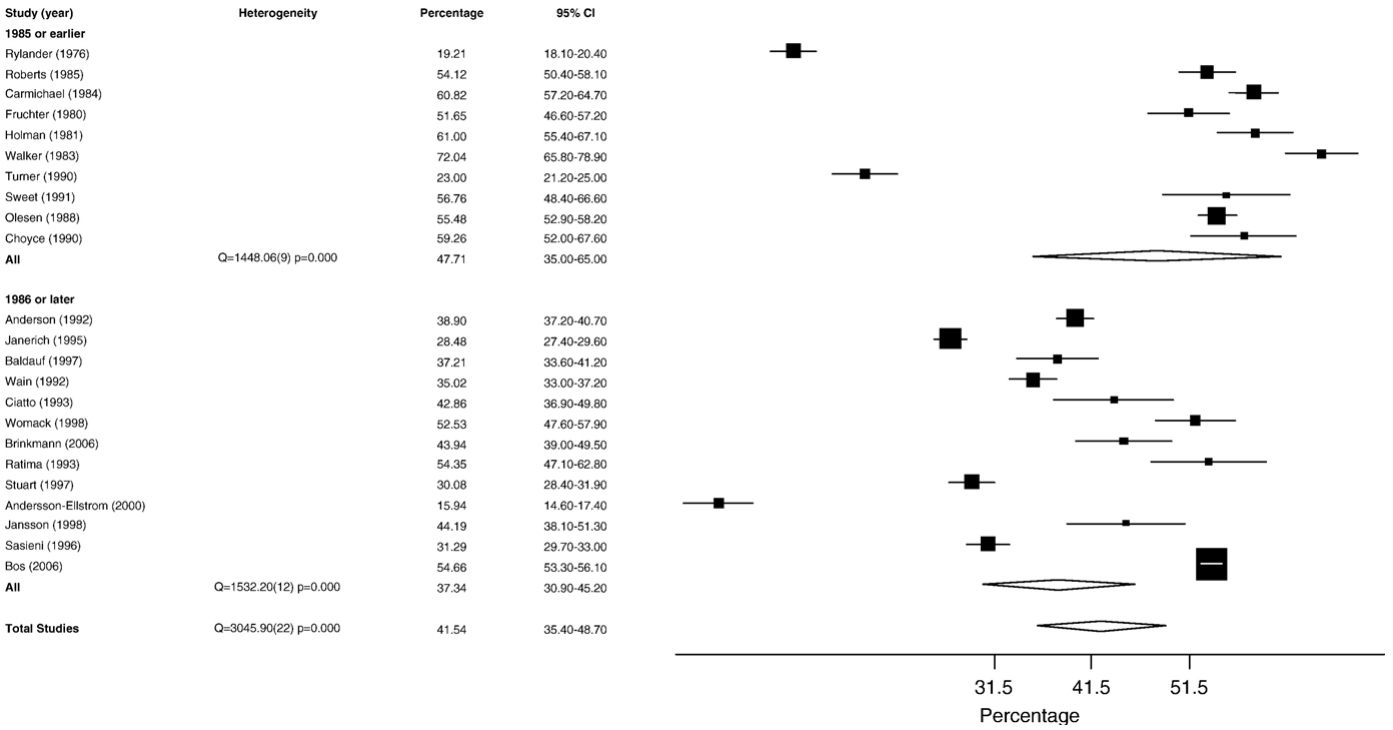

Figure 4.3. Percentages and 95% CIs from studies that examined the proportion of subjects never screened stratified by time period.

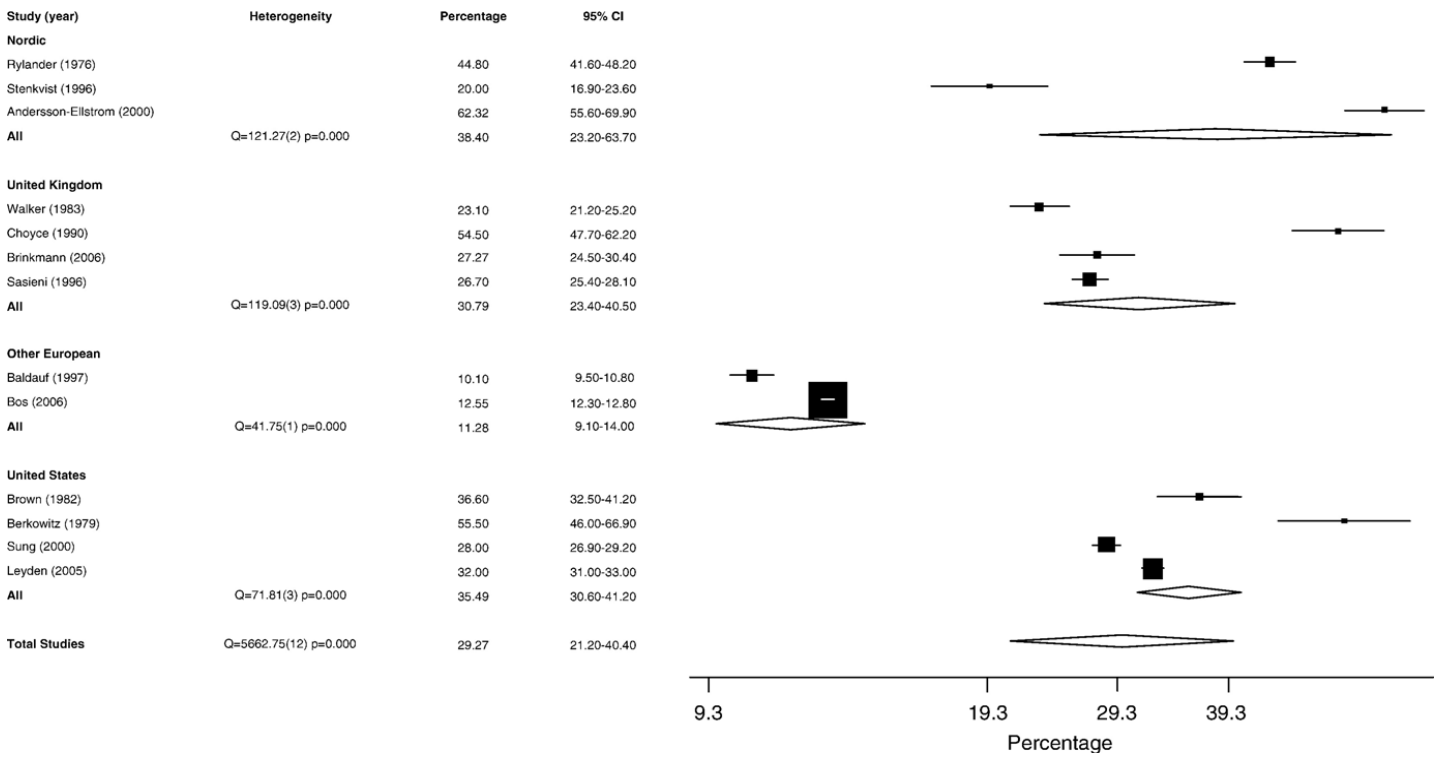

Figure 4.4. Percentages and 95% CIs from studies that examined the proportion of subjects with false-negative Pap smears.

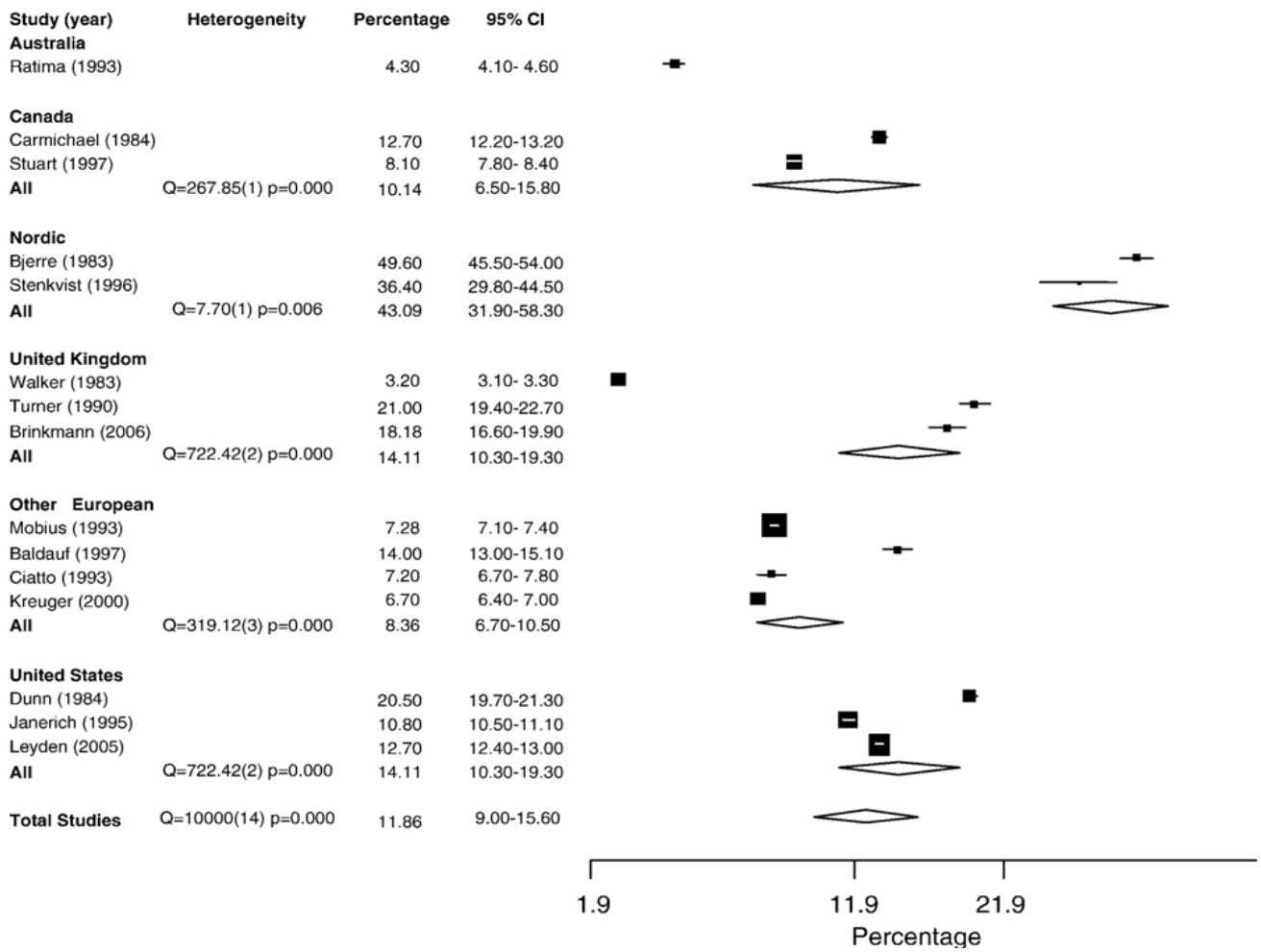

Figure 4.5. Percentages and 95% CIs from studies that examined the proportion of subjects with poor follow-up care.

4.3.3 Failure to Detect an Abnormality

Several studies assumed that negative cytological findings from one to six years before diagnosis with ICC represented false-negative results. Amongst women who were screened prior to diagnosis, 29.3% (95% CI: 21.2-40.4) had at least one negative smear prior to diagnosis. The study by Paterson et al. (1984), which examined a 10-year time period, was excluded from this analysis as it is likely that many of these smears were truly negative. As shown in Figure 4.4, the European studies by Baldauf et al. (1997) and Bos et al. (2006) seemed to have a significantly lower proportion of false-negative smears (11.3%, 95% CI: 9.1-14.0) compared to the U.S. studies (35.5%, 95% CI: 30.6-41.2).

Other studies included a review of archived Pap smears originally deemed as normal and enumerated false-negative results either in relation to the proportion of Pap slides retrieved or number of subjects for whom slides were available. As shown in Table 3.2, section I, the former studies found 20.0% to 62.5% of slides contained equivocal or dysplastic cells, carcinoma-in-situ, or invasive cancer. As individual studies either retrieved no slides for some subjects and one or more slides for other subjects, false-negative rates could not be calculated as a function of the number of ICC subjects. The latter studies examined one Pap smear per case and upon review categorized 11.1% to 33.3% of subjects as having had false-negative Pap smears. These studies were unable to retrieve smears for all women with normal cytology; hence, similarly, we were not able to determine the overall proportion of cervical cancer cases that could be attributed to a failure in detection.

Few studies examined the possibility of under-calling of cytology or poor quality slides. Proportions varied widely, with an estimated 21.0% and 90.5% of the abnormal slides being undercalled (Table 4.2, section II). As shown in section I, in a few instances, the quality of the archived Pap smears was also assessed within the cytologic review. The percentage of cytologically “normal” slides deemed to be of inadequate quality upon review varied less, with estimates ranging from 20.0% to 38.5%. The study by Kristensen and colleagues (1991) was the exception with 2.1% of “normal” slides being deemed as inadequate specimens.

Table 4.2. Review of archived Pap smears by different studies as indicative of false-negative, undercalled, or inconsistent results

First Author	# of subjects	Total # of Negative Smears retrieved	Time interval prior to diagnosis (years)	% (n slides or women)	Results of Review
I) Cytologic Review of 'Normal' Pap Slides					
A) In terms of Slides					
Stuart (1997)	--[a]	104	5	43.3 (45)	ASCUS, LSIL, HSIL, ICC
Roberts (1985)	5	8	2	62.5 (5)	malignant or dysplastic cells
				37.5 (3)	Inadequate sampling of squamocolumnar junction
Berkowitz (1979)	10	13	2	61.5 (8)	Dysplastic, CIS, probable cancer
				38.5 (5)	inadequate cellularity
Jansson (1998)	--	10	6	60.0 (6)	Pap II
				20.0 (2)	Too scanty
				20.0 (2)	Negative
Walker (1983)	--	11	5	27.3 (3)	Suggestive of CIS or possible ICC
				27.3 (3)	Normal and inadequate
				45.4 (5)	Normal and adequate
Kenter (1996)	22	30	3.5	53.3 (16)	>=Pap IIIA and adequate
				20.0 (6)	Pap I or Pap II
				26.7 (8)	Unsatisfactory
Kristensen (1991)	58	96	3	40.6 (39)	Atypical, CIN or cancer
				57.3 (55)	Normal and adequate
				2.1 (2)	Inadequate
B) In terms of Subjects					
Stuart (1997)	246		3	17.1(42)	"false-negative"
Holman (1981)	6		1	33.3 (2)	Slight atypia
Wain (1992)	51		2	31.3 (16)	CIS or invasive. Adequate
				7.8 (4)	Inadequate
Womack (1998)	18		5	11.1 (2)	Abnormal and Adequate
				16.7 (3)	Inadeqeuate
				72.2 (13)	Normal and Adequate
Janerich (1995)	137		3	21.2 (29)	Misread as normal
Ciatto (1993)	3		5	33.3 (1)	Severe dysplasia
				33.3 (1)	Inadequate

Table 4.2. continued

First Author	# of subjects	Total # of Abnormal Smears retrieved	Time interval prior to diagnosis (years)	% (n slides or women)	Initial Cytology /Results of Review,
II) Cytologic Review of 'Abnormal' Pap Slides					
A) In terms of Slides					
Kenter (1996)	19	21	3.5	90.5 (19)	Pap IIIA / Pap IIIB
				9.5 (2)	Pap IIIA / Pap IIIA
Kristensen (1991)	--	186	3	78.5 (146)	CIN and adequate / CIN and adequate
				21.0 (39)	CIN / Cancer
				0.5 (1)	Inadequate
B) In terms of Subjects					
Womack (1998)	3		5	33.3 (1)	Borderline abnormality / severe dyskaryosis
Holman (1981)	6		1	59.7 (4)	Slight atypia / dyskaryosis or suspicion of malignancy
					Dyskaryosis / suspicion of malignancy

[a] indicates that the data was not provided in article

4.3.4 Failure to Follow-Up

Subjects who were appropriately screened in the past, had truly abnormal cytology prior to diagnosis and still developed ICC can be considered as having a failure in their follow-up care. An abnormal Pap smear should have triggered appropriate diagnostic action within a reasonable time period and likewise, an identified precursor lesion should have been appropriately treated within a timely fashion. An average 11.9% (95% CI: 9.0-15.6) of subjects who had a recent abnormal smear had poor follow-up (Bjerre et al., 1983; Walker et al., 1983; Carmichael et al., 1984; Dunn et al., 1984; Turner et al., 1990; Ciatto et al., 1993; Mobius et al., 1993; Ratima et al., 1993; Janerich et al., 1995; Stenkvist et al., 1996; Baldauf et al., 1997; Stuart et al., 1997; Kreuger et al., 2000; Brinkmann et al., 2005; Leyden et al., 2005). There was statistically significant variation among studies (p=0.000). Figure 4.5 shows that subjects residing in Nordic countries had a greater probability of having poor follow-up (43.1%, 95% CI: 31.9-58.3) compared to women in

the U.S. (14.1%, 95% CI: 10.3-19.3). The other variables examined did not appear to be significant predictors of follow-up variation.

4.4 Discussion

4.4.1 Summary of Results

A deficient screening history was the most common process failure along the cancer care continuum attributable to the development of ICC, with an overall 54% of women with inadequate screening intervals and 42% of women specifically never screened. The stratified analysis revealed that a greater proportion of ICC patients had been screened at least once over their lifetimes in recent studies than in earlier ones. The growing body of evidence surrounding the effectiveness of the Pap smear at reducing incidence and mortality from cervical cancer may have been the primary factor responsible for the increased uptake in use. This knowledge, in conjunction with the historically observed poor screening histories of selected groups, has led to development of various interventions to enhance Pap smear uptake (Marcus et al., 1998).

In contrast, the overall proportion of women with inadequate screening histories did not appear to vary with time. In light of the above increased ever-screening experience in recent studies, this finding is consistent with the notion that although a woman has been screened in the past, it does not necessarily mean that she will continue to return for screening in the future. Further, it has been shown that women with normal cytologic results tend to underestimate their future risks of developing cervical neoplasia (Chingang et al., 2005) and hence, may postpone or forego future screening. This underscores the importance of a computerized system to track Pap testing and to appropriately recall women for screening. The effectiveness of this intervention is supported by the higher frequency of adherence to appropriate screening frequencies found in populations with invitation-based screening programs. Interestingly, invitation-based screening did not differentially affect the proportion of women who were never screened. It has been suggested that women who have never been screened have such a strong resistance to

screening that they may require a multi-intervention approach to recruitment, including not only invitation letters but also subsequent reminder letters, invitations via the telephone, and the offer of a specific appointment for screening (Wilson and Leeming, 1987).

The proportion of women never screened did not vary significantly among geographic regions. Hence, there may be universal similarities amongst women who have access to screening but nonetheless are inadequately screened. For instance, many studies found an increased likelihood of poor screening with advancing age (Fruchter et al., 1980; Choyce and McAvoy, 1990; Nasca et al., 1991; Sweet et al., 1991; Hogenmiller et al., 1994; Janerich et al., 1995; Kenter et al., 1996; Baldauf et al., 1997; Stuart et al., 1997; Sung et al., 2000). This may be a result of misguided beliefs and practices by both women and the health care system. Studies have shown that older women make less frequent visits to gynecologists (Cohen et al., 1992), are less likely to have knowledge about the Pap test (Siahpush and Singh, 2002), and family practitioners are less likely to recommend Pap testing to older women (Cohen et al., 1992). Moreover, this age variation may be a consequence of recommendations regarding the appropriate age at which to cease cervical screening. Although recommendations do vary somewhat by professional organizations, screening is generally not encouraged for women starting from their sixth or seventh decade of life (IARC, 2005; Morrison, 1994). To some extent this age trend may also reflect a cohort effect in that these older women belonged to a generation that had not yet realized the importance of receiving regular Pap screening. This observation may change to a degree in the future since current generations are better screened than in the past.

Most studies included in this review were either conducted in ethnically homogeneous populations or did not examine the influence of race/ethnicity on screening use. One U.S. study found that minority women were more likely to have been poorly screened for cervical cancer than non-minority women (Kreuger and Beerman, 2000). Initially, it could be surmised that monetary constraints were the impediment to screening as lack of health insurance has been shown to adversely affect the receipt of preventive services

(Mandelblatt et al., 1999). However, as these subjects were long-term members of an HMO, money was not a barrier to screening. Hence, although health insurance coverage does remove the economic barrier to preventive care, it does not guarantee subjects will receive appropriate screening (Leyden et al., 2005; Chattopadhyay et al., 2005; O'Malley et al., 2002). In contrast, Leyden et al. (2005) did not find an association between poor screening and ethnicity at the individual-level but they did find that neighbourhood-level variables influenced the screening habits of women. Specifically, women with poor screening histories tended to live in neighbourhoods characterized by high-poverty and low level education compared to women with appropriate screening histories.

Some studies found that women with poor screening histories did receive other medical care, whether within the same HMO or in other health care facilities, prior to diagnosis with ICC (Fruchter et al., 1980; Brown and Barker, 1982; Kinney et al., 1998; Leyden et al., 2005). These medical visits all represent opportunities when cervical screening could have taken place and may potentially have led to the detection of an intraepithelial cervical lesion or to an early ICC diagnosis.

The proportion of Pap smears originally labelled as cytologically normal that were categorized as false-negatives upon review or those normal Pap smears not reviewed but simply presumed to be false-negative varied widely among studies. The different time intervals studies examined, the varying quality of cytologic services in different regions or hospitals, and small sample sizes may be partly responsible for this variation. On average, 29.3% of women had false-negative cytologic findings within a few years of diagnosis. The conventional Pap test has a high false-negative rate, with an estimated mean sensitivity of 47% for CIN 1 and worse (Nanda et al., 2000) and 53% for CIN 2 and worse lesions (Cuzick et al., IJC 2006). Fortunately, as noted above, period repetition of the Pap test has been found to improve the sensitivity (Nanda et al., 2000). Except for outliers (Baldauf et al., 1997; Bos et al., 2006), the proportion of false negative smears did not vary significantly between geographic regions.

Although a much lower proportion of ICC cases was attributable to poor follow-up, it is

important to realize that without appropriate follow-up for abnormal test results the incidence of cervical cancer will not decline. Study subjects with ICC in Nordic countries had a much higher chance of being categorized as having had poor follow-up care compared to American subjects. This indicates that as failures to screen decline, the relative proportion of failures attributable to factors "downstream" from screening will increase proportionally if not also addressed.

There may be instances when the development of ICC in women with appropriate screening histories may not be a result of failures in care. In fact, an estimated 5% of cases in this meta-analysis could not be attributed to any failure in care. It has been suggested that the Pap test has a lower sensitivity for the detection of adenocarcinomas (Scheiden et al., 2004). Hence, glandular lesions are often missed, especially when they do not involve the transformation zone but rather are located higher in the endocervical canal (Kalir et al., 2005). As a result, the studies included in this meta-analysis found that as the proportion of women being screened increased over time, more squamous cell carcinomas were detected at the precursor stage and hence, the relative proportion of invasive cervical adenocarcinomas increased. In addition, many studies included in this meta-analysis assumed that women who had normal Pap smears within a few years of diagnosis must have had false-negative Paps. It is possible that a small minority of those women had rapidly progressing cancers that developed so rapidly as to be missed even though they were screened at appropriate frequencies (Miller, 1995).

4.4.2 Study Limitations and Strengths

This study had some limitations. The meta-analysis revealed significant heterogeneity between the studies; hence, overall summary estimates should be interpreted with caution. In addition, this study considered the possibility that subjects experienced only one failure in care along the continuum, but in actuality a subject may have had multiple points of failure. Also, it must be noted that screening, follow-up, and treatment guidelines and cytologic norms vary by region, country, and era. We did not take these differences into consideration when enumerating the failures of care for two reasons.

First, few studies explicitly discussed these guidelines and second, studies presented data in a given manner that did not necessarily allow us to harmonize results according to common specifications. Hence, the categorization of what constitutes a failure may vary by study. In this meta-analysis we attempted to reproduce the context of failures according to specific circumstances of time and place, as interpreted in the original studies. Thus, results may not be directly applicable to the general population of women in a given geographical setting. Further, it must be taken into consideration that this study was limited to cases of ICC and hence, results may not necessarily be generalizable to all women who are clients of screening. Conversely, by focusing on the ultimate untoward outcome, rather than less severe lesions, we were able to enumerate the most cogent process-of-care failures (Williamson, 1971). Further, the stratification allowed us to visualize the degree to which several factors affected the failures in care and the nature of the relationships.

4.5 Rationale for Current Study

This current study evolved from the observation that despite the availability of Pap screening and the means of managing cytologic abnormalities and histologic pre-invasive lesions, there are still many Canadians diagnosed with invasive cervical cancer every year. In fact, it is the 3rd most common neoplasm among Canadian women between the ages of 20-49 years. Upon reviewing the literature, I found some previously conducted studies that attempted to examine the processes of care that women with invasive cancer had prior to diagnosis. This led to the publication of the review and meta-analysis article discussed above.

Although the studies included in this meta-analysis provided valuable information they did have some limitations. Most studies were limited to only assessing the failures in Pap screening; they defined the proportion of subjects who were never screened and/or the proportion of subjects who were not screened within a given period before final diagnosis with cervical cancer. A few studies ventured further than this and assessed the

follow-up of abnormal Pap smears. This was done in a cursory manner as studies did not separately examine the acceptability of the procedures used to manage the cytologic abnormalities and the timing of the follow-up of these abnormalities. In addition, none of the previous studies included an examination of the management of pre-invasive lesions. Although, according to this meta-analysis, a relatively small proportion of failures in care can be attributed to poor follow-up of abnormal Pap smears, it is still important to closely examine the details of this failure in care and to also examine the processes of care downstream in the cancer care continuum (Figure 3.1). Further, it is imperative to determine the circumstances surrounding those subjects who were adequately screened in the past but nonetheless still developed cervical cancer. Moreover, some previous studies were hospital or clinic-based. These may have provided biased results if the patient referral pattern to that hospital differs from the surrounding catchment area and thus, may give a skewed picture of the failures in care that occurred in the base-population. In addition, several studies that determined the lifetime screening histories of subjects did not actually interview subjects and hence, cannot ensure that true lifetime screening histories of subjects were captured. I hope to have addressed these issues in this current study.

5. METHODOLOGY

5.1 Study Overview

The study objective was examined in the context of a case-control study. Cases were Montreal or Laval residents diagnosed with invasive cervical cancer between 1998 and 2004. They were identified through two sources: the Fichier des tumeurs du Québec, which is the provincial population-based cancer registry (henceforth, it will be referred to as the tumour registry) and the medical records departments of relevant hospitals. Two control groups were used: One control group consisted of females residing in Montreal or Laval who responded to the 2003 Canadian Community Health Survey (CCHS). A second control group consisted of a randomly chosen group of women, without cervical cancer, who were obtained from the Régie de l'assurance maladie du Québec (RAMQ). These controls were matched to the cervical cancer cases according to age and place of residence.

Cervical Pap screening, diagnostic procedures and pre-invasive lesion treatment histories for cases were obtained from hospital medical charts, hospital cytology and pathology laboratories, subject and proxy interviews, and physician questionnaires. The processes of care that each case received within 5 years before diagnosis were then assessed as per explicit medical review criteria, which were based on clinical practice guidelines and consensus by clinical co-investigators. The first set of controls above was used in the investigations of the association between subject demographic characteristics and cervical cancer and also the association between screening histories and cervical cancer. The second set of controls was used to examine the health services use of cases within 5 years prior to diagnosis. Note that throughout this document the terms “study subjects”, “subjects”, or “cases” will be used to refer to women diagnosed with cervical cancer.

5.2 Method of Quality Assessment

The strategy for quality assessment used in this study was based on the “negative indexes” method (Rutstein et al., 1976; Mushlin et al., 1978; Heineken et al., 1985). This method identifies potentially preventable cases of disease or death, so called sentinel

health outcomes, and then searches back in time in the processes of care to determine reasons for these failures. The negative indexes method is believed to be an optimal method of assessment as it has a greater ability to determine those factors which, if rectified, might be able to produce significant improvement in health (Williamson, 1971).

A performance measure is a tool that generates a quantitative measure of the quality of care and it consists of five elements, which must be specified as they pertain to the current quality assessment being conducted (Agency for health care policy and Research, 1995):

1) The medical review criteria. 2) The cases to whom the criteria will be applied. 3) Specification of the data to be collected. 4) The data collection methods. 5) The definition of the data analysis procedures. These five elements will be discussed throughout the methodology and statistical analysis sections.

5.3 Study Subjects

5.3.1 Subject Inclusion Criteria

The cases were women diagnosed with invasive, including microinvasive, cervical cancer. Specifically, the inclusion criteria were as follows:

1) The cervix was the primary cancer site.

2) The cancer must have been histologically-confirmed. This confirmation was based upon the findings of one or more of the following procedures: cervical biopsy, cone biopsy, endocervical curettage (ECC), loop electrosurgical excision procedure (LEEP), or hysterectomy. In those cases for which we did not find histologic confirmation of cervical cancer, confirmation from hospital gynecologic tumour boards, the reports of which were available in medical charts, were accepted as proof.

3) The cancer must have been diagnosed between January 1, 1998 and December 31, 2004.

4) If the subject had a recurrence of cervical cancer, the first incidence of cervical cancer must have occurred between 1998 and 2004. We were not interested in cervical cancer recurrences, if any, which occurred after this first incidence.

5) The subject must have been diagnosed at a hospital in Montreal or Laval, Quebec.
6) The subject must have been residing in one of these regions at diagnosis.
7) The subject must have been residing in Montreal or Laval for a minimum five years prior to diagnosis. Although we did not assess the quality of care for women who lived in Montreal or Laval for less than five years prior to diagnosis, we did administer a short-version of the subject questionnaire to these women (or next of kin). Hence, allowing us to examine the self-reported (or proxy-reported) cervical screening histories and sociodemographics of these recent immigrants from other parts of the province and from outside Quebec.
The regional and temporal criteria noted in criteria 5 to 7 enabled us to investigate the health services use of long-term residents of this defined region. Further, they had a practical reason; namely, as the study centre was located in Montreal, it was more feasible for us to collect data from the regions noted.

5.3.2 Identification of Study Subjects

The tumour registry was one source of case identification. This registry is a centralized database of incident cases of cancer that occur in the province of Quebec. It identifies cancer cases through death files, palliative care centres, the federal Canadian Cancer Registry, hospitalisation files, and through inter-provincial exchanges of cancer data (Personal communication, Monsieur Michel Beaupré of the Fichier des tumeurs du Québec). For this study, the tumour registry used the International Classification of Diseases (ICD), Ninth Revision, codes 180.0-180.9 to identify women diagnosed with cervical cancer at a Montreal or Laval hospital between 1998 and 2004 who had a home address located in either of these two regions at the time of diagnosis. The tumour registry specifically provided us with the following data for each subject: first and last names; RAMQ number; year of diagnosis; name of hospital where diagnosed with cervical cancer; medical chart number at the hospital of diagnosis; and the region of residence at diagnosis (Montreal or Laval). The tumour registry was not able to confirm the duration of residence in these areas. Confirmation of this information was obtained from medical charts, lab reports, and subject or proxy interviews. In addition, the tumour

registry was not able to determine with complete certainty whether it was a subject's first incidence of cervical cancer. As per its operating procedures, recurrences would be disallowed because the registry takes into account the histological codes used in the ICD system, which identifies when a case is simply a secondary recurrence. Hence, a second cervical cancer diagnosis in someone already included in the registry as a cervical cancer case would be flagged as a recurrence. That said, the registry cannot exclude recurrent cases that are inappropriately miscoded histologically by the hospital, if the registry does not already have an entry for the same patient as a first cervical cancer primary. Confirmation of these data were obtained from medical charts, laboratory reports, and physician questionnaires.

It should be noted that there is quite a long lag time between actual diagnoses of cervical cancer cases and the tumour registry receiving the data from its multiple sources, collating the data, cleaning it, and transmitting it. We experienced the longest wait time for the list of cases diagnosed in 2004, which was transmitted to us 3 years after this in late 2007.

A second source of subject ascertainment was the medical records departments of those hospitals located in Montreal and Laval that provided diagnostic follow-up and treatment services for women with cervical pre-invasive lesions and cervical cancer (Table 5.1). These were also the hospitals that had cytologists that read Pap tests. The medical records departments used ICD-9 codes 180.0-180.9 to identify women admitted or discharged from the hospital with invasive cervical cancer between 1998 and 2004. They were further instructed to limit their search to women with addresses located in Montreal or Laval at that time. Besides providing us with the names of potential study subjects, they also gave us their RAMQ numbers, hospital chart numbers, dates of hospital arrival and/or discharge with cancer, and postal codes of their residences at that time.

Table 5.1. Hospitals offering cervical cancer diagnostic and treatment services

Hôpital Notre-Dame	Hôpital Sacré-Cœur
Hôpital St. Luc	Hôpital Maisonneuve-Rosemont
Hôpital Hôtel-Dieu	Hôpital Santa Cabrini
Royal Victoria Hospital	Hôpital Jean Talon
Montreal General Hospital	Hôpital Lasalle
St. Mary's Hospital	Hôpital Verdun
Sir Mortimer B. Davis Jewish General Hospital	Hôpital Fleury
Hôpital Ste-Justine	Hôpital Lachine
Lakeshore General Hospital	Cite de la Santé De Laval

5.4 Period of Observation

We started by determining each subject's date of diagnosis with cervical cancer, which was considered their index date. Specifically, this was the date of the first procedure (e.g. cervical biopsy, conization, LEEP, ECC) that provided histologic proof of invasive cervical cancer. If cervical invasion was only determined upon hysterectomy or upon autopsy, then the dates of these procedures were considered the diagnostic dates. The five years preceding the index date formed the main observation period (i.e. the time window) for each subject. Any Pap screening, diagnostic procedures and treatments for cervical intra-epithelial lesions that took place during the total 5-year observation period were documented. As depicted in Figure 5.1, each period of observation was divided into two contiguous time intervals: 1) the pre-diagnostic period and 2) the diagnostic period. The lower boundary of the diagnostic period was the index date. The upper boundary of the diagnostic period was the date of the "trigger" Pap, which was the first abnormal Pap smear (within that five year period) that eventually led to the final diagnosis of invasive cervical cancer. In addition, the Pap must have been the only procedure performed on that day in order to be considered the trigger Pap. The diagnostic period was that time interval during which subjects should have received acceptable follow-up care for their abnormal Pap tests in an acceptable time frame and ideally, invasion should have been circumvented as the subject was treated for a pre-invasive lesion. The pre-diagnostic period extended back in time from the date of the trigger Pap to the beginning of the observation period. Pap tests done during this pre-diagnostic period were considered to be done for screening purposes and not to have been part of the work-up towards cervical

cancer diagnosis. Pap screening conducted prior to the pre-diagnostic period was also documented as to allow for ascertainment of lifetime screening history.

The trigger Pap test was not found for 132 subjects, and if there were Pap smears found, they were all cytologically normal. Hence, we were not able to define the diagnostic and pre-diagnostic period for them. However, we would still be able to discern the time window of observation since the date of diagnosis with cervical cancer, which demarcates the lower boundary of the observation period, would be known and the upper boundary of the observation period would be the time point 5 years prior to the date of diagnosis

The observation period for quality assessment was limited to a 5-year term for several reasons. As screening guidelines typically recommend annual screening or triennial screening, the 5-year observation period gave us adequate time over which to assess the adherence to screening recommendations. As noted above, the examination of subjects' screening histories were not limited to this five year period but rather, we attempted to examine screening histories over the women's lifetimes. Further, this 5-year period provided us with adequate time over which to assess the quality of care at other points along the cancer care continuum, not only screening. In addition, care or lack of care many years prior to diagnosis, for example 30 to 40 years ago, would not likely have had an influence on the eventual development of cervical cancer. For practical reasons, it would not have been possible or even unwieldy to obtain screening and follow-up histories from such a long time in the past. First, most labs would not have data available from such an early time period as computerized files would most likely not exist and paper copies of lab results may no longer be available. Second, the further back we look in time, especially for those subjects diagnosed in 1998, the more likely it would have been that subjects moved from across the province or from other parts of the country or from abroad, which would have made it impossible for us to search for data. In addition, it has been estimated that within a 5-year period 5.5% of mild dysplasia will progress to moderate dysplasia or worse and about 25.1% of moderate dysplasia will progress to severe dysplasia or worse if not treated (Holowaty et al., 1999). Hence, as all study

subjects developed cancer, this time interval is long enough to allow for the observation of failures in care.

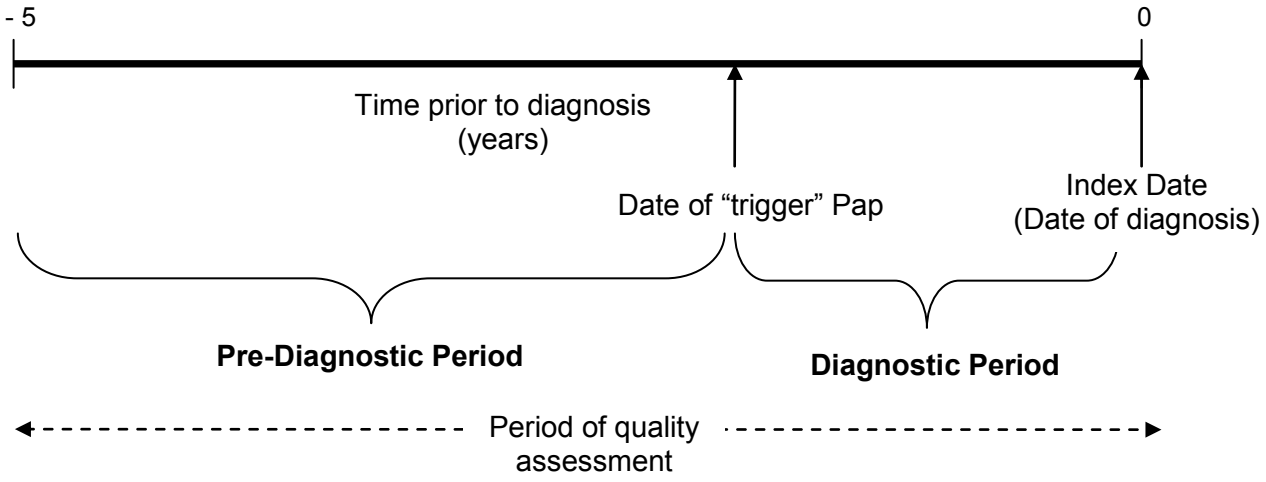

Figure 5.1. Periods of observation for the assessment of quality of care

5.4.1 Identifying the Trigger Pap Test and Other Pap Tests

As noted above, a subject's trigger Pap test was the first abnormal Pap smear result that occurred within the 5 year observation period (see the example below). Hence, if there was a sequence of consecutive abnormal Pap tests the first one would be considered the trigger Pap test and any subsequent abnormal Pap tests (or normal ones) would be considered as occurring during the diagnostic period and would not be part of the categorization of screening histories. Further, in order to be considered a trigger Pap test, it must have been the only procedure conducted on that day. Thus, if, for example, a colposcopy was conducted on the same day as a Pap test that was ultimately deemed to be abnormal then that Pap smear would not be considered the trigger Pap. Instead, I would have concluded that the trigger Pap was not found. As I needed the exact date of a trigger Pap test, they were identified through laboratory reports, either received directly from cytology laboratories, found within hospital medical charts, or provided to us by physicians. The identification of any other Pap tests would have been through laboratory

reports, hospital medical charts, subject or proxy interviews, and physician questionnaires. (These sources of data are discussed in detail in Section 5.5 below). It should be stressed that even though a trigger Pap test was not identified for a subject, her time period of observation could still be determined and her screening history could still be defined based upon the other sources of data. In the example below (Figure 5.2), the first abnormal Pap test within the 5 year observation period was taken on August 2, 2003; hence, this is the trigger Pap test.

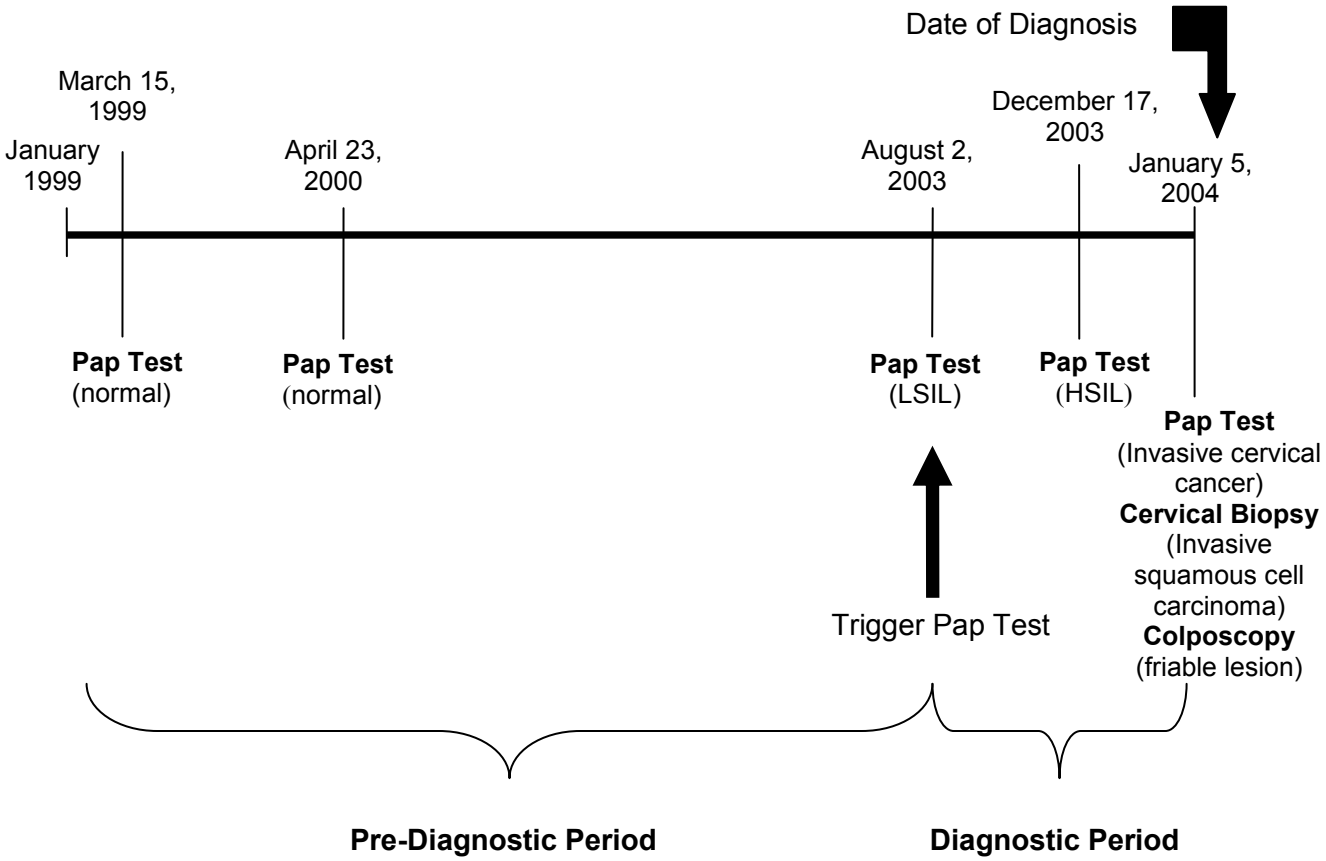

Figure 5.2. An example of identifying the trigger Pap test

5.5 Data Collection

Data were collected from several sources. Primary data sources included 1) hospital medical charts, 2) hospital cytology and pathology lab reports, 3) questionnaire-based telephone interviews of subjects or their next-of-kin if the subject was deceased at time of

interview or if the subject was not physically or mentally able to participate in the interview, and 4) physician self-administered questionnaires. Data collection from these primary sources started in 2004 and extended until 2008. The sequence of data collection steps from the primary sources of data is depicted in Figure 5.3 below.

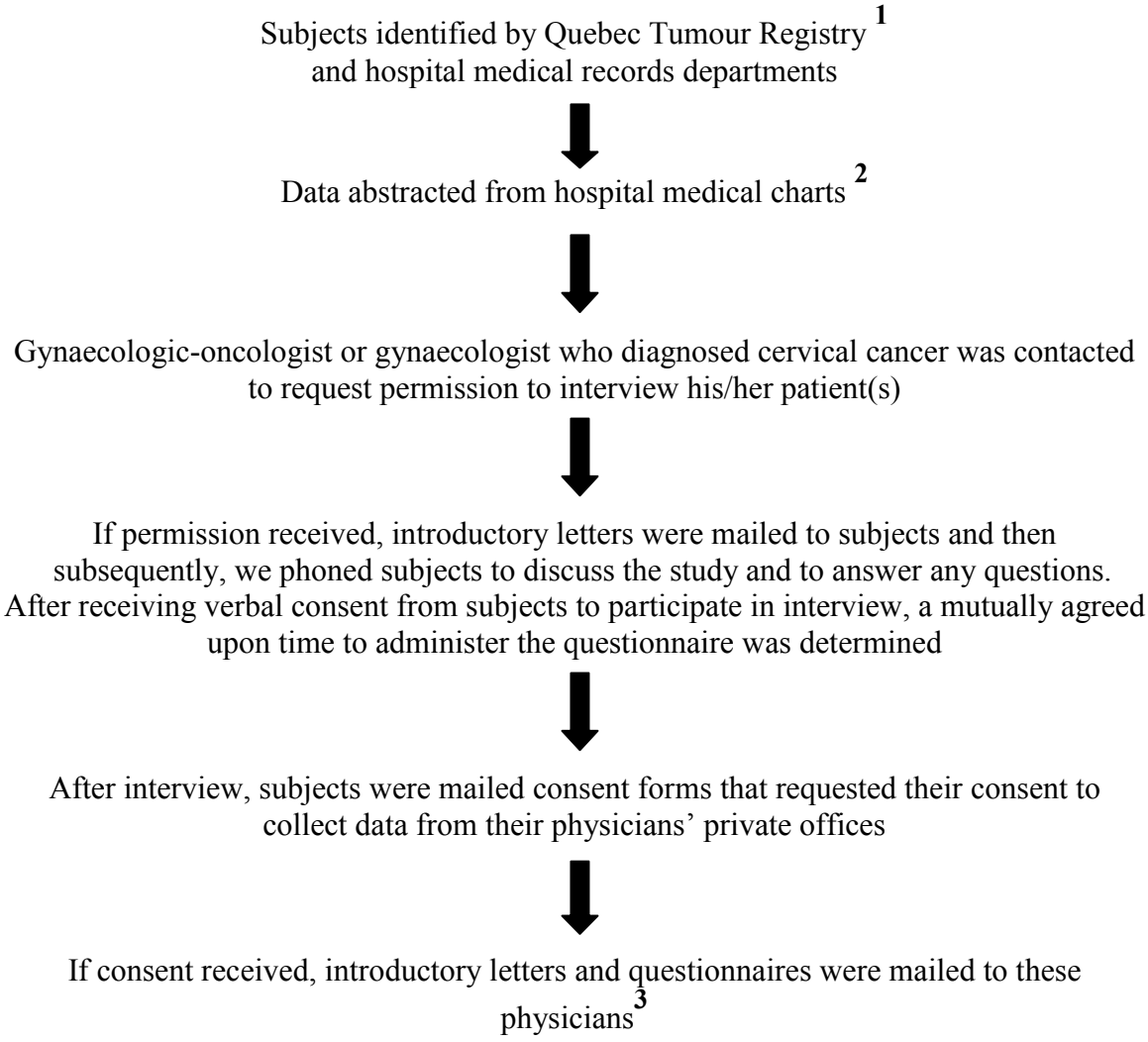

Figure 5.3. Sequence of data collection steps from primary data sources

[1]The use of the word "subjects" refers to women diagnosed with cervical cancer. This figure refers only to these women.

[2]Subject consent was not required to collect data from hospital medical charts or laboratories, according to the ethics boards of McGill University and all other hospitals involved in this study. Chart abstraction for each subject started at the hospital where she was diagnosed with cervical cancer. Chart abstraction was on-going throughout the data collection phase of the study.

[3]Collection of data from physicians was on-going as additional physicians were identified over time.

Secondary sources of data consisted of 1) the 2003 Canadian Community Health Survey (CCHS) (cycle 2.1), 2) provincial physician medical-billing records from the RAMQ, and 3) the 2001 Canadian Census.

5.5.1 Hospital Medical Charts

5.5.1.1 Development of chart abstraction tool and training of chart abstractors

The data collection phase began with the abstraction of data from the hospital medical charts of each subject using a form that was especially designed for this study (Appendix 2). This chart abstraction form was pilot tested and revised over time through its application in the field. Specifically, we used the form to abstract data from randomly chosen medical charts at different hospitals over several sessions. The final version of the abstraction tool allowed for easy and efficient recording of the following information from hospital medical charts: Names of family physicians, gynecologists, and gynecologist-oncologists of each subject; dates, results, and quality of all Pap tests found (as long as they were done prior to final diagnosis), including the names of the physicians who took the samples and the laboratories where they were read; dates and results of cervical cancer diagnostic procedures, and treatments for pre-invasive lesions, including the names of the physicians who performed the procedures and the labs where the specimens were examined; the stage, histology, and treatment received for the invasive cancer; the type and duration of any symptoms; and the presence of any co-morbidities. We also noted the current contact information for subjects, including addresses, home phone numbers, cell phone numbers, and work phone numbers. Their address at the time of cancer diagnosis was also recorded in order to verify place of residence at that time. The names and phone numbers for all of their emergency contacts were also recorded.

Chart abstraction was done mainly by a nurse having many years of clinical experience in a hospital environment. Data collection was also done by me, and in the early phase of the data collection, a gynecologic-oncology resident also reviewed medical charts. All chart abstractors were trained to extract the required data from medical charts. As part of this training, I provided each abstractor with a written and an oral summary of the study.

As a group, we discussed the epidemiology of cervical cancer including its screening and treatment options and its progression from precursor lesions to invasion, and the meaning of some of the medical terminology in more detail. We discussed the specific variables to be obtained from the charts and we reviewed the abstraction tool in detail and how to complete it. In addition, practical training sessions were conducted at various hospitals, during which time actual medical charts were searched for the relevant data and it was recorded using the chart abstraction tool.

After the initial training period, all chart abstractors independently extracted data from several charts at various times. The reliability of data extraction from medical charts was assessed by determining the degree of agreement between different abstractors independently reviewing the same charts and for each individual abstractor re-reviewing the same charts on two occasions. This is explained in greater detail in the statistical analysis, section 5.9.2 and the results are shown in Appendix 3.

5.5.1.2 Abstraction of data from medical charts

For each subject, chart abstraction started by reviewing the hospital medical chart at the hospital where each was diagnosed with cervical cancer. The names of these hospitals were provided to us by the cancer registry. We also reviewed each subjects' charts at the hospital medical records departments that identified them as cervical cancer cases. Information from the medical charts and from all other sources of data, which will be discussed below, informed us as to which other hospitals we ought to review medical charts for each subject. For instance, we reviewed charts at those hospitals where subjects received any type of medical care in the past, which was not necessarily related to the cervix, and we also reviewed subject's charts at those hospitals that were located near to these ones. Further, we reviewed medical charts at hospitals that were located in close proximity to the subject's residence at diagnosis and also those hospitals close to the office(s) of her physician(s). From the physician questionnaire, we also determined which hospital lab(s) physicians sent Pap smears to be read and we obtained data both from those labs and also reviewed the medical charts at those hospitals. Further, we took

a given hospital's or physician's referral patterns for cervical treatment into account. That is, physicians tended to refer patients to the same hospital for follow-up care of an abnormal Pap or cervical diagnostic test. In addition, all subjects had their medical charts reviewed at the McGill University Health Centre hospitals (Royal Victoria, Montreal General) or the MUHC-affiliated hospital, Sir Mortimer B. Davis Jewish General, if they initially received care at a hospital that is considered more English in terms of its predominant language of operation. Similarly, charts were reviewed at all of the Centre Hospitalier de l'universite de Montreal hospitals (Hotel Dieu, St. Luc, Notre-Dame) if initial health care was from a French-language institute. It should be noted that, as approved by the ethics committees of McGill University and of the participating hospitals, informed consent was not required from study subjects in order to abstract data from their hospital medical charts.

While abstracting data about cervical cytology, diagnostic and treatment procedures, we made a distinction between the procedural data found in actual lab reports present in the medical charts and the procedural data found as hand-written notes or in type-written correspondence.

All chart abstraction forms were reviewed by me on a regular basis throughout the duration of the data collection phase. This allowed me to determine the specific hospitals where data should be abstracted for each subject. Further, if there were any questions that arose regarding specific cases they were rectified by either re-auditing the appropriate medical charts or querying the cytologist or pathologist at that relevant lab for answers.

5.5.2 Hospital Cytology/Pathology Laboratories

When the data collection started in 2004, there were 13 hospital-based labs in Montreal and one on the island of Laval that provided cervical cytology and pathology services. Some of the hospital centres had a centralized lab. In previous years, some labs had ceased to provide Pap cytology services as they were not reading the minimum annual

number of slides as mandated by the Walton report (Deschamps et al., 2001). Pap cytology services of these labs were then transferred to other larger existing labs.

For each specific subject, we attempted to obtain lab reports from the hospitals where we had already reviewed their medical charts as described above in section *5.5.1.2*. Before retrieving data from hospital labs, I discussed the study with the chief pathologist or head cytotechnologist of each lab and received agreement from them to provide us with lab reports for our study subjects. We specifically, obtained the dates and results of Pap tests, and cervical diagnostic procedures and treatments for subjects. We did not limit data collection to procedures done within the five-year window of observation prior to cancer diagnosis; instead, we retrieved all previous lab reports available for each subject. Lab reports were obtained from these hospitals in one of two ways, depending on the wishes of the lab management: 1) I provided the lab with the names and RAMQ numbers of the study subjects and lab personnel retrieved the lab reports for us. This option often resulted in relatively long time delays, on the order of several weeks or months, as we waited for lab personnel to retrieve lab reports. 2) We personally went to the labs to retrieve the reports on our own. These labs' files were either available in a computerized database or they were available in a paper repository. Data collection from hospital labs occurred in several batches over the course of the study.

5.5.3 Study Subject Questionnaire

An interviewer-administered structured questionnaire was designed to obtain the following information from study subjects (Appendix 4): 1) To confirm that subjects resided in Montreal or Laval at diagnosis and for a minimum 5 consecutive years prior to diagnosis with invasive cervical cancer. 2) Names, office locations, and genders of the family physicians and/or gynecologists they received care from prior to diagnosis, if any. This enabled us to contact all the health providers each subject had in order to obtain a more complete pre-diagnostic medical history (if we received subject consent). 3) Pap screening history, including frequency, year(s), results, and names of physician(s) who collected the cytologic sample were obtained. Reasons for poor screening frequency,

preferences for the gender, general age, and type of physician to conduct Pap smears were also obtained. 4) Possession of physiological symptoms related to cervical cancer, and the duration of those symptoms, were also queried. We were also interested in determining whether it was the existence of symptoms that led to the visit that ultimately resulted in the discovery of invasive cancer, or rather was it simply a visit for a routine Pap smear, a regular check-up visit, or a visit for another reason. 5) Self-perceived general health, smoking history, and the existence of any chronic morbidities prior to diagnosis were determined. 6) Basic sociodemographic characteristics were also obtained.

