The effect of hormone replacement therapy on the risk of colorectal cancer in postmenopausal women

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ABSTRACT

In this thesis we examine the effect of hormone replacement therapy (HRT) on the risk of colorectal cancer. Also examined are the effects of oral versus transdermal estrogen replacement therapy, methods of defining estrogen exposure, selection bias, and trends in the use of HRT over the last two decades.

A nested case-control study was conducted using records from Saskatchewan Health's administrative databases. Information on covariates not available from the databases was collected during interviews, from a subgroup of subjects. Incidence density sampling was used to age match controls (four per case, N= 12,116) to each of 3,059 cases accrued in the province from 1981 to 1998.

Short and long durations of HRT use (<5 years and ≥ 5 years) were associated with odds ratios (OR) of 0.86 (0.76 – 0.97) and 0.78 (95% CI: 0.64 – 0.86), respectively. Stratification according to history of having had a screening sigmoidoscopy did not eliminate the observed protective effect. Important differences were not seen between more recent HRT use (< 5 and < 10 years), compared with more distant past use (≥ 5 and ≥ 10 years).

The use of various definitions of estrogen exposure produced ORs ranging from 0.78 to 0.99 which are similar to results from almost two dozen observational studies conducted over the past two decades indicating that this is an important source of variability that needs to be considered.

The study of independent effects of oral and transdermal estrogens revealed a protective effect of transdermal estrogen that was much greater than that of oral estrogen and which has not previously been reported. A protective effect remained when women who had used oral estrogen only were used as the reference group.

Data pertaining to lifestyle factors collected by interview appeared not to alter ORs for HRT and colorectal cancer. However, due to extremely low response rates in the

interview phase of the study, 30% among cases and 18% among controls, we were unable to conclude whether or not confounding was eliminated.

An important finding of research is the strong observed protective effect of transdermal estrogen replacement therapy. This demonstrates the importance of taking into consideration the mode of estrogen delivery in studies where the associations between HRT use and health outcomes are examined.

ABRÉGÉ

Cette thèse a été consacrée à l'étude des effets de l'exposition aux hormones de remplacement (HRT) sur le risque du cancer colorectal. Les sujets suivants ont également été étudiés : comparaison des effets de l'exposition aux œstrogènes oraux et transdermiques, conséquences méthodologiques sur les résultats d'utiliser différentes définitions pour décrire l'exposition aux oestrogènes et étude de la tendance concernant l'utilisation des HRT au cours des vingt dernières années.

Il s'agit d'une étude cas-témoin réalisée en utilisant les bases de données administratives de la Saskatchewan. Pour chaque cas (N=3,059) dans la période 1981-1998, quatre témoins (n=12,166) ont été sélectionnées, appareillées sur l'âge. L'information concernant des variables importantes non contenues dans les bases de données ont été recueillies par interrogatoire d'un groupe de sujets sélectionnés.

L'exposition brève (< 5 ans) ou longue (≥ 5 ans) aux HRT a été trouvée protectrice du risque de cancer colorectal avec des odds ratios (ORs) de 0.86 (0.76-0.97) et 0.78 (0.64-0.86), respectivement. L'ajustement sur la réalisation d'une sigmoidscopie ne change pas ces résultats. La période d'exposition, récente (< 5 ou < 10 ans) ou plus anciennes (≥ 5 ans ou ≥ 10 ans) ne change pas les résultats.

L'utilisation de différentes définitions pour l'exposition aux HRT entraîne des variations de l'OR entre 0.78 et 0.99. Cette amplitude correspond à celle observée dans les études épidémiologiques publiées sur le sujet, ce qui démontre l'importance d'une bonne définition dans ce type d'étude.

L'étude a montré également que l'exposition aux oestrogènes transdermiques était associée à un effet protecteur nettement supérieur à celui des oestrogènes oraux.

Les données collectées par interrogatoire sur le style de vie ne modifient pas la relation entre HRT et cancer colorectal. Ce résultat est cependant difficile à interpréter à cause du faible taux de réponse : 30% chez les cas et 18% chez les témoins.

En conclusion, le résultat le plus important de ce travail est la découverte d'un fort effet protecteur des oestrogènes transdermiques. Ce résultat invite à prendre en compte le mode d'administration quand on étudie l'effet des HRT.

Statement of originality

Several elements of this thesis constitute original scholarship and are a contribution to new knowledge in both substantive and methodological aspect of the study of the health effects of hormone replacement therapy (HRT).

Large, outpatient prescription drug dispensing databases have not previously been exploited to describe trends in the use of HRT to the extent employed in this thesis. The methods used have been borrowed from descriptive epidemiology, but their application to pharmacoepidemiology as outlined in the descriptive papers presented here involved much contemplation. The studies demonstrate how administrative databases can be efficiently used to generate population-based statistics as they pertain to patterns of drug use. Prior to this work, patterns of HRT use among postmenopausal women in the Canadian population had not been reported.

This is the first study where the impact of the variability in the definition of exposure to estrogen replacement therapy on the estimate of colorectal cancer risk has been examined. This brings attention to, and further understanding of, an important aspect of study design in pharmacoepidemiolgy, particularly in an area of research where there is much inconsistency in results.

Finally, this is the first study to demonstrate an important difference between the effects of oral and transdermal estrogen on the risk of colorectal cancer in postmenopausal women. The protective effect of transdermal estrogen is greater in magnitude than previously reported for HRT. Our findings demonstrate the importance of considering the mode of estrogen delivery in studies where the health effects of HRT are studied.

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Acknowledgements

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Contribution of Authors

This thesis by manuscript includes one research letter and four manuscripts. In addition, there is a comprehensive review of the literature, a detailed methods section, a results section (results not presented in the manuscripts), a final discussion and a conclusion.

Dr. Jean-Paul Collet conceived of the overall idea to apply the nested case-control study design with two-phase sampling to the investigation of the question of the effect of hormone replacement therapy on the risk of colorectal cancer. In addition, he recognized that the Saskatchewan Heath healthcare databases would be ideal data sources for this project. He is the principle investigator on the grant submitted funded by the National Cancer Institute of the United States. Manuscript co-authors Drs. JF Boivin, JA Hanley are co-investigators on the grant application.

The candidate reviewed the literature, identified the issues and wrote the grant application that resulted in the funding of this project. She is identified in the grant as the doctoral student working on the project. The candidate was responsible for the development of the protocol and all administrative duties related to it.

The candidate planned the fieldwork, using as a model previous work conducted by the research team. Together with Dr. MaryRose Stang at Saskatchewan Health they trained interviewers and monitored the quality of the work. The candidate took several trips to Saskatchewan in order to facilitate the implementation of fieldwork plans.

The candidate initiated the research for all of the manuscripts in this thesis. She conceptualized the objectives, design, and planned all of the statistical analyses. In addition, the she was responsible for deciding on and the defining of variables to be studied, interpreting and reporting of the research results. The candidate wrote the initial drafts of all the manuscripts and was responsible for revising them to incorporate co-authors suggestions.

The co-authors Drs. JP Collet, JF Boivin, and JA Hanley have critically reviewed the manuscripts, provided feedback and have been available for consultation throughout this doctoral research.

Ms. Andrea Benedetti was responsible for the database management for all of the work on this project. Under my direction she wrote computer programs for the data cleaning and the organization of the data. She has played a major role in facilitating all the work in the manuscripts and Phase 2 work with her programming skills. In-depth discussions with her with regard to programming inevitably resulted in an important intellectual contribution from her.

Disclaimer

This study is based in part on data provided by the Saskatchewan Department of Health. The interpretation and conclusions contained herein do not necessarily represent those of the Government of Saskatchewan or the Saskatchewan Department of Health.

CHAPTER 1. INTRODUCTION

1.1 Rationale

In Canada colorectal cancer is the third most frequently diagnosed cancer in women and despite a fairly good prognosis with early detection, it remains the third cause of cancer mortality.[1] Although age-standardized incidence and mortality rates have been declining since the mid-1980s, the number of new cases diagnosed each year continues grow as the population ages.

Screening with fecal occult blood testing, sigmoidoscopy, and colonoscopy have been shown to decrease colorectal cancer incidence and mortality.[2-4] All of these procedures however, are associated with problems of lack of compliance, incomplete detection, cost and occasional morbidity.[5] Chemoprevention and prevention through lifestyle changes remain attractive and important strategies to reduce the burden of colorectal cancer.[6]

The hypothesis that female reproductive hormones, specifically estrogens, protect against colorectal cancer originated with observations almost 30 years ago, that nuns had elevated mortality rates of colorectal cancer.[7] With the integration of the present knowledge of cellular metabolism, genetics and the complex pathophysiology of colorectal cancer Potter[8] and others[9,10] have proposed sophisticated and plausible mechanisms that link hormonal factors with the etiology of this disease in women. While 30 years of research has identified exogenous estrogen as a promising chemoprotective agent, we still do not have conclusive evidence to confirm this.

The Canadian female population is aging and growing in number. The number of peri- and postmenopausal women taking hormone-replacement therapy (HRT) to treat symptoms experienced during menopause or to prevent osteoporosis, is increasing.[11] An even greater number will be faced with having to decide whether or not to take HRT. Clarifying the role of HRT in the etiology of colorectal cancer is important to women's health and our understanding of the risk-benefit profile of HRT.

Studies conducted to investigate the effect of HRT, and other reproductive factors on colorectal cancer risk have been limited by both observational and experimental study designs. In addition, many of the potential risk and protective factors that can confound the HRT-colorectal cancer association, such as diet, smoking, the use of non-steroidal antiinflammatory drugs (NSAIDs) and physical activity are challenging exposures to measure. It is possible that many of these covariates exert their influence decades prior to colorectal cancer diagnosis, during the initiation of carcinogenesis, further complicating the task of quantifying these exposures in relation to the disease occurrence. Not surprisingly, therefore, many epidemiological studies examining the association between HRT and colorectal cancer have not been completely convincing and questions remain, particularly with regard to the possibility of residual confounding playing a role in the observed protective effect of HRT.

In this population-based nested case-control study we analyzed highly accurate estrogen dispensing data in relation to the incidence of colorectal cancer in Saskatchewan women. This detailed prescription data was prospectively documented in the provincial out-patient prescription drug plan database which was established in 1976. We were able to distinguish between various estrogen formulations and we had access to complete information on prescribed NSAIDs and other broad categories of prescribed drugs. Information with regard to the use of sigmoidoscopy and frequency of physician visits was available from other healthcare databases. Information on diet, physical activity, weight and reproductive history was collected during telephone interviews and the use of mailed self-administered questionnaires from a sample of study subjects.

The two-phase sampling design that we used was originally proposed two decades ago by Walker[12] and White[13] in order to increase the efficiency of data collection pertaining to covariates. The design is ideal for studies in populations where there is extensive documentation available on the main exposure and disease of interest. We used a balanced sampling design, where sampling is conditional on both disease and exposure status, thus further increasing statistical efficiency. The selection bias introduced during sampling is removed by correcting for the sampling fractions that vary with exposure and

disease status, as described by Collet et al[14] an Breslow and Cain.[15] Using the first phase data the variance is also corrected

1.2 Study objectives

The aims and objectives of the study outlined below include the original objectives as described in the grant application for this research and additional objectives that have been identified and considered important to pursue during the course of the study.

1.2.1 General aims

The general aim of the study was to test the hypothesis that exposure to HRT exerts an independent protective effect to reduce the risk of colorectal cancer in postmenopausal women.

1.2.2 Specific Aims

Specific objectives of the study were:

1) To determine the strength of association over varying durations of use and dosage.
2) To determine the effect of timing of HRT exposure.
3) To determine the association between specific formulations of HRT and the risk of colorectal cancer in women.

1.2.3 Additional Aims

Additional aims of study were:

1) To describe trends in the use of hormone replacement therapy in the Canadian population.
2) To describe health related characteristics of peri- and postmenopausal women.
3) To determine the impact of varying the definition of estrogen exposure on the estimation of measures of effect.

1.3 Overview of thesis

This thesis consists of a comprehensive review of the literature (Chapter 2), a methods section (Chapter 3), four manuscripts and one research letter addressing the objectives

stated above (Chapters 4 to 7). A separate results section describes findings not presented in the manuscripts (Chapter 8). A final discussion and conclusion section are presented in Chapter 9 and 10.

In Chapter 4, two papers *Use of hormone replacement therapy by postmenopausal women in Saskatchewan: 1981 to 1997*s and *Trends in the use of hormone replacement therapy by postmenopausal women in Saskatchewan: 1980 to 1997,* descriptive statistics of HRT use are presented. This is the first examination of changes in patterns of HRT use, over an extended period of time by Canadian women.

The third manuscript, *Health related behavior and use of hormone replacement therapy,* examines the differences and similarities between HRT users and nonusers in postmenopausal women among women with and without colorectal cancer in an effort to identify unknown covariates that may be confounders or effect modifiers in the HRT - colorectal cancer association.

The fourth manuscript, *The effect of oral and transdermal estrogen replacement therapy on the risk of colorectal cancer in postmenopausal women,* examines the independent effects of oral versus transdermal estrogen on colorectal cancer risk.

The fifth, *Defining estrogen exposure in longitudinal studies: Impact on measures of effect,* is an examination of various methods that have been used to quantify estrogen exposure and their impact on the estimation of colorectal cancer risk.

Results pertaining to the interview phase of the study are presented in Chapter 8, in addition to a further examination of the effect of HRT on the risk of colorectal cancer. Chapter 9 and 10 follow with the discussion and conclusion.

CHAPTER 2. BACKGROUND AND REVIEW OF THE LITERATURE

In this Chapter, I will provide an overview of the epidemiology of colorectal cancer and risk factors associated with it. This is followed by a review of the existing evidence for and against the hypothesis that HRT is protective for colorectal cancer.

2.1 Burden of disease

It is estimated that approximately 17,200 new colorectal cancer cases, 7,900 of them women, will be diagnosed in Canada in 2001.[1] The estimated 2001 age-standardized incidence rate in females is 38.0 per 100,000, and the age-standardized mortality rate is 13.6 per 100,000. This is surpassed only by rates for lung and breast cancer.[1]

During the past 15 years the age-standardized rates of colorectal cancer have been declining in both sexes: 19% in women and 8% in men. However, due to the growth and aging of the population, the number of new cases diagnosed each year continues to increase. Colorectal cancer also remains the third most common cancer and cause of cancer death, underscoring its important contribution to cancer burden in Canada [1].

Until recently, statistics pertaining to colorectal cancer sub-site incidence had been limited. Sex specific trends however, are now being reported.[16,17] In both men and women over the age of 60, the highest rates of incidence are reported for proximal tumors, followed by rectal and distal cancers.[17] During the past 50 years there has been a gradual shift in the location of carcinomas from the rectum and left (distal) colon towards the right (proximal) colon. The pattern is evident in Canada[1] and several other countries[18] and is more apparent in women than in men. The etiology of this shift is not entirely clear but may be due in part to a greater decline in distal colon and rectal cancer than in proximal colon cancer (Figure 2.1).[1]

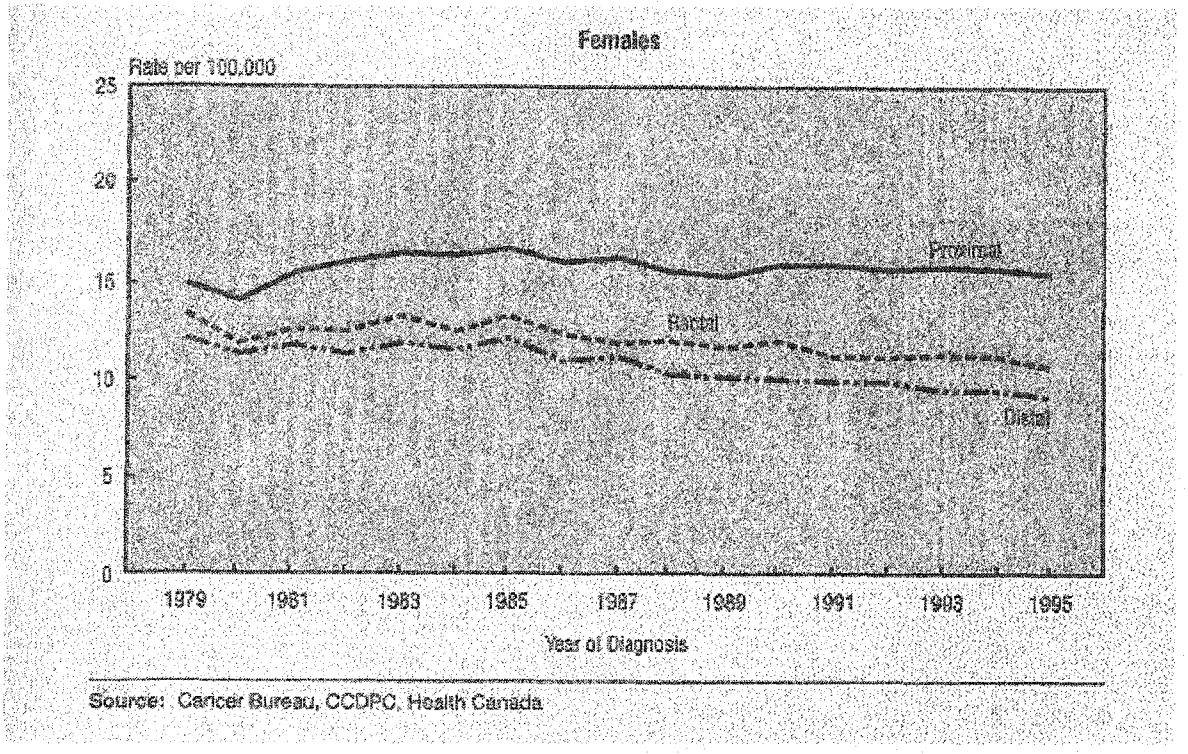

Figure 2.1 Age-standardized incidence rates for colorectal cancers by subsite, Canada, 1979 – 1995.
Source: Canadian Cancer Statistics 2001, National Cancer Instutute of Canada[1].

Mortality and survival rates have been gradually improving during the last two decades as a result of improvements in diagnostic tools and treatment. As in the case of incidence rates, the improvement has been more evident in women.[19] A 'death to new case' ratio has been suggested as a way of classifying cancer prognosis. Among women the colorectal cancer death to new case ratio is 0.37, which is interpreted as a fairly good prognosis[1]. Nevertheless, the five-year survival among women diagnosed with colon cancer is around 60%, underscoring the importance of prevention.[17] In geographical areas where screening is common, rectal cancer has a slightly better overall survival.[8]

2.2 Epidemiology of colorectal cancer

Incidence rates of colorectal cancer vary approximately 20-fold around the world, with countries in the Western world having the highest rates.[20] Canada and the United States hold intermediate positions for both males and females.[8,21] Several decades ago Doll and Peto estimated that as much as 85% of colorectal cancers may be attributed to environmental factors.[22] More recently Platz et al. estimated that in men more than 70%

of colon cancer cases can be attributed to diet and lifestyle factors.[23] For women the estimates may be similar.

Experts have attributed recently declining incidence rates of colorectal cancer, in both Canada and the United States, to population-based prevention programs.[1,17,24,25] However, there is debate over which lifestyle and health factors are responsible for this decline.[26-28] Earlier detection and an increase in the removal of premalignant polyps likely play important roles[19] and experts agree that these practices should continue to be vigorously promoted. At the same time there is also agreement that colorectal cancer is largely preventable and many risk factors are modifiable.

2.3 Natural history of colorectal cancer

2.3.1 The adenoma-adenocarcinoma sequence

The development of colorectal cancer is a multi-step process that involves the genetic mutation of normal tissues, along with their proliferation and growth. There is convincing indirect evidence for this pathogenetic process that is characterized by the 'adenoma-adenocarcinoma sequence.' Most, but not all carcinomas develop from precursor polyps.[18] Not all colonic polyps are adenomas but only adenomatous polyps have the potential to develop into invasive cancer. Some colonic polyps are hyperplastic and are not cancerous. From colonoscopic polypectomy specimens it has been estimated that only about 1 to 3% of adenomas develop into adenocarcinomas.[19,29]

Adenomatous polyps are the most common type of polyps and are found in approximately 33% of the general population by age 50, and 50% of the population by 70 years of age[30] when the incidence of colorectal cancer also peaks. While only 6% of adults will develop colon cancer, autopsy studies have shown as much as 10 to 33% of the population have developed colonic polyps by death. Increased rates of colorectal carcinoma have been reported in patients with adenomas compared with the general population. In addition, the anatomic sites of adenomas typically parallel the distribution of colorectal carcinomas.[31]

The transformation from adenomatous polyp to invasive cancer is thought to take as long as 10 to 20 years.[19,29] Evidence to support the existence of this latent time period is provided by observations made prior to the availability of colonoscopy for the removal of colonic polyps without laparotomy. A large proportion of polyps that had been identified by barium enema and left untreated, were observed to develop into invasive carcinomas 20 years later. Ademomatous polyps and carcinomas also appear to share many genetic similarities and to have many risk factors in common.[19,29]

2.3.2 Colorectal tumor staging

Dukes proposed a widely used classification for colorectal tumors based on the two prognostic features: the depth of direct invasion and metastasis to regional lymph nodes. The four stages are: Dukes' A lesions, where the growth is confined to the bowel wall; Dukes' B lesions, where the tumor has progressed through the full thickness of the bowel wall; Dukes' C lesions, where regional lymph nodes are involved; and Dukes' D, where distant metastases has occurred.[18] Other staging systems such as the TNM (tumor, node, metastasis) classification roughly correspond to the Dukes' staging system facilitating conversions from one system to the other.[29]

All classification systems are limited by observer variation since pathological changes occur along a continuum and may not fall into obvious classification categories. The reproducibility of colorectal cancer staging is therefore problematic.[29]

2.4 Risk factors for colorectal cancer

Doll and Peto have suggested that 85% of colorectal cancer cases in the United States might be prevented by changes in diet and lifestyle.[22] The research effort devoted to identifying risk factors of colorectal cancer is therefore not surprising. Many suspected risk factors for colorectal cancer were first recognized in ecological data.[32,33] The potential problems of confounding in these studies are well recognized and as expected, observational and experimental studies have not provided the evidence needed to confirm many early hypotheses. Further complicating our understanding of the etiology of colorectal cancer is the inconsistency of results from observational and experimental

studies[33] for many risk factors. In fact, several decades ago dietary fibre and fat intake were accepted by many experts as playing important roles in the etiology of colorectal cancer. More recently the supporting scientific evidence has been downgraded from a classification of 'convincing' to a more uncertain 'possible'. Due to the volume of published research in this area, many of the risk factors I will discuss below are 'dynamic' in their status as protective or risk factors in the etiology of colorectal cancer. In addition, new hypotheses have emerged to identify new additions to the risk factor list, such as calcium, folate and Vitamin D. These have just begun to be investigated with regard to their role in the etiology of colorectal cancer.[32]

In the following discussion I will summarize the evidence for suspected risk factors for colorectal cancer, and where evidence is available, I will refer to their association with the risk of colorectal cancer in postmenopausal women. I will classify risk factors according to the classification for the strength of scientific evidence in support of causal relationships: convincing, probable, possible and insufficient, as proposed by the *American Institute for Cancer research (AICR).*[34]

2.4.1 Known risk factors

2.4.1.1 Family history

Several inherited syndromes and genes are known to predispose individuals to colorectal cancer. Familial adenomatous polyposis, Gardner syndrome and hereditary nonpolyposis colorectal cancer are a few of the rare inherited syndromes with high incidence rates of colorectal cancer.[35] It has also been suggested that, in women, a family history of breast, ovarian, and endometrial cancer may be related to an increase risk of colon cancer.[20]

About 10 to 20% of individuals, who develop colon cancer, have a first-degree relative with colorectal cancer.[36] A twofold risk of developing cancer is associated with a family history of an affected first-degree relative. When more relatives are affected the risk is even higher. This effect of family history appears to be greatest among those under age 45 years of age. Separating the genetic effects from those of the environment and shared family lifestyles remains an important research question.

2.4.1.2 Inflammatory bowel disease

Inflammatory bowel diseases such as ulcerative colitis and Crohns disease have been estimated to increase the risk of colon cancer eight to 30-fold [20]. In these diseases chronic inflammation leads to hyperproliferation in the colonic mucosa which can lead to neoplastic changes. In the United States however, they account for less than one percent of all colon cancers.

2.4.2 Probable risk factors

2.4.2.1 Meat intake

Food groups, as well as specific nutrients have been implicated in altering the risk of colorectal cancer. There is debate with regard to the strength of the evidence in support of the hypothesis that a high red meat intake increases the risk of colon cancer, however, the AICR has classified it as 'probable'.[8,34]

Of more than two dozen observational studies conducted to investigate this association about half of the findings are consistent with an increase in risk and the other half with no association. A decrease in risk has also been shown.[34] Uncertainty with regard to the role of meat intake in the etiology of colorectal cancer is related to difficulty in determining how much of the increase in the observed risk is due to meat consumption and how much may be due to an inadequate intake of fruit and vegetables and nutrients that may contain protective substances inherent in these foods.[37] Many people who consume large amounts of meat consume very little in the way of fruit and vegetables and vice versa.[20] Heterogeneity among studies has also led to conflicting results. In studies, 'meat' can be defined as 'all meat', to include red meat, processed meat, cured meat, fatty meat, lean meat and the proportions of these different types of meat can vary in the diets of various populations. In addition, the cooking process of meat may alter substances found in meat, thereby modifying its carcinogenic potential.

In a recent meta-analysis Sandhu et al[38] reviewed prospective observational studies that investigated the association between meat consumption and colorectal rectal. Case-

control and ecological studies were excluded, as were studies where meat consumption was not quantified. Results from thirteen published studies were included in the analysis. Risk estimates were determined for 'all meat', 'processed meat', and 'red meat'. For 'all meat' and 'red meat', daily intake of a 100-g portions were associated with random-effects rate ratios of 1.14 (95% CI: 1.04 – 1.25) and 1.17 (95% CI: 1.05 – 1.31), respectively. For a 25-g portion of processed meat the estimated rate ratio was 1.49 (95% CI: 1.22 – 1.81). For comparable categories of exposure the summary ORs tended to be higher for studies reporting colorectal cancer incidence as study end-points, and for studies where dietary validation studies had been conducted and ORs adjusted for total energy intake.

Diets high in red meat increase the production of secondary bile acids which have been demonstrated in animal studies to be cytotoxic to colonic cells causing hyperproliferation of the colorectal epithelium and the promotion of tumor formation.[30] While the fatty acid content in red meat may exert its effect through this mechanism, additional risk may result from substances produced during cooking. Heterocyclic aromatic amines (HCA), potent mutagens, are formed in meat and fish during typical household cooking practices and have been reported to be associated with an increase in colorectal cancer risk[39] and an increase in the prevalence of adenomatous polyps.[40] Other mutagenic substances found in some processed meat products include *N*-nitroso compounds, nitrosamines and polycyclic aromatic hydrocarbons.

A proposed mechanism that is consistent with the genetic model of colon carcinogenisis pertains to acetyltransferase enzymes which are involved in the detoxification of several carcinogenic arlyamines. In addition, HCAs require metabolic activation to function as mutgens. With meat consumption, genetic predisposition for the enzymes involved in this activation may modify the risk for colorectal cancer. Colorectal cancer patients have been found to have differences in these metabolizing enzymes that are under genetic control. Risk of developing colon cancer may therefore be influenced by the inheritance of genes that regulate the metabolizing enzymes as well as exposure to food mutagens.[35]

2.4.2.2 Alcohol intake

Alcohol is known to inhibit DNA repair.[41] There is strong but not entirely consistent evidence to suggest that alcohol increases the risk of colorectal cancer in men.[33,42,43] The evidence is even less consistent for women, but only a few studies examining the association between alcohol consumption and colorectal cancer have included women.

A dose-response trend has been observed in studies, with as little as one drink a day increasing risk.[44] In a population-based case-control study, Meyer and White[44] observed statistically significant increases in ORs (1.0, 1.3, 1.8 and 2.5) for colon cancer, among middle-aged women, with increasing alcohol intake from 0, <10, 10-29, and ≥30 g/day. The authors reported finding similar associations among men.

Some of the inconsistencies may be due to differences in study methods. For example the effect of alcohol may be exacerbated by low folate and methionine levels and these dietary constituents may not always be well measured in studies.[42] In addition, not all studies have used alcohol abstainers as the reference group and in many studies exposure status is defined by membership in specific groups such as those with a history of alcohol abuse.

None of the studies have demonstrated that any one source of alcohol is associated with greater risk than the other.[34]

2.4.3 Possible risk factors

2.4.3.1 Body size

Studies investigating the effect of body size or weight on the risk of colorectal cancer are complicated by potential confounding by difficult to measure covariates such as physical activity, and dietary intake. Other issues complicating the ability to obtain a valid estimate of the association between body weight and colorectal cancer pertain to identifying the appropriate parameter reflecting the effect of body weight. Body mass index (BMI), central adiposity and weight gain or loss, are all important, but different indicators of body weight status and size.

Studying the body weight-colorectal cancer risk association is further complicated by the fact that subjects frequently need to recall what their weight was prior to their diagnosis of colorectal cancer. The relevant period of exposure may be very early in life and may be difficult to recall with accuracy, especially by people who have experienced numerous weight fluctuations. In the Harvard Growth Study, where height and weight was recorded during adolescence, and colorectal cancer ascertained 55 years later, it was found that a high body mass index (BMI) during adolescence was associated with a 6-fold increase in the risk of colorectal cancer in men. No association was found between adolescent high BMI and colorectal cancer in women.[45] The study is of interest because of the long period of follow-up, however, was limited by large losses to follow-up and the lack of information pertaining to weight change during adult years, and covariates such as diet and physical activity.

Bird et al [46]studied the association between obesity and history of weight changes and the prevalence of adenomatous polyps of the distal colon and rectum in a case-control study of men and women who had undergone sigmoidoscopies. BMIs greater than 23.5, adult weight gains of 1.5 to 4.5 kg, and at least one large weight change greater than 4.5 kg were associated with significantly elevated ORs. This case-control study was matched on sex and effect modification by sex was not reported.

Martinez[47] reported the effect of body weight on the risk of colon cancer using data from the Nurses' Health Study (NHS). Leisure time physical activity, diet, smoking, postmenopausal estrogen use, and aspirin use were prospectively measured biennially. Women who had had BMIs of greater than 29 had multivariate adjusted RRs of 1.45 (95% CI: 1.02 - 2.07), 1.96 (95% CI: 1.18 - 3.25) and 1.26 (95% CI: 0.71 - 2.23), for colon, distal and proximal colon cancers, compared to women with BMIs less than 21. A tendency toward higher risk of colon cancer with increasing waist-to-hip ratio (WHR) was also observed, but RRs were not statistically significant. A 20 kg weight gain from age 18 was associated with a RR of 1.56 (95% CI: 0.97 - 2.47) for distal colon cancers and a RRs for proximal colon cancers.

The study by Martinez provides important evidence in support of an independent effect of excess body weight as measured by BMI to increase the risk of colon cancer in women. A similar increase in the risk of colorectal ademoma among women with high BMIs was reported by the NHS investigators.[48] Nonetheless, a possible limitation of the Nurses' Health Study might be that only leisure activity was measured in all of the studies. If women are misclassified with regard to total activity the effect of high BMI could conceivably be due to residual confounding from total activity. Although occupational activity in women may generally be uninformative because of narrow levels of activity, nurses are a group where occupational activity may indeed vary depending on the whether clinical or administrative work is engaged in. In addition, whether the level of total physical activity modifies the effect of BMI has not been explored. In men there is evidence to suggest that high BMI increases colon cancer risk only in men who are physically inactive.[49]

The suggestive association between WHR and colon cancer risk reported by Martinez[47] is interesting and has been reported previously in women[50] but remains to be confirmed. It has been hypothesized that abdominal obesity is more relevant for colorectal cancer risk than an increase in generalized body fat. Hyperinsulinemia and other growth-related factors associated with abdominal obesity are known to promote tumor growth and may promote colorectal tumor growth.[10] Again, the association between WHR and colorectal cancer risk appears to be stronger in men.[51] If central adiposity is more important than generalized obesity in the development of colon cancer then the weaker effect of BMI may reflect misclassification of the relevant indicator of obesity and a lower prevalence of the relevant exposure in women compared with men. Indeed, in studies where BMI was the only marker of obesity, the association observed between BMI and incidence of colorectal cancer has been stronger for men than for women.[52,53] Giovannucci et al[48] found that women with high BMI and high WHR were at greater risk of large colon adenoma (multivariate adjusted RR=1.99, 95% CI: 0.98 - 4.05) than women with only one of these characteristics.

Murphy et al[54] examined the association between BMI and colon cancer mortality in a cohort of men and women participating in the American Cancer Society's Cancer Prevention Study II. As in other studies of colon cancer incidence the association between BMI and mortality was stronger in men than in women. Women with a BMI of 30 or greater had a RR of 1.25 (95%CI: 1.06 – 1.46) compared with women with a BMI less than 25. Further, women who reported drinking one alcoholic drink per day a BMI of 30 or greater was associated with a RR of 2.49 (95%: 1.53 – 4.03). Among non drinkers there was no association between BMI and mortality.

One study has reported that an increased stature may be associated with rectal adenomas[48] in women. Similar findings have been observed in men.[51] As in the case of weight, the association is complicated by the difficulty of separating the effects of various covariates, such as genetic factors and nutrition during development.[20]

2.4.3.2 Tobacco

It has been well established that tobacco smoke is a major source of a number of carcinogens, including heterocyclic amines, polycyclic hydrocarbons and nitrosamines. It is not presently known whether these substances enter the blood stream and then target colonic tissues, but animal models are currently being used to investigate whether this occurs.[8]

In a recent meta-analysis Giovanucci examined the studies that have investigated the association between smoking and colorectal cancer.[55] In both men and women the evidence suggests that cumulative exposure to cigarette smoking over long periods of time may increase colorectal cancer risk. In addition, smoking during adolescence and young adulthood appears to increase risk. This pattern appears to be suggestive of an initiator role for tobacco in colorectal carcinogensis.[55]

Early reports from the Nurses' Health Study indicated that the risk of colorectal cancer was increased only slightly and it was not significant. More recent results support a 2-fold increase in the risk of colorectal cancer with history of having smoked in the distant

past (30 to 40 years previously).[56] Other recent studies have reported similar increases in risk.[57,58] Giovannucci[55] has suggested that the lack of association between smoking and colorectal cancer among women in earlier studies is due to the lower prevalence of long-term female smokers in these earlier studies.

Nevertheless, while results for the association between colorectal cancer and smoking have not been consistent, studies investigating the effect of cigarette smoking on adenomatous polyps have all been consistent in demonstrating an increase in risk.[8,59,60]

2.5 Protective factors for colorectal cancer

2.5.1 Known protective factors

2.5.1.1 NSAIDs

Almost all nonexperimental studies examining the effect of NSAIDs on colorectal cancer risk have demonstrated a reduction in risk of about 50% following extended NSAIDs use.[61,62] Animal studies support these findings.[30] Only one randomized trial has been conducted to date and the authors did not find a protective effect.[63] Although the authors caution that 'confounding by indication' may explain the discrepancy between the results of observational and the randomized controlled trials, an alternative explanation is that the treatment period in the trial was too short. The minimum dose and duration of use necessary to confer protection is still being debated, although in the Nurses' Health Study as little as two aspirin per week for a period of 20 years lowered colorectal cancer risk by 44%.[62] In addition, Collet et al observed that a protective effect was observed only 10 years after of NSAIDs exposure.[61]

Only a few studies have examined the effect of NSAIDs other than aspirin. Collet et al[61] combined aspirin with other NSAIDs in the analyses but did not determine the effect of individual compounds. Studies in rodents, however, have demonstrated that indomethacin, sulindac, piroxicam, and celecoxib (a COX-2 inhibitor) inhibit carcinogenesis. COX-2 inhibition produces effects on epithelial proliferation and apoptosis and angiogenesis.[8,30]

2.5.1.2 Physical activity

Physical activity has been consistently associated with a decrease in the risk of colon cancer.[8] Although the focus has been on occupational activity, studies examining the effect of leisure time[47] and total activity have also shown a reduced risk for the more active groups. Of 20 observational studies (9 cohort; 11 case-control) only two reported not observing an association, one reported an increase in risk with higher activity and the remaining 17 reported a risk reduction.[8]

Several mechanisms have been proposed to explain the protective effect of physical activity for colorectal cancer. These include a decrease in stool transit time as a result of an increase in the stumulation of colonic peristalsis which decreases the time that dietary carcinogens and bile acids reside in the colon.[8] Recently, interest has developed in the effect of exercise on endocrine and metabolic profiles. Increased physical activity has been found to produce a characteristic lower level of insulin by increasing insulin sensitivity, lower levels of glucose, trigycerides and growth factors. This 'milieu' is less favourable to the growth of cancer in general. It is also of interest that, the effect of exercise appears to be maximized in individuals with normal body weight.

Alterations in immune function and prostaglandin synthesis have also been observed. In men and in women, Martinez et al[64] observed that rectal mucosa prostaglandin levels were inversely associated with physical activity and directly associated with BMI. Prostaglandins have been shown to be capable of stimulating insulin secretion, and it has also been shown that they regulate insulin-like growth factor-I (IGF-I) (see Section 2.7), thus suggesting another plausible biological mechanism by which exercise decreases colorectal cancer risk.

Physical activity is the strongest modifiable lifestyle risk factor for colorectal cancer. According to a statistics based on Health Canada's 1996/97, National Population Health Survey only 21% of the population were found to be active, 23% were moderately active, and 57% were inactive.[65] Thirteen and 16 % of women 45 to 54 and 55 to 64 years of age, respectively, were classified as active and 63 and 60 % were classified as inactive.

The burden of colon cancer could be greatly reduced with increases in the population physical activity.

2.5.2 Probable protective factors

2.5.2.1 Fruit and vegetables

Many case-control studies have reported that high vegetable consumption protects against colorectal cancer in both men and women.[32] Results from two recent large cohort studies, the Nurses' Health Study and the Health Professionals' Follow-up Study have not confirmed these results.[66]

Vegetables contain numerous potential anticarcinogenicagents which have properties that could conceivably be protective for colorectal cancer, but their biologic actions have not been completely described. In addition, many of these substances such as carotenoids, phenols, flavinoids, isothiocyanates, and indoles have not been well measured in foods and often co-exist in the same foods[67] making it an epidemiologic challenge to study their independent effects.

For several decades fibre was thought to be the promising protective nutrient[33,68], however, results from large prospective cohort and intervention studies have not provided evidence to support this hypothesis.[69,70] Initial results from the EPIC study suggest that there is a strong independent protective effect of fibre.[71] The investigators have suggested that the greater variability in fruit and vegetable intake found within the EPIC study populations have created a more favourable environment within which to study the association.

2.5.2.2 Folic acid

Observational studies have found lower incidences of colorectal cancer[9,72] and colorectal adenomas[73] among women whose diets were high in dietary folate. Some evidence suggests that the use of multivitamins containing folic acid may be more beneficial in reducing the risk of colon cancer than the folate derived from dietary intake.[74,75] In a population-based case-control study, the risk of colon cancer was halved among men and

women who reported taking multivitamin supplements on a daily basis compared with those who never took supplements.[74] In the Nurses' Health Study, women who had used folate containing vitamin supplements for at least 15 years had relative risks of 0.25 (95% CI: 0.13 to 0.51) for developing colon cancer compared with women who had never taken multivitamins. Interestingly, women in this study whose diets were high in folate but who never took multivitamins did not have a significant reduction in risk[75], suggesting that the effect occurs independent of clinically important folate deficiency. Folate from supplements may be more effective in protecting against colon cancer because of the generally higher dose and bioavailability from this source.[76]

The mechanism by which folate exerts its protective effect is not well understood, however folic acid and its metabolites, 5,10-methyenetetrahydrofolate and 5-methyltetrahydrofolate are critical components in the synthesis of DNA. It is thought that chronic folate deficiency may lead to abnormalities in DNA synthesis or repair.[30] A low dietary folate intake in combination with low methionnine and high alcohol intake may predispose individuals to even greater colon cancer risk.[73]

2.5.2.3 Calcium and vitamin D

More recently, a hypothesis has been proposed implicating calcium and vitamin D as possible chemoprotective agents in colorectal cancer, although studies to date have yielded inconsistent results.[77,78] Major problems encountered in these studies relate to the difficulty of accurately measuring calcium intake and the potential confounding effect of other dietary substances.

Convincing supportive evidence however is provided by a randomized controlled trial where individuals with histories of colorectal ademonas were randomly assigned to receive either daily supplements of 3.0 g of calcium carbonate (1200 mg of elemental calcium) or a placebo. Endoscopic examinations begun one and four years following the initiation of the study demonstrated a significant protective effect of RR =0.85 (0.74 to 0.98), observed as early as one year.[79]

It is thought that calcium may inhibit colon carcinogenesis by binding bile acids and fatty acids in the bowel lumen or directly by inhibiting colonic epithelial cell proliferation.[30]

2.5.3 Possible protective factors

2.5.3.1 Reproductive factors

Several decades ago Fraumeni et al[7] first observed that nuns experienced more known hormone-associated cancers, including colon cancer. Inspired by his work, and based on the known epidemiology and pathophysiology of colon cancer, McMichael and Potter proposed a hypothesis implicating a number of reproductive risk factors in the development of colon cancer.[80] They proposed that higher parity, early age at first birth, and use of oral contraceptives each independently reduced the risk of colon cancer as a result of associated changes in the hormonal milieu. Results from the more than 20 observational studies conducted to investigate the effect of reproductive factors on colorectal cancer risk, suggest that parity and early age at first birth do not appear to be protective for colorectal cancer.[8]

The use of exogenous hormones is briefly discussed below and in more detail in the review devoted to the the association between HRT and colorectal cancer.

2.5.3.2 Exogenous hormone use

Two dozen observational studies have investigated the effect of postmenopausal HRT on the risk of colorectal cancer. While current and ever use of HRT have been generally associated with approximately 30% reduction of colorectal cancer, results for distant past use have been less consistent. In addition, the effect of duration of use, dosage and use of various formulations and routes of delivery have not been well studied, primarily as a result of the limited ability to study these questions within traditional observational and experimental study design constraints. The Women's Health Initiative currently underway is designed to test the effect of only estrogen one formulation and dose on cardiovascular disease.[81] Although colorectal cancer will be ascertained to test the effect of other exposures, the study may not have adequate power to evaluate the effect of estrogen on risk.

Some of the inconsistencies in results may be due to variations in study design elements such as the definition of estrogen exposure, and the studies being conducted in different populations. Although suspicions exist that the HRT colorectal association in the majority of studies have been confounded by unmeasured or poorly measured covariates, the effect of adjusting for well measured covariates in well designed studies, such as the Nurses' Health Study, has not altered estimates of association importantly.[82]

Studies investigating the association between oral contraceptive use and colorectal cancer have provided only weak evidence to support a protective effect. The Nurses' Cohort Study is one of the few studies where a protective effect of oral contraceptive use has been observed.[83] Women using oral contraceptives for at least 8 years were observed to have a 40% reduction in colorectal cancer compared with women who had never used oral contraceptives.

Indirect and direct mechanisms have been proposed whereby estrogen may exert a protective effect on colorectal cancer risk. Exogenous estrogen is known to reduce bile acid production which has been hypothesized to initiate or promote malignant changes in the colonic epithelium. Exogenous estrogen may also alter DNA methylation and thereby directly influence colon cancer risk. Estrogen recepter (ER) hypermethylation increases with age (resulting in the silencing of the ER gene) possibly due to declining endogenous estrogen levels. It is not yet known why the loss of the ER protein is critical to colonic epithelial cells.[8]

Oral estrogen is also known to decrease serum levels of insulin-like growth factor-1, an important mitogen which may be associated with colon cancer.[10]

2.6 Screening sigmoidoscopies

Screening by flexible sigmoidoscopy may be considered as a method of primary prevention for colon cancer since not only do the tests have the ability to detect colon cancer but also remove precancerous polyps.[19] Flexible sigmoidoscopies have two

lengths: 35 and 60cm, both of which have 85% sensitivity within the regions they visualize.[19] It has been estimated that approximately one quarter of colorectal cancers (rectosigmoid region) may be detected with a rigid sigmoidoscope and about two-thirds with the 65-cm. flexible sigmoidoscope (distal colorectal lesions).[84] Several studies have demonstrated that rates of colorectal cancer are reduced in patients who have undergone polypectomy.[85, 86]

In addition, recent studies have demonstrated that men who had had sigmoidoscopies (flexible) were at a 40% lower risk of developing colorectal cancer and 50 % lower risk of dying from it.[87] When the men with cancers were classified according to whether they had proximal or distal colon cancers the risk reduction with sigmoidoscopy was seen only for distal colon cancers and not proximal tumors. These later tumors are not visualized by sigmoidoscopy.[87] The reduction in colon cancer mortality is seen whether an individual has a sigmoidoscopy ten years or two years prior to diagnosis. Whether a similar protective effect is observed in women has not been investigated.

Over the past several decades a change in the distribution of colorectal tumors has been observed with a decrease in rectal carcinomas and an increase in the percentage of proximal colon carcinaomas. This change in distribution has been hypothesized to be due to environmental factors that have increased the overall risk of colorectal cancer or to a change in the population age distribution since proximal colonic tumors are more common in people over 65 years of age. At the same time the decrease in the incidence of sigmoid colon and rectal cancer may be due to an increase in the prevalence of screening and an increase in the number of individuals undergoing polypectomies.[84]

2.7 Biological evidence and plausibility that estrogen is protective for colorectal cancer

The carcinogenic effect of bile acids on the colonic mucosa has been demonstrated.[88,89] It has also been observed that exogenous estrogens decrease concentrations of bile acids which may reduce the potential for these acids to promote tumors in the colon.[90-93]

In addition, Potter et al[94], have recently suggested a mechanism based on the work of Issa et al[95], whereby exogenous estrogens exerts a direct effect on colonic mucosa. Estrogen receptors have been identified in both human colorectal carcinomas and adjacent normal mucosa and there is some evidence from in vitro studies suggesting that estrogens may inhibit the growth of human colon cancer cells.[96,97] They may therefore play an important role in the growth of colon carcinoma cells. Although these mechanisms have been suggested for the protective effects of HRT[80], randomized controlled trials and experimental studies in animals which could potentially support or disprove the hypothesed overall effects are still lacking.

More recent evidence supporting the biologic plausibility of the protective effect of estrogen for colorectal cancer comes from studies demonstrating that in postmenopausal women, the use of oral estrogen reduces serum insulin-like growth factor-1 (IGF-1) levels.[98] IGF-I is known to be a potent mitogen and high circulating levels have been associated with an increased risk of for several common cancers, including those of the breast[99], prostate[100], lung and colorectum.[101,102] IGF-I not only stimulates cell proliferation but also inhibits apoptosis, and plays a role in cell differentiation.[103] It is interesting that nutrition, physical activity and body weight also play a role in the expression and production of IGF-I.[103] The proposed mechanism that links IGF-I to tumor development may thus provide insights into the interaction of various lifestyle and behavioral factors which are hypothesized to play a role in the prevention or progression of cancer.

IGF-I is regulated by growth hormone (GH) but the expression of IGF-I is influenced by various hormones including estrogen.[103] Levels of IGF-I change throughout the lifecycle, with an increase occurring from birth to puberty and a decline occurring with age thereafter. Age related changes are regulated by GH. IGF-I exerts its action by interacting with a specific IGF-I receptor (IGF-IR) found on cell membranes and regulated by specific binding proteins. The expression of IGF-IR is also stimulated by GH, estrogen, and a number of other hormones and nutrition.[103]

More than 99% of the IGF-I in the circulation is bound to IGF binding proteins (IGFBP), mainly IGFBP-3. The blood levels of IGF-I are fairly stable within individuals but interindividual levels of IGF-I and IGFBP-3 vary considerably. Most circulating IGFs and IGFBP-3 are synthesized in the liver. Although it is known that determinants of this variation include dietary and lifestyle factors, much remains to be learned about their independent effects.

2.8 Review of the epidemiological evidence for the chemoprotective effect of HRT on the risk of colorectal cancer incidence in postmenopausal women.

International variations in the incidence rates of colorectal cancer are known to exist. It has been suggested that as much as 85% of these cancers may be attributed to environmental factors.[22] Canada and the United States have among the highest rates in the world. In addition, colorectal is the third cause of cancer mortality in women.[21] A women's lifetime risk of being diagnosed with colorectal cancer is just under 6.0% and the lifetime risk of dying of colorectal cancer is approximately 2.7%.[35]

Thirty years ago Fraumeni et al.[7] observed that nuns had elevated mortality rates of colon cancer. Following this it was postulated that hormonal and reproductive factors play important roles in the etiology of this disease in women. Temporal trends in the incidence of colorectal cancer in the United States are also compatible with the hormone-colorectal cancer hypothesis. While the incidence rates were increasing in men, from 1950 to 1984, rates in women were gradually decreasing[1]. It has been suggested that the estrogen from oral contraceptives and HRT have played a role in the decreasing trend seen in women.

A number of biological mechanisms have been suggested to explain the protective effect of exogenous estrogen. One of the first proposed mechanisms was that estrogens reduce the secretion of bile acids.[80] In animal models, bile acids have been shown to promote colon cancer.[104] Others have suggested that there may be direct effects of exogenous estrogens on estrogen receptors in the colonic mucosa.[8] More recently, attention has focused on the effect of estrogens on the growth hormone/insulin-like growth factor axis

(GH/IGF-I), because of the potential role of IGF-I in cancer development.[103] Conclusive evidence, however, linking these proposed mechanisms to a true protective effect of estrogen against colorectal cancer is still lacking.

Evidence for an important protective role of oral contraceptives for colorectal cancer is weak. This may in part be due to a true lack of effect, or it may reflect the difficulty of studying the association between an exposure that is prevalent in premenopausal women and a disease that is prevalent in postmenopausal women.

The evidence supporting the chemoprotective effect of HRT, on the other hand, has been more promising, but nonetheless not completely convincing. To date, eighteen observational studies, six cohort and twelve case-control studies, have been conducted. Although some of these studies are methodologically strong, questions remain with regard to the evidence for, or against a protective effect of HRT for colorectal cancer. In studies where a protective effect is observed the suspicion remains that confounding may be responsible for some or all of the observed protective effect, even in the well designed studies.

All published case-control and cohort studies were reviewed. Only studies where the outcome was the incidence of colorectal cancer were considered. A case-control study conducted by Davis et al[105], was omitted from this review because the colorectal cancer cases ascertained were prevalent cases. Another study by Calle et al[106] where fatal colorectal cancer was the outcome, was also not included in this review.[106] A published abstract by Rosenberg et al[107], never published as a manuscript was excluded due to the lack of detail provided with regard to study design, exposure definition and results.[107] In addition, a study by Wu-Williams[108] was also excluded because HRT was not distinguished from other hormones that might have been used.

Only results from the Nurses' Health Study (NHS) at 14 years of follow-up[82] are described here with some reference to results published earlier at 12 years of follow-up.[109] Of the two publications one year apart[50,110], from the Iowa Women's Health Study,

only the most recently published study is reported here. Two publications by Fernandez et al[111,112] are considered because of a substantial increase in the number of cases and controls included in the analysis of the second publication.

In this systematic review I will examine the quality of the evidence provided by published studies examining the association between HRT and the incidence of colorectal cancer. The objectives of the review are:

1) To evaluate the strength of the evidence from each study with particular attention to the issue of confounding.
2) To identify differences that may explain the inconsistency of some of the results.
3) To identify specific research questions that remain unanswered and are essential for our understanding of the association between HRT and colorectal cancer.

2.8.1 Cohort Studies

Six cohort studies are described in **Table 2.1**.[82,110,113-116] All are large studies, many with several hundred thousand participants and duration of follow-up ranging from 4 to 14 years. With the exception of the study conducted by Adami[115], all of the studies were carried out in the US and Canada among women who varied in age. None of the studies included women younger than 35 years of age. One study relied completely on a large population-based prescription drug database for the ascertainment of HRT[114], and another study relied in part on a pharmacy database.[115] All of the other studies relied on self-reported use of HRT by women.

Of the two[82,110] cohort studies reporting a protective effect of HRT for colorectal cancer, the NHS had the longest follow-up, at 14 years. This study had the largest population of postmenopausal women and had the most comprehensive and rigorous measurement of confounding variables. Self-reports of hormone use including estrogen dose, and duration of use, were determined by questionnaire beginning in 1980 and updated biennially, with mailed questionnaires, until 1994. Detailed histories of dietary intake, alcohol intake, leisure physical activity, use of vitamins, NSAIDs and oral contraceptives (OCs) use were ascertained biennially and used to estimate the adjusted RR for HRT use.

From 1980 to 1994, 470 cases of colorectal cancer (366 with colon cancer and 104 with rectal cancer) were identified. Current HRT use was associated with a multivariate-adjusted RR of 0.64 (95% CI: 0.48-0.85) for colon cancer. Long duration of use, ≥ 5 years, among current HRT users was not associated with greater protection (RR, 0.72, 95% CI: 0.53 to 0.96) than shorter duration of current use (RR, 0.56, 95% CI: 0.39 to 0.83). Past HRT use, defined as ≥ 5 years since last use, was not associated with a reduced risk of colorectal cancer (RR, 0.92, 95% CI: 0.71 to 1.21). A protective effect was not observed among long-term past users (RR, 0.90, 95% CI: 0.62 to 1.30). These results were consistent with results reported by the investigators at 12 years of follow-up [109], however, the analysis with two additional years of follow-up, allowed for additional analyses. Subsite analyses provided some evidence to support a stronger protective effect for current HRT use and proximal colon cancer (RR, 0.56, 95% CI: 0.35 to 0.91) than for the distal colon (RR, 0.79, 95% CI: 0.50 to 1.25). Also of interest in this study was the finding that women in the highest quintile of body mass index (BMI > 29 kg/m^2), had the greatest protection against colorectal cancer with current HRT use (age-adjusted RR, 0.51, 95% CI: 0.28 to 0.93) and there was no relation between HRT and colorectal cancer among women in the lowest BMI quintile.

An additional question the investigators were able to address with the more recent study was whether women who were using HRT, underwent screening more frequently than nonusers and whether this could explain some of the observed protective effect of HRT. When women who reported ever having undergone screening sigmoidoscopy were excluded from the study, the strength of the association between hormone use and colorectal cancer remained unchanged.

The authors only report the use of oral conjugated estrogen among women in the NHS, presumably because other formulations were not used. Although most of the women took 0.625 mg of estrogen, there was some suggestion of increasing protection with increasing estrogen dose. The RR among current HRT users receiving a dose of 0.3 mg of estrogen was 0.99 (95% CI: 0.57 to 1.70) and for women taking 1.25 mg or more the RR was 0.48 (95% CI: 0.25 to 0.90).

Whether or not selection bias is responsible for the protective effect observed in the NHS must still be addressed. The NHS is well designed with extensive and detailed prospective measurement of important covariates. Nevertheless, diet and physical activity cannot be measured without substantial error. In fact, only leisure activity was ascertained in this study. It cannot be assumed that occupational activity among nurses is homogeneous. In fact, there might be tremendous variation depending on whether administrative or clinical work is engaged in. Since physical activity is the strongest risk factor for colorectal cancer[34] this incomplete measurement might result in residual confounding of the association between HRT and colorectal cancer.

Socio-economic status (SES) is another covariate that is difficult to measure and HRT users have also been reported to be wealthier and of a higher SES than nonusers. It is generally accepted that SES is an important predictor of disease incidence and mortality.[117] Yet the identification of specific measurable factors for which education and economic status may be markers remains to be elusive. Several recent studies have demonstrated the complexity with which SES exerts it impact on various aspects of health.[118,119] They demonstrate that the measurement of several SES indicators over a lifetime, may provide a better understanding of the full impact of SES on health and disease. SES characteristics of participants in the NHS are not addressed perhaps because it is assumed that SES in this occupational group would be fairly homogeneous. However, even among nurses there are large disparities of wealth and differences in SES, due to varying total family incomes. Total family income can also change substantially over time particularly for women affected by divorce. Confounding due to SES therefore cannot be completely ruled out even in an extremely well designed study such as the NHS.

The second largest cohort study conducted to date is an examination of data from the Breast Cancer Detection Demonstration Project (BCDDP) in the US.[113] Troisi et al. reported findings from a 7.7 year follow-up of 40,464 postmenopausal women 41-80 years of age who were a subset of the women volunteers participating in the BCDDP,

between 1973 and 1980. At baseline, the participants were interviewed with regard to menopausal hormone use, reproductive factors, age at menopause and type of menopause. Information was also collected on the use and duration of use of oral contraceptives, level of education and body mass index. Annual follow-up interviews were conducted to update the use of menopausal hormones. Data pertaining to diet and physical activity was not collected. Cancer cases were determined by self-report and death certificates, and of these, 83% were followed up with pathology reports.

Troisi et al. reported a RR of 0.99 [95% CI: 0.79 to 0.1.20] for colorectal cancer among HRT ever-users. Results for ever-use were similar when cancers of the colon and rectum were analyzed separately, but for proximal colon cancer, the risk appeared to be slightly elevated (RR, 1.70 [95% CI: 1.00 to 2.70]). Recent HRT use, defined as hormone use up to one year before diagnosis, was associated with a slight, but not statistically significant reduction in the risk of colorectal cancer (RR, 0.78 [95% CI: 0.55 to 1.10]). The risk reduction appeared to be greater for distal colon (RR, 0.68 [95% CI: 0.29 to 1.60). There was a non significant increase in risk for the proximal colon (RR, 1.50 [95% CI: 0.80 to 3.0]).

It is interesting to speculate why there might be such a discrepancy between the results from the NHS and the BCDDP studies. Although in the NHS, the investigators were able to adjust for diet and physical activity, the degree to which they were able to do so had little impact on estimated RRs. Therefore, lack of information pertaining to these lifestyle variables is not likely to explain the different results.

The women in the BCDDP were volunteers in a breast cancer screening program and therefore may be different from the general population in terms of having healthier lifestyle and health habits. Some of these women may have volunteered because of knowledge of their own increase in breast cancer risk. As a result this group of women may have been even more health conscious than usual volunteers. In fact, elsewhere, the authors have reported that compared with US white females, the all-cause standardized mortality rate for this cohort was 0.42.[120]

HRT users may self-select themselves to request HRT prescriptions from their physicians who in turn comply with the request. One might hypothesize that in a population comprised of a more homogeneous health conscious group, an observed protective effect that is due to a 'healthy user bias' would be less apparent than in a population with more diverse health habits and lifestyles. The lack of association observed between HRT and colorectal cancer in the BCDDP study is particularly interesting and would support the theory that the observed protective effect of HRT is indeed a function of selection bias rather than a true effect.

Two cohort studies have the distinction of obtaining information on HRT use from computerized prescription drug databases[114,115]; but only one was able to do so for the entire period of follow-up.[114] Risch and Howe[114] in a cohort study in Saskatchewan identified all women residing in the province in 1976 between the ages of 43 and 49, and followed them for 14 years for the development of colorectal cancer. Incidence of colorectal cancer was ascertained from the records of the Saskatchewan Cancer Agency. Other than OCs, which were also ascertained from the prescription drug plan database, information on other potential covariates was not available. Women identified as ever users of estrogen replacement therapy had a RR of 1.04 (95% CI: 0.74 to 1.46) for colorectal cancer. For colon cancer the RR risk was elevated but not statistically significant (age-adjusted RR, 1.29 [95% CI: 0.86 to 1.93]). Ever use of estrogen and proximal and distal cancers were associated with age-adjusted RRs of 1.17 (95% CI: 0.60 to 2.25) and 1.51 (95% CI: 0.90 to 2.54). Ever use of estrogen appeared to be protective for the rectum but the RR was not statistically significant (age-adjusted RR= 0.64; 95% CI: 0.33 to 1.22).

In this study, person-years in the unexposed category of estrogen use accrued until 3.5 years after the first prescription of estrogen, so that 3.5 years of exposure for each woman who eventually used HRT was included in the reference category of person-years. This 'lag time' was based on the investigators' belief that this period of time was necessary for HRT to exert its biological effect on the genesis of colon cancer. Although quite

plausible, it may also explain why their findings are not consistent with results from some other studies, particularly where a strong protective effect was observed among current HRT users as in the NHS.

Adami et al also reported not observing an effect of HRT on colorectal cancer incidence among women in a Swedish cohort (RR=0.95; 95% CI: 0.77 to 1.16).[115] A combination of interview and pharmacy database information was used to determine HRT use. A complete profile of HRT use was determined only for a subgroup of the population (1/30 of about 23,000 women) who were interviewed. Therefore, there is potential for substantial misclassification of HRT use. Some information was available from the interviewed sub-group with regard to reproductive history and lifestyle factors but this information was not used to control for confounding. Screening habits of the population were unknown.

The Iowa Women's Health Study is a cohort which had enrolled over 40,000 postmenopausal women in 1995. Women were interviewed at baseline only for the collection of information pertaining to on HRT use, diet, exercise, reproductive and medical history, anthropometrics and sociodemographic data. Results for the association between HRT and colon cancer were reported after 6 years of follow-up.[110] Less than five years of 'current' HRT use was found to be more protective for colon cancer (OR=0.31; 95% CI: 0.10 to 0.98), than longer term use (OR=0.92; 95% CI: 0.57 to 1.50). These results support findings similar to those reported by the NHS.[82]

One other cohort study of 11, 888 (numbers include males) individuals in a California retirement community was conducted to investigate the association between various exposures and colorectal cancer. Among women an association between HRT use and colorectal cancer was not found, but the follow-up was only four years.

In all of these studies, with the exception of the studies by Risch[115] and Adami[114], investigators have relied on the self-reported use of estrogen and hormone replacement therapy. Although it has been demonstrated that reports of ever use of HRT are fairly

accurate[121], more detailed information appears to be poorly reported.[122,123] West et al[122] have reported that details such as the name and dose of estrogen preparations are also poorly recalled, although this was studied with regard to past, not current use. Buist et al[124] reported that 10% women of reporting 'current use' of HRT had no evidence of having filled an HRT prescription as determined by records in a computerized pharmacy database.

Grodstein et al. have not validated self-reported hormone use in the NHS, however, they state that they are confident that the reports are accurate because their study participants are registered nurses who have demonstrated an interest in medical research. Indeed, this may be true for nurses but the accuracy of self-reports from nonmedically trained populations still needs to be viewed with skepticism. In case-control studies the accuracy of the reports may be further compromised and erroneous with regard to the duration and timing of hormone exposure.

2.8.1.1 Summary of the evidence from cohort studies

The results from cohort studies are inconclusive. The strongest evidence is from the NHS which suggests that current and recent HRT use is associated with a protective effect for colorectal cancer. Other studies have also reported that colorectal cancer risk is reduced with current use of HRT. Duration of use doesn't appear to be associated with additional risk reduction even among current users. Convincing evidence for risk reduction with distant past use is lacking.

2.8.2 Case-Control Studies

Twelve case-control studies have been conducted since 1981 to examine the association between colorectal cancer and HRT use[111,112,125-134] **(Table 2.2)**. Nine of these studies were population-based studies[125-130,132-134] and three were hospital based studies.[111,112,131]

All of these studies identified only incident cases of colorectal cancer, most of them through cancer registries[125-128,130,132,133] and a few through hospital pathology reports.[111,112,129] With the exception of the study conducted by Jacobs et al[126], where a

pharmacy database was used as the source of HRT exposure, investigators on all other caase-control studies obtained information with regard to HRT by interviewing subjects.

In many of the studies the associations have been adjusted for suspected colorectal cancer covariates: diet, physical activity, smoking, weight, reproductive history[112,125,127,128,130,131]. Several of the studies also ascertained OC use and adjusted for its effect[111,112,128,130,131], but only one found a statistically significant inverse association between OC use and colorectal cancer OR=0.58 [95% CI: 0.36-0.92][112].

Recently, Prihartono et al[125] published results from a case-control study of 404 cases and their matched controls. They found a reduction of colon cancer risk with recent HRT use (OR= 0.60 [95%: 0.40 to 1.00]), with 5 or more years of use (OR= 0.50 [95% CI: 0.30 – 0.90] and 10 or more years of use (OR=0.40, [95% CI: 0.20 – 0.80]). HRT users in this study were more likely to have had a sigmoidoscopy or fecal occult blood test than were nonusers. However, the inverse association remained after the ORs were adjusted for screening in multivariate analysis and following stratification. In addition, an inverse association was also observed among women whose cancers were detected at tumor stages II-IV. One might argue that a detection bias is more likely to play a role in the diagnosis of cancers at Stage 1. The authors did not find an association between HRT use and rectal cancer. The reported participation rate of 65 and 66% for cases and controls, respectively carries with it the potential for introducing selection bias.

In a study using the pharmacy database of the Group Health Cooperative of Puget Sound (GHC) in Washington state, to ascertain detailed information pertaining to HRT use Jacobs et al[126] reported not finding an association between HRT use and colon cancer. Estrogen use five and ten years prior to the designated reference date was associated with age-adjusted ORs of 0.85 (95% CI: 0.57 – 1.27) and 1.07 (95% CI: 0.61 – 1.86) for 1-749 estrogen tablets (equivalent to approximately 2 to 3 years of exposure). For more intense exposure of ≥ 750 estrogen tablets for the same time periods the ORs were 0.97 (95% CI: 0.68 – 1.40) and 1.11 (95% CI: 0.69 – 1.80). Data collected from GHC members on some limited lifestyle and reproductive factors were used to adjust for potential

confounding but did not change ORs by more than 5%. Additional data from members also provided information on HRT use prior to 1977, when the GHC pharmacy database was established. The authors used this information to calculate lifetime use of HRT and again did not find an association between HRT and colon cancer for duration of 10 or more years of use among current use (during the year prior to the reference index date) and former users (no use during the year prior to the reference date).

In contrast to the above results, Kampman et al[128] reported finding evidence that suggests that recent HRT use is associated with a protective of colon cancer (adjusted OR= 0.71, 95% CI: 0.56-0.89), while former use was not (OR=0.99, 95% CI: 0.80-1.40). A detailed assessment of potential covariates was also assessed in this study. HRT users were more likely to have taken multivitamins and aspirin, to have smoked in the past, and to have lower BMIs, fewer pregnancies, fewer livebirths, and more frequently reported OC use, hysterectomies and oopherectomies. Although the number of sigmoidoscopies did not differ significantly between ever- and never-users of HRT, ever-users had undergone more sigmoidoscopies because of symptoms. Adjusting for this and other differences in the multivariate model, however, did not change the results.

In agreement with the results reported by Kampman et al[128], Newcomb and Storer[127] reported a protective effect for recent (OR=0.54 [0.36-0.81]) but not for former HRT users (OR=0.85, 95% CI: 0.63-1.15). These results, adjusted for history of screening sigmoidoscopy, rule out screening as a source of bias.

Fernandez et al[111] reported results that were combined from two large hospital-based case-control studies conducted in Italy. Ever-use of HRT was protective for cancers of both the colon (OR=0.64, 95% CI: 0.46 – 0.88) and rectum (OR=0.46, 95% CI: 0.29 – 0.72). Last use of HRT ≥ 10 years prior to the index dates was associated with similar protective effects for both the colon (OR=0.53, 95% CI: 0.33 – 0.83) and rectum (OR=0.52, 95% CI: 0.30 – 0.90). In an earlier report the authors reported similar findings for time since last use but for colorectal cancers combined.[112] The investigators did not

have access to the use of screening information and were therefore were unable to control for screening bias.

Only one other study, also a hospital-based case-control study reported a statistically significant protective effect of HRT for rectal cancer.[131] Other studies that have examined this association report no effect of HRT on rectal cancer.[106,125,127,129] Two of these latter studies were able to control for screening which did not change the observed protective effect for colon cancer, nor the lack of protective effect for the incidence of rectal cancer. This finding is an additional argument that would suggest that surveillance bias does not contribute to the protective effect observed for colorectal cancer. One might expect that if surveillance due to removal of precancerous polyps was responsible for the observed protective effect of colon cancer, it would also be present for rectal cancer.

2.8.2.1 Summary of evidence from case-control studies

Case-control studies examining the association between HRT and colorectal cancer have lead to great variation in results from apparent reductions in risk by as much as 50% to no impact on the estimated measures of effect. One of the studies reporting a strongly protective effect of HRT is greatly limited by case and control response rates of less than 70%, which could introduce selection bias.[125] All of the case-control studies reporting a protective effect of HRT rely on self-reported HRT use which has been demonstrated to result in some misclassification of HRT use.[122,124]

The only case-control study clearly not affected by selection bias as a result of response rates and misclassification of the HRT exposure, has been the study conducted by Jacobs et al.[126] Since this study did not find an association between HRT use and incidence of colorectal cancer, the evidence in support of the hypothesis that HRT protects against colorectal cancer, remains unconvincing.

2.8.3 Meta-analyses of studies examining the effect of HRT on colorectal cancer

Four meta-analyses have been conducted using the results from published observational studies.[135,136 137,138] Only one of these studies, published several years before the others, did not find evidence to support a protective effect of HRT for colorectal cancer risk (RR=0.92: 95% CI, 0.74 to 1.15).[135] The other studies reported summary estimates that supported colorectal cancer risk reduction of about 20 to 33% with HRT use.[136-138] These meta-analyses also reported that the protective effect appeared to be strongest and greatest in magnitude for current HRT use, with RR from RR 0.65 (95% CI, 0.54 to 0.79)[137] to 0.67 (95% CI, 0.59 to 0.77).[136] Hébert-Croteau also found that summary estimates for duration of use appeared to have a dose-response gradient from short duration (RR=0.84: 95% CI, 0.73 to 0.97) to longer duration (RR=0.69: 95% CI, 0.58 to 0.82), however a trend test was not carried out and the estimates were not adjusted for recency of use. Grodstein et al[138] on the other hand did not find that summary estimates for duration of use were supportive of a dose-response trend. They however, only included in their analyses results pertaining to current users.

Hébert-Croteau[137] analyzed the studies by chronology and observed that although studies conducted after 1990 exhibited more heterogeneity across studies, point estimates from studies during this time period were more supportive of a protective effect. These studies tended to be larger with more comprehensive measurement of potential confounding variables and adjustment for them. There remained important methodological differences between the studies however and these differences included varying definitions and methods of HRT exposure assessment. In addition, as discussed in the previous section on cohort studies, while the NHS updated covariate and exposure information biennially[82], two of the large cohort studies published after 1990 had only baseline measurements of HRT use and covariate patterns.[106,110] One of these latter studies also assessed the impact of HRT on fatal colorectal cancer rather than incidence.[106]

While these meta-analyses were able to investigate the effects of ever-use, recency of HRT use, and duration of therapy, and to a limited degree whether point estimates varied by cancer sub-site, there was insufficient published data to assess the effects of dose, the effect of estrogen opposed and unopposed by progesterone, and the effect of different

formulations. All investigators remarked on the observed heterogeneity among the studies and all calculated RR and 95% CIs using variance-based methods based on a random-effects model. Grodstein et al[138] however, reported results based on a fixed-effects model claiming that the results were similar to the results obtained with the random effects model.

2.8.4 Concluding remarks

Despite eighteen observational studies reporting results on HRT use and risk of colorectal cancer, we can still only speculate about the association. A summary of the results are presented in **Table 2.3**. The evidence appears to suggest that there may be a slight protective effect, however, the suspicions of either selection bias or other forms of bias make it difficult to quantify this effect.

The suspicions of selection bias are unlikely to be fully dispelled until results from large randomized clinical trials, like the Women's Health Initiative, are available.[81] Although currently underway, results from this 9 year intervention study, with an anticipated 5 year posttrial follow-up, will not be available for several years.[139] In the mean time, additional evidence from well-designed observational studies, in conjunction with evidence from molecular biology need to be relied upon in order to further delineate the true benefit of exogenous postmenopausal estrogen.

Errors in estimated dose, duration of use, formulation, as well as chronological timing of exposure are important problems which may be encountered in all case-control studies where subjects are the source of information pertaining to the exposure of a medication, or in this case hormones. Where exposure in the distant past is of interest, error or non differential misclassification is more likely to be a problem. This is likely to bias the measure of effect towards the null.[140] Retrospective measurement of hormones and other types of exposure may also be subject to differential misclassification as a result of recall bias. Since it is not known whether women with colorectal cancer would be more or less likely to recall having used hormones it is difficult to estimate in which direction the point estimates would be biased.

Methodological variations in the measurement of exposure, ability to control for confounding variables, variability in the characteristics of populations studied, and small sample sizes, may explain the inconsistencies from studies. In addition, the variability in the definitions of HRT exposure probably also played prominently in producing some diversity in results. 'HRT' can be defined as estrogen only, or estrogen and progestin and within these definitions formulations may vary.[114,141] This may or may not be considered in the ascertainment, analysis and descriptive report of the exposure.

The effect of specific estrogen formulations on the risk of colorectal cancer has been virtually ignored in studies examining the association between HRT and colorectal cancer. In addition, refining definitions of HRT exposure need to be explored so that the complex patterns of use that include facets of timing and dosage can be adequately studied.

2.9 The effect of hormone replacement therapy on the survival of postmenopausal women diagnosed with colorectal cancer.

Two studies have examined the association between the use of HRT and survival among postmenopausal women diagnosed with colorectal cancer.[106,142] In addition, two publications from a Swedish study have examined the association between cause-specific mortality rates, including colorectal cancer and HRT.[143,144]

In a 7 year follow-up of 422,373 women, selected from the Cancer Prevention Study II (CPS-II), Calle et al.[106] reported a fatal colon cancer RR of 0.71[95% CI: 0.61-0.83] for 'ever use' of estrogen replacement therapy. They also report that the strongest effect was among current users (RR=0.55; 95% CI: 0.40 to 0.76). There was a dose-response trend with duration of use, among both current and former estrogen users *(p for trend =0.0001)*. As the authors point out, the observed association with estrogen use could reflect increased survival among HRT users because of the association of estrogen use with other attributes of a healthy lifestyle. Point estimates were minimally affected when

adjustments were made for family history, type of menopause, age at menopause, use of OCs, diet, physical activity, obesity, aspirin use, smoking, and race.

An interesting finding in this study was the observation that the lowest risk was observed among current long-term HRT users (RR=0.45;95% CI:0.28-0.71), defined as women who were using estrogen at the time they were interviewed (baseline), and had used HRT for ≥ 11 years prior to that time. In addition, there was a statistically significant dose-response trend with duration of use in both current and former estrogen users, defined as women who had stopped at least one year prior to baseline (P for trend = .0001). All exposure information including estrogen use was obtained by interviewing subjects at baseline only and was not updated. It can be assumed therefore although not explicitly stated in the description of the study, that HRT exposure during the 7 years of follow-up was ignored.

An important limitation of this study was the fact that the investigators did not have information on sigmoidoscopy and other colon cancer screening procedures. If women who had been taking HRT at baseline or shortly prior to baseline were under more intensive surveillance because of lifestyle characteristics it is possible that women diagnosed with colon cancer were diagnosed at an earlier stage. Therefore, a reduced mortality among HRT users might merely reflect a better prognosis as a result of earlier diagnosis rather than an effect of HRT on tumor progression. The authors admit that given the short period of follow-up, 7 years, colon cancer deaths may not have represented all cases. They also calculate that based on data from Barrett-Connor[145] with regard to a difference in screening behavior between HRT users and nonusers and a projected reduction in mortality of 50% due to early diagnosis, the expected reduction in risk of mortality among current estrogen users due to early diagnosis would be expected to be about 8.0% resulting in a RR of 0.92. The authors conclude that an increase in surveillance would not necessarily explain the entire magnitude of reduction in mortality that they had observed among HRT users. By using calculations from the Barrett-Connor[145] study these authors however may be under-estimating the difference in screening behavior between HRT users and nonusers. The population studied by Barrett-

Connor[145] comprised of upper-middle-class California residents. Over 90% of these women had visited their physician the year prior to the study. The subjects in the study by Calle had been recruited from 50 states, the District of Columbia and Puerto Rico and it is questionable whether the findings of Barrett-Connor[145] are generalisable to this population. As a result the lack of data pertaining to colon cancer surveillance and stage of cancer diagnosis remains an important limitation of this study.

In another, more recent study Slattery et al[142] investigated the effect of hormone replacement therapy on the survival in 801 postmenopausal women diagnosed with primary adenocarcinoma of the colon cancer between 1991 and 1994. Women were interviewed for history of HRT use, screening history, cancer stage at diagnosis, reproductive, family and medical history, dietary intake, physical activity, education, use of NSAIDs, smoking status and BMI. Follow up for vital status ranged from 2 to 83 months. Cause of death was determined using death certificates obtained form tumor registries.

After adjusting for disease stage, age at time of diagnosis, study center and BMI, women who ever used HRT were observed to have a 30 to 40% reduction in mortality from colon cancer (RR=0.6, [95% CI: 0.4 to 0.9]). An even greater reduction was observed among women who had used HRT for 4 or more years (RR=0.5, [95% CI: 0.3 to 0.9]). Also of interest in this study was that after stratifying on high and low levels of BMI, physical activity, dietary fiber, folate, sigmoidoscopy, NSAIDs, alcohol use and smoking history, the association between HRT and survival had a tendency to be strengthened slightly in the stratum more protective for colorectal cancer. For example women with 'low' BMIs were less likely to die from colon cancer than women with 'high' BMIs (RR=0.5, [95% CI: 0.3 to 1.0] vs 0.7, [95% CI: 0.4 to 1.2], for high and low BMIs respectively). Associations between HRT and survival among women with high and low intake of dietary folate were RR=0.5 (95% CI: 0.3 to 0.9) and 0.8 (95% CI: 0.5 to 1.4), for high and low folate intake respectively. The RR for HRT and survival among women who had a history of having had a sigmoidoscopy was 0.5 (95% CI: 0.3 to 1.0) and among women who had not had a sigmoidoscopy the RR was 0.7, (95% CI: 0.4 to 1.0).

Results from this study provide some evidence to support the hypothesis that women who have used HRT prior to diagnosis may have a better prognosis over the short-term (up to 6 years), following diagnosis of colon cancer. In addition, various covariates known to be risk factors for colorectal cancer may be effect modifiers for the association between HRT and survival from colon cancer.

Investigators from the Swedish Uppsala cohort of about 23,000 women have reported a standardized mortality ratio (SMR) of 0.7 (95% CI: 0.5 to 0.9) for colon cancer mortality among women receiving HRT.[143,144] Screening behaviour and information on lifestyle covariates however were not available in this study.

Mechanisms whereby HRT improves survival among women with diagnosed colon cancer have been proposed. It is possible that HRT users who develop colorectal cancer, develop less aggressive tumors as has been suggested for breast cancer.[146] It is also possible that estrogen slows the progression of the tumor since in vitro studies have shown that estrogen inhibits cell growth in human cancer cell lines.[97]

Neverthless, a limitation common to all of the studies to date that have examined the association between HRT and survival is that information has not been available with regard to treatment following diagnosis. While it may be assumed that all women diagnosed with colorectal cancer receive appropriate treatment, it is possible that women who have chosen to take HRT in the past also make treatment choices that are different from women who had never taken HRT. HRT users may also have access to a quality of care that is different from nonusers, given the demonstrated association between HRT use and socioeconomic status. Until this information is available and accounted for in the analysis of these studies we cannot be certain that the observed effect of HRT on survival is not confounded by cancer therapy.

TABLE 2.1 HORMONE REPLACEMENT THERAPY AND COLORECTAL CANCER: COHORT STUDIES

Author/Year	Study population	Exposure	Outcome	Covariates measured	Relative Risk [95% CI]	Comments
Grodstein et al. 1998[82]	59,002 postmenopausal nurses, 14 yrs of F/U from 1980 (601,503 person-years).	Self-reports of type, dose and duration of use E and P use; biennial updates.	366 colon and 104 rectal cancer cases	Dietary calcium, intake of red meat, folate, methionine; aspirin; alcohol use; age; BMI; physical activity; OC use; smoking; history of colonoscopy and sigmoidoscopy; family history.	Multivariate-adjusted RRs: current HRT use, 0.65 [0.50-.83]; past use 0.84 [0.67-1.05]; ≥ 5 years since last use 0.92 [0.70-1.21]; ≥ 5 years duration of use 0.72 [0.53-0.96]; proximal tumor 0.56 [0.35-0.91]; distal tumor 0.79 [0.67-1.05].	Protective effect similar for colon and rectal cancer; dose-response effect of estrogen suggested; only oral HRT formulation ascertained.
Troisi et al., 1997[113]	40,464 US volunteers in the BCDDP; postmenopausal women, 41- 80 years, F/U 7.7 years; annual updates	Self-reports of HRT hormone use, no distinction between E and P; creams not ascertained; women begin HRT year before diagnosis classified as a nonusers.	Case identification by self-report and death certificate; 83% confirmed by pathology report.	Parity; type of menopause; age at menopause; OC use; BMI.	Ever use HRT: 0.99; recent use 0.78 [0.55-1.1]; duration of use and years since cessation (< and ≥ 5 years), not associated with altered risk except for suggestion of some reduced risk for recent users of ≥5 years 0.75 [0.50-1.1].	Similar null effect of HRT for colon and rectum; possible confounding from unmeasured covariates (diet, physical activity).
Risch et al., 1995[114]	32,973 women 43-49 years of age, residing in Saskatchewan, Canada in 1976.	Strength, dosage information for all E, P obtained from Saskatchewan out-patient prescription drug plan database 1976-87.	230 incident colorectal cancer cases identified from 1976-90; distal and proximal colon cancers distinguished	Dispensed oral OCs.	Age-adjusted RRs: colon 1.29 [0.86-1.93]; distal colon 1.51[0.90-2.54].	Information on potential confounding factors not available; no data on use of screening services.
Folsom et al. 1995[110]	Iowa Women's Health Study 41,837 PM women 55-69 years; 6 year F/U.	Questionnaire: baseline and past use of E other than OCs; specific preparations not determined; E use updated 1987, 1989 & 1992	Site-specific cancer incidence (1986-91) State Health Registry.	Age, BMI, marital status, physical activity, alcohol use, smoking, WHR, and parity.	Colon cancer: multivariate adjusted current HRT use: RR 0.73 (0.47-1.14); colon cancer incidence, current and ≤5 year use: RR 0.31 (0.10-0.98); current and >5 year use: RR 0.92 (0.57-1.50).	Short follow-up

Author/Year	Study population	Exposure	Outcome	Covariates Measured	Relative Risk [95% CI]	Comments
Adami et al. 1989[115]	23,244 Swedish women; ≥35 years of age; F/U average 6.7 years	Prescription records for 3 year period: E, dose, formulation, quantity and date of purchase; questionnaire on E, repeated 1982 and 1984	Large bowel cancer identified using the National Cancer Registry	Limited information on reproductive history and other lifestyle factors obtained from 1/30 of sub-population.	Colon and rectum RR=0.95[0.77-1.16].	Confounding by diet, activity and other covariates; complete E data available for the 1/30 of cohort; potential for misclassification of E
Wu et al. 1987[116]	White, upper-middle class retirement community.	Questionnaire: self-reported E use.	Pathology report of diagnosis for colorectal cancer.	Demographic data, medical history; diet, vitamin, coffee and alcohol intake, physical activity.	Estrogen use < 8 years: age-adjusted RR = 0.98[0.5-1.8], ≥8 years RR = 1.02[0.6-1.8].	62% response rate to questionnaire; 4 year follow-up.

HRT, hormone replacement therapy; E, estrogen; P, progestins.

TABLE 2.2 HORMONE REPLACEMENT THERAPY AND COLORECTAL CANCER: CASE-CONTROL STUDIES

Author	Study Population	Exposure	Outcome	Covariates Measured	Relative Risk [95% CI]	Comments
Prihartono et al.2000[125]	Massachusetts women 40 to 69 years of age; 292 cases, 292 controls.	Self-reported hormone use: date started, duration of use, name of drug.	Incident cases large bowel cancer from tumor registry of 71 Massachusetts hospitals; staging available.	Demographic data, anthropometric data, physical activity, diet, family reproductive and menstrual history, NSAIDs use, history of sigmoidoscopy and screening.	Colon cancer: time since last use, <1 year 0.6[0.4-1.0]; ≥10 years use, 0.4[0.2-0.8]; ≥1 year since last use, and duration of ≥5 years, 0.5[0.1-1.7]; Stage II-IV only, 0.6[0.3-1.2].	HRT use <1 month classified as never use. Rectal cancer risk not reduced with HRT.
Jacobs et al. 1999[126]	Washington State women 55 to 79 years of age; members of a health maintenance organization; 441 cases, 2,180 controls.	Prescription data from computerized pharmacy database: patient identifier, tablet quantity, dosage, and formulation.	Colon cancer cases from the Surveillance Epidemiology and End Results Registry.	Breast cancer screening questionnaire completed by all women beginning in 1984: lifetime HRT use, anthropometric data, reproductive history, smoking status.	Colon cancer, age-adjusted: <750 tablets, 0.85[0.57-1.27]; ≥750 tablets, 0.97[0.68-1.40] during a five year period prior to reference date.	Reference date one year before index date; women who had filled only one prescription of HRT were classified as never users; no data on diet, alcohol, physical activity and screening endoscopy.
Fernandez et al. 1998[111]	4646 Italian women < 75 yrs; 1536 cases.	Self-reported HRT use.	Histologically confirmed incident colon cancers (994) and rectal cancer (542).	Self-reported data: sociodemographic characteristics, smoking, alcohol and coffee consumption, selected food intake and medical history.	Duration of HRT use >2 years: colon cancer: 0.47 [0.25-0.89]; rectal 0.35[0.14-0.90]; time since last use ≥10 yrs: colon 0.50 [0.32-0.78]; rectal 0.54[0.31-0.92].	Protective effect of HRT less marked in women without family history of colorectal cancer; mutivariate adjusted RR lower than age-adjusted RR;
Kampman et al. 1997[128]	2014 population-based women 30-79 yrs of age.	Self-reports by interview for duration of E, P use.	894 incident cases identified through tumor registries.	Age at diagnosis, family and reproductive history, lifetime physical activity, diet, BMI, aspirin and OCs use, focus on year 2 yrs prior to index date.	Adjusted OR for recent HRT use and colon cancer: 0.71 [0.56-0.89]; lowest risks for women without a family history; HRT effect stronger among women with ↓ BMIs	Users and nonusers of HRT did not differ in lifetime physical activity; did not distinguish between HRT formulations

Fernandez et al. 1996[112]	Italy; hospital-based; 1985-92; 709 cases, 992 controls.	Self-reports of non-contraceptive E use for HRT; timing of use and brand name noted.	Histologically confirmed incident colorectal cases	Self-reports: sociodemographic data, lifestyle habits, food intake, reproductive factors, OC use.	Colorectal cancer and duration of HRT use >2 years: 0.25 (0.08 – 0.77); time since last use >10 yrs: 0.39 (0.20-0.75).	Physical activity not acsertained; limited power; results for colon and rectal cancer similar in risk pattern.
Newcomb and Storer, 1995[127]	2316 female Wisconsin residents, 30-74 yrs of age.	Self-reported HRT use: age started and stopped, duration of use, formulation ascertained by telephone interview.	694 incident colon and rectal cancer cases identified through a cancer registry	Telephone interview to collect data on early life physical activity, diet, alcohol, smoking, weight, medical history.	Colon cancer: recent use, adjusted RR 0.54 [0.36-0.80]; proximal colon cancer 0.43 [0.22-0.84]; rectal cancer 0.90 (0.53-1.52); ↑ duration of HRT use associated with ↓ colon cancer [P for trend =.002]; decreasing time since last use inversely associated with colon cancer [P for trend <.001]	Potential for misclassification of E use; authors suggest HRT use may be inversely associated with survival
Jacobs et al 1994[130]	387 white female residents of Seattle area 30 - 62 years	Telephone interview for use of HRT (formulation not determined).	193 colon cancer cases identified from SEER registry.	Reproductive factors, medical history, diet, and physical activity obtained interview.	> 5yrs use HRT: colon cancer 0.47, (0.24-0.94); current use at ref. date 0.53 [0.29-0.96]; use of HRT >5 years: proximal 0.23 [0.09-0.61], distal 0.74 [0.34-1.60].	Distinction not made between HRT and other hormones i.e. thyroid.
Gerhardsson et al., 1992[129]	Population-based, 575 Swedish women born between 1907 and 1946.	Self-reports of HRT use in hospital (cases) and mailed questionnaires (controls).	299 incident cases identified	Reproductive factors, diet during previous 5 yrs (FFQ), weight, height, physical activity.	Colorectal cancer and HRT, 0.4 (0.2-0.9).	Adjustment for diet, BMI, and physical activity no influence on results.

Peters et al., 1990[132]	654, 45-70 year old (71% of those originally identified), white women, race and neighborhood-matched controls to cases.	Self-reported use of hormones.	327 incident colon cancer cases; data from Cancer Surveillance Program on stage, subsite, date of diagnosis.	Interview for diet over previous 15 years, weight and physical activity during previous 30 years, medical and reproductive history.	- <5 years of HRT use: OR = 1.44 [0.80 - 2.62].	Case responders were better educated, more had had at least one pregnancy.
Furner et al., 1989[131]	298, 45-74 yrs old married, white women in Illinois hospitals, 90 cases, 208 controls.	Self-administered, questionnaires for OC and HRT use; age at first use, duration, type of preparation.	90 cases, primary adenocarcinoma, diagnosed between Jan. 1980 - Dec. 1983	Reproductive history.	HRT use and colon cancer OR=0.50[0.28-0.87]; rectum 0.2[0.03-0.77].	Potential for confounding by lifestyle factors.
Potter et al., 1983[133]	466, 30-74 year old; Australian women, population-based.	Self-reported non-OC hormone use.	155 incident colon and rectal cancer cases from National Cancer Registry 1970-80.	Reproductive history, OC use; self-reported anthropometric data.	No associations found	Small sample size, definition of hormone use vague.
Weiss et al., 1981[134]	850 women population-based.	Self-reports with aid of color displays, of non-OC estrogens 1 yr post diagnosis.	143 colon and rectal cancer cases	Reproductive and medical history.	No associations found.	Small sample size; 39 % of the cases not interviewed; no lifestyle data.

HRT, hormone replacement therapy; E, estrogen; P, progestins.

TABLE 2.3 HORMONE REPLACEMENT THERAPY AND COLORECTAL CANCER: SUMMARY OF STUDY RESULTS.

Study	Main results	Timing	Duration	Subsite	Information on sigmoidoscopy
Prihartono et al. 2000[125]	Recent and long duration of use protective.	< and ≥ 1 year since last use	< and ≥ 5 yrs of use; ≥ 10 yrs	Reduced risk for C, no association with R.	Protective effect remained among women without sigmoidoscopy
Jacobs et al. 1999[126]	No effect.	Recent/former.	<10 years ≥10 years	PC, DC no association.	No data.
Grodstein et al[82]	Protective for current and recent use only.	Current Recency of use: last use < and ≥ 5 years ago	< and ≥ 5 years	C, R similar protective effect, PC ↓ risk; DC ↓ risk NS	Protective effect remained among women without sigmoidoscopy
Fernandez et al.[111]	Protective	< 10 years ago ≥ 10 years ago	≤ 2 years > 2 years	C, R similar results PC, DC information incomplete for participants	No data
Troisi et al[113]	No effect.	Recency of use: last use < and ≥ 5 years ago. Recent/past /former	<5 and ≥5 years	NS ↑ in risk for PC, NS ↓ in risk for DC and R.	No data
Kampman eet al[128]	Protective for recent use.	Recent/former	Short	PC, DC no difference	Protective effect remained among women without sigmoidoscopy.

Furner et al[131]	Protective	Ever use		C, R association appeared to be stronger for R	No data
Fernandez et al[112]	Protective	Recent/past	Long	Colorectal	No data
Gerhardsson et al[129]	Protective	Ever use		PC significance DC no association	No data
Jacobs et al[130]	Protective	Current/former	≤ and >5 years	C, PC, DC distinguished	No data
Newcomb et al[127]	Protective for recent use.	Recent/former	Short/long	C association; PC and DC numbers small but suggestion that stronger impact of recent use on PC; R no association	Protective effect remained among women without sigmoidoscopy.
Adami et al[115]	No effect	Recent	Short	Large bowel	No data
Wu et al[116]	No effect	Past	< and ≥ 8 years	C, R, PC, DC distinguished	No data
Risch et al[114]	No effect	Past		PC, DC, R distinguished	No data
Folsom et al[110]	Protective	Current/former	≤ and >5 years	No data.	No data
Peters et al[132]	No effect.		<5, 5-14,≥15 years		No data
Potter et al[133]	No effect.				No data
Weiss et al[134]	No effect.		≤ and >5 years		No data

C, colon; R, rectum; PC, proximal colon; DC, distal colon.

CHAPTER 3. METHODS

3.1 Overview and rationale for selection of study design

Pharmacoepidmiology studies often rely on large population-based administrative healthcare databases for sources of prescription drug information. These databases are valuable resources in research because of the detailed documentation of data with regard to the prescription drug, formulation, dose, quantity dispensed, and date of drug dispensing. There is often potential to link the prescription drug records with databases that contain information on health outcomes and use of health services. Due to their prospective documentation, often over decades, they are particularly appealing in epidemiological research.

Nevertheless, many exposure-disease associations are confounded by lifestyle, medical and family history, and sociodemographic factors; information generally not documented in these databases. Epidemiologists have therefore sought methods to overcome the limitations of healthcare databases by creating study designs that supplement database information with data collected from other sources such as subject interviews or patient medical records.[115,147,148]

Several decades ago, White[13] and Walker[12] described a study design that is based on a method of sampling conditional on disease and exposure status of potential study participants. The objective is to obtain a sub-sample of subjects from whom information pertaining to covariates can be collected. In order for this design to be efficient it is assumed that data pertaining to the main exposure(s) and outcome(s) of interest are available for all subjects in the database. The entire study population is referred to as Phase 1. Once these subjects are classified according to exposure and disease status various sampling strategies can be employed and subject selection for Phase 2 can take place.