The identification of the relevant items to include in this questionnaire came from several sources. First, there were items that were more administrative in nature that were essential for us to obtain information for. These included item numbers 1 and 2 listed above. Second, the subject questionnaire was another source of identification of subjects' Pap screening histories. This self-reported or proxy-reported data provided us with more complete screening histories for subjects. Third, an extensive search was done of the literature surrounding women's demographic characteristics and behavioural variables associated with Pap screening use and the adherence to recommendations for the follow-up of abnormal Pap smears. Lastly, experts in the field of gynaecologic-oncology were consulted in order to identify further areas of importance to query.

5.5.3.1 Pilot testing of questionnaire

After the questionnaire was developed it was first scrutinized by study clinical and research colleagues and revised per suggestions received. It was then pilot-tested before being administered to study subjects. The pilot-testing was done to ensure maximal comprehension and clarity of the questions; to optimize the sequence of the questions; to test skip-patterns; and to assess the best lay-out of questions. The questionnaire was administered to women who came from the same study base as women who would encompass the actual study subjects (Woodward et al., 1991). Namely, these were women diagnosed at one of two major Montreal hospitals with invasive cervical cancer who were residing in these regions at diagnosis. They were diagnosed in 1997 and hence,

these women would have been included in the larger study if they had been diagnosed with cervical cancer a year later. The names of these women were obtained from the cancer registry. Prior to contacting these subjects, we reviewed their hospital medical charts at their hospitals of diagnosis in order to obtain the names of their physicians, to obtain their contact information, to confirm diagnosis with cervical cancer, and to determine their age at diagnosis and the stage of their cancer. The chart review also allowed us to choose subjects for the pilot-testing that were from a wide-range of ages at diagnosis. The sixteen women who participated in the interview ranged in age from 37 to 75 years, with a mean age of 50.2 years and a median age of 46 years. We also chose women from the whole spectrum of cancer stages. We chose women diagnosed at a hospital which is affiliated with one of the major English speaking universities in Montreal and women diagnosed at one of the major French speaking university hospitals. Hence, allowing us to pilot test both the French and English versions of the questionnaire. Amongst, women who participated in the interview, 6 (37.5%) were conducted in English and 10 (62.5%) were conducted in French.

Prior to contacting subjects, the gynecologist or gynecologic-oncologist who treated them was asked for permission to contact his/her patient and, if permission was received, to determine whether the subject was alive and to confirm current telephone numbers. After receiving permission, the interviewer then contacted each subject by telephone. An interview script in both English and French was prepared in advance for this initial subject contact (Appendix 5). During this initial contact, the following information was communicated to subjects: The name of the interviewer; the fact that the subject's name was obtained from the Quebec Tumour Registry; permission to contact her had been obtained from her treating physician; researchers affiliated with McGill University and the University of Montreal were conducting this study; the purpose of the study; and their role in the pre-testing of the questionnaire. The interviewer answered any questions the subject had and if the subject agreed to participate in the pre-testing, she was informed that she would be receiving a letter in the mail that would give more detail about the study (Appendix 6). Mailing addresses were confirmed at that time. Also, women were

asked for the most convenient time for them to be interviewed and also for the language they would feel most comfortable having the interview.

Prior to conducting these subject interviews, the interviewers conducted several mock interviews, with study personnel playing the role of study subjects. Many different scenarios that interviewers may experience were presented and the appropriate responses to these various situations were discussed. This allowed interviewers to hone their interviewing skills and to better respond to questions or situations that may arise during the interviews. The mock interviews also enabled interviewers to become more familiar with the questionnaire itself, which helped with a smoother execution of the interviews.

We were able to administer the questionnaire to 16 of the 30 women we attempted to contact, which gave us a response rate of 53.3%. Reasons for non-participation in the interview included: 1 (3.3%) dead, 1 (3.3%) language barrier, 1 (3.3%) interview scheduled but not kept, 1 (3.3%) not available for interview for other reason, and 10 (33.3%) wrong contact information.

After each interview subjects were asked their opinions about the questionnaire (Appendix 7). This allowed us to determine subject comprehension and acceptability of specific questions. We also asked for general comments about the questionnaire and about whether they would agree, if they were study subjects, to having their archived Pap smears retrieved and reviewed and whether they would allow us to obtain further screening and treatment history from their physicians. Results were as follows:

1. 16 (100%) said there were no difficult questions to answer.
2. 15 (94%) said there were no questions they would rather not answer. 1 (6%) said there was one question she would rather not answer (i.e. Was she ever pregnant before?).
3. 14 (88%) said they would allow us to retrieve their archived Pap smears. 2 (13%) said no.
4. 15 (94%) would allow us to obtain further data from their physicians. 1 (6%) said no.

5. No one thought the interview was too long.

After each interview, I reviewed the responses and I modified the questionnaire as per these comments and responses. Feedback was also elicited from the interviewers as to any issues that they felt may impede the effective administration of the interview. Pilot-testing continued until we felt no further modifications were forthcoming.

5.5.3.2 Administration of subject questionnaire

As with the pilot-testing of the questionnaire, each subject's diagnosing gynaecologic-oncologist or gynaecologist, was contacted for written permission to interview his patient(s). Each physician was faxed a letter that provided some background information delineating the scope of this health issue, described the purpose of the study, and outlined the patient's role in the study. Along with this letter physicians were also sent a form that they were asked to complete and fax back to the study office (Appendix 8). Using this form, physicians or their secretaries recorded the most recent mailing address and telephone number of each subject, confirmed their vital status, and signed the form giving us permission to contact their patients. If the subject had died before the start of this study, we requested permission to contact a next of kin. We decided to use fax as the mode of document transmission with physicians, instead of postal mail, as the former method would expedite the process of receiving permission. If the form was not returned to us in a timely manner, physicians were contacted over the phone. Messages were left with physicians' secretaries explaining the nature of our request and our desire for them to return the completed form to our office regardless of whether they granted us permission or not. If the permission form was still not returned to us, we again contacted physician's offices. If after a minimum three attempts this physician still did not return the form, one of our physician study collaborators contacted the physician to explain the study and to request that they return the form to us. If finally, permission was never granted, that particular subject, or her next of kin, was not contacted for the interview. This also meant that her physicians were not contacted to complete the physician questionnaire since consent do to so would not have been received from these subjects or next of kin.

After receiving permission from a subject's physician, the subject was then mailed a one-page introductory letter inviting them to participate in a study about "women's health issues". It should be noted that subject addresses and phone numbers were obtained via the following sources: abstraction of data from hospital medical charts (Appendix 2) and the physician permission to contact patients form (Appendix 8). Addresses were also provided by the RAMQ.

In order to protect the confidentiality of subjects, this letter did not disclose the particularities of the study and it did not mention that the subject had been diagnosed with cervical cancer in the past. Confidentiality could have been potentially breached if, for instance, a subject moved from her last known place of residence and the introductory letter was sent to the wrong address. This letter stated that the subject's physician, who was personally named within the letter, gave us permission to contact her for the study and that the study nurse would contact her in a few weeks to complete a brief telephone interview. Subjects were invited to call our study centre if they wished further information prior to being contacted by the study nurse. There were four slightly different versions of this introductory letter depending on the recipient of the letter and the wishes of the hospital ethical review boards (Appendix 9-12): There were two different letters for subjects and two for the next-of-kin of deceased subjects depending one whether we mailed the letter or whether her physician or the hospital director of professional services sent it on our behalf. These were available in French and English. If the subject was dead, the protocol was slightly different as we first phoned the next-of-kin to briefly explain the study. We then offered to mail them the introductory letter and to then phone them back at a later time to determine if they wished to participate in the interview.

Within one and half to two weeks after mailing the introductory letter, the study nurse phoned each subject or next-of-kin. There were five possible outcomes of these initial attempts to contact subjects or next of kin:

1) No one answered the phone and there was no answering machine or voice-mail. In this case, subjects or next of kin were phoned up to 6 times on different days of the week at various times of the day and evening, including weekends. Every effort was made to reach study subjects or next-of-kin so as to maximize the response rate. First, as noted in section 5.5.1.1, we recorded each subject's address and phone number, including cell phone numbers and work numbers from medical charts or lab reports. We also took note of the names, relationships and phone numbers of all emergency contacts. Hence, if we were not able to contact subjects, we then contacted one of these people to enquire about the whereabouts of that person. Second, as noted in section 5.5.5, the RAMQ provided us with the current address of each subject, according to their files. With this locator information, we attempted to ascertain the telephone numbers of subjects using the internet site: Canada411 (http://findaperson.canada411.ca/). If needed, this site was also searched for current contact information using the names of subjects and emergency contacts.

2) If there was no one home when we phoned and there was an answering machine or voice-mail, we left a message. If the subject or next of kin did not return the phone call, the study nurse phoned back at least 3 times. Phone messages were non-descript so as to respect subject confidentiality. All subjects and next of kin for whom initial contact was not made were again phoned a few months later in the hopes we would now be able to reach them for the interview.

3) The subject was not at home at the time of the initial phone contact but someone else living at the residence answered the phone and confirmed that this person lived at that location. The follow-up procedure was the same as noted for outcome #2 above.

4) If it was determined during the initial phone call that a particular phone number was no longer in service or it was simply the wrong number, then we followed the same search procedures noted for #1 above.

5) When the study nurse was able to make contact with subjects or proxies over the phone, she introduced herself, introduced the nature of the research project, explained what participation would entail, and reassured respondents that any information they provided would be confidential (Appendix 13). Then the nurse answered any questions that subjects had regarding the study. Verbal consent for the interview was then obtained

and, if willing, the person was interviewed at that time or, if they preferred, at another mutually agreed upon time. Interviews were conducted at any time of the day, including evening and weekends, and were conducted in English, French, and Spanish as per the preference of the respondents.

After administering the questionnaire, the interviewer explained to interview participants that they would be receiving a consent form in the mail. The purpose of the informed consent was explained; namely, to receive permission to contact each subject's physician(s) to obtain further data about their cervical screening history and to retrieve archived Pap smears to be reviewed. The consent form was available in English or French and it was available in different versions depending on the person interviewed (subject or next of kin). The consent forms also varied based on the requirements of the individual ethics boards of the hospitals where they were diagnosed (Appendix 14). The mailing address of participants was confirmed at the end of the interview and a consent form was mailed with a self-addressed stamped envelope. If consent forms were not returned to the study office in a timely manner, then subjects were followed-up with a phone call to remind them to return the form to us. If participants declined to return the form during one of these reminder phone calls or simply never returned the consent form, then their participation ceased at that point. That is, we did not approach their physicians for data.

5.5.4 Physician Questionnaire

We also attempted to obtain data from all family physicians and gynecologists that each subject had at any point prior to their cervical cancer diagnosis. Physicians were not contacted if they used the medical charts located in the hospital medical archives. The names of subjects' physicians were found in the hospital medical charts, the subject interview, and the cytology and pathology laboratory reports. Physicians were also identified from the physician questionnaire as there was a question that enquired about any other physicians the subject may have had prior to diagnosis. Physicians were only

contacted to respond to the questionnaire if subjects or next of kin gave us signed consent to do so.

Prior to starting this phase of the study, a meeting was held with several study clinical co-investigators to discuss the best way to proceed with obtaining data from doctors' private files. Meeting attendees included a family physician, a gynecologic-oncologist, a clinician-researcher, study nurse, and study principal investigator. It was decided that physicians would prefer to send us the data we requested instead of having study personnel search through their files to find the data; hence, a self-administered questionnaire was designed.

Physicians were sent a separate copy of the questionnaire for each subject for whom they had provided medical care (Appendix 15). The main purpose of this questionnaire was to obtain the dates and results of all Pap tests and follow-up procedures for abnormal cervical test results that subjects had. Physicians either entered this data directly onto the questionnaire and/or they sent us the actual lab reports. The following items were also mailed to physicians along with the questionnaire: 1) An introductory letter that stated the purpose and importance of this study, the information we required from the physicians, the importance of their participation to the success of this study, and the confidentiality of the information they provided to us. This letter was personally addressed to each physician. Depending on the medical specialty of the physician they were either sent a letter undersigned by one of the family physician or gynecologist study co-investigators (Appendix 16 and 17). 2) A copy of an article published in L'actualité médicale, which is a periodical directed towards Quebec medical professionals. This article, which was published just prior to the start of this phase of the study, discussed the study and stressed the importance of physician participation (Gourde, 2006) (Appendix 18). 3) A copy of each subject's or proxy's signed consent form was also included. This gave us permission to retrieve data from their physicians. 4) A letter written by one of the study co-investigators, who is a medical officer with the Institut National de Santé Publique du Québec (Appendix 19). This letter discussed the importance of this study and urged the participation of all physicians. This package of documents was mailed to each

physician in an envelope labeled confidential. Each physician's current mailing address was obtained from the Annual Medical Directory (Collège des médecins du Québec, 2004) and confirmed by calling their office before mailing the documents. Doctors were asked to fax the completed questionnaire back to our office using the fax cover-page marked 'Confidential'. Physicians were also given the options of either mailing the completed questionnaire and other documents back to our study offices or requesting that one of the study personnel come to obtain the data directly from their office medical charts.

If questionnaires were not returned to us in a timely fashion, physicians' offices were phoned to remind physicians to complete the questionnaire. Offices were phoned up to 15 times over several months on various days of the week if no one answered the phone (and there was no answering machine) or if the phone line was busy. If the phone was answered, messages were left with receptionists or on answering machines reminding physicians to complete our questionnaire. We also offered to come to the office to retrieve the data from the medical charts if the physician preferred. If requested, we re-sent all the documents to a physician's office. Finally, if we left messages with receptionists and we still did not receive data from physicians, we again phoned their offices at least 3 more times to request their participation. If after all these attempts we still did not have participation or any response from the physician we concluded that he/she did not wish to participate.

5.5.5 Administrative Data from the RAMQ

In Canada, physicians make monetary claims to the provincial government for health services delivered to their patients using specific medical act codes. The governmental body responsible for this in Quebec is the RAMQ. Before requesting data from the RAMQ, we were obligated to receive permission to do so from another provincial entity called the Commission d'accès a l'information du Québec (CAI). We obtained three separate sets of data from the RAMQ.

1) Listing of all medical acts cases received within 5 years

First, I provided the RAMQ with the names, RAMQ numbers, birth dates, and dates of diagnosis for all subjects who resided in Montreal and/or Laval for at least 5 years prior to diagnosis. The RAMQ then provided us with a spreadsheet of all subject-level data identified by RAMQ number. Specifically, I obtained a listing of medical acts (denoted by medical act codes) that each subject had within 5 year prior to diagnosis with cervical cancer, including the date of each act and the medical specialty of the physician who performed each act.

This chronological record of contacts with the health care system provided by the RAMQ was used to supplement the process of care history we obtained from the other sources of data listed above. Table 5.2 lists RAMQ medical act codes relevant to cervical follow-up care along with their description. Unfortunately, there is no RAMQ medical act code unique to the performance of a Pap test. Instead, the medical act codes used to bill for a medical examination that includes a Pap test are general in nature and not unique to this procedure. For instance, a physician who did a Pap test could bill the RAMQ for a 'main visit', a 'follow-up visit', a 'complete examination', or an 'ordinary examination'. Hence, I was not able to determine Pap screening history from the data provided by the RAMQ.

2) Matched case-control study

The data above not only gave us a chronological sequence of the medical procedures performed prior to cervical cancer diagnosis for each subject but also it allowed us to investigate the health services use of each subject prior to their diagnosis with cervical cancer. The use of health services by study subjects prior to their cervical cancer diagnosis was compared with that of a similar group of women without cervical cancer. This was done using data also obtained from the RAMQ. For this second installment of data from the RAMQ, I provided them with the names, RAMQ numbers, birth dates, region of residence at diagnosis (i.e. Montreal or Laval), and date of diagnosis of study cases, which was considered the index date. We requested from the RAMQ a random

Table 5.2. Description of RAMQ medical act codes specific to the cervix

RAMQ medical act codes	Medical act descriptions
6146	Diagnostic conization of cervix
6074 / 6075	Colposcopy, including all biopsy sites, endocervical curettage, uterine biopsy curettage, cryosurgery and electrocoagulation of lesion.
6811	Treatment of cervix, including visit for cancerous or precancerous lesion. Surgical excision or laser.
172	Curettage of endocervix
6270/6265	Hysterectomy
6145	Dilation and biopsy curettage with or without polypectomy or cauterization.

sample of women individually matched (1:1) to our cases of cervical cancer within 5-year age groups. That is, each control must have been within the same age group as their matched case on the index date of their matched case. In addition, she must have lived in the same region at the matched case on the index date. Then, as with our study subjects, the RAMQ provided us with a spreadsheet containing the dates of all medical acts that these controls had five years prior the index date. We were also provided with the procedural code of each medical act, the medical specialty of the physician who performed each act, the age category of each control, and the identity of her matched study subject. Each control was anonymous and only identified by a unique identifier.

3) Subject contact information

Third, I also wished to receive the most recent telephone number for each subject from the RAMQ since this contact information was needed for the telephone-administered subject questionnaire. Although I did obtain contact information from the abstraction of hospital medical charts and from their physicians who granted us permission to contact them, it was often no longer valid as the person had moved since then. Unfortunately, CAI did not approve this request; instead, the RAMQ was granted permission to provide us with what they considered to be the most recent mailing address of each subject. As

discussed in section 5.5.3.2, we used these addresses to search for phone numbers using the internet site, Canada411.

5.5.6 Canadian Community Health Survey (CCHS)

In order to constitute a control group against which we could compare our patients' screening utilization data I used the CCHS, cycle 2.1 (2003). The CCHS is a cross-sectional survey conducted by Statistics Canada in conjunction with Health Canada, the Canadian Institutes for Health Information, and provincial and territorial ministries of health. The objective of the survey was to collect information about health status, health determinants, and health care utilization practices of the Canadian population. It was specifically aimed at individuals residing in private dwellings who were ages 12 years or older. Those living on Indian reserves or crown lands, institutionalized individuals, full-time members of the Canadian Armed Forces, and residents of some remote regions were excluded from sampling. The CCHS covers an estimated 98% of the Canadian population at least 12 years of age. Both personal and telephone interviews were done. The survey is only administered to the subjects chosen, that is, there are no proxy interviews done. Participation is voluntary (Canadian Community Health Survey 2003. User Guide for the Public Use Microdata File, January 2005). The respondents of this survey acted like a comparison group for the subjects of our study.

5.5.7 Canadian Census

We obtained census-tract level data from the 2001 Canadian Census. Specifically, we first determined the census-tract of each subject's place of residence using the 6 digit postal-codes of their address where they were living when diagnosed with cervical cancer. Then we obtained the descriptive statistics for the highest education levels and household income levels based on these census tracts. Although we did enquire about education levels and incomes in the subject questionnaire, we did not obtain data for all subjects. The census data allowed us to describe all the study subjects with regards to these important sociodemographic variables.

5.6 Quality of Care Assessment

Published clinical practice guidelines were translated into explicit medical review criteria. When published guidelines were not available, consensus amongst investigators was used to define "good care". These are shown in narrative form in Appendix 20. Data from all sources, specifically the dates and results of all Pap tests, diagnostic procedures, and treatments for pre-invasive cervical lesions, were collated into a chronological history for each individual subject. Then the review criteria were applied to each case one at a time and based on these criteria, each subject's care was categorized in terms of her Pap screening history, the management of abnormal Pap smears, and the treatment of biopsy-confirmed pre-invasive lesions. Assessment of screening history was done by me and the assessment of the follow-up of abnormal Pap smears and the cervical lesions was done by me in collaboration with a gynecologist. When there was discord between any assessments we had made, we discussed it and came to a consensus. Those subjects who were not resident in Montreal or Laval for a minimum of 5 years before diagnosis were not included in the quality of care assessment.

5.6.1 Assessment of Pap Screening History

Each subject's lifetime screening history was first categorized as never screened or ever screened as depicted in Figures 5.4 and 5.5. Data from the following sources, if available for an individual subject, were used to categorize screening histories: abstraction of data from hospital medical charts, retrieval of laboratory reports from hospital cytology and pathology labs, subject or proxy questionnaires, and physician questionnaires. It should be noted that even though a case was deceased, data retrieval was still attempted from all these sources.

For the categorization of screening history I was not interested in the cascade of abnormal Paps done within the diagnostic period; hence, categorization of subjects' screening histories did not consider the trigger Pap or any subsequent Pap tests done. Instead, we were interested in those Paps done as part of routine screening. Subjects classified as being "ever" screened had a Pap classified as normal or benign atypia, according to the

Dysplasia/CIS nomenclature; normal or inflammatory atypia, according to the CIN nomenclature, and within normal limits or benign cellular changes, according to the Bethesda system, during the pre-diagnostic period and/or had Paps of any result before the pre-diagnostic period. In contrast, subjects were categorized as never screened if I did not find any evidence of Pap screening within the pre-diagnostic period and prior to the pre-diagnostic period. In addition, in order to be classified as never screened, subjects or next of kin must have stated during the interview that they were never screened during their lifetime.

I was not able to categorize the lifetime screening history of some subjects as ever or never screened when all the following circumstances took place: 1) No lab reports of Pap smears were found during the pre-diagnostic period or prior to the pre-diagnostic period. 2) The subject's hospital medical charts did not have any informative annotations that provided an indication of Pap screening history. 3) The subject's physician did not complete a questionnaire or if the physician did complete a questionnaire, he did not know the subject's recent or lifetime screening history. 4) The subject or proxy was not interviewed. If there was an interview, the respondent did not know or could not remember the lifetime screening history.

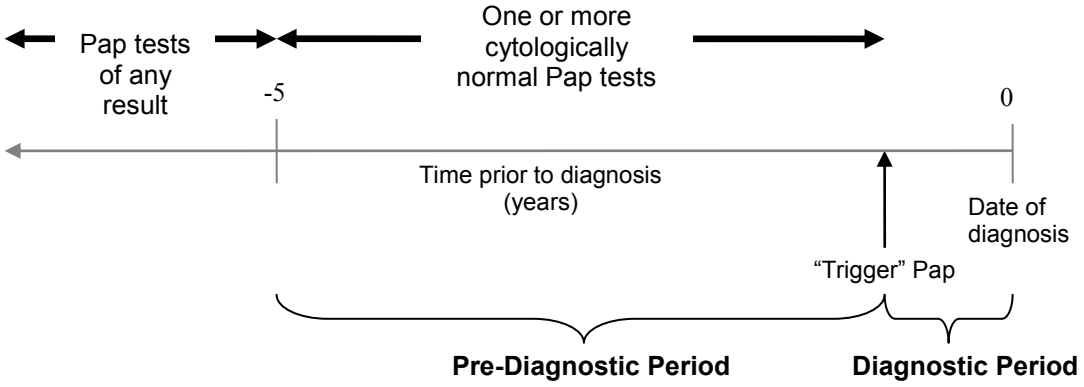

Figure 5.4. Definition of ever screened

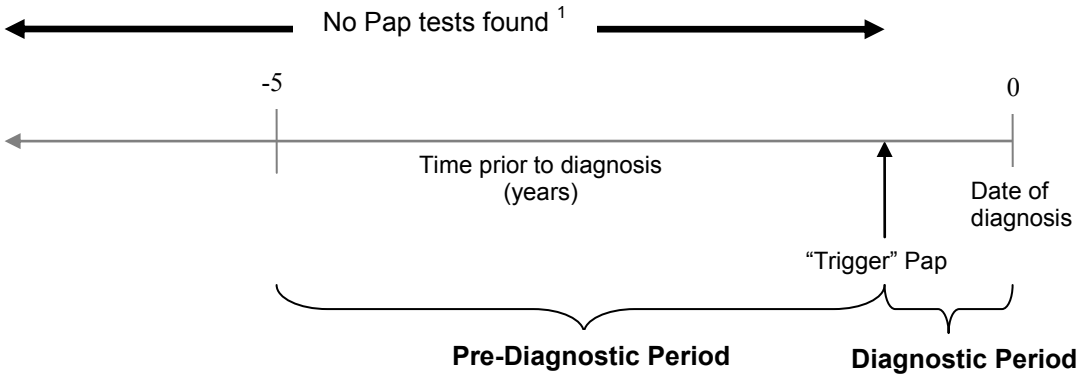

Figure 5.5. Definition of never screened

[1] In addition, the subject or proxy must have completed the subject questionnaire and must have stated that they were never screened.

Those subjects classified as ever screened were then further categorized based on the time interval between the date of diagnosis and either the last Pap smear considered normal (if it was during the pre-diagnostic period) or the last Pap of any result (if it was prior to the pre-diagnostic period). Specifically, they were categorized as being screened less than 3 years (<3 years), 3 to less than 5 years (3 to < 5 years), and greater than or equal to 5 years prior to diagnosis (≥5 years).

Similarly, among those subjects who were screened in the past, there were instances when the time since the last normal Pap smear could not be classified. This occurred when all the following conditions existed for a subject: 1) The lab reports and medical chart reviews did not find any Pap smears during the pre-diagnostic period or earlier. 2) No physician questionnaires were completed. 3) No subject (or proxy) interviews occurred. 4) Chart annotations were non-informative as they were vague and did not allow for the determination of timing of last Pap but they did give us an indication that the subject was screened at some point in her life. Examples of such annotations include "The patient had regular Paps." And "Patient always had normal cytology."

In addition to categorizing the overall screening histories and the timing of the last Pap smear, these screening categories were further qualified as "definite", "probable", or "possible" (Figure 5.6). These qualifiers indicate the veracity of the sources of data that were used to determine screening history (as discussed above). That is, these qualifiers are an indication of the degree of confidence we had that the data was correct. The potential sources of screening history, listed in declining level of quality, included primary sources (lab reports, which were either obtained directly from hospital labs, found in the medical charts, or sent to us by physicians) and secondary sources (physician questionnaires, annotations within the medical charts, subject interviews and next-of-kin interviews). If only data from lab reports were available to allow for the determination of a given screening history, then it was described as either "definite" or "probable". It was defined as "definite" if screening data within the pre-diagnostic period was found (and hence, timing of the last normal Pap was either <3 years or 3 to <5 years prior to diagnosis) and as "probable" if screening history was not found within the pre-diagnostic period but history was found prior to the pre-diagnostic period (and hence, timing of last Pap was deemed to be ≥5 years ago). The use of the term "probable" (not definite) was to indicate that even if data was not found during the pre-diagnostic period by the lab reports that it may be just missing.

If there was data available from both lab reports and from secondary sources, and there was concordance between this available data, then a subject's screening history was labeled as "definite". If there was discordance between the screening history as obtained by the lab reports and the other sources, then the source that indicated that the subject was screened at some point was used to define the subject's screening history. If this screening history was based on the data from lab reports then the history was qualified as "definite." If the history was based on data from secondary sources, it was categorized as "probable" or "possible" depending on the source (as noted below). This was the same situation if only secondary sources of data were available. If all secondary sources were in concordance regarding the subject's screening history, then it was qualified as "probable." If there was discordance between these secondary sources of

data, then the most reliable source was used to categorize screening. These secondary sources are listed below in order of decreasing reliability: doctor questionnaire, chart annotations, subject interview, and proxy interview. Screening histories based on these sources were categorized as "probable", except for those based on a proxy interview, which were categorized as "possible".

It should be noted that screening history was also assessed for women older than 69 years of age as the guidelines recommend the cessation of screening for women older than 69 only if they had a minimum of two Pap smears deemed satisfactory and cytologically normal in the previous nine years and they never had a biopsy-confirmed precursor lesion. As this could not be determined with certainty, it was decided to include this age group in the assessment of screening histories.

5.6.2 Failures in Detection of Cytological Abnormalities

In an attempt to ascertain if false negative Pap smears may have led to delays in diagnosis or prevention of cervical cancer, the last normal Pap smear that subjects had within 2 years before their date of invasive cervical cancer diagnosis, if any, was identified. They may have been done prior to or after the trigger Pap test. If a subject had more than one normal Pap smear within this two year period, only the last Pap smear was counted. Pap smears were identified by actual lab reports either found within medical charts or sent directly to us by labs or physicians. Pap smear results were then categorized into the following cumulative categories: within 6 months of final diagnosis, within 1 year of diagnosis, and within 2 years before diagnosis. The assumption here is that normal Pap smears found within up to two years of diagnosis with invasive cancer were actually false-negative Pap results.

It should be noted that I had originally planned to retrieve archived Pap smears from hospital labs to have them re-read by a cytotechnologist. This was an attempt to determine if those Pap smears that were originally classified as cytologically normal were

indeed abnormal. This was not feasible for the following reasons: 1) Consent to retrieve Pap smears was required from subjects and/or the next of kin. Of the 568 subjects residing in Montreal or Laval for a minimum 5 years before diagnosis, signed consent to retrieve archived Pap smears was received from only 39.6% (n=225) of them. 2) As will be discussed in the Limitations section of this thesis, when collating the collected data from all the various sources it was found that many subjects had missing data, in particular, Pap test results. 3) Several labs would have had great difficulty retrieving the archived Pap smears, which were either within storage in an incongruous location within the hospital and/or in storage at a location external to the hospital. 4) Some pathologists were resistant to providing us with these Pap smears, although we assured them that our study personnel would pick them up from the hospital, personally bring them to the cytotechnologist who would be reviewing them, and then return them to the hospital.

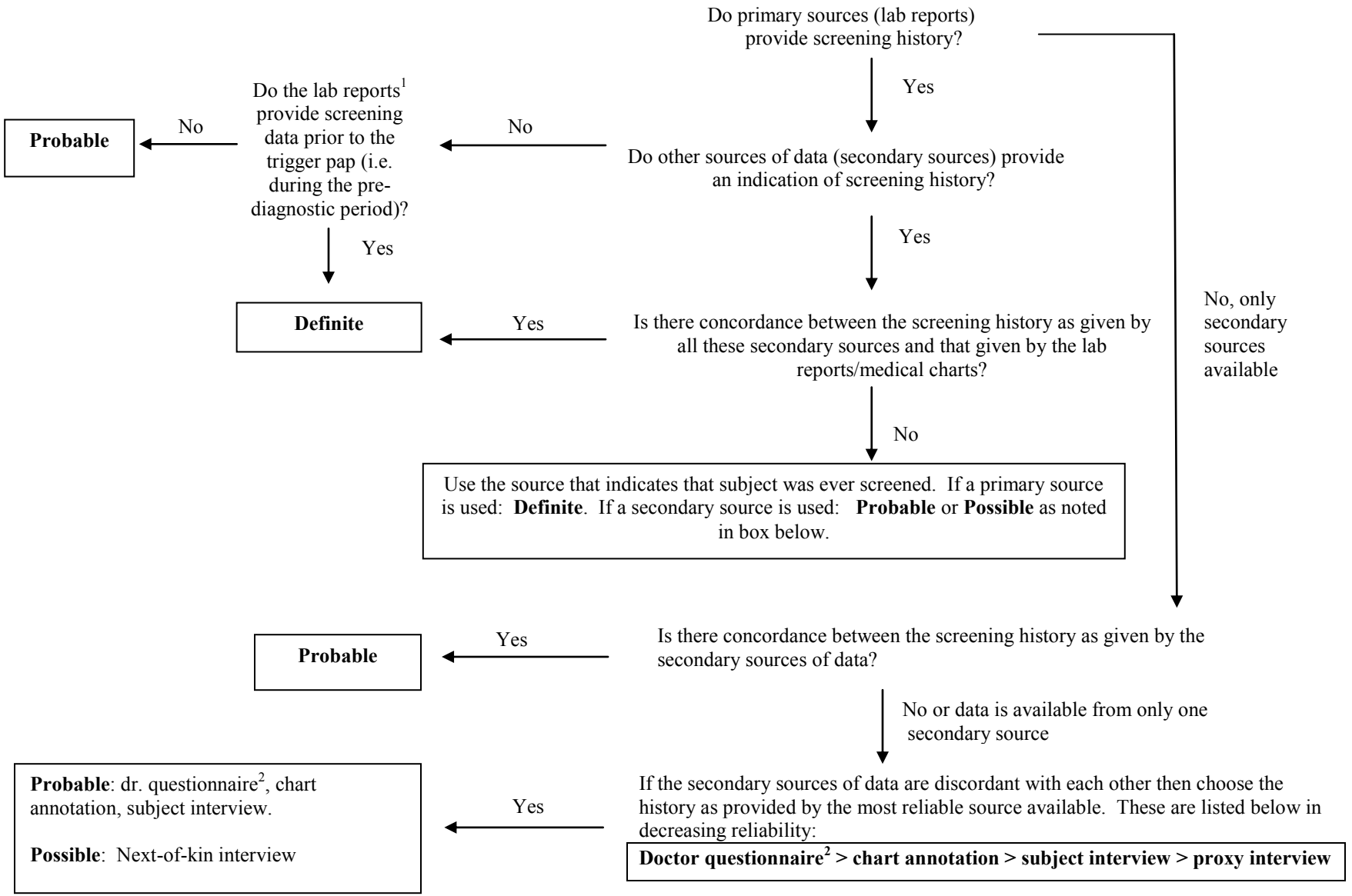

Figure 5.6. Procedure used to qualify the reliability of subject screening histories

[1]Lab reports are received from the lab or found in the hospital medical charts or sent by subjects' doctors along with the doctor questionnaire

[2] Dr. completes questionnaire and did not send actual lab reports to the researchers.

5.6.3 Quality Assessment of Follow-up of Abnormal Pap Smears

The quality assessment of the next two points along the cancer control continuum referred to the processes of care that occurred during the diagnostic period of each subject's period of observation (Figure 3.1). This assessment was based on the medical criteria outlined in Appendix 20. When assessing the quality of care, we started by comparing the chronological listing of medical acts provided to us by the RAMQ for each subject, specifically those done by gynecologists and family physicians, with the processes of care that we obtained through the abstraction of medical chart data and from lab reports provided by labs and by physicians. This comparison provided us with a more complete picture of each subject's history. Specifically, the RAMQ medical act codes provided us with some of the follow-up procedures that subjects underwent (Table 5.2). For instance, reports of colposcopic follow-up were often not found in medical charts but there was a RAMQ code for colposcopies so we would know if and when one was done. Further, if our data sources did not find any follow-up procedures and the RAMQ data also showed that there was no follow-up, then we had more confidence in our data. In addition, if there were one or more gynecology visits following an abnormal Pap test and the physician billed the RAMQ using a very generic medical exam and also our own search for data did not find any procedures being conducted on those dates, we were not able to assess the quality of care as data may have been missing. That is, a repeat Pap test may or may not have been done but we had no proof of this. Of course, as noted above in section 5.5.5, there is no specific RAMQ code for the performance of a Pap test.

Appendix 21 shows an example of the quality assessment of the processes of care for one study subject. The assessment of the quality of the follow-up of abnormal Pap smears entailed classifying two entities. First, the actual processes of care (i.e. the procedures performed) that took place after the first abnormal Pap test within the five year period were assessed. For each subject, the first abnormal Pap smear and the subsequent repeat Pap smears and/or colposcopy, along with the concomitant biopsy, ECC, and/or cone, if any, were considered to be one follow-up event. This event was the focus of the assessment and it was classified as acceptable or not acceptable. A given subject may

have had more than one abnormal Pap test during the five years prior to diagnosis (excluding those occurring within the same event) and hence, more than one follow-up event; each of which were assessed separately. The reasons for categorizing each event as unacceptable were also noted.

Second, the timing of the processes of care were also assessed and categorized as acceptable or not acceptable if the processes of care were deemed acceptable in the first place. We also defined the quality of the timing of care if the processes of care were deemed as unacceptable. In this case, the time referred to the number of days between the date of the abnormal Pap test and the date of the eventual acceptable follow-up care, if it occurred. For instance, if the appropriate follow-up procedure was a colposcopy but a Pap test was repeated first and then a colposcopy was done at a subsequent visit, this would be considered as unacceptable processes of care. However, we would determine the number of days between the initial Pap test and the colposcopy. This would allow us to conclude that even though unnecessary procedures were done, they delayed or did not unduly delay the receipt of appropriate care since the timing was within acceptable limits.

The acceptable time interval between abnormal Pap smear and the colposcopy was not provided within the clinical guidelines. Based on consultation with clinical co-investigators who are involved in the care of women with cervical abnormalities, we came to a consensus regarding appropriate time intervals (Table 5.3). These time intervals were then incorporated into the medical review criteria. When these time guidelines were applied to individual cases, we gave an up to plus 10 day leeway for the limits below when determining acceptability of timing.

For some subjects we were not able to assess the quality of management of the abnormal Pap if the abnormal Pap prior to the colposcopy/biopsy was not found (assuming there was a prior Pap test done), if the first or only abnormal Pap found showed invasion, or if all prior Pap tests were deemed normal. For these subjects, their follow-up of abnormal Pap smear histories were categorized as “cannot define”.

Table 5.3. Acceptable time intervals between abnormal Pap smear and repeat Pap smear and follow-up colposcopy, based on consensus

Pap Smear Result	Time to repeat Pap test
ASCUS-favouring reactive process	6 months
ASCUS-unqualified, ASC-US	3 months
LSIL	3 months

Pap Smear Result	Time to colposcopy
HSIL, AIS, AGUS, ASC-H, ASCUS-favouring neoplasia, ASCUS-neoplastic process cannot be excluded	3 months

5.6.4 Quality Assessment of Treatment of Pre-Invasive Cervical Lesions

Next, we assessed the appropriateness of the processes of care following a cervical lesion detected by a tissue-based method, such as cervical biopsy, ECC, or cone. As above, an event started with the detection of this cervical lesion and included any subsequent procedures and ended with treatment of that lesion. In analogy to the assessment of follow-up of abnormal Pap smears, the follow-up of pre-invasive lesions also involved classifying both the processes of care and the timing of those processes as acceptable or not acceptable. The acceptable time intervals for follow-up, which were determined by consensus, are listed in Table 5.4. Again, a subject may have had more than one such event and each was assessed separately. As our interest was ultimately in the prevention of invasive disease, we focused on processes of care occurring prior to the histologic detection of cervical invasion; hence, our assessment ended when invasive cancer was histologically confirmed.

Table 5.4. Acceptable time intervals between abnormal biopsy and treatment, based on consensus

Biopsy Result	Time to treatment
CIN I	3 months
CIN II, CIN III	1 month

5.7 Data Quality Control and Security

Quality control occurred at various phases of the study, which included the data collection phase, the data entry phase, and the pre-analysis phase. As discussed above, research personnel were trained and re-trained to abstract data and the reliability of data abstraction was investigated. Further, we had two high quality reliable sources of data, namely medical charts and lab reports. Also, 13.7% of hospital medical charts for subjects meeting the study inclusion criteria were reviewed at least twice. All data entry into our study electronic database was done by me and the research nurse. This included lab reports, medical chart data, subject questionnaires, and physician questionnaires. All data entry was independently double-checked by two other research personnel by comparing database entries with the original documents. Any errors or queries regarding the entered data were investigated and rectified. Prior to the analysis stage, various analyses, such as cross-tabulations and basic descriptive statistics, were done to search for errors in data entry.

In addition, subject's identities were not included in the study database, as subject data were identified only by a personal identification number. Further, all analyses used these identification numbers.

All data were stored in the project office in locked filing cabinets that only the principal study personnel had access to. The study database and other electronic study-related documents were stored in a secure file within the McGill Division of Cancer

Epidemiology's computer network. Again, only the study principal investigator, study coordinator, and research nurse had access to this site.

5.8 Ethical Considerations

Prior to starting this study, approval was obtained from the ethical review boards of McGill University and all 18 relevant hospitals. These were renewed on an annual basis. As noted above, we received written consent from physicians before contacting subjects or next-of-kin to administer the questionnaire. Verbal consent was received from subjects or next-of-kin to administer the questionnaire after we provided a written letter describing the study and answered any questions respondents had. Informed signed consent was requested from respondents to allow us to contact their physicians to retrieve further data and to retrieve archived Pap smears. CAI approved the receipt of data from the Quebec tumour registry and the RAMQ. Informed consent from study subjects was not required for researchers to abstract data from hospital medical charts. Rather, the approval of the ethical review boards noted above and also the permission of the director of professional services of each hospital was required to retrieve data from hospital medical charts.

Prior to conducting this study we also had to receive special dispensation from the Collège du Médecins du Québec for this study. (This letter was considered confidential by the Collège du Médecins du Québec and hence, it is not included in the Appendix of this thesis. It is on file in our study office.) Specifically, it was initially requested of us that we disclose any instances of unacceptable care to those subjects involved. As this is a research study and it is meant to provide results that ultimately lead to improvements in the provision of health services, this was not something we wished to do. Further, as our data were tabulated and analyzed with anonymous subject identification numbers, it was not possible to ascertain the specific person or physician associated with the instance of poor care. In addition, it was not possible for us to assign "blame" for the poor care to subjects, physicians or labs as data pertaining to physician recommendations for follow-

up care, subject adherence to recommendations, and lab turn-over times were not available.

5.9 Statistical Analysis

A comprehensive description of all the variables used in the descriptive analyses and the regression models in this thesis can be found in Appendix 22.

5.9.1 Sources of Study Subjects

The preliminary step of this study was the identification of study subjects. Subjects identified by the tumour registry and subjects identified by the medical records department of each hospital listed in Table 5.1 were matched by their first name, last name, and RAMQ numbers. As depicted by the Venn diagram (Figure 5.7), I then determined the total number of cases identified by each source, the number of cases identified exclusively by one source but not by the other, and the number of cases identified by both sources. The tumour registry and hospital medical records departments had been instructed to identify subjects who fulfilled the following criteria: 1) Diagnosed with histologically confirmed cervical cancer. 2) Diagnosed between 1998 and 2004. 3) Residing in Montreal or Laval at diagnosis. 4) Diagnosed at or admitted to a Montreal or Laval hospital. Using the subject-level data obtained from hospital medical charts, hospital labs, the subject (or proxy) interviews, and the physician questionnaires I was able to determine if the study inclusion criteria were actually fulfilled by each potential subject. I then determined the number of subjects fulfilling these four criteria according to their source of ascertainment. The medical records departments would not be able to determine the fulfillment of the following subject criteria: 1) Residence in Montreal or Laval for a minimum five years. 2) First occurrence of cervical cancer diagnosis. The tumour registry would not be able to determine fulfillment of the first criterion and it would not be able to determine fulfillment of the second criterion with complete certainty. Hence, these two criteria were not part of our request from these two sources. Again, the data collected was used to calculate the number of identified subjects fulfilling

all six of these inclusion criteria stratified by their source of ascertainment. In a separate analysis, the frequency of subjects not meeting each specific criterion was enumerated according to the source(s) of case identification.

The accuracy of invasive cervical cancer case ascertainment was calculated for each of the two sources. This was done without regards to the other subject inclusion criteria. Sensitivity is the proportion of diseased persons for whom upon the application of a specific test are deemed as disease positive. Positive Predictive Value (PPV) is the

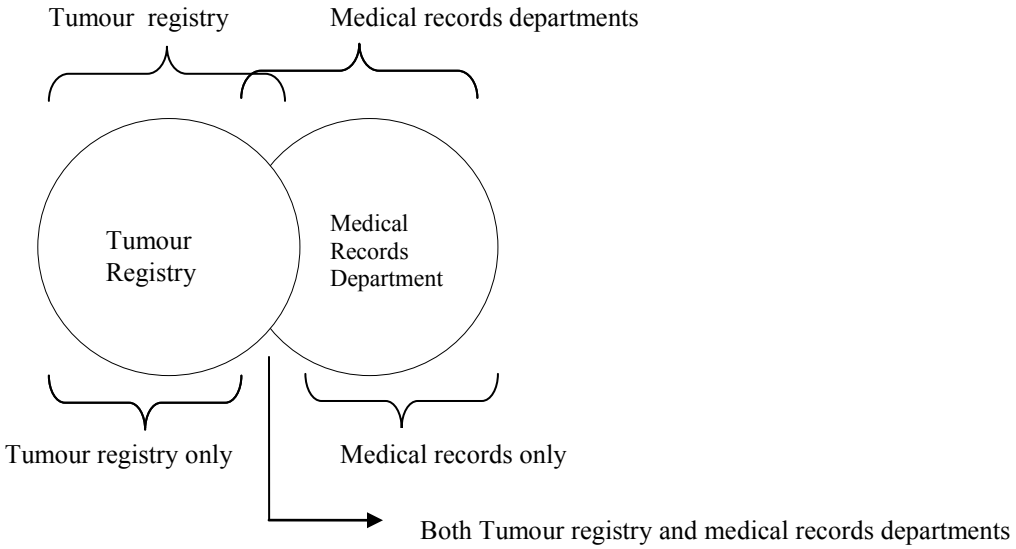

Figure 5.7. Sources of cervical cancer case ascertainment

proportion of subjects with a positive test result who truly have the disease of interest. With regards to this study, sensitivity was the proportion of women with histologically confirmed invasive cervical cancer (according to the "gold standard") who were identified by one or both of the sources as being cervical cancer cases. The "gold standard" for histological identification of disease status was laboratory reports. These documents were either found in hospital medical charts upon review by researchers or provided directly to us by hospital labs or by physicians. PPV was the proportion of subjects identified as cervical cancer cases by one or both sources that were deemed to be true cervical cancer cases by the "gold standard". The true positive cases were those cases identified by the cancer registry or hospital medical records departments and verified as cervical cancer cases by lab reports. False-positives were cases identified as

cervical cancer cases by the cancer registry or hospital medical records departments but not verified as a case by lab reports.

5.9.2 Reliability of Medical Chart Abstraction

We assessed the reliability of data extraction from medical charts both when the same charts were reviewed on more than one occasion by the same abstractor (i.e. intra-rater reliability) or the same charts were independently reviewed by different abstractors (i.e. inter-rater reliability). The levels of agreement were then examined for several variables obtained at different points in time. To this end, overall agreement was calculated for each pair of abstractors. Overall agreement is the number of cases of agreement divided by the total number of cases observed (Booth et al., 1994). As some degree of agreement can be attributed to chance, a more dependable measure of agreement is the kappa statistic: $k = (P_o - P_e)/(1 - P_e)$, where P_o is the observed proportion of agreement and P_e the proportion of agreement expected by chance (Fleiss, 1981). The kappa statistic is essentially the residual proportion of agreement following the omission of agreement due to chance (Booth et al., 1994). Abstractor agreement was assessed for the following variables: 1) number of Pap smears, 2) number of cervical biopsies, 3) number of colposcopies, 4) stage of cancer, 5) histology of cancer, 6) node status, 7) presence of symptoms of cervical cancer (yes/none found), and 8) presence of co-morbidities (yes/none found), and 9) description of definitive appointment that led to diagnosis (for routine screening or for symptoms). In general, the strength of agreement provided by a kappa statistic were interpreted as follows: kappa values >0.8 were deemed to have almost perfect agreement; k=0.61-0.80 represent substantial agreement; k=0.41-0.60 represents moderate agreement; k=0.21-0.40 indicates fair agreement (Landis et al., 1977).

5.9.3 Characteristics of Cases

The description of study subjects was derived from both the review of hospital medical charts and from the subject questionnaire. These provided data pertaining to subject demographic characteristics, characteristics pertaining to the cancer itself, reported screening history and behaviour, physician preferences, and general health. Data

obtained were mostly categorical in nature and were presented as frequencies and proportions per each level of category. Continuous data were either presented as means or medians, or categorized and presented as numbers and proportions.

Subject descriptive data obtained from the review of medical charts were also used for several sub-analyses. Specifically, this data was used to compare the characteristics of participants and non-participants in the subject interview. It was also used to compare the characteristics of those subjects whose lifetime screening histories could be categorized as ever or never screening and those whose histories could not be categorized.

5.9.4 Association between Subject Demographics and Incidence of Diagnosis of Cervical Cancer

Logistic regression was used to estimate the odds ratios (ORs) and 95% confidence intervals (CI) for the associations between several subject demographic characteristics and the diagnosis of cervical cancer, using separate bivariate models for each demographic characteristic. Multiple logistic regression is a method of statistical modeling used to determine the relationship between more than one independent variable (x_1, x_2…,x_k) and a dependent variable (Y), which is dichotomous in nature. The logistic model, which is shown below in its linear logit or log odds form, describes the probability of occurrence of one of two possible outcomes of the dependent variable (Kleinbaum et al., 1998). The OR is obtained from the logistic model by comparing the odds for one category by the odds of the other category. This is also obtained by exponentiating the coefficient of the independent variable in the logistic model (for a univariate model).

$$\text{Logit } [\text{pr}(Y=1)] = \beta_0 + \sum_{J=1}^{k} \beta_j X_j$$

In this specific set of analyses, the subjects of this study, namely, women diagnosed with invasive cervical cancer, formed the case group and the respondents of the CCHS survey comprised the comparison group. In an attempt to have a control group that was from

the same study base as the cases, we limited the control group to respondents who were living in Montreal or Laval at the time of the survey. The independent variables in these logistic regression analyses were the demographic characteristics of the subjects. These were categorical variables that included the following: marital status, education level, birthplace, duration of time resident in Canada for immigrants, language of conversation, employment status, giving birth in prior five years, having a regular physician, having a chronic medical condition, and smoking history. The demographic characteristics of the cancer cases were obtained through the interviewer-administered questionnaire and the characteristics of the comparison group were obtained via the CCHS survey. These predictors were categorical in nature and were entered in the models as dummy (or indicator) variables. For each predictor variable, there are k-1 dummy variables defined, where k refers to the number of categories or levels for that specific variable, and the dummy variables are typically assigned a value of 1 or 0 (Kleinbaum et al., 1998). The categorizations of these variables, which are shown in Table 6.9, are self-explanatory with the exception of the "highest level of education" variable and the "Had a regular doctor" variable. The education variable includes the following levels: 1) less than secondary graduation (<grade 6, high school incomplete), 2) secondary school graduation (Collège d'enseignement général et professionnel (CEGEP) incomplete, high school complete), 3) some post-secondary education (CEGEP complete, university undergraduate degree incomplete), 4) post-secondary degree/diploma (technical school complete, university undergraduate degree complete, university graduate school complete or incomplete). The variable "Had a regular doctor" referred to possession of a physician of any specialty who was seen on a regular basis. The dependent variable was a dichotomous variable with CCHS respondents coded as 0 and cervical cancer cases coded as 1. In order to control for confounding by age, the categorical variable age was included in each model. Age was coded in 13 five-year categories (20-24, 25-29, 30-34,...75-79, >=80 years) and entered into the models as dummy variables. For case subjects, the age variable referred to the age at diagnosis with cervical cancer and for control subjects, it was the age at the time of survey participation.

The logistic regression modeling described above was repeated in a case-only analysis in order to examine the relationship between subjects' demographic characteristics and the degree of cervical cancer invasion at diagnosis. These analyses were restricted to those study subjects with invasive cancer. Each subject was classified as being diagnosed with localized, regional, or distant cervical cancer, according to the staging categories devised by the Surveillance Epidemiology and End Results (SEER) Program (Young et al., 2001). In comparison to FIGO staging nomenclature, SEERs category 'localized' cervical cancer includes FIGO stages IA1, IA2, IB; 'regional' cancer encompasses stages IIA, IIB, IIIA, IIIB; and 'distant' cancer includes stage IV. Like above, age-adjusted bivariate models were created for each demographic variable. In these models, the dependent variable was dichotomized as follows: localized cancer (coded as 0) and regional or distant cancer (coded as 1). The independent variables were the same demographic characteristics included in the models above. Age was again entered into each model as dummy variables divided into 13 five-year intervals.

5.9.5 Proportions of Procedural Processes of Care Identified by Each Data Source

As discussed within the methods section, the identification of procedural processes of care occurred through the following sources: 1) Lab reports received directly from hospital cytology and pathology labs. 2) The abstraction of data from hospital medical files. 3) Data obtained from subjects' physicians. 4) Annotations found within hospital medical charts. 5) Telephone-administered questionnaires that were completed either by the subject or a proxy. I determined the sources of identification for each Pap test and diagnostic test that each subject had prior to diagnosis. The procedures examined were as follows: Pap smears, colposcopy, cervical biopsy, cervical conization, and endocervical curettage. For each of these procedures, I determined the proportion of the total number of that specific procedure that was identified by each of the sources listed above. The same analysis was repeated but it was now limited to those specific incidences of each procedure exclusively identified by only one of the sources.

5.9.6 Screening History and Invasive Cervical Cancer

Descriptive statistics (i.e. frequencies and proportions) were used to describe the lifetime Pap screening histories (ever or never screened) and the time since the last Pap test of study subjects. As discussed within the methods section, classification of subjects' individual screening histories was cumulatively based on information obtained from all sources of data. Screening histories were also stratified by the qualifiers definite, probable, and possible.

Logistic regression was also used to model the association between screening history and cervical cancer. The dependent variable, which was dichotomous, included the study subjects (coded as 1) and the respondents of the CCHS survey (coded as 0) were the comparison group. CCHS respondents were limited to women residing in Montreal or Laval at the time of the survey. Pap screening history, the independent variable, was categorized in three different ways: 1) lifetime screening history (never screened, ever screened, and subjects for whom their lifetime screening history could not be classified as ever or never screened). 2) Time since last Pap (amongst subjects ever screened) (<3 years, 3 to <5 years, ≥5 years). 3) Screening history adequacy (adequate and inadequate). For study subjects, inadequate screening included subjects never screened, those screened within 5 years of diagnosis (but not within 3years), those screened >5 years before diagnosis and those subjects for whom we could not determine whether they were ever or never screened but we were able to determine that they were not screened within 5 years before diagnosis. Omitted from this definition were subjects who were categorized as ever screened but the timing of their last normal Pap smear could not be defined (n=6). Similarly, for CCHS respondents, the inadequate screening category included women never screened and those who were last screened 3 to <5 years or ≥5 years ago. Adequate screening refers to women screened within 3 years of diagnosis. Three analyses were done for each of the three Pap screening history variables, each being restricted to a different subgroup of subjects based on the source of screening histories. First, I examined these associations when screening history was based on all sources of data. The next analysis was limited to those subjects whose screening histories were qualified as "definite". Lastly, I restricted analyses to screening histories based solely on subject

and proxy responses to the questionnaire. All models were adjusted for age at diagnosis for cervical cancer cases and age at survey administration for CCHS respondents. Age was categorized in 5-year categories (20-24, 25-29…≥80 years).

These same analyses were repeated in a case-only analysis in which cases were defined by the stage of their cancer. As above, cancer stage was according to the SEER summary staging (localized, regional, or distant), with regional and distant cancers being grouped together (coded as 1) and localized cancers as another group (coded as 0). Screening history, presented as lifetime screening, time since last Pap, and overall adequacy of screening history, were the independent variables. Bivariate models were created adjusted for subject age at diagnosis. Age, as above, was categorized into 5 year intervals and was included in each model.

5.9.7 Quality Assessment of Follow-Up of Abnormal Pap Smears and Cervical Lesions

As noted in section 5.6.2, quality of care of the follow-up of abnormal Pap smears were first assessed with respect to the follow-up procedures done and then in terms of the interval of time between the abnormal Pap and follow-up. Medical criteria, in Appendix 20, were applied to the processes of care and they were categorized separately as acceptable or not acceptable. This assessment of care was summarized in two ways. First, we presented results in terms of the total number of events, without regards to the individual. Events were classified as acceptable, not acceptable, or cannot assess. This last classification means that either the abnormal Pap was missing or the data following the abnormal Pap was missing, which precluded the assessment of that event. It should be noted that we also defined the quality of the timing of care if the processes of care were deemed unacceptable. In this case, the time referred to the number of days between the date of the Pap test and the date of the eventual acceptable follow-up care. Second, results were presented in terms of the individual subjects. Since subjects could have more than one event during that five year period, the results were summarized in a cumulative-manner. Specifically, subject-level results were categorized as follows: 1) All follow-up events for subject were acceptable. 2) Subject had at least one not

acceptable follow-up event. This category means that any of the other events (if there were any) were acceptable, not acceptable or could not be assessed. 3) Subject had at least one acceptable event and at least one event that could not be assessed. 4) All follow-up events for subjects could not be assessed. These categorizations were applied separately in the assessment of the procedure used to follow-up the abnormal Pap and also the timing of the follow-up.