An obvious approach is to sample an equal proportion of subjects randomly from each disease-exposure category of a two by two contingency table. However, the power of the study in this scenario, would be limited by the cell with the smallest number of observations. This strategy, therefore, is not very efficient since it would entail data

collection from a large number of individuals, where the additional information would not enhance the power of the study.

White[13] has suggested an alternative sampling scheme where the objective is to increase study efficiency with the collection of information from an equal number of individuals from each cell. This is accomplished with over-sampling of subjects from cells with fewer observations and comparatively, under-sampling from cells with a large number of observations. This approach has been referred to as a 'balanced design'. The effects of this biased sampling are then removed in the analysis with appropriate analytic corrections for the sampling fractions and variance.[15,149]

In this study we obtained outcome and exposure information from several Saskatchewan Health health care administrative databases, for all of the subjects in our study, as well as information on a number of covariates. We felt that given the large number of lifestyle covariates implicated as potential confounders in the association between HRT and colorectal cancer, the two-phase 'balanced design' sampling method would be the most efficient approach to investigate this relationship.

3.2 Study design

A historical nested case-control study design was used with two-phase sampling. The source population for this study consisted of women registered with Saskatchewan Health. The study population comprised of women ≥50 years of age and older, residing in Saskatchewan between January 1, 1981 and July 1, 1998, registered with Saskatchewan Health for a minimum of 5 years and eligible for prescription drug benefits. Only individuals without a history of cancer as verified by Saskatchewan Cancer Agency records (except for non-melanoma skin cancer and carcinoma in situ of the cervix), were included in the study.

3.2 Phase 1

Women living in the province of Saskatchewan, and eligible for prescription drug benefits between January 1, 1981 and June 30, 1998 were the source population for this

study. The province of Saskatchewan has a publicly funded health system with services provided by the provincial Department of Health (Saskatchewan Health) and 32 district health boards. All residents are eligible for benefits except about 1% of the population whose health-care benefits are funded by the federal government. All health beneficiaries are eligible for outpatient prescription drug benefits except those who receive drug benefits through the federal government, about 4% of women.[150]

Each individual registered with Saskatchewan Health is assigned a Health Services Number (HSN). The HSN is a lifetime number, that uniquely identifies each resident and enables the linkage of healthcare databases. The population registry of Saskatchewan Health contains daily updated demographic statistics on the entire covered population. The accuracy of the registry is verified continuously, by a variety of mechanisms and inconsistencies are followed up with manual checks.[151]

Several electronic administrative databases are currently maintained by Saskatchewan Health. The out-patient prescription drug database dates back to 1975 and the physician and hospital services databases date back to the 1970s. Due to the comprehensiveness of the population covered and the tenure of the records the databases have been widely used for research purposes.

Phase 1 of this study consisted of data extraction from several electronic records: files of the SCA registry, the out-patient prescription drug and the physician services files of Saskatchewan Health. Data pertaining to colorectal cancer, prescription drug history (estrogen and progesterone replacement therapy, oral contraceptives, NSAIDs, and cardiovascular disease, central nervous system, other hormones and vitamins), frequency of physician visits and sigmoidoscopy services were extracted from the databases for all subjects in the study.

3.3.1 Data sources for Phase 1

3.3.1.1 Outpatient prescription drug data

The electronic database of the Saskatchewan out-patient prescription Drug Plan has been in existence since September 1, 1975. The Drug Plan began as a fixed copayment

program (i.e., a beneficiary paid the pharmacist a maximum of $2.00 per prescription). The payment scheme has changed several times over its tenure. The current payment scheme is a family-based semi-annual deductible plus co-insurance with special programs for the financially compromised.

Prescription drugs covered by the Drug Plan are listed in the Saskatchewan Formulary.[152] Non formulary drugs are not covered by the Drug Plan and are therefore not captured in the database. Some non formulary drugs, have restricted coverage and appear on the Exception Drug Status list. In 1996 for example, transdermal estrogen was transferred from unrestricted to restricted coverage. Since then physicians or pharmacists have had to request individual approval for transdermal estrogen based on a woman's demonstrated intolerance to oral estrogen. With approval the prescription is covered by the Drug Plan and captured in the database.

The database contains detailed records pertaining to out-patient prescription drugs: a unique patient identification number, the date of dispensing, the class of the drug as classified by American Hospital Formulary System classification, the identity of the drug, the number of units dispensed, strength (mg/pill, mL, tablet or other unit), and dosage form (e.g., tablet, oral liquid).[153] The recommended daily dose, duration of treatment, treatment indication and patient compliance are not documented in the database. Nor does the database include information on nonformulary prescription drugs, drugs given to patients during hospitalisations, sample drugs given directly to patients by physicians during consultation and drugs bought over the counter without prescriptions. Drugs prescribed from July 1, 1987 to December 31, 1988 are not available because the payment scheme was nonassigned (i.e., beneficiaries submitted claims rather than the pharmacists and only after the deductible was reached) for this period.

For each subject a profile of drug usage was constructed covering the period of time up to 20 years before the index date. All estrogen containing drugs administered for hormone replacement and oral contraception via transdermal, parenteral, oral and vaginal routes were ascertained. Prescribed oral contraceptives were ascertained because of their

potential role in confounding or effect modification in the association between HRT and colorectal cancer.

In addition to oral contraceptives, detailed prescription drug information was obtained for prescribed NSAIDs, an important potential confounding variable. The use of other prescribed drugs were also ascertained but only as broad classes of drugs used to treat cardiovascular, central nervous system and endocrine disorders. In addition, prescribed vitamin supplements were also ascertained.

3.3.1.2 Sigmoidoscopy services and physician visits

For all subjects, history of having had a sigmoidoscopy and the frequency of physician visits were ascertained from the physician services database of Saskatchewan Health for each of the five years prior to a subjects index date. Sigmoidoscopies with or without polypectomy could not be distinguished from each other. Physician visits were counted on an annual basis and recorded as visits to the general practitioners, obstetrician/gynecologist, endocrinologists, general surgeons, and oncologists.

3.3.1.3 Methods of data linkage

Data were extracted and linked from the various Saskatchewan Health databases by employees at Saskatchewan Health, using a unique identifier. All data released to investigators in Montreal were de-identified. A study identification number, unique to this study, was assigned to subjects by Saskatchewan Health. This allowed for the analysis at the individual level while maintaining confidentiality.

3.4 Phase 2

3.4.1 Identification and selection of colorectal cancer cases

Colorectal cancer cases diagnosed and reported to the SCA between January 1, 1981 and June 30, 1998, were identified using the International Classification of Diseases for Oncology, 2nd revision, Geneva: WHO, 1990 codes (C18.0, C18.2 to C18.9, C19.9, C20.9, C21.8). Tumor staging (Dukes, Astler-Colter, Clark's, Urology) at the time of cancer diagnosis was also provided. A provincial legislation mandates reporting to the

cancer registry all individuals in the province diagnosed with cancer. The records are therefore virtually 100% complete.

The records of the SCA were also used to exclude individuals with cancers (other than nonmelanoma skin cancer and cancer of the cervix in situ), diagnosed prior to colorectal cancer and these individuals were not selected as cases. Cancer diagnoses have been documented in the electronic database of the SCA since 1967, which facilitates the process of verifying the absence of cancer history dating back to that time.

3.4.2 Identification and selection of controls

The electronic records of Saskatchewan Health were used to age match controls (± 1 year) to each identified case. A control had to have been living in Saskatchewan at the time the colorectal cancer case (to whom she was matched) was diagnosed with cancer (index date). At that time the control also had to have been registered with Saskatchewan Health for at least five years. For each case, 16 potential controls were randomly sampled using incidence density sampling, with replacement, from the pool of eligible controls. These controls were screened for the absence of a history of diagnosed cancer prior to a specific index date, using records of the SCA. Women identified as having had cancer prior to their index dates were excluded as potential controls. Controls who did not have histories of cancer prior to their index dates were retained and from them, four controls per case were randomly sampled without replacement. A woman selected as a control once, could again be selected as a control a second time and could also become a case at a later date.

3.4.3 Recruitment of subjects for Phase 2

As described in the *Section 3.0 Overview and rationale for selection of study design*, the purpose of Phase 2 was to recruit a sub-sample of subjects in order to collect information on covariates not documented in the health care databases. For statistical efficiency, a 'balanced design' was used whereby the sampling was conditional on disease and HRT exposure status.

A random sample of exposed and unexposed cases and controls, still living in 1999, were sampled from the subgroup of subjects with index dates in 1990 or later. Although we had initially planned to sample from the subgroup with index dates in 1994 and later, the number of exposed cases during these years was too few to provide adequate power for the study. Including subjects with index dates prior to 1990 was also not feasible since a greater proportion of these cases had died. A decision was made not to attempt to contact spouses of deceased women for interviews and provision of proxy information on covariates because of the evidence that indicates that husbands substantially misreport their wives' reproductive histories[154] and are unreliable with regard to reporting information pertaining to diet, alcohol and amount smoked.[155]

Study identification numbers for cases and controls were sent to Dr. MaryRose Stang at Saskatchewan Health. The protocol for the mailing of study letters, pamphlets and questionnaires to potential study participants was based on methods proposed by Dillman.[156]

Two periods of recruitment took place. The first mailing targeted colon cancer cases and their prospective controls during the summer of 1999 and the second targeted rectal cancer cases and their controls during the spring of 2000.

3.4.4 Protocol for contacting cases and obtaining consent for interviews

Primary care physicians were contacted in order to obtain permission to contact their cancer patients. Letters were sent out by the SCA, and followed-up with reminders three weeks later. Patients were not contacted if their physician's either failed to respond or refused to provide permission to have their patients contacted. Once permission was obtained from a physician the patient was contacted by mail.

During the first recruitment period, cases were sent information about the study (pamphlet), a letter inviting them to participate, two consent forms (one for their records at home) and a stamped and addressed envelope for returning consent forms. For the second recruitment, the pamphlet describing the study and the cover letters were modified, as was the mailing protocol in an attempt to increase response rates.

Subjects were asked to return by mail a signed consent form in a self-addressed envelop if they wished to participate, or a blank consent form if they did not wish to participate. During the first recruitment period cover letters implicitly stated that the return of an unsigned consent form in the stamped addressed envelop would be considered a clear refusal to participate. This statement was removed from the cover letter during the second recruitment period.

Subjects who did not respond to the first mailing, received the same package for a second time three weeks later, and they also received copies of the self-administered questionnaires. Ten days following the second mailing non-responders were contacted by telephone by a Saskatchewan Health employee. If subjects could not be reached up to ten attempts were made to contact them by phone. Subjects who refused to participate were removed from the mailing list and were not contacted again.

Subjects who returned signed consent forms were contacted for interviews during the time of day and day of the week that they had indicated as convenient for them on the consent form. Individuals who had consented to participate but could not be reached by phone on a first attempt were called numerous times. Attempts were also made to correct incorrect addresses with checks against other Saskatchewan Health databases.

Interviewers were trained as described below and were blinded to the disease status of the subject.

3.4.5 Protocol for contacting controls and obtaining consent for interviews

Controls were contacted by mail without permission from their physicians. The contents of the first package, the reminder, and the questionnaires were the same as described for cases. As outlined in the protocol for the cases, controls who did not respond following the second mailing were contacted by phone in an attempt to recruit them. Subjects who refused to participate were removed from the mailing list and those who agreed to participate were contacted for interviews by Saskatchewan Health employees.

3.4.6 Sample size and power calculations for Phase 2.

The sample size and power calculations for Phase 2 were based on the number of colon cancer cases that we anticipated would be diagnosed by 1998. We projected that approximately 650 of the eligible cases would have been diagnosed in the 5 years 1994-1998. We assumed that the prevalence of long-term (5-year) estrogen exposure among these cases would be about 15%, and that these 650 cases would therefore include almost 100 with long-term exposure. As many of these 100 'exposed' cases (50 to be conservative), as possible, together with a random sample of 150 of the 550 'unexposed' cases, 150 exposed controls, and 150 unexposed controls, were anticipated to be interviewed during phase-two in order to obtain detailed information on potential confounding variables (a total of 500 interviews). The equal numbers in the 3 other categories (the 'balanced design' with 150 in each) were chosen to optimize precision.[13] The numbers of exposed cases available to be interviewed [and indeed the power of the combined phase-one and -two data] is dependent on the actual prevalence of exposure, and so below we illustrate power calculations for an estimated range from 5% to 25%.

Following the published formulae for sample size and power calculations for phase-two designs[157], we projected the statistical power of the combined two phases (phase 1: all 650 cases and 2600 controls from 1994-98; phase 2: the 500 selected from these) under a number of scenarios concerning confounding variables and we based calculations on the worst case scenario.

The table below gives the range of statistical power (as a percentage) for the two-phase design, in which the ORs obtained in the second phase are adjusted. It is expressed as a function of the prevalence of exposure among the controls and the measure of effect of the exposure (RR, i.e. relative risk), and is based on alpha = 0.05, two-sided.

Table 3.1 Statistical power (%) for combined phase-one and -two analyses, with 650/2600 cases/controls from 1994-1998 providing phase-one data and n_{ec}/150/150/150 of these providing phase-two data. Power is given as a function of the prevalence of exposure and true relative risk.

	RELATIVE RISK					
Prevalence of Exposure	**0.50**	**0.55**	**0.60**	**0.65**	**0.70**	**0.75**
25%	100	99	96	89	77	60
20%	99	98	94	85	72	55
15%	98	95	89	78	64	47
10%	94	87	78	66	52	38
5%	76	67	56	45	34	25

*The "n_{ec}/150/150/150" refers to the plan to interview; n_{ec} will be a function of the prevalence of exposure among the 650 cases, and we assume that 50% of the exposed cases will be interviewed.[157]

With an estimated 15% prevalence of long-term estrogen exposure, 650 cases and 2600 controls in phase-one we anticipated being able to interview 150 unexposed cases, 150 exposed controls, and 150 unexposed controls and at least 50 exposed cases at phase-two. We estimated that we would have 89% power to find a significant OR of 0.60 and 78% power to find a significant OR of 0.65 ($\alpha = 0.05$).

3.4.7 Determination of exposure status for Phase 2 sampling

Women had been dispensed a dozen different estrogen replacement formulations, of varying strength and route of delivery during the past two decades. Physiological equivalences have not been established for all estrogen formulations. Therefore, a method was developed to estimate equivalences of exposure based on the therapeutic effect of estrogen for the treatment of estrogen deficiency induced degenerative changes that are experienced by postmenopausal women (e.g., osteoporosis, atrophic vaginitis, kraurosis vulvae). The 1997 Canadian Compendium of Pharmaceuticals (CPS)[158] was used as the primary source of information for identifying recommended treatment dosages. The American Hospital Formulary System Drug Information[159] and the Drug

Information for the Health Care Professional (18th ed. 1998 Vol 1) reference manuals[160] were used for formulations not listed in the CPS.

The total amount required for three months of coverage at the minimum dose was calculated for each estrogen formulation. Each woman's yearly prescription record was calculated as a proportion of this amount. Where subjects received more than one formulation per year, the proportions for all of the formulations were summed in order to estimate the level of estrogen exposure per year for each subject.

Where the total amount of estrogen dispensed was at least equivalent to the minimum required for a three month treatment period, the exposure was expressed as 100% or greater than the minimum amount. We will refer to this definition of exposure as a SUM-P3. In cases where the total amount was less than the minimum for three months of treatment the exposure was classified as less that 100% or too low to be considered exposed for Phase 2 sampling.

The following is an example of this calculation:

> A woman is dispensed 42 tablets of 0.3 mg of oral conjugated estrogens (Premarin). [The prescribed daily dose is not provided with dispensing records but it is reasonable to assume that this is a 2 months supply (21 days/month) at the minimum dose.] Several months later the same woman is dispensed 2 pack (8 patches per pack) of 25 μg/day strength estradiol-17β (Estraderm). Other HRT formulations are not dispensed that year. Three months of coverage at the **minimum dose** with these formulations would amount to 18.90 mg of conjugated estrogen and 1575 μg of estradiol-17β. Her **annual cumulative intake** and proportion of our established minimum level of exposure is calculated as follows:

Premarin	0.30 mg × 21 × 2
	= 12.60 mg/18.90 mg
	= 0.67 or 67%
Estraderm	*25 μg × 21 × 2*
	= 1050 μg/1575 μg
	= 0.67 or 67%
	SUM- P3= 1.34 or 134%

This woman would be classified as exposed during the year in which the prescriptions were dispensed. If the sum of the proportions of the minimum coverage for three months had resulted in an amount less than 1.0 she would have been classified as having had a level of exposure too low to be considered exposed.

In order to distinguish between short and long duration of use for the Phase 2 analysis the cumulative number of years of exposure was calculated by summing the number of years classified as exposed, in order to determine the duration of use. Living cases and controls were classified according to several categories of exposure: too low (less than three months exposure), 1 to 4 years exposure, and four or more years of exposure. Exposure during the two years immediately preceding index dates was not included in the calculations of SUM-P3. Women were considered to have been unexposed if they had never been dispensed estrogen replacement therapy in any form, including vaginal cream.

According to protocol subjects for Phase 2 were to be randomly sampled from all exposure categories except the category classified as 'too low' as determined by SUM-3P. The minimum level of exposure that could potentially exert a protective effect for colorectal cancer is unknown and therefore we did not want to exclude any women who might meet this minimum level. At the same time, for statistical efficiency we did not want to include women with one month of estrogen replacement therapy at the minimum dosage in phase-two interviews. Although this too could potentially have a protective

effect on cancer incidence it was considered unlikely and these women were therefore removed from exposure subgroups from which random samples for Phase 2 were drawn.

3.5 Phase 2: Questionnaires and interviews

Questionnaires for the Phase 2 data collection were modified from existing questionnaires. Subjects were interviewed with regard to past diet and past physical activity (household, occupational and leisure), reproductive and medical history and sociodemigraphic data. The questionnaires, pilot testing and the training of interviewers are described below.

Questions pertaining to family, reproductive and medical history focused on circumstances prior to index dates. For dietary intake and physical activity the period of interest was five to ten years prior to index dates.

3.5.1 Medical, reproductive and family history and sociodemographic data

A questionnaire was previously developed to collect data from subjects participating in a breast cancer case-control study.[161] This questionnaire was modified to incorporate questions relevant to colorectal cancer and HRT use and as in the previous study, designed to be administered over the telephone (Appendix I). Questions addressed medical, reproductive and family history specifically as they relate to colorectal cancer and HRT use.

A section of the questionnaire was developed to interview subjects with regard to use of HRT, OCs and over-the-counter NSAIDs. The self-reported use of the prescribed drugs was requested in order to provide information on their use during periods of time for which data were missing: drugs dispensed prior to 1976, between July 1, 1987 to December 31, 1988 and for individuals who had immigrated to the province after 1976 and after the age of 50.

Although the questionnaire was written with an embedded script, additional instructions and guides were was developed to help interviewers deal with various circumstances that might arise during the interviews.

3.5.2 Physical activity questionnaire

The physical activity questionnaire was an abbreviated version of the *Lifetime Total Physical Activity Questionnaire* developed by Friedenreich and colleagues at the Alberta Cancer Board.[162] The original questionnaire was designed to be administered in face-to-face interviews. We developed a modified version designed to be self-administered and to have subjects report their activities during a five-year period (five to ten years period prior to index dates), rather than for their entire lifetime (Appendix II). The subjects listed each activity, age started, age ended, number of months of the year, number of days in the week, and the number of hours each day that the activity was engaged in. In addition, they were asked to rate the intensity of the activity on a 4-point scale representing sedentary, light, moderate and heavy levels of activity. Examples of several common activities and their intensity scores were provided on the questionnaire to assist subjects. The classifications were those described in a Special Report of a National Heart Lung and Blood Institute Workshop on assessment methods for physical activity and physical fitness in population studies[163] and the Compendium of Physical Activities.[164]

In addition to the above questionnaire, subjects were asked to self-rate their level of physical activity. Two questions were asked with regard to their perceptions of whether or not they were much more active, somewhat more active, about the same, somewhat less active, or much less active at work, and outside of work compared to others of the same sex and age. Two additional questions were asked with regard to strenuous activities. These questions were validated in the Lipid Research Clinics studies.[165] Due to their brevity they did not greatly add to respondent burden and provided a means of validating the results from the more detailed report for activity.

3.5.2.1 Calculations for level of physical activity

For each interviewed individual, the average number of hours of light, moderate and heavy activity that had been engaged in on a weekly basis was determined for occupational, household and exercise and sports, for the five year period of interest. The following calculations as described by Friedenreich[162] were used:

Average number of hours per week spent in either occupational and household activity =

$$\sum \frac{[(\text{age finished} - \text{age started}) \times (\text{months/yr}) \times (4.33 \text{ wks/month}) \times (\text{No. of days/wk}) \times (\text{Hr/day})]/52}{\text{Number of years}}$$

For and exercise and sports =

$$\sum \frac{[(\text{age finished} - \text{age started}) \times (\text{months/yr}) \times 365 \text{ d/yr} \times (\text{No. of times/day}) \times (\text{Hr/exercise session})]/52}{\text{Number of years}}$$

For each category of activity, light, moderate, and heavy activities were calculated separately.

The number of hours engaged in during the three levels of activity intensity for the three categories of were converted to METS using the medians for METs in each category as described by Wilson et al.[163] The definition of a MET is the ratio of the associated metabolic rate for a specific activity divided by the resting metabolic rate.

3.5.3 Food frequency questionnaire

The Block 95 Food Frequency Questionnaire (FFQ) was used to measure past dietary intake (Appendix III). This questionnaire has been validated in numerous populations and validated for past dietary intake in the Baltimore Longitudinal Study.[166] This self-administered questionnaire takes about 20 minutes to complete and asks respondents to report on the frequency of intake for over 100 foods consumed during the previous year (year prior to completing the questionnaire). The questionnaire was developed using data from the U.S NHANES II population-based study of health habits in the early 1990s. Foods that had been identified as important sources of nutrients were included in the questionnaire.

For this study the questionnaire was modified to elicit food intake 5 to 10 years prior to index dates rather than during the past year (original focus of questionnaire).

The U.S. nutrient analysis database developed for the Block 95 FFQ was also modified to reflect folate, vitamin C, calcium and vitamin D content of Canadian foods during the latter part of the 1980s. Nutrient values for foods were obtained from the 1991 Canadian Nutrient File (CNF). Block Dietary Data Systems (BDDS) provided a list of foods that were fortified during the latter part of the 1980s and the early part of the 1990s. The nutrient values of these foods were checked against the values in the 1991 Canadian Nutrient File. Canadian values that were different from the U.S. values were sent to BDDS to replace the U.S values in the nutrient database. Commonly consumed Canadian foods that were identified as different from U.S. foods with regard to levels of folate, vitamin C, calcium and vitamin D content were also identified, and a list of these foods with Canadian food composition values were sent to BDDS. This modified database was used to analyze our questionnaires.

BDDS printed the questionnaires, scanned and analyzed them using the CNF modified nutrient database.

3.5.4 Life Events Calendar

A Life Events Calendar (LEC) (Appendix IV) was modified from a previously developed version (C. M. Friedenreich personal communication). The purpose of the calendar was to help subjects reconstruct the timing of important events, activities and health habits in the past. Previous studies have demonstrated that this type of memory aid is of assistance in helping subjects recall their past, and leads to a higher degree of accuracy in the reporting of events and habits.[167] The tool was exclusively for the subjects' use and they were asked not to return the completed calendar.

3.5.5 Interviewer training and interview methods

Four interviewers were hired by Saskatchewan Health to interview subjects for the study. One left early in the study and was not replaced. The remaining three interviewers conducted most of the interviews.

An intensive four-day training period was held in May 1999 organized by Dr. MaryRose Stang at Saskatchewan Health and myself. The training included discussion of issues of confidentially, respect for privacy and handling of topics considered sensitive in nature. As a group we also reviewed the questionnaires and scripted sections line by line for readability, consistency with regard to Saskatchewan Health policies and face validity. The interviewers were trained to read the questionnaire scripts as written during the interview.

Each interviewer was assigned to carry out an interview and have subjects complete the Block FFQ questionnaire. Subjects were women 50 years of age or older and they were recruited either by the interviewers or Dr. Stang. Interviewers were asked to conduct interviews only with women they did not know.

This training was followed by regular meetings between the interviewers and Dr. Stang, in order to provide an opportunity for interviewers to address outstanding questions and problems that arose prior to, and during the interview period which began in August of 1999. At a later date, the interviewers were also trained to enter the data from interviews that they had completed.

A training manual was written to provide interviewers with background information with regard to the study and design of the questionnaires. The interviewers were also provided with guidelines pertaining to the handling of missing data from the self-administered questionnaires.

3.5.5.1 Pilot testing of questionnaires

The *Medical, Reproductive and Family History and Sociodemographic Data Questionnaire,* and the LEC and FFQ questionnaire were pilot tested during the interviewer training period. Sixteen interviews were conducted by the interviewers for the pilot testing of questionnaires. The individuals interviewed during this testing were not part of the actual study. Based on feedback from interviewers the questionnaires were modified as required.

3.5.5.2 Interview protocol

As consent forms were received interviewers were systematically assigned interviews in order to keep all interviewers equally busy with subjects who needed to be contacted and interviewed. As described above a detailed script was written for interviewers to use in order to standardize interviewing methods. Interviewers were trained to follow methods that were consistent with maintaining strict confidentiality, for example to ask participants not to use cellular phones during an interview.

Individuals who had consented to participate but could not be reached by phone on a first call were called numerous times. Attempts were also made to correct incorrect addresses with checks against other Saskatchewan Health databases.

3.6 Reliability study of questionnaires

Test-retest reliability studies[168] were conducted for all self-administered questionnaires (physical activity and diet questionnaires) and the general questionnaire administered over the telephone. Upon completion of an interview, interviewers were asked to recruit subjects for the reliability study until 60 cases and 60 controls were enrolled for a total of 120 participants. Consenting participants were mailed questionnaires to complete one month after completion of the first questionnaire. An effort was also made to conduct the second telephone interview one month following the first interview.

3.7 Validation study of reporting of HRT use

The validation of self-reported HRT use was studied by comparing responses given on the questionnaire with prescription dispensing data in the database. Two one-year periods, 1985 and 1995, and two two-year periods 1985/6 and 1995/6 were compared.

For each period the subjects' response with regard to HRT use was compared with database records, using at least 1 and 2 prescriptions per period as the criteria for exposure. This was done because the questionnaire specifically asked women to only report at least 3 months of HRT use. A woman could have received a prescription for two months and accordingly would have accurately reported being a nonuser as defined on the questionnaire.

3.8 Data entry and data management

During the first recruitment period, the interviewers were trained to carry out data entry for their completed interviews. During the second recruitment period a data entry clerk was hired to enter the collected data.

A web-site data entry program developed by Michel Beland (Computer Programmer, Randomized Clinical Trial Unit) at the Montreal Jewish General Hospital was used for data entry. A secure web-site requiring an identification number and a password allowed access to the site. Interviewers had access to the site for data entry only. They did not have privileges to modify the data once they had submitted the questionnaire. Entered data were entered completely denominalized, identified only by study identification numbers. Contact information (addresses, phone numbers) was not entered.

Following initial data entry, the data were entered for the second time by a trained secretarial clerk at Saskatchewan Health. Upon completion of the double data entry Dr. Stang checked for discordance between the two entries. She was the only individual in addition to the programmer with privileges to modify the entered data.

Once the errors were picked up with double data entry and corrected by Dr. Stang, we checked the corrected data at the Jewish General Hospital for implausible and questionable responses. With the identification number and password the web-site could be accessed in Montreal (or anywhere in the world), permitting the viewing of the entered data. In Montreal we downloaded the data directly into SAS files. Outstanding problems were discussed with Dr. Stang who consulted the original records. All completed questionnaires were kept on site at Saskatchewan Health at all times.

3.9 Analysis of reliability

The intraclass correlation coefficient (ICC) was calculated for all variables on the questionnaires measured on an interval scale using a two-way, random effects analysis of variance. Reliability can be defined as follows:

$$ICC = \text{true variance}/(\text{true variance} + \text{error variance})$$

A measurement is considered more reliable if a greater proportion of the total observed variance is represented by the true score variance.[169]

3.10 Imputation for missing prescription drug dispensing information

All study subjects registered with Saskatchewan Health and eligible for prescription drug benefits during 1987 and 1988 had incomplete prescription drug dispensing data for up to 1.5 years (records not entered in database). Two methods of imputation were employed and evaluated. In the first case if a woman had received a prescription for estrogen during the year before July 1,1987 and during the year after December 31,1988 she was considered to have been exposed during the period of missing information. Otherwise, she was considered unexposed.

A second less rigorous method was also tested where a woman was considered exposed if a prescription had been dispensed on only one side of the period with missing data and otherwise considered unexposed.

By creating four hypothetical 1-year blocks of missing data and using the database information as the 'true status', the sensitivity, specificity and kappa statistic were calculated for this method of imputation. The sensitivity of the method was calculated as the proportion of truly exposed women who were identified as exposed and the specificity as the proportion of correctly identified unexposed women. The years selected were: 1983, 1984, 1993 and 1994.

3.11 Data Analysis

3.11.1 Statistical analysis of Phase 1

The analyses carried out in the manuscripts included in this thesis were done using Phase 1 data only. The statistical methods are briefly outlined here and described in more detail in each manuscript. Additional analyses addressing the question of the effect of HRT on colorectal cancer risk, using Phase 1 data only but not presented in manuscript form are also described here.

Methods commonly employed in descriptive epidemiology are used in the CMAJ Research Letter and the first manuscript Trends in the use of hormone replacement therapy by women in Saskatchewan: 1980 to 1997. These include the calculation of prevalence and incidence of HRT use, and age-standardized prevalence rates using direct standardization. Ninety-five percent confidence limits were calculated using exact and large sample Gaussian approximations as appropriate.[170]

In the second manuscript describing health related behavior and HRT use, unconditional logistic regression was carried out to determine whether or not covariates in the database were associated with HRT use among cases and controls. The outcome in this analysis, HRT use, was dichotomized as ever/never use. Prescription drugs, sigmiodoscopies and frequency of physician visits were the covariates of interest. Associations were expressed as ORs with 95% confidence intervals.

The third manuscript is an examination of the effect of various definitions of estrogen exposure on measures of effect for HRT and incidence of colorectal cancer. Conditional logistic regression was used to estimate ORs and 95% CIs.

In the fourth manuscript, the effect of transdermal (TDE) and oral estrogen (OE) on the risk of colorectal cancer is examined. Conditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CI). In a second analysis in this manuscript unconditional logistic regression was used in order to allow for the comparison of women exposed to transdermal estrogen with women who had used oral estrogen (the latter served as the reference group). For duration of use, a test for linear

trend was carried out with duration of use converted to an ordinal variable and treated as continuous variable.

The Phase 1 and Phase 2 results are presented in Chapter 8. The Phase 1 data was analyzed using conditional logistic regression to estimate ORs and 95% CI. Analyses were conducted to determine the effect of duration of use (<5 and ≥5 years of use), time since last use (current use, within 2 years of use, at least 5 years prior to the index date, at least 10 years prior to the index date) and dose response. All analyses except where stated otherwise were carried out with an assumed reference data of two years prior to the index date, where the exposure during the two years prior to the index date was ignored.

Information on various potential covariates were available for all Phase 1 subjects. Detailed dispensing information was available for the use of oral contraceptives, and prescription NSAIDs. Dispensing records for the use of drugs to treat cardiovascular diseases, central nervous system drugs (excluding NSAIDs), gastrointestinal drugs, anti-infective drugs and prescription vitamins, were also provided for Phase 1 subjects but these drugs were identified only by their therapeutic classification as described in the Saskatchewan Drug Plan Formulary.[152]

In addition to prescription drugs, the use of sigmoidoscopies during the five year period prior to the index date and physician visits during the same period of time were also available for all Phase 1 subjects.

Dietary intake of total fat, folate, vitamin D, and calcium, servings of meat, fruit and vegetables were identified a priori as potential confounding variables for which data had been collected for the Phase 2 analysis. The total amount of physical activity expressed as energy expenditure (leisure, occupational and household), body mass index, alcohol intake and smoking status were other covariates considered in the Phase 2 analysis. Variables were considered to be confounding variables if they had an impact of 10% or more on the ORs for estrogen and colorectal cancer.

3.11.2 Statistical analysis of Phase 2

A statistical analysis program (SAS macro) was written for the analysis of Phase 2 data. Since sampling for Phase 2 subjects was conditional on exposure and disease status in order to achieve a near 'balanced design', adjusted ORs using data collected during Phase 2 remained biased unless corrected for sampling fractions that varied with each exposure/disease category.

The SAS macro was written by Dr. Nandini Dendukuri. The program adjusted the main exposure regression coefficients for covariates collected in Phase 2 using unconditional logistic regression. The bias that was introduced during the 'balanced design' sampling, which resulted in different sampling fractions for each exposure/disease category, was also corrected in this analysis. A corrected variance based on information from both Phase 1 and 2 was also computed. Calculations involved in these steps have been described by Collet et al.[14] and Cain[149] and are shown below:

Figure 3.1 Correction of logistic regression drug exposure parameter estimate and its variance.

$$B = B_{2,Logistic} + \log \left[\frac{N_1 N_4 n_2 n_3}{N_2 N_3 n_1 n_4} \right]$$

$$B = B_{2,Logistic} + \log (S_2) + \log (S_3) - \log (S_1) + \log (S_4)$$

$$Var (B) = Var (B_1) + Var (B_{2,Logistic}) - Var (B_{2crude})$$

$$= \frac{1}{N_1} + \frac{1}{N_2} + \frac{1}{N_3} + \frac{1}{N_4} + Var (B_{2,Logistic}) - \left[\frac{1}{n_1} + \frac{1}{n_2} + \frac{1}{n_3} + \frac{1}{n_4} \right]$$

N_i = Observed number of individuals from the i^{th} disease and exposure group in Phase 1.

n_i = Number of individuals sampled from the i^{th} disease and exposure group.

B = Log OR, corrected for Phase 2 sampling and adjusted for confounding variables used in logistic regression of Phase 2 data.

B_1 = Crude log OR from Phase 1 data.

$B_{2,crude}$ = Log OR from crude Phase 2 data.

$B_{2,logistic}$ = Log OR from Phase 2 adjusted for covariates in logistic regression model.

S_i = Sampling fraction for each exposure/disease category = $\frac{n_i}{N}$

Taken from: Collet et al [14].

3.12 Ethical review and confidentiality

The study was reviewed and approved by the Research Ethics Committees of the Sir Mortimer B. Davis-Jewish General Hospital, the University Advisory Committee on Ethics in Human Experimentation at the University of Saskatchewan and the Data Access Review Committee of Saskatchewan Health. The study was annually reviewed and approved between the 1998 and 2001 and received continuing approval from the two ethics committees. In addition, a Single Project Assurance was obtained from the US

National Cancer Institute, National Institutes of Health, the agency that funded this project.

Strict confidentiality was maintained throughout the study. Data extraction from electronic databases was carried out by Saskatchewan Health and Saskatchewan Cancer Agency (SCA) employees, who were the only ones to have access to the mailing addresses and phone numbers of subjects. Telephone interviews were conducted by Saskatchewan Health employees. All Saskatchewan employees had to sign an oath to handle all personal data with strict confidentiality. All data released by Saskatchewan Health were de-identified and limited to variables required for the analysis.

Chapter 4. THE USE OF HORMONE REPLACEMENT THERAPY

4.1 Research letter: Use of postmenopausal estrogen replacement therapy in Saskatchewan from 1981 to 1997

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"Use of postmenopausal estrogen replacement therapy from 1981 to 1997"— Reprinted from, *CMAJ* 22 January 2002; 166(2) Page(s) 187-188 by permission of the publisher,

During the past two decades, the health risks and benefits of estrogen replacement therapy (ERT) have been the focus of intensive research and scientific debate. Recommendations for its use by asymptomatic postmenopausal women are nevertheless still limited by many questions that remain unanswered[171]. In spite of the uncertainty surrounding its overall impact on health, US data indicate that the prevalence of hormone use has been steadily increasing since the 1980s[172]. Longitudinal population-based Canadian data describing ERT use by postmenopausal women are lacking. We therefore examined the trends in the prevalence of estrogen use by peri- and postmenopausal women from 1981 to 1997.

Saskatchewan Health's computerized prescription drug plan database was used as the source of drug dispensing information for this study[151]. Women, living in Saskatchewan between 1981 and 1997 were sampled from Saskatchewan Health records to participate in two population-based case-control studies[161,173], and the controls formed a cohort of peri- and postmenopausal women for this analysis. At the time of sampling, they were 45 years of age and older, had not been diagnosed with cancer (except for non melanoma skin cancer and cancer of the cervix in situ), had had a minimum of five years registration with Saskatchewan Health and were eligible for out-patient prescription drug plan benefits.

The study was approved by the Research Ethics Committee of the Jewish General Hospital, the University Advisory Committee on Ethics in Human Experimentation of the University of Saskatchewan, and the Data Access Review Committee of Saskatchewan Health. All data released by Saskatchewan Health were de-identified and limited to the variables required for the analysis.

The type, strength and quantities of estrogen dispensed to study women between 1976 and 1997 were compiled by Saskatchewan Health. For each woman in the study, estrogen dispensing data were available for a minimum of 5 years beginning in 1976, or later if she had immigrated to the province at a later date and were terminated at death, emigration from the province or the end of the case-control study for which she had been sampled, whichever came first.

The age-standardized prevalences of estrogen use were calculated for 1981, 1984, 1989, 1994 and 1997 using direct standardization. Saskatchewan Census data from 1996 were used to provide the standard age distribution of women 45 years of age and older[174]. The age-specific proportions of women who had been dispensed at least one prescription of estrogen were also calculated for each of the five calendar years listed above.

Age-standardized prevalence of estrogen use increased substantially over time, from 5.1% in 1981, to 5.3% in 1984, 7.7% in 1989, 13.1% in 1994 and 15.4% in 1997.

Increases in age-specific proportions of women receiving at least one prescription of estrogen for the years 1981 (n=28,261), 1984(n=29,594), 1989(n=29,708), 1994(n=27,240) and 1997(n=8,836) are shown in **Figure 4.1**. The highest prevalence of ERT use occurred among women 50 to 54 years of age and ranged from 10.8% [95% CI: 9.8 to 11.8] in 1981 to 30.6% [95% CI: 24.7 to 36.5] in 1997. An increase in estrogen use over time, however, is apparent in all age groups, even in women over 65 years of age.

Our data demonstrate that important increases have occurred in the prevalence of estrogen use throughout the 1980s and the 1990s. As expected, peak estrogen use occurred consistently among women between the ages of 50 and 54 years, coinciding with the onset of menopausal symptoms for most women. With the exception of the prevention of osteoporotic bone fractures [175], the role of ERT in the prevention of various chronic diseases remains to be clearly defined. Results from the Heart and Estrogen/Progestin Replacement[176], and the Estrogen Replacement and Atherosclerosis [177] studies have challenged the hypothesis that ERT reduces the risk of coronary heart disease in women with existing coronary disease. Whether these findings impact on women's decision making with regard to the use of hormone replacement therapy will be of interest to clinicians.

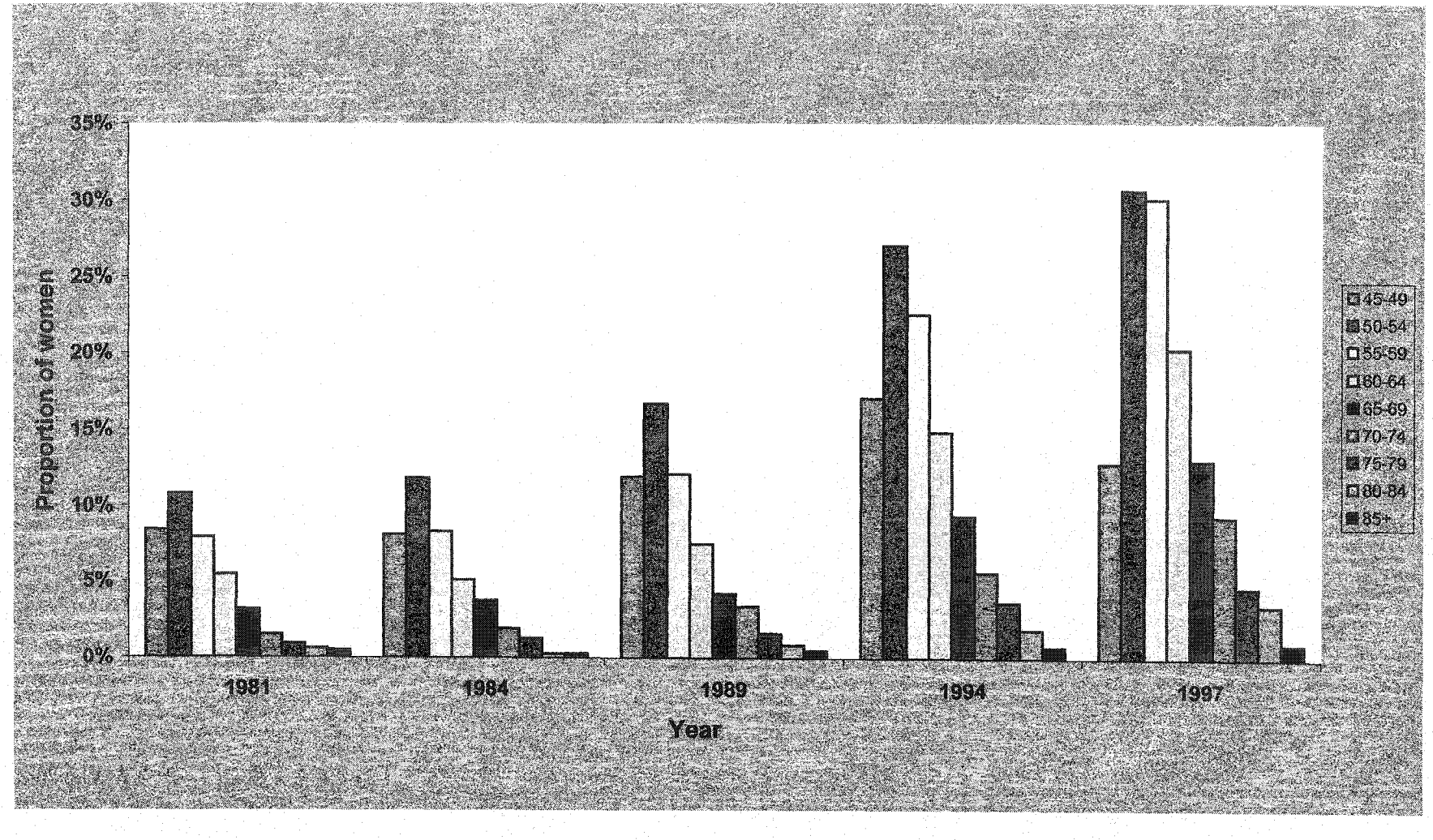
35%
30%
25%
20%
15%
10%
5%
0%
Proportion of Women
1981
1984
1989
1994
1997
Year
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85+

Fig. 1: Age-specific proportions of women 45 years of age and older who were dispensed at least one prescription of estrogen during the years 1981, 1984, 1989, 1994, and 1997.

4.2 MANUSCRIPT # 1: TRENDS IN THE USE OF HORMONE REPLACEMENT THERAPY BY WOMEN IN SASKATCHEWAN FROM 1980 TO 1997

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Abstract

Background: Canadian data describing trends in the use of hormone replacement therapy (HRT) are lacking. We describe patterns of HRT use in Saskatchewan from 1980 to 1997.

Methods: We analyzed data from the Saskatchewan out-patient prescription Drug Plan database, to determine HRT use by women 45 years of age and older. The number of women receiving new HRT prescriptions and continuing treatment for five years was determined for 1980-2 and 1990-2.

Results: The age-standardized rate of new estrogen prescriptions increased from 10.8 per 1000 woman-years during 1980-2, to 22.5 per 1000 woman-years during 1990-2. The proportion of women using estrogen for five consecutive years increased dramatically among women 55 to 59 years of age from 1980-2, to 1990-2 (6.0% [95% CI: 2.2 to 12.6] to 43.3% [95% CI: 33.1 to 53.5]).

Interpretation: Since 1980 there has been an increase in the number of new HRT prescriptions. Longer-term HRT use by peri- and postmenopausal women has also increased in Saskatchewan.

Key words: hormone replacement therapy, menopause

Résumé

Contexte : Il n'existe pas de données canadiennes sur l'évolution de l'utilisation des hormones de remplacement (HR). Notre étude décrit l'utilisation de ces hormones en Saskatchewan au cours de la période 1980-1997.

Méthode : Nous avons analysé les données provenant de la base provinciale sur les prescriptions de médicaments. Les nombres de femmes ayant reçu une nouvelle prescription d'HR et de celles ayant poursuivi un traitement continu pendant 5 ans ont été comparés pour les périodes 1980-82 et 1990-92.

Résultats : Le taux standardisé pour l'âge des nouvelles utilisatrices d'HR passe de 10.8/1000 femmes-années en 1980-82 à 22.5/1000 pour la période 1990-92. La proportion de femmes utilisant le HR cinq années consécutives augmente considérablement pour la catégorie d'âge 55 à 59 ans de 6.0% (IC 95% : 2.2 – 12.6) à 43.3% (33.1 – 53.5) pour les périodes 1980-82 et 1990 – 92, respectivement.

Interprétation : On constate que depuis 1980 le nombre de femmes qui utilisent les HR est en forte augmentation. Par ailleurs, le nombre de femmes qui utilisent les HR de manière prolongée également augmenté de manière considérable.

INTRODUCTION

Clinical trials of estrogen replacement preparations have been conducted since the 1940s when they became available for postmenopausal use in the United States [178]. During the past two decades the research focusing on the health risks and benefits of hormone replacement therapy (HRT) has intensified. Nevertheless, the debate regarding the role of HRT in women's health continues. [171,179,180]

Experts generally agree that HRT protects against the development of osteoporosis and reduces the risk of bone fractures.[175,180] Also well established is the increase in the risk of uterine cancer associated with unopposed estrogen.[181,182] The role of HRT in the primary and secondary prevention of coronary artery disease, on the other hand, continues to be scrutinized, with recent results from randomized controlled trials adding to the confusion and controversy.[177,183-186] Similarly, the HRT risk associated with breast cancer requires further study.[187-189]

Despite an unclear net health benefit of HRT for asymptomatic postmenopausal women, the prevalence of HRT use has been increasing in the United States.[141] Survey results describing HRT use by Canadian women have been limited to the ascertainment of current use, or to use by women with specific medical conditions.[190,191] Reports describing trends in the use of HRT in the general population are lacking.

The objective of this study was to describe the changes in the incidence and duration of peri-and postmenopausal estrogen and progesterone use from 1980 to 1997.