This same procedure and categorizations were also applied to the quality assessment of the follow-up of abnormal cervical lesions. A large number of subjects were not included in this assessment as they were not diagnosed with a pre-invasive lesion within five years prior to diagnosis, rather the only lesion found was the invasive cancer.

5.9.8 Examination of the Time from First Abnormal Pap Smear to the Follow-Up Colposcopy Among Cases

The length of time between the first abnormal Pap test during the observation period (trigger Pap) and the follow-up colposcopy was then examined. This was done using the Kaplan-Meier method as there were censored data. The date of the trigger Pap test and the follow-up colposcopy for each subject were first identified. If the trigger Pap was found, the number of days between the date of this Pap and the date of the colposcopy was calculated. Those subjects for whom I did not determine the date of the trigger Pap were omitted from this analysis. It should be noted that for these omitted subjects there may not have actually been a trigger Pap test done. This may have been the case if, for example, a woman had never been screened within her lifetime or had not been screened for several decades and she had been experiencing vaginal bleeding for a period of time without seeking medical attention for her symptoms. The cervical neoplasia may have eventually advanced to such a degree that she was haemorrhaging and sought care in an emergency ward. In this case, a Pap test would not have been possible or would not have been relevant at this point as the tumour may have completely obscured the cervix and the bleeding may have been so profuse as to disallow the adequate sampling of the

cervix. Instead, more drastic measures of diagnosis would have taken place, such as an immediate colposcopy.

If the colposcopy was not found through review of hospital medical charts or from information provided by physicians, it was found in the subject-level chronological itemization of medical acts provided by the RAMQ. The RAMQ medical act code for performing a first colposcopy is 6074. Subjects who did not have a colposcopy were censored at the date of their hysterectomy. The subjects for whom I did not determine their colposcopy date and I also could not determine the date of their hysterectomy were also omitted from this analysis. Two Kaplan-Meier curves were plotted specifically depicting the cumulative probability of failure of cervical cancer patients. That is, the probability of having a colposcopy at each point in time. The first Kaplan-Meier curve was stratified by the cytologic results of the trigger Pap tests. The second curve was stratified by whether the follow-up by colposcopy was mandatory or not according to guidelines. Pap results of ASC-US and LSIL should be followed-up by a repeat Pap; hence, they were deemed colposcopy optional. All higher cytology grades are considered colposcopy mandatory. These data were used to determine the mean and median number of days from the trigger Pap to the colposcopy by Pap result. The log-rank test was used to compare the survival curves among the strata in the stratified Kaplan-Meier plots. This is a nonparametric test that involves the comparison of the observed and expected number of events for each group (Peto et al., 1977). A p-value is then calculated to assess the statistical significance of differences between the survival curves.

Next, I examined the determinants of the length of time between the trigger Pap smear and the subsequent colposcopy using linear regression. Multiple linear regression is a regression modeling technique used to assess the association between one or more exposure variables on an outcome variable that is continuous, while simultaneously controlling for the effect of all other variables in the model. The general formula for a regression line is as follows:

$$E(Y)= \beta_0 + \sum_{J=1}^{k} \beta_j X_j$$

In this analysis, the dependent variable was time (measured in days) between the trigger Pap and the follow-up colposcopy. It was modelled as a continuous variable. Prior to analysis, the assumptions of linear regression were examined using a plot of the residuals versus fitted values of the dependent variable. These assumptions were as follows (Kleinbaum et al., 1998): 1) Homoscedasticity: The variance of Y is the same for all X's. 2) Linearity: The mean value of Y for given X's is a linear function. 3) Normality: For given X's, Y is normally distributed. The plot showed that the data was in violation of these assumptions. The dependent variable was then transformed by taking the natural log of each value. The residual plot now revealed a scatter of values that was more symmetrical in shape with an equal spread of data on either side of zero.

All models included subject demographics and physician characteristics as independent variables. The subject-level variables were categorical and were entered as dummy variables into the models. These characteristics were from the responses to the subject questionnaire and they were previously defined. There were 3 independent variables related to physicians: 1) Medical specialty of the physician who sampled the cervix for that first Pap test that was cytologically abnormal. 2) Gender of the physician who performed this trigger Pap. 3) The time between this physician's year of graduation from medical school and the year of the trigger Pap. The year of graduation was obtained from the annual medical directory (Collège des médecins du Québec, 2004). This variable was meant to be both a proxy measure for the age of the physician and also the amount of medical experience the physician possessed. All independent variables were categorical, either naturally categorical or continuous in nature and categorized for this analysis, and were entered into the models as dummy variables. This analysis was limited to subjects who were long-term residents of the relevant regions and completed the questionnaire (i.e. self-report or proxy-report). In addition, we must have been able to determine the date of their trigger Pap and the date of their follow-up colposcopy. There were 59 questionnaire respondents for whom we were not able to determine the date of their

trigger Pap. There was a negligible number of questionnaire respondents (n=5) for whom we knew the date of their trigger Pap but not the date of their colposcopy. These subjects were omitted from this analysis.

First, crude univariate models were created for each independent variable. Second, trivariate models adjusted for subjects' ages at time of trigger Pap and also whether the results of the trigger Pap warranted a mandatory or optional colposcopy were created. Next, a variable selection technique, specifically, backwards stepwise regression was used to ascertain the best final model as we had many possible independent variables to consider. All variables were entered in to the model and the probability of removal was set at 0.15 (Glantz et al., 2001). The resulting β-coefficients in the final model were then exponentiated in order to interpret the results.

5.9.9 Patterns of Health Services Use According to a Matched Case-Control Study

Conditional logistic regression was used to compare the health utilization histories of cervical cancer cases with their matched controls that were provided by the RAMQ (These controls were discussed in detail in section 5.5.5). The dependent variable was the case or control status. In three separate models, the independent variable was the volume of family physician visits, gynaecologist visits, and medical specialist visits (other than family physicians or gynaecologists) within the five years prior to diagnosis but before the date of the trigger Pap. For the first two analyses that focused on family physicians and gynaecologist visits, if more than one medical procedure was billed on the same day by the same type of medical professional then it was deemed as one contact with that type of physician. Similarly, for the analysis examining the frequency of contact with medical specialists other than gynecologists, the existence of several medical acts billed by the same type of specialist or by different types of medical specialist on the same day was considered as one medical visit. In order not to include medical visits that occurred as part of the final diagnostic work-up that led to the diagnosis of cervical cancer, the date of the first abnormal Pap smear (i.e. the trigger Pap) for each cancer case was considered the new index date and was then used to truncate the listing of medical

acts of each case and their matched control. Any medical acts that occurred between the date of the first abnormal Pap smear (i.e. the trigger Pap) and the date of diagnosis with cervical cancer were thus, omitted from these analyses. The medical act(s) that occurred on the date of the trigger Pap were also omitted. The date of the trigger Pap was not found for 132 of the 562 women, assuming there was one. For these cases, the medical visit, conducted either by a family physician or gynecologist, that occurred one day prior to the date of diagnosis was used as a proxy trigger Pap date. If there was a sequence of visits to family physicians or gynaecologists on consecutive days leading up to the diagnosis date, then the earliest date within that sequence was used as the proxy trigger Pap date. The volume of visits was categorized as 0, 1-2, 3-4, and >4. The trigger Pap date or its proxy date for each case was then applied to its matched control and the medical visits that the case and control subjects had prior to this date but within 5 years of the case's date of diagnosis were summed and categorized. Each model was then mutually adjusted for the number of visits to the other types of physicians as per the other models. These were entered as categorical variables, coded as above.

All statistical analyses were performed using Stata, version 10 (Stata Corporation, College Station, TX).

6. RESULTS

6.1 Identification of Study Subjects by Source

The tumour registry and hospital medical records departments identified a combined 774 potential study subjects. As outlined in Table 6.1, the tumour registry identified 656 (84.8%) of these subjects and the medical records departments identified 695 (89.8%) of them. About 75% (577) of these potential cases were identified by both sources and 25.5% (197) of subjects were ascertained by only one source. More potential cases (15.2%) were solely ascertained by hospital medical records departments compared to 10.2% identified solely by the tumour registry.

Upon review of the collected data, we found that not all 774 potential subjects initially identified fulfilled the study inclusion criteria requested of the tumour registry and medical records departments. As shown in Table 6.1, 152 subjects did not possess one or more of these criteria. Of the 622 subjects who did fulfill all of these criteria, 519 (83.4%) were identified by both the tumour registry and the medical records departments. The medical records departments and tumour registry identified 59 and 44 unique subjects, respectively. This led to a slightly larger proportion of subjects meeting the inclusion criteria being identified by medical records than the tumour registry (92.9% and 90.5%, respectively). A total of 54 additional women did not fulfill the last two inclusion criteria that were not requested of the tumour registry or medical records departments (but they did fulfill the other criteria). That is, they did not reside in the appropriate regions for 5 years or more and/or they had recurrent cervical cancer. Ultimately, a total of 568 women met all the study inclusion criteria. There was a great deal of overlap in the subjects identified by the two sources. Specifically, 85.6% (486) of eligible women were identified by both sources. The tumour registry and the medical records departments identified a minority of subjects exclusively (6.3% and 8.1%, respectively), with the latter solely identifying 10 more eligible subjects than the former source.

Upon the abstraction of data from hospital medical charts and the receipt of data from labs it was determined that 111 women of the originally identified 774 women (14.3%) did not in fact have histologically confirmed primary cervical cancer (Table 6.2). Thus, rendering it the most frequent criterion not met. Amongst, those with confirmed ICC, there were 56 incidences of women not being 5 year residents of the appropriate regions and 24 incidences of women not actually being diagnosed between 1998 and 2004. Approximately equal numbers of women either were residing outside of Montreal or Laval at diagnosis or had a recurrence of ICC during this time period (and had their first incidence of cervical cancer prior to 1998). Only 4 women were found to be diagnosed at a hospital located outside of our area of interest. It should be noted that some women did not possess more than one of the inclusion criteria and hence, they were enumerated in more than one row in Table 6.2.

Upon application of the gold standard to the total 774 potential subjects identified, 663 of them were found to be true cervical cancer cases and 111 were false positives (data not shown). As shown in Table 6.3, the hospital medical records departments identified a greater number of true positive cases compared to those identified only by the tumour registry (616 and 574, respectively) (Table 6.3). This gave rise to a higher sensitivity for ICC identification by the hospital medical records departments (92.9%) compared to the sensitivity of the tumour registry (86.5%). The PPVs for these two sources were essentially the same (88.6% and 87.5%). When both sources were considered in combination, the sensitivity for case identification was 79.4% and the positive predictive value was 91.3%.

Table 6.1. Number of subjects captured and number of subjects meeting inclusion criteria stratified by source

	No. of subjects identified by Quebec Tumour Registry (%)[1]	No. of subjects identified by Hospital Medical Records Departments (%)	No. of subjects identified only by Quebec Tumour Registry (%)	No. of subjects identified only by Hospital Medical Records Departments (%)	No. of subjects identified both by the Quebec Tumour Registry and Hospital Medical Records (%)	Total number of subjects identified, irregardless of source
Number of potential subjects captured by the Quebec Tumour Registry and/or hospital medical records departments[2]	656 (84.8)	695 (89.8)	79 (10.2)	118 (15.2)	577 (74.5)	774
Number of potential subjects who met inclusion criteria requested of the Quebec Tumour Registry and hospital medical records departments[3]	563 (90.5)	578 (92.9)	44 (7.1)	59 (9.5)	519 (83.4)	622
Number of subjects who met all the inclusion criteria[4]	522 (91.9)	532 (93.7)	36 (6.3)	46 (8.1)	486 (85.6)	568

[1] Percentage of total number of subjects identified.

[2] All names provided to us by the tumour registry and hospital medical records departments.

[3] The inclusion criteria include the following: 1) Diagnosed with histologically confirmed primary invasive cervical cancer. 2) Diagnosed between 1998 and 2004. 3) Residing in Montreal or Laval at diagnosis. 4) Diagnosed/admitted at a Montreal or Laval hospital.

[4] The additional inclusion criteria include residing in Montreal or Laval for a minimum 5 years prior to diagnosis and being the first occurrence of this disease.

Table 6.2. Subject inclusion criteria not met according to source of subject

Subject inclusion criteria	Sources of potential cases					Total number of times each criterion was not fulfilled, regardless of source
	No. of subjects identified by Quebec Tumour Registry	No. of subjects identified by Hospital Medical Records Departments	No. of subjects identified only by Quebec Tumour Registry	No. of subjects identified only by Hospital Medical Records Departments	No. of subjects identified both by the Quebec Tumour Registry and Hospital Medical Records	
	Number of times each criterion was not fulfilled by source [2]					
Histologically confirmed primary invasive cervical cancer	82	79	32	29	50	111
Diagnosed between 1998 and 2004[1]	4	22	2	20	2	24
Residing in Montreal or Laval at diagnosis[1]	6	17	0	11	6	17
Diagnosed at/Admitted to a Montreal or Laval Hospital[1]	4	3	1	0	3	4
Residing in Montreal or Laval for minimum 5 years[1]	40	50	6	16	34	56
First occurrence of invasive cervical cancer[1]	8	13	3	8	5	16

[1]Refers to subjects with confirmed histologically confirmed primary invasive cervical cancer upon review of lab reports found in hospital medical charts and/or received directly from cytology/pathology laboratory files.

[2]An individual subject may not fulfill more than one inclusion criterion.

Table 6.3. Accuracy of primary invasive cervical cancer subjects identified by the Quebec Tumour Registry and/or hospital medical records departments[1]

Approaches to Identify Cervical Cancer Subjects	Frequencies				Ascertainment Accuracy (%)	
	True Positive	True Negative	False Positive	False Negative	Sensitivity	Positive Predictive Value
Number subjects identified by Quebec Tumour Registry	574	29	82	89	86.5	87.5
Number subjects identified by hospital medical records departments	616	32	79	47	92.9	88.6
Number subjects identified both by the Quebec Tumour Registry and hospital medical records departments	527	61	50	136	79.4	91.3

[1] This table refers only to the correct identification of invasive cervical cancer cases. It does not refer to fulfillment of the other inclusion criteria. The gold-standard were lab reports found in hospital medical charts and/or lab reports obtained directly from hospital cytology/pathology laboratory files.

6.2 Hospital Medical Charts and Lab Reports

Over the course of the data collection phase, we requested a total of 3,443 patient charts from hospital medical records departments or colposcopy departments to abstract. Of these requests, there were 1,884 medical charts that actually existed. Of those 568 subjects who met all inclusion criteria, including residing in Montreal or Laval for a minimum 5 years prior to diagnosis, there were 3,266 requests made for medical charts. This was a median of 6.0 requests for charts per subject. Of these requests made, a total of 1,770 charts existed and were reviewed. As previously noted, in most instances we did not know whether subjects had medical charts at given hospitals so we made a request to the medical records technicians at hospitals and they would do a search to see whether charts existed at that specific hospital. This was the same situation for obtaining data from labs. We requested lab reports for a total of 3,449 subjects and 1,119 lab reports existed. If we consider only those subjects who met the study criteria, 3,280 lab reports were requested and 1,055 existed.

6.2.1 Assessment of Reliability of Medical Chart Abstraction

As noted above, the reliability of the chart abstraction was measured at several points during the data collection phase. Both percentage agreement and kappa statistics were calculated for nine variables for both inter and intra-rater reliability. These were initially deemed to be relatively poor for certain variables, especially for the number of colposcopies per subject. Several practical training sessions with all abstractors as a group were conducted. At these sessions we meticulously went through each hospital medical chart and used the chart abstraction form to record the requested data. We also discussed what the sources of disagreement were between abstractors or between successive reviews done by the same abstractor. These sessions also allowed for further exchange of substantive information and yielded many suggestions regarding a more effective lay-out for the abstraction form. Subsequent measures of reliability greatly improved. The details of the assessment of reliability of chart abstraction can be found in Appendix 3. Also, please see section 5.7 for further discussion regarding the quality of data.

6.2.2 Demographic Characteristics of Subjects as Determined by Medical Chart Review

Table 6.4 displays the sociodemographic and clinical characteristics of study subjects as obtained by review of hospital medical charts. Essentially equal numbers of cervical cancer cases were identified each year with the greatest proportion of cervical cancer cases in the year 2000 (n=99) and then the frequency slightly declined temporally, with 72 cases in the year 2004 (n=72). This seeming pattern may be real (depending on the population sizes in each of these years and trends in rates) or it may merely be a result of random fluctuations. The majority of cases lived in Montreal (87.0%) compared with 13.0% who lived in Laval. The median age at diagnosis was 52 years and the range was 22 years to 94 years. The majority of subjects had symptoms of cervical cancer (70.2%), although the presence or absence of symptoms was not found within the hospital medical charts in 20.8% of subjects. This inability to confirm the presence or absence of a given subject characteristic from the medical chart due to data not being found within medical charts also occurred with other variables. Further, the absence of information was not considered to indicate the non-possession of a given characteristic. Amongst those women who had symptoms, the most common was vaginal bleeding. Namely, 17.0% of women suffered post-coital vaginal bleeding, 25.3% had inter-menstrual vaginal bleeding and 50.1% had post-menopausal vaginal bleeding. It should be noted that many women had more than one symptom of cervical cancer. A large percentage (23.8%) of women experienced pain of some nature, effecting either the pelvis, abdomen, back, legs or an unspecified location. The presence of symptoms caused more than one-third of subjects to seek medical care that culminated in their cervical cancer diagnosis. About 41.4% of subjects had a co-morbidity, although this information was unknown for 58.6% of subjects. Almost 26.9% of subjects were current smokers at time of cervical cancer diagnosis and 24.5% of subjects had family member(s) who had developed some type of cancer in the past. The relevant data for these two variables was not found in the medical chart(s) of the majority of subjects; specifically, 64.6% and 74.5%, respectively.

In terms of the cancer itself, about 15.7% of cancers were FIGO stage IA1, which involves less than 3 mm of stromal invasion, and the greatest percentage (30.5%) were stage IB cancers, which means that invasion was more than 5 mm but was limited to the pelvic area. A very small minority of cancers (2.6%) were not staged. Either staging was not found within hospital

medical charts or data was not available to allow researchers to ascertain the cancer stage. The most prevalent histologic type of cervical cancer was squamous cell carcinoma, comprising 72.2% of cases. Adenocarcinoma was the second most common histologic type (21.7%) and the remaining cancers were adenosquamous (2.8%) and other less common types. Few subjects lived in census tracts where the median income was less than $30,000 or $70,000 or more. Subjects lived in census tracts where a median of 15.2% of residents had a university degree.

Table 6.4. Characteristics of study subjects as determined by hospital chart review [1]

Variable	n[2]	%
Year of diagnosis		
1998	74	13.0
1999	82	14.4
2000	99	17.4
2001	86	15.1
2002	78	13.7
2003	77	13.6
2004	72	12.7
Place of residence at diagnosis		
Montreal	494	87.0
Laval	74	13.0
Age at diagnosis (years)		
20-29	23	4.0
30-39	91	16.0
40-49	137	24.1
50-59	103	18.1
60-69	76	13.4
70-79	86	15.1
≥80	52	9.2
Median	52	
Mean	55	
Range	22-94	
Presence of symptoms[3]		
Yes	399	70.2
No	51	9.0
Unknown[4]	118	20.8
If symptoms present, type of symptoms[5]		
Vaginal discharge	69	17.3
Between menstrual period vaginal bleeding	101	25.3
Post-menopausal vaginal bleeding	200	50.1
Vaginal bleeding following sexual intercourse	68	17.0
Heavy and/or prolonged menstrual bleeding	12	3.0
Abnormal vaginal bleeding, type unspecified	5	1.3
Loss of appetite	15	3.8
Weight loss	64	16.0
Fatigue	18	4.5
Pain (pelvic, abdominal, back, and/or leg, or unspecified location)	95	23.8
Other symptoms	45	11.3

Table 6.4. continued

Variable	n	%
Reason for appointment that led to the diagnosis of ICC		
Specifically for presence of symptoms	214	37.7
Routine medical check-up	68	12.0
Condition unrelated to cervical cancer	5	0.9
Unknown	281	49.5
Presence of other co-morbidities		
Yes	235	41.4
Unknown	333	58.6
Smoking status at time of diagnosis		
Current	153	26.9
Former	29	5.1
Never	1	0.2
Not smoking at diagnosis, unclear if former or never smoker	18	3.2
Unknown	367	64.6
Family history of any type of cancer		
Yes	139	24.5
No	6	1.1
Unknown	423	74.5
Stage of cervical cancer		
IA1	89	15.7
IA2	31	5.5
IB	173	30.5
II	113	19.9
III	105	18.5
IV	42	7.4
Unknown	15	2.6
Histology of cervical tumour		
Squamous cell	410	72.2
Adenocarcinoma	123	21.7
Adenosquamous	16	2.8
Other less common types	14	2.5
Unknown	5	0.9
Median income level (by census tract)[6]		
<$30,000	21	3.7
$30,000-39,999	119	21.0
$40,000-49,999	149	26.2
$50,000-59,999	127	22.4
$60,000-69,999	64	11.3
$70,000 or more	71	12.5
Missing	17	3.0
Completed university degree (% by census tract)[6]		
Median	15	
Mean	20	
Range	2-63	

Table 6.4. continued

[1] Subjects diagnosed with non-recurrent histologically-confirmed invasive cervical cancer between 1998 and 2004 at a Montreal or Laval hospital. Subjects must have been residing in Montreal or Laval at diagnosis and for a minimum 5-year time period. N=568.
[2] n (%) refers to the number and percentage of subjects falling within each category except when median, mean, and range are noted. Percentages may not add up to 100 due to rounding of numbers.
[3] Symptoms of cervical cancer include the following: abnormal vaginal discharge, inter-menstrual vaginal bleeding, post-menopausal vaginal bleeding, heavy and/or prolonged menses, post-coital vaginal bleeding, loss of appetite, weight loss, fatigue, pain (pelvic, abdominal, back, and/or leg), and other less common symptoms. The category "other symptoms" include anemia, dyspareunia, dysuria, hematuria, rectal bleeding, urinary/renal tract problems, ascites, vesicovaginal fistula.
[4] Unknown means that the data indicating the presence or absence of a particular characteristic were not found in the medical chart.
[5] Subject may have had more than one symptom (N=399).
[6] Data were obtained from the 2001 Canadian Census. Data not available for 17 subjects.

6.3 Subject Questionnaire

6.3.1 Participation with Subject Questionnaire

A total of 605 study subjects were eligible for the questionnaire. These were women who met all the inclusion criteria noted on page 40 but they may or may not have been living in Montreal or Laval for at least 5 years. As shown in Figure 6.1, 46 eligible subjects were not contacted for the interview for one of the mutually-exclusive reasons listed in Table 6.5. The majority of these reasons could be attributed to decisions made by either the hospital ethics boards or subjects' physicians regarding the entry of subjects into this study. The greatest proportion of subjects (32.6%) was not contacted for the interview because the ethics board of the hospital at which they were diagnosed refused to allow us to contact the next of kin of deceased subjects. In addition, a large proportion of subjects were not contacted due to physicians not granting us permission to contact their patients (13.0%) or their family members (15.2%), or simply not responding to our request for permission to interview their patient(s) (6.5%). In 13.0% of cases, the subject had died and the name of a next of kin was not found within hospital medical charts and was not provided by her physician when we requested permission for the interview. Upon review of hospital medical charts, we determined that 4 subjects (8.7%) had physical limitations or mental impairments that would not enable them to successfully participate in our interview.

We attempted to contact 559 of the eligible subjects or their next of kin for the interview (Figure 6.1). Of these subjects (or their next of kin), 197 of them were not interviewed. As tabulated in Table 6.6, the main reasons for non-participation were an inability to locate subjects (22.3%) or their next of kin (29.9%). Upon telephoning these subjects either the interviewer was informed by the person who answered the phone that this was not the subject's residence or the phone-line was not in service or the phone was never answered upon repeated calls to that phone number. In 8.0% (n=16) of cases, we determined that we had subjects' correct residences but we never made direct contact with them even though we left messages on telephone answering machines and/or with other members of the household. In some instances, contact was successfully made with subjects or next of kin; however, 20.3% and 9.6% of subjects and next of kin, respectively, refused to participate in the interview. The two least common reasons for non-participation were subjects or next-of-kin who did not speak French, English, or Spanish, and next-of-kin who felt that they did not have sufficient knowledge of the subject's medical and demographic history to participate in the interview. Ultimately, 362 interviews were conducted; 289 with study subjects and 73 with proxies. Of the 362 interviews done, only 32 were more recent residents of these areas; thus, only their screening history and demographic information were obtained during the interview. Three-hundred and thirty of these subjects resided in Montreal or Laval for at least 5 years before diagnosis and hence, were administered the unabridged version of the questionnaire. Of these long-term residents of Montreal or Laval, 78.5% (n=259) of the interviews were completed by the study subjects and 21.5% (n=71) of the interviews were completed by proxies. In the end, there were 568 (=259+71+238) subjects diagnosed with cervical cancer and who met all inclusion criteria.

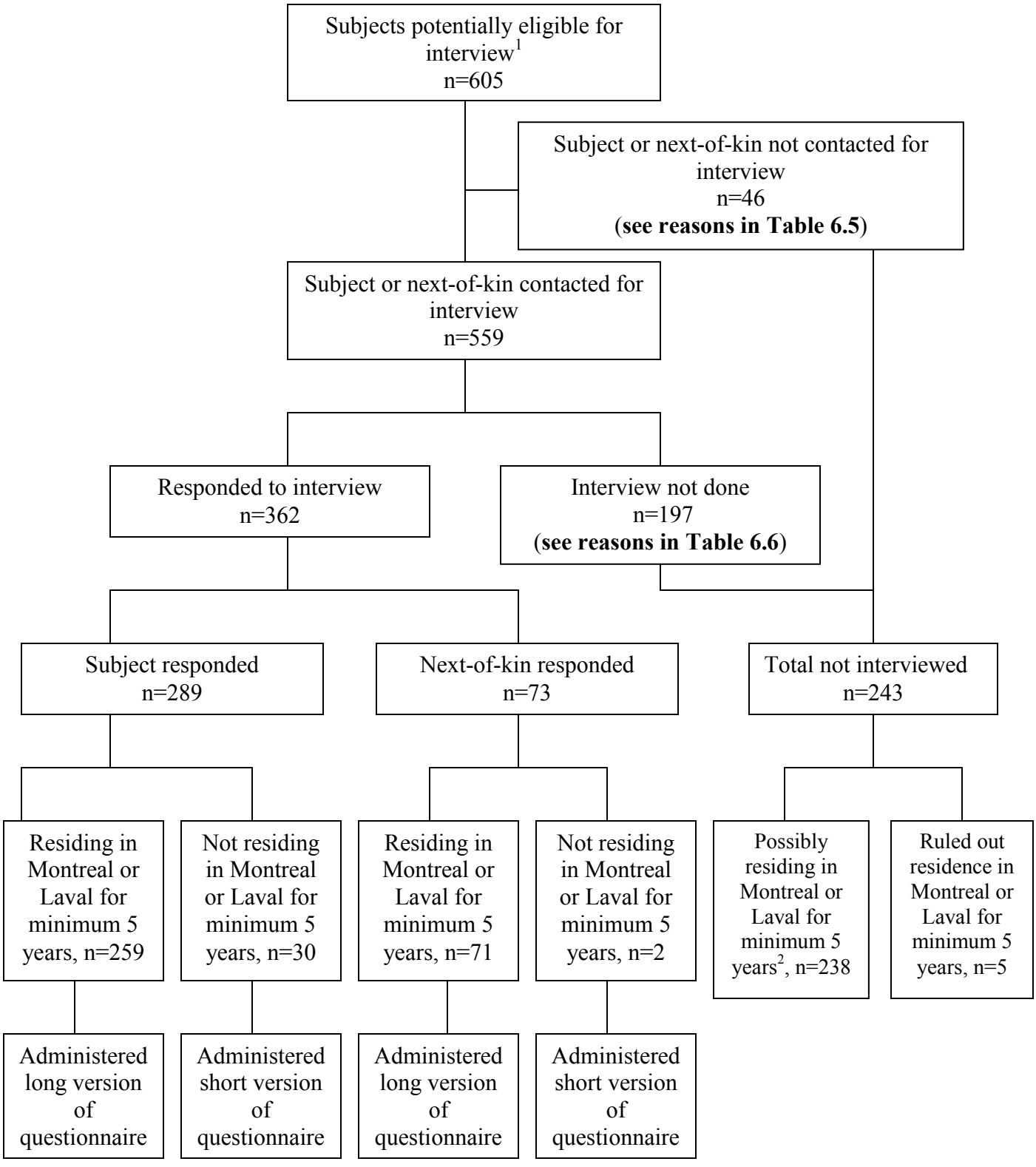

Figure 6.1. Subject questionnaire participation

[1] Subjects satisfied all study inclusion criteria but it was not known, in some instances, whether they resided in Montreal or Laval for minimum five years

[2]There was no evidence found in the sources of data available to suggest that these subjects were not living in Montreal or Laval for at least five years before the diagnosis of cervical cancer.

Table 6.5. Reasons eligible subjects or their next-of-kin were not contacted to administer the questionnaire

Reason	Number (%)
Subject was dead at time of interview and next of kin was not known.	6 (13.0)
Hospital ethics review board did not allow researchers to contact next of kin to administer interview.	15 (32.6)
Physician did not allow researchers to contact next of kin to administer interview.	7 (15.2)
Physician did not allow researchers to contact study subjects to administer interview.	6 (13.0)
Subject not physically or mentally able to participate in interview.	4 (8.7)
Physician did not respond to our request for permission to interview his/her patient.	3 (6.5)
Identity of subject's physician was not known.	2 (4.3)
Identity of subject's physician was known but he or she could not be located.	1 (2.2)
Subject was pursuing legal action against physician.	1 (2.2)
Subject was not aware of cervical cancer diagnosis.	1 (2.2)
Total	46

Table 6.6. Reasons why subjects or next of kin whom researchers attempted to contact did not participate in interview

Reason	Number (%)
Subject could not be located.	44 (22.3)
Subject refused to participate in the interview.	40 (20.3)
Subject was telephoned but she did not return the messages.	16 (8.0)
Next of kin could not be located.	59 (29.9)
Next of kin refused to participate in the interview.	19 (9.6)
Next of kin did not possess adequate information to participate in the interview.	5 (2.5)
Language barrier with subject or proxy.	14 (7.1)
Total	197

Ultimately, the overall response rate for the subject questionnaire was (362/605)×100=59.8%. The denominator of the response rate includes all possible subjects who could be interviewed (Galea et al., 2007). Here, the denominator includes the number of completed interviews; the number of subjects or proxies contacted but no interview was done; and the number of subjects or proxies who were not contacted for the interview. The cooperation rate, which only considers those subjects contacted, was (362/559)×100=64.8% (The American Association for Public Opinion Research. 2011). That is, amongst those contacted for the interview, almost 65% of subjects or proxies agreed to the interview.

6.3.2 Characteristics of Subjects According to Participation and Non-Participation with the Questionnaire

Table 6.7 shows that there were some differences between respondents and non-respondents of the subject questionnaire. In comparison with non-respondents of the questionnaire, those subjects who responded to the questionnaire themselves or had a proxy respond to the questionnaire tended to be younger in age (median age 50.0 and 58.4 years, respectively), were diagnosed at an earlier stage, were less likely to have symptoms of cervical cancer, and if they had symptoms, a routine medical check-up was more likely to have been the event that eventually precipitated the work-up towards the cancer diagnosis. There did not appear to be important differences between these two groups in terms of year of diagnosis, residence at diagnosis, smoking status, family history of cancer, tumour histology, or median income or education-level by census tract.

Table 6.7. Comparison of the characteristics of study subjects who were or who were not interviewed [1]

Variable	Subject or proxy Interviewed n (%)	Subject or proxy not interviewed n (%)
Total	330	238
Year of diagnosis		
1998	43 (13.0)	31 (13.0)
1999	43 (13.0)	39 (16.4)
2000	54 (16.4)	45 (18.9)
2001	50 (15.2)	36 (15.1)
2002	51 (15.5)	27 (11.3)
2003	48 (14.6)	29 (12.2)
2004	41 (12.4)	31 (13.0)
Place of residence at diagnosis		
Montreal	280 (84.9)	214 (89.9)
Laval	50 (15.2)	24 (10.1)
Age at diagnosis (years)		
20-29	15 (4.6)	8 (3.4)
30-39	62 (18.8)	29 (12.2)
40-49	84 (25.5)	53 (22.3)
50-59	70 (21.2)	33 (13.9)
60-69	41 (12.4)	35 (14.7)
70-79	42 (12.7)	44 (18.5)
≥80	16 (4.9)	36 (15.1)
Median	50.0	58.4
Mean	51.8	58.6
Range	21.9-90.4	24.2-93.6
Presence of symptoms[2]		
Yes	216 (65.5)	183 (76.9)
No	42 (12.7)	9 (3.8)
Unknown[3]	72 (21.8)	46 (19.3)
Reason for appointment that led to the diagnosis of ICC		
Specifically for presence of symptoms	108 (32.7)	106 (44.5)
Routine medical check-up	50 (15.2)	18 (7.6)
Condition unrelated to cervical cancer	1 (0.3)	4 (1.7)
Unknown	171 (51.8)	110 (46.2)
Presence of other co-morbidities		
Yes	117 (35.5)	115 (48.3)
Unknown	213 (64.6)	123 (51.7)

Table 6.7. continued

Variable	Subject or proxy Interviewed n (%)	Subject or proxy not interviewed n (%)
Smoking status at time of diagnosis		
Current	91 (27.6)	63 (26.5)
Former	18 (5.5)	11 (4.6)
Never	1 (0.3)	0
Not smoking at diagnosis, unclear if former/never	11 (3.3)	7 (2.9)
Unknown	209 (63.3)	157 (66.0)
Family history of any type of cancer		
Yes	90 (27.3)	49 (20.6)
No	3 (0.9)	3 (1.3)
Unknown	237 (71.8)	186 (78.2)
Stage of cervical cancer		
IA1	65 (19.7)	24 (10.1)
IA2	20 (6.1)	11 (4.6)
IB	118 (35.8)	55 (23.1)
II	60 (18.2)	53 (22.3)
III	42 (12.7)	63 (26.5)
IV	18 (5.5)	24 (10.1)
Unknown	7 (2.1)	8 (3.4)
Histology of cervical tumour		
Squamous cell	234 (70.9)	176 (74.0)
Adenocarcinoma	81 (24.6)	42 (17.7)
Adenosquamous	7 (2.1)	9 (3.8)
Other less common types	7 (2.1)	7 (2.9)
Unknown	1 (0.3)	4 (1.7)
Median income level (by census tract)[4]		
<$30,000	14 (4.2)	7 (2.9)
$30,000-39,999	61 (18.5)	58 (24.4)
$40,000-49,999	95 (28.8)	54 (22.7)
$50,000-59,999	72 (21.8)	55 (23.1)
$60,000-69,999	37 (11.2)	27 (11.3)
$70,000 or more	46 (13.9)	25 (10.5)
Missing	5 (1.5)	12 (5.0)
Completed university degree (% by census tract)[4]		
Median	16.0	13.5
Mean	20.5	18.8
Range	2.0-63.1	1.6-57.4

[1] Characteristics were obtained by review of hospital medical charts and from the 2001 Canadian Census. This table refers to subjects diagnosed with non-recurrent histologically-confirmed invasive cervical cancer between 1998

and 2004 at a Montreal or Laval hospital. Subjects must have been residing in Montreal or Laval at diagnosis and for a minimum 5-year time period. Participants refer to subjects or next-of-kin who were contacted and responded to our questionnaire. Non-participants refer to subjects or next-of-kin who either were not contacted to participate in the interview or we attempted to contact them but they were not interviewed.

[2] Symptoms of cervical cancer include the following: abnormal vaginal discharge, inter-menstrual vaginal bleeding, post-menopausal vaginal bleeding, heavy and/or prolonged menses, post-coital vaginal bleeding, loss of appetite, weight loss, fatigue, pain (pelvic, abdominal, back, and/or leg), and other less common symptoms. The category "other symptoms" include anemia, dyspareunia, dysuria, hematuria, rectal bleeding, urinary/renal tract problems, ascites, vesicovaginal fistula.

[3] Unknown means that the data indicating the presence or absence of a particular characteristic were not found in the medical chart.

[4] Data were obtained from the 2001 Canadian Census. Data not available for 17 subjects.

6.3.3 Demographic Characteristics of Subjects as Determined by Questionnaire

Table 6.8 displays the demographic characteristics of study subjects as obtained during the interview. These were either personally reported by the study subject or by a proxy. Study subjects had a mean age of 51.1 years and a median age of 48.2 years of age, which reflects the younger age distribution of questionnaire respondents compared to all study subjects. The majority of subjects (84.5%) resided in Montreal at diagnosis. About 91% of subjects resided in these regions for at least five years prior to diagnosis. Of the 32 subjects not residing in Montreal or Laval for five years, most subjects lived between 3 and 4 years within these regions. Almost 71% of subjects were Canadian-born. Immigrants were mainly from European countries (48.1%), with a large proportion from Asia (14.4%) or the Caribbean (13.5%). Immigrants lived in Canada between less than 1 year up to 77 years before their cervical cancer diagnosis, with a mean and median of 23.0 years and 20.0 years living in Canada, respectively. Over half of the subjects identified themselves as French-Canadian or as having partly French-Canadian heritage. About 35% of subjects were married, 21.0% were divorced or separated, 18.5% were single, 16.9% were in a common-law relationship, and 8.6% were widowed. Most subjects were able to converse in French only (39.5%) and a smaller proportion was bilingual, specifically, being able to converse in both French and English but not in a third language (28.5%). An estimated 59% of women only spoke French at home. More than half of subjects were employed when they were diagnosed with cervical cancer. An almost equal proportion of women had less than a high school education as had some post-secondary education. Approximately, 33% of subjects or proxy interviewees refused to answer the question regarding household income or did not know the answer. The greatest proportions of subjects had household incomes between $10-

20,000 (14.4%) and greater than $60,000 (19.3%) and lived in 2-person households (38.1%). Essentially equal proportions were current smokers or never smokers, with the smallest proportion being former smokers.

Table 6.8. Sociodemographic characteristics of study subjects as determined by questionnaire[1]

Variable	n [2]	%
Age at diagnosis (years)[3]		
mean	51.1	
median	48.2	
range	21.9-90.4	
City of residence at diagnosis		
Montreal	306	84.5
Laval	56	15.5
City of residence within 5 years prior to diagnosis		
Montreal	282	77.9
Laval	48	13.3
Other	32	8.8
If not residing in Montreal or Laval for minimum 5 years prior to diagnosis, number of years in these regions (N=32)		
<1	3	9.4
1 to <2	8	25.0
2 to <3	7	21.9
3 to <4	11	34.4
4 to <5	3	9.4
Immigrant status		
Born in Canada	256	70.7
Not born in Canada	104	28.7
Do not know/remember	2	0.6
If not Canadian born, place of birth (N=104)		
Europe	50	48.1
Asia	15	14.4
Caribbean	14	13.5
Africa	9	8.7
Central America	8	7.7
South America	4	3.8
United States	3	2.9
Mexico	1	1.0

Table 6.8. continued

Variable	n	%
If not Canadian born, number of years in Canada prior to diagnosis (N=92)[4]		
mean	23.0	
median	20.0	
range	<1-77 years	
Cultural Background		
French-Canadian or French-Canadian mix	205	56.6
Other	146	40.3
Do not know/remember	11	3.0
Marital status		
Legally married (not separated)	126	34.8
Common-law	61	16.9
Divorced/ Separated	76	21.0
Single	67	18.5
Widowed	31	8.6
Do not know/remember	1	0.3
Language of conversation		
English only	23	6.4
English and another language(s) but not French	14	3.9
French only	143	39.5
French and another language(s) but not English	30	8.3
Both English and French and another language(s)	33	9.1
Both English and French but not a 3rd language	103	28.5
Neither English nor French	14	3.9
Do not know/remember	2	0.6
Language spoken most often at home		
English only	62	17.1
English and another language(s) but not French	4	1.1
French only	212	58.6
French and another language(s) but not English	14	3.9
Both English and French and another language	4	1.1
Both English and French but not a 3rd language	13	3.6
Neither English nor French	51	14.1
Do not know/remember	2	0.6
Employment status		
Employed	206	56.9
Unemployed	20	5.5
Housewife	47	13.0
Retired	77	21.3
Student	8	2.2
Do not know/remember	4	1.1

Table 6.8. continued

Variable	n	%
Highest level of education		
Less than high school	107	29.6
High school graduate	57	15.8
Some post-secondary education	113	31.2
University undergraduate degree complete	52	14.4
University graduate degree complete	17	4.7
Do not know/remember or refuses to answer	16	4.4
Household income ($)		
<10,000	8	2.2
10-20,000	52	14.4
21-30,000	37	10.2
31-40,000	36	9.9
41-50,000	26	7.2
51-60,000	11	3.0
>60,000	70	19.3
Social assistance/ welfare	4	1.1
Do not know/ remember or refuses to answer	118	32.6
Number of people in household		
1	72	19.9
2	138	38.1
3	53	14.6
4	60	16.6
5	27	7.5
6	4	1.1
7	2	0.6
I don't know/remember	6	1.7
Smoking status at diagnosis (N=330)[5]		
Current	123	37.3
Former	73	22.1
Never	131	39.7
Do not know/remember	3	0.9

[1] Subjects of this analysis include all women who responded or proxy responded to the questionnaire. Subjects may or may not have resided in Montreal or Laval for minimum 5 years prior to diagnosis. The exception was the question regarding smoking status, which was only asked of long-term residents of these regions. A total of 362 subjects or proxies responded to the questionnaire. The denominator for the percentages was 362, unless noted otherwise within the table.

[2] n (%) refers to the number and percentage of subjects falling within each category except when median, mean, and range are noted.

[3] Age at diagnosis was not obtained from the subject interview but instead it was determined using the birth date and date at diagnosis obtained from hospital medical charts and/or lab reports

[4] Data missing for 12 subjects.

[5] This question was only asked of subjects residing in Montreal or Laval for at least 5 years.

6.3.4 Association between Subject Demographics and Cervical Cancer

As is shown in Table 6.9, women with cervical cancer were more likely to have certain characteristics compared to those without cervical cancer. It was found that women not born in Canada were more likely to develop cervical cancer compared to Canadian-born women (OR 1.4, 95% CI 1.1-1.8). This risk amongst immigrants appeared to dissipate the longer they resided in Canada, although results were not statistically significance (OR 0.7, 95% CI 0.3-1.3). Women in common-law relationships (OR 1.6, 95% CI 1.1-2.3) or those possessing some post-secondary education (but not completed) (OR 2.4, 95% CI 1.6-3.6) were at greater risk of cervical cancer. Women who spoke English or French (but not both) or who spoke neither English nor French were all at an enhanced risk of cervical cancer. The latter group had the greatest risk with an estimated OR of 4.5 (95% CI 2.3-9.1). The following variables appeared to confer some protection against cervical cancer: the completion of a post-secondary degree (OR 0.3, 95% CI 0.2-0.4), being a former smoker (OR 0.4, 95% CI 0.3-0.6), having a regular doctor of any specialty (OR 0.5, 95% CI 0.4-0.7), and having a chronic health condition (OR 0.07, 95% CI 0.06-0.10).

When the same analysis was repeated but was now limited to women with invasive cervical cancer, some sociodemographic differences were found between subjects based on the progression of their cervical cancer, which is shown in Table 6.10. Being widowed, separated or divorced (OR 1.9, 95% CI 1.1-3.5) or being a current smoker (OR 2.1, 95% CI 1.2-3.8) were both associated with a greater risk of regional or distant cancer. Possession of a post-secondary degree (OR 0.5, 95%CI 0.2-0.9) was associated with a much higher probability of a localized cancer at diagnosis compared to women who did not graduate from secondary school. Amongst non-Canadian born women, those residing in Canada for 10 or more years had a much lower likelihood of being diagnosed at a late cancer stage compared to more recent immigrants (OR 0.2, 95% CI 0-0.8).

Table 6.9. Association between subject demographic characteristics and invasive cervical cancer, as measured by odds ratios

Characteristic	No. of Study Subjects[1] (%)	No. of CCHS respondents[2] (%)	Adjusted OR (95% CI)[3]
Place of birth			
Canada	256 (71.1)	1442 (77.4)	referent
Other	104 (28.9)	421 (22.6)	1.4 (1.1-1.8)
If not Canadian born, number of years in Canada			
0-9 years	22 (23.9)	109 (26.4)	referent
10 or more years	70 (76.1)	304 (73.6)	0.7 (0.3-1.3)
Marital Status			
Married	126 (34.9)	662 (33.5)	referent
Common-law	61 (16.9)	215 (10.9)	1.6 (1.1-2.3)
Widowed/Separated/Divorced	107 (29.6)	587 (29.7)	1.1 (0.8-1.4)
Single	67 (18.6)	513 (25.9)	0.9 (0.6-1.2)
Language of conversation			
Both English and French (may speak other language)	136 (37.8)	1034 (55.4)	referent
English (not French, may speak other language)	37 (10.3)	153 (8.2)	2.0 (1.4-3.1)
French (not English, may speak other language)	173 (48.1)	653 (35.0)	2.1 (1.6-2.7)
Neither English nor French	14 (3.9)	28 (1.5)	4.5 (2.3-9.1)
Employment status			
Employed	206 (57.5)	940 (58.1)	referent
Unemployed/housewife	67 (18.7)	284 (17.5)	1.0 (0.7-1.4)
Student	8 (2.2)	41 (2.5)	1.7 (0.8-4.0)
Retired	77 (21.5)	354 (21.9)	0.4 (0.3-0.7)
Highest level of education			
Less than secondary graduation	107 (30.9)	498 (25.5)	referent
Secondary school graduation	72 (20.8)	251 (12.9)	0.9 (0.6-1.3)
Some post-secondary education	68 (19.4)	105 (5.4)	2.4 (1.6-3.6)
Post-secondary degree/diploma	99 (28.6)	1096 (56.2)	0.3 (0.2-0.4)
Smoking status			
Never	131(40.1)	676 (34.2)	referent
Current	123 (37.6)	537 (27.2)	1.1 (0.8-1.5)
Former	73 (22.3)	763 (38.6)	0.4 (0.3-0.6)

Table 6.9. continued

Characteristic	No. of Study Subjects (%)	No. of CCHS respondents (%)	Adjusted OR (95% CI)
Child birth in previous 5 years			
No	294 (89.4)	887 (82.7)	referent
Yes	35 (10.6)	186 (17.3)	1.3 (0.9-2.1)
Had regular doctor			
No	95 (29.7)	408 (20.6)	referent
Yes	225 (70.3)	1574 (79.4)	0.5 (0.4-0.7)
Chronic condition			
No	246 (75.5)	448 (22.6)	referent
Yes	80 (24.5)	1534 (77.4)	0.07 (0.06-0.10)

[1] Study subjects are the women with invasive cervical cancer for whom we had data from the subject interview. These women may or may not have lived in Montreal or Laval for at least five years (N=362). Numbers may not add up to 362 for certain questions due to non-responses. The last four analyses listed in the table include only those women residing in Montreal or Laval for a minimum of five years since only these women were administered the long version of the questionnaire (N=330).

[2] CCHS refers to the Canadian Community Health Survey. These analyses included women living in Montreal or Laval who responded to the CCHS Survey (N=1984).

[3] All analyses were adjusted for age at diagnosis for cervical cancer cases and age at time of survey administration for CCHS respondents. Age was categorized in 5 year intervals (20-24, 25-29, 30-34..., >=80 years).

Table 6.10. Association between subject demographic characteristics and advanced cervical cancer, as measured by odds ratios[1]

Characteristic	No. of Distant cancer cases (%)[2]	No. of Regional cancer cases (%)[2]	No. of Localized cancer cases (%)[2]	Adjusted OR (95% CI)[3]
Place of birth				
Canada	13 (72.2)	81 (72.3)	157 (69.8)	referent
Other	5 (27.8)	29 (25.9)	68 (30.2)	0.6 (0.3-1.0)
If not Canadian born, number of years in Canada				
0-9 years	0	8 (33.3)	14 (22.6)	referent
10 or more years	4 (100.0)	16 (66.7)	48 (77.4)	0.2 (0-0.8)
Marital Status				
Married	7 (38.9)	32 (28.8)	83 (36.9)	referent
Common-law	1 (5.6)	16 (14.4)	43 (19.1)	1.8 (0.8-4.0)
Widowed/Separated/Divorced	6 (33.3)	47 (42.3)	52 (23.1)	1.9 (1.1-3.5)
Single	4 (22.2)	16 (14.4)	47 (20.9)	1.6 (0.8-3.3)
Language of conversation				
Both English and French (may speak other language)	6 (33.3)	36 (32.7)	92 (40.9)	referent
English (not French, may speak other language)	2 (11.1)	11 (10.0)	24 (10.7)	0.6 (0.3-1.5)
French (not English, may speak other language)	9 (50.0)	57 (51.8)	103 (45.8)	1.1 (0.6-1.9)
Neither English nor French	1 (5.6)	6 (5.5)	6 (2.7)	0.9 (0.3-3.2)
Employment status				
Employed	9 (50.0)	47 (42.7)	147 (65.9)	referent
Unemployed/housewife	3 (16.7)	26 (23.6)	36 (16.1)	1.8 (1.0-3.5)
Student	0	0	8 (3.6)	NA
Retired	6 (33.3)	37 (33.6)	32 (14.3)	1.0 (0.4-2.4)
Highest level of education				
Less than secondary graduation	8 (47.1)	44 (42.7)	50 (22.8)	referent
Secondary school graduation	3 (17.6)	21 (20.4)	33 (15.1)	1.1 (0.5-2.4)
Some post-secondary education	3 (17.6)	12 (11.7)	28 (12.8)	1.0 (0.4-2.3)
Post-secondary degree/diploma	3 (17.6)	26 (25.2)	108 (49.3)	0.5 (0.2-0.9)

Table 6.10. continued

Characteristic	No. of Distant cancer cases (%)[2]	No. of Regional cancer cases (%)[2]	No. of Localized cancer cases (%)[2]	Adjusted OR (95% CI)[3]
Annual household income ($)				
≤20,000	1 (14.3)	23 (34.8)	40 (23.8)	referent
21-40,000	1 (14.3)	23 (34.8)	47 (28.0)	1.0 (0.5-2.3)
41-60,000	4 (57.1)	6 (9.1)	27 (16.1)	0.8 (0.3-2.2)
>60,000	1 (14.3)	14 (21.2)	54 (32.1)	0.6 (0.2-1.4)
Child birth in previous 5 years				
No	18 (100.0)	99 (98.0)	170 (83.7)	referent
Yes	0	2 (2.0)	33 (16.3)	0.3 (0.1-1.4)
Had regular doctor				
No	8 (47.1)	38 (39.2)	48 (24.1)	referent
Yes	9 (52.9)	59 (60.8)	151 (75.9)	0.6 (0.4-1.1)
Chronic condition				
No	14 (77.8)	74 (74.0)	155 (77.1)	referent
Yes	4 (22.2)	26 (26.0)	46 (22.9)	0.7 (0.4-1.2)
Smoking status				
Never	7 (38.9)	35 (35.4)	85 (41.9)	referent
Current	8 (44.4)	43 (43.4)	70 (34.5)	2.1 (1.2-3.8)
Former	3 (16.7)	21 (21.2)	48 (23.6)	1.1 (0.5-2.1)

[1] Study subjects are the women with invasive cervical cancer for whom we had data from the subject interview and for whom cancer staging was available. They may or may not have resided in Montreal or Laval for a minimum 5 years prior to diagnosis (N for distant cancer=18, N for regional cancer=112, N for localized cancer=225). The last four characteristics refer only to those women who lived in Montreal or Laval for a minimum five years prior to diagnosis (N for distant cancer=18, N for regional cancer=102, N for localized cancer=203).

[2] Staging refers to the SEER summary staging. Localized refers to FIGO staging IA1, IA2, IB. Regional refers to FIGO staging IIA, IIB, IIIA, IIIB. Distant refers to FIGO staging IV.

[3] In these analyses, distant and regional cancers were combined into one group and localized cancers were another group. All analyses were adjusted for age at diagnosis for cervical cancer cases. Age was categorized in 5 year intervals (20-24, 25-29, 30-34..., >=80 years).

6.3.5 Other Subject Questionnaire Results

6.3.5.1 Pap screening knowledge, screening history, physician preferences and cervical cancer symptoms of study subjects

At the time of the interview, 83% of study subjects knew what a Pap test was (Table 6.11). About 51% of respondents reported that they had a Pap test within five years before diagnosis. The most common reason for not being screened was "I never imagined that I would ever develop cervical cancer". Other frequent reasons for no screening included not having a physician, not knowing the purpose of the Pap test, and being busy. About 38% of subjects claimed to be screened every year and 14.1% were never screened. Sixty-five percent of subjects did not have a Pap test deemed abnormal prior to the five-year interval before diagnosis. In general, the majority of subjects did not have a preference for the sex, the age, or medical specialty of the physician who performed their Pap test. If subjects did have a preference, most of them said they would have their Pap tests done even though they could not find a physician with these specific characteristics. Seventy percent of subjects experienced symptoms of cervical cancer. The most frequent symptoms included vaginal bleeding, either post-menopausal (37.2%) or inter-menstrual bleeding (28.6%), and pain, which either affected the pelvis, abdomen, back and/or legs (32.5%). The presence of symptoms led 54.8% of subjects to seek medical attention that eventually led to diagnosis of cervical cancer. Forty percent of subjects went to their physicians for a routine medical check-up.

6.3.5.2 Health status and physician-use behaviour

As shown in Table 6.12, most subjects classified their general health as either "good" or "very good". About 66% of women had a family physician or gynecologist from whom they would receive care. The majority of subjects (74.5%) did not have a chronic condition. Amongst those women who did have a chronic condition, hypertension (20.0%) and diabetes (18.8%) were the most common. Over 80% of subjects with chronic conditions were followed regularly by a physician, who was most likely a family physician (61.5%). Depressed immunity was uncommon among subjects. Almost 42% of subjects claimed to visit their doctors for non-gynaecologic care once a year. Only 10.6% of subjects were pregnant within the five-year interval prior to their cervical cancer diagnosis and 71.4% of them had only one pregnancy

during that period. An estimated 14.3% of these women believed that their pregnancy delayed the receipt of follow-up Pap tests of diagnostic tests for cervical cancer.

Table 6.11. Pap screening knowledge, screening history, physician preferences and cervical cancer symptoms as reported during interview[1]

Variable	n	%
Subject had knowledge of Pap testing at interview (N=289)[2] *		
Yes	240	83.0
No	49	17.0
Did subject have Pap tests within 5 years of diagnosis? (N=362)*		
Yes	184	50.8
No	149	41.2
Do not know/remember	29	8.0
Reason for not being screened within 5 years of diagnosis (N=136)[3]		
Did not know what pap test was for	38	27.9
Felt embarrassed	21	15.4
Afraid it would hurt	13	9.6
Never imagined I would develop cervical cancer	73	53.7
Forgot to do have Pap	27	19.9
My physician did not tell me I needed a Pap smear	24	17.6
I knew I needed a Pap test but my physician did not do Pap tests	6	4.4
I did not have a physician	40	29.4
Inconvenient office hours	5	3.7
I was busy	33	24.3
Thought Pap tests were only for women who had symptoms	18	13.2
Lifetime frequency of Pap smears (N=362)*		
Every 6 months	4	1.1
Every year	137	37.8
Every 2 years	30	8.3
Every 3 years	14	3.9
Every 4 years	5	1.4
Every 5 years	1	0.3
Frequency unknown but screened in past	36	9.9
Never	51	14.1
I don't know/remember	84	23.2

Table 6.11. continued

Variable	n	%
Besides Paps done within 5 years of diagnosis, did you have any abnormal Paps throughout your lifetime? (N=227)		
Yes	46	20.3
No	148	65.2
I don't know/remember	33	14.5
Did it matter if the physician performing the gynaecologic exam or Pap test was male or female?		
Yes, female	60	18.2
Yes, male	5	1.5
Did not matter	205	62.1
Do not know or remember	60	18.2
If the sex of the physician mattered, what if you could not find a physician of that sex? (N=65)		
Have pap smear anyway	58	89.2
Not have a pap smear	4	6.2
Do not know or remember	3	4.6
Did it matter if the physician performing the gynaecologic exam or Pap test was older or younger?		
Yes, older	32	9.7
Yes, younger	5	1.5
Did not matter	232	70.3
Do not know or remember	61	18.5
If the age of the physician mattered, what if you could not find a physician of that age? (N=37)		
Have pap smear anyway	32	86.5
Not have a pap smear	1	2.7
Do not know or remember	3	8.1
Other (I would have found one)	1	2.7
Did the type of physician performing the gynaecologic exam or Pap test matter?		
Yes, family physician	13	3.9
Yes, gynecologist	66	20.0
Did not matter	192	58.2
Do not know/ remember	59	17.9

Table 6.11. continued

Variable	n	%
If the type of physician mattered, what if you could not find that caregiver? (N=79)		
Have pap smear anyway	66	83.5
Not have a pap smear	2	2.5
Do not know or remember	10	12.7
Other (I would have found one)	1	1.3
Presence of symptoms		
Yes	231	70.0
No	94	28.5
Do not know/remember	5	1.5
If symptoms present, type of symptoms (N=231)[3]		
Vaginal discharge	51	22.1
Between menstrual period vaginal bleeding	66	28.6
Post-menopausal vaginal bleeding	86	37.2
Vaginal bleeding following sexual intercourse	55	23.8
Heavy and/or prolonged menstrual bleeding	34	14.7
Pain (pelvic, abdominal, back, and/or leg)	75	32.5
Other less common symptoms	21	9.1
Reason for visit that eventually led to cervical cancer diagnosis		
Specifically because of symptoms	181	54.8
Routine medical check-up	133	40.3
Condition or procedure unrelated to cervical cancer	8	2.4
Other reason	2	0.6
Do not know/remember	6	1.8

[1] Subjects of this analysis are women residing in Montreal or Laval for a minimum 5 years before diagnosis with ICC (N=330). The exceptions are those questions denoted with an asterisk. These questions were also asked of subjects who did not live in these regions for at least 5 years.
[2] This question refers to self-reports only (not proxy reports).
[3] Subjects may choose more than one reason.

Table 6.12. Health Status and physician-use behaviour of study subjects as reported during interview (N=330)[1]

Variable	n	%
General health		
Poor	2	0.6
Fair	37	11.2
Good	174	52.7
Very good	113	34.2
Does not know/remember	4	1.2
Family physician or gynaecologist within 5 years of diagnosis		
Yes	217	65.8
No	105	31.8
Does not know/remember	8	2.4
Presence of chronic disease		
No	246	74.5
Yes	80	24.2
Does not know/remember	4	1.2
Type of chronic condition (N=80)		
Hypertension	16	20.0
Diabetes	15	18.8
Heart problems	6	7.5
Thyroid condition	5	6.3
High cholesterol	4	5.0
Cancer	3	3.8
Other less common conditions	31	38.8
Being seen by doctor for chronic condition on regular basis (N=80)		
Yes	65	81.3
No	10	12.5
Does not know/remember	5	6.3
Type of doctor providing care for chronic condition (N=65)		
General practitioner/family doctor	40	61.5
Endocrinologist	5	7.7
Psychiatrist or psychologist	3	4.6
Cardiologist	3	4.6
Other medical specialty	8	12.3
Does not know/remember	6	9.2
Depressed immunity (N=330)		
Yes	2	0.6
No	310	93.9
Does not know/remember	18	5.5

Table 6.12. continued

Variable	N	%
Frequency of doctor visits for non-gynecologic care		
Once a month	7	2.1
Every 2 months	5	1.5
Every 3 months	16	4.8
Every 4 months	5	1.5
Every 5 months	1	0.3
Every 6 months	23	7.0
Once a year	137	41.5
Every 2 years	1	0.3
Never	32	9.7
If necessary/when sick/Does not know	103	31.2
Pregnancies within 5 years prior to cervical cancer diagnosis		
Yes	35	10.6
No	294	89.1
I don't know/remember	1	0.3
If pregnant within 5 years prior to cervical cancer diagnosis, the number of pregnancies (N=35)		
1	25	71.4
2	8	22.9
3	1	2.9
Does not know/remember	1	2.9
Lifetime number of pregnancies (including those within 5 years prior to diagnosis)		
0	54	16.4
1	44	13.3
2	87	26.4
3	55	16.7
4	27	8.2
5	24	7.3
>=6	31	9.4
Does not know/remember	8	2.4
Did pregnancy within 5 years of diagnosis delay the receipt of Pap tests or diagnostic tests for cervical cancer? (N=35)		
Yes	5	14.3
No	15	42.9
Does not know/remember	15	42.9

[1] Subjects of this analysis are women residing in Montreal or Laval for a minimum 5 years before diagnosis with ICC (N=330).

6.4 Physician Questionnaire

As shown in Figure 6.2, 330 subjects or their next of kin responded to the subject questionnaire. Of these respondents, 221 (67.0%) gave us signed consent to contact any of their physicians to obtain further information regarding their cervical screening and treatment history. We obtained data for 87 of these subjects (39.4%). For these 221 subjects, we made a total of 329 requests to physicians for data. It should be noted that a subject may have had more than one physician so we sent each of them a questionnaire. Likewise, an individual physician could have had more than one of our study subjects as a patient and hence, he/she received a request for data for more than one subject. Of 329 questionnaires we mailed out, we received data for 150 (45.6%) of them. This data retrieval occurred in the following ways: 1) Physicians completed the questionnaire and may or may not have sent us lab reports too. 2) Physicians did not complete the questionnaire and only sent us lab reports. 3) Physicians phoned the study office to relay the requested data to us via the telephone. 4) Upon the request of the physician, we personally went to the physician's office to retrieve the pertinent data from the subject's medical file.

Data was not received for 134 subjects or a total of 179 individual requests to physicians. The reasons for not receiving data are tabulated in Table 6.13. For 40.2% of these 179 requests, the reasons for the non-response were not known. In those cases, the physicians did not respond to our repeated requests to complete the questionnaire and they did not contact our office to offer a reason as to why they did not want to participate. The rest of the physicians contacted the study research office by telephone or fax but did not send data. The most common reason (43.6%) was that no medical chart was found for the patient in that office. This was the case if the chart was thrown out since the subject had not been seen by the physician for a given period of time, typically five years or more, or simply, the physician stated he did not know this subject. Other less common reasons were as follows: 1) The physician only saw the patient at diagnosis or after her diagnosis with cervical cancer. 2) The physician had retired, had died or no longer practiced at a given clinic and hence, he did not have access to the medical chart. 3) The physician does not have personal office charts but rather uses the charts at the hospital. Hence, we requested these charts directly from the pertinent hospital medical records departments and reviewed them. 4) Upon the request of the physician, the researcher attempted to retrieve data from physicians'

offices but either there was no chart for that particular subject or there was no data pertaining to cervical cancer.

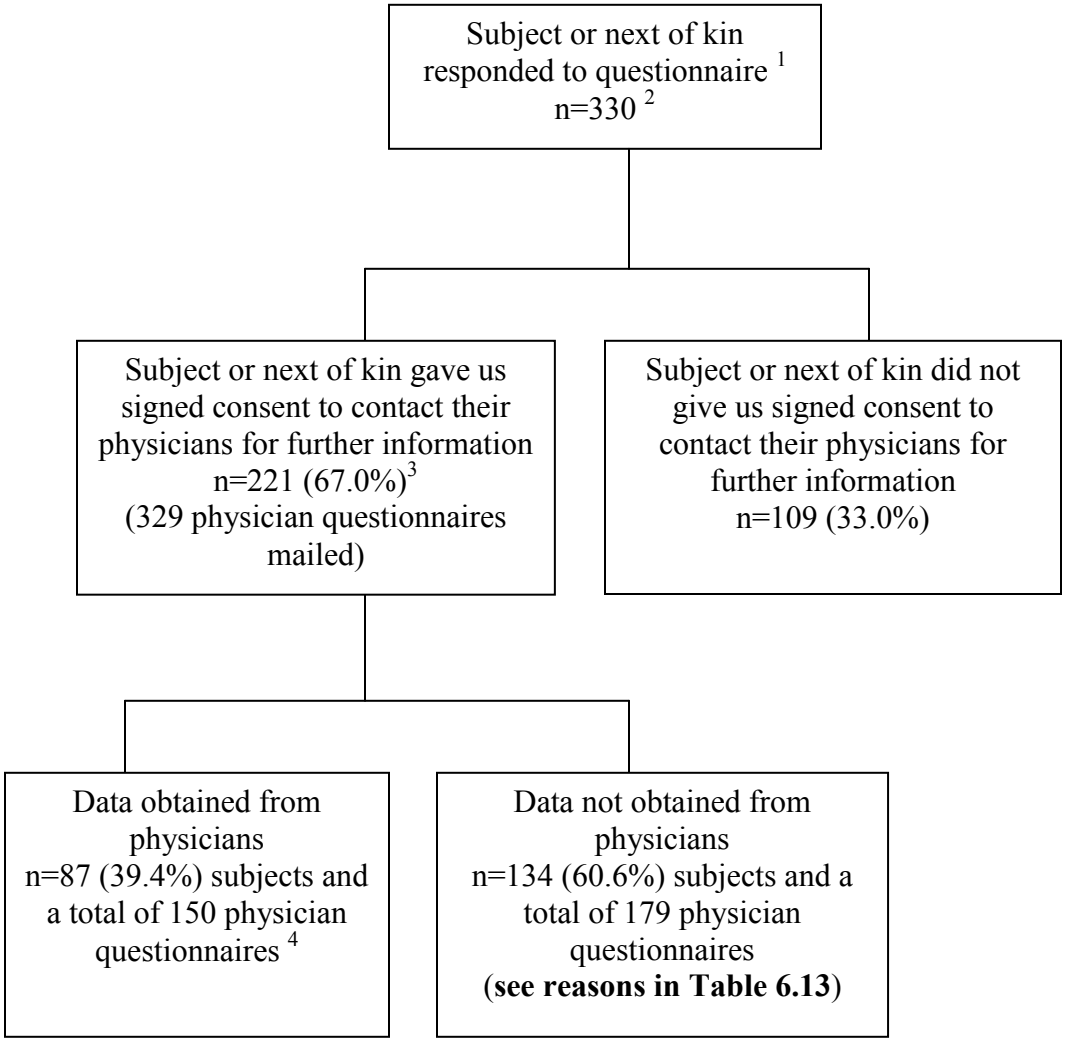

Figure 6.2. Physician questionnaire participation

[1] This refers to women residing in Montreal or Laval for a minimum 5 years prior to diagnosis.
[2] Numbers within this figure refer to the number of subjects, unless otherwise stated.
[3] Percentages within this table are based on the total number of subjects one level above.
[4] Physicians either completed the questionnaire and/or sent us lab documents or they relayed the requested information to us over the telephone or the researcher personally obtained the data from the physician's office medical files. Data was either received for one or more physician.

Table 6.13. Reasons physicians did not complete questionnaire or provide documents

Reason	Number incidences (%)
Physician contacted the study office and stated the following: He/She does not know the subject or he/she has thrown out the chart for this subject as he/she does not keep charts for longer than five years.	78 (43.6)
Reason not known. Physicians did not respond to our request to complete the questionnaire.	72 (40.2)
Physician does not have his own office medical charts. Instead, the data should be found within the hospital medical files.	12 (6.7)
Physician only provided medical care to these subjects at diagnosis or after diagnosis with cervical cancer or did not provide care related to cervical cancer.	7 (3.9)
Physician has retired or has died.	6 (3.4)
Study research personnel reviewed the physician's office medical charts but either there was no chart for subjects or no data was found related to cervical cancer.	3 (1.7)
Physician too busy to complete questionnaire.	1 (0.6)
Total	179

6.5 Comparison of Sources of Data

As displayed in Table 6.14, the most fruitful sources of data for all procedures were hospital labs and hospital medical charts. The hospital labs identified 64.0% (1051) of the total 1643 Pap tests we found and 41.8% (686) were found in medical charts. It should be noted that a given proportion of each of these procedures were identified by more than one source. In general, a slightly greater percentage of the other procedures were identified by reviewing hospital medical charts in comparison to that obtained from the hospital lab. The data obtained from the physician questionnaire and chart annotations provided essentially equal percentages of Pap tests but the former identified a greater proportion of all the other procedures except for cones. The

study subjects provided us with the year of only 34.5% of the Pap tests and proxies with only 3.2% of Pap tests.

It should be noted that some of the labs that should have been searched for data for specific subjects were not contacted. This was the case since one lab refused to participate in our study, another lab required written consent from subjects, and over time some labs that had initially provided us with lab reports were no longer willing to do so. Hence, proportions calculated above for the various sources are probably a slight overestimate of what they would be, assuming that some new unidentified procedures would be found if all labs could be searched without these barriers.

Table 6.15 shows the numbers of procedures that were uniquely identified by each source. Labs were the most likely to identify Pap tests that were not found by the other sources of data. Subjects also exclusively ascertained a large proportion of Pap smears (26.6%) during the interview. Almost 84% of all colposcopies identified by only one source were identified through the review of medical charts. Slightly more cervical biopsies and cones were exclusively identified by medical charts than labs. Only four more ECCs were solely identified by labs compared to medical charts.

Table 6.14. Proportion of procedures identified by different data sources

Procedure	Total number of procedures	Number of procedures identified by source (% of total)[1]					
		Laboratory	Hospital Medical Chart	Physician Questionnaire	Hospital Medical Chart Annotations	Questionnaire completed by Study Subject[2]	Questionnaire completed by Proxy[2]
Pap Tests	1643	1051 (64.0)	686 (41.8)	231 (14.1)	241 (14.7)	567 (34.5)	52 (3.2)
Colposcopy	322	NA[3]	264 (82.0)	67 (20.8)	37 (11.5)	NA	NA
Cervical biopsy	697	533 (76.5)	559 (80.2)	77 (11.1)	55 (7.9)	NA	NA
Cervical conization	179	147 (82.1)	156 (87.2)	23 (12.9)	42 (23.5)	NA	NA
Endocervical curettage	431	318 (73.8)	310 (71.9)	62 (14.4)	20 (4.6)	NA	NA

Abbreviation: NA, not applicable

[1] Numbers do not add up to the total number of procedures listed in the second column since the same given procedure may have been identified by multiple sources.

[2] The subject questionnaire only enquired about Pap screening history.

[3] A colposcopy is a visual examination that does not involve laboratory review.

Table 6.15. Proportion of procedures exclusively identified by a single source

Procedure	Total number of procedures exclusively identified via a single source	Number of procedures only identified by one source (% of total)					
		Laboratory	Hospital Medical Chart	Physician Questionnaire	Hospital Medical Chart Annotations	Questionnaire completed by Study Subject	Questionnaire completed by Proxy
Pap Tests	745	324 (43.5)	129 (17.3)	33 (4.4)	37 (5.0)	198 (26.6)	24 (3.2)
Colposcopy	264	NA	221 (83.7)	31 (11.7)	12 (4.5)	NA	NA
Cervical biopsy	238	106 (44.5)	122 (51.3)	7 (2.9)	3 (1.3)	NA	NA
Cervical conization	40	17 (42.5)	22 (55.0)	0	1 (2.5)	NA	NA
Endocervical curettage	186	89 (47.8)	85 (45.7)	11 (5.9)	1 (0.5)	NA	NA

Abbreviation: NA, not applicable

6.6 Assessment of Pap Screening Histories

6.6.1 Subject Pap Screening Histories

As shown in Table 6.16, the majority of women (whose screening histories could be classified based on the available data) were screened at least once during their lifetime. Specifically, 90% of these subjects were "ever" screened and about 10% of women were "never" screened. Of those women who were ever screened, an almost equal proportion was screened within less than 3 years and 5 years or more before cancer diagnosis (40.3% and 43.1%, respectively). An estimated 16.6% of these women were screened between 3 and less than 5 years before diagnosis. We were not able to determine the timing of the last Pap smear for 6 subjects who were classified as ever screened.

A greater proportion of women categorized as "ever screened" (63.0%) or "never screened" (82.1%) were qualified as being "definite" in terms of the degree of assurance we had with the Pap screening categorization rather than "probable" or "possible". When timing since last Pap test was classified, the majority of those women screened 5 or more years before diagnosis were qualified as "definite". About half of the other timing categories were qualified as "definite" or "probable".

Based on the data collected, we were not able to categorize 161 subjects as being ever or never screened during their lifetimes. Table 6.17 shows that there were some demographic differences between these 161 subjects and the 407 subjects we were able to categorize as ever or never screened. The non-classified group were significantly older in age (median age 67.0 vs. 48.4, respectively), diagnosed at a more advanced stage, lived in lower-income census tracts, more likely to have had symptoms of cervical cancer, and more likely to reside in a census tract with a lower-level of university graduates (median 12.3% vs. 16.5%, respectively), and much less likely to have personally responded to or have had a proxy respond to the subject questionnaire (21.7% vs. 72.5%, respectively).

Table 6.16. Subject Pap screening histories stratified by level of uncertainty as to categorization

Pap Screening History[1]	Categorization Qualifiers[2]			Total N (%, 95% CI)[4]
	Definite n (%)	Probable n (%)	Possible n (%)	
Ever or Never screened				
Ever Screened	232 (63.0)	127 (34.5)	9 (2.4)	368 (90.4, 87.5-93.3)
Never Screened	32 (82.1)	5 (12.8)	2 (5.1)	39 (9.6, 6.7-12.5)
Subjects not classified as ever or never screened[3]	NA	NA	NA	161
Time since last Pap amongst those Ever screened				
< 3 years	71 (48.6)	70 (47.9)	5 (3.4)	146 (40.3, 35.3-45.4)
3 to < 5 years	28 (46.7)	29 (48.3)	3 (5.0)	60 (16.6, 12.7-20.4)
≥5 years	131 (84.0)	24 (15.4)	1 (0.6)	156 (43.1, 38.0-48.2)
Subjects classified as ever screened but not able to classify time since last Pap	NA	NA	NA	6

[1] These definitions of ever screened, never screened and timing of last Pap were based on the results of potentially all four sources of screening history. Those women who did not live in Montreal or Laval for a minimum 5 years prior to diagnosis were omitted from these analyses (n=37).

[2] These qualifiers have been defined in Figure 5.5 and within the text on page 68.

[3] Based on available data, the screening histories of 161 women could not be classified as "ever" or "never" screened. However, it was determined that they were not screened within five years prior to diagnosis with cervical cancer.

[4] The denominator is the total of those subjects whose screening histories we were able to categorize.

Table 6.17. Characteristics of subjects who could not be defined as being 'ever' or 'never' screened in the past versus those subjects who were defined as 'ever' or 'never' screened[1]

Variable	Subjects not categorized n (%)	Subjects categorized n (%)
Total	161	407
Year of diagnosis		
1998	22 (13.7)	52 (12.8)
1999	26 (16.1)	56 (13.8)
2000	33 (20.5)	66 (16.2)
2001	18 (11.2)	68 (16.7)
2002	24 (14.9)	54 (13.3)
2003	16 (9.9)	61 (15.0)
2004	22 (13.7)	50 (12.3)
Place of residence at diagnosis		
Montreal	138 (85.7)	356 (87.5)
Laval	23 (14.3)	51 (12.5)
Age at diagnosis (years)		
Median	67.0	48.4
Mean	63.2	51.3
Range	25.0-93.6	21.9-90.4
Stage		
IA1	18 (11.2)	71 (17.4)
IA2	6 (3.7)	25 (6.1)
IB	39 (24.2)	134 (32.9)
II	30 (18.6)	83 (20.4)
III	39 (24.2)	66 (16.2)
IV	20 (12.4)	22 (5.4)
Unknown	9 (5.6)	6 (1.5)
Histology		
Squamous cell	124 (77.0)	286 (70.3)
Adenocarcinoma	25 (15.5)	98 (24.1)
Adenosquamous	6 (3.7)	10 (2.5)
Other less common types	3 (1.9)	11 (2.7)
Unknown	3 (1.9)	2 (0.5)
Median income level (by census tract)[2]		
<$30,000	5 (3.1)	16 (3.9)
$30,000-39,999	45 (28.0)	74 (18.2)
$40,000-49,999	45 (28.0)	104 (25.6)
$50,000-59,999	30 (18.6)	97 (23.8)
$60,000-69,999	17 (10.6)	47 (11.5)
$70,000 or more	11 (6.8)	60 (14.7)
Missing	8 (5.0)	9 (2.2)

Table 6.17. continued

Variable	Subjects not categorized n (%)	Subject categorized n (%)
Proportion with university degree (% for census tract)[2]		
Median	12.3	16.5
Mean	17.4	20.7
Range	2.0-60.2	1.6-63.1
Presence of symptoms[3]		
Yes	124 (77.0)	275 (67.6)
No	6 (3.7)	45 (11.1)
Unknown[4]	31 (19.3)	87 (21.4)
Responded to questionnaire		
Yes	35 (21.7)	295 (72.5)
No	126 (78.3)	112 (27.5)

[1] Subjects diagnosed with non-recurrent histologically-confirmed invasive cervical cancer between 1998 and 2004 at a Montreal or Laval hospital. Subjects must have been residing in Montreal or Laval at diagnosis and for a minimum 5-year time period.

[2] Data were obtained from the 2003 Canadian Census. Data not available for 17 subjects.

[3] Symptoms of cervical cancer include the following: abnormal vaginal discharge, inter-menstrual vaginal bleeding, post-menopausal vaginal bleeding, heavy and/or prolonged menses, post-coital vaginal bleeding, loss of appetite, weight loss, fatigue, pain (pelvic, abdominal, back, and/or leg), and other less common symptoms. The category "other symptoms" include anemia, dyspareunia, dysuria, hematuria, rectal bleeding, urinary/renal tract problems, ascites, vesicovaginal fistula.

[4] Unknown means that the data indicating the presence or absence of a particular characteristic were not found in the medical chart.

6.6.2 Association between Pap Screening History and Cervical Cancer

Counter to what was expected, being ever screened within your lifetime was associated with an increased risk of developing invasive cancer compared to being never screened (OR 1.6, 95% CI 1.1-2.3) (Table 6.18). The analysis was then repeated and study subjects were restricted to those whose screening categorization was classified as "definite". Again, this relationship was positive in direction; however, the point estimate diminished in magnitude and lost its statistical significance (OR 1.2, 95% CI 0.8-1.8). The analysis was again repeated and screening history was now limited to that obtained solely from the subject questionnaire. It was found that being ever screened was protective against developing cervical cancer, although statistical significance was not reached (OR 0.7, 95% CI 0.5-1.0). When timing of the last Pap was examined, it was found that the greater the time interval since the last Pap, the greater the risk of cervical cancer. The highest odds ratios and widest gradient between the time intervals was found when limited to study subjects whose screening categorization was deemed as definite. All three analyses found that an adequate screening history (i.e. being screened within last 3 years) was protective against cervical cancer. The lowest point estimate was found in the analysis limited to subjects with a "definite" screening history.

When the same analysis was now limited to only subjects with cervical cancer, the point estimates of all three analyses, although not statistically significant, indicated that being never screened was associated with a greater risk of more advanced cancer compared to women who were ever screened (Table 6.19). The analysis that was limited to women with screening histories deemed as "definite" found that women screened 5 or more years before diagnosis were more than two-fold more likely to have a more advanced cancer (OR 2.6, 95% CI 1.3-5.3) compared to women screened within 3 years of diagnosis. All three analyses found that women with adequate screening histories were more likely to be diagnosed at an earlier stage of cancer, although only the analysis restricted to women with "definite" screening histories was statistically significant (OR 0.5, 95% CI 0.2-0.9).

Table 6.18. Association between Pap screening history and invasive cervical cancer

Pap Screening History	Pap screening history of study subjects based on all sources of data			Pap screening history of study subjects based on all sources of data and screening history reliability deemed "definite"		Pap screening history of study subjects based on subject self-reported or proxy-reported results	
	No. Study Subjects[1] (%)	No. CCHS respondents[2] (%)	Adjusted OR (95% CI) [6]	No. Study Subjects[1] (%)	Adjusted OR (95% CI) [6]	No. Study Subjects[1] (%)	Adjusted OR (95% CI) [6]
Never or Ever Screened							
Never	39 (9.6)	319 (16.7)	referent	32 (12.1)	referent	43 (15.3)	referent
Ever	368 (90.4)	1593 (83.3)	1.6 (1.1-2.3)	232 (87.9)	1.2 (0.8-1.8)	239 (84.8)	0.7 (0.5-1.0)
Subjects not classified as ever or never screened[3]	161	NA	NA	NA	NA	NA	NA
Timing since last Pap amongst those Ever screened[4]							
<3 years	146 (40.3)	1252 (79.0)	referent	71 (30.9)	referent	113 (56.8)	referent
3to <5 years	60 (16.6)	68 (4.3)	8.2 (5.4-12.3)	28 (12.2)	7.9 (4.7-13.3)	20 (10.1)	3.3 (1.9-5.7)
≥5 years	156 (43.1)	264 (16.7)	7.3 (5.3-9.8)	131 (57.0)	14.4 (9.9-20.9)	66 (33.2)	4.8 (3.2-7.0)
Subjects classified as ever screened but not able to classify time since last Pap	6	NA	NA	NA	NA	NA	NA
Overall screening history adequacy[5]							
Inadequate	416 (74.0)	651 (34.2)	Referent	191 (72.9)	referent	129 (53.3)	referent
Adequate	146 (26.0)	1252 (65.8)	0.2 (0.1-0.2)	71 (27.1)	0.1 (0.1-0.2)	113 (46.7)	0.3 (0.3-0.4)

[1] This analysis includes only those study subjects who lived in Montreal or Laval for a minimum 5 years prior to diagnosis of invasive cervical cancer (N=568).
[2] CCHS refers to the Canadian Community Health Survey. These analyses include women living in Montreal or Laval who responded to the Canadian Community Health Survey (N=1912). Nine respondents who characterized themselves as being ever screened did not know the time since their last Pap.
[3] Based on available data, the screening histories of 161 women could not be classified as "ever" or "never" screened. However, it was determined that they were not screened within five years prior to diagnosis with cervical cancer.
[4] Timing since last Pap test refers to those women who were "ever" screened in the past.

Table 6.18. continued

[5] The category "Inadequate screening" for study subjects includes subjects never screened, those screened within 5 years of diagnosis (but not within 3 years), those screened greater than 5 years before diagnosis, and those subjects for whom we could not determine whether they were ever or never screened but we were able to determine that they were not screened within 5 years before diagnosis. Subjects who were categorized as ever screened but the timing of their last normal Pap smear could not be defined were omitted (n=6). For CCHS respondents, inadequate screening refers to women never screened and those 3-<5 years and ≥5 years since last Pap. "Adequate screening" refers to women screened within 3 years of diagnosis. Adequacy was based on prevailing clinical practice guidelines.

[6] All analyses were adjusted for age at diagnosis for ICC cases and age at survey administration for CCHS respondents. Age was categorized in 5 year intervals (20-24, 25-29, 30-34..., ≥80 years).

Table 6.19. Association between Pap screening history and cervical cancer stage[1]

Pap Screening History	Pap screening history of study subjects based on all sources of data			Pap screening history based on all sources of data and screening history reliability deemed "definite"			Pap screening history based on self-reported or proxy-reported results		
	No. of Regional and Distant cancer cases (%)[2]	No. of Localized cancer cases (%)[2]	Adjusted OR (95% CI)[6]	No. of Regional and Distant cancer cases (%)[2]	No. of Localized cancer cases (%)[2]	Adjusted OR (95% CI)[6]	No. of Regional and Distant cancer cases (%)[2]	No. of Localized cancer cases (%)[2]	Adjusted OR (95% CI)[6]
Never or Ever Screened									
Ever	151 (56.9)	217 (74.1)	referent	94 (81.0)	138 (93.2)	referent	62 (72.1)	159 (89.3)	referent
Never	26 (8.8)	13 (4.4)	1.8 (0.9-4.0)	22 (19.0)	10 (6.8)	1.9 (0.8-4.7)	24 (27.9)	19 (10.7)	1.6 (0.7-3.6)
Subjects not classified as ever or never screened[3]	98 (34.2)	63 (21.5)	1.4 (0.9-2.2)	NA	NA	NA	NA	NA	NA
Timing since last Pap among those Ever screened[4]									
< 3 years	50 (33.1)	96 (44.2)	referent	19 (20.2)	52 (37.7)	referent	29 (47.5)	84 (60.9)	referent
3 to <5 years	16 (10.6)	44 (20.3)	0.6 (0.3-1.2)	7 (7.4)	21 (15.2)	1.0 (0.3-2.8)	4 (6.6)	16 (11.6)	0.8 (0.2-2.7)
≥5 years	83 (55.0)	73 (33.6)	1.7 (1.0-2.8)	68 (72.3)	63 (45.7)	2.6 (1.3-5.3)	28 (45.9)	38 (27.5)	1.4 (0.7-3.0)
Subjects classified as "Ever" screened but not able to classify time since last Pap	2 (1.3)	4 (1.8)	0.6 (0.1-3.8)	NA	NA	NA	NA	NA	NA
Overall screening history adequacy[5]									
Inadequate	223 (81.7)	193 (66.8)	referent	110 (85.4)	109 (67.7)	referent	56 (65.9)	73 (46.5)	referent
Adequate	50 (18.3)	96 (33.2)	0.7 (0.5-1.1)	19 (14.6)	52 (32.3)	0.5 (0.2-0.9)	29 (34.1)	84 (53.5)	0.7 (0.4-1.3)

Table 6.19. continued

[1] This analysis includes only those study subjects who lived in Montreal or Laval for a minimum 5 years prior to diagnosis of invasive cervical cancer (N=568).
[2] Staging refers the SEER summary staging. Localized refers to FIGO staging IA1, IA2, IB. Regional refers to FIGO staging IIA, IIB, IIIA, IIIB. Distant refers to FIGO staging IV.
[3] Based on available data, the screening histories of 161 women could not be classified as "ever" or "never" screened. However, it was determined that they were not screened within five years prior to diagnosis with cervical cancer.
[4] Timing since last Pap test refers to those women who were "ever" screened in the past.
[5] The category "Inadequate screening" for study subjects includes subjects never screened, those screened within 5 years of diagnosis (but not within 3 years), and those screened greater than 5 years before diagnosis. "Adequate screening" refers to women screened within 3 years of diagnosis. Adequacy was based on prevailing clinical practice guidelines.
[6] All analyses were adjusted for age at diagnosis. Age was categorized in 5 year intervals (20-24, 25-29, 30-34..., ≥80 years).

6.7 Failures in Detection of Cytological Abnormalities

Normal Pap smears were found for only 34 subjects within 1 year prior to diagnosis and a cumulative 74 subjects within 2 years prior to diagnosis, either before or after the trigger Pap smear. It is believed that these values are underestimates of the true number of subjects with normal Pap smears within these time periods due to missing data. As noted in Section 5.6.2, failures in detection of cytological abnormalities were based on lab reports either found within medical charts or sent directly to us from labs or physicians' offices; specifically, we did not use subject or proxy reports of normal Pap smears in this analysis. As shown in Table 6.16, the screening histories could not be defined for 161 subjects and hence, no lab reports were found for these women. Hence, I was not able to determine the proportion of subjects who potentially had a false negative Pap smear.

6.8 Assessment of Follow-Up of Abnormal Pap Smears

6.8.1 Quality Assessment of the Follow-Up of Abnormal Pap Smears by Total Number of Events

6.8.1.1 Assessment of processes of care and timing of processes of care

Upon reviewing the processes of care of all eligible subjects, we found that there were a total of 611 incidences of abnormal Pap smears that should have received some follow-up care (Table 6.20). In terms of the processes of care that occurred after each abnormal Pap smear, 293 (48.0%) of these 611 events were classified as acceptable, according to the clinical criteria we developed, and 38 (6.2%) events were not acceptable. Note, events are units of follow-up that start with an abnormal Pap smear and are followed by (if there is follow-up) one or more procedures, such as a repeat Pap test or a colposcopy. The acceptability of the processes of care could not be assessed for 280 (45.8%) of these abnormal Pap smears for the following reasons: 1) No Pap tests were found in the five years prior to the date of histologic diagnosis. 2) Only Pap tests without cytologic abnormalities were found for the five years. 3) Data following the abnormal Pap test appeared to be missing. This would be the case if according to the record of medical acts provided to us by the RAMQ, there were one or more gynecology visits that took place after the initial visit during which the abnormal Pap test was taken. However, we did not find any procedures done at these subsequent visit(s) and the RAMQ medical act codes billed for those visits were general in nature and hence, did not provide us with the identity of the procedures performed.

When we only considered the 331 events for which we had sufficient data to assess the courses of care, we found that 88.5% (85.1%-92.0%) of the follow-up of these abnormal Pap smears were acceptable in terms of the procedures performed and 11.5% (8.3%-14.9%) were not acceptable.

As shown in Table 6.20, we found that 215 (35.2%) of these 611 events were managed in an acceptable time frame and 113 (18.5%) experienced an unacceptable delay in follow-up based on our criteria. It should be noted that it was possible for the follow-up of an abnormal Pap smear to have been deemed unacceptable in terms of the procedures performed but the timing of the

follow-up be categorized as acceptable. This would be the case if, for example, a Pap smear was repeated subsequent to an abnormal Pap rather than a colposcopy being done immediately as per the review criteria. And the colposcopy was then done after that repeat Pap test. The assessment referred to the time between the abnormal Pap and the performance of the recommended acceptable procedure.

As with the assessment of the processes of care, a large proportion (46.3%) of the assessment of the timing of these processes could not be assessed. When we only considered those events without missing data, we found that 65.5% (95% CI 60.4-70.7%) and 34.5% (95% CI 29.3-39.6%) were handled in an acceptable and unacceptable time frame, respectively.

Figure 6.3 shows that amongst the 293 incidences of abnormal Pap tests that were managed acceptably, the majority (70.2%) of this occurred at an acceptable time frame. However, it was found that about 1/3 of these incidences had a time delay in being followed-up.

Table 6.20. Quality assessment of the follow-up of abnormal Pap smears by the total number of events[1]

	Processes of Care			Timing of the Processes of Care[3]		
Acceptability of follow-up of abnormal Pap smears[2]	Total Number of Events	% (95% CI) based on total number of events (denominator=611)	% (95% CI) based on number of events for which assessment was possible (denominator=331)	Total Number of Events	% (95% CI) based on total number of events (denominator=611)	% (95% CI) based on number of events for which assessment was possible (denominator=328)
Acceptable	293	48.0 (44.0-51.9)	88.5 (85.1-92.0)	215	35.2 (31.4-39.0)	65.5 (60.4-70.7)
Not acceptable	38	6.2 (4.3-8.1)	11.5 (8.3-14.9)	113	18.5 (15.4-21.6)	34.5 (29.3-39.6)
Cannot assess (abnormal Pap was missing or data following the abnormal Pap were missing)	280	45.8 (41.9-49.8)	NA	283[4]	46.3 (42.4-50.3)	NA
Total	611			611		

[1] Events are units of follow-up that start with an abnormal Pap smear and are followed by (if there is follow-up) one or more procedures, such as a repeat Pap test or a colposcopy. Some subjects had more than one event within the five years prior to diagnosis.
[2] Acceptability was based on adherence to SOGC guidelines (1998) and consensus by clinical co-investigators
[3] We also defined the quality of the timing of care if the processes of care were deemed as unacceptable. In this case, the time referred to the number of days between the date of the abnormal Pap smear and the date of the eventual acceptable follow-up care, if it occurred.
[4] There were three process of care events assessed as "not acceptable" that had no follow-up care and hence, the timing of the processes of care could not be assessed.

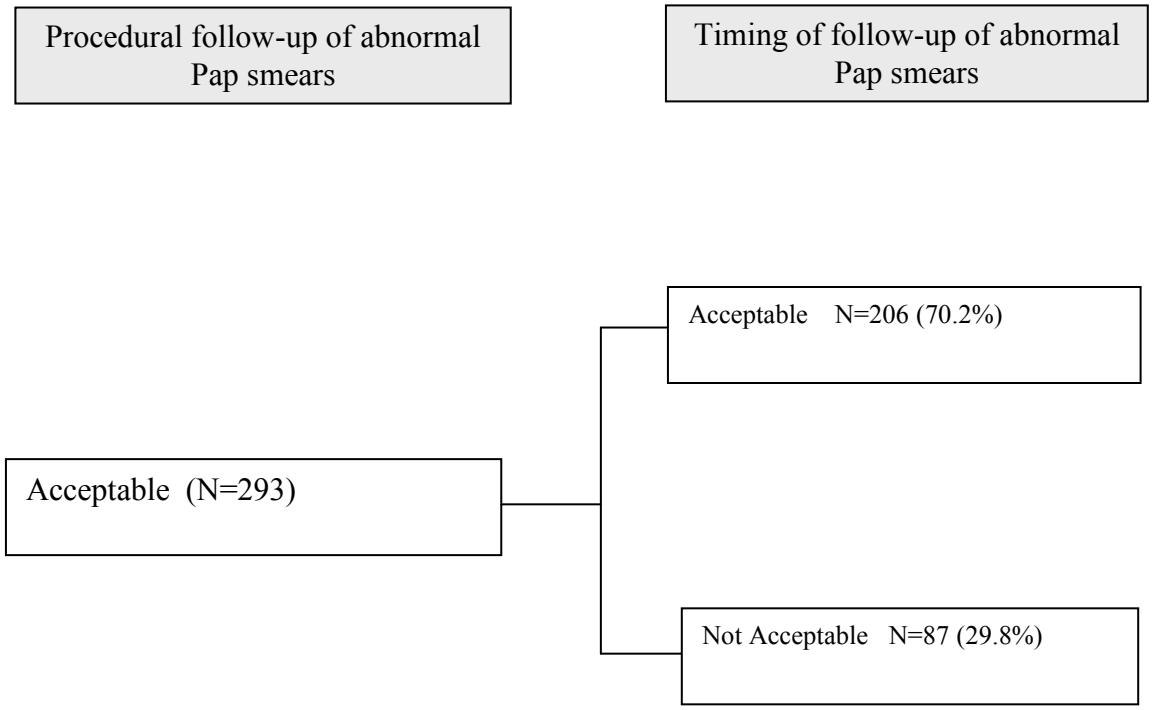

Figure 6.3. Acceptable procedural follow-up of cytologically abnormal Pap smears by the acceptability of the timing of follow-up based on number of events

6.8.1.2 Reasons for unacceptable processes of care

Table 6.21 lists the reasons that the follow-up care of 38 abnormal Pap smears were deemed to be unacceptable. The most common reason (65.8%) was the repeat of a Pap test, either once or multiple times, when the guidelines recommend the performance of a colposcopy. The second most frequent reason was similar in nature. In these latter 6 events (15.8%), a repeat Pap test was done as per the recommendations for an initial LSIL or ASC-US Pap test. It again revealed cytologic abnormalities and, at this point, colposcopic investigation was warranted. However, in these cases Pap tests were again subsequently repeated.

Table 6.21. Reasons for quality assessment of abnormal Pap smears deemed "not acceptable" (N=38)

Reasons follow-up case classified as "not acceptable"	Number (%)
Subject had a Pap smear result (HSIL, AIS, AGUS, ASC-H, ASCUS-favouring neoplasia) that according to guidelines required a follow-up colposcopy. Instead, a Pap smear was repeated. A colposcopy may have been done after the first repeat Pap smear or a Pap smear may have been repeated one to two times more before the colposcopy was eventually done.	25 (65.8)
Subject had a Pap smear result (ASCUS-NOS or LSIL) for which a repeat Pap smear is recommended by the guidelines. The Pap smear was repeated and it also was abnormal. According to the guidelines, the subject now should have been sent for a colposcopy. Instead a Pap smear was done again.	6 (15.8)
Subject was pregnant at time of the abnormal Pap smear and there was no follow-up during the pregnancy. One subject had LSIL and Pap smear was repeated 9 months post-partum. Another subject had an HSIL Pap that was followed by a Pap, colposcopy and biopsy 7 months post-partum. The third subject had an AGUS Pap that was followed by a Pap smear one year post-partum.	3 (7.9)
No follow-up	3 (7.9)
Subject had an HSIL Pap and was sent for an immediate cone, without undergoing a colposcopy first.	1 (2.6)

6.8.2 Quality Assessment of the Follow-Up of Abnormal Pap Smears Based on Study Subjects

Table 6.22 displays the results of our quality assessment of the follow-up of abnormal Pap smears, which are the same results discussed above and shown in table 6.20, but in this current table the data are presented on a per subject basis. It should be noted that one subject may have had multiple abnormal Pap tests prior to diagnosis and hence, we would have assessed the follow-up care of each of these abnormal Pap tests. Due to this, we categorized each subject's follow-up on a cumulative basis as it would be possible, for instance, for one subject to have the follow-up of one abnormal Pap deemed to be acceptable and that of another one deemed to be unacceptable. Of the 568 study subjects, 45.6% of them had one or more abnormal Pap tests that were all followed-up acceptably and 6.5% had at least one abnormal Pap test that was not managed appropriately. This latter group may have also had one or more abnormal Paps that were acceptably managed. There were also 264 women for whom the processes of care following the abnormal Pap test could not be assessed. If we only consider those women whose history was entirely assessed, we found that an estimated 87.5% of subjects had follow-up events that were all considered acceptable and 12.5% had at least one event that was deemed unacceptable.

In terms of timing of the processes of care, we found that 32.7% of subjects were managed in a timely manner and 19.0% had at least one abnormal Pap smear that was not managed in an acceptable time frame. About half of the subjects (47.0%) had missing data and hence, the timing of their follow-up care could not be reviewed. Without considering those subjects with missing data, 63.3% of the study subjects were managed in a timely manner and 36.7% of study subjects had at least one event of unacceptable timing of follow-up care.

Table 6.22. Quality assessment of the procedures used for the follow-up of abnormal Pap smears and the timing analyzed using subjects as the units of analysis

	Processes of Care			Timing of Processes		
Subject cumulative acceptability of follow-up of abnormal Pap smears[1]	Number of subjects	% (95% CI) based on total number of subjects (denominator=568)	% (95% CI) based on number of subjects with either all "acceptable" follow-up events or ≥1 "not acceptable" follow-up events (denominator=296)	Number of subjects	% (95% CI) based on total number of subjects (denominator=568)	% (95% CI) based on number of subjects with either all "acceptable" follow-up events or ≥1 "not acceptable" follow-up events (denominator=294)
All follow-up events for subject were "acceptable"	259	45.6 (41.5-49.7)	87.5 (83.7-91.3)	186	32.7 (28.9-36.6)	63.3 (57.7-68.8)
Subject had at least one "not acceptable" follow-up event	37	6.5 (4.5-8.5)	12.5 (8.7-16.3)	108	19.0 (15.8-22.3)	36.7 (31.2-42.3)
Subject had 1 or more acceptable events and 1 or more events that could not be assessed[2]	8	1.4 (0.4-2.4)	NA	7	1.2 (0.3-2.1)	NA
All follow-up events for subject could not be assessed[2]	264	46.5 (42.4-50.6)	NA	267	47.0 (42.9-51.1)	NA
Total	568			568		

[1] Acceptability was based on adherence to SOGC guidelines (1998) and consensus by clinical co-investigators. Cumulative acceptability refers to each subject's follow-up history within 5 years prior to their diagnosis with cervical cancer. All categories are mutually exclusive and each subject is represented only once within the table.

[2] An event was categorized as "cannot assess" if the trigger Pap was missing or data following the trigger/abnormal Pap were missing or there was no follow-up of an abnormal Pap.

6.8.3 The Relationship between Pap Screening History and the Quality of Follow-Up of Abnormal Pap Smears

As shown in Figure 6.4, subjects with a pre-diagnostic Pap screening history deemed to be adequate were more likely to have all instances of abnormal Pap tests managed appropriately in terms of the processes conducted compared to those subjects with an inadequate pre-diagnostic Pap screening history (54.1% and 42.1%, respectively). Likewise, those subjects who had adequate screening histories and acceptable procedural follow-up of abnormal Pap smears were more likely to have all abnormal Pap smears followed on an acceptable time frame compared to subjects who had inadequate screening histories and acceptable procedural management of abnormal Pap smears (70.9% and 67.4%, respectively).

6.8.4 Time between Trigger Pap and Colposcopy

We were able to determine the dates of the first abnormal Pap test within the 5-year time-window of observation and the dates of the follow-up colposcopy for 293 subjects. As displayed in Table 6.23, the mean and median time between the sampling of the cervix for this Pap test and the performance of a colposcopy were 6 months and 2 months, respectively. As displayed in Figures 6.5 and 6.6, the longest time intervals were found for women who had cytologic abnormalities for which follow-up by Pap tests, rather than immediate colposcopy, are recommended according to the guidelines. Specifically, abnormalities deemed to be LSIL had a median follow-up time until colposcopy of 5 months and ASC-US Paps had a median of 4 months until colposcopy. Pap smears with cytological abnormalities categorized as AIS or invasive cancer were the most expediently followed-up results, with median follow-up times of 1 month. High grade cytologic abnormalities, including HSIL and ASC-H, had time intervals between sampling and colposcopy that were intermediate to the extremes noted above. The median follow-times for HSIL and ASC-H Paps were 2 months. The differences between groups were significant as the p-value obtained from the log-rank tests were <0.0001.

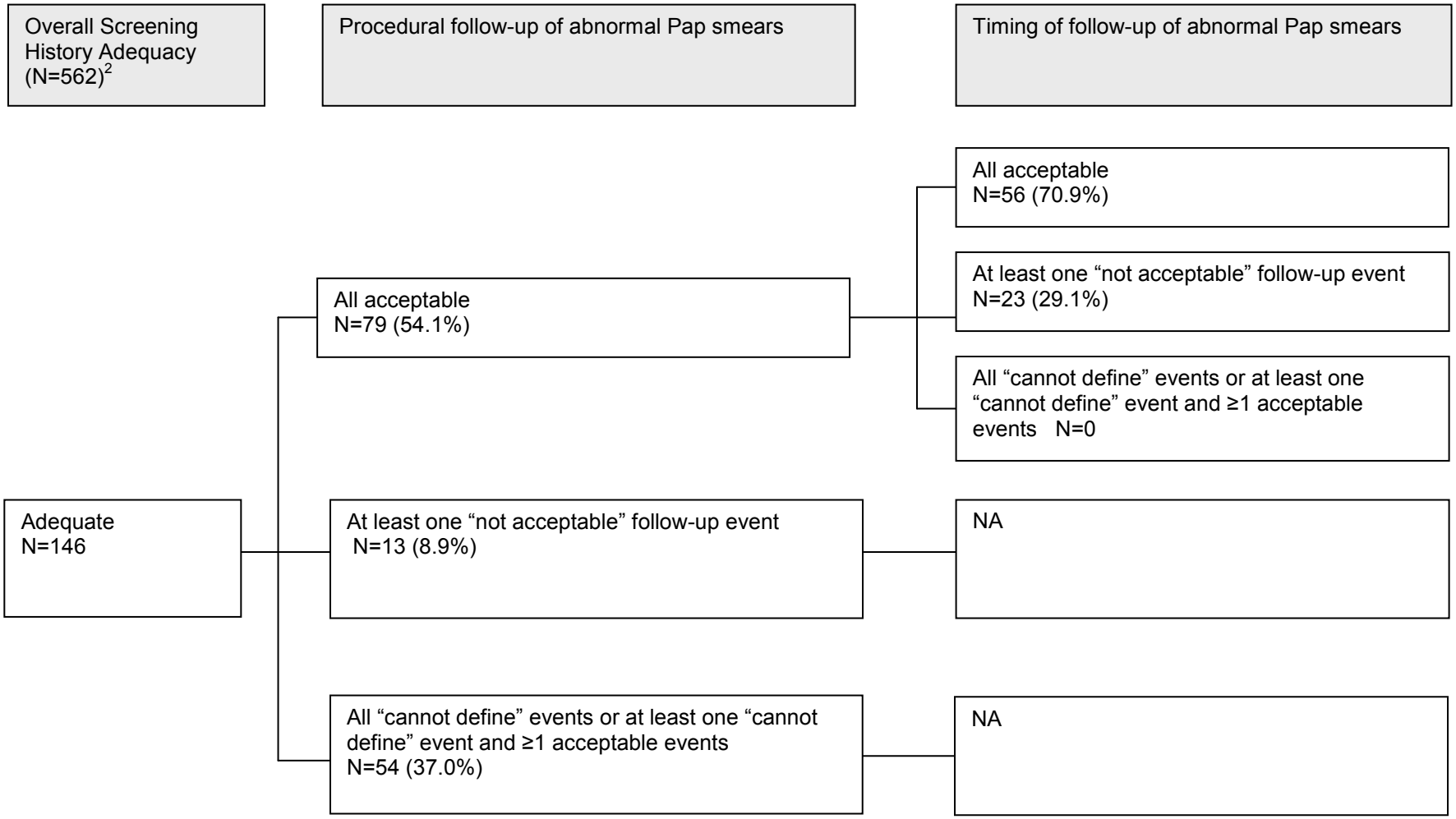

Figure 6.4. The relationship between the quality of Pap screening history and the quality of the follow-up of abnormal Pap smears[1]

[1] The unit of analysis is the subject.

[2] The total number of subjects is 562 since 6 subjects were classified as "ever" screened but the time since last Pap was not known. Inadequate screening includes the following subjects: never screened, screened 3-<5 years, screened ≥5 years, and subjects for whom we could not determine whether they were ever or never screened but we were able to determine that they were not screened within 5 years of diagnosis. Adequate screening refers to women screened <3 years before diagnosis.

Figure 6.4. continued

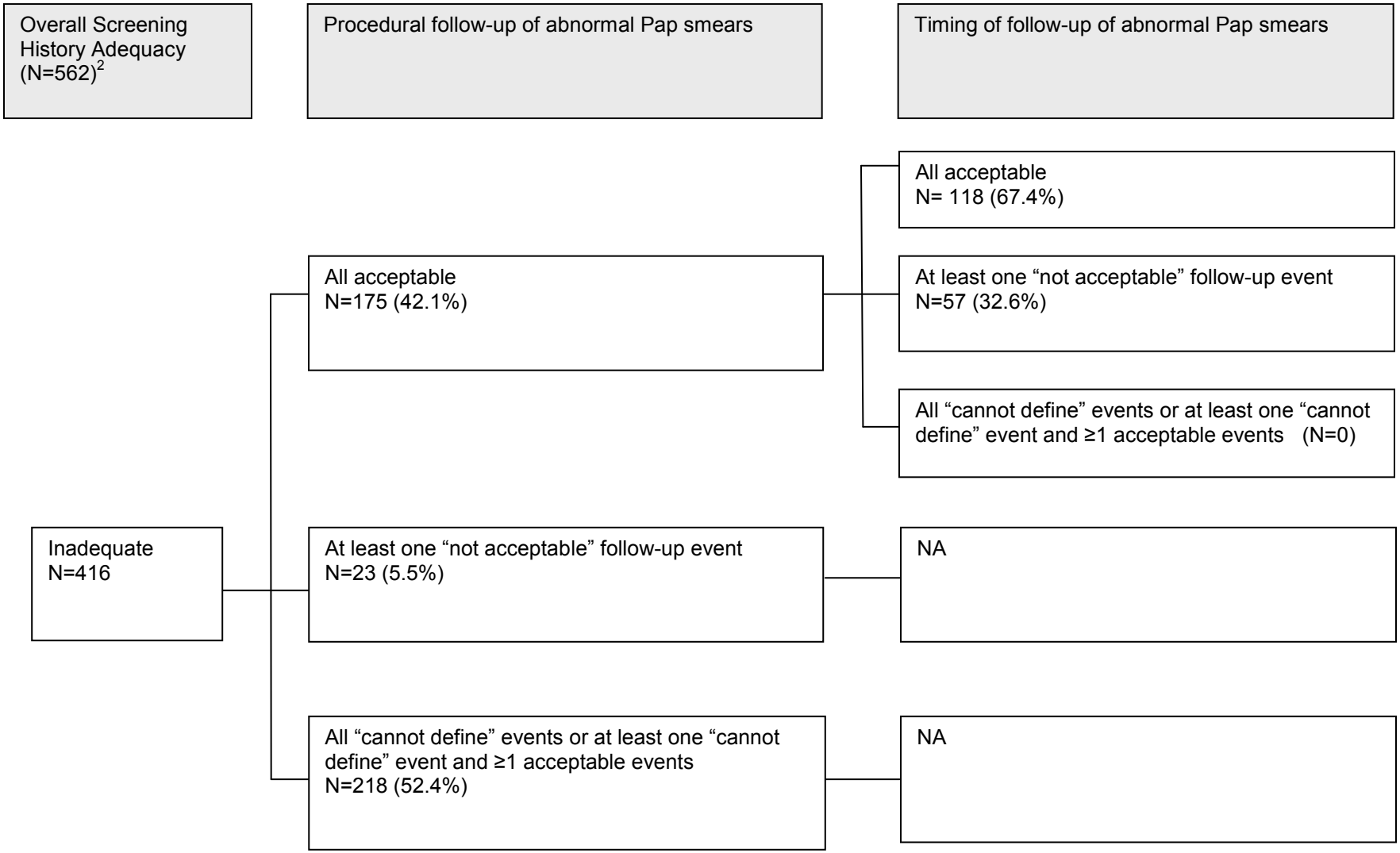

Table 6.23. Time interval between the first abnormal Pap test (trigger Pap[1]) and the follow-up colposcopy stratified by the result of the trigger Pap

Result of Pap Test	Number of Subjects (%)	Number of colposcopies	Number of days or months (as noted) between trigger Pap and colposcopy		
			Range	Mean (95% CI) (months)	Median (95% CI) (months)
Overall	293[1]	285	1 day - 65 months	6 (5-8)	2 (1-3)
ASC-US	36 (12.3)	35	1 day - 53 months	12 (7-17)	4 (3-8)
AGC & AGC-favour neoplastic	33 (11.3)	29	3 days- 59 months	7 (2-12)	3 (2-4)
ASC-H	3 (1.0)	3	24 days - 3 months	2 (1-3)	2 (1-ND)
LSIL	12 (4.1)	12	19 days - 65 months	18 (5-31)	5 (2-46)
AIS	5 (1.7)	5	1 day - 2 months	1 (0.3-2)	1 (0.03-ND)
HSIL	93 (31.7)	91	1 day - 63 months	6 (3-8)	2 (1-3)
Invasive	77 (26.3)	76	1 days - 13 months	1 (0.7-2)	1(0.4-1)
Other[2]	18 (6.1)	18	5 days - 48 months	5 (0.3-10)	2(1-3)
Grade of abnormality unknown	16 (5.5)	16	1 day- 46 months	12 (6-19)	4 (2-17)

Abbreviation: ND, not determined

[1] The trigger Pap is the first abnormal pap that a subject had within 5 years prior to her diagnosis with cervical cancer. The trigger Pap was found for 293 women.