MATERIALS AND METHODS

Study population

Saskatchewan Health's computerized databases were used as sources of health care information for this study; the Saskatchewan Health databases and their use in population-based studies have been described elsewhere.[151,192] Women, sampled from Saskatchewan Health records, participated as controls in two case-control studies.[161,173] They formed a cohort of peri- and postmenopausal women for this study. Women were

45 years of age and older, did not have histories of cancer diagnosis (except for non melanoma skin cancer and cancer of the cervix in situ), had had a minimum of five years registration with Saskatchewan Health and were eligible for prescription drug benefits. Only about four percent of the women in Saskatchewan, are excluded from the program as they are covered by Federal jurisdiction.[150] The absence of cancer diagnosis was verified using Saskatchewan Cancer Agency records dating back to 1970.

The women had been matched on age (± 1 year) to breast and colorectal cancer cases diagnosed between 1981 and 1997 and assigned index dates (the date of cancer diagnosis for the matching case). The resulting artificial age distribution was accounted for in the analysis (see below). No other matching criteria or restriction had been used in the selection of these controls. The studies were approved by the Research Ethics Committee of the Jewish General Hospital, the University Advisory Committee on Ethics in Human Experimentation of the University of Saskatchewan, and the Data Access Review Committee of Saskatchewan Health. All data released by Saskatchewan Health were de-identified and limited to the variables required for the analysis.

Ascertainment and definitions of estrogen and progesterone use

The type, strength and quantities of the estrogen and progesterone that were dispensed to study women between 1976 and 1997 were compiled by Saskatchewan Health.

For each woman in the study, dispensing data were available for a minimum of 5 years beginning in 1976, or later, if she had immigrated to the province at a later date. Records were terminated in either 1995, or 1997 (the year when data extraction from the outpatient prescription drug database ended for the two case-control studies) or earlier, for women who had died or emigrated from the province prior to these dates.

Delivery routes of estrogen

The use of oral, transdermal, or injectable estrogen was determined for the years 1981, 1984, 1989, 1994 and 1997. Each proportion was calculated with the numerator comprising the number of women receiving prescriptions for a specified route of

administration. The total number of women receiving estrogen prescriptions in the cohort that year formed the denominator. A woman was counted in more than one category in a given year and therefore appeared in more than one numerator and twice in the denominator, if she had received estrogen prescriptions with different modes of delivery. This, however, affected less than one percent of the women during the years examined.

Rate of new estrogen use

Age-specific rates of new estrogen users, and the prevalence of five consecutive years of use among new users were determined for the time periods 1980 to 1982 and 1990 to 1992. A new estrogen user was defined as a woman who had received a first prescription of estrogen during these time intervals. The number of woman-years for each woman in the cohort previously unexposed to estrogen was calculated from the beginning of the time period, or the date of entry into the cohort, whichever occurred last. Woman-year accumulation was terminated on the day a woman received a prescription, died, left the province, or at the end of the period, whichever occurred first. An age-standardized incidence rate was also calculated for 1990-1992 using the 1980-1982 age-specific woman-years distribution as the standard.

Progesterone use among new estrogen users

The proportion of women who had received at least one progesterone prescription within three years following a new estrogen prescription, was determined for the 1980-1982 and 1990-1992 time periods. In addition, the proportion receiving progesterone prescriptions for the entire five-year period was also determined.

Statistical analysis

Calculation of confidence intervals

Ninety-five percent confidence limits were calculated for proportions of five-year progesterone use and rates of new estrogen use using exact and large sample Gaussian approximations as appropriate[170]. All statistical analyses were carried out using Excel software. SAS (SAS Institute, Version 8, 1999) was used for database management.

RESULTS

During the years 1981 and 1984, 99% of users had used oral estrogen; one percent had received estrogen injections. During years 1989 and 1994, 80.0% of women were using oral estrogen, 0.5% were using injections, and 19.5% were using transdermal estrogen. Transdermal estrogen first appeared on the Saskatchewan Formulary in 1989, but was transferred to the Exception Drug Status Program (EDSP) in 1996. This change in formulary status required physicians to request approval for transdermal estrogen based on a woman's demonstrated intolerance to oral estrogen. As a result, only two percent of eligible female beneficiaries received transdermal estrogen in 1997.

Rate of new estrogen use

The age-standardized rate of having filled a new estrogen prescription increased from 10.8 per 1000 woman-years, from 1980 to 1982 to 22.5 per 1000 woman-years, from 1990 to 1992. Age-specific rates of first prescriptions in the 1990s were about twice the rates in the 1980s, in all age categories **(Figure 1)**. In the 45 to 49 year age group, the category with the highest start rate, there was an increase from 30.7 per 1000 woman-years [95% CI: 26.9 to 34.9] during the 1980s, to 64.2 per 1000 woman-years [95% CI: 56.6 to 72.5] during the 1990s. The increasing trend was apparent in all age groups including among women 85 years of age and older.

A greater proportion of new users in the 1990s continued to use HRT for five consecutive years compared with those a decade earlier. The increases were most dramatic in the 55 to 59 year age group where 6.0% [95% CI: 2.2 to 12.6] of women used HRT for at least five years during the 1980s compared with 43.3% [95% CI: 33.1 to 53.5] during the early 1990s.

Progesterone use among new estrogen users

Equally striking is the increase in the use of progesterone among new users during the early 1990s compared with the early 1980s, when generally, unopposed estrogen had been prescribed. The proportion of women receiving at least one prescription of progesterone within the three years following the first estrogen prescription in the 1990s

ranged from a minimum of 16.7% in the 75 to 79 year age category, to a peak of 55.5% in the 45 to 49 year age group. Among five-year estrogen users, in 1990, 48.7% [95% CI: 33.0 to 64.4] of women 55 to 59 years of age, received progesterone prescriptions for each of the five years.

DISCUSSION

The data confirm that HRT use has increased markedly from the 1980s to the 1990s. As expected, peak estrogen use occurred between 50 and 54 years of age, coinciding with the onset of menopausal symptoms for most women. Recently, however, more women 65 years of age and older have been prescribed new and repeat HRT prescriptions. This is consistent with recommendations published in several practice guidelines which have until recently advocated HRT not only for the treatment of menopausal symptoms, but also for the prevention of osteoporosis.[175,193,194] Similar trends have been observed in the United States.[141,172]

The prevalence of HRT use has been reported in two Canadian studies.[190,195] In the 1994 National Population Health Survey, conducted by Statistics Canada, a nationally representative sample of women, 45 to 64 years of age, were interviewed with regard to HRT use during the month prior to the interview. The prevalence was highest at 33% among women 50 to 54 years of age, followed by 23% and 18% for women 55 to 59 and 60 to 64 years of age.[190] Pavletic and Metge[195] reported 1995 age-specific prevalence rates of 23, 22 and 14% for Manitoban women 50 to 54, 55 to 59 and 60 to 64 years of age. The Saskatchewan prevalence rates of 27, 23, and 15% for the same age groups are closer to the Manitoba results than to the reported national rates. Some regional differences in the use of HRT are not surprising and have also been observed in the United States.[172,196] In Canada, regional differences in the prevalence of lifestyle habits have been observed[197] and the underlying determinants of these differences may also play a role in a woman's decision to take HRT.

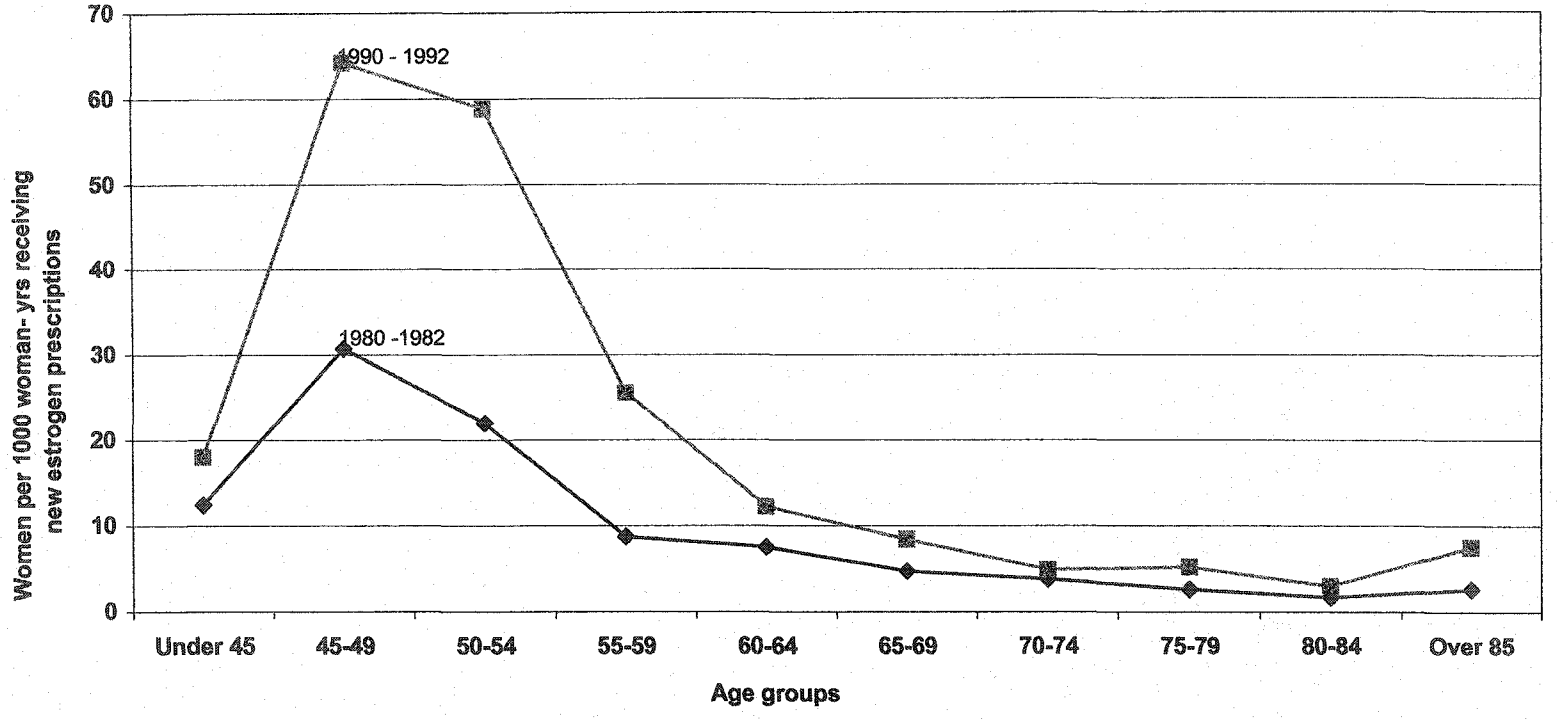
Records from Saskatchewan Health indicate that more than 50% of new estrogen users in the early 1990s were receiving unopposed estrogen. The increased risk of endometrial

cancer associated with the use of unopposed estrogen has been extensively documented and therefore[181,182,198-200] a combined estrogen-progestin regimen has been recommended in practice guidelines for women who have not had hysterectomies.[193,194] In the original case-control study, from which this cohort of women was drawn, a random sample of women had consented to participate in telephone interviews in order to obtain information pertaining to their medical and reproductive histories, including hysterectomy status. Sixty-two of these women were among the women we identified as new estrogen users in the early 1990s. Thirty-one of these women had been dispensed estrogen opposed by progesterone and 31 had been dispensed estrogen only. Of the women receiving estrogen-progesterone regimens 26 (84%) reported to have had an intact uterus. Of the women receiving unopposed estrogen 25 (81%), reported to have had hysterectomies. Thus our data thus suggest that most women are being prescribed HRT according to HRT guideline recommendations. This is consistent with the findings of Elinson et al.[201] who recently surveyed physicians' HRT prescribing practices in Ontario. Nonetheless, a small number of women who are receiving unopposed estrogen have not had a hysterectomy. In addition, sixteen percent of women are perhaps receiving progesterone without benefit. Given the small number of women for whom we have hysterectomy status data, our findings warrant further examination in future studies.

Important strengths of this study are the population-based sampling design with very few exclusion criteria, and the use of age-specific rates. Results therefore are generalizable to the provincial population of peri- and postmenopausal women. Also, due to the low rate of immigration and emigration of women 45 years of age and older, complete drug dispensing records from 1976 to 1997 were compiled for 78% of the women. It should be noted, however, that the outpatient prescription drug database does not capture drugs administered during hospitalization, and there is incomplete capture from July 1, 1987 to December 31, 1988 because of an administrative change. These limitations, however, do not impact on the validity of our results because HRT is almost always prescribed on an outpatient basis and our analyses were carefully designed so as to avoid reliance on data from the time period for which dispensing records are lacking.

We can expect that practice guidelines for prescribing HRT will continue to undergo revision as advancements in medical science add to our understanding of the risks and benefits associated with short and long-term HRT use. Prescription drug databases, such as the Saskatchewan Health database, can help us determine with a high degree of accuracy and efficiency the extent to which these changes have an impact on the pattern of HRT use at the population level.

Figure 1. The number of women per 1000 woman-years, receiving new estrogen prescriptions during the period from 1980 to 1982, and during the period from 1990 to 1992.



CHAPTER 5.

5.1 MANUSCRIPT #2: HEALTH RELATED BEHAVIOR AND THE USE OF HORMONE REPLACEMENT THERAPY

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Abstract

Background: Describing lifestyle and health behaviours associated with HRT use is of value to investigators designing epidemiological studies that examine health risks and benefits of HRT.

Methods: Data from the Saskatchewan Health population-based databases were used to study differences between postmenopausal HRT users and nonusers among colorectal cases and women without diagnosed cancer. HRT use, oral contraceptives (OCs), cardiovascular system (CV) drugs, central nervous system (CNS) drugs, prescribed NSAIDs and vitamins, were ascertained from the out-patient prescription drug database. Frequency of physician visits and use of sigmoidoscopies were also determined.

Results: Among women without diagnosed cancer, HRT was associated with past use of medication for the cardiovascular system (OR=1.26, 95%CI:1.13-1.40), CNS drugs (OR=2.02, 95%CI:1.78-2.30), NSAIDs (OR=1.26, 95%CI:1.10-1.45) and prescribed vitamins (OR=1.35, 95%CI:1.20-1.52). In this group women using HRT were also more likely to have had a sigmoidoscopy three to five years prior to assigned index dates (OR=1.30, 95%CI:1.11-1.52) and visited their physicians more often during the 5th year prior to their assigned index date. Similar results were observed among women diagnosed with colorectal cancer, except that HRT use was not associated with having had a sigmoidoscopy.

Discussion: Describing health-related differences between HRT users and nonusers in various populations is of value in identifying factors that may contribute to selection bias in studies of the health benefits of HRT.

Key words: hormone replacement therapy, health behaviour, selection bias, colorectal cancer, administrative health care databases, population-based health care databases, Saskatchewan.

Introduction

Results from observational studies indicate that women who use hormone replacement therapy (HRT) have a reduced risk of cardiovascular disease[202], cancer[136-138]and have lower rates of all cause mortality.[120] Concerns, however, have been raised with regard to the validity of the observed effects due to the possible presence of selection bias.[120,145,203] In observational studies it is possible to control for selection bias if differences between HRT users and nonusers are measured and considered in the statistical analyses. In order to do this, however, a priori knowledge of potential confounding factors is required.

Matthews et al[204] compared premenopausal lifestyle and cardiovascular disease risk factor characteristics of subsequent HRT users with those of nonusers and found that women who later became HRT users were better educated, had higher levels of leisure activity, were more likely to consume alcohol, were leaner and had lower levels of fasting insulin than women who remained nonusers. A number of other studies have confirmed that women who use HRT are more likely to have healthier lifestyle and health behaviors that may reduce their susceptibility some degenerative diseases.[120,124,145,172,203,205-207]

During the past two decades observational studies have examined the association between HRT and colorectal cancer and although the results are not consistent, the weight of the evidence appears to support a 20 to 30% reduction in colorectal cancer among HRT users. A causal association, however, has not been generally accepted by experts.[208] Results from well-designed observational studies such as the Nurses' Health Study (NHS), in which great attempts have been made to carefully measure potential known covariates, indicate that age-adjusted measures of association do not vary by more than 5% from multi-variate adjusted ORs.[82] Results from the NHS and other observational studies with extensive control of confounding continue to support the hypothesis that HRT is protective for colorectal cancer. Nevertheless, the possibility remains that these results are affected by residual confounding due to an inability to accurately measure important lifestyle factors, or due to the presence of yet unidentified important covariates.

It is worthwhile therefore, to continue studying the differences between HRT users and nonusers in a variety of populations. Most studies examining these differences to date have been conducted in the general population or among women assumed to be healthy. Whether associations between HRT use and various covariates are similar among women without colorectal cancer and women who subsequently develop colorectal cancer has not been investigated. Exploring such differences would be useful in the identification of potential covariates that need to be considered in the design of future studies examining the association between HRT use and colorectal cancer.

Objectives

To examine the differences in health related behavior between HRT users and nonusers among women not diagnosed with cancer and women who subsequently develop colorectal cancer.

Methods

Study population

Data for this analysis was originally compiled for a nested case-control study designed to examine the effect of HRT on colorectal cancer risk in postmenopausal women. The records from the Saskatchewan Cancer Agency Registry (SCA) had been used to identify histologically confirmed cases ≥ 45 years of age, from 1981 to mid-1998. These records, in existence since 1970 were also used to confirm the absence of previous cancer diagnoses amongst cases and the absence of cancer diagnoses in the women identified as controls described below (except for non melamoma skin cancer and cancer of the cervix in situ).

Women who had not been diagnosed with cancer, as confirmed by the SCA, had been matched to colorectal cancer cases on birth month and year (±1 year) and sampled, from the population-based Saskatchewan Health records using incidence density sampling. These women had served as controls in the original nested case-control study. In order to be eligible for the original study, both cases and controls had to have been registered with Saskatchewan Health for at least five years at the time of sampling.

Ascertainment of HRT and prescription drugs

Prescription drugs dispensed to women prior to their assigned index date (date of colorectal cancer diagnosis for cases and their age-matched controls), were ascertained using records of the Saskatchewan out-patient prescription drug plan dating back to 1976. Women, who prior to their assigned index date had received at least one prescription of estrogen replacement therapy in the form of a transdermal estrogen patch, estrogen injection and oral estrogen were considered to be ever users of hormone replacement therapy (HRT).

The past ever use of oral contraceptives (OCs), cardiovascular system (CVS) drugs, central nervous system (CNS) drugs (not including NSAIDs, see below), other hormones, and vitamins obtained by prescription were also determined using the out-patient prescription drug plan records. NSAIDs use, was determined and categorized according to when prescriptions had been dispensed during three separate time periods: up to five years prior to the index date, six to ten years, and 11 to 15 years prior to index dates. With the exception of oral contraceptives and NSAIDs, drugs were identified by broad classification rather than individual drugs.

Ascertainment of use of sigmoidoscopy and frequency of physician visits

Data pertaining to the use of sigmoidoscopies and frequency of physician visits were obtained for a five year period prior to index dates, from the Saskatchewan Hospital Services and Medical Care Insurance Branch databases.

Data analysis

The women with colorectal cancer and women who had been identified as controls were classified as ever or never having used HRT. Associations between HRT use and covariates were estimated using logistic regression in separate analyses for the women with and without colorectal cancer. Results are expressed as age-adjusted odds ratios (ORs) and 95% confidence intervals (CI). All ORs, are also adjusted for four blocks of calendar time according to the assigned index dates of the women (before 1986, 1986 to

1990, 1991 to 1994, and 1995 to 1998), ever/never use of prescription drugs previously mentioned above, and having had a sigmoidoscopy 3 to 5 years prior to index dates and frequency of physician visits during the 5th year prior to the index dates.

The studies were approved by the Research Ethics Committee of the Jewish General Hospital, the University Advisory Committee on Ethics in Human Experimentation of the University of Saskatchewan, and the Data Access Review Committee of Saskatchewan Health. All data released by Saskatchewan Health were de-identified and limited to the variables required for the analysis.

RESULTS

13,216 women had been sampled as controls and 3,338 women had been identified as having received a diagnosis of colorectal cancer. 191 controls were excluded from the control group in this analysis because they were diagnosed with colorectal cancer subsequent to their index date.

Health-related characteristics associated with HRT use among women without cancer and women who were subsequently diagnosed with colorectal cancer are presented in **Table 5.1**. Odds ratios are adjusted for age and all variables listed. Using the period before 1986 as a reference period, all other time periods were associated with an increased in HRT use. In both groups there appears to be a three-fold increase in the probability of HRT use in 1995 compared with the time prior to 1986 (OR=2.90;95 percent CI: 2.49 to 3.37 for controls) and (OR=2.78; 95 percent CI: 2.04 to 3.80 for cases).

Among colorectal cancer cases, there was an association between HRT use and OC use, (OR=1.55, 95 percent CI: 0.93 to 2.58). Among women without cancer there was no association between HRT use and OC use. Women without cancer who had used HRT were 20% more likely to have received medications prescribed for the cardiovascular system (OR=1.26; 95 percent CI: 1.13 to 1.40). HRT users in both groups were 30% more likely to take prescribed vitamins, and twice as likely to take CNS drugs. HRT users in both groups were also more likely to have received prescriptions for NSAIDs,

but the magnitude of the association was greatest during 6 to 10 years prior to the index dates (OR=1.26; 95 percent CI: 1.10 to 1.45 and OR=1.50; 95 percent CI: 1.14 to 1.98 for controls and cases respectively). An association between HRT and the use of other prescribed hormones was not observed.

Among women without colorectal cancer HRT use was associated with having had a sigmoidoscopy 3 to 5 years prior to index dates, OR=1.31 (95 percent CI: 1.11 to 1.56). Among cases, an association between HRT and sigmoidoscopy was not observed, OR= 0.90(CI: 0.64 to 1.27). An association between frequent physician visits and HRT use during the 5th prior to the index date was also stronger and greater in magnitude among the controls compared with cases especially for 15 or more visits during that year (OR=2.03; 95 percent CI: 1.74 to 2.38 vs. OR=1.61; 95 percent CI: 1.19 to 2.18 for controls and cases respectively).

Table 5.1. Health related behavior associated with HRT use among healthy women and women subsequently diagnosed with colorectal cancer.

Covariates	*Adjusted Odds Ratios* and 95% Confidence Intervals*	
	Healthy Women	*Colorectal Cases*
Calendar time of index date	*(N = 13,025)*	*(N=3,338)*
before 1986	1.00	1.00
1986-1990	1.30 (1.02 - 1.54)	1.18 (0.84 - 1.67)
1991-1994	1.93 (1.62 - 2.81)	1.62 (1.13 - 2.33)
1995-1998	2.90 (2.44 - 3.37)	2.78 (2.04 – 3.80)
Oral Contraceptives		
Never	1.00	1.00
Ever	0.84 (0.64 - 1.10)	1.55 (0.93 –2.58)
Cardiovascular Drugs		
Never	1.00	1.00
Ever	1.26 (1.13 - 1.40)	1.18 (0.95 - 1.46)
Central Nervous System Drugs		
Never	1.00	1.00
Ever	2.02 (1.78 - 2.30)	2.03 (1.58 – 2.61)
Other hormones		
Never	1.00	1.00
Ever	1.13 (1.02 - 1.25)	1.04 (0.84 - 1.28)
Vitamins		
Never	1.00	1.00
Ever	1.35 (1.20 - 1.52)	1.42 (1.09 - 1.81)
NSAIDs use in past		
Never	1.00	1.00
1 to 5 yrs.	1.25 (1.12 - 1.39)	1.18 (0.94 - 1.47)
6 to 10 yrs.	1.26 (1.10 - 1.45)	1.50 (1.14 - 1.98)
11 to 15 yrs.	1.22 (1.07 - 1.39)	1.39 (1.07 - 1.82)
Sigmoidoscopy in past 3 to 5 yrs prior to the index date		
Never	1.00	1.00
Ever	1.30 (1.11 - 1.52)	0.90 (0.64 - 1.27)
Number of physician visits during the 5th year prior to index date		
2 or less	1.00	1.00
3 to 7	1.38 (1.20 - 1.60)	0.91 (0.69 - 1.20)
8 to 14	1.70 (1.46 - 1.98)	1.72 (1.29 - 2.30)
15 or more	2.03 (1.74 - 2.38)	1.61 (1.19 - 2.18)

* Odds ratios adjusted for age and all variables listed.

DISCUSSION

Differences in health behavior exist between HRT users and nonusers in healthy populations. It has been hypothesized that some of these differences are responsible for the observed lower risk of cardiovascular disease and colorectal cancer among HRT users.

Our data confirm that among women without cancer diagnoses in the general population, health behaviors that may prevent chronic disease, such as the use of vitamins, NSAIDs, screening sigmoidoscopy and frequency of physician visits are more likely to occur among HRT users. With the exception of having had a sigmoidoscopy three to five years prior to index dates, associations between HRT and these covariates were also seen among women who subsequently developed colorectal cancer.

HRT use among women not diagnosed with cancer appeared to be associated with the dispensing of drugs intended to treat cardiovascular system disorders. This is consistent with results from studies that describe physician prescribing practices. Newton et al[209] reported an association between the frequency of prescribing HRT and the belief that HRT prevents cardiovascular disease (CVD). This study, and ours predate the publication of results from the Heart and Estrogen/Progestin Replacement Study (HERS), which indicates that women with existing CVD may not benefit from HRT for secondary prevention and may be at an increased risk of experiencing thromboembolic events.[183] Prior to the publication of these findings, practice guidelines and some expert groups had advocated prescribing HRT to women with coronary artery disease in order to the optimize secondary prevention management.[191,193,198]

Women who were prescribed HRT were twice as likely to be prescribed CNS medications. A large proportion of these medications are antidepressants, although narcotic analgesics were also included in this category. Studies have generally not found an association between menopause and depression.[210,211] In a study of 581 women between 45 and 54 years of age Bosworth et al[212] did not find an association between menopausal status and depressive symptoms but did report higher rates of depressive

symptoms among women experiencing climacteric symptoms. A similar association between climacteric symptoms and depressive symptoms may exist among women in this population, hence explaining the strong association between CNS medications and HRT.

Exploring and understanding the associations between health-related behavior and HRT use is important for improving the design and analysis of observational studies. The associations between certain health behaviors and HRT use among controls and colorectal cases indicate the presence of variables that may confound the association between HRT and colorectal cancer, if they are also associated with colorectal cancer. In this study prescription vitamins and NSAIDs would qualify as potential confounding variables. Although CNS drugs are strongly associated with HRT use, they have not been implicated in colorectal cancer. They may however be potential confounding variable in studies where there is another outcome of interest.

HRT users in both groups tend to frequent their physician more often than nonusers as far back as five years prior to their assigned index date. It has been hsuggested that the frequency of physician visits may serve as a marker for other health related characteristics that could be associated with the outcome and may be used to control for confounding indirectly. With regard to colorectal cancer, women who visit their physicians frequently, may have more access to screening procedures such as sigmoidoscopy. It is of interest that independent of the frequency of physician visits, HRT users among women who had not been diagnosed with cancer were more likely to have had a sigmoidoscopy three to five years prior index dates. We do not have information pertaining to whether or not polypectomies were performed at the same time as sigmoidoscopies. In some women they likely were, and for these women the procedure would have conferred protection against colorectal cancer. Since an association was not seen between HRT use and having had a sigmoidoscopy three to five years prior to the index date among women with colorectal cancer we may conclude that this factor might be an effect modifier for the association between HRT and colorectal cancer. As discussed by Ray and Griffin[148], associations between an exposure and covariate which differ between cases and controls is suggestive of an interaction between

the covariate and the exposure. Indeed, it has previously been shown that women taking HRT have more screening sigmoidoscopies performed than women not taking HRT.[82] It has previously been suggested but not demonstrated that in studies examining the association between HRT and colorectal there may exist an interaction between having had a sigmiodoscopy and HRT. This data supports this hypothesis.

It is known that HRT users tend to be healthier, more affluent and engage in healthier lifestyle habits. As a result, the protective effect observed in some studies examining the impact of HRT on colorectal cancer risk has been viewed with skepticism. Paradoxically, attempts to adjust for potential confounding variables have generally not altered estimates of a protective effect of HRT for colorectal cancer. In designing future epidemiological studies therefore, we need to focus on measuring covariates with greater accuracy, and also on identifying covariates, perhaps currently not known.

Our results confirm that there are health related differences between women who use HRT and those who do not, among women with and without colorectal cancer. Additional research is required in order to identify other differences that may exist. Such information would increase our understanding of selection bias and the extent to which it may be responsible for the observed protective effect of HRT on colorectal cancer, if indeed it is present.

CHAPTER 6. DEFINING HORMONE REPLACEMENT THERAPY IN LONGITUDINAL STUDIES: IMPACT ON MEASURES OF EFFECT

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ABSTRACT

Studies have used various methods of defining estrogen exposure to investigate the health risks and benefits of hormone replacement therapy (HRT). Data from a nested-case control study, that examined the effect of HRT on colorectal cancer risk, were obtained to verify whether or not varying exposure definition had an impact on the estimation of risk ratios (RR). Records from an out-patient prescription drug plan database were used to ascertain all HRT prescriptions dispensed to cases (N=3,059), prior to colorectal cancer diagnosis and to controls (N=12,116), prior to their assigned index dates. Definitions of HRT exposure reported in the literature, have included prescription counts, tablet counts, and the ascertainment of conjugated estrogen only. A fourth method based on proportions of a calculated minimum exposure (SUM-P3 and SUM-P12) was also calculated for comparison. Differences produced by varying exposure definition were studied with reference to the following durations of use: ever use, 1 to 4, and ≥ 5 yr of HRT exposure. Conditional logistic regression (incidence density sampling and age-matching) was used to estimate RRs and 95% confidence intervals (CI). Regression models were adjusted for having had a sigmiodoscopy 3 to 5 years prior to index dates. RRs for ever use of HRT ranged from 0.72 (95% CI: 0.60 to 0.88) to 0.88 (95% CI: 0.77 to 1.01). For 1 to 4 yr use, the range was from 0.72 (95% CI: 0.52 to 1.00) to 0.89 (95% CI: 0.77 to 1.04). For ≥ 5 year HRT use, the RR ranged from: 0.78 (95% CI: 0.64 to 0.95) to 0.98 (95% CI: 0.42 to 2.26). The various methods used to define HRT exposure in pharmacoepidemiology studies can produce variability in measures of association between HRT and colorectal cancer and lead one to reject or accept the hypothesis that HRT is protective. This diversity across studies however, does not explain all of the variability of measures of effect reported in the literature.

Introduction

Eighteen observational studies, examining the association between hormone replacement therapy (HRT) and colorectal cancer, have been published during the past two decades. Some of these studies suggest that HRT reduces the risk of colorectal cancer by 20 to 30% [82,111,112,125,127-131]. Others have not found a clear association between HRT and colorectal cancer risk[110,113-116,126,132-134].

HRT is available in several formulations, routes of delivery, and dosage. Estrogen is prescribed alone or combined with progesterone. Observational studies examining the effect of HRT on the risk of colorectal cancer have relied primarily on self-report [82,106,110-113,116,125,127-134]. In a few studies investigators have used medical records, prescription drug databases [114,126] or a combination of these methods and self-reports as sources of information for the determination of HRT use[115]. The source of information pertaining to HRT exposure determines the detail with which it is described and the accuracy with which its effect as a chemoprotective agent for colorectal cancer risk can be determined. The extent to which the variability in the definitions of HRT contributes to the variability of the reported effect of HRT on the risk of colorectal cancer in longitudinal studies has not been explored.

The objective of this study was to examine the impact of varying the definition of HRT use on the estimation of colorectal cancer. The published literature focusing on the relationship between HRT and risk of colorectal cancer was reviewed. Definitions of HRT use were identified in these studies and were applied to estrogen and progesterone dispensing data obtained from an extensive and detailed out-patient population-based administrative prescription drug plan database.

SUBJECTS AND METHODS

Data from a nested case-control study, designed to examine the effect of HRT on the risk of colorectal cancer incidence, were used in this analysis.

Study population

Peri-and postmenopausal women 50 years of age and older, living in Saskatchewan between January 1, 1981 and June 31, 1998 formed the study population. Women eligible for the case-control study included women without cancer diagnoses prior to index dates (except for non melanoma skin cancer and cancer of the cervix in situ) and women with at least five years of registration with Saskatchewan Health. The Saskatchewan Cancer Agency registry (SCA), which has been in existence since 1932 and computerized since 1970[213], verified that participants did not have previous cancer diagnoses. About 4 % of women in the population are covered by Federal programs and are therefore excluded from provincial jurisdiction [153].

Cases

Histologically confirmed colorectal cancer cases, identified by ICDO codes: C18.0, C18.2-C18.9, C19.9, C20.9 and C21.8 were eligible for the study. Cases diagnosed between 1981 and mid-1998 were ascertained from the SCA registry (N=3,059 colorectal cancers; 2123 colon and 936 rectal cancers). Cases are identified through pathology reports and physician service claims and the registry reported to be one of the most complete in Canada[213].

Controls

Four controls per case (N=12,116) were sampled from the out-patient prescription drug plan database using incidence density sampling. Controls living in Saskatchewan at the time of the cancer diagnosis of cases diagnosed between 1981 and 1997 for cases were matched on month and year of birth (± 1 year).

Ascertainment of estrogen exposure

For each woman in the study, HRT dispensing information was available for a minimum of 5 years, beginning between 1976 and 1993, depending on when she turned 50 years of age, and whether she immigrated to the province after 1981. All sources of HRT were ascertained: oral tablets, transdermal patches, vaginal creams and rings. The type of

formulation, drug strength and number of estrogen and progesterone units (tablets, capsules) dispensed to cases and controls prior to their index dates were obtained from the records of the out-patient prescription drug plan database, originally established in 1975. Exposure records were terminated on the date of colorectal cancer diagnosis for cases and on corresponding index dates for their respective controls.

Ascertainment of sigmoidoscopy use

The Medical Care Insurance Branch Databases were used to identify women who had had a sigmoidoscopy three to five years prior to the assigned index date.

Published definitions of estrogen exposure

Studies investigating the impact of estrogen on colorectal cancer risk were identified using a computerized search of the Medline and Cancerlit databases. Studies published between 1975 and 2000 were considered. Medical-subject-headings 'colorectal, colon, and rectal neoplasm' or textword terms 'colorectal, colon, and rectal cancer' and medical-subject-headings 'estrogen, estrogen replacement therapy' or textword terms or 'hormone replacement therapy, postmenopausal hormones', were used to identify publications. References cited in these publications were also scanned to identify studies. A total of 21 publications, 7 cohort and 14 case-control studies were identified and reviewed.

Three common methods of defining estrogen exposure were identified in the published literature: prescription counts, tablet counts, and the restriction of estrogen exposure to specific formulations. These methods were applied to our data from the out-patient prescription drug database as described below. In addition, for purposes of comparison another method that include information pertaining to the number of units (tablets) prescribed and dose per prescription was also calculated.

Definitions of estrogen exposure

Prescription counts

Using the definition of 'one prescription per year', a woman was considered exposed if she had received at least one oral or transdermal estrogen prescription per year for the

specified period of time. A definition of two prescriptions per year was also used to classify exposure. For this latter analysis, women receiving only one prescription per year were excluded from both exposed and unexposed groups.

A category of exposure for women receiving estrogen opposed by progesterone was also created. In this case women receiving estrogen alone were excluded from this analysis.

Oral estrogen tablet count

Oral estrogen tablets were counted and women dispensed a cumulative amount of at least 252 tablets were considered exposed; women receiving less were excluded. This was considered to be equivalent to at least one year of exposure (under the assumption that at least 21 pills were required for a one month supply).

Conjugated equine estrogens

Only women who had received oral conjugated equine estrogens (CEE) were classified as having been exposed. Three definitions of exposure were considered in this category: i) at least one prescription per year; ii) at least two prescriptions per year and; iii) at least 252 tablets of CEEs per year. Women who received transdermal estrogen were excluded from the exposed and unexposed groups.

Proportion of minimum exposure (SUM-P3 and SUM-P12)

Prescriptions were ascertained for all oral and transdermal forms of estrogen. The strength and quantity of estrogen that was dispensed to each woman during each year was determined and averaged over a three month and 12 month period. The amount of estrogen that a woman received was expressed as the proportion of the minimum dose prescribed to her for the specified period of time. If a woman received prescriptions for more than one formulation the proportions for the formulations were calculated individually and then summed. A woman was considered exposed for the year if the sum of the proportions equalled one for the three month period or for the entire year. A proportion of one for either three months or one year represented HRT coverage equivalent to the minimum daily amount that could be prescribed to a woman for the

treatment of postmenopausal symptoms for the specified period of time. We will refer to these definitions of exposure as the SUM-P3 and SUM-P12 for the three and twelve month coverage.

Data analysis

The impact of HRT was studied using the following time and duration specifications: 'ever use', 1 to 4 years of use, and ≥5 year use prior to index dates. These specified times were selected because they were used most frequently in the published literature and therefore the results could be compared with results from the present study. Conditional logistic regression was used to estimate RRs and 95 % confidence intervals (CIs). All estrogen exposure categories were calculated with the exclusion of exposure during the two years prior to index dates. Reference categories for all exposure groups were women who had never been exposed to oral, or transdermal estrogen patches prior to the two years immediately preceding index dates. Women who received prescriptions for vaginal creams and rings were considered to be unexposed because including them did not have an impact on point estimates and the amount that enters the systemic circulation is not well documented. Odds ratios were adjusted for sigmiodoscopy 3 to 5 years prior to index dates. Analyses are reported for colorectal and for colon and rectal cancer incidences separately. All statistical analyses were carried out using SAS software (SAS Institute, Version 8, 1999).

RESULTS

The effect of varying definitions of ever use of HRT, on the risk of colorectal cancer incidence is outlined in **Table 6.1.** For colorectal cancer, all odds ratios were 1.0 or less, ranging from 0.72 to 0.88. Seven of the 9 definitions produced statistically significant results: 1 prescription per year of estrogen only (OR=0.84 [95 % CI: 0.75 - 0.94]), 2 prescriptions per year of estrogen only (OR=0.86 [95 % CI: 0.76 - 0.98]), 1 prescription of CEE only (OR=0.86 [95 % CI: 0.76 - 0.97]), pill counts of 252 per year of all formulations of estrogen (OR=0.72 [95 % CI: 0.60 - 0.88]), pill counts of CEE only (OR=0.76 [95 % CI: 0.62 - 0.93], and the SUM-P3 (OR=0.83 [95 % CI: 0.74 - 0.94]).

Similar methods of defining exposure status produced similar point estimates regardless of intensity of exposure. For example 1 and 2 prescriptions of estrogen per year resulted in similar point estimates as did 1 and 2 prescriptions of CEE, and both SUM-P3 and SUM-P12. Tablet counts that included all estrogen formulations appeared to be just slightly more protective than tablet counts of CEE only.

Similar results were obtained for the associations between ever use of HRT and colon cancer incidence, with all ORs less than 1.0, ranging from 0.73 to 0.86 and 6 of 9 definitions resulting in significant results. Estimates of association were more variable for rectal cancer (ORs from 0.65 to 0.92) and only one association was statistically significant.

In **Table 6.2** the associations between colorectal cancer and 1 to 4 years of HRT use, are presented. Again for colorectal cancer, ORs are below 1.0, ranging from 0.70 to 0.89. Six of the nine associations estimated for colorectal cancer were statistically significant. The greatest variability was seen for the estimates of ORs for rectal cancer (ORs from 0.66 to 1.01). Similar methods of defining exposure again produced similar results, regardless of exposure intensity.

The ORs for colorectal cancer and HRT use for ≥5 years appear to be less variable than for shorter durations of use **Table 6.3.** As a result of fewer longer term estrogen users, the confidence intervals were also wider. Estimates for rectal cancer had the greatest amount of variability and the widest confidence intervals.

DISCUSSION

This study was designed to examine the impact of varying the definition of HRT exposure on the estimation of colorectal cancer risk in postmenopausal women. With the exception of the minimum defined daily dose, all definitions of estrogen exposure that were used were methods identified in publications examining the association between HRT and colorectal cancer. Our results, are consistent with the majority of published results which report relative risks below 1.0, and generally supporting a risk reduction of

about 20% to 30% among women who use HRT, although some studies have reported a greater reduction in risk (Table 4). The only source of variation in our study is that due to variation in the definition of exposure. This study demonstrates the importance of examining in detail how exposure is defined in HRT studies. Other potential sources of variability between studies were not addressed in this analysis and include other such factors as the timing of exposure and adjustment for covariates in addition to having had a sigmoidoscopy. However, as the timing of HRT exposure has not been extensively studied and adjustment for covariates has generally not altered point estimates, the inconsistencies between studies cannot be attributed to these differences.

Our results indicate that defining estrogen exposure as 1 or 2 prescriptions does not lead to differences in results for measures of association. Although some differences in point estimates exist between the methods of 'counting tablets' and 'counting prescriptions', the magnitude of differences appear to decrease with five or more years of hormone use. Neither of these methods however incorporate information pertaining to estrogen dose into the definition of exposure, as do the calculations for the SUM-P3 and SUM-P12. The inclusion of this detail in the definition of exposure, however, did not produce results that varied greatly from definitions where only prescriptions were counted. Since we calculated a daily dose based on the minimum amount that might be prescribed daily it would be reasonable to assume results with the 3 month SUM-P3 classification would essentially be similar to the '1 prescription per year' classification and the SUM-P12 would be similar to the '2 prescription per year' classification of exposure.

The definition of estrogen opposed by progesterone produced risk estimates that were somewhat lower than risk estimates with other definitions for 'ever use' and 1 to 4 years of use. For five or more years of use the definition of opposed estrogen produced higher risk estimates. It is possible that the effect of opposed estrogen on the risk of colorectal cancer is different from unopposed estrogen. However, fewer women fall into this category, confidence intervals are wider and point estimates for opposed estrogen are therefore prone to greater random fluctuation. An alternative explanation is that women prescribed unopposed estrogen are different from women prescribed opposed estrogen.

Current practice guidelines recommend restricting the prescribing of unopposed estrogen to women who have had hysterectomies[193,194]. Indeed, data from interviews of a sub-sample of women in our study population confirms that 81% of women receiving unopposed estrogen during the 1990s have had hysterectomies [214].

In **Table 6.4.** results from some recent cohort and case-control studies are described. For 'ever use' of HRT, only the case-control study by Fernandez et al [111] reported a protective effect for colorectal cancer, OR 0.64 (95 % CI: 0.46 to 0.88). Other case-control studies also reported ORs which appeared to be protective but not statistically significant [128,130]. A protective effect for 1 to 4 years of HRT use was also reported by Fernandez et al [111] (OR= 0.70 (95 % CI: 0.48 to 0.88)). Two case-control studies reported statistically significant protective effects associated with HRT use of five years or more 0.52 (95 % CI: 0.27 to 0.99) [111]and 0.47 (95 % CI: 0.24 to 0.91) [130].

With the exception of two of the studies presented in Table 4[114] and [126], the remaining studies had relied on self-reported use of HRT. Although self-reporting of HRT use has been reported to be quite accurate by some investigators[205], misclassification is likely to occur with reporting of duration of use, particularly in the distant past, adding another potential source of variation in the estimation of the effect of HRT in these studies.

A sub-sample of 464 women interviewed for the case-control study from which this data were obtained, were asked to recall HRT use throughout the 1980s and 1990s (data not presented). When responses were compared with database dispensing records, kappa statistics varied from 0.59 to 0.69. As expected, recall of more recent HRT use was better (kappa>0.65), than recall of HRT use in the distant past. Thirty to forty percent of women identified as having been dispensed a prescription during the years in question, reported no use. These results might in part reflect a pattern of not taking a dispensed prescription, however, the reporting was similar for women who had been dispensed only one and women who had been dispensed more than one prescription, suggesting under-reporting due to poor recall.

Over-reporting appeared to be less of a problem with only 3 to 5 % of women reporting HRT use in the absence of dispensing records for the time in question. While this discrepancy may represent an error in recall of the timing of the prescription dispensed, Buist et al[124] have also reported that almost 10% of women reporting 'current' HRT use, had no evidence of filling a prescription for HRT when compared with a computerized pharmacy database. West et al[122] have reported that details such as the name and dose of estrogen preparations are also poorly recalled. In their comparison of interview data with a pharmacy database they found that 78% of women recalled the name of HRT preparations used but only 26% recalled the name and dose. Additional validation studies of HRT self-reporting should be conducted in order to determine its usefulness and perhaps limitations in observational studies, particularly where the impact of specific patterns of use or formulations are being studied.

As in the case of the HRT-cardiovascular disease hypothesis, there has been a suspicion that some of the protective effects attributed to HRT, may in fact be due to characteristics of women who self-selected themselves to receive HRT [145,203,204]. These suspicions are not likely to be fully dispelled until results from large randomized clinical trials, like the Women's Health Initiative, are available. Although currently underway, results from this 9 year intervention study, with an anticipated 5 year post-trial follow-up, will not be available for several years [81,139]. In the mean time, evidence from well-designed observational studies, require further examination to delineate the true effect of exogenous postmenopausal estrogen. Such an examination can provide important insight into methods that will improve the design of future studies and the interpretation of results from existing studies.

While the existence of these administrative prescription drug databases present exciting opportunities in research they also presents investigators with new methodological challenges. The challenge facing investigators using observational designs to study the impact of HRT on health outcomes, is to find definitions of HRT exposure that can best represent exposure to this therapy with a high degree of accuracy. The maintenance of large prescription drug databases provide epidemiologists with the opportunity to do this.

In conclusion, our results demonstrate, that with the use of a large out-patient prescription drug database, some variability is introduced by varying the definition of HRT exposure. However, the results appear to be less variable than results from studies where self-reported use is relied upon.

TABLE 6.1 IMPACT OF EVER USE OF HRT ON THE RISK OF COLON AND RECTAL CANCER USING SEVERAL DEFINITIONS OF HRT EXPOSURE.

Definition of HRT exposure	*RR* (95% CI)* *Colorectal* n= 15,175	*Colon* n=10,534	*Rectal* n=4,641
1 PRESCRIPTION OF ESTROGEN PER YEAR	0.84 (0.75 - 0.94)	0.81 (0.71 - 0.93)	0.90 (0.74 - 1.09)
2 PRESCRIPTIONS OF ESTROGEN PER YEAR	0.86 (0.76 - 0.98)	0.83 (0.72 – 0.97)	0.89 0.73 - 1.10)
1 PRESCRIPTION OF CEE PER YEAR**	0.86 (0.76 - 0.97)	0.85 (0.73 - 0.98)	0.89 (0.73 - 1.10)
2 PRESCRIPTIONS OF CEE PER YEAR**	0.88 (0.77 - 1.01)	0.86 (0.73 - 1.01)	.92 (0.73 - 1.16)
ALL TABLETS (252/yr)	0.72 (0.60 - 0.88)	0.76 (0.60 - 0.96)	0.65 (0.45 - 0.93)
CEE TABLETS (252/yr)**	0.76 (0.62 - 0.93)	0.80 (0.63 - 1.02)	0.67 (0.46 – 0.97)
SUM-P3	0.84 (0.74 - 0.94)	0.82 (0.71 - 0.95)	0.86 (0.70 - 1.05)
SUM-P12	0.85 (0.74 – 0.98)	0.83 (0.70 – 0.98)	0.89 (0.70 – 1.13)
1 PRESCRIPTION PER YEAR (estrogen & progesterone)	0.75 (0.55 - 1.02)	0.73 (0.49 - 1.08)	0.79 (0.48 - 1.31)

** RR adjusted for age and having had a sigmoidoscopy 3 to 5 years prior to index dates; exposure status during 2 year period prior to index date not included in calculations.*

** Other HRT users deleted: colorectal n= 14176; colon n= 9843; rectal =4333.

TABLE 6.2 IMPACT OF 1 TO 4 YEAR USE OF HRT ON THE RISK OF COLON AND RECTAL CANCER INCIDENCE USING SEVERAL DEFINITIONS OF HRT EXPOSURE.