[2] In this table, the category "Other" refers to those Pap results that did not fit into one of the other categories above.

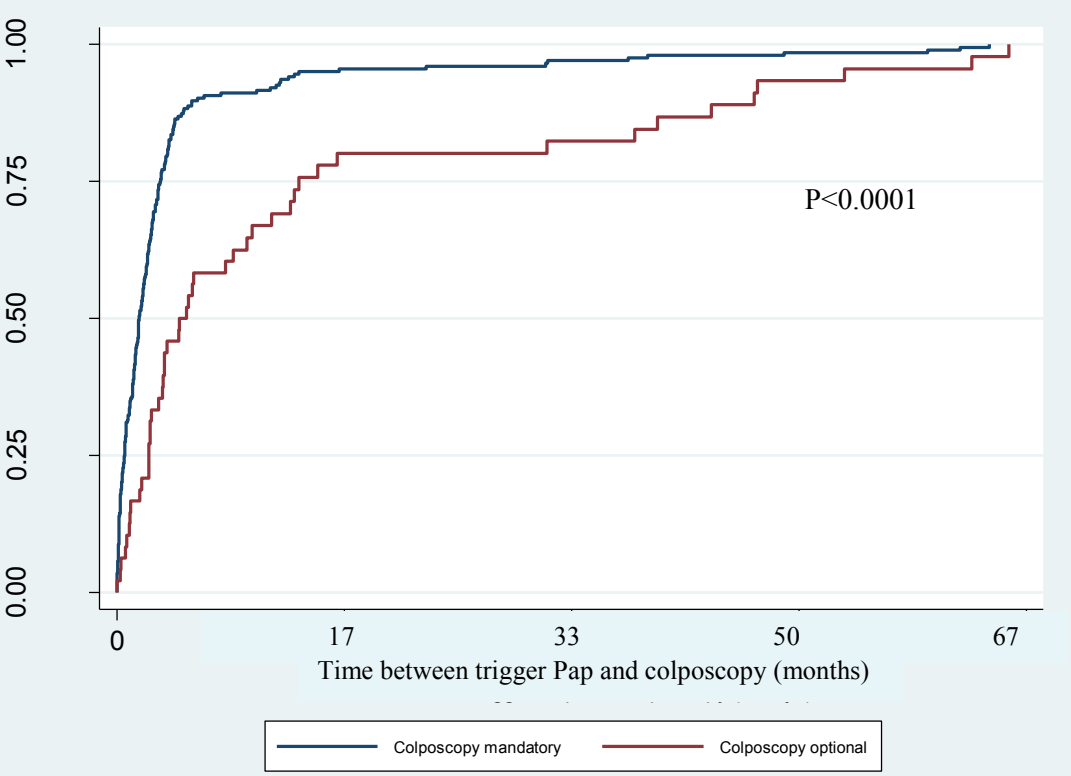

Figure 6.5. Distribution of time to colposcopy, separately for those where, according to guidelines, colposcopy is or is not considered mandatory

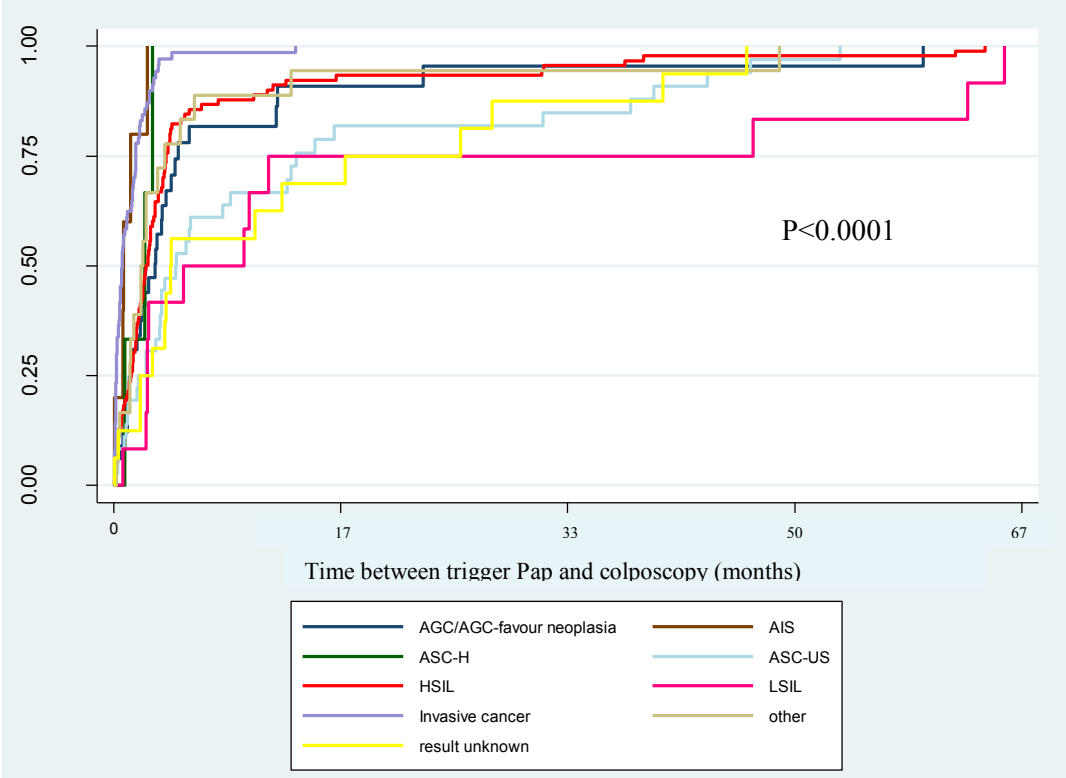

Figure 6.6. Distribution of time to colposcopy, separately by result of trigger Pap test

6.8.5 Determinants of Time between Trigger Pap and Colposcopy

Table 6.24 shows that there were a few characteristics pertaining to subjects or their physicians that were associated with the time interval between the first abnormal Pap test and the performance of the colposcopy. The final multivariate model, which was adjusted for subject age at diagnosis and also whether the severity of the cytologic abnormality required a colposcopy or not, found that women between the ages of 20 and 34 waited an average of 3 times longer for a colposcopy than women 55 years of age or older. Also, women who spoke neither French nor English waited 4 times longer for a colpscopy than women who spoke both languages. Women who had a family physician perform the trigger Pap test waited 2 times longer for a colposcopy than women who had a gynaecologist perform the trigger Pap test.

6.9 Assessment of Follow-Up of Cervical Lesions

6.9.1 Quality Assessment of the Follow-Up of Cervical Lesions by Total Number of Events

6.9.1.1 Assessment of processes of care and the timing of processes of care

As presented in Table 6.25, 16.1% (95% CI 11.4-20.8) of the treatment of pre-invasive cervical lesion events which we were able to assess were classified as not acceptable and 83.9% (95% CI 79.2-88.6) were deemed acceptable. Approximately equal numbers of follow-up events were deemed as acceptable and not acceptable in terms of the time interval between detection of the lesion and treatment. Like with the assessment of abnormal Pap smears, there were also some events that could not be assessed as data appeared to be missing; although, there were many fewer such events for the follow-up of cervical lesions.

When we exclusively examined the cervical lesions that had acceptable procedural management (n=198), we found that 43.4% of them were not managed in an acceptable time frame (Figure 6.7). This represents a greater proportion of time delays compared to the time delays encountered during the follow-up of abnormal Pap smears (Figure 6.3).

Table 6.24. Determinants of time between first abnormal Pap smear (trigger Pap)[1] and colposcopy

Variable	Categories	n (%)	Median time between trigger Pap and colposcopy (days)	Fitted ratio of medians [2] (95% CI)		
				Crude univariate models	Models adjusted for age and follow-up required [3]	Multivariate Model
Age at time of trigger Pap (years)	20-34	30 (16)	110	4.8 (2.5-9.5)	--	3.2 (1.6-6.3)
	35-44	56 (30)	73	2.5 (1.4-4.5)	--	2.0 (1.1-3.5)
	45-54	47 (25)	53	2.1 (1.2-3.8)	--	1.8 (1.0-3.2)
	55 to max	55 (29)	41	referent	--	referent
Required follow-up based on severity of Pap results	Colposcopy mandatory	142 (76)	53	referent	--	referent
	Colposcopy optional	31 (17)	102	2.8 (1.5-5.1)	--	1.7 (0.9-3.2)
	Grade of abnormality unknown	15 (8)	125	3.5 (1.5-8.1)	--	2.7 (1.2-5.8)
Language(s) of conversation	French and English	77 (41)	58	referent	referent	referent
	English only	21 (11)	70	0.8 (0.4-1.7)	1.0 (0.5-2.1)	--
	French only	83 (44)	73	1.5 (0.9-2.4)	1.5 (0.9-2.3)	--
	Neither French nor English	5 (3)	158	3.5 (0.8-15.2)	5.1 (1.3-20.1)	4.0 (1.1-14.9)
	Missing [3]	2 (1)	43	1 (0.1-1.2)	1.8 (0.2-14.4)	9.1 (0.7-119.1)
Highest level of education	High school or less	84 (45)	57	referent	referent	referent
	Some post-secondary education	54 (29)	74	1.4(0.8-2.3)	1.1 (0.7-1.9)	--
	University undergraduate degree complete	36 (19)	87	2.2 (1.2-4.1)	1.6 (0.9-2.9)	1.5 (0.9-2.7)
	University graduate degree complete	9 (5)	48	1.2 (0.4-3.7)	1.1 (0.4-3.2)	--
	Missing	5 (3)	14	0.3(0.1-1.2)	0.4 (0.1-1.6)	0.2 (0-0.9)
Has Chronic Disease	No	144 (77)	74	referent	referent	--
	Yes	42 (22)	40	0.5 (0.3-0.9)	0.8 (0.5-1.5)	--
	Missing	2 (1)	53	0.5 (0.1-4.6)	0.9 (0.1-7.2)	--
Employment Status	Employed	123 (65)	70	referent	referent	--
	Unemployed	9 (5)	78	1.0 (0.3-2.7)	1.2 (0.4-3.4)	--
	Not in labour force	55 (29)	43	0.5 (0.3- 0.9)	0.8 (0.5-1.5)	--
Place of Birth	Born in Canada	134 (71)	73	referent	referent	--
	Not born in Canada	52 (28)	52	0.7 (0.4-1.1)	0.7 (0.5-1.2)	--
	Missing	2 (1)	43	0.7 (0.1-7.2)	1.3 (0.2-10.5)	--

Table 6.24. continued

Variable	Categories	n (%)	Median time between trigger Pap and colposcopy (days	Fitted ratio of medians [2] (95% CI)		
				Crude univariate models	Models adjusted for age and follow-up required [3]	Multivariate Model
Household income ($)	<=20,000	33 (18)	72	referent	referent	--
	21-40,000	38 (20)	65	0.6 (0.3-1.2)	0.6 (0.3-1.2)	--
	41-60,000	21 (11)	79	1.5 (0.6-3.6)	1.2 (0.5-2.7)	--
	>60,000	43 (23)	80	1.0 (0.5-2.0)	0.8 (0.4-1.6)	--
	Missing	53 (28)	50	0.6 (0.3-1.2)	0.9 (0.4-1.7)	--
Marital Status	Legally married	69 (37)	57	referent	referent	--
	Common-law	37 (20)	76	1.7 (0.9-3.2)	1.3 (0.7-2.6)	--
	Divorced, separated, or widowed	44 (23)	60	1.0 (0.6-1.9)	1.4 (0.8-2.6)	--
	Single	37 (20)	79	2.1 (1.1-4.0)	1.7 (0.9-3.1)	--
Medical specialty of physician who performed the trigger Pap	Gynaecologist	124 (66)	57	referent	referent	referent
	Family physician	56 (30)	78	2.0 (1.2-3.2)	1.9 (1.2-3.0)	2.0 (1.3-3.2)
	Missing	8 (4)	319	8.6 (3.0-24.3)	3.8 (1.2-11.6)	4.1 (1.4-12.3)
Gender of physician who performed the trigger Pap	Male	94 (50)	55	referent	referent	--
	Female	56 (30)	72	1.6 (0.9-2.6)	1.3 (0.8-2.2)	--
	Missing	38 (20)	75	1.6 (0.9-2.9)	1.0 (0.5-1.8)	--
Time between physician's year of medical school graduation and year of trigger Pap (years)	5-19	40(21)	59	referent	referent	referent
	20-28	46 (25)	59	0.9 (0.4-1.8)	0.8 (0.4-1.6)	--
	29-35	37 (20)	70	0.9 (0.4-1.9)	1.0 (0.5-2.0)	--
	36-49	26 (14)	71	1.3 (0.6-2.8)	1.4 (0.7-2.9)	1.7 (0.9-3.2)
	Missing	39 (21)	76	1.5 (0.7-3.1)	1.0 (0.5-2.0)	--

[1] The trigger Pap is the first abnormal Pap smear that a subject within 5 years prior to diagnosis with cervical cancer. [2] from linear regression using exponentiated β. [3] Trivariate models adjusted for age at time of trigger Pap and the severity of Pap results based on whether colposcopic examination was mandatory or optional. -- indicates that the specific category was not kept in the model. The category "Missing" means that respondents to the subject questionnaire did not know or remember the information for that specific question. "Missing" also indicates that the specific physician data or Pap smear result was not found during the data collection phase of the study.

Table 6.25. Quality assessment of the follow-up of pre-invasive cervical lesions by the total number of events[1]

	Processes of Care			Timing of Processes of Care[3]		
Acceptability of follow-up of cervical lesions[2]	Total Number of Events	% (95% CI) based on total number of events (denominator=609)	% (95% CI) based on number of events for which assessment was possible (denominator=237)	Total Number of Events	% (95% CI) based on total number of events (denominator=609)	% (95% CI) based on number of events for which assessment was possible (denominator=235)
Acceptable	198	32.5 (28.8-36.2)	83.5 (78.9-88.3)	116	19.0 (15.9-22.2)	49.4 (42.9-55.8)
Not acceptable	39	6.4 (4.5-8.4)	16.5 (11.7-21.2)	119	19.5 (16.4-22.7)	50.6 (44.2-57.1)
Cannot assess as data is missing	28	4.6 (2.9-6.3)	NA	30	4.9 (3.2-6.6)	NA
Not applicable, lesion is cervical cancer	344	56.5 (52.5-60.4)	NA	344	56.5 (52.5-60.4)	NA
Total	609			609		

[1] Events are units that start with a histologically detected lesion and end with treatment, such as conization.
[2] Acceptability was based on adherence to SOGC guidelines, 1998 and consensus by clinical co-investigators
[3] We also defined the quality of the timing of care if the processes of care were deemed as unacceptable. In this case, the time referred to the number of days between the date of the procedure that provided histological confirmation of the cervical lesion and the date of the eventual acceptable follow-up care, if it occurred.

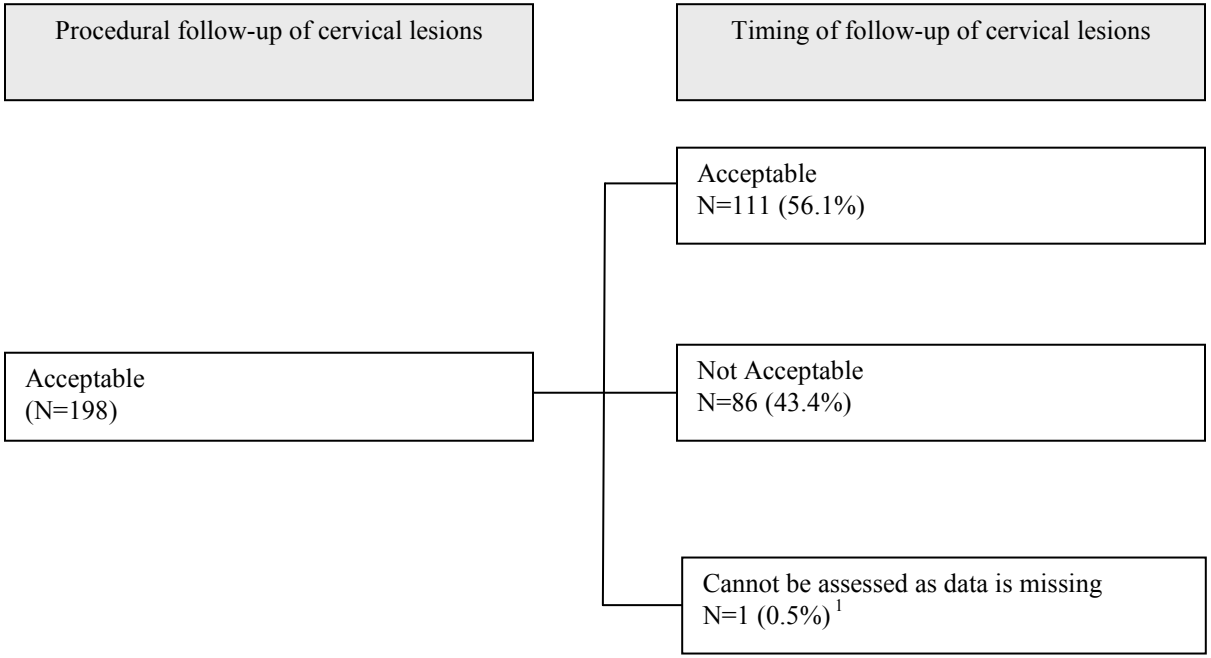

Figure 6.7. Acceptable procedural follow-up of cervical lesions by the acceptability of the timing of follow-up based on number of events

[1]One event was deemed acceptable in terms of the procedures but the exact date of that follow-up procedure was not known.

6.9.1.2 Reasons for unacceptable processes of care

Similar to the follow-up of cytologically abnormal Pap smears, the major reason for the unacceptable follow-up of histologically confirmed cervical lesions was the unnecessary repetition of procedures (i.e. biopsies, cones, etc.) instead of immediately performing the recommended subsequent treatment (Table 6.26).

Table 6.26. Reasons for quality assessment of abnormal cervical lesions deemed "not acceptable"

Reasons follow-up case classified as "not acceptable"	Number (%)
Subject had a diagnostic procedure (i.e. biopsy, ECC, or cone) that showed the presence of a cervical lesion that should have been treated. Instead, the Pap test and/or the diagnostic procedure were repeated once or in some instances, more than once or other diagnostic procedures were performed. The lesion was eventually treated.	38 (97.4%)
Patient had a cervical biopsy deemed to be CIN II/III. She then had a sub-total hysterectomy. The cervix should have been treated via excision of the lesion.	1 (2.6%)

6.9.2 Quality Assessment of the Follow-Up of Pre-Invasive Cervical Lesions Based on Study Subjects

More than half of subjects did not have a pre-invasive lesion within 5 years of diagnosis. Table 6.27 displays the assessment of the follow-up of cervical pre-invasive lesions based on the individual subject. It shows the subjects' cumulative histories as some subjects had more than one cervical lesion prior to final diagnosis. Of those whose follow-up histories could be assessed, 19.4% (95% CI 13.9-24.9) had at least one follow-up event classified as not acceptable

and approximately half of subjects (52.5%, 95% CI 45.5-59.4) had at least one follow-up event that was not followed in an acceptable time frame.

6.9.3 The Relationship between Pap Screening History and the Quality of Follow-Up of Pre-Invasive Cervical Lesions

Figure 6.8 shows that subjects with an adequate screening history were more likely to have a greater proportion of follow-up of lesion events deemed to be acceptable in terms of procedures performed compared to subjects who had an inadequate screening history (39% versus 24.5%, respectively). Those subjects with both acceptable screening histories and acceptable procedural follow-up of lesions had a greater proportion of delays in management compared to subjects with inadequate screening histories and acceptable procedural management of lesions (49.1% vs. 40.2%).

6.10 Patterns of Health Services Use According to a Matched Case-Control Study

Table 6.28 and Figure 6.9 show the association between the number of physician visits prior to the first abnormal Pap test and the risk of developing cervical cancer. Age-matched and region-matched control subjects were obtained from the RAMQ. The time-windows were the same length for each case and their matched control. Women with cervical cancer were more likely have had a greater number of family physician visits and medical specialist visits prior to their first abnormal Pap test than women without cervical cancer. Conversely, women with cervical cancer were less likely to have had gynaecologist visits during this time period.

Table 6.27. Quality assessment of the procedures used for the follow-up of pre-invasive cervical lesions and the timing analyzed by number of subjects

	Processes of Care			Timing of Processes		
Subject cumulative acceptability of follow-up of cervical lesions[1]	Number of subjects	% (95% CI) based on total number of subjects (denominator=568)	% (95% CI) based on number of subjects with either all "acceptable" follow-up events or ≥1 "not acceptable" follow-up events (denominator=201)	Number of subjects	% (95% CI) based on total number of subjects (denominator=568)	% (95% CI) based on number of subjects with either all "acceptable" follow-up events or ≥1 "not acceptable" follow-up events (denominator=202)
All follow-up events for subject were "acceptable"	162	28.5 (24.8-32.2)	80.6 (75.1-86.1)	96	16.9 (13.8-20.0)	47.5 (40.6-54.5)
Subject had at least one "not acceptable" follow-up event	39	6.9 (4.8-9.0)	19.4 (13.9-24.9)	106	18.7 (15.4-21.9)	52.5 (45.5-59.4)
Subject had 1 or more acceptable events and 1 or more events that could not be assessed[2]	5	0.9 (0.1-1.7)	NA	2	0.4 (-0.1-0.8)	NA
All follow-up events for subject could not be assessed[2]	23	4.0 (2.4-5.7)	NA	25	4.4 (2.7-6.1)	NA
The only lesion prior to treatment was invasive cancer	339	59.7 (55.6-63.7)	NA	339	59.7 (55.6-63.7)	NA
Total	568			568		

[1] Acceptability was based on adherence to SOGC guidelines (1998) and consensus by clinical co-investigators. Cumulative acceptability refers to each subject's follow-up history within 5 years prior to their diagnosis with cervical cancer. All categories are mutually exclusive and each subject is represented only once within the table. [2] An event was categorized as "cannot assess" if data following the detection of the cervical lesion was missing.

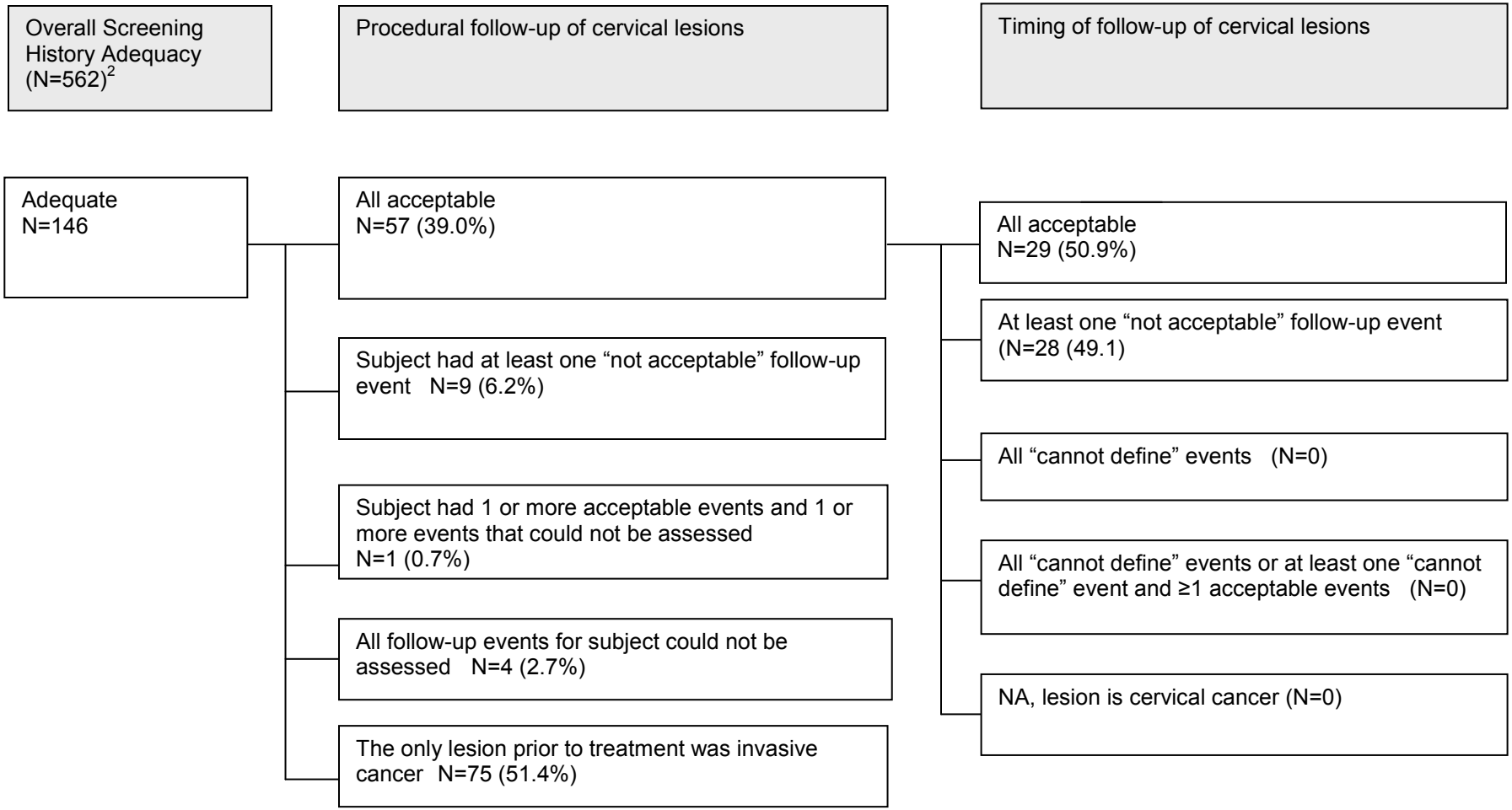

Figure 6.8. The relationship between the quality of Pap screening history and the quality of the follow-up of cervical lesions[1]

[1] The unit of analysis is the subject.

[2] The total number of subjects is 562 since 6 subjects were classified as "ever" screened but the time since last Pap was not known. Inadequate screening includes the following subjects: never screened, screened 3-<5 years, screened ≥5 years, and subjects for whom we could not determine whether they were ever or never screened but we were able to determine that they were not screened within 5 years of diagnosis. Adequate screening refers to women screened <3 years before diagnosis.

Figure 6.8. continued

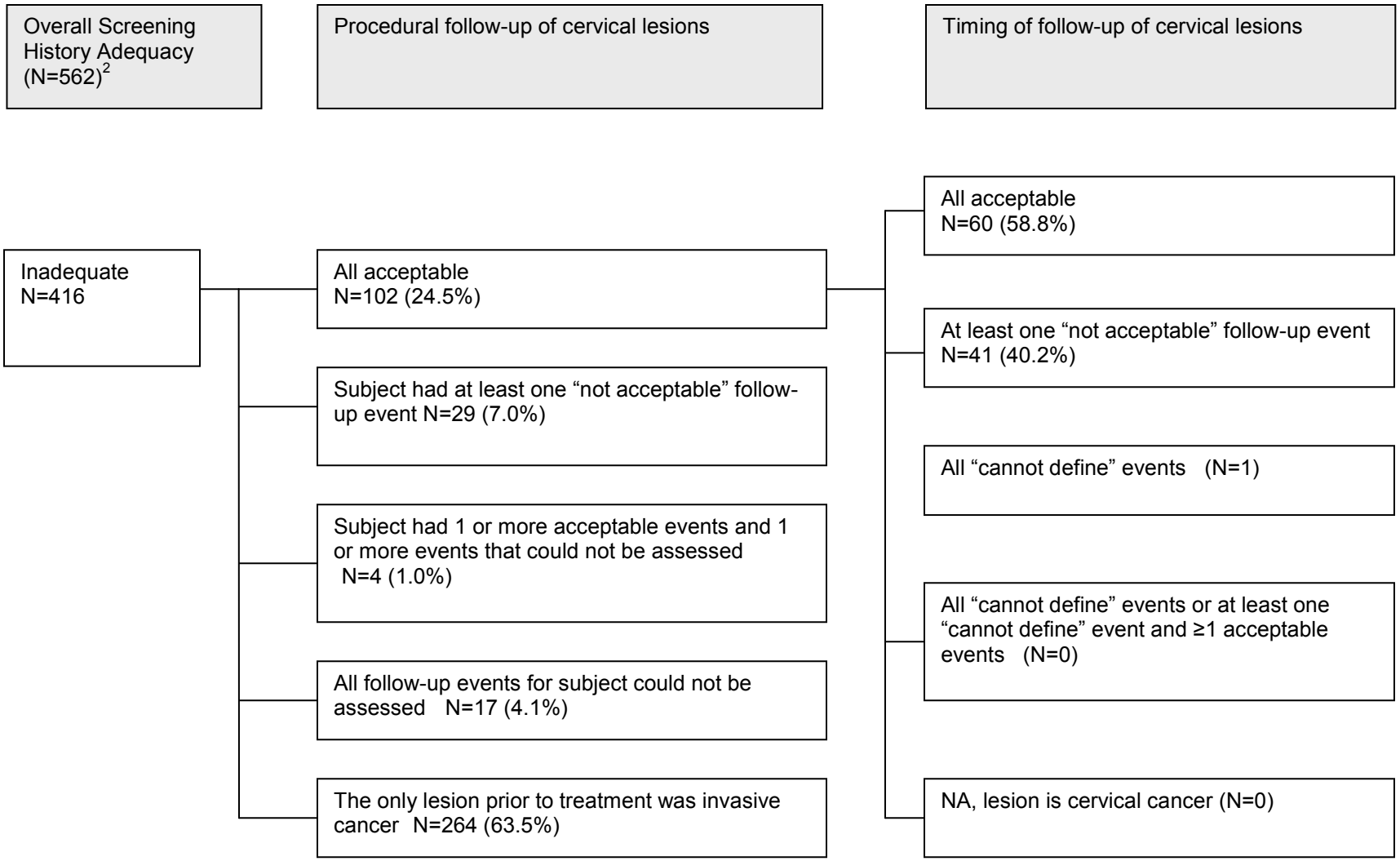

Table 6.28. Association between number of physician visits prior to first abnormal Pap test and risk of developing cervical cancer [2]

Total number of visits to physicians during time interval of interest	No. of Study Subjects (%)[1]	No. of Non-cervical cancer controls (%)[1]	OR (95% CI)	OR adjusted for number of visits to other types of physicians (95% CI)[3]
Family physician visits				
0	54 (9.6)	146 (26.0)	referent	referent
1-2	65 (11.6)	53 (9.4)	4.8 (2.7-8.4)	3.6 (2.0-6.6)
3-4	55 (9.8)	49 (8.7)	4.4 (2.4-7.9)	3.4 (1.8-6.6)
>4	388 (69.0)	314 (55.9)	5.2 (3.3-8.2)	4.3 (2.4-7.6)
Gynaecologist visits				
0	355 (63.2)	345 (61.4)	referent	referent
1-2	110 (19.6)	75 (13.4)	1.4 (1.0-1.9)	0.9 (0.6-1.3)
3-4	38 (6.8)	58 (10.3)	0.6 (0.4-0.9)	0.4 (0.2-0.7)
>4	59 (10.5)	84 (15.0)	0.7 (0.5-1.0)	0.5 (0.3-0.7)
Medical specialist (other than gynecologists) visits				
0	86 (15.3)	172 (30.6)	referent	referent
1-2	110 (19.6)	67 (11.9)	4.1 (2.6-6.4)	2.4 (1.4-4.0)
3-4	65 (11.6)	47 (8.4)	3.6 (2.2-5.9)	2.0 (1.1-3.5)
>4	301 (53.6)	276 (49.1)	2.8 (1.9-4.0)	1.7 (1.0-2.8)

[1] There were 568 study subjects (i.e. cases) who met our study inclusion criteria. For each case, the RAMQ randomly chose one control subject matched for region of residence and same age (within 5 year age category) on the index date (i.e. date of cervical cancer diagnosis) of her matched case. Six cases did not have RAMQ medicare numbers and hence, matched controls were not obtained for these subjects. Hence, there were 562 cases and 562 controls.

[2] For cases, this analysis includes the number of physician visits during the time interval demarcated at its lower boundary by the date of the case's first abnormal Pap smear (trigger Pap) and at its upper boundary by the date 5 years prior to diagnosis with cervical cancer. For those cases for whom a trigger Pap date was not found, the medical visit just prior to their date of histologic diagnosis with cervical cancer was used as a proxy trigger Pap date. If there was a sequence of visits on consecutive days just prior to the trigger Pap date then the date of the earliest visit within that sequence was used. Each RAMQ control had the same corresponding time window as their matched case. That is, the date of the trigger Pap smear for the case was used as the lower boundary of the control's time window and the period five years prior to the matched case's diagnosis date was the upper boundary.

[3] Each model was mutually adjusted for the number of visits to other types of physicians in the table. All visits are categorized as 0, 1-2, 3-4, >4.

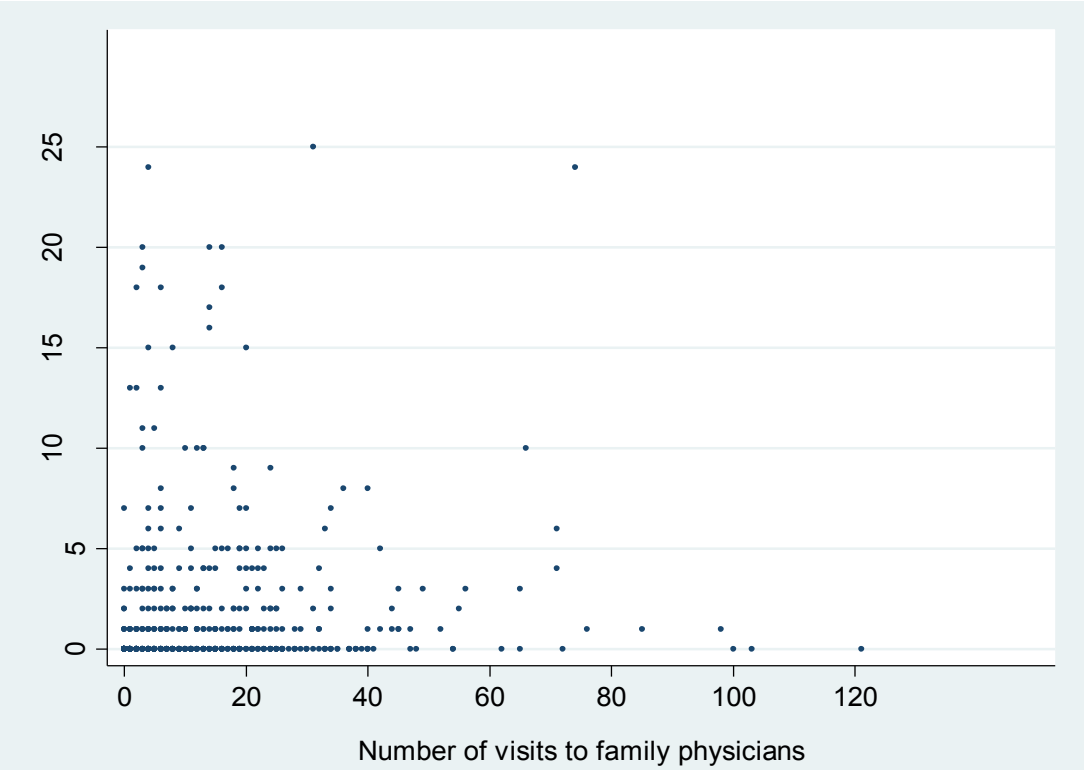

Figure 6.9. Number of visits to gynaecologists versus number of visits to family physicians by cases prior to their first abnormal Pap test

7. DISCUSSION

7.1 Summary of Results

This study examined the acceptability of the processes of care that women with cervical cancer received within 5 years prior to their diagnosis. Cases were diagnosed with invasive cervical cancer at a Montreal or Laval hospital between 1998 and 2004, and were residing in Montreal or Laval at that time. Based on the cases for which there were adequate data to assess quality of care, 90% of women with invasive cervical cancer were 'ever' screened and 10% were 'never' screened. Of the women categorized as 'ever' screened, about 43% of them were not screened within 5 years before diagnosis. Almost 13% of subjects and 36.7% of subjects with an abnormal Pap smear had at least one follow-up event that was considered unacceptable procedure-wise and in terms of a time delay, respectively. It was also found that the quality of care was more likely to be unacceptable for subjects with a pre-invasive lesion, in terms of procedures performed and the timing of those procedures, compared to those with an abnormal Pap smear. Specifically, in terms of procedures performed and the timing of those procedures, 19.4% and 52.5% of subjects had at least one unacceptable event during the follow-up of a cervical lesion, respectively.

7.2 More Detailed Results of Study

7.2.1 Characteristics of Cervical Cancer Cases

According to data obtained from the subject questionnaire, the majority of women with cervical cancer were born in Canada, legally married, employed, spoke French only or both French and English, either had less than a high school level education or some post-secondary education, and the largest percentage had a household income of more than $60,000 annually. As the distribution of demographic characteristics of any sub-group is inherently linked to that of the greater population from which they arose, this distribution of characteristics possessed by the cancer cases may not be necessarily associated with those at an increased risk of developing cervical cancer. When cases were compared to the CCHS respondents, it was found that immigrants were at a higher risk of cervical cancer than non-immigrants; women in common-law

relationships were at a higher risk than married women; women who spoke neither French nor English were at a greater risk than women who spoke both French and English; and women with some post-secondary education were at a greater risk than women with less than a secondary school education. Those who had a regular doctor, completed a post-secondary degree, and had a chronic disease were at lower risk of cervical cancer.

Interestingly, many of these characteristics are congruent with subject-level determinants of Pap smear screening. Specifically, previous studies have found that the following characteristics are associated with never being screened or not being screened recently: being an immigrant, less educated, lower income, never married, older age, living in non-metropolitan areas, certain ethnic groups, and less insured (Goel, 1994; Lee et al., 1998). Hence, perhaps it would be most prudent to especially target women with these characteristics with various initiatives to improve their screening rates and to ensure that they are not lost to follow-up. The most efficient scenario would be to institute a population-based provincial organized screening program with invitations for screening and an appropriate recall system.

It should be noted that the demographic characteristics derived from the subject questionnaire may offer a skewed representation of women diagnosed with cervical cancer. The respondents to the questionnaire were younger in age, diagnosed at an earlier stage, and less likely to have symptoms than non-respondents. Hence, selection bias may have affected the internal validity of these results.

7.2.2 Assessment of Pap Screening History

Based on all sources of data, this study found that the vast majority of subjects (90%) were screened at least once in their lifetime and only 10% were never screened. These findings are in sharp contrast to the results of the meta-analysis presented in Chapter 4, which estimated that only 58.5% of women with cervical cancer were ever screened and 41.5% of women with cervical cancer were never screened before diagnosis. There may be an underestimate of the true proportion of study cases that were never screened and concomitantly, an overestimate of the proportion ever screened. This underestimation of the proportion of subjects never screened may be explained by the fact that in order for a woman to be classified as never screened, she or

her next of kin must have participated in the interview and it must have been specifically stated that she was never screened. I did find that the unclassified subjects (n=161) were less likely to have participated in the subject interview than those subjects whose screening histories were classified (21.7% vs. 72.5%, respectively). Thus, if there were no lab reports for Pap smears done prior to the trigger Pap, no informative data from medical charts or physician questionnaires regarding Pap smear use, and no subject or proxy interview (or if there was an interview, the subject's screening history was not known), this subject's lifetime screening use would not be categorized as never screened. Instead, their screening histories would not be classifiable. In sum, it is more likely that unclassified subjects were actually never screened than ever screened.

The subjects whose lifetime screening histories could not be classified as ever or never screened were demographically different than those subjects whose screening histories were categorized as ever or never screened. The unclassified subjects tended to be older in age, resided in lower income and education-level census tracts, were more likely to have symptoms of cervical cancer, and were diagnosed at more advanced stages. As noted above, these characteristics are also descriptive of those women who tend to have poor screening histories. Hence, it could be surmised that the majority of subjects whose lifetime screening histories could not be assessed based on the available data, were indeed more likely to have been never screened. It is possible that selection bias occurred since a large segment of the study cases, who possessed characteristics associated with poor Pap screening use, were essentially omitted from the assessment of screening activity. This resulted in an assessment of lifetime screening largely based on a subset of the cases whom were younger in age, diagnosed at an earlier stage, and more likely to live in higher income and higher-education level census tracts, and hence, more likely to have been screened sometime in the past. This provides further proof that this study may have underestimated the proportion of study subjects never screened.

When the Pap screening histories of the cervical cancer cases and the CCHS respondents were compared, especially when the effects of bias were considered, the results emphasized how crucial screening is to the prevention of cervical cancer. The analyses not only found that being ever screened was protective against developing cervical cancer but also, they showed the even

greater importance of regular Pap screening. Specifically, the analysis that was limited to screening histories deemed as "definite" found that women screened 5 or more years prior to diagnosis were at a much greater risk of cervical cancer than those screened recently.

This study also showed that an acceptable screening history is not only associated with a reduced risk of cervical cancer but also with diagnosis of cervical cancer at an earlier stage. Specifically, using cases diagnosed with localized cancer as an internal comparison group, all analyses found that subjects never screened or those whose last Pap smear was 5 or more years prior to diagnosis were at a greater risk of regional and distant cervical cancer compared to those screened within the last 3 years. However, in most instances, except for the results obtained by screening data classified as "definite", statistical significance was not reached. This non-significance may have been due to sparse numbers in these analyses.

Earlier cancer diagnosis lends itself to treatments that are less physically destructive, which is not only less taxing for women to undergo but also more conducive to maintaining fertility and a better quality of life (Tierney et al., 2010). Further, earlier diagnosis implies a better prognosis. The estimated 5-year survival rates for stage I cervical cancer is 85% and it declines to 11% for stage IV cancer (Herbst et al., 1997)

7.2.3 Other Potential Biases

In addition, the results of these analyses also highlighted the effect of using different sources of data to classify screening use. When the information obtained from all the sources of data were used to classify the screening use of the cancer cases, women who were screened at least once in their lifetimes were more likely to have cervical cancer, which is contrary to the literature. These spurious results were most likely due to differential misclassification bias as there was a more exhaustive search for data to determine the screening history of women with cervical cancer compared to control subjects. For cervical cancer cases, data was obtained from lab reports, medical charts, physician questionnaire, and self-reports from subjects or responses from a proxy. The lifetime screening histories of the control group were only based on responses to the following question in the CCHS survey: Have you ever had a Pap test? It appears that there was

most likely a greater tendency to categorize cases as being ever screened compared to the controls, producing an over-estimate and reversal of the true association in this analysis. The estimated OR slightly declined when based on those screening histories deemed to be "definite". This is probably a reflection of the superior reliability of the data sources, namely, lab reports, used to classify screening use in that particular analysis, although, misclassification may still be present. When the lifetime screening histories of the cancer cases were exclusively based on the responses to the subject questionnaire, it was found that the association was more consistent with what would be expected. That is, being screened at least once was protective against cervical cancer.

When the time since the last Pap test was examined, it was found in all three analyses that in general, the longer the time since one's last Pap, the greater was the risk of cervical cancer. The analysis based on all sources of data may have been affected by differential misclassification bias which again, was due to a more in-depth search for data for cancer cases. The largest associations, at least for the category ≥5 years, and the greatest difference between categories were found for the analysis limited to screening categorizations deemed to be "definite". This again is most likely a reflection of the greater reliability of the data used to characterize the screening use of cancer cases but differential misclassification may still be present. The smallest odds ratios and the smallest gradient between categories were found for the analysis based solely on the responses to the subject questionnaire. Non-differential misclassification, due to the following biases, may have resulted in an estimate that was skewed towards the null. Recall bias may have occurred as cases and controls may have inaccurately recalled their past screening history to a similar degree. Further, the literature has shown that women tend to underestimate the time since their last Pap smear and they recall Pap testing as occurring more recently than it actually did (McPhee et al., 2002); a phenomenon called telescoping (Newell et al., 2000; Rauscher et al., 2008). Social desirability response bias may have also occurred. This refers to the tendency of subjects to provide what they believe is the socially desired response so as to present themselves in a positive light (Johnson et al., 2005).

The variable "adequacy of screening history" was an amalgamation of the two previous screening variables. Hence, similar to above, the analysis examining the association between the

adequacy of a subjects screening and cervical cancer based on all sources of data may have also been affected by differential misclassification. The analysis based on screening histories classified as "definite" were based on the results of lab reports and thus, were more reliable but were still affected by differential misclassification. The analysis based solely on the questionnaire was most likely influenced by non-differential misclassification, which would have biased the point estimates towards the null and resulted in an underestimate of the true association.

In all these analyses that examined the association between screening history and cervical cancer development, the potential confounding effect of subject age was adjusted for in each model. Age was rather finely categorized into 5-year age intervals; however, there is still the possibility that age-adjustment was incomplete and a small degree of residual confounding remained.

7.2.4 Proxy Respondents to Subject Questionnaire

As noted within the results section, 22% of the interviews for long-term residents were completed by proxy-respondents. There were a few important differences between those respondents who responded to the questionnaire and those who had a proxy respond (data not shown). Study subjects for whom a proxy responded to the interview tended to be older at diagnosis, more likely to have experienced symptoms of cervical cancer, more likely to have a chronic disease, more likely to have never smoked, and more likely to be diagnosed at a more advanced stage. Proxy respondents were much less likely to know the past screening histories of subjects compared to subjects themselves; specifically, 53.5% (n=38) of proxies did not know if subjects was ever or never screened and only 10.8% (n=28) of subjects did not know if they had been ever or never screened. Of those subjects and proxies who knew their own or their next of kin's screening history, subjects who had proxies respond for them were more likely to be never screened compared to subjects who responded themselves (36.0% and 13.0%, respectively). These results provided credibility to both the screening results obtained from proxy respondents and also to the screening results based solely on the questionnaire as it is expected that older women and women diagnosed at a later stage would be more likely to have died and hence, more likely to have never been screened during their lifetime.

Screening history classifications that were based only upon data obtained from proxy interviews were qualified with the term "possible". The term possible indicated that this source of data was of the lowest quality and showed that we had the least among of confidence that it was correct compared to classifications based upon other more reliable sources of data.

7.2.5 Assessment of the Follow-up of Abnormal Pap Smears

A minority of subjects who had one or more abnormal Pap smears prior to diagnosis had at least one follow-up event that was deemed unacceptable (12.5%, 95% CI 8.7%-16.3%); a larger proportion of subjects did not receive their care in a timely manner per consensus (36.7%, 95% CI 31.2%-42.3%). The most common reason for poor follow-up of an abnormal Pap smear was the unnecessary repetition of Pap smears when an immediate colposcopy was recommended according to the guidelines. This occurred, in most instances, as a patient with an abnormal Pap smear was referred from one physician to another for follow-up; for example, from a family physician to a gynaecologist or from a gynaecologist to a gynaecologic-oncologist. This second physician then repeated the Pap test once or twice before performing a colposcopy. In some instances, this repetition of Pap smears was done by the first physician before referral. A delay in referral for a colposcopy due to unnecessary repeat cytological investigation has also been observed by previous studies (Turner et al., 1990; Brinkmann et al., 2005; Janerich et al., 1995; Kreuger et al., 2000; Mobius et al., 1993) and could reflect health providers' lack of confidence in isolated Pap smear reports.

7.2.6 Patient-Level Impediments to the Follow-up of Abnormal Pap Smears

Studies have investigated the patient-level barriers to timely follow-up of abnormal cervical cytology and have developed quite elaborate multi-factorial models to explain the reasons for these temporal delays in appropriate care. It has been determined that a woman's adherence with management recommendations for an abnormal Pap smear is influenced by her beliefs and knowledge regarding health, cancer, and the Pap test. These include the following: beliefs about the risk of cervical cancer and fears surrounding a cancer diagnosis; concerns regarding the effect of treatment on femininity; knowledge about Pap smears and perceptions of the seriousness of the Pap test results; understanding the purpose of a colposcopy; understanding the necessity of and familiarity with treatment; and family history of disease (Paskett et al., 1990;

Nelson et al., 2002). More utilitarian issues may also have an effect on these delays such as monetary costs, time constraints, lack of transportation, and child-care issues (Paskett et al., 1990; Lerman et al., 1992). Although there is consensus in the literature regarding these more practical factors, another study found that several of these variables were not barriers to the follow-up of abnormal cytology (McKee et al., 1999). The observation that patients with abnormal Pap cytology were often delaying their return for follow-up or not returning altogether has led to the development of various interventions to improve the follow-up of abnormal Pap smears. As noted previously, these include such things as counseling over the telephone, mail or telephone reminders, vouchers for public transportation, and providing patients with educational brochures (Khanna et al., 2001; Yabroff et al., 2000; Marcus et al., 1998; Miller et al., 1997; Stewart et al., 1994).

Although the results of studies have been variable, generally, women who are less likely to return for follow-up of an abnormal Pap smear have the following demographic characteristics: younger age, unmarried, lower education level, less severe cytologic abnormality, and fewer health issues (McKee et al., 1999; Michielutte et al., 1985; Khanna et al., 2001). In this current study, one patient-related variable that was a statistically significant predictor of the time between having an abnormal Pap smear and receiving a colposcopy was the language of conversation. Specifically, women who spoke neither French nor English had a longer time interval between the abnormal Pap and the subsequent colposcopy compared to women who spoke both languages. Hence, it could be surmised that not speaking one of the main languages in a given population acts as a barrier to the timely management of an abnormal Pap smear. Further, I found that younger subjects waited longer for a colposcopy than older subjects.

7.2.7 Physician-Level Impediments to the Follow-up of Abnormal Pap Smears

Research into abnormal cytology follow-up delays appears to have focused almost exclusively at the level of the patient. In this study, I found that the physician may also play a role in these poor follow-up outcomes. Specifically, it is the physician who decides to unnecessarily repeat Pap smears even though an immediate colposcopy is warranted. As noted above, this often happened prior to a family physician referring his/her patient to a gynaecologist or a gynaecologic-oncologist because of an abnormal Pap result. Perhaps, the family physician may

have wanted to confirm the result of the first abnormal Pap test prior to transferring his patient so as to not escalate the diagnostic work-up unnecessarily. Likewise, the gynaecologist who received this patient may also have repeated the Pap (instead of doing an immediate colposcopy) in order to confirm the result of the prior Pap(s) so as to not do an unnecessary colposcopy.

This current study found that subjects who had a family physician do the original abnormal Pap smear tended to wait twice as long for a colposcopy than those subjects who had a gynaecologist do the original Pap test. In corroboration with this, a study by Kupets and colleagues (2011) found that gynaecologists were more likely, compared to other physicians, to provide "appropriate" management for abnormal Pap smear results. Further, another study also found that gynecologists tended to provide colposcopies sooner than did other physicians (Kuo et al., 2010).

7.2.8 Assessment of the Treatment of Pre-Invasive Cervical Lesions

This current study also found that subjects with pre-invasive lesions were more likely to receive unacceptable care in terms of both procedures (19.4%, 95% CI 13.9-24.9) and timing (52.4%, 95% CI 45.5-59.4), than observed for the follow-up of abnormal Pap smears. Similar to that found for the follow-up of abnormal Pap smears, the unacceptable care of cervical lesions was in all instances, except one, due to the unnecessary repetition of a biopsy, cone or endocervical curettage that had already detected a lesion. The research on patients' compliance with treatment recommendations after colposcopic treatment has been much less intense than that examining compliance after an abnormal Pap smear. As far as I could tell, there have been no studies that specifically examined the reasons that patients had for not complying with treatment recommendations. It has been shown that women's demographic characteristics (for example, age, ethnicity, smoking history, parity, age at first intercourse) and the severity of the initial Pap smear results were not associated with compliance (Laedtke et al., 1992; Massad et al., 1999). It has been found that the severity of the cervical lesion was associated with patient compliance with follow-up recommendations, with women diagnosed with lower grade pre-invasive lesions being more likely to be non-compliant than those with high grade lesions (Eger et al., 1996).

7.2.9 Health Services Use in Cervical Cancer Cases and Controls

7.2.9.1 Visits to gynaecologists

In terms of health services use, women with cervical cancer tended to have fewer visits with gynaecologists within their pre-diagnostic period, but more visits with family physicians compared to women without cervical cancer. Studies have found that gynaecologists may be more likely to perform Pap tests than family physicians (Lurie et al., 1993; Camirand et al., 1995). From this, it could be surmised that since women with cervical cancer had less contact with gynaecologists than did women without cervical cancer, it rendered the former group less likely to be screened and, as a result, at a greater risk of developing invasive cervical cancer.

In addition, it has been suggested that gynaecologists may not be more likely to perform Pap tests but instead, women who wish to have Pap smears preferentially go to gynaecologists, rather than family physicians, to have them done. The literature has shown that 51% of women tend to prefer gynaecologists to perform their Pap tests, although many did not have a preference (34%) (Pemberton et al., 1998; Lurie et al., 1993). In contrast, in this current study, 20.0% of cancer cases who responded to the subject questionnaire stated that they preferred a gynaecologist to perform their Pap tests, 3.9% preferred a family physician, and more than half of these respondents (58.2%) had no preference as to the specialty of the physician for their screening. This large proportion of indifference among cancer cases could be a reflection of the tendency for these subjects not to seek screening at all. This indifference may also be reflected by about half of cancer subjects stating that they were not screened within 5 years of diagnosis because they never imagined they would develop cervical cancer. This may instead be simply a lack of knowledge about Pap screening as almost 30% of cancer cases stated that they were not screened prior to diagnosis because they did not know the purpose of Pap testing. Even after diagnosis with cervical cancer, 17.0% of study subjects who responded to the questionnaire themselves (not proxy respondents) claimed not to have any knowledge of Pap testing.

Interestingly, previous studies have also found that in addition to gynaecologists, female physicians and older physicians (when mutually adjusted for each other and subject age in the model) are also more likely to perform Pap tests (Lurie et al., 1993). Again, the respondents of

the subject questionnaire did not have any partiality as to the gender or age of the physician who performed Pap tests.

7.2.9.2 Visits to family physicians

These results indicate that family physicians have ample opportunity to offer their patients Pap tests and to educate their patients about the importance of regular Pap screening. This should be done even when patients go to their physician for non-gynaecologic care. As noted before, when Quebec physicians perform a Pap test during a medical visit they are not actually specifically paid for that act. It has been suggested that instituting a RAMQ billing code specific to the performance of Pap tests may offer an incentive for more family physicians to perform screening (Mayrand et al., 2009).