		RR (95% CI)*	
Definition of HRT exposure	***Colorectal***	***Colon***	***Rectal***
1 PRESCRIPTION OF ESTROGEN PER YEAR	0.86 (0.76 - 0.97)	0.80 (0.68- 0.93)	0.99 (0.80 - 1.22)
2 PRESCRIPTIONS OF ESTROGEN PER YEAR	0.87 (0.75 - 1.01)	0.80 (0.67 - 0.96)	1.01 (0.79 - 1.29)
1 PRESCRIPTION OF CEE PER YEAR**	0.87 (0.76 - 0.99)	0.81 (0.69 - 0.96)	0.99 (0.79 - 1.45)
2 PRESCRIPTIONS OF CEE PER YEAR**	0.89 (0.77 - 1.04)	0.84 (0.69 - 1.02)	1.01 (0.78 - 1.31)
ALL TABLETS (252/yr)	0.70 (0.56- 0.88)	0.72 (0.55 – 0.94)	0.66 (0.44 - 0.99)
CEE TABLETS (252/yr)**	0.75 (0.59 - 0.94)	0.77 (0.58 - 1.02)	0.68 (0.45 - 1.03)
SUM-P3	0.85 (0.74 - 0.97)	0.80 (0.68 - 0.94)	0.95 (0.76 - 1.19)
SUM-P12	0.84 (0.64 – 1.04)	0.76 (0.69 – 1.22)	1.01 (0.36 – 0.96)
1 PRESCRIPTION PER YEAR (estrogen & progesterone)	0.72 (0.52 - 1.00)	0.72 (0.48 - 1.09)	0.78 (0.43 - 1.25)

** RR adjusted for age and having had a sigmoidoscopy 3 to 5 years prior to index dates; exposure status during 2 year period prior to index date not included in calculations.*

** Other HRT users deleted: colorectal n= 14176; colon n= 9843; rectal =4333.

TABLE 6.3 IMPACT OF ≥ 5 YEARS OF HRT USE ON THE RISK OF COLON AND RECTAL CANCER INCIDENCE USING SEVERAL DEFINITIONS OF HRT EXPOSURE.

		RR (95% CI)*	
Definition of HRT exposure	***Colorectal***	***Colon***	***Rectal***
1 PRESCRIPTION OF ESTROGEN PER YEAR	0.78 (0.64 - 0.95)	0.84 (0.66 - 1.06)	0.66(0.45 - 0.95)
2 PRESCRIPTIONS OF ESTROGEN PER YEAR	0.79 (0.63 - 0.98)	0.85 (0.65 - 1.10)	0.66 (0.43 - 1.00)
1 PRESCRIPTIONS OF CEE PER YEAR **	0.84 (0.68 - 1.03)	0.94 (0.73 - 1.20)	0.63 (0.42 - 0.95)
2 PRESCRIPTIONS OF CEE PER YEAR **	0.85 (0.67 - 1.07)	0.91 (0.69 - 1.20)	0.70 (0.45 - 1.10)
ALL TABLETS (252/yr)	0.80 (0.55 - 1.16)	0.89 (0.57 - 1.36)	0.60 (0.28 - 1.28)
CEE TABLETS (252/yr)**	0.80 (0.54 - 1.18)	0.91 (0.60 - 1.41)	0.63 (0.29 - 1.35)
SUM-P3	0.79 (0.65 - 0.97)	0.86 (0.68 - 1.10)	0.65 (0.44 - 0.96)
SUM-P12	0.82 (0.64 – 1.04)	0.92 (0.70 – 1.22)	0.59 (0.36 – 0.96)
1 PRESCRIPTION PER YEAR (estrogen & progesterone)	0.98 (0.42 - 2.26)	0.81 (0.28 - 2.41)	1.35 (0.36 - 5.11)

** RR adjusted for age and having had a sigmoidoscopy 3 to 5 years prior to index dates; exposure status during 2 year period prior to index date not included in calculations.*

** Other HRT users deleted: colorectal n= 14176; colon n= 9843; rectal =4333.

TABLE 6.4 ESTROGEN EXPOSURE DEFINITIONS AND RESULTS FROM STUDIES EXAMINING THE ASSOCIATION BETWEEN HRT AND RISK OF COLON CANCER.

Cohort Studies	*Source of HRT exposure*	*Definition of HRT*	*RR (95% CI) for colon cancer* *Ever use*	*1 to 4 year use*	*≥ 5 year use*
GRODSTEIN et al. 1998[82]	Self-report	CEE	0.84 (0.65 - 1.08)	0.89 (0.59 - 1.34)	
TROISI et al. 1997[113]	Self-report		1.10 (0.81 - 1.60)	1.30 (0.65 - 2.70)	0.70 (0.37 - 1.30)
RISCH & HOWE 1995[114]	Dispensing data (Saskatchewan)	Oral HRT only Tablet counts Prescription counts	1.29 (0.86 - 1.93)	1.26 (0.55 - 2.88)	1.33 (0.70 - 2.49)
Case-control Studies					
PRIHARTONO et al 2000[125]	Self-report		0.60 (0.40 - 1.00)	0.80 (0.40 – 1.70)	0.50 (0.30 -1.00)
JACOBS et al. 1999[126]	Pharmacy database	CEE Tablet counts Prescription counts	0.85 (0,57-1.27)	0.97 (0.68 – 1.40)	0.98 (0.64-1.50)
FERNANDES et al. 1998[111]	Self-report		0.64 (0.46 - 0.88) (≤ 2 years)	0.70 (0.48 - 0.88) (> 2 years)	0.52 (0.27 - 0.99)
KAMPMAN et al. 1997[128]	Self-report		0.77 (0.64 - 1.32)		
JACOBS et al 1994[130]	Self-report		0.60 (0.35 - 1.01)	0.72 (0.39 - 1.32)	0.47 (0.24 - 0.91)

CHAPTER 7. THE EFFECT OF TRANSDERMAL AND ORAL ESTROGENREPLACEMENT THERAPY ON COLORECTAL CANCER RISK IN POSTMENOPAUSAL WOMEN

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Abstract

Background: Observational studies suggest that estrogen replacement therapy (ERT) may be protective for colorectal cancer, however results have been inconsistent. Whether the association between ERT and colorectal cancer risk is affected by the route of administration, oral or transdermal, has not been studied.

Objective: To determine the effect of oral and transdermal estrogen administration on the risk of colorectal cancer risk in postmenopausal women.

Methods: Data from a nested case-control study, designed to investigate the effect of ERT on colorectal cancer was analyzed. Colorectal cancer cases diagnosed between 1990 (N=1,675) were identified using Saskatchewan Cancer Agency records. Four controls per case were age matched to cases, using incidence density sampling. Women were $\geq$ 50 years of age, and all were eligible to be covered by the Saskatchewan out-patient prescription drug plan. Records from the prescription drug plan database were used to ascertain past estrogen prescriptions dispensed to study subjects. Women were grouped according to history of estrogen use: transdermal (primarily estradiol;TDE), oral (primarily conjugated estrogens; OE). Conditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs).

Results: Compared to women who had never used HRT, ORs for <3 and $\geq$3 years of TDE use and colorectal cancer were 0.35 (95% CI: 0.13, 0.98) and 0.18 (95% CI: 0.02, 1.33), respectively. For the same duration of use, ORs for OE use were 0.94 (95% CI: 0.78, 1.12) and 0.85 (95% CI: 0.70, 1.03).

Conclusion: The risk reduction that we observed for colorectal cancer with TDE was greater in magnitude than that which has been reported for ERT in the past. Metabolic differences between ERT administered via different routes may be associated with different levels of protection.

INTRODUCTION

The risks and benefits of estrogen replacement therapy (ERT) have been the focus of research and sometimes heated debate during the past two decades. Expert opinion regarding the net benefit of ERT and its role in the prevention of chronic disease in postmenopausal women has swayed from enthusiastic support to great reservation[179,193,215].

Although negative results have been published [50,114,115,126], the majority of observational studies suggest that hormone replacement therapy is protective for colorectal cancer in postmenopausal women [82,110,111,125,127,128,130,131,144]. All of the studies have focused almost exclusively on the use of oral estrogen. This may be due in part to the higher prevalence of oral estrogen use among women, compared with transdermal estrogen. However, since the availability of transdermal estrogen in the mid-1980s in both Canada and the US, its use has been increasing [141,214]. In the province of Saskatchewan (Canada), we found that by 1990, 20% of all ERT users were using transdermal estrogen[214].

Estrogen delivered by oral and transdermal routes result in metabolic differences. Following oral estrogen administration a large proportion of the estradiol is metabolized to estrone resulting in a serum estradiol/estrone ratio of 1:4[216,217]. Following transdermal estrogen administration, the presystemic metabolism of estradiol to estrone is avoided, resulting in a serum estradiol/estrone ratio that compares favourably with the 2:1 ratio reported in fertile women[178]. This biological difference, and other known [218]and still to be clarified differences between oral and transdermal estrogen administration[219], may confer different effects on colorectal cancer risk. Our main objective in this study was to examine the effect of transdermal and oral estrogen administration on the risk of colorectal cancer in postmenopausal women.

METHODS

Population

Data from a population-based nested case-control study was analyzed to investigate the effect of oral and transdermal estrogen on the risk of colorectal cancer risk in postmenopausal women in Saskatchewan, a province in Canada. Saskatchewan Health (SH) is a provincial government department that, among other responsibilities, maintains publicly funded computerized health care databases. These databases were used as sources of health care information for this study. About 4 percent of women in the population are covered by Federal programs and are therefore excluded from provincial jurisdiction[150]. The remaining women are eligible for, and registered with SH for medical care and prescription drug financial coverage. The SH computerized databases and their use in population-based studies have been described elsewhere[151,192].

Study subjects

Women, 50 years of age and older, diagnosed with histologically confirmed colorectal cancer between 1990 and mid-1998 were identified using records from the Saskatchewan Cancer Agency (SCA). Four controls per case were sampled from SH electronic records using incidence density sampling. Controls living in Saskatchewan at the time cases were diagnosed (the index date) were matched to cases on month and year of birth (± 1 year).

Women were eligible if they had had at least five years of registration with SH and if prior to the index date they had not been diagnosed with cancer (except for non melanoma skin cancer and cancer of the cervix in situ). This was verified against records of the SCA computerized database dating back to 1970. Physicians are reimbursed for providing treatment to cancer patients, only if patients are registered with the SCA. The reporting of cancer cases is therefore highly accurate.

Ascertainment of estrogen exposure

Dispensing data was available for oral, transdermal patch, and creams forms of estrogen. For each woman in the study, the type of formulation, strength and number of estrogen units dispensed, prior to index dates, were obtained from the records of the outpatient prescription drug plan database, originally established in 1975. Prescription drug

dispensing data was ascertained for each subject from the time she turned 50 years of age or the time that prescription drug coverage began, whichever occurred last, and until the date of colorectal cancer diagnosis for cases or assigned index dates for controls.

Definitions of estrogen exposure

Women were classified according to history of ERT use: transdermal (TDE) use only, or use of TDE with a history of OE use; oral (OE) estrogen use alone, or use of OE with a history of TDE use. Exposure to ERT prior to the index date was ignored because there was a concern and some evidence to suggest that women who begin to feel unwell, discontinue ERT, leaving only healthy women as ERT users [120]. A woman was identified as 'ever' having used estrogen if she had received at least one prescription of estrogen prior to her index date, excluding the two years immediately preceding it. Women who had used ERT exclusively during the two years prior to their index dates or women who had received prescriptions for estrogen containing vaginal creams or rings only, were identified. This permitted analyses to be carried out with their inclusion or exclusion from the reference groups.

The cumulative number of years of oral and transdermal estrogen exposure was determined using one and two prescriptions per year as definitions of exposure. Duration of use was further classified according to short-term (<3 years) or longer term use (≥3 years).

Ascertainment of covariates

The use of oral contraceptives, cardiovascular system (CVS) drugs, central nervous system (CNS) drugs, and prescription nonnsteroidal anti-inflammatory drugs (NSAIDs) and vitamins, and other hormones were also ascertained from the outpatient prescription drug plan database for the period of time preceding index dates. History of having had a sigmoidoscopy and the frequency of physician visits during the five-year period prior to index dates were ascertained for all cases and controls using records of the medical care insurance branch database.

Statistical analysis

Conditional logistic regression was used to calculate crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs). Backward and forward model selection methods were used to identify the best regression model. The confounding effect of each covariate that had been identified a priori, was assessed using a criteria of 10% or more change in the ORs for OE or TDE.

All the analyses were repeated among subjects who had not had a sigmoidoscopy three to five years prior to the index date. The analyses could not be carried out among women who had had sigmoidoscopies during this period of time because too few women had had the procedure.

An unmatched analysis was conducted to study the impact of TDE on the risk of colorectal cancer, among ERT users. In this analysis cases and controls exposed to TDE were compared with women who had used exclusively OE. Age-adjusted ORs and 95% confidence intervals (CI) were calculated using unconditional logistic regression.

A test for linear trend was carried out for the duration of ERT use by redefining short and longer duration (<3 or ≥ 3 years) of TDE and OE use, as ordinal variables and assessing their level of significance in a logistic regression model. All statistical analyses were carried out using SAS software (SAS Institute, Version 8, 1999).

RESULTS

The health-related characteristics of 1675 women diagnosed with colorectal cancer and 6571 controls are outlined in **Table 7.1**. Cases and controls had a mean age of 73.4 years. Not surprisingly, important differences existed between cases and controls with regard to the proportion that had had a sigmoidoscopy during the year immediately preceding the index date (70.0 % vs. 2.5 % for cases and controls, respectively). During the year preceding the index date, 65.5 % of cases also visited their physician 15 times or more, compared with 29.8% of controls. Minor differences were found between cases and controls with regard to having had a sigmoidoscopy and the frequency of physician

visits during the 2 to 5 years preceding index dates. The prevalence of prescription vitamin, cardiovascular and CNS drug use did not differ between cases and controls. There was a tendency for controls to use more NSAIDs during the three five-year periods prior to index dates.

Prescription drug use only minimally altered ORs for estrogen and colorectal cancer (less than 10%) and therefore only age-adjusted ORs are presented. ORs for the incidence of colorectal cancer were controlled for age with matching, or where matching was broken, adjusted for age by including age in the regression model. All associations are presented for the entire study population as well as for women who had not had sigmoidoscopies three to five years prior to index dates.

'Ever' use of OE, was associated with an OR of 0.89 (95% CI: 0.78 to 1.02) **Table 7.2.** The 'ever' use of TDE was associated with an OR of 0.62 (95% CI: 0.41 to 0.93). Among women who had 'ever' used only TDE, the OR associated with colorectal cancer was 0.29 (95% CI: 0.12 to 0.73). The ORs for 'ever' use of OE and TDE among women who had not had sigmoidoscopies was not markedly different from that of the entire sample,.

Colorectal cancer risk associated with duration of oral estrogen use is outlined in **Table 7.3**. Neither short-term, less than 3 years of use, nor longer duration of more than 3 years of OE use, was associated with colorectal cancer risk among women who in the past had used OE exclusively, or who had also used TDE estrogen. The tests for linear trend were almost significant (p for trend = 0.06). Similar results were obtained for women who had not had sigmoidoscopies three to five years prior to index dates.

The above analyses were carried out with one prescription per year qualifying as an exposed year. When 2 prescriptions per year were counted as exposed, women who used OE only, had ORs of 0.97 (95% CI: 0.79 to 1.19), and 0.83 (95% CI: 0.67 to 1.02) for short and longer duration of use. Among women without sigmoidoscopies these results were 1.06 (95% CI: 0.85 to 1.31), and 0.87 (95% CI: 0.70 to 1.09). Removing women

who had used ERT only during the two years prior to the index date, from the reference group, had no effect on altering results. Similarly, removing vaginal estrogen cream users only from the reference group had no effect .

For TDE users, some of whom had used OE in the past, the ORs were 0.70 (95% CI: 0.45 to 1.10) for less than three years of use, and 0.39 (95% CI: 0.15 to 0.99) for three or more years of use **(Table 7.4)**. The linear test for trend was statistically significant (p for trend = 0.02). For TDE users only, less than three years use was associated with an OR of 0.35 (95% CI: 0.13 to 0.98), and 0.18 (95% CI: 0.02 to 1.33) for 3 or more years of use (p for trend = 0.03). Among women who had not had sigmoidoscopies three to five years prior to the index dates, the same durations of TDE use only was associated with ORs of 0.28 (95% CI: 0.09 to 0.91), and 0.22 (95% CI: 0.03 to 1.67).

When '2 prescriptions per year' was used as the definition of exposure, women who had used TDE only, had ORs of 0.29 (95% CI: 0.11 to 0.88), and 0.25 (95% CI: 0.07 to 0.85) for short and longer durations of use. Among women without sigmoidoscopies these results were 0.29 (95% CI: 0.10 to 0.88), and 0.16 (95% CI: 0.04 to 0.70). As in the case of OE, removing the women who had used ERT during the two years prior to the index date only, or vaginal cream only, from the reference group, had no effect on altering results.

An analysis was carried out to determine the association between transdermal estrogen use and colorectal cancer risk among ERT users (cases N=353; controls N=1547) **(Table 7.5).** Women using oral estrogen only were in the reference category. Among TDE users, some of whom had also used OE, short and longer durations of use was associated with an OR of 0.78 and 0.45, respectively. Among women who had used TDE only, short and longer durations of use were associated with ORs of 0.38 and 0.20. Dose-response effects were observed for the two groups (p for trend=0.05 and 0.04, respectively). Among women who had not had sigmoidoscopies, TDE use only was associated with ORs of 0.30 and OR=0.24.

Discussion

We observed a protective effect of transdermal estrogen replacement therapy for colorectal cancer in postmenopausal women. The reduction in risk of at least 60% for women using only transdermal estrogen, is greater in magnitude than has been reported in studies investigating the association between oral estrogen replacement therapy and colorectal cancer.

The results from published studies have been inconsistent, with several studies reporting no effect of ERT [50,114,115,126]. The weight of the evidence however, appears to support a 20 to 30% risk reduction of colorectal cancer with the use of oral conjugated estrogens [82,110,111,125,127,128,130,131,144]. Four meta-analyses have been conducted to date using results from published observational studies [135-138]. Only one of these studies, published several years before the others, did not find evidence supportive of a protective effect of ERT for colorectal cancer risk (RR=0.92: 95% CI, 0.74 to 1.15)[135]. The other studies reported summary estimates that supported colorectal cancer risk reduction of about 20 to 33% with ERT use [136-138].

We did not find strong evidence of a protective effect of oral conjugated estrogen use for colorectal cancer, but all of our point estimates are below one and some are of borderline statistical significance. In assigning exposure status, we assumed reference dates 2 years prior to the diagnosis of colorectal cancer for cases and therefore we either ignored exposure during the 2 years prior to index dates or identified women who only used ERT during this period of time and removed them from the reference group. This did not affect our results.

Although our results for the effect of oral estrogen were not adjusted for all potential covariates including diet and physical activity, we were able to investigate the impact of some important covariates, obtained from prospectively recorded healthcare databases, on the odds ratios for transdermal and oral estrogen. The impact of the use of prescription NSAIDs, the use of oral contraceptives and the frequency of physician visits prior to index dates had a negligible effect on odds ratios. These results are consistent

with results from the Nurses Health Study, where numerous covariates including diet, physical activity and reproductive history have been prospectively documented. In that study adjustment for these covariates resulted in less than a 5% change in the estimated relative risk for oral estrogen and colorectal cancer[82]. This lack of impact of covariates on measures of association has also been reported by other investigators [111,125,128].

We also report results from our analysis among women who had not had a sigmoidoscopy during the three to five year period prior to index dates. All ORs remained strongly protective for transdermal estrogen some associations became even more protective. We consider at this time period to be a 'screening' sigmoidoscopy rather than a 'diagnostic' procedure. The impact of having had a sigmoidoscopy during this time could conceivably have a protective effect, if premalignant polyps are removed [85]. This effect could be attributed to HRT, if women using HRT are also are more likely to have this procedure performed. As previously mentioned the number of women who had had sigmoidoscopies performed during this time prior to index dates was too few to permit analysis in this group. However, since in the absence of a screening sigmoidoscopy, results for ERT remain protective we can rule out the impact of having this procedure substantially affecting our results.

The estimates for colorectal cancer risk among women using oral and transdermal estrogen use, may be confounded by covariates not measured in our study, particularly in the analyses where the reference groups are women unexposed to estrogen. Women choosing to use hormone replacement therapy (HRT) are known to be different from women choosing to not use HRT and it has been suggested that some of these differences may be responsible for its observed protective effect on colorectal cancer and other chronic diseases[145,172,204]. However, as mentioned above, even in a well designed large prospective study such as the Nurses' Health Study where all known covariates are measured, crude relative risks are not very different from multi-variate relative risks. Many of the healthy lifestyle characteristics attributed to HRT users are likely to be present in both oral and transdermal estrogen users. Whether or not additional health related differences exist between transdermal and oral estrogen users has been studied

very little. Ettinger et al studied differences between transdermal and oral estrogen users with regard to continuation of estrogen therapy [220]. He reports that age and compliance were comparable among transdermal and oral estrogen users. It is unlikely, that differences, if they exist, would be as extreme as the differences between ERT users and nonusers. In the analysis of the effect of transdermal estrogen on colorectal cancer risk compared with oral estrogen, we therefore eliminate an important potential for bias. As in the analysis where HRT nonusers are the reference group, the protective effect of transdermal estrogen remains.

Our study is limited by the fact that we only have a small number of women with colorectal cancer who are exposed to transdermal estrogen. If however, transdermal estrogen is truly protective we can always expect to have fewer cases exposed than controlsand we did observe significant results even with this small number of exposed cases. Nonetheless, in order to study the effect of the duration of transdermal estrogen use adequately, a larger population with a longer history of trandermal estrogen use must be studied.

Several strengths and advantages of this study are worth mentioning. First, we have highly accurate estrogen exposure and outcome data, prospectively documented for all of our subjects. This avoids the potential problem of violations of temporal order, which can plague case-control studies. Second, we have accurate data from healthcare databases for all of our subjects, with regard to the dispensing of several other prescription drugs, and history of having had a sigmoidoscopy.

Finally, indirect and direct mechanisms have been proposed to explain the protective effect of endogenous and exogenous effects of estrogen on colorectal cancer. Plasma estrogens from endogenous and exogenous are known to influence bile acid composition [90,93,221]. It has also been observed that exogenous estrogens decrease concentrations of bile acids which may reduce the potential for these acids to promote tumors in the colon[90,91,93]. The carcinogenic effect of bile acids on the colonic mucosa has been demonstrated[88].

More recent evidence supporting the biologic plausibility for the protective effect of estrogen for colorectal cancer comes from studies demonstrating that in postmenopausal women, the use of estrogen reduces serum insulin-like growth factor-1 (IGF-I) levels[98]. IGF-I is known to be a potent mitogen and high circulating levels have been associated with an increased risk of for several common cancers, including those of colorectal cancer [101,102]. IGF-I is regulated by growth hormone (GH) but the expression of IGF-I is influenced by various hormones including estrogen [103]. Oral estrogen has been observed to reduce IGF-I levels and increase growth hormone levels. The reported effects of transdermal estradiol on IGF-I production and GH levels have been inconsistent. Campagnoli et al [219] recently reported observing a bimodal effect of transdermal estrogen, which was dependent on basal IGF-I levels. Following six months of treatment an increase in IGF-I levels was observed when basal levels were low. In the presence of high basal IGF-I levels, IGF-I tended to decrease. Further study is warranted in order to clarify the effects of oral and transdermal estrogen on the IGF-I/GH axis, and if differences exist, their impact on clinical outcomes.

Other metabolic differences between transdermal and oral estrogen have also been reported. The induction of hepatic protein synthesis (sex hormone-binding globulin, corticosteroid-binding globulin, thyroxine-binding globulin, transferrin, ceruloplasmin, apolipoprotein A1, rennin substrate and various coagulation and fibrinolysis factors) during oral estrogen administration is avoided with transdermal estrogen administration[218,222]. The estradiol/estrone ratio produced with transdermal etrogen administration is closer to premenopausal levels than is the ratio produced with oral estrogen administration [178,217,218]. In addition, with the transdermal estrogen patch the amount of estrogen released is constant and the peaks and troughs characteristic of oral estrogen are avoided[217]. The clinical relevance of these different biological properties is an area that requires study.

In summary, the important reduction in colorectal cancer risk with transdermal estrogen use, has not previously been reported. The difference in effect between TDE and OE is striking and should lead to further research in this field.

Table 7.1. Health-related characteristics of cases and controls.

	Cases n=1675		Controls n=6571	
	N	%	N	%
Age at index date (mean)	73.4		73.4	
Ever use of prescription drugs prior to index date				
Cardiovascular drugs	1139	68.0	4298	65.4
Central nervous system drugs	1216	72.6	4834	73.6
Oral contraceptives	35	2.1	121	1.5
Other hormones and substitutes	636	38.0	2537	38.6
Vitamins	292	17.4	1210	18.4
NSAIDs use in yrs before the index date: **1-5**	869	51.9	3703	56.4
6-10	920	54.9	3844	58.5
11-15	917	54.8	3721	56.6
History of sigmoidoscopy or colonoscopy				
Year before the index	1179	70.39	161	2.45
2-5 yrs "	170	10.2	546	8.3
3-5 yrs "	128	7.6	417	6.3
Frequency of doctor visits in year before index date:				
0-2	46	2.8	1265	19.3
3-7	111	6.6	1681	25.6
8-14	421	25.1	1669	25.4
15+	1097	65.5	1956	29.8
Frequency of doctor visits 2-5 years before index date:				
0-9	207	12.4	855	13.0
10-24	351	21.0	1360	20.7
25-59	694	41.4	2575	39.2
60+	423	25.3	1781	27.1

Table 7.2 Odds ratios and 95% confidence intervals for incidence of colorectal cancer associated with ever use of oral and transdermal estrogen administration in postmenopausal women.

	Cases N=1675	Controls N=6571	Crude OR*	95%CI	Among women who had not had a sigmoidoscopy§ N=7701	95%CI
Unexposed	1322	5024	1.00		1.00	
Oral†	348	1484	0.89	0.78-1.02	0.94	0.81-1.09
Transdermal†	29	172	0.62	0.41-0.93	0.60	0.39-0.94
Transdermal only	5	63	0.29	0.12-0.73	0.26	0.10-0.73

† May have used other HRTs.

* Cases and controls matched on age.

§ Sigmoidoscopy 3 to 5 years prior to the index date.

Table 7.3 Odds ratios and 95% confidence intervals for incidence of colorectal cancer associated with duration of oral estrogen in postmenopausal women.

	Cases N=1675	Controls N=6571	Crude OR*	95%CI	p for trend	Among women who had not had a sigmoidoscopy N=7701	95%CI
Oral estrogen†							
Unexposed	1322	5024	1.00			1.00	
< 3 years	188	755	0.94	0.79-1.12		0.99	0.82-1.19
≥ 3 years	160	729	0.84	0.69-1.01	0.06	0.85	0.70-1.04
Oral estrogen only							
Unexposed	1322	5024	1.00			1.00	
< 3 years	176	712	0.94	0.78-1.12		0.98	0.81-1.18
≥ 3 years	148	663	0.85	0.70-1.03	0.06	0.88	0.72-1.08

† May have used transdermal estrogen.

* Cases and controls matched on age.

§ Sigmoidoscopy 3 to 5 years prior to the index date.

Table 7.4 Odds ratios and 95% confidence intervals for incidence of colorectal cancer and duration of transdermal estrogen use.

	Cases N=1675	Controls N=6571	Crude OR*	95%CI	p for trend	Among women who had not had a sigmoidoscopy N=7701	95%CI
Transdermal estrogen†							
Unexposed	1322	5024	1.00			1.00	
< 3 years	24	126	0.70	0.45-1.10		0.72	0.45-1.15
≥ 3 years	5	46	0.39	0.15-0.99	0.02	0.27	0.08-0.88
Transdermal estrogen only							
Unexposed	1322	5024	1.00			1.00	
< 3 years	4	43	0.35	0.13-0.98		0.28	0.09-0.91
≥ 3 years	1	20	0.18	0.02-1.33	0.03	0.22	0.03-1.67

† May have used oral estrogen. * Cases and controls matched on age. § Sigmoidoscopy 3 to 5 years prior to the index date.

Table 7.5 **Odds ratios and 95% confidence intervals for incidence of colorectal cancer associated with duration of transdermal estrogen among postmenopausal women estrogen users (oral estrogen users are the reference group).**

	Cases N=353	Controls N=1547	Age adjusted OR	95%CI	p for trend	Among women who had not had a sigmoidoscopy N=1740	95%CI
Transdermal estrogen†						1.00	
Oral	324	1375	1.00				
< 3 years	24	126	0.78	0.50-1.24		0.78	0.48-1.26
≥ 3 years	5	46	0.45	0.18-1.13	0.05	0.30	0.09-1.01
Transdermal estrogen only							
Oral	324	1375	1.00			1.00	
< 3 years	4	43	0.38	0.14-1.08		0.30	0.09-0.99
≥ 3 years	1	20	0.20	0.03-1.53	0.04	0.24	0.03-1.80

† May also have used oral estrogen.
§ Sigmoidoscopy 3 to 5 years prior to the index date.

CHAPTER 8. RESULTS

This section is a presentation of the results pertinent to this doctoral research and not already presented in the manuscripts. All of the Phase 2 results, as well as the Phase 1 results for the effect of HRT on the risk of colorectal cancer are presented in this section.

8.1 Phase 1 sample

The drug file with 4,015,796 records and the subject file with 16,554 records were received in March 1999 from Saskatchewan Health. Data on the frequency of physician visits and sigmoidoscopy procedures were sent in May 1999.

8.1.1 Subject file

For each subject in the subject file we received the following information: identification number, identification to indicate the case to which a control was matched, date of birth, the coverage enrollment date (1976, immigration, age at which subject turned 45 years of age), the coverage termination date (death, emigration, or December 31, 1998), date of cancer diagnosis, date of death, primary and secondary causes of death, ICDO-2 code, behavior, and disease staging (Dukes, Astler-Coller, Clark's, Urology).

A total of 16,554 subjects were included in the database phase of the study: 3,338 women with colorectal cancer, accrued between January 1, 1981 and November 1998; 13,025 controls age matched to cases, 191 of whom later developed colorectal cancer. At the time of data extraction a total of 5,429 subjects had died (1,881 cases and 3,648 controls). The mean age of the subjects was 71.8 years, with a range of 45 to 100 years of age.

The mean period of coverage with Saskatchewan Health was 13.9 $\pm$ 5.1 years, with a range from 5 to 22 years.

The method of sampling for controls, incidence density sampling with replacement, allowed controls to be sampled more that once: 646 were selected twice, 36 were selected three times, 1 subject was selected four times.

All cases had primary colon (C19.9, C20.9, C21.8) and rectal cancers (C18.0, C18.2 to C18.9). Behavior and morphology codes were provided for all cases: 3,059 cases had a behavior code of 3 and 279 had behavior codes of 1 (neoplasms of uncertain behavior) or 2 (in situ neoplasms). This latter group and their controls were eliminated from analyses.

Information on tumor staging was not available for all cancer cases. Four percent of cases were Dukes' stage A, 32% were stage B, 23% were stage C and 9% were stage D. Approximately 32% of cases had not been staged.

8.1.2 Prescription drug file

Prescription drug information was provided with the following details for each subject in the study: dispensing date, drug category, dosage form (capsule, vaginal cream, tablet, transdermal etc), strength of prescription ingredients and quantity dispensed.

Twelve different estrogen replacement formulations had been dispensed to women for the treatment of menopausal symptoms between 1976 and 1998 (there were 13 formulations identified from the Saskatchewan Formularies for this time period but no prescriptions for estrone/estrone sulfate were dispensed). Two different types of progesterone had been prescribed to oppose estrogen during menopause. Eleven different oral contraceptive containing estrogen had been prescribed (there were 14 categories but no prescriptions dispensed for three categories). 21 different NSAIDs had been prescribed during the entire period. Dispensing data for other drugs were provided as broad classifications: cardiovascular drugs, central nervous system drugs (less NSAIDs), electrolyte, caloric and water balance drugs, gastrointestinal drugs, other hormones and substitutes and vitamins.

8.2 Imputation

As described in section 3.8.2 we tested two methods of imputation to deal with the missing estrogen dispensing data for the period from July 1,1987 to December 31, 1988. The out-patient prescription-drug dispensing records had not been linked to individual identifiers for this period of time and therefore data is universally absent for all residents

identifiers for this period of time and therefore data is universally absent for everyone who had been receiving benefits. In one method, prescriptions had to have been dispensed within one year, both before and after the period of missing data, for a woman to be classified as exposed during the period in question. Validation of this method indicated that very few women were misclassified. The method was tested by comparing the results for calculated sensitivity and specificity, using four separate years where the data was available from the database as a 'gold standard'. The calculated sensitivity and specificity for each of four years tested was almost 100%. The kappa statistics for agreement between the predicted and actual estrogen exposure during the years 1983, 1984, 1993, and 1994 were 0.93 (95% CI: 0.91 to 0.95), 0.95 (95% CI: 0.93 to 0.97), 0.98 (95% CI: 0.96 to 0.99) and 0.97 (95% CI: 0.95 to 0.99), respectively.

The second less rigorous method of imputation, where the criteria for exposure classification during the gap of missing information was having had a dispensed prescription either the year before or the year after the gap, performed less well with the sensitivity test and kappa statistic. The sensitivity results of this method for the years 1983, 1984, 1993, and 1994 were 71%, 72%, 87% and 73%. Results for specificity were close to 100%. The results for the kappa statistic were 0.58 (95% CI: 0.52 to 0.64), 0.70 (95% CI: 0.63 to 0.76), 0.72 (95% CI: 0.68 to 0.76), and 0.76 (95% CI: 0.71 to 0.80) for the same years respectively.

The first more rigorous method was therefore selected as the method to assign exposure status to women for the 1.5- year period with missing database data.

8.3 Identification of cases and controls for Phase 2 sample

Living colorectal cancer cases and their controls with index dates between 1990 and mid-1998 were classified according to estrogen exposure status in order to select cases and controls by level of exposure, for the Phase 2 sample. The following estrogen exposure categories were established: unexposed, less than three months of estrogen use, use of estrogen for at least three months per year for a duration of 1 to 4 years, use of estrogen for at least three months of the year for a duration of $\geq$5 years of use, and use of vaginal

estrogen cream only. Exposure was defined by the method used to calculate SUM-P, as described in Chapter 3. Section 3.3.2 method.

The exposure status for all living colorectal cases and controls with index dates between 1990 and 1998 are presented in **Table 8.1.** For the colon cancer cases and controls (first period of recruitment) an attempt was made to recruit all unexposed cases, and those exposed to estrogen 1 to 4 and more than 5 years. Because we had a large number of controls, a random sample was selected from the categories unexposed and 1 to 4 years of exposure (numbers selected appear in parentheses). All the controls with exposure for 5 or more years were contacted by mail for recruitment. All rectal cancer cases and all their controls were contacted by mail for recruitment.

TABLE 8.1 Living colon and rectal cancer cases and their controls with index dates from 1990 to 1998 classified according to estrogen exposure status.

EXPOSURE CLASSIFICATION (SUM-P3)	COLON CANCER Case	Controls	Total	RECTAL CANCER Cases	Controls	Total
Exposure categories from which subjects were sampled for phase-two recruitment						
Unexposed	358	2409 (400)	2767	167	400	567
1-4 years use	68	487 (203)	571	29	164	193
≥ 5 year use	32	197 (197)	229	15	92	107
Total	458	3093 (800)	3567	211	656	867
Exposure categories from which subjects were not sampled for phase-two recruitment						
Exposure only during 2 yrs Prior to index date	16	72	88	9	39	48
< 1 year	8	90	98	2	40	42
Cream use only	83	462	545	39	155	194
All subjects	549	3645	4210	261	890	1151

In parentheses the number of controls randomly selected for mailing contact list; all cases were selected for recruitment.

8.4 Response rates of cases and controls sampled for Phase 2

Subjects for the phase 2 sample were enrolled during two periods of recruitment: July to November of 1999 and March to August 2000. During the first period, colon cancer cases and their controls were recruited and during the second period rectal cancer cases and their controls were recruited.

Some subjects sampled for Phase 2 recruitment had died during the interval between the time the data were complied and recruitment began. Also during that time some controls had been diagnosed with cancer (necessitating the SCA to contact physicians first), and some cards were returned by physicians indicating that the beneficiary had left the province. These changes are summarized in **Table 8.2.**

TABLE 8.2 Number of subjects identified for phase-two and contacted by mail during the first and second recruitment periods.

Recruitment period	**July 1999**			**March 2000**		
Initial diseases status assignment	**Cases**	**Controls**	**Total**	**Cases**	**Controls**	**Total**
	458	**800**	**1,258**	**211**	**656**	**867**
Died, moved	-19	-28	-47	-29	-58	-87
First	**439**	**772**	**1,211**	**182**	**598**	**780**
subtotal						
Controls with Ca (including one subject serving as both case and control) to SCA	+24*	-24*		30	-30	
	463	**748**	**1,211**	**212**	**568**	**780**
Subtotal						
Duplicate (case also serving as control) or returned to SH	-1			-30	+30	
	462	**748**	**1,210**	**180**	**600**	**780**
Total						

*These individual were controls in our study but they were diagmosed with cancer after the index date. They were therefore contacted by the Saskatchewan Cancer Agency.

The total number of physicians contacted by the SCA was less than the number of cases because many physicians had more than one case as a patient. 88 and 25 colon and rectal cancer cases could not be contacted for recruitment because their physicians advised

against it for the following reasons: death, too ill, dementia, had problems with memory, hearing or had difficulty with language.

TABLE 8.3 Response results provided by physicians and colon and rectal cancer cases contacted by the Saskatchewan Cancer Agency (SCA)

Consent	July 1999	March 2000	Total
Physician refusal	88	25	113
Patient refusal	235	70	305
Total refusal	323	95	418
Consent	139	50	189
Nonresponder	0	32	32
TOTAL	462	177	639

Of the cases whose physicians agreed to have SCA contact them, 189 consented to be interviewed, while 305 subjects refused to participate **Table 8.3**.

Table 8.4 outlines the participation rates for the study with a break down for response rate by first, and second recruitment periods, and exposure and disease status. These numbers do not reflect the changes in the disease status at the time of recruitment (24 controls developed cancer and were contacted by SCA; 1 control also served as a case) but rather the status that they had within the study. Of the controls contacted directly by mail requesting them to participate in Phase 2, 250 gave their consent. Of the controls who refused or did not respond, approximately 20% gave such reasons as illness, dementia, death and difficulty with hearing or language. The remaining subjects did not provide a reason for non-participation or expressed disinterest.

A total of 439 subjects were interviewed for the study. The overall participation rate was 30% for cases and 22% for controls. During the first recruitment period there was a variation in response by exposure and disease status, with the response rate being highest amongst the exposed cases (60.0%) and lowest amongst the unexposed controls (10.2%). During the first recruitment we had designed a pamphlet describing the study entitled, *Hormone Replacement Therapy and Colon Cancer Study*. We became concerned that subjects who had not used HRT or had not been diagnosed with colon cancer were making a decision not to participate in the study before reading the pamphlet. For the

second recruitment we decided to change the title of the pamphlet to *Lifestyle and Risk of Colon and Rectal Cancer in Women*. Although we were unsuccessful in increasing the overall response rate during this period, exposure and disease status appeared to be less influential in the decision making of subject's with regard to participation than during the previous period.

Table 8.4 Response rate from both first and second recruitment periods.

Both recruitments combined

Consent			CASES		CONTROLS		TOTAL	
Yes	***Exposure***	***No***	129	27%	87	12%	215	
		Low	25	31%	78	22%	103	
		High	35	61%	85	30%	120	
		Subtotal	**189**	**30%**	**250**	**18%**	**438**	**22%**
No	***Exposure***	***No***	314		564		878	
		Low	53		234		287	
		High	18		175		193	
		Subtotal	385	62%	973	71%	1,358	68%
No response	***Exposure***	***No***	35		77		112	
		Low	11		43		54	
		High	4		23		27	
		Subtotal	50	8%	143	10%	193	10%
Total			624	100%	1,366	100%	1,989	100%

PHASE 2 SAMPLE: SUBJECTS WITH INDEX DATES FROM 1990 to 1998

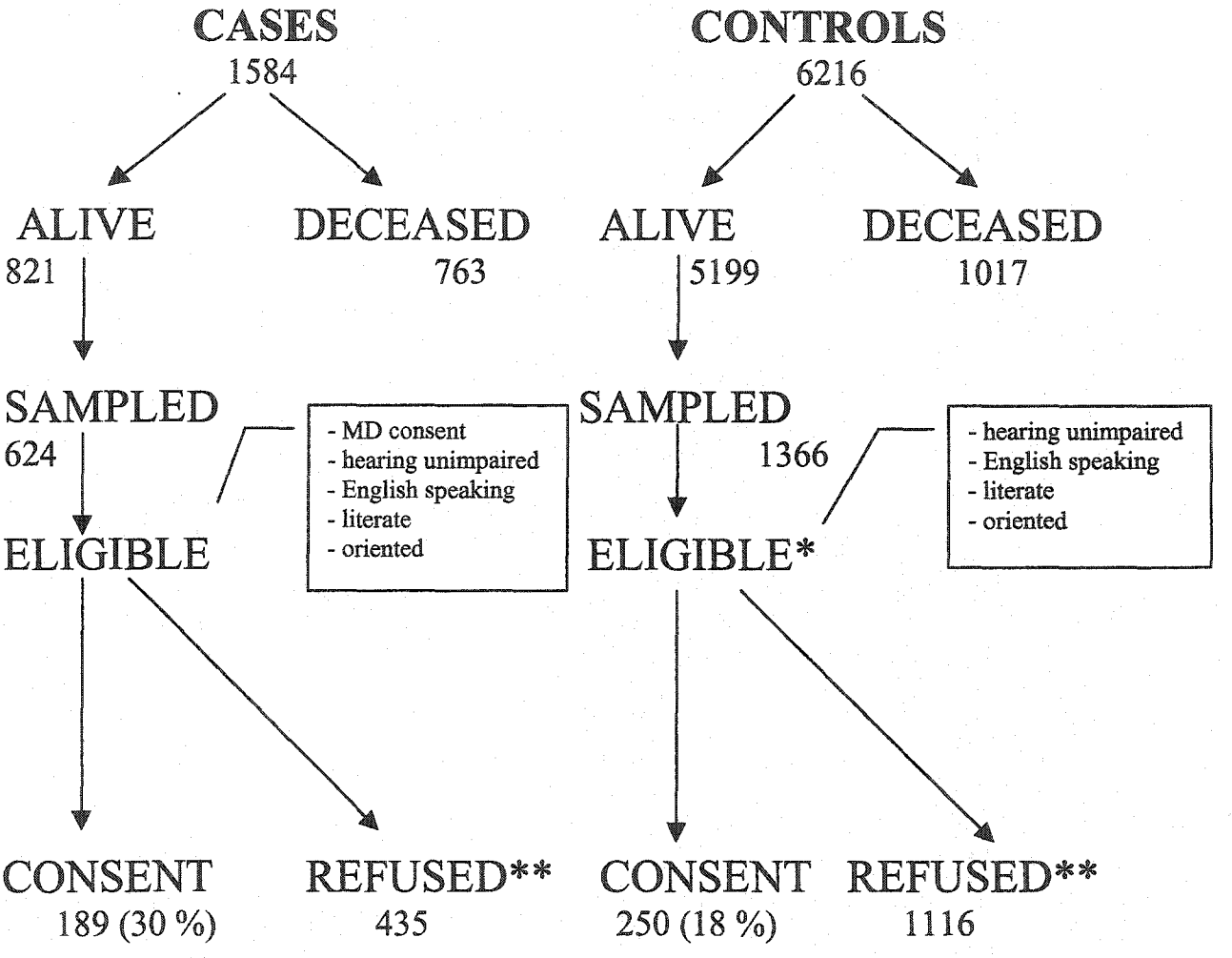


Figure 8.1 Diagram showing sampling and participation rates for Phase 2 subjects.

* Approximately 20% of subjects who refused to participate gave illness, dementia, death and difficulty with hearing or language as reasons for refusal. The remaining subjects did not provide a reason for non-participation or expressed disinterest.
** Refused or did not respond.

8.5 Characteristics of Phase 1 and Phase 2 subjects

The characteristics of the Phase 1 and Phase 2 subjects are outlined in Table 8.5 and Table 8.6. Using data on covariates that were provided for all subjects in the database (prescription drugs, use of sigmoidoscopies and physician visits) the characteristics of subjects who consented to participate in Phase 2 of the study were compared with the characteristics of the entire study population. In addition, comparisons were made between living and deceased subjects with index dates in 1990 and later. Whether a subject was living or dceased refers to their status in 1999 at the time of recruitment for Phase 2. We did not interview proxy respondents for people who had died and therefore whether or not differences between these groups existed was of interest to us.

8.5.1 Controls

Table 8.5 outlines the prevalence of prescription drug use (HRT, OCs, cardiovascular drugs, central nervous system drugs, other hormones, prescription vitamins and NSAIDs), use of sigmoidoscopies and frequency of physician visits two to five years prior to the index date among control subjects. Results are provided for all control subjects as a group, and separately for the following subgroups: subjects with index dates before and after 1990; living and dead subjects with index dates after 1990; living subjects who were requested by mail to participate in Phase 2 of the study; subjects who consented to participate (actual Phase 2 sample) and those who had refused.

Age-adjusted prevalences are provided for the sub-groups with index dates in 1990 or later, those with index dates after 1990 and had died by 1999 and those still living in 1999. For standardization the age-distribution for the entire study population and rates from the sub-populations were used.

The mean age of the entire group of control subjects was 73 years. The prevalence of HRT use increased from 15% in the women with index dates before 1990 to 25% (age-adjusted 26%) in the women with index dates after 1990. Women with index dates after 1990 also took more drugs for the cardiovascular system (age-adjusted, 64% vs. 59%)

Table 8.5 Use of prescription drugs and health care services by various subgroups of controls.

	All controls		ID ≥1990 (age-adj)			ID <1990		ID ≥1990; Alive (age-adj)			ID ≥1990; deceased (age-adj)			Requested to participate		Consent provided		Refused	
Variable	N	%	N	%		N	%	N	%		N		%	N	%	N	%	N	%
Mean Age	73		74			72		72			82			70		65		71	
HRT																			
Never	9662	80	4658	75		5004	85	3767	72		891		88	742	51	87	35	655	54
Ever	2454	20	1558	25	(26)	896	15	1432	28	27	126	12	(20)	714	49	163	65	551	46
Oral Contraceptives																			
Never	11924	98	6110	98		5814	99	5096	98		1014		99	1420	98	239	96	1181	98
Ever	192	2.0	106	2	(2)	86	1	103	2	2	3	<1	(1)	36	2	11	4	25	2
Cardiovascular Drugs																			
Never	4580	38	2151	35		2429	41	1939	37		212		21	551	38	105	42	446	37
Ever	7536	62	4065	65	(64)	3471	59	3260	63	63	805	79	(69)	905	62	145	58	760	63
Central Nervous System Drugs																			
Never	3336	28	1638	26		1698	29	1469	28		169		17	399	27	74	30	325	27
Ever	8780	72	4578	74	(73)	4202	71	3730	72	72	848	83	(81)	1057	73	176	70	881	73
Other hormones																			
Never	8046	66	3821	62		4225	72	3247	63		574		56	904	62	153	61	751	62
Ever	4070	34	2395	39	(38)	1675	28	1952	37	38	443	44	(40)	552	38	97	39	455	38
Vitamins																			
Never	9968	82	5066	82		4902	83	4326	83		740		73	1216	84	213	85	1003	83
Ever	2148	18	1150	18	(18)	998	17	873	19	17	277	27	(25)	240	16	37	15	203	17
NSAIDs use in past																			
Never																			
1 to 5 yrs.	4471	37	1837	30	(30)	2634	45	1668	32	32	169	17	(13)	462	32	97	39	365	30
6 to 10 yrs.	2823	23	1128	18	(18)	1695	29	786	15	15	342	34	(33)	230	16	32	13	198	16
11 to 15 yrs	2657	22	2657	43	(43)			2188	42	42	469	46	(42)	600	41	98	40	502	42
Sigmoidoscopy in past 2 to 5 yrs.																			
Never	11160	92	5695	92		5465	93	4760	92		935		92	1330	91	222	89	1108	92
Ever	956	8	521	8	(8)	435	7	439	8	8	82	8	(8)	126	9	28	11	98	8
Number of physician visits																			
2 or less	648	5	310	5	(5)	338	6	275	5	5	35	3	(6)	73	5	4	2	69	6
3 to 7	810	7	344	6	(6)	466	8	311	6	6	33	3	(4)	71	5	9	4	62	5
8 to 14	1228	10	583	9	(10)	645	11	516	10	10	67	7	(8)	134	9	27	10	107	9
15 or more	9430	78	4979	80	(80)	4451	75	4097	79	79	882	87	(82)	1178	81	210	84	968	80

Note: To calculate the age-adjusted percent the rates from sub-populations and the age-distribution of the full population is used.

Table 8.6 Use of prescription drugs and health care services by various subgroups of cases.

	All cases		ID ≥ 1990 (age-adj)			ID <990		ID ≥1990; alive (age-adj)			ID ≥1990; deceased (age-adj)			Requested to participate		Consent provided		Refused	
Variable	N	%	N	%		N	%	N	%		N	%	%	N	%	N	%	N	%
Mean Age	73		74			72		71			76			71		67		73.	
Stage (HRT no use)																			
A	213	8.4	141	11		72	6	114	19		27	4		84	17	26	21	58	16
B	675	27	358	28		317	25	252	41		106	16		209	42	61	49	148	40
C	568	22	325	26		243	19	148	24		177	27		116	24	25	20	91	25
D	227	9	125	10		102	8	13	2		112	17		13	3	0	0	13	4
?	863	34	311	25		552	43	88	14		223	35		70	14	12	10	58	16
Stage (HRT use)																			
A	51	10	37	11		14	8	32	16		5	4		27	15	8	12	19	17
B	148	29	108	33		40	21	94	46		14	12		83	47	37	57	46	41
C	135	26	77	24		58	31	44	21		33	28		35	20	14	22	21	19
D	48	9	39	12		9	5	2	1		37	31		2	1	0	0.0	2	2
?	131	26	63	19.		68	36	34	17		29	25		30	17	6	9	24	21
HRT																			
Never	2506	82	1227	78		1279	87	592	72		635	83		487	73	124	66	363	77
Ever	553	18	357	23	(24)	196	13	229	28	26	128	17	(20)	176	27	65	34	111	23
Oral Contraceptives																			
Never	3004	98	1553	98		1451	98	798	97		755	99		644	97	184	97	440	97
Ever	55	2	31	2	(2)	24	2	23	3	3	8	1	(2)	19	3	5	3	14	3
Cardiovascular Drugs																			
Never	1116	37	502	32		614	42	288	35		214	28		239	36	75	40	164	35
Ever	1943	64	1082	68	(67)	861	58	533	65	66	549	72	(69)	424	64	114	60	310	65
Central Nervous System Drugs																			
Never	861	28	436	28		425	29	248	30		188	25		211	32	65	34	146	31
Ever	2198	72	1148	73	(72)	1050	71	573	70	69	575	75	(74)	452	68	124	66	328	69
Other hormones																			
Never	2060	67	985	62		1075	73	528	64		457	60		428	65	133	70	295	62
Ever	999	33	599	38	(37)	400	27	293	36	36	306	40	(38)	236	35	56	30	179	38
Vitamins																			
Never	2528	83	1298	82		1230	83	693	84		605	79		566	85	169	89	397	84
Ever	531	17	286	18	(18)	245	17	128	16	16	158	21	(18)	97	15	20	11	77	16
NSAIDs use in past																			
Never																			
1 to 5 yrs.	1025	34	377	24	(24)	648	44	224	27	28	153	20	(20)	183	28	48	25	135	28
6 to 10 yrs.	701	23	302	19	(19)	399	27	125	15	15	177	23	(23)	100	15	29	15	71	15
11 to 15 yrs	651	21	651	41	(41)			321	39	39	330	43	(42)	257	39	63	33	194	41
Sigmoidoscopy in past.																			
2 to 5 yrs Never	2764	90	1429	90		1335	91	744	91		685	90		602	91	175	93	427	90
Ever	295	10	155	10	(10)	140	9	77	9	9	78	10	(11)	61	9	14	7	47	10
Number of physician																			

Visits	2 or less	157	5	74	5	(5)	83	6	34	4	4	40	5	(6)	33	5	11	6	22	5
	3 to 7	210	7	87	6	(6)	123	8	50	6	5	37	5	(5)	41	6	10	5	31	6
	8 to 14	313	10	136	9	(9)	177	12	77	9	9	59	8	(9)	58	9	17	9	41	9
	15 or more	2379	78	1287	81	(81)	1092	74	660	80	80	627	82	(80)	531	81	151	80	380	80

Note: To calculate the age-adjusted percent the rates from sub-populations and the age-distribution of the full population is used.

and other hormones (age-adjusted, 38% vs. 28%) compared with women with index dates prior to 1990. Other differences were not observed between these two groups.

Subjects who had died after 1990 were notably the oldest of the sub-groups with a mean age of 82 years. The age-adjusted prevalence of ever use of HRT among the deceased controls was 20% compared with 27 % for those who were alive. Those who had died had used more cardiovascular system (age-adjusted, 69% vs. 63%) and more central nervous system drugs (age-adjusted, 81% vs. 72%), as well as more vitamins (25% vs. 17%). Other differences between these two control groups were not observed.

Controls requested to participate were fairly equally divided between 'ever' HRT users and 'never' users as a result of the sampling that was conditional on exposure and that had as an objective a 'balanced design'. Otherwise, women who were requested to participate were similar in characteristics as a group to the women who had index dates after 1990.

Of subjects who consented to participate in Phase 2 an even higher proportion in this group were HRT users than in the subgroup originally requested to participate, and much higher than in the group who refused to participate in Phase 2 (65% vs 46%). Women consenting to participate were the youngest of the sub-groups (mean age of 65 years). Women who consented used slightly less cardiovascular and central nervous system medication than women who refused but other differences between those who consented and those who refused were minimal.

8.5.2 Cases

Characteristics of cases using the same sub-group classifications were also determined **(Table 8.6)**. In addition, the tumor stage (Dukes' classification) at which colorectal cancer was diagnosed was determined within each group. The mean age of the cases was 73 years, the same as that of the controls, as would be expected since controls were age-matched to cases.

In all subjects the prevalence of pathologic staging was similar between HRT users and nonusers, however, nonusers had a higher prevalence of unstaged cancers compared with HRT users. After 1990 a lower proportion of cancers were unstaged in both HRT users and nonusers but a higher proportion remained unstaged among HRT never users. More of the women still living in 1999 and more of the cases who had consented to participate had been diagnosed with colorectal cancer at stages A and B compared with all subjects, those who had died and those with index dates before 1990. There were negligible differences between HRT users and nonusers with regard to staging at diagnosis.

As observed among the controls, cases with index dates in 1990 or later tended to use more cardiovascular drugs (age-adjusted, 67%) than did cases with index dates before 1990 (58%), and more 'other hormones' (age-adjusted, 37% vs 27%). Other differences were not observed between these two groups.

Women who had died were the oldest group of cases (76 years of age), but they were not as old as the controls who had died. As observed among controls, deceased cases with index dates in 1990 or later, were less likely to have taken HRT than those still alive (age-adjusted, 20% vs.26%). Unlike the controls there were only slight differences between those alive and deceased with regard to use of cardiovascular drugs, other hormones and prescribed vitamins. Those who had died appeared to have used more medications for the central nervous system than those alive (age-adjusted, 74% vs. 69%).

Due to the smaller number of cases exposed to HRT, we could not achieve a 'balanced design' and thus the proportions of HRT users and nonusers among the cases requested to participate are not equal as had occurred with the controls (27% HRT users). Proportionally more exposed cases than unexposed cases however consented to participate (34%) in Phase 2.

The group consenting to participate was the youngest of the case groups (mean age of 67 years), and slightly older than the controls who had consented. Those who had refused to participate tended to use more prescribed medications including other hormones (38%

vs.30%), more vitamins (16% vs. 11%) and more NSAIDs in the distant past (41% vs. 33%), compared with those who had consented.

In summary there are differences between women with index dates before 1990 and those after 1990 in terms of prescription drug use. These differences are present among cases and controls. There were also differences in prescription drug use between subjects who had died by 1999 and those still living among both cases and controls, but the differences were less in the former. Cases and controls who provided consent to participate in Phase 2 were the youngest of the sub-groups. Consenting controls had a similar drug use profile to the entire group of controls, whereas consenting cases tended to use slightly less prescribed drugs. Consenting cases also had a higher prevalence of stage A and B cancers, and no one in this group had been diagnosed with cancer at stage D.

8.6 Phase 2 subjects: Interview results

189 cases and 250 controls completed the main questionnaire. 23 controls either became cases or were controls more than once.

Table 8.7 Number of subjects who completed the general, physical activity and Block Food Frequency Questionnaires

Questionnaire	Total N	Cases N	Controls N
General Questionnaire	438	188	250
Physical Activity Questionnaire	366	154	212
Block Nutrition Questionnaire	364	153	211

A copy of the telephone questionnaire that was used to collect data from the Phase 2 subjects pertaining to medical, reproductive, and family history can be found in Appendix 1. **Table 8.8** outlines the health, lifestyle and sociodemographic characteristics of cases and controls that were interviewed during Phase 2 of the study.

8.6.1 Characteristics of cases and controls in Phase 2

Medical, reproductive and family history

Of the cases who responded to the question with regard to a diagnosis of cancer prior to the index date just under 10% of cases responded affirmatively (n=17). Six of these cancers were reported to be nonmelanoma skin cancer, 7 were reported as 'other', and 4 women did not specify a category. Five of seven women reporting having received a diagnosis of cancer classified as 'other' prior to the index date, reported having this diagnosis within one year of the index date. Of the remaining two women, one reported being diagnosed with breast cancer in 1951 and the other reported being diagnosed with bowel cancer in 1997. It was decided not to remove these subjects from the study because the accuracy of the self-reporting was not known and we felt that treating the Phase 2 subjects differently from Phase 1 with regard to verifying disease status might invalidate the study.

None of the controls reported having received cancer diagnoses prior to the index dates.

19 and 21% of the cases and controls reported having had a colonoscopy or sigmoidoscopy prior to the index date. 26 and 12% of these women reported to have had polyps removed.

The reported mean age at first menstrual period was 13 years of age, for both cases and controls. 98% of cases and almost 100% (99.6%) of controls reported to be menopausal at the time of the interview. The age at menopause was reported to be 48 and 47 years of age, for cases and controls, respectively. 92 and 93% of cases and controls reported having had at least one pregnancy. The mean number of pregnancies was 4 for both cases and controls. 41 % of cases reported having had a hysterectomy at a mean age of 50 years and 44% of controls reported having had a hysterectomy at a mean age of 45. 26 and 30% of cases and controls reported having had oopherectomies at mean ages of 46 and 45 years of age.

21 and 17% of cases and controls had at least one first degree relative who had been diagnosed with colorectal cancer.

Anthropometric data

Maximum and minimum mean body weights since the age of 25 were 75kg and 55kg for both cases and controls, however, more cases (75%) than controls (67%) reported having had a stable weight for most of the time since age 25. Mean body mass index (BMI) was 25 and 26 kg/m^2 for cases and controls

Tobacco and alcohol use

54% and 53% of cases and controls reported having smoked in the past. 86% and 84% of these cases and controls reported having smoked for longer than a year.

On average, cases and controls reported drinking less than 2 drinks per week throughout the four five-year periods. When only subjects who reported drinking alcohol were counted in the denominator the average drink per person was generally just over two drinks per week.

Use of hormone replacement therapy and oral contraceptives (OCs)

25% and 56% of cases and controls had used HRT for at least 3 months. The mean duration of use was 98 months (8.2 years) for cases and 120 months (10 years) for controls. The majority of women reported having received a prescription for HRT for the treatment of menopausal symptoms, 87% and 94%, for cases and controls, respectively. In addition, many reported prevention of osteoporosis as being a factor for beginning HRT (20% of cases and 30% of controls). 10% and 11% of cases and controls reported the prevention of cardiovascular disease also being a reason for taking HRT.

Of women who reported taking HRT, 100 of cases reported to have received prescriptions for estrogen and 41% received prescriptions for progesterone. 99% of controls reported to have received estrogen and 44% reported to have received progesterone.

Of women who had not been prescribed HRT 12% of cases and 22% of controls had considered taking HRT and of these 68% of cases and 72% of controls reported that they had decided not to take HRT because of health concerns.

Of women who took HRT 100% of the cases and 97% of controls stated that they had taken HRT as prescribed.

36% of cases and 31% of controls reported having used oral contraceptives in the past.

Use of NSAIDs

The mean number of total NSAIDs tablets taken by controls was slightly more than the number used by cases during the four 5-yr periods prior to the index date.

Sociodemographic data

Important differences were not noted between cases and controls with regard to marital status, education and other sociodemographic factors.

Physical activity

The mean MET-hours/week per year of occupational activity reported by cases and controls, respectively, was 52 to 65 MET-hours during the five-year period 5 to 10 years prior to their index dates. 18 and 15 MET-hours/week per year was reported for exercise and 66 and 48 MET-hours/week per year was reported for household activity by cases and controls respectively.

Cases reported engaging in 24, 5, and 1 hours per week of light, moderate, and heavy activity. Controls reported engaging in 21, 6 and <1 hours of light, moderate, and heavy activity. Most people rated themselves as 'somewhat more active' (31% of cases and 31% of controls) or 'about the same' (32% of cases and 29% of controls) with regard to level of physical activity at work, compared to others of the same sex and age. The pattern of

self-rating was similar for physical activity outside of work. 24% of cases and 34% of controls reported to engage regularly in stenuous activity or hard physical labour. 23% of cases and 33% of controls engaged in exercise or labour at least three times a week.

Dietary intake

153 cases and 211 controls completed the Block Food Frequency Questionnaire reporting on their intake for the five-year period 5 to 10 years prior to the index date. Calcium (mg), folate (μg), vitamin D (IU), protein (mg), fibre (g), fat (g), and frequency of the number of servings of meat, fruit, fat, grains and vegetables consumed were divided into quartiles. The percent of calories derived from alcohol was divided into tertiles.

The intake of cases and controls were quite similar, although some minor differences were observed. More cases than controls were in the upper two quartiles of nutrient intake for calcium, folate and vitamin D. More cases than controls were in the highest quartile for number of daily servings of meat, fat, grains and vegetables and consequently in the upper quartile for intake of grams of fat and fibre. More controls than cases were in the highest quartile for the number of daily servings of fruit intake and the upper tertile for percent of calories derived from alcohol.

Table 8.8 Health, lifestyle and sociodemographic characteristics of cases and controls

Characteristic	Cases n	Cases %	Cases N=189 missing	Controls n	Controls %	Controls N=275 missing
Medical History						
Cancer before ID (%)	17	9	12	0	0	10
Type of cancer: (denominator=subjects with reported cancer before ID)						
Cancer of cervix-in –situ (%)	0	0	1	0	0	0
Non-melanoma skin cancer (%)	6	46	4	0	0	0
Other (%)	7	54	4	0	0	0
Colonoscopy or sigmoidoscopy prior to ID (%)	34	19	12	51	21	12
Polyps removed (denom=women reporting colonoscopy pre-ID) (%)	8	26	3	6	12	2
Reproductive history						
Age at first menstrual period (Mean (SD))	170	13(2)	19	236	13(2)	16
Menopausal at the time of interview (%)	172	98	14	241	100	10
Age at menopause (Mean (SD))	150	48(6)	22	223	47(7)	18
Ever pregnant (%)	162	92	12	224	93	10
Number of pregnancies (among those with at least 1 pregnancy) (Mean)	162	4(2)	0	224	4(2)	0
Hysterectomy (%)	72	41	12	106	44	10
Age at hysterectomy (Mean (SD))	68	50(12	4	103	45(9)	3
Prior to index date?						
Hysterectomy due to cancer (%)	4	6	6	0	0	7
Other medical reasons for hysterectomy (%)	62	94	6	99	100.0	7
Oopherectomy (%)	44	26	19	70	30	16
Bilateral (%)	14	33	2	17	25	2
Age at surgery (Mean (SD))	42	46(12	2	68	45(9)	2
Family History						
At least one first degree relative with colorectal cancer (%)	37	21	13	41	17	13

Characteristic	n	Cases %	N=189 missing	n	Controls %	N=275 missing
Anthropometric data						
Maximum weight (kg) (Mean (SD))	176	75(14	13	241	75(14)	9
Minimum weight (kg) (Mean)	175	55	14	242	55	10
Stable weight (%)	133	75	12	161	67	11
BMI (mean) (Usual weight/Height^2)	174	25	15	241	26	11
[0-20[	14	8		15	6	
[20-25[	89	51		111	46	
[25-27]	29	17		49	20	
]27-++	42	24		66	27	
Tobacco use						
Ever smoked (%)	95	54	12	128	53	10
Ever smoked for a period longer than one year (among ever-smokers) (%)	82	86	0	108	84	0
Alcohol use						
Average number of drinks per week among all subjects						
5-year period immediately preceding ID	172	1.7	17	230	1.7	22
6 to 10 years prior to the ID	172	1.7	17	231	1.6	21
11 to 15 years prior to ID	168	1.5	21	234	1.6	18
16 to 20 years prior to ID	171	1.3	18	234	1.6	18
Average number of drinks per week among drinkers						
5-year period immediately preceding ID	126	2.3	17	178	2.2	22
6 to 10 years prior to the ID	129	2.2	17	181	2.1	21
11 to 15 years prior to ID	123	2.0	21	183	2.1	18
16 to 20 years prior to ID	125	1.8	18	183	2.0	18
Postmenopausal hormones						
Ever use of hormones for period of three months (%)	45	25	12	135	56	10

Characteristic	n	Cases %	N=189 missing	n	Controls %	N=275 missing
Duration of use among users only (months)						
Mean	44	98	0	130	120	0
Median	44	71	0	130	88	0
Mean start year	44	1978	0	127	1979	3
Reason for prescribing (Among women who reported taking HRT)						
Symptoms of menopause (%)	39	87	0	121	94	6
Prevention or treatment of osteoporosis (%)	9	20	0	38	30	7
Prevention of cardiovascular disease (%)	4	10	3	14	11	11
Prescription included estrogen (Among women who reported taking HRT) (%)	41	100	4	121	99	13
Prescription included progesterone (Among women who reported taking HRT) (%)	12	41	16	42	44	40
Considered taking hormones (denom=women who did not take HRT) (%)	15	12	5	21	22	11
Decided to not take hormones based on a health concerns (denom=women who did not take HRT but considered taking HRT)	7	58	3	13	72	3
Took HRT as prescribed	42	100	2	124	97	2
Did not take hormones as prescribed	0	0	2	4	3	2
Reasons for not taking hormones as prescribed (among subjects reporting non-compliance)						
Difficulty remembering to take HRT	0	0	0	1	25	0
Did not tolerate HRT	0	0	0	2	50	0
Use of oral contraceptives						
Ever prescribed oral contraceptives	63	36	12	81	31	15
Duration of use (months)						
Mean	60	50	129	76	65	176
Median	60	24	129	78	48	176
Starting year	60	1965	129	79	1966	174
History of NSAIDs exposure						
NSAIDs -5-yr period prior to ID (Mean total pills)	177	502	12	241	662	11
NSAIDs -6 to 10 years immediately before ID (Mean total pills)	177	485	12	241	536	11
NSAIDs -11 to 15 years before ID (Mean total pills)	177	343	12	241	358	11
NSAIDs -16 to 20 years before ID (Mean total pills)	177	298	12	241	402	11

Characteristic	n	Cases %	N=189 missing	n	Controls %	N=275 missing
Sociodemographic Data						
Marital status:						
Single	4	2		7	3	
Married	124	70		164	69	
Common law	0	0		2	<1	
Widowed	46	26		56	24	
Separated or divorced	3	2		9	4	
Unknown			12			14
Highest level of education prior to index date						
None	3	2		2	<1	
Elementary School	70	40		86	36	
High School	42	24		47	20	
Trade/Technical School/College	45	25		68	29	
University attended: not completed	9	5		18	8	
University: degree obtained	8	5		18	8	
Unknown			12			12
Size of community lived in:						
Rural	86	49		124	52	
In a small city	28	16		31	13	
In a large city	63	36		85	35	
Unknown			11			12
Prior to index date type of living arrangement						
Own	153	86		204	85	
Rent	24	14		35	15	
Board	0	0		0	0	
Unknown			11			13
Family income			20			26
<$20,000/year	46	27		52	23	
$20,000-$35,000	57	34		74	33	
$35,000-$50,000	40	24		59	26	
$50,000-$75,000	19	11		22	10	
>$75,000	5	3		14	6	
Refuses to respond	2	1		5	2	
Physical activity						
MET –hours/week per year -occupational	154	52	35	212	65	40
MET –hours/week per year - exercise	154	18	35	212	15	40
MET –hours/week per year household	154	66	35	212	48	40
MET –hours/week per year (Mean)	154	135	35	212	128	40
	154	25	35	212	21	40

Characteristic	n	Cases %	N=189 missing	n	Controls %	N=275 missing
Avg hrs/wk of any LIGHT activity						
Avg hrs/wk of any MODERATE activity	154	5	35	212	6	40
Avg hrs/wk of any HEAVY activity	154	1	35	212	<1	40
In general at work, how would you rate yourself as to the amount of physical activity you had participated in compared with others of your age and sex?			36			41
Much more active	15	10		39	19	
Somewhat more active	47	31		65	31	
About the same	49	32		61	29	
Somewhat less active	9	6		9	4	
Much less active	3	2		6	3	
Not applicable	30	20		31	15	
Outside of work, how would you rate yourself as to the amount of physical activity you had participated in compared with others of your age and sex?			35			41
Much more active	21	14		38	18	
Somewhat more active	49	32		76	36	
About the same	59	38		60	28	
Somewhat less active	21	14		31	15	
Much less active	4	3		6	3	
Did you regularly engage in strenuous activity or hard physical labour?	36	24	36	72	34	42
Did you exercise or labour at least three times a week?	35	23	36	71	34	42
Dietary intake						
Mean energy intake kcal/d		1675			1648	
Mean calcium intake (mg)/d		743			728	
Calcium <= 480	41	26.8	36	51	24.2	41
480 < Calcium <= 680	33	21.6	36	57	27.0	41
680 < Calcium <= 937	40	26.1	36	52	24.6	41
937 > Calcium	39	25.5	36	51	24.2	41
Mean folate intake (μg)/d		198			204	
Folate <= 154	41	26.8	36	50	23.7	41
154 < Folate <= 195	32	20.9	36	59	28.0	41
195 < Folate <= 239	42	27.5	36	48	22.8	41
239 > Folate	38	24.8	36	54	25.6	41

Characteristic	n	Cases %	N=189 missing	n	Controls %	N=275 missing
Mean vitamin D intake (IU)/d		221			211	
Vitamin D <= 134	37	24.2	36	54	25.6	41
134 < Vitamin D <= 192	34	22.2	36	56	26.5	41
192 < Vitamin D <= 272	41	26.8	36	52	24.6	41
272 > Vitamin D	41	26.8	36	49	23.2	41
Mean protein intake (g)/d		71			70	
Protein (g) <= 52	41	26.8	36	49	23.2	41
52 < Protein <= 66	38	24.8	36	54	25.6	41
66 < Protein <= 86.	30	19.6	36	62	29.4	41
86 > Protein	44	28.8	36	46	21.8	41
Mean fiber intake (g)/d		15			15	
Fiber <= 11.8	43	28.1	36	48	22.8	41
11.8 < Fiber <= 14.9	34	22.2	36	59	28.0	41
14.9 < Fiber <= 18.3	35	22.9	36	55	26.1	41
18.3 < Fiber	41	26.8	36	49	23.2	41
Mean fat intake g/d		76			73	
Total Fat <= 52.8	38	24.8	36	51	24.2	41
52.8 < Total Fat <= 69.1	37	24.2	36	56	26.5	41
69.1 < Total Fat <= 89.3	38	24.8	36	54	25.6	41
89.3 < Total Fat	40	26.1	36	50	23.7	41
Mean number of servings/d		1.9			1.9	
Meat Servings <= 1.3	47	30.7	36	54	25.6	41
1.3 < Meat Servings <= 1.7	40	26.1	36	51	24.2	41
1.7 < Meat Servings <= 2.4	29	19.0	36	61	28.9	41
2.4 < Meat Servings	37	24.2	36	45	21.3	41
Mean number of servings/d		1.6			1.7	
Fruit Servings <= 1	56	36.6	36	60	28.4	41
1 < Fruit Servings <= 1.5	32	20.9	36	50	23.7	41
1.5 < Fruit Servings <= 2	31	20.3	36	38	18.0	41
2.3 < Fruit servings	34	22.2	36	63	29.9	41
Mean number of servings/d		4.0			4.0	
Fat Servings <= 2.7	39	25.5	36	54	25.6	41
2.7 < Fat Servings <= 3.8	30	19.6	36	53	25.1	41
3.8 < Fat Servings <= 4.8	43	28.1	36	58	27.5	41
4.8 < Fat Servings	41	26.8	36	46	21.8	41
Mean number of servings/d		4.8			4.6	
Grain Servings <= 3.3	34	22.2	36	54	25.6	41
3.3 < Grain Servings <= 4.4	36	23.5	36	62	29.4	41
4.4 < Grain Servings <= 5.7	45	29.4	36	47	22.3	41
5.7 < Grain Servings	38	24.8	36	48	22.8	41
Mean number of servings/d		3.2			3.2	
Vegetable Servings <= 2.3	34	22.2	36	43	20.4	41
2.3 < Vegetable Servings <= 3.1	45	29.4	36	67	31.8	41
3.1 < Vegetable Servings <= 3.8	28	18.3	36	45	21.3	41

Characteristic	n	Cases %	N=189 missing	n	Controls %	N=275 missing
3.8 < Vegetable Servings	46	30.1	36	56	26.5	41
Mean fat intake g/d		76			73	
Total Fat <= 52.8	38	24.8	36	51	24.2	41
52.8 < Total Fat <= 69.1	37	24.2	36	56	26.5	41
69.1 < Total Fat <= 89.3	38	24.8	36	54	25.6	41
89.3 < Total Fat	40	26.1	36	50	23.7	41
Percent Of Calories From Alcohol <= 0	86	56.2	36	105	49.8	41
0 < Percent Of Calories From Alcohol <= 1.2	34	22.2	36	52	24.6	41
1.2 < Percent Of Calories From Alcohol	33	21.6	36	54	25.6	41

8.7 Reliability studies

8.7.1 Reliability of main questionnaire

The kappa statistic was used to determine the reliability of reporting of characteristics measured in a dichotomous variable. The reporting of menopausal status was 0.80 (lower 95% confidence limit (CL): 0.41). The reliability of reporting for relatives with cancer, hysterectomy status, oopherectomy and ever having smoked were all above 0.9 with only minor differences between cases and controls.

The reliability of reporting 'ever' having used OCs and HRT were 0.87 (lower 95% CL: 0.79) and 0.91 (lower 95% CL: 0.85), with controls reporting slightly better than cases. The reliability of reporting the use of HRT during the specific years 1985 and 1995 and the two-year periods of 1985/6 and 1995/6 were 0.69 (lower 95% CL: 0.54), 0.75 (lower 95% CL: 0.60), 0.73 (lower 95% CL: 0.59) and 0.77 (lower 95% CL: 0.64). The reliability of reporting was not consistently different between cases and controls.

Using a weighted kappa statistic the reliability of reporting of the number of alcoholic drinks per week (0, 1 to 6, 7 to 13 and more than 14) ranged from 0.63 (lower 95% CL: 0.49) for the most distant past intake, 16 to 20 years prior to the index date, to 0.72 (lower 95% CL: 0.62) for intake during the 5 year period prior to the index date.

8.7.2 Reliability of dietary questionnaire

Intraclass correlation coefficients (ICCs) were calculated to estimate the reliability of food and nutrient reporting as measured by the Block Food Frequency Questionnaire (see Methods sections 3.3.4.2 and 3.71). The reliability of reporting the number of servings of food ranged from 0.47 for grain products to 0.69 for servings of meat per day (Table 8.9). The reporting nutrients of interest in colorectal cancer, ranged from 0.69 for protein to 0.79 for total fat.

Table 8.9 Intraclass correlation coefficients (ICC) and lower confidence limits (CL) for the reliability of reporting of food and nutrient intake on the Block Questionnaire.

Food groups servings/day	ICC	95% CL
Dairy products	0.67	0.63
Fat	0.67	0.63
Fruit	0.61	0.56
Grain	0.47	0.41
Meat	0.69	0.65
Vegetables	0.61	0.56
Nutrient intake/day		
Calories (kcal)	0.79	0.76
Protein (g)	0.69	0.65
Total fat (g)	0.79	0.76
Calcium (g)	0.71	0.67
Vitamin D (IU)	0.71	0.67
Folate ((μg)	0.71	0.67
Total dietary fiber	0.70	0.66

8.7.3 Reliability of physical activity questionnaire

ICCs were calculated for the reliability of reporting occupational, household and exercise physical activity for the five-year period 5 to 10 years prior to index dates. ICC ranged from a low 0.12 for MET-hours/week of household activity to 0.72 MET-hours/week of occupational activity. The ICCs for exercise and total MET-hours/week was 0.22 to 0.37.

8.8 Validation of reporting hormone reoplacement therapy use

As described in section 3.5, the reporting of HRT use was validated using the prescription drug database as the 'gold standard'. Reporting for the single years 1985, 1995 resulted in kappa statistics of 0.64 and 0.67 respectively. The dispensing of one prescription during the specified year was sufficient to be classified as exposed in the database. When a

criteria of at least two prescriptions per year was used in order to be classified as exposed the kappa statistic was 0.67 for both years. This approach was taken because the women were asked to report HRT use for the years where they had used HRT for at least three months. For the two-year periods 1985/6 and 1995/6 where reporting of HRT use was compared with the presence of at least 1 dispensed prescription during the two year period, kappas were 0.61 and 0.69.

8.9 The effect of hormone replacement therapy on the risk of colorectal cancer

8.9.1 Analysis of Phase 1

In **Table 8.10** the results for the association between colorectal, colon and rectal cancer and ever use and duration of HRT use among women who were using HRT during the year immediately preceding the index date, are presented. HRT exposure is defined as the dispensing of one prescription per year. Conditional logistic regression is used except in the analyses among women with a history of having had a sigmoidoscopy where unconditional logistic regression is used with an interaction term for short and long duration of HRT use and history of having had a sigmoidoscopy.

Ever use of HRT was associated with a protective effect that was statistically significant (OR and 95% confidence interval (CI), of 0.79 (0.65 – 0.95). Short-term current use (<5 yrs), was not associated with a protective effect (OR, 95% CI: 0.92 (0.68 – 1.24) but longer term use was associated with an OR of 0.71 (95% CI: 0.56 – 91). Similar findings were observed for the association between HRT and colon cancer among current users. ORs for rectal cancer were slightly lower with wider CIs, and the same trend with duration use. Similar results were obtained among women who had not had a history of sigmoidoscopy (3 to 5 years prior to index date).

Very few women had had screening sigmoidoscopies and therefore confidence intervals for ORs were much wider. The association between HRT and colorectal cancer, however, appeared to follow the same pattern with duration of use as in the previous analyses.

In **Table 8.11** the same analysis is carried out, however the reference date for determining exposure status was the time prior to two years before the index date. ORs for 'ever' use and duration of use were more consistent than among current users. For colorectal cancer the ORs were all protective (0.78 ≥5yrs use to 0.84 'ever' use) and statistically significant. For rectal cancer long duration of use (≥5yrs) appeared to be protective (OR, 0.65(95% CI: 0.45 – 0.95), but short duration of use was not. Results among women with histories of having had a sigmoidoscopy were similar. Women with

histories of having had a screening sigmoidoscopy had lower ORs which were significant for colorectal cancer and 'ever' (OR, 0.59(95% CI: 0.40 – 0.87), and short duration of use (OR, 0.55 (95% CI: 0.35 – 0.88).

In Table **8.12,** the association between colorectal cancer and time since last HRT use is presented. There was a slight tendency for more recent HRT use to be more protective than distant past use (<5 yrs vs. ≥ 5yrs and <10 yrs vs. ≥ 10 yrs) but the differences were not large for colorectal and colon cancer. The differences between more recent and distant past HRT use were greater for rectal cancer (OR, 0.80 (95% CI: 0.61 – 1.04), for <5 yrs and (OR, 0.94 (95% CI: 0.81 – 1.04), for ≥5yrs. The results were similar among women without a history of screening sigmoidoscopy but ORs were lower among women with histories of a sigmoidoscopy particularly for HRT use within five years of the index date ((OR, 0.57 (95% CI: 0.33 – 0.96) for colorectal cancer and (OR, 0.52 (95% CI: 0.28 – 0.96),for colon cancer).

In **Table 8.13** results are presented for the association between colorectal cancer and oral conjugated estrogen. This analysis was conducted in view of the different effects of oral and transdermal estrogen on colorectal cancer risk (Chapter 7). Exposure was defined as SUM-P3 and SUM-P12 as dicussed in Chapter 3, section 3.3.2. Exposure during the two years prior to the index date was not counted in the determination of the level of exposure. Both levels of intensity of exposure (SUM-P3 and SUM-P12) had similar effects on colorectal cancer, colon and rectal cancer risk. Duration of estrogen use did not alter estimates of colorectal cancer risk, which tended to be around 0.85, with borderline significance. For colon and rectal cancer risk <5 yrs of estrogen use had the opposite effects, lowering ORs for rectal cancer risk (ORs, 0.95 to 0.64 (95% CI: 0.42 – 0.96 with SUM-P3) and increasing the ORs for colon cancer (ORs, 0.81 to 0.95 (95% CI: 0.74 – 1.22).

In **Table 8.14** the effect of age on the association between oral conjugated estrogen and colorectal cancer is studied. Estrogen appeared to have a protective effect in women

under 70 years of age, similar in magnitude to previous analyses but the protective effect disappeared among older women.

8.9.2 Phase 2 analyses

Results from Phase 2 analyses are presented in **Table 8.15**. Results for the association between short and long duration of HRT use (exposure defined as SUM-P3) and colorectal cancer are consistently reproduced with an analysis of the Phase 1 data (1981 – 1998 or using only subject with index dates in 1990 or later) using conditional logistic regression, unconditional logistic regression with age in the regression model and unconditional logistic regression using the Phase 2 subjects and correcting for the sampling fraction and standard error (as described in Chapter 3, section 3.8), but without age in the Phase 2 model. This demonstrates that the age distribution of Phase 2 subjects is different for that of the database population whether all subjects are considered to be Phase 1 or just subjects with index dates from 1990 and later. Using the Phase 2 sample age distribution therefore leads to a bias in the estimates of the association between HRT and colorectal cancer.

When age-adjusted estimates of colorectal cancer risk were determined with short and long duration of HRT use for all subjects with index dates between 1981 and 1998, the ORs were slightly different from the ORs obtained by using only database subjects with index dates in 1990 and later (for longer duration of use, 0.80 (95% CI: 0.65 – 0.98) and 0.86 (95% CI: 0.67 – 1.09). Since we had sampled only from subjects with index dates in 1990 and later, and we have evidence suggesting that these subjects were slightly different from the entire population **(Tables 8.5 and Tables 8.6)**, in the following analyses we considered Phase 1 subjects to be subjects with index dates in 1990 and later.

Since we had information on prescription drug NSAIDs use and history of having had a sigmoidoscopy the effect of including these covariates in the regression model was assessed as an additional means of attempting to determine whether the Phase 2 subjects were representative of the Phase 1 subjects or not. When these covariates were included in the Phase 2 regression models, without age, the estimates of colorectal cancer risk with

HRT use were similar to those obtained for Phase 1 indicating that bias was not introduced, confirming that with regard to these covariates the Phase 2 sample was representative of Phase 1.

Table 8.15 presents results examining the association between HRT exposure and risk of colorectal cancer among Phase 2 subjects adjusting for various lifestyle covariates: body mass index (BMI), total physical activity, and dietary intake for the five-year period 5 to 10 years prior to the index date. Although ORs for the covariates are presented they are not valid estimates of their association with colorectal cancer because they are not adjusted for sampling fractions.

All variables were categorized and dummy variables created with the lowest category serving as the reference group. Neither adjustment for physical activity, BMI nor any of the nutrients or food groups resulted in important changes in the estimated association between colorectal cancer and HRT. Given the low response rates it is difficult to determine whether these estimates are truly adjusted or whether confounding is still present.

Table 8.10 Odds ratios for colorectal cancer and hormone replacement therapy: Ever use and duration of use among current users only.

	Colorectal cancer			Colon cancer			Rectal cancer		
Hormone use	**N Cases**	**Controls**	**OR (95% CI)**	**N Cases**	**Controls**	**OR (95% CI)**	**N Cases**	**Controls**	**OR (95% CI)**
	n 3059	*n* 12116		*n* 2123	*n* 8411		*n* 936	*n* 3705	
Current HRT users only and duration of use among current users (1 prescriptions per year)									
Ever	139	680	0.79 (0.65 – 0.95)	93	445	0.81 (0.64 – 1.03)	46	235	0.74 (0.53 – 1.03)
<5 yrs	58	243	0.92 (0.68 – 1.24)	37	152	0.95 (0.65 – 1.37)	21	91	0.87 (0.53 – 1.43)
≥5yrs	81	437	0.71 (0.56 – 0.91)	56	293	0.74 (0.55 – 1.00)	25	144	0.66 (0.43 – 1.02)
Women without history of screening sigmoidoscopy									
	n	n 2851	n 11371	n 1964	n 7884		n 887	n 3487	
Ever	125	610	0.81 (0.66 – 1.00)	83	395	0.84 (0.65 – 1.08)	42	215	0.77 (0.54 – 1.09)
<5 yrs	52	223	0.95 (0.69 – 1.30)	33	137	0.98 (0.66 – 1.45)	19	86	0.90 (0.53 – 1.51)
≥5yrs	73	387	0.74 (0.57 – 0.96)	50	258	0.76 (0.56 – 1.05)	23	129	0.57 (0.13 – 2.58)
*Women with history of screening sigmoidoscopy**									
		n 208	n 745	n 159	n 527		n 49	n 218	
Ever	14	70	0.69 (0.38 – 1.25)	10	50	0.64 (0.31 – 1.29)	4	20	0.87 (0.28 – 2.68)
<5 yrs	6	20	1.05 (0.42 – 2.65)	4	15	0.86 (0.28 – 2.63)	2	5	1.76 (0.33 – 9.35)
≥5yrs	8	50	0.55 (0.26 – 1.18)	6	35	0.54 (0.23 – 1.33)	2	15	0.57 (0.12 – 2.62)

* Age-adjusted ORs estimate using unconditional logistic regression and interaction term (screening sigmoidoscopy =1) .

Table 8.11 Odds ratios for colorectal cancer and hormone replacement therapy: ever use and duration of use .

	Colorectal cancer			Colon cancer			Rectal cancer		
Hormone use	**N Cases**	**Controls**	**OR (95% CI)**	**N Cases**	**Controls**	**OR (95% CI)**	**N Cases**	**Controls**	**OR (95% CI)**
	n 3059	*n* 12116		*n* 2123	*n* 8411		*n* 936	*n* 3705	
Duration of use (1 prescriptions per year)*									
Ever	513	2307	0.84 (0.75 – 0.94)	340	1565	0.81 (0.71 – 0.93)	173	7[illegible]	0.74 (0.53 – 1.03)
<5 yrs	383	1682	0.86 (0.76 – 0.97)	246	1148	0.80 (0.69 – 0.94)	137	534	0.99 (0.80 – 1.22)
≥5yrs	130	625	0.78 (0.64 – 0.96)	94	417	0.85 (0.67 – 1.07)	36	208	0.65 (0.45 – 0.95)
Women without history of screening sigmoidoscopy									
		n 2851	n 11371	n 1964	n 7884		n 887	n 3487	
Ever	475	2104	0.81 (0.66 – 1.00)	310	1423	0.84 (0.72 – 0.97)	165	681	0.96 (0.79 – 1.18)
<5 yrs	359	1543	0.87 (0.78 – 0.98)	225	1050	0.82 (0.70 – 0.97)	134	493	1.09 (0.88 – 1.36)
≥5yrs	116	561	0.79 (0.64 – 0.98)	85	373	0.87 (0.68 – 1.12)	31	188	0.64 (0.43 – 0.95)
*Women with history of screening sigmoidoscopy***									
		n 208	n 745	n 159	n 527		n 49	n 218	
Ever	38	203	0.59 (0.40 – 0.87)	30	142	0.62 (0.40 – 0.97)	8	61	0.50 (0.22 – 1.13)
<5 yrs	24	139	0.55 (0.35 – 0.88)	21	98	0.65 (0.39 – 1.08)	5	41	0.27 (0.08 – 0.91)
≥5yrs	14	64	0.74 (0.41 – 1.35)	9	44	0.63 (0.30 – 1.32)	3	20	1.12 (0.40 – 3.14)

*Exposure during two years prior to index date not counted.

** Age-adjusted ORs estimate using unconditional logistic regression and interaction term (screening sigmoidoscopy =1).

Table 8.12 Odds ratios for colorectal cancer and hormone replacement therapy: Time since last use

	Colorectal cancer			Colon cancer			Rectal cancer		
	N Cases	Controls	OR (95% CI)	N Cases	Controls	OR (95% CI)	N Cases	Controls	OR (95% CI)
Time since last use (1 prescription per year)									
	n 3059	*n* 12116		*n* 2123	*n* 8411		*n* 936	*n* 3705	
Ever use	553	2454	0.85 (0.76 – 0.95)	369	1654	0.84 (0.74 – 0.96)	184	800	0.88 (0.73 – 1.05)
<5 yrs	230	1056	0.82 (0.70 – 0.96)	151	682	0.83 (0.69 – 1.01)	79	374	0.80 (0.61 – 1.04)
≥5yrs	323	1398	0.88 (0.77 – 1.00)	218	972	0.84 (0.72 – 0.99)	105	426	0.94 (0.81 – 1.04)
<10 yrs	346	1580	0.83 (0.73 – 0.94)	223	1022	0.82 (0.70 – 0.97)	123	558	0.84 (0.67 – 1.04)
≥10yrs	207	874	0.89 (0.76 – 1.05)	146	632	0.87 (0.71 – 1.01)	61	242	0.96 (0.71 – 1.31)
Women without history of screening sigmoidoscopy									
<5 yrs	212	952	0.85 (0.73 – 1.00)	138	607	0.88 (0.72 – 1.07)	74	345	0.81 (0.62 – 1.07)
≥5yrs	300	1288	0.90 (0.78 – 1.03)	199	897	0.86 (0.73 – 1.01)	101	391	0.94 (0.81 – 1.04)
*Women with history of screening sigmoidoscopy**									
<5 yrs	18	104	0.57 (0.33 – 0.96)	13	75	0.52 (0.28 – 0.96)	4	29	0.73 (0.27 – 1.99)
≥5yrs	23	110	0.69 (0.43 – 1.12)	19	75	0.79 (0.46 – 1.36)	5	35	0.94 (0.81 – 1.04)

* Age-adjusted ORs estimate using unconditional logistic regression and interaction term (screening sigmoidoscopy =1).

Table 8.13 Odds ratios for colorectal cancer and use of oral conjugated estrogen.

	Colorectal cancer			Colon cancer			Rectal cancer		
	Cases n=2861	Controls n=11315	OR (95% CI)	Cases n=1989	Controls n=7854	OR (95% CI)	Cases n= 872	Controls n= 3461	OR (95% CI)
Conjugated estrogen									
SUM –P3*									
Unexposed	2414	9344	1.00	1689	6509	1.00	725	2835	1.00
<5 yrs	299	1321	0.86 (0.74 – 0.98)	193	902	0.81 (0.68 – 0.96)	106	419	0.95 (0.75 – 1.20)
≥5 yrs	113	515	0.84 (0.68 – 1.05)	85	349	0.95 (0.74 – 1.22)	28	166	0.64 (0.42 – 0.96)
SUM –P12*									
Unexposed	2414	9344	1.00	1689	6509	1.00	725	2835	1.00
<5 yrs	193	859	0.85 (0.72 – 1.01)	120	588	0.78 (0.63 – 0.96)	73	271	1.00 (0.76 – 1.32)
≥5 yrs	81	370	0.85 (0.66 – 1.09)	62	247	0.98 (0.73 – 1.31)	19	123	0.59 (0.36 – 1.25)

* Exposure during two years prior to index date not counted.

Table 8.14 Odds ratios for colorectal cancer and use of oral conjugated estrogen: The effect of age

	Colorectal cancer		
	Cases n=2861	**Controls n=11315**	**OR (95% CI)**
≤ 70 years of age			
SUM –P12*			
Unexposed	883	3322	1.00
Ever	181	851	0.79 (0.66 – 0.95)
<5 yrs	128	601	0.77 (0.63 – 0.95)
≥5 yrs	53	250	0.78 (0.57 – 1.06)
> 70 years of age			
SUM –P12*			
Unexposed	1531	6022	1.00
Ever	93	378	0.99 (0.77 – 1.24)
<5 yrs	65	258	1.00 (0.75 – 1.34)
≥5 yrs	28	120	0.93 (0.61 – 1.42)

* Exposure during two years prior to index date not counted.