7.2.9.3 Visits to medical specialists

Women with cervical cancer were also found to have had more visits to medical specialists (other than gynaecologists) before diagnosis than had the non-cervical cancer control subjects. Perhaps, women with cervical cancer, compared to the controls, tended to have more severe morbidities or were more likely to have morbidities that required consultation and treatment by specialists. The research surrounding the relationship between cancer screening and chronic disease suggests that women with a chronic condition undergo screening less often than women without a chronic disease (Kiefe et al., 1998; Hsia et al., 2000). It has been suggested that physicians are less likely to screen for cancer if it is believed that the chronic disease has shortened the life expectancy of a patient. Further, perhaps, the management of a patient's chronic disease becomes the physician's sole focus of attention and screening is just not the priority. Hence, this may explain the lower screening rate of cervical cancer cases prior to their cancer diagnosis compared to controls. It should be noted that the conjecture that cervical cancer cases have a greater frequency of chronic disease than controls is counter to one of the other findings of our study; specifically, our study found that cervical cancer cases were less likely to have a chronic disease than the CCHS controls. That analysis, though, was based on a sub-group that tended to be younger in age than those not interviewed and hence, would be less likely to possess a chronic condition.

7.2.10 Identification of Cervical Cancer Cases

Typically, population-based cancer registries are maintained and used to identify incident cancer cases for surveillance and research purposes. In an attempt to enhance the capture of cancer cases various other data repositories that are typically collected for administrative purposes have been investigated as potential sources of cancer cases. These include such databases as Medicare claims data in the United States (Cooper et al., 1999; Freeman et al., 2000; Nattinger et al., 2004) and hospital discharge data files (Penberthy et al., 2003; Baldi et al., 2008). Studies have examined the possibility of these secondary sources of cancer cases either acting as an adjunct source of cases along with a cancer registry or potentially replacing cancer registries as primary sources of case capture (Penberthy et al., 2003).

For this study, the tumour registry of Quebec was the primary source for cervical cancer case identification. This study also used a secondary source to capture the cancer cases: the hospital discharge files accessed through medical records departments. The PPVs of these two sources were essentially the same (i.e. 87.5% for the tumour registry and 88.6% for medical records departments) and indicate that these sources were essentially both equally and highly accurate at correctly ascertaining incident cervical cancer cases. The medical records departments had a greater number of true positives and were able to identify a greater number of cancer cases than did the tumour registry, which is reflected in the larger sensitivity for the former source.

When assessing case identification with the accompanying criteria requested, the medical records departments identified a much greater number of unique cases compared to the cancer registry (118 versus to 79 cases, respectively). However, a much greater proportion of those unique cases originally identified by medical records were found not to meet the criteria that I stipulated for the cases than did the cancer registry. Of these criteria, 59 of the cases identified by medical records, but not by the cancer registry, met the criteria we requested of both sources. And 44 cases uniquely identified by the cancer registry fulfilled these criteria. As a result, the medical records departments collectively identified slightly more eligible subjects for this study than did the cancer registry.

These data show us that cervical cancer case ascertainment by the tumour registry is not 100% complete, which is counter to the results of a 2003 study conducted by the Institut national de santé publique du Québec that evaluated the completeness of the cancer registry (Brisson et al., 2004). This study identified new cervical cancer cases diagnosed in 1996 by reviewing pathology reports at a sample of hospitals. Among the 16 cases found at the hospitals, the tumour registry was able to identify all 16 cases. It should be stressed that this study had a very small sample size.

These findings suggest that supplementation of cervical cancer case capture by the tumour registry using medical records departments is an accurate method. I would not use only one of these sources and not the other to identify cervical cancer cases as in the end there were 36 and 46 unique cases identified by the cancer registry and medical records departments, respectively. In addition, obtaining data from the medical records departments was an easy and cost-effective method to ascertain cases. There was no direct monetary cost in the sense that I did not pay to retrieve the lists of potential study subjects from the hospitals. However, there was a cost in terms of the time spent reviewing medical charts of those extra cases uniquely identified by medical records departments, which subsequently were found not to meet our inclusion criteria. This expenditure of time, of course, translated into payment of the salary for the chart abstractor.

7.3 Limitations of Study

Although the present study represents one of the largest audit investigations ever conducted on the process of care of women who developed cervical cancer some important limitations must be recognized. The various sources of data used for this study had inadequacies that may have prevented us from obtaining the complete processes of care related to cervical screening and management of abnormal cytology results and pre-invasive lesions for some subjects.

7.3.1 Abstraction of Data from Hospital Medical Charts

One major source of data was patient hospital medical charts and, in fact, the literature has shown that the abstraction of data from medical charts is the most common source of data for the measurement of quality (Rubin et al., 1992; Gilbert et al., 1996). Unfortunately, using medical

charts to obtain process of care data has its limitations: handwritten entries may be illegible, lab reports may be missing, and charts, in general, may be poorly organized and data may be inaccurate and incomplete (Tsai et al., 2008; Luck et al., 2000). All of these shortcomings were experienced when reviewing medical charts for this study. Further, as was found in this current study, medical charts may not include valuable data such as patient characteristics and health behaviour and knowledge (Skinner et al., 2005). This made it difficult to fully characterize study subjects. This speaks to the necessity of having more uniformity, between hospitals and even between patients within the same hospital, in terms of the personal information obtained about patients. This is important not only for research purposes but also to be able to provide better comprehensive care of patients. And finally, the process of chart abstraction can be time consuming and expensive, which has also been established in a previous study (Downey et al., 2004). In addition, I also found that the breadth of data regarding medical procedures specific to cervical cancer found in charts varied by hospital. In order to overcome these weaknesses associated with data collection via medical chart abstraction, we used multiple data sources, as suggested by the literature (Luck et al., 2000). Specifically, we also used administrative data (i.e. RAMQ medical billing data), lab reports directly obtained from labs and physicians, and interviewed subjects and/or next of kin.

Despite the limitations attributed to obtaining data from medical charts, we obtained a considerable amount of data from them. Specifically, of those individual procedures uniquely identified through only one data source, medical record abstraction identified 83.7% of the colposcopies, 45.7% of ECCs, 51.3% of cervical biopsies, and 55.0% of cones. Moreover, subject and next-of-kin contact information, names of physicians, and cancer stage were almost exclusively obtained from medical charts.

7.3.2 Cytology/Pathology Laboratories

Like medical charts, cytology/pathology laboratories were also quite a robust source of data for this study as they identified the majority of most procedures for subjects. However, there were shortcomings to obtaining data from labs because of the impediments to us accessing data from

labs and also the extent of data available from the individual labs. Some examples of these barriers to data collection from labs are as follows:

1) Most labs had results in a computerized database, which were searched for lab reports for our study, and if available, they were printed. However, many labs had not transferred the results from earlier time periods into their computerized systems or had not retained those earlier lab reports. For example, one lab did not have data available in their computerized system for procedures conducted before 1998. Similarly, another lab had not transferred procedures done before 2002 into their electronic database, and another lab, for procedures conducted before 2003. These labs instructed us that we should review the hospital medical charts for lab reports from the earlier time periods. Unfortunately, these lab reports were not always found in the medical charts, if there were actually any procedures done. One hospital lab was not computerized at all but rather had cytology and pathology reports in paper form. This non-computerized repository was manually searched by me and our study nurse to determine if reports existed for subjects.

2) The head pathologist of one hospital lab refused to participate in our study, even after being personally contacted on several occasions by the study principal investigator, a study clinical co-investigator who is also a pathologist, and me. Hence, lab reports were not directly received from this lab. However, a few reports of procedures read at this particular lab were transmitted to us by physicians or were found in the medical records department of that hospital.

3) One lab only retained reports for Pap tests that were deemed to be abnormal and the lab reports for Pap smears that were cytologically normal were sent to the physician who performed that Pap test. The challenges of retrieving data from physicians' offices are described below.

4) Many labs only provided us with the abridged form of the original lab reports. These reports often did not contain the name of the physician who performed the individual Pap tests or other procedures, and did not include the dates that cervical cytology and tissue samples were sent to the lab, the dates they were reviewed, and the dates that results were returned to the physician.

5) One lab would only retrieve lab reports for subjects if the subject or next of kin had given us

prior consent to do so.

6) In most cases, hospital lab personnel retrieved data for our study as they would not permit us to personally access their computerized databases.

The data collection from labs was an extremely protracted process as each lab had to be approached several times during our data collection phase to request that they search for lab reports for given subjects. Each lab was contacted several times for the following reasons: We received the names of study subjects in multiple batches from the tumour registry over several years; hence, as new names were provided to us we gave them to the appropriate labs. Also, as additional data were retrieved for each subject (from all sources of data) it enabled us to determine which other hospital labs should be searched for reports for each given subject that had not been previously searched. Most labs were amenable to searching their files and providing us with reports on multiple occasions; however, eventually there were some labs that ultimately refused to continue to do so. It should be noted that we offered to pay lab personnel to retrieve data for us but only one lab agreed to do so on a regular basis and another lab only did this once. Labs often suffered from a lack of staff and heavy workloads and thus, they were not willing to accept this additional work. On the whole, as lab personnel were retrieving data for us gratis we often had extended waiting time before we received the data and also, we had to limit the number of subject names for whom we required them to search for at a given time. Hence, we were not able to search each lab for the existence of lab reports for all 568 study subjects, which would have been ideal. Instead, we took cues from the data we had from all sources to determine which labs should be searched for each individual subject. Again, the use of several data sources presumably helped to minimize the data omissions that may have occurred during the data collection from the labs.

We only searched for cytology reports at public labs located in hospitals. Potentially, some Pap smear results could have been interpreted at private labs and these may have been missed by our data collection efforts. However, we believe that any Pap smear omissions would have been negligible since there were very few private cytology labs in existence at our time period of interest. In addition, women who would have paid for these services at a private lab would more

likely be of a higher socio-economic status and hence, at a lower risk of cervical cancer and unlikely to have been a subject in this study. Further, we did attempt to retrieve test procedure results from the files of private physicians' offices; thus, if there were any tests reviewed at private labs, these may have been provided to us by physicians we contacted.

The search for cervical cytology and pathology reports was concentrated in hospitals located on the Islands of Montreal and Laval; these are listed in Table 5.1. It is possible that some study subjects may have had screening and procedural follow-up at hospitals or clinics in other regions of Quebec that are in close proximity to Montreal or even a distance from Montreal. We limited these possibilities by including in the study only women residing in Montreal or Laval for a minimum 5 years prior to diagnosis. As previously noted, during the data collection phase we attempted to determine where each subject may have had Pap tests reviewed based on cues found in medical charts and from data obtained by subjects, their next of kin, or their physicians. Based on this information, we determined that some subjects may potentially have had Pap smears reviewed at two hospitals that were outside of Montreal and Laval. The labs at these two hospitals were contacted and they searched for any relevant data for the specified subjects. Lab reports were found for a negligible number of these subjects at these two hospitals.

7.3.3 Subject Questionnaire

The subject questionnaire was another source of data. Although we used several tactics in our study in an attempt to maximize the response rate of the questionnaire, its biggest drawback was its low response rate, which based on the overall number of eligible subjects was 59.8%. This response rate is comparable to those studies included in the meta-analysis that interviewed subjects with cervical cancer (and provided response rates) (Stuart et al., 1997; Nasca et al., 1991; Ratima, 1993; Ciatto et al., 1993). Those studies had response rates that ranged from 50.4% to 60.9%, with one outlier of 72.4% (Janerich et al., 1995). Of the subjects or next of kin whom we attempted to contact to administer the questionnaire, the most common reason for no interview being done was not being able to locate a subject or next of kin. This may have been less of an issue if interviews were done closer to the date of diagnosis as it would have been less likely that subjects (or next of kin) would have moved or died. Interestingly, the literature has

shown that, in general, participation in research involving telephone surveys has declined in the last decade, which may also partly explain the low response rate (Braunsberger et al., 2007).

The relatively low response rate meant that no questionnaire data were obtained for 238 subjects who resided in Montreal or Laval for a minimum 5 years. In some instances, this hindered our ability to categorize the screening use of a large number of study subjects in terms of being ever or never being screened in the past. We also found that those subjects interviewed were a specific subgroup of the cases and hence, any analyses done using the data from the questionnaire may suffer from poor internal validity.

Despite the poor response rate and the disadvantages of using self-reported screening rates, it is still imperative that such studies obtain data directly from subjects or proxies, especially if a similar study as this one is conducted in a population without a centralized computerized repository of lab results. For this study, the responses to the questionnaire allowed us to confirm subject fulfillment of inclusion criteria and to determine demographic characteristics (which were often missing from medical charts, as noted previously), health seeking behaviour, and names of physicians. The interview also provided information that allowed us to assess screening histories. However, despite the utility of the questionnaire, self-reports should not be solely relied on as a means of determining screening histories due to the reasons discussed above. In addition, women may not be able to discern between Pap screening that occurred as part of normal screening practice and Pap tests that were done as part of the work-up towards the final diagnosis with cervical cancer. Further, women may mistakenly report having a Pap smear during a routine gynaecologic exam that did not actually include Pap testing (Rauscher et al., 2008).

7.3.4 Physician Questionnaire

Data collection from physicians was hindered by various factors and resulted in poor retrieval of data. Prior to contacting physicians for data, we had to receive signed consent from study subjects to do so. Consent was received from 221 (70%) of subjects (or next of kin) who were long-term residents of Montreal or Laval, and for these 221 subjects, data was received for only

87 (39.4%) of them. Of the 329 questionnaires I mailed to physicians, only 150 (45.6%) questionnaires were returned. A major impediment to the retrieval of data from physicians was medical charts being discarded since the patient had not been seen by that physician for over 5 years. This factor was something that was beyond our control and it could only have been circumvented to a large degree by conducting this study closer in time to the subjects' diagnosis dates. Another major impediment was physicians not responding to the questionnaire, even though we incorporated various strategies in our study in an attempt to maximize the response rates. Studies have shown that, historically, the questionnaire response rates for physicians are quite low (Thorpe et al., 2009). A review study that examined 321 mailed surveys published over a one-year period in medical journals found a mean response rate of 54% for physicians (Kellerman et al., 2001).

It has been suggested that physicians' essentially are not willing to or able to complete surveys due to their already busy schedules (Kaner et al., 1998). This may be, at least in part, one of the reasons for the non-response found in this study. Further, the physician questionnaire requested information for specific patients; it was not simply a survey of physicians' personal beliefs or practices, for example. Rather, completion of this questionnaire required physicians or their staff to search for a medical file for a given patient(s) and to provide responses pertaining to that given patient(s). In addition, the medical file had to be searched for the appropriate lab reports and physicians had to either transcribe the dates and results of these procedures on to the questionnaire and/or fax lab reports along with the completed questionnaire to our study office. We did offer physicians the option to have one of our research personnel come to their office to personally retrieve the data from their files but only 11 physicians (24 subject charts) agreed to this option. Another possible explanation for the poor response from physicians was a sense of suspicion that some physicians had towards this study as they may have felt that study researchers were attempting to blame them for any unacceptable care that we found. I tried to alleviate this feeling in the introductory letter we mailed to all physicians along with the questionnaire (Appendix 16 and 17). This letter clearly states that we are not interested in laying blame for any instances of poor care found and that data will be analyzed without any personally identifiers.

7.3.5 Data Obtained from the RAMQ

The medical billing data obtained from the RAMQ provided us with a listing of the medical acts subjects had prior to diagnosis. These data allowed us to develop a better sense of the processes of care that each woman had leading up to diagnosis. Using this RAMQ data I was sometimes able to identify procedural care that was not identified by the other sources of data. For instance, physician reports of colposcopies were often not found with hospital medical charts, or if they were found, they were often illegible. The RAMQ data were able to inform us that a colposcopy was performed. This source of data also has its limitations. As noted above, there is no RAMQ billing code specific to the performance of a Pap test. Further, the other RAMQ billing codes noted in Table 5.2, were often not unique to a specific procedure. For instance, code 6145 is described as "Dilation and biopsy curettage with or without polypectomy or cauterization" in the RAMQ billing guide but in my experience, on separate occasions it has referred to an endometrial biopsy, an ECC, or a cervical biopsy. Also, there were instances that we found data from other sources, for example, lab reports, but these procedures were not captured by the RAMQ. It has been shown that about 10.5% of medical services provided by salaried physicians are missed by the RAMQ (Ionescu-Ittu et al., 2007). Hence, relying solely on the data available from the RAMQ may, in some instances, not provide a complete or accurate picture of a subject's processes of care.

7.3.6 Canadian Community Health Survey

The respondents of the CCHS survey were used as a comparison group in several of the analyses. For these analyses, it was assumed that these women had not been diagnosed with cervical cancer at the time of the survey or prior to the survey, which I believe is a reasonable assumption. It should be considered that the CCHS survey used 3 types of sampling frames (area frames, a list frame of telephone numbers, and random digit dialing) to select the sample of households within the health regions constituting each province. A total of 27,599 persons (male and female) living in Quebec responded to the CCHS survey (Canadian Community Health Survey 2003. User Guide for the Public Use Microdata File, January 2005.). In this current study, we found that there were from 72 to 99 cases of cervical cancer diagnosed in Montreal or

Laval annually. It is theoretically possible that some women with cervical cancer took part in the survey, but in comparison to the numeric breadth of the survey and the intricate sampling techniques used, this would be an extremely small probability.

7.3.7 Other Study Limitations

Despite the individual limitations of all the sources of data, they each uniquely identified procedures and provided data that were not identified by one of the other sources. However, our inability to assess the quality of care of many study subjects and the time consuming data collection, especially medical chart abstraction and data collection from labs, undertaken for this study underscores the necessity of having a centralized computerized information system for Pap tests and other screening and treatment procedures. This information system would be invaluable for the appropriate recall of women at specified intervals for screening and follow-up care and it could be used for surveillance activities.

Another limitation was the use of existing lab pathology reports to confirm that study subjects were diagnosed with invasive cervical cancer. It would have been prudent to have retrieved those tissue samples and have them reviewed by a pathologist to confirm the diagnosis of invasive cervical cancer. However, such a review of slides would have been exceedingly expensive. Also, this retrieval of pathology slides would most likely not have been feasible as there was a great deal of difficulty to retrieve archived Pap smears, and this attempt was eventually abandoned for this current study.

In addition, the lack of data for specific study cases led to their omission from given analyses. For instance, as noted previously, in some instances we were not able to assess the quality of the procedural care or timing of the care as data was not found. This may have skewed the results. In terms of the assessment of Pap screening history, as discussed above, this lack of data and subsequent inability to characterize the lifetime screening histories of several subjects, may have led to an underestimation of the proportion of subjects never screened.

An additional limitation of this study was the inability to determine who was responsible for the unacceptable care that was found, especially for the follow-up care. For example, if there was an unacceptable amount of time between the sampling for a Pap smear (that turned out to be abnormal) and the follow-up procedure (a repeat Pap test or colposcopy) then there are several entities that could be responsible for this delay. The time delay could be attributed to the cytology lab. For instance, there could have been an inordinate amount of time between the lab receiving a Pap test, the cytologist reviewing it, and the result being sent back to the physician. However, as noted above, almost all of the lab reports we obtained did not provide us with the necessary data to determine to whom the poor care could be attributed to. The blame may lie with the physician. Perhaps, the physician simply took a long time to review the results from the lab and/or to contact the patient to return for follow-up. It would be difficult to determine this. It may be noted within the physician medical charts but writing within charts was often illegible, physicians may be reticent about providing this data (if it was actually present) and simply, many old charts had been discarded by physicians. Maybe, the patient delayed returning for follow-up care based on personal reasons. Again, the date the patient was first contacted to discuss follow-up procedures may have been noted within the medical chart but for the reasons just noted, this data may not be retrievable. It may be a good idea to obtain the reasons for the delay from the patient but it may be difficult to do so if these procedures occurred many years ago (as in our study). Further, patients may not understand the medical procedures we would wish to discuss with them. Lastly, maybe there was a delay in scheduling a colposcopy or other treatments due to a lack of operating rooms available or perhaps, due to a limited number of physicians trained to perform these procedures.

The duration of time between the date of the trigger Pap smear and the final diagnosis with cervical cancer corresponds to the diagnostic period depicted in Figure 5.1. This is the time window during which the follow-up of abnormal Pap smears and pre-invasive lesions were assessed. For subjects for whom we were able to determine the date of the first abnormal Pap smear, the mean and median duration of the diagnostic period were 305 days and 90 days, respectively, with a minimum duration of 1 day and maximum duration of 2122 days. Hence, for some subjects, the diagnostic period included one or more abnormal Pap smears and a follow-up event that occurred several months or years prior to final diagnosis and that upon

assessment was deemed to be unacceptable, or the management of a pre-invasive lesion may have been classified as not acceptable. These episodes of poor care may have impeded the prevention of neoplastic invasion or prevented the detection of cancer at an earlier stage. In some other cases, the incidence of unacceptable care occurred at such a brief time interval before diagnosis that this care would not have had any effect on the progression of an intra-epithelial lesion to invasion. However, it is legitimate to examine the processes of care for these subjects with very short diagnostic periods as the study objective was to assess the quality of care women received prior to their diagnosis with invasive cervical cancer. Further, despite the specific situation, each patient should receive appropriate care from her physician as per accepted clinical practice.

7.4 Strengths of Study

Despite the limitations discussed above, this study had several strengths. First, this was a population-based study; and hence, results have greater validity than a hospital or clinic- based study. Second, I am confident that complete cervical cancer case capture was attained for the specified geographic regions and time periods of interest as two sources of data were independently searched. Third, unlike the studies included within the meta-analysis, this study involved an in-depth search for process of care data using several data sources, each of which uniquely identified procedural data. This data collection also included an interview of cancer cases, which few other studies have done. This allowed us to obtain self-reported screening histories, demographic information, and allowed us to broaden and refine the search for further data. In addition, this study assessed the quality of screening history, like other studies presented in the meta-analysis did, but it went beyond this to assess two downstream types of care along the cancer care continuum; specifically, the follow-up of abnormal Pap smears and the management of pre-invasive lesions. Also, I separately considered both the procedural acceptability of the care and the timeliness of the follow-up. Further, quality assessment was based on a priori defined explicit medical review criteria, which renders the study results more reliable and reproducible. In addition, I was able to characterize the source population from which the cases arose, which allowed for the estimation of rate ratios through the calculation of

odds ratios. This also allowed me to examine the health services use of cases by using matched controls obtained from the RAMQ.

7.5 Conclusion

Despite the limitations of this study and the study being largely restricted to women with cancer, these results do show that there were many women whose processes of care prior to diagnosis with invasive cervical cancer were not acceptable, according to medical criteria, either in terms of the actual processes of care, the timing of the processes, or both. Although, it cannot be concluded that these poor instances of care played a role in the development of invasive cervical cancer, they may have possibly led to diagnosis at a later stage. At the very least, the inappropriate repetition of Pap tests, colposcopies, and other diagnostic procedures, and temporal delays in follow-up must have heightened the level of anxiety that these women already felt due to their abnormal test results.

In addition, the study results also highlight the potential responsibility that physicians, laboratories, the health care system, and women also, had in the occurrences of these instances of unacceptable care. Based on the study results, physician behavior regarding the appropriate recall of patients for screening and follow-up of abnormalities, the appropriate management procedures and timing of these procedures should be addressed in the form of continuing education. Perhaps, laboratory quality improvement initiatives may need to be instituted to examine and improve the turn-over time of cytology and pathology specimens. Delays in performing colposcopies or other surgical treatments of the cervix due to poor availability of surgical space at hospitals or poor availability of gynaecologists who are trained to perform these procedures should also be examined. Future research may be required to examine these issues in greater depth using a more general group of non-cancer study subjects in the context of a prospective study.

7.6 Recommendations from Study

1. This study has highlighted the importance of being screened on a regular basis, not simply being screened once in one's lifetime, in order to prevent the development of invasive cervical cancer or even for the earlier diagnosis of cancer. This leads to the recommendation for an organized population-based screening program in Quebec. This program should have the means to recall women on a regular basis for their Pap smears.
2. This leads to the following recommendation: the creation of a centralized computerized database. Besides being a repository for Pap smear results, this database would be necessary in order to invite women to initiate Pap screening and for the appropriate recall of women for subsequent Pap smears. It could also be used for surveillance and research purposes.
3. In addition, this computerized system could be used not only to recall women for screening but also to recall women in a timely fashion for colposcopies and the treatment of pre-invasive lesions.
4. Further, this computerized system could be used to specifically target those women who are less likely to be screened or more likely to have a longer wait-time for a colposcopy. For instance, immigrants and women who do not speak French or English.
5. More educating of physicians regarding the importance of Pap testing, the quick referral of women with abnormal Pap smears, and the guidelines surrounding the management of cervical cytologic abnormalities and pre-invasive lesions.
6. Further studies have to be conducted to ascertain the role that women, physicians, and the health care system play in the failures of processes of care.
7. With the upcoming changes to cervical cancer screening practices in Canada (see below for the rationale for such changes), it is imperative that screening organization be properly dimensioned to prevent unequal access to care and to be able to monitor loss of compliance. The new molecular technologies that will be used in cervical cancer screening will require longer screening intervals and record linkage to vaccination registries. This underscores the importance of a comprehensive database that links all components of the process of care.

8. THE RELEVANCE OF STUDY RESULTS IN THE CHANGING CERVICAL CANCER PREVENTION ENVIRONMENT

In Quebec during the time frame of this study, cervical cancer prevention was exclusively based on the traditional Pap smear. Since that time, other prevention techniques have come into existence. With the realization that cervical cancer is caused by an infection with a high-risk type of HPV (Walboomers et al., 1999; Franco et al., 1999), the realm of cervical cancer prevention has gradually changed and has continued to evolve. This development has led to changes to the established paradigm of secondary prevention of cervical cancer that was based on detection of a cytologic change in cervical cells via the Pap smear to one increasingly incorporating the detection of high-risk HPV DNA in cervical cellular samples and primary prevention via a prophylactic HPV vaccine.

HPV DNA testing has its roots in the research domain and subsequently, it has found utility in the clinical setting as a screening tool for cervical cancer. The two main commercially available HPV DNA protocols are the Hybrid Capture system and the Polymerase Chain Reaction protocol; the former is the test most widely used. HPV testing is most commonly used in two scenarios: First, in the triage of ASC-US Pap tests, which is a descriptor used to indicate that the cytologic results are ambiguous. Instead of repeating the Pap test in 3 to 6 month intervals and then performing a colposcopy if an abnormality is found, the patient is sent immediately for an HPV test after the initial ASC-US Pap test, which reduces the need for the repetition of Pap tests. This will avoid needlessly sending all women for multiple Pap tests and for more in-depth follow-up. It will also determine which women are at greatest risk of having a cervical abnormality. This test is recommended for women age 30 and over, as HPV infections become less transient with age rendering women more at risk for cancer (Castle et al., 2005). Second, HPV testing is also increasingly being considered for primary screening, which involves using the HPV tests alone or combined with cytology. Studies have shown that HPV testing has a much higher sensitivity, is more amenable to automation and being reproduced than cytologic screening but it has a lower specificity and is not indicated for women younger than 30 years of age (Mayrand et al., 2007; Ronco et al., 2008).

Only a small number of hospitals in Quebec offer HPV testing and it is used almost solely for the triage of ASC-US Pap tests. It is available at some private labs at a cost of about $100, which may be prohibitive for many women (Mayrand et al., 2009), especially those who are most likely to develop cervical cancer.

There are two HPV prophylactic vaccines licensed in Canada that both offer protection against HPV types 16 and 18, which are causally associated with 70% of cervical cancers (Munoz et al., 2004). These two vaccines have achieved almost 100% efficacy in the prevention of incident infections and precancerous lesions in clinical trials (Franco et al., 2008). In 2008, a school-based vaccination program was initiated that targeted girls in Grade 4 of elementary school and girls in Level 3 of high school, with vaccination in the clinical setting for females ages 18 or younger who were missed by the school program (Comité sur l'immunisation du Québec, 2008). As the HPV vaccine is preventative in nature, in order to achieve maximal reduction in cervical cancer incidence on a population-wide scale, it is most effective to target young females who are sexually naive and hence, most likely not yet exposed to these high-risk types of HPV. However, it is still imperative that screening with the Pap test continues for vaccinated females for several reasons: These vaccines are not useful against prevalent HPV infections. Further, the current vaccines only protect against 2 high-risk HPV types so vaccinated women are still at risk of cervical cancer caused by the other types. Moreover, there is the potential for the niche currently occupied by HPV types 16 and 18 to be filled by other less prevalent high-risk HPV types as the former types become less common. In addition, most vaccinated females are under the age of 18, so it will take up to 20 years until we realize the influence of vaccination on substantially reducing the incidence of cervical cancer (Bosch et al., 2008). In the future, screening algorithms will have to be modified for vaccinated women (Franco & Cuzick, 2008) but there is currently no evidence available to propose changes to current screening schedules (Mayrand et al., 2009).

These novel techniques for primary and secondary prevention of cervical cancer will eventually lead to major changes to the current screening schedules and follow-up algorithms in the future. However, in the present and near future, screening via the Pap test, with or without HPV testing, will continue to be the main tool in the prevention of cervical cancer amongst women of all ages

in Montreal, including among females who are vaccinated as teenagers. And, of course, detected cervical lesions will still need to be followed-up and treated in an appropriate and timely manner. Thus, it is imperative that the current system of cervical cancer prevention via the Pap test be overhauled to prevent these failures in care from occurring.

.

References

Agency for health care policy and research. Using clinical practice guidelines to evaluate quality of care. Volume 2: Methods. U.S. Department of Health and Human Services, Public Health Service. March 1995.

Anderson GH, Benedet JL, Le Riche JC, Matisic JP, Thompson JE. Invasive cancer of the cervix in British Columbia: A review of the demography and screening histories of 437 cases seen from 1985-1988. Obstet Gynecol 1992; 80: 1-4.

Andersson-Ellstrom A, Seidal T, Grannas M, Hagmar B. The pap-smear history of women with invasive cervical squamous carcinoma. A case-control study from Sweden. Acta Obstet Gynecol Scand 2000; 79: 221-226.

Ashton CM, Kuykendall DH, Johnson ML, and Wray JP. An empirical assessment of the validity of explicit and implicit process-of-care criteria for quality assessment. Med Care 1999; 37(8): 798-808.

Atkins K. HPV: from the cervical smear to the research bench to the court room. Clin Leadersh Manag Rev 2003; 17: 341-345.

Attwood ME, Woodman CB, Luesley D, Jordan JA. Previous cytology in patients with invasive carcinoma of the cervix. Acta Cytol 1985; 29: 108-110.

Baldauf JJ, Dreyfus M, Ritter J, Meyer P, Philippe E. Screening histories of incidence cases of cervical cancer and high grade SIL: A comparison. Acta Cytol 1997; 41: 1431-1438.

Baldi I, Vicari P, Di Cuonzo D, Zanetti R, Pagano E, Rosato R, Sacerdote C, Segnan N, Merletti F, Ciccone G. A high positive predictive value algorithm using hospital administrative data identified incident cancer cases. J Clin Epidemiol 2008; 61: 373-379.

Berkowitz RS, Ehrmann RL, Lavizzo-Mourey R, Knapp RC. Invasive cervical carcinoma in young women. Gynecol Oncol 1979; 8: 311-316.

Bjerre B, Johansson S. Invasive cervical cancer in a cytologically screened population. Acta Obstet Gynecol Scand 1983; 62: 569-574.

Booth B, Ludke RL, Fisher EM. Reliability of a utilization review instrument in a large field study. Am J Med Qual 1994; 9: 68-72.

Bos AB, Rebolj M, Habbema JD, van Ballegooijen M. Nonattendance is still the main limitation for the effectiveness of screening for cervical cancer in the Netherlands. Int J Cancer 2006; 119: 2372-2375.

Bosch FX, Castellsague X, de Sanjose S. HPV and cervical cancer: screening or vaccination? Br J Cancer 2008; 98: 15-21.

Bosch FX, Munoz N. The viral etiology of cervical cancer. Virus Res 2002; 89: 183-190.

Braunsberger K, Wybenga H, Gates R. A comparison of reliability between telephone and web-based surveys. J Bus Res 2007; 60: 758-764.

Brien SE, Dixon E, Ghali WA. Measuring and reporting on quality in health care: A framework and road map for improving care. J Surg Oncol 2009; 99: 462-466.

Brinkmann D, Gladman MA, Norman S, Lawton, FG. Why do women still develop cancer of the cervix despite the existence of a national screening programme? Eur J Obstet Gynecol Reprod Biol 2005; 119: 123-124.

Brisson J, Major D, Pelletier E. Evaluation of the completeness of the Fichier des Tumeurs du Québec. Institut National de Santé Publique Du Québec. 2004.

Brook R, McGlynn E, Cleary P. Quality of health care, part 2: measuring quality of care. N Engl J Med 1996; 335: 966-970.

Brown RK, Barker WH. Pap smear screening and invasive cervical cancer. J Fam Pract 1982; 15: 875-879.

Buetow SA, Roland M. Clinical governance: bridging the gap between managerial and clinical approached to quality of care. Quality in Health Care 1999; 8: 184-190.

Camirand J, Potvin L, Beland F. Pap recency: modeling women's characteristics and their patterns of medical care use. Prev Med 1995; 24: 259-269.

Canadian Cancer Society's Steering Committee: Canadian Cancer Statistics 2010. Toronto: Canadian Cancer Society, 2010.

Canadian Community Health Survey 2003. User Guide for the Public Use Microdata File, January 2005.

Carmichael JA, Jeffrey JF, Steele HD, Ohlke ID. The cytologic history of 245 patients developing invasive cervical carcinoma. Am J Obstet Gynecol 1984; 148: 685-690.

Castellsagué X, Muñoz N. Chapter 3: Cofactors in human papillomavirus carcinogenesis-role of parity, oral contraceptives, and tobacco smoking. J Natl Cancer Inst Monogr 2003; 31: 20-28.

Castle PE, Schiffman M, Herrero R, Hildesheim A, Rodriguez AC, Bratti MC, Sherman ME, Wacholder S, Tarone R, Burk RD. A prospective study of age trends in cervical human papillomavirus acquisition and persistence in Guanacaste, Costa Rica. J Infect Dis 2005; 191: 1808-1816.

Champagne R, Contandriopoulos AP, Pineault R. A health care evaluation framework. Health

Manage Forum 1986; 7: 57-65.

Chattopadhyay SK, Ebrahim SH, Tao G, McKenna M. Use of cervical cancer screening among insured women: the extent of missed opportunities. Health Policy 2005; 73: 194-201.

Chingang LC, Bischof U, Andall-Brereton G, Razum O. 'Have a Pap smear!'-doctors, their clients, and opportunistic cervical cancer screening. Int J STD AIDS 2005; 16: 233-236.

Choyce A, McAvoy B.R. Cervical cancer screening and registration—are they working? J Epidemiol Community Health 1990; 44: 52-54.

Ciatto S, Grazzini G, Cecchini S, Iossa A. Screening history of incident cases of invasive carcinoma of the cervix. Florence District 1988-1989. Tumori 1993; 79: 311-313.

Closs SJ, Cheater FM. Audit or research-what is the difference? J of Clinical Nursing 1996; 5: 249-56.

Cohen MM, Roos NP, MacWilliam L,Wajda A. Assessing physicians' compliance with guidelines for Papanicolaou testing. Med Care 1992; 30: 514-528.

Collège des médecins du Québec. L'Annuaire médical Québec 2003-2004. Québec, QC: Collège des médecins du Québec, 2003.

Comité sur l'immunisation du Québec. Prevention by vaccination of diseases attributable to the human papilloma virus in Québec. Summary, recommendations and synthesis of facts. Institut national de santé publique du Québec, 2008.

Contandriopoulos AP, Champagne F, Denis JL, Avargues MC. Evaluation in the health sector: concepts and methods. Rev Epidemiol Sante Publique 2000; 48: 517-539.

Cooper GS, Yuan Z, Stange KC, Dennis LK, Amini SB, Rimm AA. The sensitivity of medicare claims data for case ascertainment of six common cancers. Med Care 1999; 37: 436-444.

Cuzick J, Clavel C, Petry K.-U, Meijer C, Hoyer H, Ratnam S, Szarewski A, Birembaut P, Kulasingam S, Sasieni P, Iftner T. Overview of the European and North American studies on HPV testing in primary cervical cancer screening. Int J Cancer 2006; 119: 1095-1101.

Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Smith GD, Altman DG, eds. Systematic reviews in health care: meta-analysis in context. London, England: BMJ Publishing Group, 2001: 285-312.

Deschamps M, Band PR, Xu N. Le dépistage du cancer du col utérin : État de situation dans le région Montreal-Centre et recommandations pour le mis en œuvre d'un programme de dépistage. Régie régionale de la santé et des services sociaux de Montreal-Centre. Montréal, 2001.

Donabedian A. Evaluating the quality of medical care. Milbank Memorial Fund Quarterly Supplement 1966; 44: 166-206.

Donabedian A. The quality of medical care. Science 1978; 200: 856-8640.

Donabedian A. Explorations in quality assessment monitoring. Vol I: The definitions of quality and approaches to its assessment. Health Administration Press. Ann Arbor, 1980.

Donabedian A. Criteria, norms, and standards of quality: What do they mean? Am J Public Health 1981; 71: 409-412.

Donabedian A. The quality of care: how can it be assessed? JAMA 1988; 260: 1743-1748.

Downey L, Lafferty WE, Tao G, Irwin KL. Evaluating the quality of sexual health care provided to adolescents in medicaid managed care: a comparison of two data sources. Am J of Med Qual 2004; 19: 2-11.

Dunn JE, Schweitzer V. The relationship of cervical cytology to the incidence of invasive cervical cancer and mortality in Alameda County, California, 1960 to 1974. Am J Obstet Gynecol 1981; 139: 868-876.

Dunn JE, Crocker DW, Rube IF, Erickson CC, Coleman SA. Cervical cancer occurrence in Memphis and Shelby County, Tennessee, during 25 years of its cervical cytology screening program. Am J Obstet Gynecol 1984; 150: 861-864.

Eger RR, Peipert JF. Risk factors for noncompliance in a colposcopy clinic. J Reprod Med 1996; 41: 671-674.

Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002 cancer incidence. Mortality and prevalence worldwide. IARC CancerBase No. 5, version 2.0. Lyon: IARC Press, 2004.

Fleiss JL. Statistical methods for rates and proportions, Ed. 2 New York, NY: John Wiley, 1981.

Franco EL, Rohan TE, Villa LL. Epidemiologic evidence and human papillomavirus infection as a necessary cause of cervical cancer. J Natl Cancer Inst 1999; 91: 506-511.

Franco EL, Duarte-Franco E, Ferenczy A. Cervical cancer: epidemiology, prevention, and the role of human papillomavirus infection. CMAJ 2001; 164: 1017-1024.

Franco EL, Duarte-Franco E, Rohan TE. Evidence-based policy recommendations on cancer screening and prevention. Cancer Detect Prev 2002; 26: 350-361.

Franco EL, Ferenczy A. Chapter 16. Cervix. In: Franco EL, Rohan TE, eds. Cancer precursors: epidemiology, detection, and prevention. New York, NY: Springer-Verlag, 2002: 249-286.

Franco EL, Cuzick J. Cervical cancer screening following prophylactic human papillomavirus vaccination. Vaccine 2008; 26S: A16-23.

Freeman JL, Zhang D, Freeman DH, Goodwin JS. An approach to identifying incident breast cancer cases using Medicare claims data. J Clin Epidemiol 2000; 53: 605-614.

Fruchter RG, Boyce J, Hunt M. Missed opportunities for early diagnosis of cancer of the cervix. Am J Public Health 1980; 70: 418-420.

Galea S, Tracy M. Participation rates in epidemiologic studies. Ann Epidemiol 2007; 17: 643-653.

Garnick DW, Horgan CM, Chalk M. Performance measures for alcohol and other drug services. Alcohol Res Health 2006; 29: 19-26.

Gilbert EH, Lowenstein SR, Koziol-McLain J, Barta DC, Steiner J. Chart review in emergency medicine research: where are the methods? Ann Emerg Med 1996; 27: 305-308.

Glantz SA, Slinker BK. Primer of applied regression and analysis of variance, second edition. McGraw-Hill, Inc New York. 2001.

Goel V. Factors associated with cervical cancer screening: Results from the Ontario Health Survey. Can J Public Health 1994; 85: 125-127.

Gourde S. Une étude exhaustive sur le cancer du col utérin: La collaboration des médecins est essentielle. L'actualité médicale 2006; 10: 70.

Gustafsson L, Pontén J, Zack M, Adami HO. International incidence rates of invasive cervical cancer after introduction of cytological screening. Cancer Causes Control 1997; 8: 755-763.

Health Canada. Cervical cancer screening in Canada: 1998 surveillance report. Ottawa: Public Works and Government Services Canada, 2002.

Heineken PA, Charles G, Stimson DH, Wenell C, Stimson RH. The use of negative indexes of health to evaluate quality of care in a primary-care group practice. Med Care 1985; 23: 198-208.

Herbst AL. Chapter 28. Malignant diseases of the cervix. In: Mishell DR, Stenchever MA, Droegemueller W, Herbst AL, eds. Comprehensive Gynecology. St. Louis, Missouri: Mosby, 1997: 848.

Hogenmiller JR, Smith ML , Stephens LC, McIntosh DG. Patterns of Pap smear screening in women diagnosed with invasive cervical cancer. J Gynecol Surg 1994; 10: 247-253.

Holman CD, McCartney AJ, Hyde KL, Armstrong BK. Cervical cytology histories of 100 women with invasive carcinoma of the cervix. Med J Aust 1981; 2: 597-598.

Holowaty P, Miller AB, Rohan T, To T. Natural history of dysplasia of the uterine cervix. J Natl Cancer Inst 1999; 91: 252-258.

Hsia J, Kemper E, Kiefe C, Zapka J, Sofaer S, Pettinger M, Bowen D, Limacher M, Lillington L, Mason E. The importance of health insurance as a determinant of cancer screening: evidence

from the Women's Health Initiative. Prev Med 2000; 31: 261–270.

IARC. IARC handbooks of cancer prevention. Cervix cancer screening, vol. 10. Lyon, France: International Agency for Research on Cancer Press, 2005.

Ionescu-Ittu R, McCusker J, Ciampi A, Vadeboncoeur AM, Larouche D, Verdon J, Pineault R. Continuity of primary care and emergency department utilization among elderly people. CMAJ 2007; 177: 1362-1368.

Janerich DT, Hadjimichael O, Schwartz PE, Lowell DM, Meigs JW, Merino MJ, Flannery JT, Polednak AP. The screening histories of women with invasive cervical cancer, Connecticut. Am J Public Health 1995; 85: 791-794.

Jansson A, Gustafsson M, Wilander E. Efficiency of cytological screening for detection of cervical squamous carcinoma: a study in the county of Uppsala 1991-1994. Uppsala J Med Sci 1998; 103: 147-154.

Johnson TP, O'Rourke DP, Burris JE, Warnecke RB. An investigation of the effects of social desirability on the validity of self-reports of cancer screening behaviours. Med Care 2005; 43: 565-573.

Jordan JA, Singer A, Jones H, Sahafi MI (editors). The Cervix. Chapter 31. The management of cervical intraepithelial neoplasia (squamous). Shafi MI, Jordan JA, Singer A. pages 462-485. Blackwell Publishing Massachusetts, 2006.

Kalir T, Simsir A, Demopoulos HB, Demopoulos RI. Obstacles to the early detection of endocervical adenocarcinoma. Int J Gynecol Pathol 2005; 24: 399-403.

Kaner E, Haighton C, McAvoy B. So much post, so busy with practice—so, no time! A telephone survey of general practitioners' reasons for not participating in postal questionnaire surveys. Br J Gen Pract 1998; 48: 1067–1069.

Kazandjian VA. The contribution of epidemiology to CQI: a commentary. Int J Qual Health Care 1996; 8: 351-357.

Kellerman SE, Herold J. Physician response to surveys: a review of the literature. Am J Prev Med 2001; 20: 61-67.

Kenter GG, Schoonderwald EM, Koelma IA, Arentz N, Hermans J, Fleuren G. The cytological screening history of 469 patients with squamous cell carcinoma of the cervix uteri; does interval carcinoma exist? Acta Obstet Gynecol Scand 1996; 75: 400-403.

Khanna N, Phillips MD. Adherence to care plan in women with abnormal Papanicolaou smears: a review of barriers and interventions. J Am Board Fam Pract 2001; 14: 123-130.

Kiefe CI, Funkhouser E, Fouad MN, May DS. Chronic disease as a barrier to breast and cervical cancer screening. J Gen Intern Med 1998; 13: 357-365.

Kinney W, Sung HY, Kearney KA, Miller M, Sawaya G, Hiatt RA. Missed opportunities for cervical cancer screening of HMO members developing invasive cervical cancer (ICC). Gynecol Oncol 1998; 71: 428-430.

Kitchener HC, Castle PE, Cox JT. Chapter 7: Achievements and limitations of cervical cytology screening. Vaccine 2006; 24S3: S3/63-S3/70.

Kjaer SK, van den Brule AJC, Paull G, Svare EI, Sherman ME, Thomsen BL, Suntum M, Bock JE, Poll PA, Meijer CJ. Type specific persistence of high risk human papillomavirus (HPV) as indicator of high grade cervical squamous intraepithelial lesions in young women: population based prospective follow up study. BMJ 2002; 325: 572-578.

Kleinbaum DG, Kupper LL, Muller KE, Nizam A. Applied regression analysis and other multivariable methods. Toronto, Ontario: Duxbury Press, 1998.

Koss LG. The Papanicolaou test for cervical cancer detection. A triump and a tragedy. JAMA 1989; 261: 737-743.

Kreuger FA, Beerman H. The screening history of women with cervical cancer in the Rotterdam area. Eur J Epidemiol 2000; 16: 641-645.

Kristensen GB, Skyggebjerg KD, Holund B, Holm K, Hansen MK. Analysis of cervical smears obtained within three years of the diagnosis of invasive cervical cancer. Acta Cytol 1991; 35: 47-50.

Kuo TM, Benard VB, Berkman ND, Martin CK, Richardson LC. Timing of colposcopy after cervical cytologic abnormalities. Obstet Gynecol 2010; 115: 629-636.

Kupets R, Paszat L. Physician and patient factors associated with follow up of high grade dysplasias of the cervix: a population-based study. Gynecol Oncol 2011; 120: 63-67.

Laedtke TW, Dignan M. Compliance with therapy for cervical dysplasia among women of low socioeconomic status. Southern Medical Journal 1992; 85: 5-8.

Laffel G, Blumenthal D. The case for using industrial quality management science in health care organizations. JAMA 1989; 262: 2869-2873.

Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977; 33: 671-679.

Lee J, Parsons GF, Gentleman JF. Falling short of pap test guidelines. Health Reports 1998; 10: 9-19.

Lerman C, Hanjani P, Caputo C, Miller S, Delmoor E, Nolte S, Engstrom P. Telephone counseling improves adherence to colposcopy among lower-income minority women. J Clin Oncol 1992; 10: 330-333.

Leyden WA, Manos MM, Geiger AM, Weinmann S, Mouchawar J, Bischoff K, Yood MU, Gilbert J, Taplin SH. Cervical cancer in women with comprehensive health care access: attributable factors in the screening process. J Natl Cancer Inst 2005; 97: 675-683.

Lohr KN, ed. Medicare: a strategy for quality assurance. Washington, D.C.: National Academy Press, 1990.

Lozano R. Comparison of computer-assisted and manual screening of cervical cytology. Gynecol Oncol 2007; 104: 134-138.

Luck J, Peabody JW, Dresselhaus TR, Lee M, Glassman P. How well does chart abstraction measure quality? A prospective comparison of standardized patients with the medical record. Am J Med 2000; 108: 642-649.

Lurie N, Slater J, McGovern P, Ekstrum J, Quam L, Margolis K. Preventive care for women. Does the sex of the physician matter? N Engl J Med 1993; 329: 478-482.

Mandelblatt JS, Yabroff KR, Kerner JF. Equitable access to cancer services: a review of barriers to quality care. Cancer 1999; 86: 2378-2390.

Mant J. Process versus outcome indicators in the assessment of quality of care. Int journal for quality in health care 2001; 13: 475-480.

Marcus AC, Crane LA. A review of cervical cancer screening intervention research: implications for public health programs and future research. Prev Med 1998; 27: 13-31.

Massad S, Meyer PM. Predicting compliance with follow-up recommendations after colposcopy among indigent urban women. Obstet Gynecol 1999; 94: 71-76.

Mayrand MH, Duarte-Franco E, Rodrigues I, Walter SD, Hanley J, Ferenczy A, Ratnam S, Coutlée F, Franco EL. Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. N Engl J Med 2007; 357: 1579-1588.

Mayrand MH, Goggin P. Recommendations on optimizing cervical cancer screening in Québec. Institut National de Santé Publique Du Québec, January 2009.

McCrory DC, Matchar DB, Bastian L, Datta S, Hasselblad V, Hickey J, et al. *Evaluation of cervical cytology*. Evidence report/technology assessment no 5; AHCPR publ no 99-E010. Rockville, MD: Agency for Health Care Policy and Research, 1999.

McKee MD, Lurio J, Marantz P, Burton W, Mulvihill M. Barriers to follow-up of abnormal Papanicolaou smears in an urban community health centre. Arch Fam Med 1999; 8: 129-134.

McPhee SJ, Nguyen TT, Shema SJ, Nguyen B, Somkin C, Vo P, Pasick R. Validation of recall of breast and cervical cancer screening by women in an ethnically diverse population. Prev Med 2002; 35: 463-473.

Michielutte R, Diseker RA, Young L, May WJ. Noncompliance in screening follow-up among family planning clinic patients with cervical dysplasia. Prev Med 1985; 14: 248-257.

Miller AB. Failures of cervical cancer screening. Am J Public Health 1995; 85: 761-762.

Miller AB, Anderson G, Brisson J, Laidlaw J, Le Pitre N, Malcolmson P, Mirwaldt P, Stuart G, Sullivan W. Report of a National Workshop on Screening for Cancer of the Cervix. CMAJ 1991; 145: 1301-1325.

Miller SM, Siejak KK, Schroeder CM, Lerman C, Hernandez E, Helm CW. Enhancing adherence following abnormal Pap smears among low-income minority women: a preventive telephone counseling strategy. J Natl Cancer Inst 1997; 89: 703-708.

Mobius G. Cytological early detection of cervical carcinoma: possibilities and limitations: analysis of failures. J Cancer Res Clin Oncol 1993; 119: 513-521.

Morrison BJ. Screening for cervical cancer. In: Canadian Task Force on the Periodic Health Examination. Canadian guide to clinical preventive health care. Ottawa: Health Canada, 1994:870-881.

Munoz N, Bosch FX, Castellsague X, Diaz M, de Sanjose S, Hammouda D, Shah KV, Meijer CJ. Against which human papillomavirus types shall we vaccinate and screen ? The international perspective. Int J Cancer 2004; 111: 278-285.

Mushlin AI, Appel FA, Barr DM. Quality assurance in primary care: a strategy based on outcome assessment. J of Community Health 1978; 3: 292-305.

Nanda K, McCrory DC, Myers ER, Bastian LA, Hasselblad V, Hickey JD, Matchar DB. Accuracy of the papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review. Ann Intern Med 2000; 132: 810-819.

Nasca PC, Ellish N, Caputo TA, Saboda K, Metzer B. An epidemiologic study of Pap screening histories in women with invasive carcinomas of the uterine cervix. NY State J Med 1991; 91: 152-156.

National Cancer Institute Workshop. The 1988 Bethesda System for reporting cervical/vaginal cytologic diagnoses. JAMA 1989; 262: 931-934.

National Cancer Institute Workshop. The Bethesda System for reporting cervical/vaginal cytologic diagnoses: revised after the second National Cancer Institute Workshop, April 29-30, 1991. Acta Cytol 1993; 37: 115-124.

Nattinger AB, Laud PW, Barjorunaite R, Sparapani RA, Freeman JL. An algorithm for the use of Medicare claims data to identify women with incident breast cancer. Health Serv Res 2004; 39: 1733-1749.

Nelson k, Geiger AM, Mangione CM. Effect of health beliefs on delays in care for abnormal cervical cytology in a multi-ethnic population. J Gen Intern Med 2002; 17: 709-716.

Newell S, Girgis A, Sanson-Fisher R, Ireland M. Accuracy of patients' recall of pap and cholesterol screening. Am J Public Health 2000; 90: 1431-1435.

Nygard JF, Nygard M, Skare GB, Thoresen SO. Screening histories of women with CIN 2/3 compared with women diagnosed with invasive cervical cancer: a retrospective analysis of the Norwegian Coordinated Cervical Cancer Screening Program. Cancer Causes Control 2005; 16: 463-474.

Olesen F. Prophylactic cytological investigation for cervical cancer in relation to stage at diagnosis: a study of 420 women in Denmark. J R Coll Gen Pract 1988; 38: 356-359.

O'Malley AS, Forrest CB, Mandelblatt J. Adherence of low-income women to cancer screening recommendations. J Gen Intern Med 2002; 17: 144-154.

Papanicolaou GN. Atlas of exfoliative cytology. New York, NY: The Commonwealth Fund, 1954.

Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB, eds. Cancer incidence in five continents, vol. VIII, No. 155. Lyon, France: IARC Press, 2002.

Parkin DM, Bray F. Chapter 2: The burden of HPV-related cancers. Vaccine 2006; 24S3: S3/11-S3/25.

Paskett EC, Carter WB, Chu J, White E. Compliance behaviour in women with abnormal Pap smears: developing and testing a decision model. Med Care 1990; 28: 643-656.

Paterson MEL, Peel KR, Joslin CAF. Cervical smear histories of 500 women with invasive cervical cancer in Yorkshire. Br Med J 1984; 289: 896-898.

Pemberton AG, Margolis KL, Mink PJ, McGovern PG, Lurie N. Women's preferences for specialists who provide cancer screening and general medical care. J Gen Intern Med 1998; 13: 624-626.

Penberthy L, McClish D, Pugh A, Smith W, Manning C, Retchin S. Using hospital discharge files to enhance cancer surveillance. Am J Epidemiol 2003; 158: 27-34.

Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, Mantel N, McPherson K, Peto J, Smith PG. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Br J Cancer 1977; 35: 1-39.

Ratima K, Paul C, Skegg DCG. Cervical smear histories of Maori women developing invasive cervical cancer. NZ Med J 1993; 106: 519-521.

Rauscher GH, Johnson TP, Cho YI, Walk JA. Accuracy of self-reported cancer screening histories: a meta-analysis. Cancer Epidemiol Biomarkers Prev 2008; 17: 748-757.

Reagan JW, Hamonic MJ. The cellular pathology in carcinoma in situ: a cytohistolopathological correlation. Cancer 1956; 9: 385-402.

Renwick PA. Quality assurance in health care: The theoretical context. Int J of Health Care Quality Assurance 1992; 5: 29-34.

Richart RM. Natural history of cervical intraepithelial neoplasia. Clin Obstet Gynecol 1968; 5: 748-784.

Richart RM. A modified terminology for cervical intraepithelial neoplasia. Obstet Gynecol 1990; 75: 131-133.

Roberts AW, Lane DA, Buntine D, Wright RG. Invasive carcinoma of the cervix in young women. Med J Aust 1985; 143: 333-335.