Table 8.15 Odds ratios and 95% CIs for colorectal cancer and HRT (SUM-P) for Phase 1 and Phase 2 subjects.

HRT	Cases n=3059	Control n=21116	Conditional LR ORs (95% CIs)	Unconditional LR ORs (95% CIs)	Cases n=188	Controls n=250	Unconditional LR with correction for sampling fraction and standard error.
Phase 1					**Phase 2**		
All subjects: 1981 – 1998			**Age-matched**	No adjustment for age			
Crude							
Unexposed	2608	10077	1.00	1.00	128	88	1.00
1 – 4 years	330	1467	0.85 (0.75 – 0.97)	0.87 (0.77 – 0.99)	25	78	0.87 (0.77 – 0.99)
≥ 5 years	121	572	0.80 (0.65 – 0.98)	0.82 (0.67 – 1.00)	35	85	0.82 (0.66 – 1.00)
				Age-adjusted			
Unexposed	2608	10077		1.00	128	88	1.00
1 – 4 years	330	1467		0.86 (0.76 – 0.98)	25	78	0.93 (0.79 – 1.08)
≥ 5 years	121	572		0.81 (0.66 – 0.99)	35	85	0.84 (0.68 – 1.03)
Subjects with index dates in 1990 or later.				No adjustment for age			
Unexposed	1296	4926	1.00	1.00	128	87	1.00
1 – 4 years	201	909	0.83 (0.70 – 0.98)	0.84 (0.71 – 0.99)	25	78	0.84 (0.71 – 0.99)
≥ 5 years	87	381	0.86 (0.67 – 1.09)	0.87 (0.68 – 1.04)	35	85	0.87 (0.68 – 1.10)
				Age-adjusted			
Unexposed	1296	4926		1.00	128	87	1.00
1 – 4 years	201	909		0.83 (0.70 – 0.98)	25	78	0.89 (0.74 – 1.07)
≥ 5 years	87	381		0.86 (0.67 – 1.09)	35	85	0.89 (0.70 – 1.14)

Table 8.15 continued

HRT	Cases n=3059	Control n=21116	Conditional LR ORs (95% CIs)	Unconditional LR ORs (95% CIs)	Cases n=188	Controls n=250	Unconditional LR with correction for sampling fraction and standard error.
Phase 1						**Phase 2**	
Adjusting for age and NSAIDs use 1 to 5 years prior to index dates.							
Unexposed	1296	4926	1.00	1.00	128	87	1.00
1 – 4 years	201	909	0.85 (0.72 – 1.01)	0.85 (0.72 – 1.01)	25	78	0.97 (0.80 – 1.19)
≥ 5 years	87	381	0.88 (0.69 – 1.12)	0.88 (0.69 – 1.12)	35	85	0.92 (0.71 – 1.19)
NSAIDs	396	1838	0.71 (0.61 – 0.83)	0.80 (0.71 – 0.91)	47	98	0.53 (0.34 – 0.83)
							NSAIDs only
Unexposed					128	87	1.00
1 – 4 years					25	78	0.89 (0.75 – 1.06)
≥ 5 years					35	85	0.88 (0.69 – 1.13)
NSAIDs					47	98	0.57 (0.37 – 0.88)
Adjusting for age and screening sigmoidoscopy three to five years prior to index date.							
Unexposed	1296	4926	1.00	1.00	128	87	1.00
1 – 4 years	201	909	0.82 (0.70 – 0.98)	0.83 (0.70 – 0.98)	25	78	0.89 (0.74 – 1.07)
≥ 5 years	87	381	0.85 (0.67 – 1.09)	0.85 (0.67 – 1.08)	35	85	0.89 (0.70 – 1.14)
Sigmoidoscopy	115	402	1.14 (0.92 – 1.41)	1.15 (0.92 – 1.42)	12	23	0.63 (0.29 – 1.35)
							Sigmoidoscopy only
Unexposed					128	87	1.00
1 – 4 years					25	78	0.84 (0.71 – 0.99)
≥ 5 years					35	85	0.87 (0.68 – 1.10)
Sigmoidoscopy					12	23	0.65 (0.30 – 1.39)

Table 8.16 The Effect of Phase 2 covariates on HRT point estimates with correction for sampling fractions and standard errors.

HRT and covariates from Phase 2.	Cases n=188	Controls n=250	Unconditional LR with correction for sampling fraction and standard error.
SUM- P3	**Adjusting for BMI**		
Unexposed	128	87	1.00
1 – 4 years	25	78	0.85 (0.71 – 1.00)
≥ 5 years	35	85	0.87 (0.68 – 1.11)
BMI			
<22	48	67	1.00
22 to 23	31	48	0.84 (0.46 – 1.52)
24 to 27	52	62	1.01 (0.59 – 1.71)
≥28	42	62	0.83 (0.48 – 1.43)
Missing	15	11	
	Adjusting for physical activity		
Unexposed	128	87	1.00
1 – 4 years	25	78	0.82 (0.69 – 0.98)
≥ 5 years	35	85	0.86 (0.67 – 1.09)
Physical activity			
Low (< 90 total METS-hours/week per year)	69	107	1.00
Moderate (91 to 180 total METS-hours/week per year)	41	54	0.94 (0.51 – 1.73)
High (≥181 total METS-hours/week per year)	39	51	1.30 (0.82 – 2.06)
Missing	39	38	

Table 8.16 continued

Adjusting for food groups			
Number of meat servings/d			
Unexposed	128	87	1.00
1 – 4 years	25	78	0.84 (0.71 – 1.00)
≥ 5 years	35	85	0.87 (0.67 – 1.11)
Meat servings/d			
1.5 or less	66	88	1.00
1.6 to 2.4	49	79	0.87 (0.55 – 1.39)
2.5 or more	37	44	1.20 (0.70 – 2.07)
Missing	36	39	
Adjusting for number of vegetable servings per day			
Unexposed	128	87	1.00
1 – 4 years	25	78	0.84 (0.71 – 1.00)
≥ 5 years	35	85	0.85 (0.66 – 1.09)
Vegetable servings/d			
3.0 or less	76	104	1.00
3.1 to 4.9	58	88	0.89 (0.57 – 1.38)
5.0 or more	18	19	1.44 (0.69 – 3.02)
Missing	36	39	
Adjusting for number of grain servings per day			
Unexposed	128	87	1.00
1 – 4 years	25	78	0.84 (0.71 – 1.00)
≥ 5 years	35	85	0.86 (0.67 – 1.10)
Grain servings/d			
4.5 or less	78	119	1.00
4.5 to 7.5	60	76	1.15 (0.74 – 1.79)
7.5 or more	14	16	1.25 (0.56 – 2.80)
Missing	36	39	

Table 8.16 continued

Adjusting for number of fruit servings per day			
Unexposed	128	87	1.00
1 – 4 years	25	78	0.85 (0.72 – 1.00)
≥ 5 years	35	85	0.89 (0.69 – 1.13)
Fruit servings/d			
3.0 or less	88	109	1.00
3.1 to 4.9	45	74	0.82 (0.51 – 1.30)
5.0 or more	19	28	0.90 (0.46 – 1.74)
Missing	36	39	
Adjusting for number of fat servings per day			
Unexposed	128	87	1.00
1 – 4 years	25	78	0.84 (0.71 – 1.00)
≥ 5 years	35	85	0.85 (0.67 – 1.09)
Fat servings/day			
3.5 or less	60	103	1.00
3.6 to 5.9	70	83	1.28 (0.83 – 1.98)
6.0 or more	22	25	1.39 (0.71 – 2.71)
Missing	36	39	
Adjusting for percent of calories from alcohol			
Unexposed	128	87	1.00
1 – 4 years	25	78	0.85 (0.72 – 1.00)
≥ 5 years	35	85	0.88 (0.68 – 1.14)
Percent of calories from alcohol			
0	85	105	1.00
0.1 to 1.4	35	55	0.91 (0.54 – 1.52)
1.5 or more	32	51	0.92 (0.54 – 1.58)
Missing	36	39	

Table 8.15 continued

Adjusting for nutrient intake

Adjusting for calcium intake (mg/d)

Unexposed	128	87	1.00
1 – 4 years	25	78	0.85 (0.72 – 1.00)
≥ 5 years	35	85	0.84 (0.66 – 1.09)
Calcium intake (mg/d)			
600 or less	61	89	1.00
601 to 999	58	83	0.95 (0.61 – 1.50)
1000 or more	33	39	1.29 (0.73 – 2.29)
Missing	36	39	

Adjusting for vitamin D intake (IU per day)

Unexposed	128	87	1.00
1 – 4 years	25	78	0.85 (0.72 – 1.01)
≥ 5 years	35	85	0.83 (0.64 – 1.07)
Vitamin D intake (IU/d)			
200 or less	75	118	1.00
201 to 399	64	77	1.33 (0.85 – 2.07)
400 or more	13	16	1.26 (0.55 – 2.68)
Missing	36	39	

Adjusting for folate intake (µg per day)

Unexposed	128	87	1.00
1 – 4 years	25	78	0.83 (0.70 – 0.98)
≥ 5 years	35	85	0.87 (0.68 – 1.12)
Folate intake (µg/d)			
180 or less	67	85	1.00
181 to 249	52	84	0.81 (0.51 – 1.29)
250 or more	33	42	1.14 (0.65 – 2.01)
Missing	36	39	

Table 8.16 continued

Adjusting for fiber intake (g per day)

Unexposed	128	87	1.00
1 – 4 years	25	78	0.84 (0.71 – 1.00)
≥ 5 years	35	85	0.86 (0.67 – 1.10)
Fiber intake (g/d)			
15 or less	79	109	1.00
15.1 to 19.9	43	70	1.28 (0.83 – 1.98)
20 or more	30	32	1.39 (0.71 – 2.71)
Missing	36	39	

Adjusting for total fat intake (g. per day)

Unexposed	128	87	1.00
1 – 4 years	25	78	0.84 (0.71 – 1.00)
≥ 5 years	35	85	0.84 (0.65 – 1.08)
Total fat intake (g/d)			
65 or less	65	97	1.00
65.1 to 84.9	40	61	1.00 (0.61 – 1.66)
85 or more	47	53	1.38 (0.84 – 2.29)
Missing	36	39	

Shaded area refers to HRT exposure adjusted for each individual covariate specified.

CHAPTER 9. Discussion

Convincing evidence is still lacking even after several decades of research, that HRT is protective for colorectal cancer. In this thesis we are reporting new findings that add to our understanding of this challenging area of study. In addition, we have explored methodological questions pertinent not only to studies that examine the effect of HRT on the risk of colorectal cancer but also to pharmacoepidemiology in general. In this discussion I will present our substantive contribution to the area of women's health, examine our work in terms of strengths and weaknesses, discuss the methodological challenges we faced and our approach to resolving some of these difficulties.

9.1 Use of hormone replacement therapy in Saskatchewan

Estimating the prevalence of HRT use in Canada was one of the first problems we encountered in the course of developing the protocol for this study. Although US data describing patterns of HRT use are available, Canadian data have been lacking with the exception of data describing the prevalence of current HRT use, published in survey reports.[190,195] Data pertaining to the duration of HRT was not available, nor were changes in the rate of new use over time among women within various age categories. With existing questions and controversy surrounding the health effects of HRT, we felt it would be of interest to clinicians, public health experts and researchers alike, with an interested in women's health, to have Canadian data available.

In the two manuscripts in Chapter 4 we analyze data using the controls from the present and a previous population-based case-control study.[161] This latter study was designed to investigate the effect of antidepressants and NSAIDS on the risk of breast cancer and was also conducted using data from the Saskatchewan out-patient prescription drug database. Our results demonstrate how data from administrative healthcare databases can be used to describe an exposure over long periods of time, eliminating the need to embark on expensive and labour intensive data collection.

Two limitations of this analysis could have an impact on the generalizability of the results. First, in order to qualify as a control in the original case-control studies the

subjects could not have had a diagnosis of cancer at, and prior to their assigned index date. Second, they had to have had a five-year registration with Saskatchewan Health. The former limitation is unlikely to have an impact on estimates of new use and prevalence of HRT use due to the low rate of immigration into the province particularly among women 45 years of age and older.

The absence of cancer diagnosis prior to index dates probably resulted in a slightly healthier study population for this descriptive analysis than would have been obtained with random sample of women in this age group. However, the difference is not likely to be as great as may initially appear. Many of the women in fact were diagnosed with cancer during a time after their assigned index date and these women were included in our analysis. All the women in our descriptive study were therefore not cancer free. The consistency of our results with the prevalence data for women 50 to 64 years of age in Manitoba during 1995, supports our conviction that our estimates of HRT use are valid. We are confident that the various analyses demonstrate several aspects of the changes in patterns of HRT use in this population.

The results from this study highlight the importance of studying the health effects of HRT. The age-standardized prevalence estimates demonstrate that 15% of women over the age of 45 are using HRT. Our data show that more women over the age of 60 began using HRT in the 1990s than during the 1980s (Chapter 4: Figure 4.1). Data collection during Phase 2 of our study indicate that while the management of menopausal symptoms is the most common reason cited for using HRT (Chapter 8: Table 8.9) other reasons include the prevention or treatment of osteoporosis and the prevention of cardiovascular disease. Certainly women over the age of 60 are likely to be asymptomatic and likely to be taking HRT solely for disease prevention.

9.2 Health-related behaviour of HRT users

The second manuscript in this thesis, *Health related behaviour and use of hormone replacement therapy,* is an examination of the association between HRT use and covariates available for our entire study population. We examined this association in

cases and controls separately in order to identify potential confounding factors and effect modifiers. The results of this study confirm previously reported evidence that HRT users are different from nonusers in that they are more likely to use vitamin supplements and NSAIDs and visit their physicians more often regardless of disease status. Our data are limited to prescription drugs whereas most other studies have relied on self-reported use which likely represent both prescription and over the counter drugs.

Our data also indicate that HRT users are more likely to be prescribed CNS drugs and cardiovascular drugs again, regardless of disease status, although the association for the among cases is stronger among controls.

An interesting finding here is the difference in the association between HRT and sigmoidoscopy between cases and controls. It has been shown by others that HRT users are more likely to have had a screening sigmoidoscopy than nonusers. This is of interest because it has been suggested that an increase in screening and perhaps removal of adenomatous polyps will reduce the incidence of colorectal cancer among HRT users. This would thus explain an observed protective effect among HRT users.

Investigators from the Nurses Health Study have reported that 15.6% of the women taking HRT had undergone screening sigmoidoscopy compared with 11.4% of HRT nonusers. In our study 8.6% and 4.5% of users and nonusers had had sigmoidoscopies 3 to 5 years prior to index dates. For cases the percentages are 7.4 and 6.7 for HRT users and nonusers, and 8.8% and 5.5% among controls. It is possible that among cases a sigmiodoscopy 3 to 5 years prior to the index date represents a diagnostic procedure rather than a screening procedure, perhaps due to a lag time between the time the procedure was performed, confirmation of a diagnosis and its reporting to the Cancer Registry. This therefore needs to be considered in analyses since sigmoidoscopy during this time may represent a mix of two types of bias: a detection bias where HRT users with colorectal cancer are more likely to be diagnosed and a preventive procedure where polyps may be removed thus reducing the incidence of colorectal cancer among HRT users. Unfortunately, we did not have information on sigmoidoscopies for a time in the

more distant past in order to determine the association between HRT use and a sigmoidoscopy in the distant past which may in fact be a better proxy for screening. We also did not have information pertaining to the reason a women had a procedure, nor did we have information with regard to whether a polypectomy was performed or not.

It is likely that associations between HRT and sigmoidoscopy vary with population and it may be unwise to assume an understanding of the association without close scrutiny. Although in the present study including screening sigmoidoscopy in regression models did not alter point estimates perhaps because of its low prevalence, in populations with a higher prevalence of sigmoidoscopy procedures it would be important to know the timing of the procedure and its association with HRT in both cases and controls before automatically adjusting for its effect in regression modelling. In a number of studies where the effect of HRT on the risk of colorectal cancer has been investigated adjustment has been made for history of screening sigmiodoscopy, likely appropriately, although what is meant by 'screening sigmoidoscopy' is not explicitly stated.[125,127]

9.3 Defining estrogen exposure

The third manuscript in this thesis, *Defining estrogen exposure in longitudinal studies: Impact on measures of effect*, is an examination of various definitions of estrogen exposure that have been used in published studies. Due to the detailed prescription drug dispensing data documented in the database we were able to replicate these methods to determine whether inconsistencies in exposure definitions could reproduce the inconsistencies that have been reported for the effect of estrogen on the risk of colorectal cancer.

Thirty-six estrogen exposure variables were created in order to account for the various aspects of exposure that could be defined. The magnitude of variability introduced by different estimates varied with duration of HRT use and colorectal sub-site. Estimates of association between HRT use and colorectal cancer were most prone to fluctuate, by as much as 20% with variations in exposure definitions for short-term use (1 to 4 years). With longer-term use this variability was reduced by almost half.

The association between HRT and rectal cancer was more affected by variations in exposure definition than were associations with colorectal and colon cancer. This is likely due to random fluctuation due to the smaller sample size of rectal cancer subjects, compared with colon cancer subjects.

One can expect to observe the amount of variability in measures of effect seen here, between studies with different definitions of estrogen exposure even with accurate data. In most studies however, additional factors are a source of random and systematic error, further increasing the differences between study results. This highlights the importance of carefully examining the definition of exposure when study results are compared and demonstrates the difficulty inherent in studies when small effects are the focus of investigation.

9.4 Transdermal vs. oral estrogen estrogen replacement therapy

In the manuscript *The effect of transdermal and oral estrogen replacement therapy on colorectal cancer risk in postmenopausal women*, we examine the independent effect of the route of administration on the risk of colorectal cancer. We report for the first time results that indicate that transdermal estrogen is strongly protective for colorectal cancer. The reduction in risk appears to be as great as 60% with short-term use and greater with more than 3 years of transdermal estrogen use, with evidence of a dose-response effect for duration of use. The protective effect was not eliminated among women without a history of having had a sigmoidoscopy.

An important limitation of this analysis is the lack of information on lifestyle covariates that could confound the relationship. None of the prescription drug covariates for which we had information, nor the frequency of physician visits had altered the estimated ORs by a few points to two decimal places. We were however, able to demonstrate that by using women who had been exposed to oral estrogen only, as the reference group, the association between transdermal estrogen and colorectal cancer risk did not change substantially. The issues of selection bias and confounding are related to the

demonstrated differences between HRT users and nonusers. By using a group of HRT users as the reference group, presumably most of these differences are eliminated thus minimizing the potential for confounding.

The question remains whether there are differences between oral and transdermal estrogen users that would reduce the risk of colorectal cancer in the latter group of women. Such differences have not been reported in the literature. It is conceivable however, that physician prescribing patterns are such that there is a physician induced 'selection bias', such that women who use these formulations are at a reduced risk of colorectal cancer. Again, evidence suggesting this has not been reported.

Another limitation of this study is the small number of exposed cases. If however, transdermal estrogen is truly protective for colorectal cancer we will always have fewer exposed cases to study, limiting even very large population-based studies. Nevertheless, in order to adequately study the effect of duration of use and dose-response larger sample sizes will be required.

Continuing the study of the effect of the association between transdermal estrogen and colorectal cancer will not be possible in Saskatchewan, due to the removal of this prescription drug from the Full Formulary and its transfer to the Exception Drug Status Program in 1996. At the present time, in order for women to be financially covered by the Drug Plan for using transdermal estrogen, their physicians have to request approval for transdermal estrogen use based on a woman's demonstrated intolerance to oral estrogen. Interestingly, as our descriptive data demonstrate (Chapter 4), following this change in formulary status, only 2% of HRT users remained transdermal estrogen users. This would indicate that whatever reasons were present for physicians to prescribe transderamal estrogen to some women, they were not important enough to warrant continuing the practice. This is indirect evidence to suggest that indeed big differences do not exist between transdermal and oral estrogen users.

On a final note, it has been recognized for several decades that there are metabolic differences between transdermal and oral estrogen. With oral estrogen a large amount of estrogen is delivered to the liver in contrast to transdermal estrogen administration where estradiol is delivered directly into the venous circulation. The presystemic metabolism of estradiol is thus minimal with transdermal estrogen administration and results in a serum E_2/E_1 ratio similar to that found in fertile women.

Chetkowski et al[218] studied the metabolic effects of treating women with four increasing doses of transdermal estradiol (25, 50, 100, and 200 μg per 24 hours) and two doses of oral conjugated equine estrogen (0.625 and 1.25 mg per day). Both doses of oral conjugated estrogen significantly increased levels of renin substrate, thyroxine binding protein, sex-hormone-binding globulin (SHBG), and cortisol-binding globulin (CBG), compared with levels in premenopausal women and postmenopausal baseline levels. No changes in these proteins were observed with transdermal estrogen replacement.

A dose of 100 μg per 24 hours of transdermal estrogen administration increased mean estrone and estradiol levels to those comparable with the early follicular phase of the menstrual cycle during premenopause, and 200 μg per 24 hour increased estrone and estradiol concentrations that were between those in the early and late follicular phases. Conjugated estrogens raised estradiol levels above postmenopausal baseline levels, but regardless of dose, estradiol remained less than 50% of premenopausal levels. Mean plasma estrone levels, on the other hand, were substantially greater than at any time during the premenopausal menstrual cycle with oral conjugated estrogens.

Clinical studies are continuing to investigate the different effects of transdermal and oral estrogen on hormonal milieu and metabolites. We are the first to report differences in their impact on cancer risk and our results indicates that additional studies conducted to examine the long-term differences in the health consequences of estrogens delivered by different routes are warranted.

9.5 Hormone replacement therapy and risk of colorectal cancer

9.5.1 Study design issues

Eighteen observational studies have been conducted during the past two decades to examine the effect of HRT on the risk of colorectal cancer. Although many of these studies have reported observing a protective effect of HRT [82,125,127], others have not. [114,126] Adding to this uncertainty are questions pertaining to the validity of the results that support the hypothesis that HRT is protective. Women who use HRT are known be leaner, engage in more physical activity, be ex-smokers, use more NSAIDs, take vitamin supplements and be from a higher socio-economic status. Evidence from studies examining the effect of physical activity and NSAIDs on the risk of colorectal cancer have been classified as providing 'convincing' evidence to support a protective effect. Numerous dietary and other lifestyle factors have been classified as 'probable' and 'possible' risk or protective factors. These are among the most difficult covariates to measure particularly in the distant past when they are likely to have had an important effect on cancer cell initiation and growth. Because they are also highly correlated with HRT use, an unbiased estimate of the association between HRT and colorectal cancer has been a great challenge to investigators from both a substantive and a methodological perspective.

In order to answer the obvious substantive question 'is HRT causally related to a reduction in the risk of colorectal cancer in postmenopausal women' it is essential to resolve some of the methodological problems that have afflicted studies to date. In this remaining section of the discussion I will interpret the evidence from our research and describe its contribution to the substantive area of the effect of HRT on the incidence of colorectal cancer.

I will also address our attempts to deal with some of the methodological concerns in this area of research and our experience with a two-phase case-control sampling design.

Undoubtedly, selection bias is one of the most difficult problems to deal with in studies examining the health-related effects of HRT. Frequently in research an appropriate solution to this kind of methodological problem is the use of a randomized controlled trial

(RCT) design. When the outcome is a chronic disease with a long latency period, an RCT becomes less appealing and often not feasible. Intermediate end-points such as adenomatous polyps may be studied in this particular question, since they appear to share similar risk factors with colorectal cancers. This however, still requires further study.[19] In addition, most adenomatous polyps are highly prevalent in people over the age of 50, and most adenomas do not evolve into colorectal cancer.[223] The relevance to the etiology of colorectal cancer, of findings from short-term clinical trials that assess the association between risk factors and adenomas, has therefore been questioned.[223]

RCTs are also limited in design to the study of specific aspects of an exposure in a clearly defined pattern of administration, in a clearly defined population. HRT is available in many formulations and used by a large group of women with varying health and lifestyle characteristics. Observational designs are therefore alluring because of the potential to study various aspects of an exposure in a varied population over extended periods of time.

Clearly, traditional observational and experimental study designs have limited appeal in this area of study. It is with this view that we decided to use an innovative population-based nested-case control study design with two-phase sampling.

Many aspects of this study design were ideal for the investigation of the effect of HRT on the risk of colorectal cancer. The Saskatchewan Health administrative databases provided detailed population-based information on HRT over a period of 22 years. Data on colorectal cancer was available for the same period of time. In addition, other potential covariates such as history of having had a screening sigmoidoscopy, physician visits, use of NSAIDs and OCs were also available. Nonetheless, the lack of information pertaining to lifestyle covariates was a serious limitation. The two-phase sampling design presented an efficient way to collect this information.

This design has been academically discussed for several decades but its application to fieldwork has been limited. This is the second study that our research team has embarked

on used this study design and our experiences reveal the tremendous difficulty with which it is implemented. In the first study completed several years ago, and conducted in the same population, response rates were 67% among cases and 43% among controls.[161] In that study, proxy respondents were used for deceased cases and controls.

9.5.2 The effect of hormone replacemeent therapy on the risk of colorectal cancer

Can we conclude that HRT is protective for colorectal cancer? We have shown in our study of transdermal estrogen that this form of HRT appears to have a protective effect greater in magnitude than previously reported. A stronger effect of transdermal estrogen than oral estrogen is biologically plausible. Previous studies have examined the effects of oral estrogen exclusively or have not distinguished between the effects of different formulations. Our main objective was to study the overall effect of HRT on colorectal cancer and our sampling for Phase 2 was based on a calculation of HRT exposure that included all formulations regardless of route of administration. We therefore present results that examine the overall effect of HRT on the risk of colorectal cancer in addition to the specific effects of oral and trandermal estrogen.

Previous studies have demonstrated that there is a protective effect of HRT against colorectal cancer among current HRT users and no additional effect of duration of use with current use.[82,113,113] We also observed a protective effect among current HRT use but only among women long-term users (5 or more years of HRT use). Among short-term current use, a null effect was observed among all the women and among those stratified for history of having had a sigmoidoscopy. While this could be random fluctuation since the analysis among current users only was conducted with a smaller sample size, another explanation is that among these women there may be an increase in the rate of cancer detection as a result of starting HRT recently and being followed more closely than in the past. Longer-term HRT users wouldn't experience this recent change in surveillance. In similar analyses the NHS investigators have reported observing a protective effect among short (<5 yrs; OR, 0.56 (0.39 – 0.83) and long-term (<5 yrs; OR, 0.72 (0.53 – 0.96) current use without additional benefit from long-term use. However, this may reflect the fact that the difference in surveillance between HRT users and

nonusers is not as great among nurses as it is in the general population of women. Our results for ≥5 years use however, OR = 0.71(0.56 – 0.91), are consistent with their findings. Among women who did not necessarily have a prescription during the year before their index date, both short and long-term HRT use is as protective for colorectal cancer.

With regard to timing since last use more recent HRT use is associated with a more protective OR than more distant past use. These results, however, appear to be largely influenced by the results for rectal cancer. Again, this may reflect some confounding where 'recent HRT use' in relation to index date, is also more recent in chronological time and therefore reflects increasing differences over time between HRT users and nonusers with regard to preventive lifestyle habits.

The results for the effect of oral conjugated estrogen alone are consistent with a possible risk reduction of about 15% for both levels of intensity of exposure as calculated by SUM-P3 and SUM-P12. For colon cancer the protective effect was stronger for short duration of use and appeared to disappear.

Two studies have reported that age may be an effect modifier for the association between HRT and colon cancer.[125,126] Prihartono et al[125] observed an OR of 0.4 (95% CI: 0.20 to 0.90) for women 60 to 69 years of age, compared with an OR of 0.8 (95% CI: 0.20 to 2.70) for women under 60 years. That study did not include women over 69 years of age. Jacob et al reported ORs of 1.14 (95% CI: 0.71 to 1.83) between HRT and colorectal cancer among women 55 to 69 years of age and 0.79 (95% CI: 0.45 to 1.41) for women 70 to 79 years of age. In contrast to these results we found that HRT was protective for colorectal cancer among women 70 years of age and younger but not for women over 70 years. In our population since more women under the age of 70 had a history of having used HRT and more recently than the older women and more recent use appears to confer a more protective effect, these results are consistent with our other observations.

In summary, we have observed a reduction in the risk of colorectal cancer of about 20% with HRT use. We did not find any evidence of confounding by any of the covariates on which we had information for all our subjects, nor did we find evidence of confounding by any of the Phase 2 covariates. The validity of the Phase 2 information, however, is questionable. The discussion that follows addresses this concern.

9.5.3 Selection bias due to Phase 2 response rates

Despite much planning to develop a recruitment protocol that would optimize response rates our response rates were 30% for cases and 18% for controls. Questionnaires and literature describing the study were designed to be attractive, informative and at an acceptable level of literacy. Attention was given to such details as the commemorative stamp (year of the elderly) on the letter of the preliminary notice. All of these factors have been advocated for improving response rates in mail surveys.[156]

With response rates as low as ours, it becomes extremely difficult to estimate the quality of the information obtained. We have the advantage of having information on all our cases and controls for some covariates from Saskatchewan healthcare databases. It is virtually impossible to estimate the direction or magnitude of bias that a response rate as low as ours would introduce in the association between HRT and colorectal cancer. However, it is of value to identify responder and non responder characteristics so that methods can be developed to encourage a high level of participation if these types of studies are to continue.

Responders among both cases and controls were younger than those who had refused. While this pattern has been observed in other studies it is not universally true.[224,225] Eaker et al[226] reported finding a nonlinear relationship between age and response rate, with old age being a strong predictor of nonresponse. The length of the self-administered questionnaires in our study may also have deterred people from participating. In a randomized factorial study design Eaker et al[226] studied the use of various combinations of technical aspects of recruitment and found that the highest response rates were achieved with preliminary notification, a short questionnaire and no mention of telephone

contact. However, even with the most successful recruitment strategy the overall response rate in a population that included all age groups was only 56 percent, highlighting the difficulty with which response rates can be manipulated.

The average age of our population was 73 years of age. A combination of age, burden of self-administered questionnaires and telephone contact probably deterred women from participating; however, this age group may be difficult to recruit under most circumstances.

Some non responders provided reasons for not participating in the study. Many indicated that they were not interested but at least 20 percent of non respondance gave illness, dementia, death and difficulty with hearing or language as reasons for refusal. Others have reported similar problems in the recruitment of the elderly.[227]

We observed that during our first period of recruitment there was a correlation between disease, exposure status and response rate. The response rate among highly exposed cases sampled for Phase 2 (5 or more years of HRT use), was 60 percent, 29 percent among short duration HRT users and 28 percent among unexposed cases. The response rate among highly exposed controls was 26 percent, 21 percent for low exposure and 10 percent for unexposed controls. We suspected that women were quickly making a decision about whether or not to participate in our study after reading the title of the study pamphlet: *Hormone Replacement Therapy and Colorectal Cancer Study.* For the second recruitment therefore we changed the title to removed HRT form the title and replaced it with 'Lifestyle'. Following this the response rates appeared to be less related to HRT exposure and disease. The response rates among exposed cases were 29, 39 and 29 percent for high, low and unexposed. The rates for controls were 38, 19 and 17 percent for high, low and unexposed. Unfortunately, the overall response rates remained essentially unchanged.

Some investigators have reported an improvement in response rates following the enclosure of small cash incentive.[228] The authors have suggested that when these

incentives are as small as two to five dollars and are unconditional they may foster a feeling of trust. In studies where the effects of cash incentives have been examined an increase in response rates of about 20% has been observed, however, some studies have observed no effect.[229,230] As with other mailing recruitment strategies the response to cash incentives may vary by population and therefore without first conducting pilot studies we do not know whether or not such a strategies would have improved response rates. It is a strategy that needs to be considered for future work where high response rates are critical to the validity of results.

While cognizant of the enormous potential for bias due to our poor response rates, and the difficulty of ruling it out, we examined the second stage data in an effort to evaluate the impact of the data collected on point estimates of HRT use (Table 8.14). Using data from the database we compared the impact of age, prescription NSAIDs use, and history of having had a sigmoidoscopy on the HRT point estimates. We compared these results with results obtained using the data from Phase 2 with correction for the biased sampling and the standard error.

The point estimates for the association between colorectal cancer and HRT, adjusted for Phase 2, were most affected by adjusting for age using the Phase 2 age distribution. This is consistent with our observations that responders tended to be much younger than nonresponders among cases and controls and younger than the mean ages of all the cases and controls. Other important differences were not observed and neither NSAIDs nor history of screening sigmoidoscopy appeared to alter the point estimates for HRT.

None of the covariates collected during Phase 2 altered HRT point estimates more than would be expected with random fluctuation. Many of the covariates such as physical activity and intake of vegetables, calcium, vitamin D and folate were expected to attenuate an observed protective effect because of their expected association with HRT use and protective effect against colorectal cancer. Since HRT users have been demonstrated to be leaner and an elevated BMI has been associated with an increase in the risk of colorectal cancer, BMI would also be expected to attenuate a protective effect

of HRT. The percent of calories from alcohol would have been expected to reveal a more protective effect of HRT if it is truly protective because it has been demonstrated to increase the risk of colorectal cancer and HRT users have been reported more likely to drink alcohol than HRT nonusers. Many other covariates are suspected confounders but conclusive evidence is not available.

Despite the lack of evidence that covariates from the Phase 2 sample other than age are biasing point estimates, we cannot be sure that the crude point estimates are valid estimates of the association between HRT and colorectal cancer. In addition, to the potential problem of selection bias as discussed above, another concern is that 48% of cases with index dates in 1990 or later, had died by 1998. Proxy respondents were not interviewed because of evidence that suggests that husbands do not provide reliable information pertaining to their wives' reproductive histories and lifestyle habits.[154,155]

We have shown with the comparison of covariate profiles of the subjects remaining alive in 1990 with the profiles of the all subjects with index dates in 1990 and later that there are negligible differences between the groups among controls. Among cases, of those remaining alive in 1999, 60 percent had been diagnosed with colorectal cancer at Stage A or B, compared with 40 percent of cases diagnosed at these stages when all the cases with index dates in 1990 or later were considered. This over-representation of cancer cases with stage A and B was further exaggerated among the responders of whom 70 percent had been diagnosed with cancer at stages A and B.

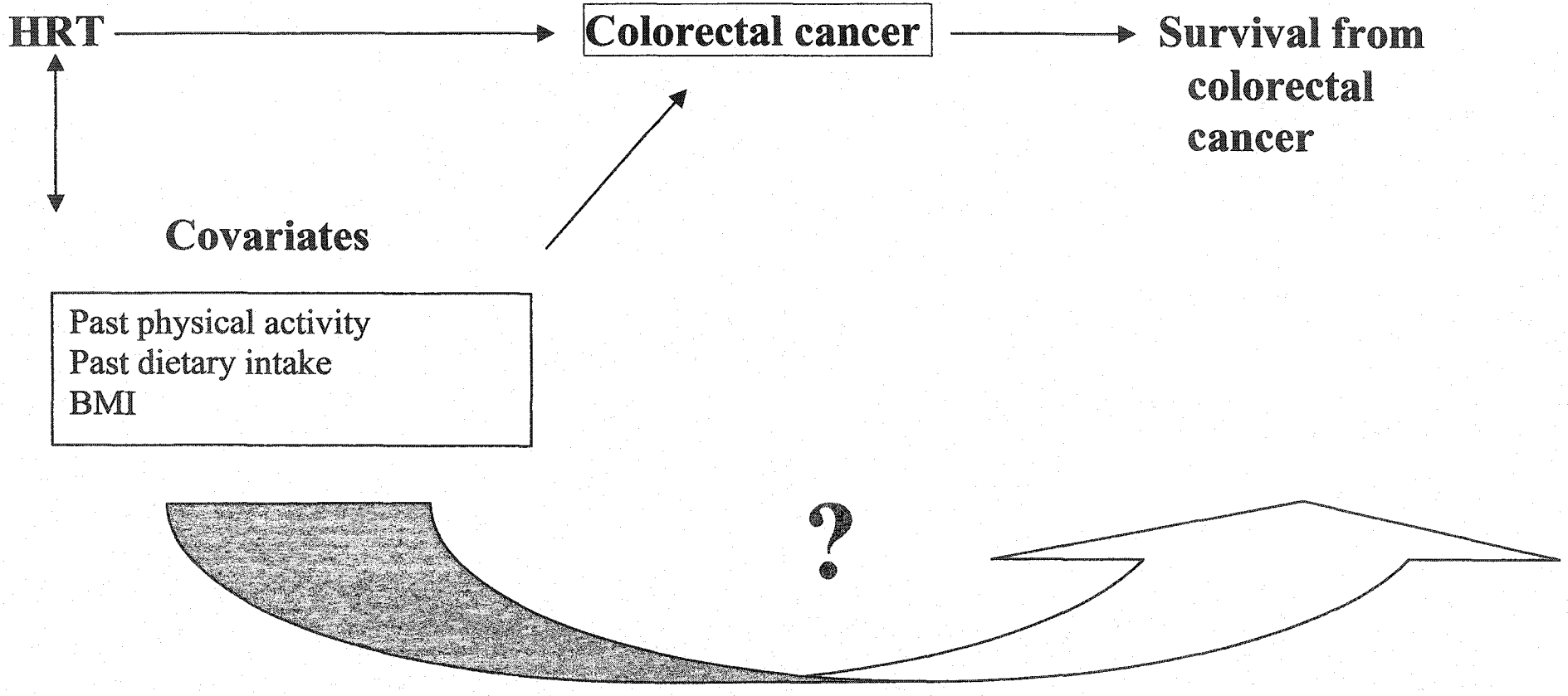
The question that this raises is whether or not cases alive in 1999, from whom we collected data on lifestyle, physical activity, anthropometrics and reproductive and medical history are similar in covariate patterns to the entire population of cases diagnosed in 1990 and later. This problem is illustrated in Figure 9.1. Several studies have provided evidence to suggest that HRT reduces the risk of mortality from colorectal cancer.[106,142-144] Slattery[142] has suggested that BMI, physical activity, dietary fiber, folate, sigmoidoscopy, NSAIDs, alcohol use and smoking history may even be effect modifiers for the association between HRT and survival. In the stratum more protective

for colorectal cancer, HRT had a greater effect in reducing the risk of dying (Chapter 2; Section 2.9). If indeed this is true, it would mean that we may be more likely to have cancer cases with more protective covariate patterns in our study population than in the base population. The covariate pattern of HRT exposed cases would reflect survival and appear to be more similar to HRT exposed controls than would truly exist if information on all cases had been available. Using this data would fail to adjust for the confounding effects of these protective factors in the association between HRT and incidence of colorectal cancer and could possibly even introduce bias depending on the magnitude of difference.

A remaining concern with the use of this two-phase sampling is whether or not the data collected from the Phase 2 subjects are representative of the base population of cases and controls. A problem can arise if the outcome, main exposure and confounding variables change over time. This could mean that the relationships between these variables could also change over time and thus adjustment using this data would bias the association between HRT and the incidence of colorectal cancer. During the past two decades changes have occurred in the prevalence of obesity, dietary and physical activity patterns of Canadians.[231,232] In addition, we know from our own descriptive study that the prevalence of HRT use has also changes over the past two decades and cancer statistics show that the incidence of colorectal cancer among women has been gradually decreasing. It is difficult to know how these changes would impact on our estimates of association between HRT and the incidence of colorectal cancer. We have minimized interference from these sources of variability by limiting our Phase 1 sample to individuals with index dates in 1990 or later. If other studies are to be conducted using this design the impact of changes in the prevalence of covariates should be examined.

Figure 9.1 Relationship of covariates to colorectal cancer incidence and survival from colorectal cancer.

Are covariate profiles of living cases with index dates in 1990 and later different from covariate profiles of those who have deceased?



Chapter 10. Conclusions

This concluding chapter summarizes the results in this doctoral research.

- More women of all ages are currently using HRT and continuing therapy for longer periods of time than a decade ago.

- Health-related differences between HRT users and nonusers are exhibited among cases and controls. Our results indicate that screening sigmoidoscopy modify the observed effect of HRT on colorectal cancer risk.

- The various definitions that have been used to define estrogen exposure can produce some variability in the estimates of the association between HRT and colorectal cancer risk when applied to data from a large detailed prescription drug dispensing database. The range in the results however is not as great as that reported in the literature where additional sources of variability play a role.

- Transdermal estrogen appears to reduce the risk of colorectal cancer by about 60 percent. This is the first time the route of estrogen administration has been examined for its independent effect on colorectal cancer risk and our work demonstrates the importance of taking into consideration the mode of delivery and possibly other aspects of formulation in the study of the effect of HRT on colorectal cancer risk.

- The population-based two-phase case-control study design is an appealing design that appears to have potential for the study of questions where traditional observational and experimental designs have been inadequate. The major limitation is poor response rates during Phase 2 of the study. Pilot testing and identification of successful incentive strategies for recruitment are required before extensive use of this design can be made.

- Our results are consistent with about a 20% risk reduction of colorectal cancer with oral HRT use. The results suggest that the protective effect of HRT appears to be stronger among women under 70 years of age.

This thesis does not provide a definitive answer to the question of whether or not HRT is protective for colorectal cancer. Our results for the effect of transdermal estrogen, however, are particularly convincing and biologically plausible. Our work has contributed to a better understanding of methodological and substantive issues related to the study of HRT and colorectal cancer risk. The insight gained from the results of this research will allow us to better plan the direction of future research in this challenging area of women's health.

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Appendix I

Main Questionnaire:
Medical, Reproductive and Sociodemographics Factors

SASKATCHEWAN-MCGILL
HORMONE REPLACEMENT THERAPY AND COLON CANCER STUDY

Interviewer ID No.: |__| **Study ID No.:** |__|__|__|__|__|__|__|

May I please speak to (subject's name)?

IF SUBJECT IS UNAVAILABLE:

Is there a convenient time I can call back? Date:_____ Time:_____

(If you are asked to identify yourself and the purpose of your call, give your full name and say that in previous communication with Mrs. _____ she indicated that this would be a good time to call her.)

IF TALKING TO SUBJECT:

Hello, I am (interviewer's first and last name), calling from Saskatchewan Health. I'm calling in connection with the Saskatchewan McGill Colon Cancer and Hormone Replacement Therapy Study.

We've received your signed consent agreeing to participate in the study and to conduct a telephone interview. I'd like to thank you for helping us with this important study. The information that you provide will be extremely valuable in increasing our understanding of women's health in relation to the use of hormones.

Is this a convenient time to carry out the telephone interview? - It'll take about 30 minutes.

IF NO: Is there a more convenient time I can call back? Date:_____ Time:_____

IF NO: Reason for refusal: _____

IF YES: As described in the pamphlet you received in the mail **(Hormone Replacement Therapy and Colon Cancer Study)**, we are carrying out a survey to study the extent to which women use postmenopausal hormones and some other medications. We are interested in knowing whether these medications play a role in the development of large bowel cancer in women. We are also studying how dietary intake, physical activity, and other lifestyle and reproductive factors are associated with the development of large bowel cancer.

Have you had a chance to complete the LIFE EVENTS CALENDAR (LEC)?

IF YES: OK, please have it handy during the interview, it'll help you answer the questions I'll be asking you.

IF NO: Would you like to complete the LEC before we do the interview or continue without it?

IF SUBJECT WANTS TO COMPLETE CALENDAR:

When would you like me to call you back? Date:_____ Time:_____

IF SUBJECT AGREES TO CONTINUE WITH INTERVIEW:

I'd like to emphasize that your replies will be kept completely confidential and I would also recommend that you not use a cell phone for this interview for reasons of confidentiality. To begin, I would like to verify your name and date of birth:

Subject's Name

_____ _____

First Name Last Name

Note to interviewers: If the subject has questions with regard to the completion of the self-administered questionnaires please tell her that you'll address them at the end of the interview.

SASKATCHEWAN-MCGILL
HORMONE REPLACEMENT THERAPY AND COLON CANCER

Interviewer ID No.: |__| **Index Date:** |__|__|__| 19|__|__| **Study ID No.:** |__|__|__|__|__|__|__|
mmm year

Some of the questions I will be asking you about your medical history and drug use refer to specific five year periods in the past. You may write them down if you wish. The four five-year periods are:

1. 19|__|__| to 19|__|__|
2. 19|__|__| to 19|__|__|
3. 19|__|__| to 19|__|__|
4. 19|__|__| to 19|__|__|

1st Data Entry: Date: |__|__| |__|__|__| 2000 **Interviewer ID No:** |__|
dd mmm

2nd Data Entry: Date: |__|__| |__|__|__| 2000 **Interviewer ID No:** |__|
dd mmm

1. DESCRIPTIVE INFORMATION

1.1 Present age of subject: |__|__| years old

1.2 D.O.B. |__|__| |__|__|__| 19|__|__|
dd mmm year

1.3 Reason for discrepancy in D.O.B.: _____

1.4 Is the subject deaf?

☐1 Yes ☐2 No IF YES, DO NOT INTERVIEW

1.5 Is the subject demented?

☐1 Yes ☐2 No IF YES, DO NOT INTERVIEW

1.6 Can the subject speak English?

☐1 Yes ☐2 No IF NO, DO NOT INTERVIEW

1.7 Interview:

☐1 accepted ☐2 refused ☐3 subject deaf, demented, unable to speak English, deceased, location unknown (exclusion criteria)

☐4 Unable to contact subject

2. DATE AND TIME OF INTERVIEW:

Date: |__|__| |__|__|__| 2000 Time |__|__|:|__|__| (24 hour system)
dd mmm year

3. MEDICAL HISTORY

Now I will ask you some questions about your medical history.

3.0 Prior to |__|__|__| 19|__|__|, (*the index date*), had you ever had a cancer diagnosis? **IF NO, OR UNKNOWN GO TO Q. 3.2.**	Yes ☐1 No ☐2 Unknown ☐3
3.1 IF YES: What type of cancer did you have? Was it…	
a) Cancer-in-situ of the cervix? *(It would have been treated by local treatment to the cervix rather than hysterectomy.)*	Yes ☐1 No ☐2 Unknown ☐3
b) Did you have skin cancer other than melanoma? (*Types: basal cell carcinoma, squamous cell carcinoma.*)	Yes ☐1 No ☐2 Unknown ☐3
c) Other, please specify:	
d) When was the cancer diagnosed?	Date: |__|__|__| 19|__|__| Unknown ☐3
3.2 Prior to |__|__|__| 19|__|__|, (*the index date*), had you ever had a colonoscopy or a sigmoidoscopy? (*If the subject doesn't know what this is explain that it's having a tube or scope inserted into the rectum to examine the large bowel.)* **IF NO GO TO Q. 4.0**	Yes ☐1 No ☐2 Unknown ☐3
IF YES: **3.2a** When did you have this done?	Date |__|__|__| 19|__|__| Unknown ☐3
3.3 a During this procedure did you have polyps removed from your bowel?	Yes ☐1 No ☐2 Unknown ☐3
IF YES: **3.3 b** When was this done?	Date |__|__|__| 19|__|__| Unknown ☐3

4. REPRODUCTIVE HISTORY

Now I will ask some questions about your reproductive history. This information is needed to further our understanding of important issues concerning women's health.