Ronco G, Giorgi-Rossi P, Carozzi F, Confortini M, Dalla PP, Del MA, Gillio-Tos A, Minucci D, Naldoni C, Rizzolo R, Schincaglia P, Volante R, Zappa M, Zorzi M, Cuzick J, Segnan N. Results at recruitment from a randomized controlled trial comparing human papillomavirus testing alone with conventional cytology as the primary cervical cancer screening test. J Natl Cancer Inst 2008; 100: 492-501.

Rubin HR, Rogers WH, Kahn KL, Rubenstein LV, Brook RH. Watching the doctor-watchers: how well do peer review organization methods detect hospital care quality problems. JAMA 1992; 267: 2349-2354.

Russell J, Crothers BA, Kaplan KJ, Zahn CM. Current cervical screening technology considerations: liquid-based cytology and automated screening. Clin Obstet Gynecol 2005; 48: 108-119.

Rutstein DD, Berenberg W, Chalmers TC, Child CG, Fishman AP, Perrin EB. Measuring the quality of medical care: a clinical method. N Engl J Med 1976; 294: 582-588.

Rylander E. Cervical cancer in women belonging to a cytologically screened population. Acta Obstet Gynecol Scand 1976; 55: 361-366.

Sasieni PD, Cuzick J, Lynch-Farmery E. Estimating the efficacy of screening of auditing smear histories of women with and without cervical cancer. The national co-ordinating network for cervical screening working group. Br J Cancer 1996; 73: 1001-1005.

Scheiden R, Wagaener C, Knolle U, Dippel W, Capesius C. Atypical glandular cells in conventional cervical smears: incidence and follow-up. BMC Cancer 2004; 19: 37.

Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. Lancet 2007; 370: 890-907.

Schlecht NF, Kulaga S, Robitaille J, Ferreira S, Santos M, Miyamura RA, Duarte-Franco E, Rohan TE, Ferenczy A, Villa LL, Franco EL. Persistent human papillomavirus infection as a predictor of cervical intraepithelial neoplasia. JAMA 2001; 286: 3106-3114.

Sellors JW, Sankaranarayanan R. Colposcopy and treatment of cervical intraepithelial neoplasia: a beginner's manual. Lyon, France: International Agency for Research on Cancer, 2003.

Siahpush M, Singh GK. Sociodemographic predictors of pap test receipt, currency and knowledge among Australian women. Prev Med 2002; 35: 362-368.

Skinner KM, Miller DR, Lincoln E, Lee A, Kazis LE. Concordance between respondent self-reports and medical records for chronic conditions: Experience from the veterans health study. J Ambul Care Manage 2005; 28: 102-110.

SOGC clinical practice guidelines. Management of the abnormal papanicolaou smear. Policy Statement No. 70, 1998.

SOGC clinical practice guidelines. Guidelines on adeoncarcinoma in situ of the cervix: clinical features and review of management. Policy Statement No. 77, 1999.

Solomon D. The 1988 bethesda system for reporting cervical/vaginal cytologic diagnoses: developed and approved at a National Cancer Institute workshop, Bethesda MD, U.S.A., December 12-13, 1988. J Reprod Med 1989; 34: 779-785.

Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, Prey M, Raab S, Sherman M, Wilbur D, Wright T Jr, Young N. The 2001 bethesda system: terminology for reporting results of cervical cytology. JAMA 2002; 287: 2114-2119.

Spence AR, Goggin P, Franco EL. Process of care failures in invasive cervical cancer: systematic review and meta-analysis. Prev Med 2007; 45: 93-106.

Steinwachs DM, Weiner JP, Shapiro S. Management information systems and quality, in Providing Quality Care: The Challenge to Clinicians, eds N. Goldfield and DB Nash. Philadelphia: American College of Physicians, 1990: 160-182.

Stenkvist B, Söderström J. Reasons for cervical cancer despite extensive screening. J Med Screen 1996; 3: 204-207.

Stewart DE, Buchegger PM, Lickrish GM, Sierra S. The effect of educational brochures on follow-up compliance in women with abnormal Papanicolaou smears. Obstet Gynecol 1994; 83: 583-585.

Stoler MH, Schiffman M, Atypical squamous cells of undetermined significance low-grade squamous intraepithelial lesion triage study (ALTS) group. Interobserver reproducibility of cervical cytologic and histologic interpretations: realistic estimates from the ASCUS-LSIL triage study. JAMA 2001; 285: 1500-1505.

Stuart GCE, McGregor SE, Duggan MA, Nation JG. Review of the screening history of Alberta women with invasive cervical cancer. CMAJ 1997; 157: 513-519.

Sung H-Y, Kearney KA, Miller M, Kinney W, Sawaya GF, Hiatt RA. Papanicolaou smear history and diagnosis of invasive cervical carcinoma among members of a large prepaid health plan. Cancer 2000; 88: 2283-2289.

Sweet L, Tesch M, Dryer D, McAleer C. A review of the cervical cytology screening history of PEI women diagnosed with carcinoma of the cervix, 1981-1986. Chron Dis Can 1991; 12: 1-3.

The American Association for Public Opinion Research. 2011. Standard Definitions: Final Dispositions of Case Codes and Outcome Rates for Surveys. 7th edition. AAPOR.

Thorpe C, Ryan B, McLean SL, Burt A, Stewart M, Brown JB, Reid GJ, Harris S. How to obtain excellent response rates when surveying physicians. Fam Pract 2009; 26: 65-68.

Tiltman AJ. The pathology of cervical tumours. Best Pract Res Clin Obstet Gynaecol 2005; 19: 485-500.

Tsai J, Bond G. A comparison of electronic records to paper records in mental health centers. Int J Qual Health Care 2008; 20: 136-143.

Turner MJ, Keane DP, Flannelly GM, Lenehan PM, Murphy JF, Foley ME. Cytological screening history of patients with early invasive cervical cancer. Ir Med J 1990; 83: 61-62.

van Wijngaarden WJ, Duncan ID, Hussain KA. Screening for cervical neoplasia in Dundee and Angus: 10 years on. Br J Obstet Gynaecol 1995; 102: 137-142.

Wain GV, Farnsworth A, Hacker NF. The papanicolaou smear histories of 237 patients with cervical cancer. Med J Aust 1992; 157: 14-16.

Walboomers JMM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, Snijders PJ, Peto J, Meijer CJ, Munoz N. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 1999; 189: 9-12.

Walker EM, Hare MJ, Cooper P. A retrospective review of cervical cytology in women developing invasive squamous cell carcinoma. Br J Obstet Gynaecol 1983; 90: 1087-1091.

Williamson JW. Evaluating quality of patient care. A strategy relating outcome and process assessment. JAMA 1971; 218: 564-569.

Wilson A, Leeming A. Cervical cytology screening: a comparison of two call systems. Br Med J 1987; 295: 181-182.

Womack C, Warren AY. Achievable laboratory standards; a review of cytology of 99 women with cervical cancer. Cytopathology 1998; 9: 171-177.

Woodward CA, Chambers LW. Guide to questionnaire construction and question writing. Ottawa: Canadian Public Health Association; 1991.

Wright TC, Cox JT, Massad LS, Carlson J, Twiggs LB, Wilkinson EJ. 2001 consensus guidelines for the management of women with cervical intraepithelial neoplasia. Am J Obstet Gynecol 2003; 189: 295-304.

Wright TC. Cervical cancer screening in the 21st century: Is it time to retire the pap smear? Clin Obstet Gynecol 2007; 50: 313-323.

Yabroff KR, Kerner JF, Mandelblatt JS. Effectiveness of interventions to improve follow-up after abnormal cervical cancer screening. Prev Med 2000; 31: 429-439.

Young JL, Roffers SD, Ries LAG, Fritz AG, Hurlbut AA (eds). SEER Summary Staging Manual-2000: Codes and Coding Instructions, National Cancer Institute, NIH Pub. No. 01-4969, Bethesda, MD, 2001.

Zapka JG, Taplin SH, Solberg LI, Manos MM. A framework for improving the quality of cancer care: the case of breast and cervical cancer screening. Cancer Epidemiol Biomarkers Prev 2003; 12: 4-13.

PREAMBLE TO APPENDICES

The documents included as Appendices, specifically, questionnaires, introductory letters, interview scripts, and consent forms, all exist in both English and French versions. In the interest of brevity, only the English versions of these documents are included here. Further, the ethics boards at each of the hospitals listed in Table 5.1 had slightly different requirements for the study subject consent forms. Further, there were separate consent forms for subjects and next of kin. Again, in order to respect space limitations, I have only included the basic consent form upon which all other forms were based.

APPENDIX 1

Cervical cytopathology nomenclature

Correspondence among reporting terminologies for cervical cytology and pathology reports

Papanicolaou class system [Papanicolaou, 1954]	**Dysplasia terminology** [Reagan et al., 1956]	**Original CIN terminology** [Richart, 1968]	**Modified CIN terminology** [Richart, 1990]	**Bethesda system (SIL terminology)** [Solomon, 1989]	**Bethesda system (SIL terminology)** [Solomon, 2002]
Class I	Normal	Normal	Normal	Within normal limits	Negative for intraepithelial lesion or malignancy
Class II	Atypia (multiple qualifiers)			Benign cellular changes (infection or repair)	
Class II	Atypia (epithelial cell abnormalities)			ASCUS with qualifier *	ASC-US or ASC-H
				AGUS with qualifier *	Atypical glandular cells**
Class II or III		Koilocytotic atypia, flat condyloma, without epithelial changes	Low grade CIN	LSIL	
Class III	Mild dysplasia or dyskaryosis	CIN grade 1	Low grade CIN	LSIL	LSIL
Class III or IV	Moderate dysplasia or dyskaryosis	CIN grade 2	High grade CIN	HSIL	HSIL
Class IV	Severe dysplasia or dyskaryosis	CIN grade 3	High grade CIN	HSIL	HSIL
Class IV or V	Carcinoma in situ	CIN grade 3	High grade CIN	HSIL	HSIL
Class V	Invasive carcinoma	Invasive carcinoma	Invasive carcinoma	Invasive carcinoma	Invasive carcinoma

Abbreviations: CIN, cervical intraepithelial neoplasia; ASCUS, atypical squamous cells of undetermined significance; AGCUS, atypical glandular cells of undetermined significance; LSIL, low grade squamous intraepithelial lesion; HSIL, high grade squamous intraepithelial lesion.

* whether a reactive or premalignant/malignant process is favoured.
**specify as endocervical, endometrial, or not otherwise specified.

Note: A revised Bethesda classification became effective in May 2001 with minor changes to the above scheme that only affected the ASCUS and benign cellular changes categories.

APPENDIX 2

Medical chart abstraction form

Study Number

Montreal Invasive Cervical Cancer Study

Chart Abstraction Form – Confidential Information Sheet

VERY IMPORTANT:
This sheet contains sensitive information; keep it secure at all times while retrieving the information. After all information is entered, file this page separately from the rest of the audit form in the locked filing cabinet, which is exclusively used for the Cervical Cancer Screening Audit Study.

Patient's Maiden Name: _____ **First Name**:_____

Married Name:_____

RAMQ#:

Patient Address: _____ Tel no.: (450) or (514) _____

_____

Other contacts:

Name:_____ Relationship: _____Tel no.: (450) or (514)_____

Name:_____ Relationship: _____Tel no.: (450) or (514)_____

Has patient lived in Mtl/Laval/South Shore at least 5 years prior to diagnosis? ☐Yes ☐No ☐DNK

Patient Date of Birth:_____/_____/_____ Origin: _____
DD MM YY

Occupation: _____ Marital status: _____

Doctors	Name	Specialty	Office location/address
Referring (1)			
Referring (2)			
Treating (1)			
Treating (2)			

AUDIT HISTORY

Date	Hospital	Dept	Chart #	Auditor

Chronological Screening and Treatment History (Prior to diagnosis with Invasive Cervical Cancer)

Date DD/MM/YY	**Procedures Performed** (Include Revisions) 1) Pap Test (slide #) * 2) HPV Test ** 3) Colposcopy/EUA 4) Endocervical Currettage 5) Biopsy 6)Treatment of precursor lesion (**Table 1**)	**Hospital Name** (For Pap test, include lab# if done at a private lab)	**Name of Physician who Performed Procedure**	**If Pap test, was the smear satisfactory or satisfactory but limited?** Yes or No. If NOT satisfactory or satisfactory but limited, give reason(s).	**Results** For Pap tests-see **Table 2**. For Colposcopy , note findings from visual inspection Even if colposcopy **NOT** done, note findings from visual inspection. If treatment was given for pre-invasive lesions, note whether margins were positive or negative. and give detail.	**Recommendations** (Note if recommendations were not followed) Include specifics and dates.

Attach additional pages if needed.

Descriptors for Page 2 (Do NOT write on this page)

* Pap Test:

- If a liquid-based Pap test (thin-prep) was done, please indicate this in the table.
  - Indicate slide #

** HPV Test:

- If HPV testing was done, please indicate if the results were positive or negative for the presence of HPV virus.
- If HPV virus was found, was it high-risk (oncogenic) or low-risk (non-oncogenic) HPV or not specified.

Table 1: Treatment for Pre-invasive Lesions

Cryotherapy
LEEP Cone or LLETZ
Cold Knife Cone ("Cone")
Trachelectomy
Hysterectomy : simple or radical

Table 2: Results of Pap test or Biopsy

- WNL (within normal limits)
- BCC (benign cellular changes)
- ASCUS,specify whether reactive or premalignant/malignant process is favoured_____
- AGUS, specify qualifiers _____
- ASC-US
- ASC-H
- Atypical glandular cells (AGC), specify as endocervical, endometrial, or not otherwise specified_____
- CIN 1
- LSIL
- CIN 2
- CIN 3
- HSIL (includes carcinoma in situ, CIN 2, CIN 3)
- Endocervical adenocarcinoma in situ (AIS)
- Invasive squamous carcinoma
- Invasive adenocarcinoma
- Invasive adenosquamous carcinoma
- Other: specify_____

The Invasive Cervical Cancer

1) Year the invasive cervical cancer was diagnosed: _____

2) Tumour Stage (Please Check one. The biopsy is the gold-standard)

√	TNM	FIGO	DESCRIPTION
	Tis	0	Carcinoma in-situ
	T1	1	Invasive cancer confined to the cervix.
	T1a	IA	A very small amount of tumour can be seen under a microscope.
	T1a1	**IA1**	Tumour has penetrated less than 3mm deep and less than 7mm wide
	T1a2	**IA2**	Tumour has penetrated 3 to 5 mm deep and less than 7 mm wide.
	T1b	IB	Includes tumours that can be seen without a microscope. Also includes tumours that cannot be seen without a microscope but are more than 7mm wide and have penetrated more than 5 mm.
	T1b1	**IB1**	Tumour is no bigger than 4 cm
	T1b2	**IB2**	Tumour is bigger than 4 cm. Tumour has spread to organs and tissues outside the cervix but is still limited to the pelvic area.
	T2	II	Invasive cancer with tumour extending beyond the Cervix and/or the upper two-thirds of the vagina, but not beyond the pelvic wall.
	T2a	**IIA**	Tumour has spread beyond the cervix to the upper part of the vagina.
	T2b	**IIB**	Tumour has spread to the tissue next to the cervix.
	T3	III	Invasive cancer with tumour spreading to the lower third of the vagina or onto the pelvic wall
	T3a	**IIIA**	Tumour has spread to the lower third of the vagina.
	T3b	**IIIB**	Tumour has spread to the pelvic wall and/or blocks the flow of urine From the kidneys to the bladder
	T4	IV	Invasive cancer with tumour spreading to other parts of the body.
	T4a	**IVA**	Tumour has spread to organs located near the cervix, such as the bladder or rectum.
	T4b	**IVB**	Tumour has spread to parts of the body far from the cervix.

a) Source of staging (e.g. nursing notes, tumour board report, biopsy, MRI etc):

_____

b) Describe the tumour (width and depth): _____

_____

c) If an MRI was done, was hydronephrosis found? □Yes □No □MRI not done

3) Lymph Node Status (Check one)

	Regional lymph nodes cannot be assessed (**if NO hysterectomy**)
	Hysterectomy performed but lymph nodes not assessed
	No regional lymph node metastasis (negative nodes)
	Regional lymph node metastasis (positive nodes).

4) Histology of the Invasive Cancer (Check one)

	Invasive squamous carcinoma
	Invasive adenocarcinoma
	Invasive adenosquamous carcinoma
	Other: specify_____

5) Treatment of Invasive Cancer (Check all that apply)

	Treatment	**Year**
	Radiation	
	Chemotherapy	
	Hysterectomy: **specify as simple or radical**	
	Cold Knife Cone	

If Patient did **NOT** receive treatment explain: _____

_____

6) Did patient have any symptoms of invasive cervical cancer?

☐ **Yes** (check all that apply) ☐ **No** (proceed to next question)

↓ **None noted in chart** (proceed to next question)

☐Abnormal vaginal bleeding, specify:
- ☐Between menstrual periods Duration/Date:_____
- ☐After intercourse Duration/Date:_____
- ☐Post-menopausal Duration/Date:_____

☐ Heavy menses Duration/Date:_____
☐ Vaginal discharge Duration/Date:_____
☐ Loss of appetite Duration/Date:_____
☐ Weight Loss Duration/Date:_____
☐ Fatigue Duration/Date:_____
☐ Pain (Back, pelvic, leg (specify)) Duration/Date:_____
☐ Other_____

7) When the pt was finally diagnosed with <u>invasive</u> cancer, was that definitive appointment for-

☐ **Routine preventive screening** ☐**Specifically because of her symptoms.**

☐ **Do not know**

8) Did patient know she was diagnosed with cervical cancer?

☐ **Yes** ☐ **No**, explain_____ ☐ **Do not know**

9) Co-Morbidities/Pre-existing conditions (i.e. things that may alter treatment or influence a cases tendency to go for screening and/or follow-up after an abnormal Pap.)

☐ History of cancer in family, specify:

_____

_____

☐ Smoking

☐ Obesity

☐ Pregnancy (List dates if within 5 years prior to diagnosis:

_____

_____

☐Other (e.g. HIV, herpes simplex virus, chlamydia, other STD, other immune suppressing conditions (such as, transplantation))

Specify:_____

☐ **None noted in chart**

10) As far as is noted in the chart, is this subject:

☐ **Alive** ⟶ As of this date:

_____/_____/_____
DD MM YR

☐ **Dead** ⟶ Date of death:

_____/_____/_____
DD MM YY

↓

Cause: ☐ Cervical cancer or ☐ Other _____
(specify)

After reviewing this chart at a specific hospital, please note other information that must be obtained about this patient (e.g. information about Pap tests done at other hospitals). This will help ensure that complete screening, diagnostic and follow-up treatment is obtained for each subject. Also, note any other information that may help explain the screening and treatment history of this patient.

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

Office Use Only:

☐ All data from this form has been entered in the database. Initials:_____

☐ Study Number has been entered on the top of each page.

☐ The confidential information sheet has been filed separately.

☐ The "next steps" for data collection for this patient has been noted in her file.

Version July 19, 2004

APPENDIX 3

Results of medical chart abstractor reliability measurements

After the initial training session at the beginning of the chart abstraction phase of the study, abstractor #1 and abstractor #2 independently reviewed data from 11 medical charts at one hospital. Table 1 shows the inter-rater percent agreements and the kappa statistics for the variables listed in section 5.9.2. Note that an early version of the chart abstraction from was used when reviewing these medical charts and it did not request for retrieval of data for the following variables: histology of the final cancer, node status, and the nature of the definitive appointment that eventually led to diagnosis.

Table 1. Measurement of inter-rater reliability for Abstractors #1 and #2

Variable	Agreement (%)	Kappa statistic
# Pap smears	81.8	0.70
# cervical biopsies	90.9	0.83
# colposcopies	72.7	0.35
Stage of cancer	54.6	0.39
Presence of symptoms of cervical cancer (Yes/none found)	72.7	0.42
Presence of co-morbidities (Yes/none found)	100.0	1.00

After the calculations were done, I met with the two abstractors. This meeting involved actually reviewing the 11 medical charts as a group while we discussed the disagreements in the collected data in order to determine their sources.

Perfect agreement was found for the presence of co-morbidities. We realized that the very low kappa statistic found for staging was due to the fact that abstractor #2 was using the available data to determine the staging on his own. We decided that it was best to take note of the width and depth of the tumour regardless of whether a stage is given and we would determine staging later if it was not found within the chart. Also, some procedures performed after the subject received treatment for the invasive cervical cancer had been abstracted, which may account for the less than perfect agreement for the number of Pap smears and the number of biopsies. A fair level agreement for the number of colposcopy examinations was also found. This was due to the fact that reports of colposcopies found in charts were often photocopies of the originals and were illegible. The performance of a colposcopy may have been noted within doctor's notes or

sometimes within the lab report of a Pap test that was done at the same visit. Abstractors were cautioned about the importance of carefully reviewing each page within charts. The moderate level of agreement for the presence of cervical cancer symptoms was due to the fact that this early version of the abstraction form did not specifically list the symptoms we were looking for.

The abstraction tool was further refined based both on the results of this initial reliability assessment and also based on suggestions from the chart abstractors on ways of improving the ease of use of the tool.

Prior to the continuation of the chart review process, a second training session was held. This training session involved all three abstractors reviewing 10 hospital medical charts together (5 charts at each of 2 hospitals) and discussing any issues and questions about the process. A revised version of the abstraction form was used for this review. All abstractors then independently reviewed 30 charts each (15 at each of 2 hospitals). It should be noted that for this activity we all used an even more recently edited and refined version of the abstraction form compared to that used for the review above. Tables 2 to 4 display the inter-rater reliabilities for each pair of abstractors.

Table 2. Measurement of inter-rater reliability for Abstractors #1 and #2

Variable	Agreement (%)	Kappa statistic
# Pap smears	100	1.00
# cervical biopsies	96.7	0.95
# colposcopies	93.3	0.71
Stage of cancer	90.0	0.89
Histology of cancer	93.3	0.89
Node status	96.7	0.90
Present of symptoms of cervical cancer (Yes/none found)	96.7	0.92
Presence of co-morbidities (Yes/none found)	83.3	0.66
Description of definitive appointment that led to diagnosis	93.3	0.88

Table 3. Measurement of inter-rater reliability for Abstractors #1 and #3

Variable	Agreement (%)	Kappa statistic
# Pap smears	96.7	0.90
# cervical biopsies	96.7	0.95
# colposcopies	93.3	0.71
Stage of cancer	86.7	0.85
Histology of cancer	96.7	0.95
Node status	93.3	0.82
Present of symptoms of cervical cancer (Yes/none found)	93.3	0.84
Presence of co-morbidities (Yes/none found)	90.0	0.74
Description of definitive appointment that led to diagnosis	86.7	0.76

Table 4. Measurement of inter-rater reliability for Abstractors #2 and #3

Variable	Agreement (%)	Kappa statistic
# Pap smears	96.7	0.90
# cervical biopsies	93.3	0.90
# colposcopies	100.0	1.00
Stage of cancer	90.0	0.88
Histology of cancer	96.7	0.94
Node status	93.3	0.87
Present of symptoms of cervical cancer (Yes/none found)	96.7	0.92
Presence of co-morbidities (Yes/none found)	73.3	0.44
Description of definitive appointment that led to diagnosis	93.3	0.87

In almost all cases the kappa statistics were greater than 0.80 and deemed to have almost perfect agreement. One exception was the stage of cancer. The poor kappa for 'stage' is again a result of one abstractor looking at the evidence and if needed, refining the stage noted in the chart. For instance, the chart may indicate that the subject had stage IB invasive cervical cancer. This abstractor may decide that it was, in fact, stage IB1 cancer. This is not a negative thing but it meant that we did not enter the same information in the audit form. In terms of 'diagnostic

trigger', there was some confusion as to the category "specifically because of her symptoms." A subject may have had symptoms prior to being diagnosed with invasive cervical cancer but the definitive appointment that led to the final diagnosis may not have been due to these symptoms. The agreement for the 'presence of co-morbidities' was deemed to have from moderate to substantial agreement depending on the abstractor pairs reviewed. In terms of the 'number of colposcopies', like before, I again stressed the importance of meticulously searching the charts for any indications of colposcopy examinations, and for all the other variables of interest.

In 3 months time, all 3 abstractors re-reviewed charts that they had previously independently reviewed. For each abstractor, intra-rater reliability was measured for each variable between the first review and the second review using percentage agreement and kappa statistics. The results are displayed in tables 5 to 7.

Table 5. Measurement of intra-rater reliability for Abstractor #1 (N=20 charts)

Variable	Agreement (%)	Kappa statistic
# Pap smears	84.2	0.72
# cervical biopsies	89.7	0.78
# colposcopies	89.5	0.61
Stage of cancer	94.7	0.93
Histology of cancer	100.0	1.00
Node status	84.2	0.76
Present of symptoms of cervical cancer (Yes/none found)	94.7	0.83
Presence of co-morbidities	100.0	1.00
Description of definitive appointment that led to diagnosis	Variable not abstracted with earlier version of abstraction form.	

Table 6. Measurement of intra-rater reliability for Abstractor #2 (N=15 charts)

Variable	Agreement (%)	Kappa statistic
# Pap smears	93.3	0.89
# cervical biopsies	93.3	0.88
# colposcopies	86.7	0.78
Stage of cancer	100.0	1.00
Histology of cancer	100.0	1.00
Node status	100.0	1.00
Present of symptoms of cervical cancer (Yes/none found)	86.7	0.72
Presence of co-morbidities	86.7	0.72
Description of definitive appointment that led to diagnosis	Variable not abstracted with earlier version of abstraction form.	

Table 7. Measurement of intra-rater reliability for Abstractor #3 (N=15 charts)

Variable	Agreement (%)	Kappa statistic
# Pap smears	89.5	0.81
# cervical biopsies	94.7	0.88
# colposcopies	94.7	0.86
Stage of cancer	100.0	1.00
Histology of cancer	100.0	1.00
Node status	84.2	0.66
Present of symptoms of cervical cancer (Yes/none found)	0.89	0.69
Presence of co-morbidities	100.0	1.00
Description of definitive appointment that led to diagnosis	Variable not abstracted with earlier version of abstraction form.	

On the whole, the measures of agreement between first and second reviews were deemed to have 'almost perfect' agreement or 'substantial' agreement for almost all variables. One reason for the less than 100% agreement could be the fact that the results of the second chart review were compared to the results of the first review, which was very early in the chart abstraction phase

when abstractors had not received extensive training and did not have as much experience with using the chart abstraction form or finding the required data within medical charts. Also, the earlier chart abstractions involved a very early and yet, unrefined version of the abstraction form. We sat down as a group to review many of the charts used to calculate these intra-rater measurements and we did find that the second review of the charts had actually produced the more reliable data. Again, abstractors were urged to take their time when reviewing charts.

Again, within about 3 months abstractor #1 re-abstracted data from a set of charts that she had previously reviewed (N=10). Intra-rater reliabilities were determined (Table 8). It should be noted that at this point, abstractor #1 was the main abstractor, abstractor #2 was no longer reviewing charts for this study, and abstractor #3 was involved in other parts of the study.

Table 8. Measurement of intra-rater reliability for Abstractor #1 (N=10 charts)

Variable	Agreement (%)	Kappa statistic
# Pap smears	100	1.00
# cervical biopsies	88.9	0.81
# colposcopies	77.8	0.55
Stage of cancer	88.9	0.85
Histology of cancer	100	1.00
Node status	88.9	0.83
Present of symptoms of cervical cancer (Yes/none found)	100	1.00
Presence of co-morbidities	77.8	0.50
Description of definitive appointment that led to diagnosis	88.9	0.83

The lowest kappa statistic was found for the number of colposcopies. They are not procedures for which a lab report is produced. As noted before, colposcopies are not well documented in medical charts and they may be easily missed. There may be a photocopy of a colposcopy report within the medical chart but it was often illegible or there was simply a note within the progress notes that stated that a colposcopy was done. We are able to identify colposcopies through the data provided to us by the RAMQ using billing code 6074 and 6075.

Measurement of abstraction reliability was again measured in one year. Abstractor #1 reviewed 10 charts (Table 9).

Table 9. Measurement of intra-rater reliability for Abstractor #1 (N=10 charts)

Variable	Agreement (%)	Kappa statistic
# Pap smears	89.0	0.71
# cervical biopsies	100.0	1.00
# colposcopies	100.0	1.00
Stage of cancer	88.9	0.73
Histology of cancer	100.0	1.00
Node status	88.9	ND
Present of symptoms of cervical cancer (Yes/none found)	77.9	0.55
Presence of co-morbidities	100.0	1.00
Description of definitive appointment that led to diagnosis	44.4	0.20

*ND, not determined

On the whole, the reliability of data abstraction was 'almost perfect'. The level of agreement was poor for three variables (the number of Pap smears, cancer stage, node status, and for the presence of symptoms). Upon review of the data, we realized that the data abstracted was exactly the same for all subjects for these four variables between the two time periods, except for one instance. These inconsistencies in data, although very few, resulted in a disproportionately low kappa statistic since there were only 10 charts re-abstracted.

APPENDIX 4

Subject questionnaire

Date entered into database: ☐ Study number: ☐☐☐

Montreal Invasive Cervical Cancer Study

Patient Questionnaire

Date Administered: _____/_____/_____ Year of diagnosis: _____ Tel. No.: _____
DD MM YY

Name of Subject : _____
(Last Name) (First Name)

Was subject assisted by another person? ❑Yes ❑No

If Yes, name and relationship of that person:

_____
(Last Name) (First Name) (Relationship)

Name of Next of Kin (if applicable):

_____
(Last Name) (First Name) (Relationship)

1. You were diagnosed with invasive cervical cancer in ____ (year). At that time you were _____ years old.

What city were you living in when diagnosed with cervical cancer?

☐ Montreal or ☐ Laval ☐ Other, _____ **end interview**

↓

2. Now let's go back 5 years before you were diagnosed with cervical cancer. Between ____ and _____ :

What city were you living in during this entire time period?

☐ Montreal or ☐ Laval → **Go to page 3**

↓

If other city _____

↓

3. What year did you move to Montreal or Laval?_____ **Go to next page**

<u>This page is for women who did NOT live in Montreal within 5 years of diagnosis.</u>

Our main interest for this study are women who lived in Montreal a minimum of 5 years before being diagnosed with cervical cancer. Since you did not live in Montreal or Laval for 5 years before your diagnosis, I'll only ask you a few more questions.

Do you know what a Pap test is?

☐ **Yes** ⟶ **Go to question 10**

☐ **No / I'm not sure / Maybe** ⟶ **Read description below**

A Pap smear, or Pap test, is a test performed to detect changes in the cells of the cervix that occur before cancer or in rare cases, to detect cancer of the cervix. The cervix is the lower part of the uterus and connects the body of the uterus to the vagina.

During a Pap test, an instrument is inserted into the vagina. This widens the vagina so that the upper portion of the vagina and the entire cervix can be seen. Your doctor then uses a small spatula or a brush, to gently scrape the surface of the cervix in order to pick up cells which are then examined under the microscope.

10. During the five years prior to being diagnosed with cervical cancer, that is between _____ and _____:

Did you have any Pap tests?

☐ **Yes** ↓ ☐ **No** ↓ ☐ **I don't know/I don't remember** ↓

25. How about your entire lifetime. In general, how often would you say you had a Pap smear? (Read out the categories. Force pts to choose a category)

☐ **Never**

☐ **Every year, _____** (explain if needed)

☐ **About every 2 years, _____** (explain if needed)

☐ **About every 3 years, _____** (explain if needed)

☐ **About every 4 years, _____** (explain if needed)

☐ **Other**, _____

☐ **I don't remember/I don't know**

⟶ **Go to Demographics section, page 14**

This page and the others are for women who DID live in Montreal within 5 years of diagnosis.

PHYSICIANS

The next section of the interview will pertain to your doctors.

4. Within 5 years before your diagnosis with cervical cancer so that's between ____ and ____(year), did you have a family doctor and/or gynaecologist who you would receive care from?

☐ **Yes** → **Go to question 6**

☐ **No** → **5. Explain why:**_____

_____

_____

→ **Go to next page**

☐ **I don't remember/I don't know** → **Go to next page**

6. What was the name of your doctor?	**7.** Was this person male or female?		**8.** Was he/she a family doctor or a gynaecologist?		**9.** Where was the office located? (Address/Street/ City/Office)
	Male	**Female**	**Family doctor/gp**	**gynaecologist**	

→ **Go to next page**

PAP SCREENING HISTORY

For the next part of the interview, I will ask you about your Pap screening history.

Do you know what a Pap test is?

☐ **Yes ⟶ Go to question 10**

☐ **No / I'm not sure / Maybe ⟶ Read description below**

Pap smear, or Pap test, is a test performed to detect changes in the cells of the cervix that occur before cancer or in rare cases, to detect cancer of the cervix. The cervix is the lower part of the uterus and connects the body of the uterus to the vagina.

During a Pap test, an instrument is inserted into the vagina. This widens the vagina so that the upper portion of the vagina and the entire cervix can be seen. Your doctor then uses a small spatula or a brush, to gently scrape the surface of the cervix in order to pick up cells which are then examined under the microscope.

⟶ Go to next page

10. So again look back 5 years prior to your diagnosis that is from _____ to _____.

Within this period of time, did you have any Pap tests**?**

☐ **I don't remember/I don't know** ⟶ ***Go to question 25***

☐ **Yes** ⟶ ***Go to question 22***

☐ **No** ⟶

Since you did not have any Pap tests within the five years we would like to understand your situation a little bit better. I'm going to read out a list of statements that may or may not pertain to your situation. Please answer either 'true', 'false' or 'maybe'. Remember that this question does not refer to your beliefs at the present time but rather <u>before</u> your diagnosis with cervical cancer.

↓

	1	2	3	4
	True	**False**	**Maybe**	**I don't remember/ I don't know**
11. I did not know what a Pap test was for.				
12. I felt embarrassed about having a Pap smear.				
13. I was afraid it would hurt.				
14. I never imagined that I would ever develop cervical cancer.				
15. I forgot to do it.				
16. My physician did not tell me that I needed a Pap smear				
17. I knew I needed a Pap test but my physician did not do Pap tests.				
18. I did not have a physician.				
19. The clinic hours were inconvenient.				
20. I just never got around to it. I was busy.				
21. I thought Pap tests were only for women who had symptoms of cervical cancer.				

⟶ ***Go to question 25***

22. Can you tell me the year of each Pap test within this 5 year period?	**23.** Was this test normal or abnormal?			**24.** What is the name of the physician who did the Pap test?
	Normal	**Abnormal**	**I don't remember/I don't know**	

25. How about your entire lifetime. In general, how often would you say you had a Pap smear? (Read out the categories. Force pts to choose a category)

- ☐ Never → **Go to question 28**
- ☐ Every year, _____ (explain if needed)
- ☐ About every 2 years, _____ (explain if needed)
- ☐ About every 3 years, _____ (explain if needed)
- ☐ About every 4 years, _____ (explain if needed)
- ☐ Other, _____
- ☐ I don't remember/I don't know → **Go to question 28**

Go to question 26

26. Besides the Pap smears you had within 5 years of diagnosis, did you have any other Pap smears that were abnormal?

☐ Yes ☐ No ☐ I don't know/I don't remember

Go to question 28

27. If yes, explain: _____

_____

_____

28. Prior to diagnosis with cervical cancer, did it matter to you if the physician performing your gynaecologic exam or your Pap test was male or female?

- ❑ No ⟶ ***Go to question 30***
- ❑ I do not remember/I do not know ⟶ ***Go to question 30***
- ❑ Yes. Please specify preferred gender: ❑ Female ❑ Male

29. If you could not find a physician of the preferred sex to perform your Pap smear or gynaecologic exam, what would you have done?

- ❑ Have the Pap smear anyway.
- ❑ I do not remember/I do not know
- ❑ Not have a Pap smear.

30. Prior to your diagnosis with cervical cancer, did it matter to you if the physician performing your gynaecologic exam or your Pap test was older or younger?

- ❑ No ⟶ ***Go to question 32***
- ❑ I do not remember/I do not know ⟶ ***Go to question 32***
- ❑ Yes. Please specify preferred gender: ❑ Older ❑ Younger

31. If you could not find a physician of the preferred age to perform your gynaecologic exam or your Pap test, what would you have done?

- ❑ Have the Pap smear anyway.
- ❑ Not have a Pap smear.
- ❑ I do not remember/I do not know

32. What type of physician/caregiver would you have preferred to perform your gynaecologic exam or your Pap test?

- ❑ Did NOT matter ⟶ **Go to question 34**
- ❑ I do not remember/I do not know ⟶ **Go to question 34**
- ❑ Family physician
- ❑ Obstetrician-gynaecologist
- ❑ Other (e.g. nurse, midwife) (specify):_____

Only read out these 3 choices.

33. If you could not find one of these caregivers to perform your gynaecologic exam or your Pap test, what would you have done?

- ❑ Have the Pap smear anyway.
- ❑ Not have a Pap smear.
- ❑ I do not remember/I do not know

34. Is there anything else that influenced your decision to obtain or not obtain a Pap smear?

_____

_____

_____

_____

_____

_____

Symptoms

The next questions refer to any symptoms of cervical cancer you may have had one year before your diagnosis with cervical cancer. I'm going to read out a list of symptoms one at a time and I'll ask you to respond 'yes' or 'no' if you had this symptom.

So at anytime between _____(year) to _____(year), did you experience…

35. Symptoms			**36.** How long did this symptom last?	**37.** Units (months/weeks/ days)
	No	**Yes**		
1. vaginal bleeding following sexual intercourse				
2. spotting between periods				
3. bleeding following menopause				
4. heavy periods				
5. unusual vaginal discharge				
6. lower back pain				
7. pelvic pain				
8. Other (specify):				

Pathway to Diagnosis

38. Now let's go back to what led to your diagnosis of cervical cancer.

What started this whole process that led to your diagnosis with cervical cancer? That is, what specifically made you seek medical attention in the first place?

Listen carefully and I'm going to read out some options. Choose the most appropriate answer.

If Had symptoms

(Check only one option)

You specifically went to a physician or the hospital because of these symptoms	
You went for a routine medical check-up	
You went to your doctor for a condition unrelated to cervical cancer	
I don't remember	
Other:	

If did NOT have symptoms

(Check only one option)

You went for a routine medical check-up	
You went to your doctor for a condition unrelated to cervical cancer	
I don't remember	
Other:	

Go to question 39

General Health Questions

The next questions refer to your general health and health practices. Again, let's go back to the period 5 years prior to your diagnosis (from _____ to _____).

39. Prior to being diagnosed with cervical cancer and prior to developing any symptoms of cervical cancer (if any), how would you describe your general health?

- ❑ Poor
- ❑ Fair
- ❑ Good
- ❑ Very good

40. Between _____ and _____(yr of diagnosis), did you have any chronic diseases or ailments that required you to see your physician on a regular basis?

☐ **Yes** → **41.** What was the illness? _____

↓

42. Were you being seen by a doctor for this illness?

☐ **Yes** ☐ **No** → **Go to question 44**

↓

43. What type of physician was he/she? _____

☐ **No** → **Go to question 44**

44. Between _____ and _____(yr of diagnosis), was your immunity depressed due to HIV/AIDS or an organ transplantation?

☐ **Yes** ☐ **No**

45. Between _____ and _____(yr of diagnosis), how often did you see a doctor over each year for things other than Pap testing or gynaecological care?

- ☐ More than once a month
- ☐ Once a month
- ☐ Every 2 months
- ☐ Every 3 months
- ☐ Every 4 months
- ☐ Every 5 months
- ☐ Every 6 months
- ☐ Once a year
- ☐ Other, _____(specify)

46. Between _____ and _____(year) did you have any pregnancies (regardless of whether the pregnancy was full term, resulted in a miscarriage, or you had an abortion)?

- ❑ **Yes ——→ Go to question 47**
- ❑ **No ——→ Go to question 50**
- ❑ **Refuses to answer ——→ Go to question 50**

47. How many total pregnancies did you have during this time period? _____

	48. Can you tell me the year that you delivered or miscarried, or had an abortion?	**49.** As far as you know, did this pregnancy delay you receiving Pap tests or diagnostic tests for cervical cancer?		
		Yes	**No**	**I don't know/I don't remember**
1st				
2nd				
3rd				
4th				

50. Now before this 5 year period, how many pregnancies did you have (regardless of whether the pregnancy was full term, resulted in a miscarriage, or you had an abortion)?

_____

51. Between _____ and _____(yr of diagnosis),how would you describe your cigarette smoking status?

- ☐ Current smoker
- ☐ Former smoker
- ☐ Never smoker
- ☐ I don't remember

52. Is there anything else you'd like to tell me about the medical care you received prior to your diagnosis with cervical cancer?

Demographic Questions

The following questions refer to your background. They will help us to better analyze our data. And as I mentioned before the information you give us will be kept completely confidential and our analysis will be done without using your name.

53. In what country were you born? _____

If born in Canada → **go to question 55.**

If NOT born in Canada → **go to question 54.**

54. What year did you arrive in Canada? _____

55. What cultural background would you say your ancestors belong to?

_____

_____

Again, let's go back to the year you were diagnosed with cervical cancer _____.

56. What language(s) did you speak well enough to conduct a conversation? (check all that apply)

❑ French ❑ English

❑ Other, specify_____

57. When you were diagnosed with cancer, what language(s) did you speak **most often** at home? (check all that apply)

❑ French ❑ English

❑ Other, specify_____

58. What was your marital status when diagnosed with cervical cancer in ____(year)?

❑ **Legally Married** (and not separated)

❑ **Common–law** (Two people of the opposite/same sex living together as a couple but not legally married to each other

❑ **Divorced** (and not living with a common-law partner)

❑ **Separated** (Still legally married and not living with a common-law partner)

❑ **Single** (Never legally married and not living with a common-law partner)

❑ **Widowed** (Was legally married and lost spouse through death. Have not remarried and not living with a common-law partner)

59. Just prior to being diagnosed with cervical cancer, were you a…

❑Student ❑Housewife ❑Unemployed ❑Employed ❑Retired

60. What was the highest level of schooling you had when diagnosed with cervical cancer?

❑ Less than grade 6
❑ High School -incomplete
❑ High School –complete
❑ CEGEP or College –incomplete
❑ CEGEP or College –complete
❑ Technical/vocational school
❑ University (undergraduate) -incomplete
❑ University (undergraduate) -complete
❑ University (graduate degree) - incomplete
❑ University (graduate degree) – complete

61. What was your total annual **household** income when diagnosed with cervical cancer?

❑<$10,000 ❑$31-40,000 ❑>$60,000
❑$10-20,000 ❑$41-50,000 ❑Refuses to answer
❑$21-30,000 ❑$51-60,000 ❑ I don't know,_____

62. What was the number of people living in your household including yourself when you were diagnosed with cervical cancer? _____

This is the end of questionnaire.
Thank you very much for answering these questions.

For women who lived in Montreal or Laval at diagnosis and lived in one of these places for minimum 5 years before diagnosis

With your permission we would like to contact your physician(s) to obtain further data about the cervical screening (if any), diagnostic care, and treatment you received before your final diagnosis with cervical cancer. We would also like to retrieve the Pap smears you had in the 5 years prior to your diagnosis of cervical cancer. The slides will be reviewed by a cytologist. We will not ask you to collect any additional samples of any kind for this study; just to let us reread the one(s) that has (ve) been kept in the laboratory.

All results from this cytology review and any other data collected will be used strictly for research purposes. Specimens and any results will have no personal identifiers attached to them.

We will be mailing you an information letter and consent form that describes this further. Please read it over and regardless of your decision, sign it and mail it back to us in the self-addressed-stamped envelope included. Also, keep one copy for yourself.
If you have any questions, feel free to call the study office (514-398-3399).

Version- November 2005

APPENDIX 5

Pilot testing of subject questionnaire: Interview script

SCRIPT FOR PILOT-TESTING OF SUBJECT QUESTIONNAIRE

Good afternoon,

My name is Claude Richard.

I am calling you from McGill University to tell you about a study we are conducting among Montreal and Laval women who were diagnosed with cervical cancer.

Your name was given to us by the Quebec Tumour Registry and we received permission to contact you from your doctor, Dr. _____, who treated you when you had your cervical cancer in _____.

This study is being conducted by researchers affiliated with McGill and the University of Montreal. And we would like to determine the course of care that women received within 5 years before being diagnosed with cervical cancer. Our purpose is to monitor the quality of diagnostic services and health care that women receive in Quebec. The final goal is to ultimately improve the services for women in the future.

Part of our study involves conducting a telephone interview with the women. Before we do this, we would like to pre-test our questionnaire and as a survivor of cervical cancer we would like you to help us with this. This questionnaire will obtain information about your physicians, your Pap screening history, and your social descriptors.

If you agree to help us I will send you an official letter giving you more details about our study.

I would like to check your mailing address with you.

I will call you back next week to find out if you have received the letter and to answer any questions you may have. I will ask you then whether you would like to participate in the pre-testing of our questionnaire. This should only take 15 minutes.

What is the best time to call you on week days?

Thank you.

APPENDIX 6

Pilot testing of subject questionnaire: Introductory letter

Study Coordinating Centre:
Eduardo L. Franco, MPH, DrPH
Principal Investigator
Dept of Epidemiology & Biostatistics
McGill University

Andrea R. Spence, MSc
Study Coordinator
Dept. of Epidemiology & Biostatistics
McGill University

Patricia Goggin, MD, MSc
Médecin-conseil
Systèmes de soins et services
Institut national de santé publique

Abdulaziz Alobaid, M.D.
Clinical Liaison
Clinical Fellow Gynecology-Oncology
CHUM – Université de Montréal

Claude Richard, R.N.
Research Nurse
McGill University

Clinical Co-Investigators:
Pierre Drouin, MD
Professeur
Service de gynécologie-oncologie
CHUM – Université de Montréal

Diane M. Provencher, MD
Chef et professeure
Service de gynécologie-oncologie
CHUM – Université de Montréal

François Lehmann, MD
Directeur
Département de médecine familiale
CHUM- Université de Montréal

Parviz Ghadirian, PhD
Director
Epidemiology Research Centre
CHUM – Université de Montréal

Michèle Deschamps, MSc
Direction de la Santé Publique
Unité de santé physique
Montréal-Centre

Lucy Gilbert, MD
Associate Professor
Division of Gynecological Oncology
McGill University

Martin G. Dawes, MD
Chair, Dept. of Family Medicine
McGill University

Alex Ferenczy, MD
Professor of Pathology & OBGYN
McGill University

* Funded by the Canadian Institutes of Health Research. Study approved by the Research Ethics Boards of McGill University and CHUM

_____, 200__

Re: Invitation to participate

Dear Ms. _____,

As explained to you by our Research Nurse, Ms Claude Richard when she phoned you, we will soon be conducting a study about cervical cancer screening in women who have been diagnosed with invasive cervical cancer in Montreal and Laval between 1998 and 2004. This study, which is funded by the Canadian Institutes of Health Research (CIHR), is being carried out by clinical scientists from McGill University, Université de Montréal, McGill University Health Centre (MUHC), Centre Hospitalier de l'Université de Montréal (CHUM), and the Institut national de santé publique. This study has received endorsement from the Departments of Gynecology & Obstetrics and Family Medicine at these institutions. Your physician, Dr._____, has given us permission to contact you.

As a survivor of invasive cervical cancer we would like you to give us your opinion concerning the approaches we plan to use in this research study. Ms Richard, will be calling you at home in the coming week or at a mutually agreed upon time. She will first administer a questionnaire to you. This questionnaire will obtain basic background information and information about screening. She will then ask you for your opinions concerning the questionnaire (For example: Were some questions difficult to understand? If so, how should they be re-worded?). The phone conversation will take about 15-20 minutes.

This study has obtained ethical approval from MUHC and CHUM and the ethics boards of various hospitals in Montreal. Your responses during the interview will be kept absolutely confidential and your identity, as a respondent, will remain anonymous. If you have any questions about the study, please feel free to contact the study's coordinating centre at (514) 398-3399.

Your opinion regarding our study is very important to us. Thank you in advance.

Yours sincerely,

Eduardo Franco, PhD
Professor and Director
Division of Cancer Epidemiology
McGill University

APPENDIX 7

Pilot testing of subject questionnaire: Post-questionnaire administration questions

Pilot-testing questions

Name of Subject: _____

Time interview started:_____ Time interview ended:_____

Thank you for answering our questionnaire, I have a few questions for you.

1. Were there any questions that were difficult to understand? Can you explain why? Do you have any suggestions as to how this question could be improved?

2. Were there any questions you would rather not answer? Can you explain why?

3. If you were participating in this study, would you give us consent to have your Pap smears retrieved and reviewed? Would you allow us to obtain further information from your physicians?

4. Was the interview too long?

Interviewer's Comments:

_____

_____

_____

_____

_____

_____

_____

_____

APPENDIX 8

Subject questionnaire: Physician permission letter and form to contact their patient

Study Coordinating Centre:
Eduardo L. Franco, MPH, DrPH
Principal Investigator
Dept of Epidemiology & Biostatistics
McGill University

Andrea R. Spence, MSc
Study Coordinator
Dept. of Epidemiology & Biostatistics
McGill University

Patricia Goggin, MD, MSc
Médecin-conseil
Systèmes de soins et services
Institut national de santé publique

Abdulaziz Alobaid, M.D.
Clinical Liaison
Clinical Fellow Gynecology-Oncology
CHUM – Université de Montréal

Claude Richard, R.N.
Research Nurse
McGill University

Clinical Co-Investigators:
Pierre Drouin, MD
Professeur
Service de gynécologie-oncologie
CHUM – Université de Montréal

Diane M. Provencher, MD
Chef et professeure
Service de gynécologie-oncologie
CHUM – Université de Montréal

François Lehmann, MD
Directeur
Département de médecine familiale
CHUM- Université de Montréal

Parviz Ghadirian, PhD
Director
Epidemiology Research Centre
CHUM – Université de Montréal

Michèle Deschamps, MSc
Direction de la Santé Publique
Unité de santé physique
Montréal-Centre

Lucy Gilbert, MD
Associate Professor
Division of Gynecological Oncology
McGill University

Martin G. Dawes, MD
Chair, Dept. of Family Medicine
McGill University

Alex Ferenczy, MD
Professor of Pathology & OBGYN
McGill University

* Funded by the Canadian Institutes of Health Research. Study approved by the Research Ethics Boards of McGill University and CHUM

*MONTREAL INVASIVE CERVICAL CANCER STUDY**

_____, 200_

Re: Authorization to contact your patients

Dear Dr. _____,

We are presently conducting a study to understand the circumstances leading to the development of invasive cervical cancer amongst women in Montreal and Laval. This study, which is funded by the Canadian Institutes of Health Research (CIHR), is being carried out by clinical scientists from McGill University, Université de Montréal, MUHC, CHUM, and the Institut national de santé publique. This study has received endorsement from the Departments of Gynecology & Obstetrics and Family Medicine at these institutions.

Study subjects are women residing in Montreal or Laval who were diagnosed with invasive cervical cancer between 1998 and 2004. We have identified them through the Quebec Tumour Registry. We wish to interview these women to obtain demographic information and to determine their Pap screening histories and their preferences regarding screening. This will be a telephone interview about 15 minutes in length conducted by our study nurse. We have attached a list of women who you treated for cervical cancer. We seek permission from you to allow us to contact them to administer the questionnaire. If the patient has died, we would like to contact a next of kin to obtain basic demographic information about the patient. **Please complete the attached form and fax it back to our study coordinating centre at (514)398-5002.**

All analyses will be done in aggregate without any personal identifiers of the physicians or the patients. We believe that our study will provide valuable information to assist policy decisions concerning cervical screening and to develop new public health initiatives that will help prevent the progression of this disease to an invasive stage. Your cooperation is <u>crucial</u> to the success of this study and we kindly ask you to join our study group. Your contribution will be acknowledged in the authorship of any publications to originate from the investigation.

This study has obtained ethical approval from MUHC and CHUM and the Ethics Boards of all hospitals in Montreal. If you have any questions about the study, please feel free to contact the study's coordinating centre at 398-6926 or any of the study investigators listed on the first page.
Thank you in advance.

Yours sincerely,

Eduardo Franco, PhD
Professor and Director
Division of Cancer Epidemiology
McGill University

Andrea Spence, MSc.
Study Coordinator
Division of Cancer Epidemiology
McGill University

Montreal Invasive Cervical Cancer Study

PERMISSION TO CONTACT PATIENT FORM

We would like to obtain your permission to contact your patients for our study. Please complete the table below:

Name of patient and RAMQ No.	Can we contact this patient?			If dead, can we contact her next of kin?
	YES you can contact her √	**Please give her address and telephone number**	**NO** You cannot contact her **(Please give reason)** √	**YES** ❑ **NO** ❑ **Please indicate name and telephone number for next of kin if possible**

Date: _____ **Hospital:** _____

Please sign below and fax this page to the study coordinating centre at (514) 398-5002.

I give you permission to contact those patients, or their next of kin, as indicated above.

_____ _____ _____

Physician's Name Signature Date

APPENDIX 9

Subject questionnaire: Introductory letter sent to subject from our study office

Study Coordinating Centre:
Eduardo L. Franco, MPH, DrPH
Principal Investigator
Dept of Epidemiology & Biostatistics
McGill University

Andrea R. Spence, MSc
Study Coordinator
Dept. of Epidemiology & Biostatistics
McGill University

Patricia Goggin, MD, MSc
Médecin-conseil
Systèmes de soins et services
Institut national de santé publique

Abdulaziz Alobaid, M.D.
Clinical Liaison
Clinical Fellow Gynecology-Oncology
CHUM – Université de Montréal

Claude Richard, R.N.
Research Nurse
McGill University

Clinical Co-Investigators:
Pierre Drouin, MD
Professeur
Service de gynécologie-oncologie
CHUM – Université de Montréal

Diane M. Provencher, MD
Chef et professeure
Service de gynécologie-oncologie
CHUM – Université de Montréal

François Lehmann, MD
Directeur
Département de médecine familiale
CHUM- Université de Montréal

Parviz Ghadirian, PhD
Director
Epidemiology Research Centre
CHUM – Université de Montréal

Michèle Deschamps, MSc
Direction de la Santé Publique
Unité de santé physique
Montréal-Centre

Lucy Gilbert, MD
Associate Professor
Division of Gynecological Oncology
McGill University

Martin G. Dawes, MD
Chair, Dept. of Family Medicine
McGill University

Alex Ferenczy, MD
Professor of Pathology & OBGYN
McGill University

* Funded by the Canadian Institutes of Health Research. Study approved by the Research Ethics Boards of McGill University and CHUM

_____, 200__

Re: Invitation to participate

Dear Ms _____,

We are presently conducting a study of women's health issues amongst women in Montreal and Laval. This study, which is funded by the Canadian Institutes of Health Research (CIHR), is being carried out by clinical scientists from McGill University, Université de Montréal, McGill University Health Centre (MUHC), Centre Hospitalier de l'Université de Montréal (CHUM), and the Institut national de santé publique. This study has received endorsement from the Departments of Gynecology & Obstetrics and Family Medicine at these institutions. Your physician, Dr. _____, has given us permission to contact you.

Our study nurse, Ms. Claude Richard will be calling you at home in the coming weeks to invite you to complete a brief telephone interview. This interview will obtain basic demographic information and information about screening. The interview will take about 10 to 15 minutes to complete. Your responses during the interview will be kept absolutely confidential and your identity, as a respondent, will remain anonymous.

This study has obtained ethical approval from MUHC and CHUM and the ethics boards of various hospitals in Montreal. If you have any questions about the study, please feel free to contact the study's coordinating centre at (514) 398-3399.

Your participation is very important to us and we hope you agree to our telephone interview.

Thank you in advance.

Yours sincerely,

Eduardo Franco, PhD
Professor and Director
Division of Cancer Epidemiology
McGill University

APPENDIX 10

Subject questionnaire: Introductory letter

sent to subject by her physician or the director of professional services

Study Coordinating Centre:
Eduardo L. Franco, MPH, DrPH
Principal Investigator
Dept of Epidemiology & Biostatistics
McGill University

Andrea R. Spence, MSc
Study Coordinator
Dept. of Epidemiology & Biostatistics
McGill University

Patricia Goggin, MD, MSc
Médecin-conseil
Systèmes de soins et services
Institut national de santé publique

Abdulaziz Alobaid, M.D.
Clinical Liaison
Clinical Fellow Gynecology-Oncology
CHUM – Université de Montréal

Claude Richard, R.N.
Research Nurse
McGill University

Clinical Co-Investigators:
Pierre Drouin, MD
Professeur
Service de gynécologie-oncologie
CHUM – Université de Montréal

Diane M. Provencher, MD
Chef et professeure
Service de gynécologie-oncologie
CHUM – Université de Montréal

François Lehmann, MD
Directeur
Département de médecine familiale
CHUM- Université de Montréal

Parviz Ghadirian, PhD
Director
Epidemiology Research Centre
CHUM – Université de Montréal

Michèle Deschamps, MSc
Direction de la Santé Publique
Unité de santé physique
Montréal-Centre

Lucy Gilbert, MD
Associate Professor
Division of Gynecological Oncology
McGill University

Martin G. Dawes, MD
Chair, Dept. of Family Medicine
McGill University

Alex Ferenczy, MD
Professor of Pathology & OBGYN
McGill University

* Funded by the Canadian Institutes of Health Research. Study approved by the Research Ethics Boards of McGill University and CHUM

_____, 200__

Re: Invitation to participate

Dear Ms. _____,

This letter is to inform you about a study of women's health issues being conducted amongst women in Montreal and Laval. This study, which is funded by the Canadian Institutes of Health Research (CIHR), is being carried out by clinical scientists from McGill University, Université de Montréal, McGill University Health Centre (MUHC), Centre Hospitalier de l'Université de Montréal (CHUM), and the Institut national de santé publique. This study has received endorsement from the Departments of Gynecology & Obstetrics and Family Medicine at these institutions.

Our study nurse, Ms. Claude Richard, will be calling you at home in the coming weeks to invite you to complete a brief telephone interview. This interview will obtain basic demographic information and information about screening. The interview will take about 10 to 15 minutes to complete. Your responses during the interview will be kept absolutely confidential and your identity, as a respondent, will remain anonymous.

This study has obtained ethical approval from MUHC and CHUM and the ethics boards of various hospitals in Montreal. If you have any questions about the study, please feel free to contact the study's coordinating centre at (514) 398-3399.

Your participation is very important and we hope you agree to the interview.

Thank you in advance.

Yours sincerely,

Dr._____

APPENDIX 11

Subject questionnaire: Introductory letter sent to next of kin from our study office

Study Coordinating Centre:
Eduardo L. Franco, MPH, DrPH
Principal Investigator
Dept of Epidemiology & Biostatistics
McGill University

Andrea R. Spence, MSc
Study Coordinator
Dept. of Epidemiology & Biostatistics
McGill University

Patricia Goggin, MD, MSc
Médecin-conseil
Systèmes de soins et services
Institut national de santé publique

Abdulaziz Alobaid, M.D.
Clinical Liaison
Clinical Fellow Gynecology-Oncology
CHUM – Université de Montréal

Claude Richard, R.N.
Research Nurse
McGill University

Clinical Co-Investigators:
Pierre Drouin, MD
Professeur
Service de gynécologie-oncologie
CHUM – Université de Montréal

Diane M. Provencher, MD
Chef et professeure
Service de gynécologie-oncologie
CHUM – Université de Montréal

François Lehmann, MD
Directeur
Département de médecine familiale
CHUM- Université de Montréal

Parviz Ghadirian, PhD
Director
Epidemiology Research Centre
CHUM – Université de Montréal

Michèle Deschamps, MSc
Direction de la Santé Publique
Unité de santé physique
Montréal-Centre

Lucy Gilbert, MD
Associate Professor
Division of Gynecological Oncology
McGill University

Martin G. Dawes, MD
Chair, Dept. of Family Medicine
McGill University

Alex Ferenczy, MD
Professor of Pathology & OBGYN
McGill University

* Funded by the Canadian Institutes of Health Research. Study approved by the Research Ethics Boards of McGill University and CHUM

_____, 200__

Re: Invitation to participate

Dear M _____,

We are presently conducting a study of women's health issues in Montreal and Laval. Dr._____ has informed us that your _____ has passed away. He has given us permission to contact you, as a next of kin, to obtain some information about her.

One of our study nurses, Ms. Claude Richard or Ms Solange Piché will be calling you at home in the coming weeks to invite you to complete a brief telephone interview. This interview will obtain basic demographic information and information about screening. The interview will take about 10 to 15 minutes to complete. Your responses during the interview will be kept absolutely confidential and your identity, as a respondent, will remain anonymous.

This study, which is funded by the Canadian Institutes of Health Research (CIHR), is being carried out by clinical scientists from McGill University, Université de Montréal, McGill University Health Centre (MUHC) and Centre Hospitalier de l'Université de Montréal (CHUM). This study has received endorsement from the Departments of Gynecology & Obstetrics and Family Medicine at these institutions. This study has obtained ethical approval from MUHC and CHUM and the ethics boards of various hospitals in Montreal.

Your participation is very important to us and we hope you agree to our telephone interview. If you have any questions about the study, please feel free to contact the study's coordinating centre at (514) 398-3399.

Thank you in advance.

Yours sincerely,

Eduardo Franco, PhD
Professor and Director
Division of Cancer Epidemiology
McGill University

APPENDIX 12

Subject questionnaire: Introductory letter

sent to next of kin by physician or the director of professional services

Study Coordinating Centre:
Eduardo L. Franco, MPH, DrPH
Principal Investigator
Dept of Epidemiology & Biostatistics
McGill University

Andrea R. Spence, MSc
Study Coordinator
Dept. of Epidemiology & Biostatistics
McGill University

Patricia Goggin, MD, MSc
Médecin-conseil
Systèmes de soins et services
Institut national de santé publique

Abdulaziz Alobaid, M.D.
Clinical Liaison
Clinical Fellow Gynecology-Oncology
CHUM – Université de Montréal

Claude Richard, R.N.
Research Nurse
McGill University

Clinical Co-Investigators:
Pierre Drouin, MD
Professeur
Service de gynécologie-oncologie
CHUM – Université de Montréal

Diane M. Provencher, MD
Chef et professeure
Service de gynécologie-oncologie
CHUM – Université de Montréal

François Lehmann, MD
Directeur
Département de médecine familiale
CHUM- Université de Montréal

Parviz Ghadirian, PhD
Director
Epidemiology Research Centre
CHUM – Université de Montréal

Michèle Deschamps, MSc
Direction de la Santé Publique
Unité de santé physique
Montréal-Centre

Lucy Gilbert, MD
Associate Professor
Division of Gynecological Oncology
McGill University

Martin G. Dawes, MD
Chair, Dept. of Family Medicine
McGill University

Alex Ferenczy, MD
Professor of Pathology & OBGYN
McGill University

* Funded by the Canadian Institutes of Health Research. Study approved by the Research Ethics Boards of McGill University and CHUM

_____, 200__

Re: Invitation to participate

Dear Ms. _____,

This letter is to inform you about a study of women's health issues being conducted by clinical scientists from McGill University, Université de Montréal, McGill University Health Centre (MUHC), Centre Hospitalier de l'Université de Montréal (CHUM) and of the Institut de santé publique. As the next of kin of Ms._____ they wish to obtain some basic information from you about her.

Our study nurse, Ms. Claude Richard, will be calling you at home in the coming weeks to invite you to complete a brief telephone interview. The interview will take about 10 to 15 minutes to complete. Your responses during the interview will be kept absolutely confidential and your identity, as a respondent, will remain anonymous.

This study, which is funded by the Canadian Institutes of Health Research (CIHR), has received endorsement from the Departments of Gynecology & Obstetrics and Family Medicine at the institutions noted above. This study has obtained ethical approval from MUHC and CHUM and the ethics boards of various hospitals in Montreal. If you have any questions about the study, please feel free to contact the study's coordinating centre at (514) 398-3399.

Your participation is very important and we hope you agree to the interview.

Thank you in advance.

Yours sincerely,

Dr._____

APPENDIX 13

Subject questionnaire: Interview script

INTERVIEW SCRIPT

Good day,

My name is Claude Richard from McGill University

I am calling you about a study we are conducting among Montreal and Laval women who were diagnosed with cervical cancer in the past. Your name was given to us by the Quebec Tumour registry and we received permission to contact you from your doctor, Dr. _____who treated you when you had cervical cancer.

Did you receive the letter from Dr. Franco (or the DESP or her treating physician) regarding the study?

I'll explain the study to you in more detail and then I'll answer any questions you may have.

This study is being conducted by researchers affiliated with McGill and the University of Montreal. And we would like to determine the course of care that women received within 5 years before being diagnosed with cervical cancer. Our purpose is to monitor the quality of diagnostic services and health care that women receive in Quebec. The goal is to ultimately improve the services for women in the future.

Your participation includes answering a questionnaire with me over the phone - that should take approximately 15 minutes. Your answers to the questionnaire will give us information about your physicians, your Pap screening history and your social descriptors. Your responses during the interview will be kept confidential and your identity will remain anonymous.

We would like to know if you would like to participate in our study and whether you have any questions you would like me to answer.

If woman agrees to interview:
Would you like to answer the questionnaire with me right away or would you like me to call you back some other day.

What is the best time to call you on weekdays? **(Make a definite appointment)**

_____

Thank you.

APPENDIX 14

Subject questionnaire: Consent form

Montreal Invasive Cervical Cancer Study

PATIENT INFORMED CONSENT FORM

PRINCIPAL INVESTIGATOR: DR. EDUARDO FRANCO, MCGILL UNIVERSITY

Purpose:

You have been asked to take part in this study because you have had cervical cancer. We would like to study the events leading up to the diagnosis of cervical cancer in Montreal and Laval women in order to develop better prevention strategies that will help other women in the future.

This is a study funded by the Canadian Institutes of Health Research (CIHR) and carried out by clinical scientists from McGill University and Université de Montréal.

Study procedures:

During the telephone interview you provided us with the names of physicians you saw within the last few years. With your authorization we would like to contact these physicians to obtain the following information: the dates and results of Pap tests, cervical cancer diagnostic tests, treatments and recommendations you may have received 5 years prior to your diagnosis of cervical cancer.

We would also like to retrieve the Pap smears you had in the 5 years prior to your diagnosis of cervical cancer. The slides will be reviewed by a cytotechnologist. We will not ask you to collect any additional samples of any kind for this study; just to let us reread the one(s) that has(ve) been kept in the laboratory.

Given what we explained above, all results from this cytology review will be used strictly for research purposes and as noted below, specimens and any results will have no personal identifiers attached to them.

Benefits:

By participating in this study, you will be contributing to our understanding of the factors surrounding a diagnosis of cervical cancer. This may help us and other researchers to develop better prevention and screening programs that would help other women in the future.

Risks:

There are no potential risks to you as a consequence of your participation in this study.

Confidentiality:

All results from the analyses we will carry out as well as the information you provided in the telephone interview will be kept completely confidential. No names or other information that could identify you as a subject will be released under any circumstances. Our study nurse will create a temporary list of names and slides numbers in order to retrieve the Pap smears. When not in use, this list will be kept locked in a secure location and the study nurse will be the only person with access to it. Once the slides are retrieved, reviewed and returned to their original labs, the list will be destroyed. There will be no instance when the list of names will be linked with the results of the slide review.

Only laboratory personnel involved with this study will have access to the Pap slides. They will be securely stored in the cytology laboratory where the review will be carried out. Slides will be returned to the appropriate cytology labs when the study is done.

Your rights:

Your right to participation/withdrawal from this study is voluntary. You may refuse to participate in the study without any negative consequences to your health care. If you agree to participate, you are free to withdraw from the study at any time. Your decision to withdraw will have no effect on your current or future medical care.

There are no costs to you, direct or indirect. All the tests will be paid out of research funds that our scientific team received from the Canadian Institutes of Health Research to conduct this study.

Ethics acceptance

The Research Ethics Board of the Royal Victoria Hospital has given us permission to conduct this research project. If you have any questions concerning your rights as a possible participant in this research, please contact the ombudsman at the Royal Victoria Hospital, at (514)934-1934 ext 35655.

Additional information:

If you would like to obtain additional information about this study you may call our research nurse, **Ms. Claude Richard** or our study coordinator, **Ms. Andrea Spence**, at **(514) 398-3399**.

MONTREAL INVASIVE CERVICAL CANCER STUDY
PATIENT INFORMED CONSENT FORM

PRINCIPAL INVESTIGATOR : DR. EDUARDO FRANCO, MCGILL UNIVERSITY

1) I give consent for my Pap smears from 19_____ to _____ to be retrieved and analyzed.

☐ **YES** ☐ **NO**

2) I give consent to the researchers to obtain from my doctors and my medical files any additional data they require for their study (cervical cancer screening, diagnostic care, treatments and recommendations).

☐ **YES** ☐ **NO**

I understand the general purpose of the study and my rights as a participant. In no way does this waive my legal rights nor release the investigators, nor involved institutions from their legal and professional responsibilities. My participation is voluntary and if I agree to participate I may withdraw my consent and discontinue my participation from the study at any time. I understand that if I decide to stop participating, there will be no negative impact on the health care I receive presently or in the future.

If you agree to participate please print your name and sign below. Kindly return this form to the researchers in the self-addressed stamped envelope enclosed with this package.

Patient's name (**Please Print Clearly**):	Signature:	Date:
Witness's name:	Signature:	Date:

We have enclosed two copies of this consent form. You may keep the unsigned copy of the consent form for your own records.

APPENDIX 15

Physician questionnaire

PLEASE TYPE OR PRINT CLEARLY

MONTREAL INVASIVE CERVICAL CANCER STUDY

DATE: _____ PHYSICIAN: _____

PATIENT (RAMQ#): _____

Diagnosed with invasive or micro-invasive cervical cancer in _____

1. Did you ever provide any medical care to this person? **(check one)**

☐ **YES** ⇨ **Go to question 2 and complete the rest of the form.**

☐ **YES, but only after her diagnosis with cervical cancer. She received care from the following doctor before her diagnosis: _____ ⇨ Go to question 2 and complete the rest of the form**

☐ **YES, but I did not retain a chart in my office. ⇨ Answer question 4 and then fax form to us.**

☐ **NO, I do not know this person. ⇨ Fax this form to us.**

☐ **NO, but she was seen by another doctor in the clinic. Please give us this doctor's name_____ ⇨ Go to question 2 and complete the rest of the form**

2. Was this her first incidence of cervical cancer (check one)?

☐ **YES** ☐ **I DON'T KNOW** ☐ **NO**, she was also diagnosed in the year _____

3. Did this patient have any other physicians from whom she may have received gynecologic care before she was diagnosed with ICC? ☐ **NO** ☐ **I DO NOT KNOW** ☐ **YES.** List their name(s) including first name: _____

4. To which laboratories do you/did you send your pap smears to be read?

_____

Fax all cervical cytology/ cervical pathology reports and this form to the study office.
Use the enclosed fax cover-page. Fax #: 514-398-5002

PLEASE TYPE OR PRINT CLEARLY

PHYSICIAN NAME: _____ PATIENT NAME: _____

5. Did this patient ever have a Pap test (**besides those done as the final work-up towards diagnosis of invasive cervical cancer**)?

☐ **YES** ⇨ Please **fax** us the cytology reports and any cervical pathology reports. ⇨ ***GO TO PAGE 3***

****** If you do NOT have the reports, please complete table on page 4**

☐ **NO**

☐ **I DO NOT KNOW**

⇨ Did you ever recommend this patient have a **Screening** Pap test prior to diagnosis with cervical cancer (this does not include those Paps done as the final work-up towards diagnosis of ICC)?

☐ **NOT SURE**

☐ **YES**. Explain _____

☐ **NO** ⇨ Choose a reason below:

☐ Patient refused pelvic exam

☐ I do not provide gynecologic exams/Pap tests

☐ This was a new patient whom I only saw just prior to her diagnosis with cervical cancer.

☐ All prior visits were emergencies or were non-gynecologic visits.

☐ Other. Please explain._____

_____

⇨ ***GO TO PAGE 3***

Fax all cervical cytology/ cervical pathology reports and this form to the study office.
Use the enclosed fax cover-page. Fax #: 514-398-5002

PLEASE TYPE OR PRINT CLEARLY

PHYSICIAN NAME: _____ PATIENT NAME: _____

6. Did this patient ever have an abnormal pap smear prior to her final work-up towards the diagnosis of ICC?

- ☐ **NO**
- ☐ **I DO NOT KNOW**
- ☐ **YES** ⇨ **Fax us the lab report**

⇨ ***GO TO PAGE 4***

PLEASE TYPE OR PRINT CLEARLY

PHYSICIAN NAME: _____ PATIENT NAME: _____

7. Follow-up Procedures for abnormal cervical test results

We are interested in the follow-up procedures that patients had for abnormal cervical test results and recommendations that you made to this patient with regards to any tests prior to their final diagnosis with (micro-) invasive cervical cancer.

Name of Procedure (include name of Doctor if not done by you) 1) Paps, 2) HPV testing, 3) colposcopy, 4) examination under anaesthesia, 5) cervical biopsy, 6) cone, 7) endocervical curettage, 8) LEEP/LOOP, 9) cryotherapy, 10) Laser therapy, 11) uterine dilation & curettage 12) endometrial biopsy.	**Date of Procedure**	**Findings of Procedure**	**Follow-up Recommendations** ***These do **NOT** refer to recommendations made by the pathologist

Fax all cervical cytology/ cervical pathology reports and this form to the study office. ⇨ ***GO TO PAGE 5***

Use the enclosed fax cover-page. Fax #: 514-398-5002

PLEASE TYPE OR PRINT CLEARLY

PHYSICIAN NAME: _____ PATIENT NAME: _____

7. Continued…

Name of Procedure (include name of Doctor if not done by you) 1) Paps, 2) HPV testing, 3) colposcopy, 4) examination under anaesthesia, 5) cervical biopsy, 6) cone, 7) endocervical curettage, 8) LEEP /LOOP, 9) cryotherapy, 10) Laser therapy, 11) uterine dilation & curettage 12) endometrial biopsy.	**Date of Procedure**	**Findings of Procedure**	**Follow-up Recommendations** ***These do NOT refer to recommendations made by the pathologist

⇨ *GO TO PAGE 6*

Fax all cervical cytology/ cervical pathology reports and this form to the study office.
Use the enclosed fax cover-page. Fax #: 514-398-5002

PLEASE TYPE OR PRINT CLEARLY

PHYSICIAN NAME: _____ PATIENT NAME: _____

8. Did this patient ever **NOT** adhere to recommendations you made or delayed complying with recommendations you made regarding the follow-up of abnormal pap results or other abnormal cervical cancer diagnostic procedures?

☐ **I DO NOT KNOW**

☐ **NO**

☐ **YES. Explain and give details** _____

_____

_____

_____

_____

_____

_____

_____

_____

THE END. THANK YOU FOR YOUR PARTICIPATION.

Fax all cervical cytology/ cervical pathology reports and this form to the study office.
Use the enclosed fax cover-page. Fax #: 514-398-5002

APPENDIX 16

Physician questionnaire: Introductory letter for family physicians

Study Coordinating Centre:
Eduardo L. Franco, MPH, DrPH
Principal Investigator
Dept of Epidemiology & Biostatistics
McGill University

Andrea R. Spence, MSc
Study Coordinator
Dept. of Epidemiology & Biostatistics
McGill University

Patricia Goggin, MD, MSc
Médecin-conseil
Systèmes de soins et services
Institut national de santé publique

Abdulaziz Alobaid, M.D.
Clinical Liaison
Clinical Fellow Gynecology-Oncology
CHUM – Université de Montréal

Claude Richard, R.N.
Research Nurse
McGill University

Clinical Co-Investigators:
Pierre Drouin, MD
Professeur
Service de gynécologie-oncologie
CHUM – Université de Montréal

Diane M. Provencher, MD
Chef et professeure
Service de gynécologie-oncologie
CHUM – Université de Montréal

François Lehmann, MD
Directeur
Département de médecine familiale
CHUM- Université de Montréal

Parviz Ghadirian, PhD
Director
Epidemiology Research Centre
CHUM – Université de Montréal

Michèle Deschamps, MSc
Direction de la Santé Publique
Unité de santé physique
Montréal-Centre

Lucy Gilbert, MD
Associate Professor
Division of Gynecological Oncology
McGill University

Martin G. Dawes, MD
Chair, Dept. of Family Medicine
McGill University

Alex Ferenczy, MD
Professor of Pathology & OBGYN
McGill University

* Funded by the Canadian Institutes of Health Research. Study approved by the Research Ethics Boards of McGill University and CHUM

*MONTREAL INVASIVE CERVICAL CANCER STUDY**

_____, 200__

Re: Obtaining Patient Data

Dear Dr. _____,

We are conducting a study to explore the care that women diagnosed with cervical cancer received prior to their diagnosis. This study has received support from the Departments of Gynecology & Obstetrics and Family Medicine at McGill and l'Université de Montréal.

The incidence and mortality rates of cervical cancer have dramatically declined in Canada over the last 50 years. This decline has been largely attributed to the introduction of Papanicolaou (Pap) cytology screening programs in the 1960s. However, despite the gains made in preventing cervical cancer there are about 1,400 new cases of preventable cervical cancer annually. We are looking into the care of all women residing in Montreal or Laval who were diagnosed with invasive cervical cancer between 1998 and 2004.

Please note that our interest is not to scrutinize the care provided by a specific physician or the care received by a specific patient. All analyses will be done in aggregate without any personal identifiers of the physicians or the patients.

Our study will provide valuable information to assist policy decisions concerning cervical screening and to develop new public health initiatives that will help prevent the progression of this disease to an invasive stage. Further, as cervical cancer prevention is undergoing revolutionary changes it is imperative that we gain a better sense of present cervical cancer screening practices in Montreal.

The hospital medical charts of the subjects have been reviewed by the study nurse to find the Pap screening history prior to diagnosis with invasive cancer, and the management/treatment of pre-invasive lesions. In many instances we did not find this information in the hospital medical chart or we found only partial information. This is the reason for us contacting you now in order to obtain this information.

Your cooperation is <u>crucial</u> to the success of this study and we kindly ask you or one of our research staff, to do the following:

1) Fax us the lab reports for the following tests that each woman had related to cervical intraepithelial lesions or invasive cervical cancer: Pap tests (conventional or liquid-based), HPV testing, endocervical curettage, cervical biopsies, cryotherapy, loop electrosurgical excision procedure (LEEP), etc.
2) Complete the two page information sheet for each patient and fax it back to the study office (514)398-5002.

If you prefer, our research nurse, Ms. Claude Richard, or the study coordinator, Andrea Spence, could drop by your office to collect the above mentioned information from your medical charts.

Below are the names of your patients who were diagnosed with cervical cancer. Please note that we have received written consent from these patients to retrieve data from their medical office chart. Find enclosed these consent forms.

Family Name	First Name	RAMQ

Your contribution will be acknowledged in the authorship of any publications to originate from this study.

This project has obtained ethical approval from MUHC and CHUM and the Ethics Boards of various hospitals in Montreal. If you have any questions about the study, please feel free to contact the study's coordinating centre at (514) 398-6926 (English) or (514)398-3399 (French).

Thank you in advance.

Yours sincerely,

Dr. Martin Dawes, MD
Chair
Department of Family Medicine
McGill University

Dr. François Lehmann, MD
Directeur
Département de médicine familiale
Université de Montréal

Eduardo Franco, PhD
Professor and Director
Division of Cancer Epidemiology
McGill University

Andrea Spence, MSc
Study Coordinator
Department of Epidemiology and Biostatistics
McGill University

APPENDIX 17

Physician questionnaire: Introductory letter for gynaecologists

Study Coordinating Centre:
Eduardo L. Franco, MPH, DrPH
Principal Investigator
Dept of Epidemiology & Biostatistics
McGill University

Andrea R. Spence, MSc
Study Coordinator
Dept. of Epidemiology & Biostatistics
McGill University

Patricia Goggin, MD, MSc
Médecin-conseil
Systèmes de soins et services
Institut national de santé publique

Abdulaziz Alobaid, M.D.
Clinical Liaison
Clinical Fellow Gynecology-Oncology
CHUM – Université de Montréal

Claude Richard, R.N.
Research Nurse
McGill University

Clinical Co-Investigators:
Pierre Drouin, MD
Professeur
Service de gynécologie-oncologie
CHUM – Université de Montréal

Diane M. Provencher, MD
Chef et professeure
Service de gynécologie-oncologie
CHUM – Université de Montréal

François Lehmann, MD
Directeur
Département de médecine familiale
CHUM- Université de Montréal

Parviz Ghadirian, PhD
Director
Epidemiology Research Centre
CHUM – Université de Montréal

Michèle Deschamps, MSc
Direction de la Santé Publique
Unité de santé physique
Montréal-Centre

Lucy Gilbert, MD
Associate Professor
Division of Gynecological Oncology
McGill University

Martin G. Dawes, MD
Chair, Dept. of Family Medicine
McGill University

Alex Ferenczy, MD
Professor of Pathology & OBGYN
McGill University

* Funded by the Canadian Institutes of Health Research. Study approved by the Research Ethics Boards of McGill University and CHUM

*MONTREAL INVASIVE CERVICAL CANCER STUDY**

_____, 200___

Re: Obtaining Patient Data

Dear Dr. _____,

We are conducting a study to explore the care that women diagnosed with cervical cancer received prior to their diagnosis. This study has received support from the Departments of Gynecology & Obstetrics and Family Medicine at McGill and l'Université de Montréal.

The incidence and mortality rates of cervical cancer have dramatically declined in Canada over the last 50 years. This decline has been largely attributed to the introduction of Papanicolaou (Pap) cytology screening programs in the 1960s. However, despite the gains made in preventing cervical cancer there are about 1,400 new cases of preventable cervical cancer annually. We are looking into the care of all women residing in Montreal or Laval who were diagnosed with invasive cervical cancer between 1998 and 2004.

Please note that our interest is not to scrutinize the care provided by a specific physician or the care received by a specific patient. All analyses will be done in aggregate without any personal identifiers of the physicians or the patients.

Our study will provide valuable information to assist policy decisions concerning cervical screening and to develop new public health initiatives that will help prevent the progression of this disease to an invasive stage. Further, as cervical cancer prevention is undergoing revolutionary changes it is imperative that we gain a better sense of present cervical cancer screening practices in Montreal.

The hospital medical charts of the subjects have been reviewed by the study nurse to find the Pap screening history prior to diagnosis with invasive cancer, and the management/treatment of pre-invasive lesions. In many instances we did not find this information in the hospital medical chart or we found only partial information. This is the reason for us contacting you now in order to obtain this information.

Your cooperation is <u>crucial</u> to the success of this study and we kindly ask you or one of our research staff, to do the following:

1) Fax us the lab reports for the following tests that each woman had related to cervical intraepithelial lesions or invasive cervical cancer: Pap tests (conventional or liquid-based), HPV testing, endocervical curettage, cervical biopsies, cryotherapy, loop electrosurgical excision procedure (LEEP), etc.
2) Complete the two page information sheet for each patient and fax it back to the study office (514) 398-5002.

If you prefer, our research nurse, Ms. Claude Richard, or the study coordinator, Andrea Spence, could drop by your office to collect the above mentioned information from your medical charts.

Below are the names of your patients who were diagnosed with cervical cancer. Please note that we have received written consent from these patients to retrieve data from their medical office chart. Find enclosed these consent forms.

Family Name	First Name	RAMQ

Your contribution will be acknowledged in the authorship of any publications to originate from this study.

This project has obtained ethical approval from MUHC and CHUM and the Ethics Boards of various hospitals in Montreal. If you have any questions about the study, please feel free to contact the study's coordinating centre at (514) 398-6926 (English) or (514)398-3399 (French).

Dr. Gerald Stanimir, MD
Director,
Division of gynecologic-oncology
McGill University
Department of Obstetrics & Gynecology
Royal Victoria Hospital

Dr. Pierre Drouin, MD
Department of gynecologic-oncology
CHUM-Hôpital Notre-Dame
Professor
Département of Obstetrics & Gynecology
Université de Montréal

Eduardo Franco, PhD
Professor and Director
Division of Cancer Epidemiology
McGill University

Andrea Spence, MSc
Study Coordinator
Department of Epidemiology and Biostatistics
McGill University

APPENDIX 18

Article published in L'actualité médicale

par Sylvie Gourde

La santé des femmes fait l'objet de recherches accrues. Nous poursuivons une série d'articles sur ce thème.

UNE ÉTUDE EXHAUSTIVE SUR LE CANCER DU COL UTÉRIN

La collaboration des médecins est essentielle

Depuis 30 ou 40 ans, le plus vieux test diagnostique pour dépister le cancer du col de l'utérus en a réduit l'incidence de 75 %. Le test Pap est en effet la recommandation officielle pour le dépistage du cancer du col utérin. Quelle femme ne le connaît pas? est-on porté à dire. Certaines femmes ignorent cependant la raison pour laquelle elles subissent régulièrement ce test et le cancer du col utérin semble ne plus être à la mode. On n'en parle plus... Et pourtant, il y a encore, en 2006, 300 cas de cancer du col de l'utérus diagnostiqués chaque année, au Québec, et 1400 au Canada! Où est la faille? Quels sont les maillons de la chaîne où se faufilent tous ces cas? C'est ce que veulent mettre au jour des chercheurs de Montréal issus de l'Université McGill, du CHUM et de la Direction de santé publique afin de dénicher les lacunes qui font en sorte que la bataille contre le cancer du col utérin n'est toujours pas gagnée.

Coordonnée par Andrea Spence, candidate au doctorat, avec la collaboration du Dr Edouardo Franco à titre de chercheur principal, tous deux de l'Université McGill, cette étude vise à analyser les raisons qui mènent au diagnostic du cancer invasif du col utérin malgré la présence d'un test de dépistage dont l'efficacité est prouvée.

CHAQUE ANNÉE, AU QUÉBEC, ON DIAGNOSTIQUE AU QUÉBEC 300 CAS DE CANCER DU COL DE L'UTÉRUS.

Quatre étapes

L'étude comprend plusieurs étapes. La première est la cueillette des données et vise à retracer tous les cancers du col utérin invasif traités à Montréal et à Laval, et ce, grâce au Registre des tumeurs du Québec. Au moment d'écrire ces lignes, 600 cas avaient été identifiés. Les femmes doivent avoir résidé à Montréal et à Laval pendant au moins cinq ans avant le diagnostic. Ces données incluent le dépistage, les interventions diagnostiques et le traitement des lésions précancéreuses. On analysera, grâce à un formulaire structuré conçu pour cette révision, tous les événements qui ont précédé le diagnostic de cancer. On obtiendra également des laboratoires concernés les rapports de tests de cytologie et de pathologie pour chaque sujet.

La deuxième étape est une entrevue avec la patiente ou avec un membre de son entourage en cas de décès. Cette entrevue complétera les données du formulaire et se fera par téléphone. Le médecin de chaque patiente sera contacté afin d'obtenir son autorisation de faire une entrevue avec la patiente. « Ici, nous éprouvons quelques difficultés avec certains médecins, dit le Dr Eduardo Franco. Ils doivent savoir et comprendre que ni les médecins, ni les patientes, ni les laboratoires, ni les hôpitaux ne seront mentionnés, identifiés ou pointés du doigt. Nous avons besoin de leur coopération. Cette étude bénéficiera à tous, car elle englobe toutes les étapes de soins. »

La troisième étape est l'obtention de données de la part des cabinets privés des médecins consultés par les patientes. Encore ici, des médecins résistent à fournir les données demandées. Ces dossiers permettront de compléter et de valider les données sur le dépistage, les procédures diagnostiques et les traitements.

La dernière étape est la récupération et la révision de tous les frottis archivés qui présentent des résultats négatifs, de bas grade ou équivoques. Tous les frottis seront révisés par un pathologiste et un chef cytologiste. Aucun ne sera identifié à une patiente donnée, les résultats ne seront pas connus des réviseurs, pas plus que le nom des laboratoires qui auront fait les premières analyses. Enfin, la patiente devra donner son accord pour que l'on récupère ces frottis.

Dépistage

« C'est la première étude à faire l'analyse de l'ensemble des femmes traitées à Montréal, explique la Dre Patricia Goggin, de l'Institut national de santé publique du Québec. Auparavant, les études n'incluaient qu'un hôpital. Nous voulons mettre sur pied un programme de dépistage du cancer du col, mais, avant d'édicter des lignes directrices, nous devons connaître la situation et cette étude nous permettra de cibler les lacunes qui entraînent encore autant de cas. Il est inexcusable aujourd'hui d'avoir des cancers invasifs du col utérin. »

C'est donc toute la chaîne du dépistage avant le diagnostic qui sera examinée à la loupe, soit tous les états précurseurs du cancer du col utérin. Il faut aussi savoir que ce ne sont pas toutes les femmes qui se prêtent au dépistage. C'est ce que montrera également l'étude. « Chez certaines femmes immigrantes, dit le Dr Franco, il n'est pas naturel de faire un dépistage quel qu'il soit. De plus, les femmes cessent de passer le test Pap vers 50 ans. Elles croient que, parce que leur période de reproduction est terminée, elles ne sont plus sujettes au cancer du col. On constate qu'entre 50 et 70 ans les femmes ne passent plus le test. »

Selon la Dre Goggin, le nouveau vaccin contre le virus du papillome humain (VPH), qui vient d'être commercialisé au Canada, ne préviendra pas tous les cas de cancer du col utérin. Même si on estime que 70 % des cancers du col sont causés par le VPH, il reste un 30 % qui, s'il n'est pas dépisté, peut faire des ravages.

On estime que les données auront été recueillies d'ici un an et demi. « C'est l'étude la plus approfondie qui ait jamais été réalisée, ajoute le Dr Franco. Mais nous avons besoin de la collaboration des médecins, que nous contacterons. Ils doivent saisir toute l'importance d'une telle étude. » ◄

CANCER DU COL DE L'UTÉRUS

L'infection par plusieurs types de VPH augmente les risques

par Véronique Robert

Les femmes infectées par plusieurs souches du virus du papillome humain (VPH) sont beaucoup plus à risque de cancer du col de l'utérus que celles qui sont infectées par une seule souche du VPH.

Telle est la conclusion d'une étude menée sous la direction de chercheurs du Centre universitaire de santé McGill. Les travaux de Franco E et coll. rapportés dans *Cancer Epidemiol Biomarkers Prev 2006*; 15 (7) : 1274-80 ont porté sur 2462 femmes âgées de 18 à 60 ans qui ont subi de multiples tests pour dépister le VPH pendant quatre ans.

Par comparaison avec les femmes non infectées au cours de la première année, celles qui ont été infectées par une seule souche de VPH voyaient leur risque de développer des lésions précancéreuses multiplié par 41. Le risque était multiplié par 92 chez celles qui étaient infectées par deux ou trois souches du virus. Cependant, il était multiplié par plus de 400 chez celles qui étaient porteuses de quatre à six souches différentes (RR: 424.0; IC 95 % 31.8-5651.8). L'association du VPH-16 (la souche ciblée par le vaccin Gardasil récemment mis au point) et du VPH-58 s'est révélée particulièrement dangereuse.

Les auteurs estiment par conséquent que l'analyse génétique des souches de VPH jumelée aux tests de Pap standard pourrait aider à identifier à un stade précoce les femmes qui sont plus à risque de développer un cancer du col de l'utérus.

APPENDIX 19

Letter written by Dr. Goggin, medical officer with the Institut National de Santé Publique du Québec

Institut national de santé publique
Québec
Systèmes de soins et services

Montréal, le 15 août 2006

Docteure, Docteur

Le cancer du col utérin constitue encore aujourd'hui un problème de santé important pour les femmes, avec quelque 300 cas par année au Québec. Il est possible de réduire encore davantage le fardeau relié à cette maladie par une attention particulière à tous les maillons de la chaîne de dépistage, soit de l'invitation à participer, jusqu'au traitement et suivi des états précurseurs de cancer observés à l'examen cytologique.

Une étude a été entreprise récemment au Québec par le Dr Eduardo Franco de l'Université McGill et ses collaborateurs, afin d'identifier et de quantifier les lacunes de notre système de dépistage et ainsi jeter les bases de véritables mécanismes d'assurance de la qualité. À l'heure où des pressions se font sentir pour améliorer la sensibilité du test de Pap conventionnel par de nouvelles technologies plus dispendieuses, il est essentiel de bien comprendre la contribution relative des lacunes reliées aux questions d'accès aux services de dépistage, aux performances comme telles du test de dépistage ou au suivi après un test anormal ou douteux.

L'Institut de santé publique du Québec (INSPQ) mène actuellement des travaux avec le ministère de la Santé et des Services sociaux afin d'améliorer la lutte contre le cancer du col utérin. Nous croyons que ce projet fournira des informations cruciales pour améliorer les services en place et définir des besoins de formation pour les intervenants du réseau. C'est pourquoi nous avons accepté de collaborer activement à ce projet. De plus, selon le protocole établi, toutes les précautions sont prises pour assurer la confidentialité des données et les analyses seront présentées de façon agrégée seulement. Le projet a reçu l'approbation du Comité d'éthique de l'Université McGill ainsi que du Centre hospitalier où votre patiente a été traitée. Il a reçu également un avis favorable de la part du Collège des médecins du Québec en ce qui concerne l'analyse des résultats sans nécessité de divulgation des faits observés aux femmes concernées ou à des instances professionnelles.

En comptant sur votre collaboration pour la réalisation de ce projet de recherche important pour la santé des femmes au Québec, je vous prie d'agréer mes salutations les meilleures.

Patricia Goggin, M.D., M. Sc.
Médecin-conseil
Institut national de santé publique du Québec

190, boulevard Crémazie Est
Montréal (Québec) H2P 1E2
Téléphone : (514) 864-1600
Télécopieur : (514) 864-1616
www.inspq.qc.ca

APPENDIX 20

Medical criteria for quality assessment

Criteria for the management of abnormal Pap smears:

1. An immediate colposcopy (and biopsy) should be done if a Pap smear is one of the following results: HSIL, AIS, AGUS, neoplastic or malignant cells, ASCUS favouring neoplasia, ASCUS-neoplastic process cannot be excluded, and ASC-H. This colposcopy should be done within 3 months of the Pap smear. If an abnormality is found, it should be treated (see below).
2. A Pap smear should be repeated if the first Pap smear is one of the following results: ASCUS unqualified, ASCUS favour reactive process, or LSIL. Pap smears should be repeated 3 times in 3 to 6 month intervals. Specifically, an, ASCUS favour reactive process Pap test should be repeated in 6 months and an ASCUS unqualified or an LSIL Pap should be repeated in 3 months. If any of them are cytologically abnormal, then a colposcopy (and biopsy) should be done. If an abnormality is found upon the colposcopy, it should be treated (see below). Note that it is also acceptable to do an immediate follow-up colposcopy if the first Pap smear is ASCUS unqualified, ASCUS favour reactive process, or LSIL.
3. If a woman is pregnant and her Pap smear is ASCUS unqualified, ASCUS favour reactive process, or LSIL then she is followed like above. If her Pap smear is a higher grade of abnormality, a colposcopy is mandatory and a biopsy is optional. An endocervical curettage should not be performed during pregnancy.

Criteria for the management of cervical lesion:

Biopsy confirmed CIN I, II or III with a technically satisfactory colposcopy can be treated by an ablative or excisional procedure. If the colposcopy is unsatisfactory, then an excisional procedure should be used. CIN I should be treated within 3 months of the colposcopy and CIN II and CIN III should be treated within 1 month of the colposcopy.

APPENDIX 21

An example of the quality assessment of the processes care for one subject

Example of Assessment of follow-up of abnormal Pap smears and treatment of pre-invasive lesions

Below is a listing of all the medical acts, provided by a gynaecologist, that one study subject had within 5 years of diagnosis.

Data Provided by the RAMQ			Data obtained from our 4 sources of data		
Date of Procedure (day/month/year)	RAMQ medical act code (description)	Medical Specialty	Procedure according to our data search	Results of the Procedure	
07/08/2001	9175 (main visit)	Gynaecologist	Pap	ASCUS, neoplastic process cannot be excluded	Follow-up of abnormal Pap smear was not acceptable
02/11/2001	9164 (follow-up visit)	Gynaecologist	Pap	ASCUS, neoplastic process cannot be excluded	
10/12/2001	9175 (main visit)	Gynaecologist	Pap	HSIL	
26/02/2002	6074 (colposcopy)	Gynaecologist	Pap Biopsy ECC	HSIL CIN II/III Neoplastic squamous epithelium consistent with CIN II/III	Treatment of pre-invasive lesion was acceptable. The timing was not acceptable.
09/04/2002	9164 (follow-up visit)	Gynaecologist	LEEP	HSIL, evidence of early invasion	

This subject had her first abnormal Pap smear (trigger Pap) on 07/08/2001. It was read as ASCUS, neoplastic process cannot be excluded. This subject should have been sent for an immediate colposcopic examination. Instead the subject had two repeat Pap smears by the same gynaecologist. She was finally sent for a colposcopy, along with a biopsy and ECC, on 26/02/2002. This was over 6 months since the first abnormal Pap smear. She then had a LEEP for the CIN II/III lesion. This was acceptable treatment of this pre-invasive lesion but there was a delay in providing this treatment. Treatment should take place within one month.

APPENDIX 22

Listing and Description of all Study Variables

Subject demographic characteristics- from subject questionnaire

Variables	Categorization	Analyses in which variable was used (shown by Table)	Definitions and Comments
Place of birth	Canada (reference group) Other	6.9, 6.10, 6.24	Where was the subject born? My main interest was whether the subject was born in Canada or not. Same variable obtained from CCHS.
City of residence at diagnosis	Montreal Laval	6.8	Used for descriptive analysis only. Used to confirm inclusion criteria, along with data from medical charts.
City of residence within 5 years prior to diagnosis	Montreal Laval Other	6.8	Used for descriptive analysis only. Used to confirm inclusion criteria, along with data from medical charts.
If not Canadian born, place of birth	Europe, Asia, Caribbean, Africa, Central America, South America, United States, Mexico	6.8	Used for descriptive analysis only.
If not Canadian born, # of years in Canada prior to diagnosis with ICC (years)	0-9 years (reference group) 10 or more years	6.8, 6.9, 6.10	Originally a continuous variable. Derived from year of diagnosis with ICC (which was the year of tissue-based confirmation of ICC diagnosis) and year of arrival in Canada (which was determined by the subject questionnaire). Same variable obtained from CCHS.
Cultural Background	French-Canadian or French-Canadian mix Other Do not know/remember	6.8	Used for Descriptive analysis only

Subject demographic characteristics- from subject questionnaire- continued

Variables	Categorization	Analyses in which variable was used (shown by Table)	Definitions and Comments
Marital status	Legally married (not separated) (reference group) Common-law Widowed/separated/divorced Single Do not know/remember	6.8, 6.9, 6.10, 6.24	Same variable obtained from CCHS.
Language of conversation	Both English and French (may speak other language) (reference group) English (not French, may speak other language) French (not English, may speak other language) Neither English nor French	6.8, 6.9, 6.10, 6.24	Language(s) spoken well enough to conduct conservation. Same variable obtained from CCHS.
Language spoken most often at home	English only English and another language(s) but not French French only French and another language(s) but not English Both English and French and another language Both English and French but not a 3rd language Neither English nor French Do not know/remember	6.8	Used for descriptive analysis only.

Subject demographic characteristics- from subject questionnaire- continued

Variables	Categorization	Analyses in which variable was used (shown by Table)	Definitions and Comments
Employment status	Employed (reference group) Unemployed/housewife Student Retired Do not know/remember	6.8, 6.9, 6.10, 6.24	Same variable obtained from CCHS.
Highest level of education	Less than secondary education (reference group) Secondary school graduation Some post-secondary education Post-secondary degree/diploma	6.8, 6.9, 6.10, 6.24	This referred to the highest level of education completed. Same variable obtained from CCHS. See footnote.*
Annual household income ($)	≤20,000 (reference group) 21-40,000 41-60,000 >60,000	6.8, 6.10, 6.24	This specifically asked about the household income. Same variable obtained from CCHS.
Number of people in household at diagnosis	Continuous variable	6.8	Used for descriptive analysis only.
Child-birth in the previous 5 years	No (reference group) Yes Do not know/remember	6.9, 6.10	Refers to 5 years before diagnosis with ICC. Same variable obtained from CCHS.
Smoking status	Never (reference group) Current Former	6.9, 6.10	Refers to smoking status at diagnosis. Same variable obtained from CCHS.

*1) less than secondary graduation (<grade 6, high school incomplete), 2) secondary school graduation (CEGEP) incomplete, high school complete), 3) some post-secondary education (CEGEP complete, university undergraduate degree incomplete), 4) post-secondary degree/diploma (technical school complete, university undergraduate degree complete, university graduate school complete or incomplete).

Subject Pap screening knowledge, screening history, physician preferences and cervical cancer symptoms- from subject questionnaire

Variables	Categorization	Analyses in which variable was used (shown by Table)	Definitions and Comments
Knowledge of Pap testing at interview	Yes No	6.11	This refers to self-reports by study subjects, not proxy responses. Refers to knowledge at the time of the interview. This question was asked of all study subjects regardless of whether they resided in Montreal or Laval for a minimum 5 years prior to diagnosis.
Did subject have Pap test within 5 years of diagnosis?	Yes No Do not know/remember	6.11	This refers to the period prior to their diagnosis with ICC. This question was asked of all study subjects regardless of whether they resided in Montreal or Laval for a minimum 5 years prior to diagnosis.
Reason for not being screened within 5 years of diagnosis.	Did not know what Pap test was for. Felt embarrassed Afraid it would hurt Never imagined that I would develop cervical cancer Forgot to do Pap test My physician did not tell me that I needed to do Pap tests I did not have a physician I was busy	6.11	Refers only to subjects who said they were not screened within 5 years of diagnosis. Subjects may choose more than one reason.

Subject Pap screening knowledge, screening history, physician preferences and cervical cancer symptoms- from subjecct questionnaire- continued

Variables	Categorization	Analyses in which variable was used (shown by Table)	Definitions and Comments
Reason for not being screened within 5 years of diagnosis- continued	My physician had inconvenient office hours I thought Pap tests were only for women who had symptoms		
Lifetime frequency of Pap smears	Every 6 months; every year; every 2 years; every 3 years; every 4 years; every 5 years; frequency unknown but screened sometime in past; never screened; do not know/remember.	6.11	This question was asked of all study subjects regardless of whether they resided in Montreal or Laval for a minimum 5 years prior to diagnosis.
Besides Paps done within 5 years of diagnosis, did you have any abnormal Paps throughout your lifetime?	Yes No Do not know /remember	6.11	
Did it matter if the physician performing the gynaecologic exam or Pap test was male or female?	Yes, female Yes, male Did not matter Do not know/remember	6.11	Refers to preference prior to diagnosis.
If the sex of the physician mattered, what if you could not find a physician of that sex?	Have pap smear anyway Not have a pap smear Do not know/ remember	6.11	Refers to preference prior to diagnosis.

Subject Pap screening knowledge, screening history, physician preferences and cervical cancer symptoms- from subject questionnaire- continued

Variables	Categorization	Analyses in which variable was used (shown by Table)	Definitions and Comments
Did it matter if the physician performing the gynaecologic exam or Pap test was older or younger?	Yes, older Yes, younger Did not matter Do not know or remember	6.11	Refers to preference prior to diagnosis.
If the age of the physician mattered, what if you could not find a physician of that age?	Have pap smear anyway Not have a pap smear Do not know or remember Other (I would have found one)	6.11	Refers to preference prior to diagnosis.
Did the type of physician performing the gynaecologic exam or Pap test matter?	Yes, family physician Yes, gynaecologist Did not matter Do not know/ remember	6.11	Refers to preference prior to diagnosis.
If the type of physician mattered, what if you could not find that caregiver?	Have pap smear anyway Not have a pap smear Do not know or remember Other (I would have found one)	6.11	Refers to preference prior to diagnosis.
Presence of Symptoms	Yes No Do not know/remember	6.11	We attempted to obtain this same data from the hospital medical charts.

Health status and physician-use behaviour of study subjects- from subject questionnaire

Variables	Categorization	Analyses in which variable was used (shown by Table)	Definitions and Comments
General health	Poor; fair; good; very good; do not know/ remember	6.12	
Did subject have a family physician or gynaecologist within 5 years of diagnosis?	Yes No Do not know/remember	6.12	If yes, the name, office location, and sex of the physician(s) was queried so that we could send this physician a questionnaire to complete (if consent was received by subject or proxy). The identity of this physician would also provide us with information as to which other hospitals to review medical charts at and which hospital labs to search for lab reports.
Presence of chronic condition	No (reference group) Yes Do not know/remember	6.9, 6.10, 6.11, 6.12, 6.24	This is for a condition that the subject would have sought medical care. Same variable obtained from CCHS.
If yes, type of chronic condition	Hypertension, diabetes, heart problems, thyroid condition, high cholesterol, other types of cancer, less common ailments	6.12	Open-ended question
Had a regular doctor	No (reference group) Yes	6.9, 6.10, 6.12	Refers to medical doctor of any specialty being seen on a regular basis. Same variable obtained from CCHS.

Subject demographic characteristics- from medical charts

Variables	Categorization	Analyses in which variable was used (shown by Table)	Definitions and Comments
Year of diagnosis	1998, 1999, 2000, 2001, 2002, 2003, 2004	6.4, 6.7	Based on the date of the first tissue based procedure that diagnosed ICC. The sources were lab reports found in medical chart or sent to us by physicians or received directly from lab.
Place of residence at diagnosis	Montreal, Laval	6.4, 6.7	Derived from address at diagnosis. Found in medical chart.
Age at diagnosis (years)	20-29, 30-39, 40-49, 30-39, 40-49, 50-59, 60-69, 70-79, ≥80,	6.4, 6.7, 6.8	A continuous variable. Categorized as noted for most analyses. Means and medians calculated for other analyses. Derived from the date of the first tissue based procedure found in lab reports that confirmed ICC and the date of birth found in medical charts. Note: the sequence of numbers comprising a subject's RAMQ number is their date of birth.
Presence of symptoms	Yes No Unknown	6.4, 6.7	Symptoms of cervical cancer are listed below. The category "unknown" means the data indicating the presence or absence of a particular variable were not found in the medical chart. This is the same for other data collected from medical charts.

Subject demographic characteristics- from medical charts

Variables	Categorization	Analyses in which variable was used (shown by Table)	Definitions and Comments
If symptoms present, type of symptom.	Vaginal discharge; between menstrual period vaginal bleeding; post-menopausal vaginal bleeding; vaginal bleeding following sexual intercourse; heavy and/or prolonged menstrual bleeding; abnormal vaginal bleeding (type unspecified); loss of appetite; weight loss; fatigue; pain; other symptoms	6.4	
Reason for appointment that led to the diagnosis of ICC	Specifically for presence of symptoms Routine medical check-up Condition unrelated to cervical cancer Unknown	6.4, 6.7	That is, what led the subject to seek medical care in the first place (before diagnosis)? It is important to note that a subject may have had symptoms of cervical cancer but these symptoms may not have been what led the subject to seek medical care.
Presence of other co-morbidities	Yes Unknown	6.4, 6.7	
Smoking status at time of diagnosis	Current Former Never Not smoking at diagnosis, unclear if former or never smoker Unknown	6.4, 6.7	Abstractors ensured that this smoking status referred to the time of diagnosis with cervical cancer
Family history of any type of cancer	Yes/ Unknown	6.4, 6.7	Any type of cancer. Type of cancer noted and relative.

Characteristics of cancer- from medical charts

Variables	Categorization	Analyses in which variable was used (shown by Table)	Definitions and Comments
Stage of cervical cancer	IA1, IA2, IB, II, III, IV, unknown	6.4, 6.7	
Histology	Squamous cell, adenocarcinoma, adenosquamous, other less common types, unknown	6.4, 6.7	

Subject demographic characteristics-from 2001 Canadian Census

Median income level ($)	<30,000/ 30,000-39,999/ 40,000-49,999/ 50,000-59,999/ 60,000-69,999/ ≥70,000/ Missing	6.4, 6.7	By census tract. This refers to the census tract that the subject resided in when diagnosed with ICC. Census tracts were obtained by using the 6-digit postal code of each subject's address. This was obtained from the address at diagnosis, which was found in the medical charts.
Completed university degree (%)	Continuous	6.4, 6.7	% by census tract

Classification of screening histories for cases[1]

Variables	Categorization	Analyses in which variable was used (shown by Table)	Definitions and comments
Ever or Never screened	Ever screened Never screened Subjects not classified as ever or never screened	6.16, 6.18, 6.19	Refers to lifetime screening histories and only to pre-diagnostic period. Data received from all possible sources were used to determine this variable. Based on available data, the screening histories of 161 women could not be classified as ever or never screened. However, it was determined that they were not screened within five year prior to diagnosis with cervical cancer.
Time since last Pap amongst those Ever screened	<3 years 3 to <5 years ≥5 years Subjects classified as ever screened but not able to classify time since last Pap	6.16, 6.18, 6.19	Refers to last Pap that occurred in the pre-diagnostic period. Time interval is measured from the date of diagnosis with ICC. Data received from all possible sources were used to determine this variable. There were six subjects for whom it was determined that they were ever screened but I was not able to determine the timing of that last Pap smear.
Overall screening history adequacy	Inadequate Adequate	6.18, 6.19	"Inadequate screening" includes subjects never screened, those screened within 5 years of diagnosis (but not within 3 years), those screened greater than 5 years before diagnosis, and those subjects for whom we could not determine whether they were ever or never screened but we were able to determine that they were not screened within 5 years before diagnosis. "Adequate screening" refers to women screened within 3 years of diagnosis.

[1] Refers only to women residing in Montreal or Laval for a minimum five year prior to diagnosis. Data obtained via hospital medical charts, hospital cytology/pathology laboratory reports, subject questionnaires, and physician questionnaires.

Physician demographic characteristics

Variables	Categorization	Analyses in which variable was used (shown by Table)	Definitions, Comments, and Sources of data
Medical specialty of physician who performed the trigger Pap	Gynaecologist Family Physician Missing	6.24	The trigger Pap smear was the first abnormal Pap smear within the 5 year observation period. The names of the physicians who performed each Pap test were obtained from laboratory reports and from abstraction of data from medical charts. The specialty of each given physician was subsequently obtained from the Medical Directory of the College des Medecins du Quebec. The missing category indicates that the identity of the physician was not known or the physician was not listed in the directory.
Gender of physician who performed the trigger Pap	Male Female Missing	6.24	Self-evident from name or obtained from subject questionnaire or physician's office staff.
Time between physician's year of medical school graduation and year of trigger Pap (years)	5-19 20-28 29-35 36-49 Missing	6.24	The year of physician's graduation from medical school was obtained from the Medical Directory of the College des Medecins du Quebec. It was categorized as follows.