4.0 Can you recall your age when you had your first menstrual period?	Yes ☐1 No ☐2 Unknown ☐3
4.1 IF YES: At what age? *(If the subject reports 2 possible years, take the mid-point of the years and round up.)*	Age: |__|__|
4.2 a Have you reached menopause (change of life)? **IF NO GO TO Q. 4.3**	Yes ☐1 No ☐2 Unknown ☐3
IF YES:	
4.2 b Can you recall when you had your last menstrual period? **IF NO GO TO Q. 4.5a**	Yes ☐1 No ☐2 Unknown ☐3
4.2 c When was that?	Date |__|__|__| 19|__|__|
4.2 d How old were you then? **GO TO Q. 4.5a**	Age: |__|__|
4.3 Are you still menstruating? **If YES GO TO Q. 4.5a**	Yes ☐1 No ☐2
IF NO:	
4.4 When did you last have a period?	Date |__|__|__| 19|__|__| Unknown ☐1
4.4 a Are you pregnant? **IF NO GO TO Q. 4.5 a**	Yes ☐1 No ☐2 Unknown ☐3
4.4 b IF YES: Is this your first pregnancy? **If NO GO TO Q. 4.5 b**	Yes ☐1 No ☐2
IF YES GO TO Q. 5.0 (FAMILY HISTORY)	

4.5 a Have you ever been pregnant? — Yes □1 No □2

If NO GO TO Q. 4.7 a

4.5 b How many times, including pregnancies which did not come to term. — Number of times ______

4.6 a Could you please tell me the month and year of all your deliveries for pregnancies that lasted 6 months or more beginning with the first. *(Please check all options that apply)*

Delivery Dates mmm/year	Full Term	Still Born	Miscarriage	Singleton
________ 19______	Yes□1 No□2	Yes□1 No□2	Yes□1 No□2	Yes□1 No□2
________ 19______	Yes□1 No□2	Yes□1 No□2	Yes□1 No□2	Yes□1 No□2
________ 19______	Yes□1 No□2	Yes□1 No□2	Yes□1 No□2	Yes□1 No□2
________ 19______	Yes□1 No□2	Yes□1 No□2	Yes□1 No□2	Yes□1 No□2
________ 19______	Yes□1 No□2	Yes□1 No□2	Yes□1 No□2	Yes□1 No□2
________ 19______	Yes□1 No□2	Yes□1 No□2	Yes□1 No□2	Yes□1 No□2
________ 19______	Yes□1 No□2	Yes□1 No□2	Yes□1 No□2	Yes□1 No□2
________ 19______	Yes□1 No□2	Yes□1 No□2	Yes□1 No□2	Yes□1 No□2
________ 19______	Yes□1 No□2	Yes□1 No□2	Yes□1 No□2	Yes□1 No□2
________ 19______	Yes□1 No□2		Yes□1 No□2 Yes□1 No□2	
Yes□1 No□2				
________ 19______	Yes□1 No□2	Yes□1 No□2	Yes□1 No□2	Yes□1 No□2
________ 19______	Yes□1 No□2	Yes□1 No□2	Yes□1 No□2	Yes□1 No□2

4.6 b So your last delivery (for pregnancy 6 months or more) was in? — ________ 19______

4.7 a Have you had your uterus surgically removed (*hysterectomy*)? — Yes □1 No □2 Unknown □3

IF NO OR UNKNOWN GO TO Q. 4.8 a

4.7 b IF YES: When did you have your surgery? — Date ________ 19______ Unknown □3

4.7 c How old were you? — Age: ______

(4.7 d Interviewer please indicate whether this was prior to ________ 19______ (the index date).) — Yes □1 No □2 Unknown □3

4.7 e What was the medical reason for your hysterectomy? ***(Interviewer please be sure to write reason if known by subject.)*** — Cancer □1 Other □2 Unknown □3

____

4.8 a Have you had one or both ovaries removed prior to ________ 19______? (*the index date*) — Yes □1 No □2 Unknown □3

IF NO GO TO Q. 5.0

4.8 b IF YES: When did you have this surgery and how old were you? — Date ________ 19______ Age: ______ Unknown □3

4.8 c Did you have both ovaries or just one removed? — Single □1 Both □2 Unknown □3

4.9 d What was the medical reason for having one or both of your ovaries removed?

____

5. FAMILY HISTORY

Next I will ask you some questions about your family history of colon cancer. Please remember that this information will be kept completely confidential.

5.0 Because we need to learn about hereditary factors, we need to know if you were adopted? **IF NO GO TO Q. 5.2**	Yes ☐1 No ☐2 Unknown ☐3
5.1 IF YES: Do you have information on the medical background of your biological family? **IF NO ASK ABOUT CHILDREN ONLY IN Q. 5.2.**	Yes ☐1 No ☐2
5.2 Have any of your parents, siblings or children been diagnosed with colon cancer? **IF NO GO TO Q. 6.**	Yes ☐1 No ☐2 Unknown ☐3
5.3 IF YES: Which ones have been diagnosed with colon cancer?	Mother: Yes ☐1 No ☐2 Unknown ☐3 Age at diagnosis: ____ Unknown ☐3 Father: Yes ☐1 No ☐2 Unknown ☐3 Age at diagnosis: ____ Unknown ☐3 Sister (s): Yes ☐1 No ☐2 Unknown ☐3 Age (s) at diagnosis: ____ ; ____ Unknown ☐3 Brother (s): Yes ☐1 No ☐2 Unknown ☐3 Age (s) at diagnosis: ____ ; ____ Unknown ☐3 Children: Yes ☐1 No ☐2 Unknown ☐3 Age (s) at diagnosis: ____ ; ____ Unknown ☐3

6. ANTHROPOMETRIC DATA

Now I will ask you a few questions about your weight history.

6.0 What is the most you've ever weighed, not counting weight during pregnancy?

Kg Lbs |__|__|__|
☐1 ☐2 Unknown ☐3

6.1 What has been your lowest body weight since age 25?

Kg Lbs |__|__|__|
☐1 ☐2 Unknown ☐3

6.2 Has your weight been stable (± 2 kg/ ± 5 lbs) for most of your adult life after age 25?

Yes No Unknown
☐1 ☐2 ☐3

6.3 What was your usual body weight during the five year period between 19|__|__| and 19|__|__| *(6-10 years prior to the index date)* ? We are interested only in the weight you maintained for the longest period of time during that time.

Kg Lbs |__|__|__|
☐1 ☐2 Unknown ☐3

6.4 How tall are you?

Cm Feet/Inches Unknown
☐1 ☐2 ☐3

|__|__|__|cm |__|__|in.

7. TOBACCO

Now I will ask you some questions about use of tobacco

7.0 Have you ever smoked cigarettes?
IF NO GO TO Q. 8.0

Yes No
☐1 ☐2

7.1 Have you ever smoked cigarettes for more than 1 year?
IF NO GO TO Q. 8.0

Yes No
☐1 ☐2

7.2 **IF YES:** Could you please describe your smoking pattern before |__|__|__| 19|__|__| (*the index date*). I'd like to know the age at which you started and the age at which you had stopped (and if you had stopped for any period of time equivalent to at least a year). |__|__| (subject's age at index date)

From age	To age	Average number per day
|__|__|	|__|__|	|__|__|
|__|__|	|__|__|	|__|__|
|__|__|	|__|__|	|__|__|
|__|__|	|__|__|	|__|__|
|__|__|	|__|__|	|__|__|
|__|__|	|__|__|	|__|__|

8. ALCOHOL

Now I will ask you about your use of alcohol in the past.

8.0 Have you consumed an alcoholic beverage on more than a dozen separate occasions during your lifetime? **IF NO GO TO Q. 9.0**	Yes ☐1 No ☐2 Unknown ☐3
8.1 During the five year period 19____ to 19____ (*immediately preceding the index date*) how frequently did you consume an alcoholic beverage? **8.2** On these occasions, on average, how many drinks did you consume? *(One drink = one pint of beer, one 4oz or 125 ml glass of wine, sherry, port or vermouth; 1 oz. or 30 ml hard liquor (1 shot). Express subject's intake in these units.)*	Per/week ☐1 Per/month ☐2 Per/year ☐3 Unknown ☐4 |_|_|_| # of days/category Unknown ☐3 |_|_|_| # of drinks/occasion
8.3 During the five year period 19____ to 19____ (*preceding the index date by 6-10 years*) how frequently did you consume an alcoholic beverage? **8.4** On these occasions, on average, how many drinks did you consume?	Per/week ☐1 Per/month ☐2 Per/year ☐3 Unknown ☐4 |_|_|_| # of days/category Unknown ☐3 |_|_|_| # of drinks/occasion
8.5 During the five year period 19____ to 19____ (*preceding the index date by 11-15 years*) how frequently did you consume an alcoholic beverage? **8.6** On these occasions, on average, how many drinks did you consume?	Per/week ☐1 Per/month ☐2 Per/year ☐3 Unknown ☐4 |_|_|_| # of days/category Unknown ☐3 |_|_|_| # of drinks/occasion
8.7 During the five year period 19____ to 19____ (*preceding the index date by 16-20 years*) how frequently did you consume an alcoholic beverage? **8.8** On these occasions, on average, how many drinks did you consume?	Per/week ☐1 Per/month ☐2 Per/year ☐3 Unknown ☐4 |_|_|_| # of days/category Unknown ☐3 |_|_|_| # of drinks/occasion

9. POSTMENOPAUSAL HORMONES

Next I would like to ask you if you ever used hormone replacement therapy.

9.0 Were you ever prescribed hormones for at least three months after menopause by a doctor before ____ 19 ___ *(the index date)*? **IF NO GO TO Q. 9.2**	Yes ☐1 No ☐2 Unknown ☐3
9.1 a **IF YES:** Was it prescribed to treat symptoms of menopause?	Yes ☐1 No ☐2 Unknown ☐3
9.1 b Was it prescribed to prevent or treat osteoporosis?	Yes ☐1 No ☐2 Unknown ☐3
9.1 c Was it prescribed to prevent cardiovascular disease?	Yes ☐1 No ☐2 Unknown ☐3
9.1 d Did the prescription include estrogen?	Yes ☐1 No ☐2 Unknown ☐3
9.1 e Did the prescription include progesterone? **GO TO Q. 9.4**	Yes ☐1 No ☐2 Unknown ☐3
9.2 **IF NO:** Had you considered taking hormones? **IF NO GO TO Q. 10**	Yes ☐1 No ☐2 Unknown ☐3
9.3 a **IF YES:** Was your decision to **NOT** take hormones due to concerns about your health? **IF NO GO TO Q. 10**	Yes ☐1 No ☐2
9.3 b **IF YES:** What type of health concerns? **GO TO Q. 10**	Please specify: _____

Interviewer ID No.: |__| **Index Date:** |__|__|__| 19|__|__| (mmm, year) **1st Data Entry ID No.:** |__| **2nd Data Entry ID No.:** |__|

9.4. Please list the name(s) of the drug(s), strength and dosage form, the calendar year(s) in which they were first prescribed and the total duration of time for which you were treated with the drug.

Drug Name	Strength	Form (pill, cream, injection, patch)	Drug Code (see code sheet Appendix I)	Year Prescribed	Duration (months)	Did you take the hormones as prescribed?
			|__|__|__|__|	19 |__|__|	|__|__|__|	Yes ☐1 No ☐2 Unknown ☐3
			|__|__|__|__|	19 |__|__|	|__|__|__|	Yes ☐1 No ☐2 Unknown ☐3
			|__|__|__|__|	19 |__|__|	|__|__|__|	Yes ☐1 No ☐2 Unknown ☐3
			|__|__|__|__|	19 |__|__|	|__|__|__|	Yes ☐1 No ☐2 Unknown ☐3
			|__|__|__|__|	19 |__|__|	|__|__|__|	Yes ☐1 No ☐2 Unknown ☐3
			|__|__|__|__|	19 |__|__|	|__|__|__|	Yes ☐1 No ☐2 Unknown ☐3
			|__|__|__|__|	19 |__|__|	|__|__|__|	Yes ☐1 No ☐2 Unknown ☐3
			|__|__|__|__|	19 |__|__|	|__|__|__|	Yes ☐1 No ☐2 Unknown ☐3
			|__|__|__|__|	19 |__|__|	|__|__|__|	Yes ☐1 No ☐2 Unknown ☐3
			|__|__|__|__|	19 |__|__|	|__|__|__|	Yes ☐1 No ☐2 Unknown ☐3
			|__|__|__|__|	19 |__|__|	|__|__|__|	Yes ☐1 No ☐2 Unknown ☐3
			|__|__|__|__|	19 |__|__|	|__|__|__|	Yes ☐1 No ☐2 Unknown ☐3
			|__|__|__|__|	19 |__|__|	|__|__|__|	Yes ☐1 No ☐2 Unknown ☐3
			|__|__|__|__|	19 |__|__|	|__|__|__|	Yes ☐1 No ☐2 Unknown ☐3
			|__|__|__|__|	19 |__|__|	|__|__|__|	Yes ☐1 No ☐2 Unknown ☐3
			|__|__|__|__|	19 |__|__|	|__|__|__|	Yes ☐1 No ☐2 Unknown ☐3

9.5 If you did not take the hormones as prescribed, why not?

a) Difficulty remembering to take HRT. Yes ☐1 No ☐2 Unknown ☐3

b) Did not tolerate HRT. Yes ☐1 No ☐2 Unknown ☐3

10. USE OF ORAL CONTRACEPTIVES

10.0 Had you ever been prescribed oral contraceptives (OC's) before |__|__|__| 19 |__|__| *(the index date)*

Yes ☐1 No ☐2 Unknown ☐3

10.1 IF YES: please list the name(s) of the OC(s), the calendar year(s) and months in which they were first prescribed and the total duration of time you took them. *(For each drug that the subject mentions write the name of the drug, afterwards find the code on the list of OC's).*

Drug Name	Drug Code (Appendix II)	Month and Year Prescribed	Duration (months)
	|__|__|__|__|	|__|__|__| 19 |__|__|	|__|__|__|
	|__|__|__|__|	|__|__|__| 19 |__|__|	|__|__|__|
	|__|__|__|__|	|__|__|__| 19 |__|__|	|__|__|__|
	|__|__|__|__|	|__|__|__| 19 |__|__|	|__|__|__|
	|__|__|__|__|	|__|__|__| 19 |__|__|	|__|__|__|
	|__|__|__|__|	|__|__|__| 19 |__|__|	|__|__|__|
	|__|__|__|__|	|__|__|__| 19 |__|__|	|__|__|__|
	|__|__|__|__|	|__|__|__| 19 |__|__|	|__|__|__|
	|__|__|__|__|	|__|__|__| 19 |__|__|	|__|__|__|
	|__|__|__|__|	|__|__|__| 19 |__|__|	|__|__|__|
	|__|__|__|__|	|__|__|__| 19 |__|__|	|__|__|__|
	|__|__|__|__|	|__|__|__| 19 |__|__|	|__|__|__|
	|__|__|__|__|	|__|__|__| 19 |__|__|	|__|__|__|
	|__|__|__|__|	|__|__|__| 19 |__|__|	|__|__|__|
	|__|__|__|__|	|__|__|__| 19 |__|__|	|__|__|__|

11. HISTORY OF NSAIDS DRUG EXPOSURES

The last group of drugs I would like to ask you about are two products that may be bought over-the-counter or with a prescription. I will ask you about your use of these drugs during the four five year periods which we discussed earlier. Once again the four five-year periods are:

11.0 Subject's index date:

|__|__|__| 19|__|__|
mmm year

11.1 Five year periods preceding the index date

1.19|__|__| to 19|__|__| *(Assume these dates are*
2.19|__|__| to 19|__|__| *from Jan. 1 to Dec. 31)*
3.19|__|__| to 19|__|__|
4.19|__|__| to 19|__|__|

The two drugs are ibuprofen and acetylsalicylic acid (Aspirin). They may be used to relieve pain and fever. They can also be used to relieve symptoms of illness, joint pains, toothaches, headaches, menstrual cramps, or pain from accidental injuries or from surgery, including dental surgery. These drugs are sold under various brand names. I will read to you a list of the more common brand names. Please listen carefully and tell me if you have used any of these drugs in the past. If I have missed any products that you think may include acetylsalicylic acid - sometimes called Aspirin or ASA – please tell me about them.

The more common brand names for Ibuprofen are:

Medication	Code	Medication	Code
Actiprofen (200mg)	IB200	Medipren (200mg)	IB200
Advil (200mg)	IB200	Motrin (200mg)	IB200
Apo-ibuprofen (200mg)	IB200	Novo-profen (200mg)	IB200
Ibuprofen (200mg)	IB200		

The more common brand names for acetylsalicylic acid or Aspirin are:

Medication	Code	Medication	Code
ASA – many companies produce generic ASA or acetylsalicylic acid products such as Safeway, Shopper's Life Brand & so on	AT325	Darvon N Compound (375 mg-Rx only)	AT375
		Ecotrin (325 mg)	AT325
		(650 mg)	AT650
AC&C (325 mg)	AT325	Entrophen (325 mg: brown)	AT325
AC with codeine (375 mg)	AT375	(500 mg: pink)	AT500
(500 mg)	AT500	(650 mg: orange)	AT650
Anacin (325 mg)	AT325	(975 mg: yellow)	AT975
(500 mg)	AT500	Excedrin (325 mg)	AT325
Anacin with Codeine (325 mg)	AT325	Fiorinal (330mg – Rx only)	AT330
Ancasal with Codeine (325 mg)	AT325	Midol (486 mg)	AT486
(375 mg)	AT375	Norgesic (385 mg)	AT385
Apo-Asen (325 mg)	AT325	Norgesic Forte (770 mg)	AT770
(650 mg)	AT650	Novasen (325mg)	AT325
Arthrinol (500 mg)	AT500	(650 mg)	AT650
Arthrisin (325 mg)	AT325	Phenaphen (325 mg – Rx only))	AT325
(650 mg)	AT650	Robaxisal (325 mg)	AT325
Arthritic Pain (650 mg)	AT650	Robaxisal C (325 mg)	AT325
Ascriptin (300 mg)	AT300	Sal Infant (150 mg)	AS150
Aspergum (225 mg)	AG225	Sal Adult (650 mg)	AS650
(325 mg)	AG325	Supasa (160 mg)	AS160
Bayer Aspirin (325 mg)	AT325	(320 mg)	AS320
Bayer Aspirin with Stomach Guard (325 mg)	AT325	(640 mg)	AS640
Bayer Aspirin Extra Strength (500 mg)	AT500	Talwin Compound (390 mg – Rx only)	AT390
Astria-SR (650 mg)	AT650	Tecnal (330 mg – Rx only)	AT330
Baby Aspirin (80 mg)	AT080	217 (325 mg)	AT325
Bufferin (325 mg)	AT325	217 Strong (500 mg)	AT500
Bufferin Extra Strength (500 mg)	AT500	222 (375 mg)	AT375
Children's Size Aspirin (80 mg)	AT080	222 Forte (500 mg)	AT500
C2 (325 mg)	AT325	282 (375 mg – Rx only)	AT375
C2 with Codeine (325 mg)	AT325	292 (375 mg – Rx only)	AT375
Coricidin (325 mg)	AT325	293 (375 mg – Rx only)	AT375
Coricidin D (325 mg)	AT325	692 (375 mg – Rx only)	AT375
Coryphen (325 mg)	AT325	Upsarin (500 mg)	AT500
(650 mg)	AT650		

11.2 During the five year period 19____ to 19____, (*immediately preceding the index date*), did you use IBUPROFEN?

Yes ☐1 No ☐2 Unknown ☐3

IF YES, please list the names

Product Name	Strength	Product Code	Pills/Day on Days When Used	Total Number of Days Use In 5 year Period

11.3 During the five year period 19 ____ to 19 ____, (*preceding the index date by 6-10 years*), did you use IBUPROFEN

Yes ☐1 No ☐2 Unknown ☐3

IF YES, please list the names

Product Name	Strength	Product Code	Pills/Day on Days When Used	Total Number of Days Use In 5 year Period

11.4 a During the five year period 19____ to 19____, (*immediately preceding the index date*), did you use ASPIRIN (*mention brand names used*)

Yes ☐1 No ☐2 Unknown ☐3

11.4 b Sources of Apririn: Prescription only ☐1 OTC only ☐2 Both prescription and OTC ☐3

IF YES, please list the names

Product Name	Strength	Product Code	Pills/Day on Days When Used	Total Number of Days Use In 5 year Period

11.5 a During the five year period 19____ to 19____, (*preceding the index date by 6-10 years*), did you use ASPIRIN (*mention brand names used*)

Yes ☐1 No ☐2 Unknown ☐3

11.5 b Sources of Apririn: Prescription only ☐1 OTC only ☐2 Both prescription and OTC ☐3

IF YES, please list the names

Product Name	Strength	Product Code	Pills/Day on Days When Used	Total Number of Days Use In 5 year Period

11.6 a During the five year period 19____ to 19____, (*preceding the index date by 11-15 years*), did you use ASPIRIN (*mention brand names used*)

Yes ☐1 No ☐2 Unknown ☐3

11.6 b Sources of Apririn: Prescription only ☐1 OTC only ☐2 Both prescription and OTC ☐3

IF YES, please list the names

Product Name	Strength	Product Code	Pills/Day on Days When Used	Total Number of Days Use In 5 year Period

11.7 a During the five year period 19____ to 19____, (*preceding the index date by 16-20 years*), did you use ASPIRIN (*mention brand names used*)

Yes ☐1 No ☐2 Unknown ☐3

11.7 b Sources of Apririn: Prescription only ☐1 OTC only ☐2 Both prescription and OTC ☐3

IF YES, please list the names

Product Name	Strength	Product Code	Pills/Day on Days When Used	Total Number of Days Use In 5 year Period

mmm year **2nd Data Entry ID No.:** |__|

12. SOCIOECONOMIC STATUS

Now, I will ask you some questions about your personal background, similar to questions that you may have been asked on a census. Please remember that your replies will be kept completely confidential and that the information you give will be used only for medical research.

12.0 Were you born in Canada? Yes ☐1 No ☐2 Unknown ☐3

12.1 IF NO: please specify what country you were born in. _____

12.2 What was your Marital Status as of |__|__|__| 19|__|__| (*index date)*?

☐1 Single (never married) ☐3 Common law ☐5 Separated or divorced

☐2 Married ☐4 Widowed ☐6 Unknown

12.3. What was the highest level of education that you completed as of |__|__|__| 19|__|__| (*index date)*?

☐1 None ☐3 High School ☐5 University attended: degree not obtained

☐2 Elementary School ☐4 Trade/Technical School/College ☐6 University: degree obtained ☐7 Unknown

12.4. In what type or size of community did you live in as of |__|__|__| 19|__|__| (*index date)*?

☐1 Rural ☐2 In a small city ☐3 In a large City ☐4 Unknown

12.5. As of |__|__|__| 19|__|__| (*index date)* did you own, rent or board (*live with others without paying rent*) in the dwelling in which you lived?

☐1 Own ☐2 Rent ☐3 Board ☐4 Unknown

12.6 a Are you an Aboriginal person, that is Metis, First Nations or Inuit? Yes ☐1 No ☐2 Unknown ☐3 ☐4 Refuses to respond

12.6 b IF NO: Canadians belong to many ethnic or cultural groups, such as Chinese, French, or Ukrainian. On coming to Canada, to which ethnic or cultural group did you or your ancestors belong? _____

12.7 As of |__|__|__| 19|__|__| (*index date)* do you know which of the following five income brackets would best describe your family's total annual income? Yes ☐1 No ☐2 Unknown ☐3 ☐4 Refuses to respond

☐1 < $20,000 / year
☐2 $20,000 - $35,000
☐3 $35,000 - $50,000
☐4 $50,000 - $75,000
☐5 > $75,000
☐6 Refuses to respond

13. INTERVIEWER'S ASSESSMENT OF INTERVIEW	
13.1 Total duration of interview to this point (Time ____:____ 24 hour system)	Total minutes ____
13.2 Assessment of Quality of Interview	Reliable ☐1 Doubtful ☐2 Unreliable ☐3

14. SELF-ADMINISTERED QUESTIONNAIRES	
IF QUESTIONNAIRES HAVE BEEN RETURNED -- REVIEW IF NECESSARY THEN GO TO Q. 14.3.	
14.1 Have you had a chance to complete the FOOD (BLOCK DIET) QUESTIONNAIRE?	Yes ☐1 No ☐2
IF YES:	
14.1a Were you able to complete all the questions?	Yes ☐1 No ☐2
14.1b Did you encounter any difficulty in answering the questions? *Respond to subjects questions with regard to the questionnaire*	Yes ☐1 No ☐2
14.2 Have you had a chance to complete the ACTIVITY QUESTIONNAIRE?	Yes ☐1 No ☐2
IF YES:	
14.2a Were you able to complete all the questions?	Yes ☐1 No ☐2
14.2b Did you encounter any difficulty in answering the questions? *Respond to participant's questions with regard to the questionnaire*	Yes ☐1 No ☐2
14.3 Did you find the Life-Events Calendar useful?	Yes ☐1 No ☐2
14.4 IF AT LEAST ONE OF THE QUESTIONNAIRES NOT COMPLETED: Can we call back when we've received your questionnaire(s) if we need to verify anything with you?	Yes ☐1 No ☐2
14.4 a IF THE SUBJECT REFUSES TO COMPLETE THE QUESTIONNAIRES: Can you tell me why you've chosen not to complete the questionnaires?	
a) too lengthy and time consuming:	Yes ☐1 No ☐2
b) too difficult to understand questions	Yes ☐1 No ☐2
c) difficult to read of poor eyesight	Yes ☐1 No ☐2
d) Other, please specify:	_____

THANK PARTICIPANT FOR HER TIME AND CONTRIBUTION TO OUR STUDY!

Time ____:____ 24 hour system Total minutes since Question 13.1 ____

Appendix II

Physical Activity Questionnaire

RECORD OF OCCUPATIONAL ACTIVITIES FROM «L_5YR2» TO «U_5YR2» THAT IS FROM AGE «L_AGE» TO AGE «U_AGE»

In the following table please list any paid or volunteer jobs you may have had **for at least 8 hours a week for 4 months of the year** from **age «L_AGE» to age «U_AGE».** Beginning with **«L_5YR2»** and ending with **«U_5YR2»,** please describe any job(s) you had, the age you started and the age you ended doing that particular job. For each job we also need to know the number of months per year, the number of days per week, the number of hours per day and the *level of the activity. **FOR EXAMPLE:** *A woman who worked as a Meals-on-Wheels volunteer for 2 **hours** a day, 5 **days** per week for the **entire 5 year period** would record this activity as appears in the table below. She would also list any other jobs if applicable.*

No.	Description of Occupational Activity	Age Started	Age Ended	No. of Months/Year	No. of Days/Week	Average Amount of Time/Day		*Level of Activity (1, 2, 3, 4)
						Hours	Minutes	
e.g.	*Meals-on-Wheels volunteer*	*«L_AGE»*	*«U_AGE »*	*12*	*5*	*2*		*2*
1								
2								
3								
4								
5								
6								

*** Levels of occupational activities are given below with some examples of activities you might have participated in – you may have been involved in others. Please list any you may have done from «L_5YR2» to «U_5YR2».**

1 = Jobs that require light physical activity such as desk work, typing, computer work, reading, light office work, driving a car or tractor, milking by machine, playing a musical instrument, shoe repair.

2 = Jobs that require moderate physical activity with no increase in heart rate and no perspiration such as standing or slow walking, lifting or carrying light objects up to 5 lbs, farming (feeding animals, milking by hand, fixing fences), sales or stock clerking.

3 = Jobs that require hard physical activity that would increase the heart rate slightly and cause light perspiration such as continuous walking, carrying light loads (5 to 10 lbs), farming (shoveling grain), construction work.

4 = Jobs that require very hard physical activity that increase the heart rate substantially and cause heavy sweating: such as rapid walking, carrying heavy loads (greater than 10 lb), mainly outdoor activity, digging ditches, barn cleaning.

PLEASE RETURN BY MAIL WHEN COMPLETED.

Office Use: INT # ___ «INDEX_YR»/«INDEX_MON» «STUDYID»

RECORD OF HOUSEHOLD ACTIVITIES FROM «L_5YR2» TO «U_5YR2» THAT IS FROM AGE «L_AGE» TO AGE «U_AGE»

In the following table we would like you to list any household or gardening activities you may may have engaged in for **at least 7 hours per week for at least 2 months** from **age «L_AGE» to age «U_AGE».** Again, please start with **«L_5YR2»** and end with **«U_5YR2».** It may help you to think about a typical day you might have had during that period of time. Then think about how many hours of household, gardening or yard work you had done on a typical day. **FOR EXAMPLE:** *A woman who spends **an average of 1 hour and 30 minutes everyday** in meal preparation would enter a record as appears in the table below. She would also list any other activities if applicable.*

No.	Description of Household Activity	Age Started	Age Ended	No. of Months/ Year	No. of Days/Week	Average Amount of Time/Day		*Level of Activity (1, 2, 3, 4)
						Hours	Minutes	
e.g.	*cooking*	*«L_AGE»*	*«U_AGE»*	*12*	*7*	*1*	*30*	*1*
1								
2								
3								
4								
5								
6								

*** Levels of household activities are given below with some examples of activities you might have participated in – you may have b**

involved in others. Please list any you may have done from «L_5YR2» to «U_5YR2».

1 = Light activities such as cooking, ironing, sewing, light auto repair, indoor painting, typing, wallpapering, writing.

2 = Moderate activities that do not require much physical effort such as pushing a stroller with child, sweeping, mopping, vacuuming, cleaning windows, scraping paint, plastering, painting outside, planting seeds, clipping hedges, raking, mowing lawn with a power mower.

3 = Hard activities that are not exhausting, increase the heart rate slightly and may cause some light perspiration such as carrying a child 5 to 10 lbs, scrubbing floors, shoveling snow or dirt, mowing lawn with a nonpower mower.

4 = Very hard activities that increase the heart rate and cause heavy sweating such as those requiring lifting, moving heavy objects, rubbing vigorously for long periods, carrying a child greater than 10 lbs, chopping wood, digging with heavy tools.

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RECORD OF EXERCISE/SPORTS ACTIVITIES FROM «L_5YR2» TO «U_5YR2» THAT IS FROM AGE «L_AGE» TO AGE «U_AGE»

In the following table please list any exercise or sports activities that you did **at least 4 times per year** from age «L_AGE» to age «U_AGE». Beginning with «L_5YR2» and ending with «U_5YR2» please list the number of times per day, of days per week, of weeks per month, of months per year, the average amount of time spent per day and the *level of the activity. (If you walked or biked to work, please report this activity as reported for the other exercise/sports activities.) **FOR EXAMPLE:** *A woman who cross-country skis **once a day, for 2 days every second weekend, 3 months of the year** would record the information as it appears in the table below. She would also list any other activities if applicable.*

No.	Description of Exercise/Sports Activity	Age Started	Age Ended	No. of Times /Day	No. of Days /Week	No. of Weeks /Month	No. of Months /Year	Average Amount of Time/Day		*Level of Activity (1, 2, 3, 4)
								Hours	Minutes	
e.g.	*cross-country skiing*	*«L_AGE»*	*«U_AGE»*	*1*	*2*	*2*	*3*	*2*		*4*
1										
2										
3										
4										
5										

*** Levels of exercise/sports activities are given below with some examples of activities you might have participated in – you may have been involved in others. Please list any you may have done from «L_5YR2» to «U_5YR2».**

1 = Light activities such as leisurely walking, bowling, golfing with a power cart, curling (if position is skip).

2 = Moderate activities that require minimal effort such as brisk walking, throwing frisbee, cycling leisurely on level ground, swimming laps (easy effort), weight lifting, sailing, golf without a power cart, curling (if position is not skip).

3 = Hard activities that are not exhausting, that increase the heart rate slightly and may cause some light perspiration such as brisk walking uphill, backpacking (on level ground), climbing hills, brisk cycling on level ground without loosing breath, tennis, downhill skiing, swimming laps (moderate effort), aerobics, ballroom or square-dancing, roller skating, ice skating, badminton.

4 = Very hard activities that increase heart rate and cause heavy sweating such as jogging, climbing hills while carrying a load, cycling (racing), field hockey, handball, cross country skiing, skindiving, squash, continuous lap swimming (maximum effort exerted), basketball.

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SUMMARY ACTIVITY QUESTIONS

1. Thinking about the things you did **in general at work**, during the time period **«L_5YR2» to «U_5YR2»**, how would you rate yourself as to the amount of physical activity you had participated in compared with others of your age and sex? (Please compare yourself to women of your age group in general rather than just women in your immediate circle of friends.)
Please circle number below which applies to you:

    1. Much more active
    2. Somewhat more active
    3. About the same
    4. Somewhat less active
    5. Much less active
    6. Not applicable

2. Now, thinking about the things you did **outside of work**, during the time period **«L_5YR2» to «U_5YR2»**, how would you rate yourself as to the amount of physical activity you had compared with others your age and sex?
Please circle number below which applies to you:

    1. Much more active
    2. Somewhat more active
    3. About the same
    4. Somewhat less active
    5. Much less active

3. Did you regularly engage in strenuous activity or hard physical labour?
Please circle number below which applies to you:

    1. Yes (if yes please answer question #4)
    2. No (if no please stop here)

4. Did you exercise or labour at least three times a week?
Please circle number below which applies to you:

    1. Yes
    2. No

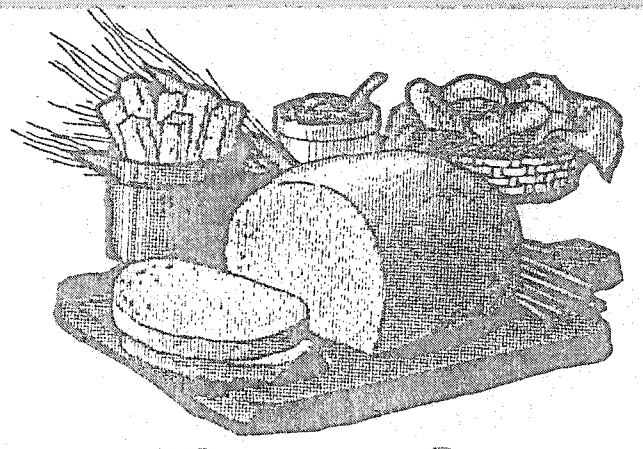
Appendix III

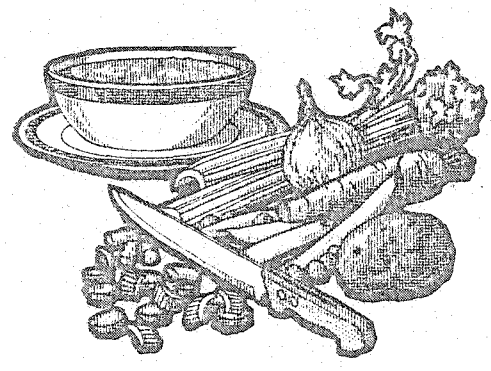
Block Food Frequency Questionnaire

Saskatchewan Health-McGill University

Hormone Replacement Therapy and Colon Cancer Study

Appendix III





FOOD QUESTIONNAIRE

We would like you to complete this questionnaire providing answers about your usual food intake for the 5-year period indicated in the box to the right. Although your intake might have varied from year to year during this time, please describe the intake that **'on average'** fits the pattern.

You will need to take about 30 minutes to complete this form. Please follow these instructions:

- Answer each question as best you can – estimate if you aren't sure.
- Use only an HB (#2), ordinary pencil.
- Be certain to completely blacken in each of your answers, and erase completely if you make any changes.
- Do not make any other marks on this form.
- If you wish to make comments, please use a separate piece of paper.

ID NUMBER

AGE

WEIGHT pounds

HEIGHT ft. in.

HHHQ.BLOCK.95.M Phone or fax: (510) 704-8514

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0343

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During the 5-year period specified on page 1 were you taking any vitamins or minerals regularly (at least once a week for a period of 3 months)?

○ No ○ Yes, fairly regularly ○ Yes, but not regularly

IF YES, WHAT DO YOU TAKE FAIRLY REGULARLY?

VITAMIN TYPE	HOW OFTEN				FOR HOW MANY YEARS?					
	DON'T TAKE	1-3 DAYS PER WEEK	4-6 DAYS PER WEEK	EVERY DAY	LESS THAN 1 YR.	1 YEAR	2 YEARS	3-4 YEARS	5-9 YEARS	10+ YEARS
Multiple Vitamins										
Regular Once-A-Day, Centrum, or Thera type	○	○	○	○	○	○	○	○	○	○
Antioxidant combination type	○	○	○	○	○	○	○	○	○	○
Single Vitamins (not part of multiple vitamins)										
Vitamin A (not beta-carotene)	○	○	○	○	○	○	○	○	○	○
Beta-carotene	○	○	○	○	○	○	○	○	○	○
Vitamin C	○	○	○	○	○	○	○	○	○	○
Vitamin E	○	○	○	○	○	○	○	○	○	○
Calcium or Tums	○	○	○	○	○	○	○	○	○	○
Iron	○	○	○	○	○	○	○	○	○	○
Folic acid, folate	○	○	○	○	○	○	○	○	○	○
Vitamin D	○	○	○	○	○	○	○	○	○	○

If you took multiple vitamins:

Did you usually take types that ○ contain minerals (iron, zinc, etc.) ○ do not contain minerals ○ Don't know

If you took Vitamin C or Vitamin E:

How many milligrams of **vitamin C** did you usually take, on the days you took it?

○ 100 ○ 250 ○ 500 ○ 750 ○ 1000 ○ 1500 ○ 2000 ○ 3000+

How many milligrams of **vitamin E** did you usually take, on the days you took it?

○ 100 ○ 200 ○ 300 ○ 400 ○ 600 ○ 800 ○ 1000 ○ 2000+

The next section is about your *usual* eating habits during the 5-year period specified on page 1.

FIRST: Mark the column to show HOW OFTEN, on the average, you ate the food during the specified 5-year period.

SECOND: Mark the column to show HOW MUCH you usually ate of each food.

- Sometimes the "how much" is asked as number of pieces, such as 1 egg, 2 eggs or 3 eggs. Mark your serving size as the number you usually ate ON THE DAYS YOU ATE IT.
- Sometimes the "how much" is asked as small-medium-large (S-M-L). A "medium" portion is shown for each food, but only as a guideline. The "medium" portion that will actually be used in the calculations is larger for men than for women, and larger for young people than for older people. Mark "small" if you think you usually ate a smaller portion of that food than other people of your age and sex. Mark "large" if you ate more of it than other people of your age and sex.

SAMPLE: This person ate one orange about twice a week, and ate a medium serving of other fruit about three times a week.

TYPE OF FOOD	HOW OFTEN								HOW MUCH			
	NEVER OR LESS THAN ONCE PER MONTH	1 PER MON.	2-3 PER MON.	1 PER WEEK	2 PER WEEK	3-4 PER WEEK	5-6 PER WEEK	EVERY DAY	MEDIUM SERVING	YOUR SERVING SIZE S	M	L
Oranges	○	○	○	○	●	○	○	○	1 medium	○ 1/2	● 1	○ 2
Other fruit	○	○	○	○	○	●	○	○	1/2 cup	○ S	● M	○ L

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TYPE OF FOOD	HOW OFTEN								HOW MUCH			
	NEVER OR LESS THAN ONCE PER MONTH	1 PER MON.	2-3 PER MON.	1 PER WEEK	2 PER WEEK	3-4 PER WEEK	5-6 PER WEEK	EVERY DAY	MEDIUM SERVING	YOUR SERVING SIZE S	M	L
EXAMPLE: Bananas	○	○	○	●	○	○	○	○	1 medium	○ 1/2	● 1	○ 2
Bananas	○	○	○	○	○	○	○	○	1 medium	○ 1/2	○ 1	○ 2
Apples, applesauce	○	○	○	○	○	○	○	○	1 medium	○ 1/2	○ 1	○ 2
Oranges (not including juice)	○	○	○	○	○	○	○	○	1 medium	○ 1/2	○ 1	○ 2
Grapefruit (not including juice)	○	○	○	○	○	○	○	○	1/2 medium	○ 1/4	○ 1/2	○ 1
Cantaloupe	○	○	○	○	○	○	○	○	1/4 medium	○ 1/8	○ 1/4	○ 1/2
Peaches, apricots (fresh, in season)	○	○	○	○	○	○	○	○	1 medium	○ 1/2	○ 1	○ 2
Peaches, apricots (canned or dried)	○	○	○	○	○	○	○	○	1 medium or 1/2 cup	○ S	○ M	○ L
Prunes, or prune juice	○	○	○	○	○	○	○	○	1/2 cup	○ S	○ M	○ L
Watermelon (in season)	○	○	○	○	○	○	○	○	1 slice	○ S	○ M	○ L
Strawberries, other berries (in season)	○	○	○	○	○	○	○	○	1/2 cup	○ S	○ M	○ L
Any other fruit, including kiwi, fruit cocktail, grapes, raisins, mangoes	○	○	○	○	○	○	○	○	1/2 cup	○ S	○ M	○ L
				1/ WEEK		3-4/ WEEK						
Fiber cereals like raisin bran, granola or shredded wheat	○	○	○	○	○	○	○	○	1 medium bowl	○ S	○ M	○ L
Sweetened cereals like frosted flakes	○	○	○	○	○	○	○	○	1 medium bowl	○ S	○ M	○ L
Other cold cereals like corn flakes or cheerios	○	○	○	○	○	○	○	○	1 medium bowl	○ S	○ M	○ L
Cooked cereal like oatmeal, oat bran or grits	○	○	○	○	○	○	○	○	1 medium bowl	○ S	○ M	○ L
Milk on cereal	○	○	○	○	○	○	○	○	1/2 cup	○ S	○ M	○ L
Breakfast bars, granola bars, power bars	○	○	○	○	○	○	○	○	1 serving	○ S	○ M	○ L
Breakfast shakes, diet shakes	○	○	○	○	○	○	○	○	1 serving	○ S	○ M	○ L
Pancakes or waffles	○	○	○	○	○	○	○	○	2 med.	○ 1	○ 2	○ 3
Eggs	○	○	○	○	○	○	○	○	1 egg=sml. 2 eggs=med.	① egg	② eggs	③ eggs
Egg substitutes, Egg Beaters, egg whites	○	○	○	○	○	○	○	○	2 eggs	① egg	② eggs	③ eggs
Sausage or bacon	○	○	○	○	○	○	○	○	2 patties or pieces	① piece	② pieces	③ pieces
Cottage cheese	○	○	○	○	○	○	○	○	1/2 cup	○ S	○ M	○ L
Other cheeses and cheese spreads (regular or lowfat)	○	○	○	○	○	○	○	○	2 slices or 2 ounces	○ 1	○ 2	○ 3
Yogurt, frozen yogurt (regular or lowfat)	○	○	○	○	○	○	○	○	8 oz. container	○ 5 oz.	○ 8 oz.	○ 10 oz.

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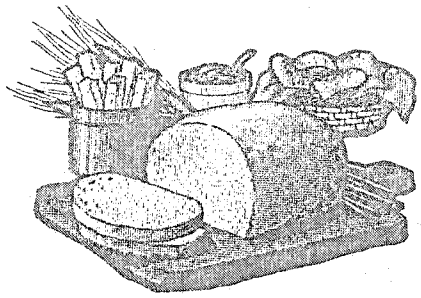
	HOW OFTEN								HOW MUCH			
	NEVER OR LESS THAN ONCE PER MONTH	1 PER MON.	2-3 PER MON.	1 PER WEEK	2 PER WEEK	3-4 PER WEEK	5-6 PER WEEK	EVERY DAY	MEDIUM SERVING	YOUR SERVING SIZE		
										S	M	L
VEGETABLES (fresh, frozen or canned, or in restaurants)												
String beans, green beans	○	○	○	○	○	○	○	○	1/2 cup	○	○	○
Peas	○	○	○	○	○	○	○	○	1/2 cup	○	○	○
Chili with beans (with or without meat)	○	○	○	○	○	○	○	○	1 cup	○	○	○
Other beans such as baked beans, pintos, kidney (not including soup)	○	○	○	○	○	○	○	○	3/4 cup	○	○	○
Corn	○	○	○	○	○	○	○	○	1/2 cup	○	○	○
Alfalfa sprouts, including on sandwiches	○	○	○	○	○	○	○	○	1/2 cup	○	○	○
Tomatoes, tomato juice	○	○	○	○	○	○	○	○	1 medium or 6 oz. glass	○	○	○
Salsa, ketchup, taco sauce	○	○	○	○	○	○	○	○	2 tablesp.	○	○	○
Broccoli	○	○	○	○	○	○	○	○	1/2 cup	○	○	○
Cauliflower or brussels sprouts	○	○	○	○	○	○	○	○	1/2 cup	○	○	○
Spinach (cooked or raw)	○	○	○	○	○	○	○	○	1/2 cup	○	○	○
Mustard greens, turnip greens, collards	○	○	○	○	○	○	○	○	1/2 cup	○	○	○
Cole slaw, cabbage	○	○	○	○	○	○	○	○	1/2 cup	○	○	○
Carrots, or mixed vegetables containing carrots	○	○	○	○	○	○	○	○	1/2 cup	○	○	○
Green salad	○	○	○	○	○	○	○	○	1 medium bowl	○	○	○
Salad dressing & mayonnaise (regular or lowfat)	○	○	○	○	○	○	○	○	2 tablesp.	○	○	○
French fries and fried potatoes	○	○	○	○	○	○	○	○	3/4 cup	○	○	○
White potatoes not fried, including boiled, baked, mashed and in potato salad	○	○	○	○	○	○	○	○	1 medium or 1/2 cup	○	○	○
Sweet potatoes, yams	○	○	○	○	○	○	○	○	1/2 cup	○	○	○
Any other vegetable, such as cooked onions, summer squash	○	○	○	○	○	○	○	○	1/2 cup	○	○	○
Butter, margarine or other fat added to veg., potatoes, etc.	○	○	○	○	○	○	○	○	2 pats	○	○	○
Tofu, bean curd	○	○	○	○	○	○	○	○	1/2 cup	○	○	○
Meat substitutes made from soy	○	○	○	○	○	○	○	○	1 cup or patty	○	○	○
	NEVER OR LESS THAN ONCE PER MONTH	1 PER MON.	2-3 PER MON.	1 PER WEEK	2 PER WEEK	3-4 PER WEEK	5-6 PER WEEK	EVERY DAY				

0343 PLEASE DO NOT WRITE IN THIS AREA

TYPE OF FOOD	HOW OFTEN								HOW MUCH			
	NEVER OR LESS THAN ONCE PER MONTH	1 PER MON.	2-3 PER MON.	1 PER WEEK	2 PER WEEK	3-4 PER WEEK	5-6 PER WEEK	EVERY DAY	MEDIUM SERVING	YOUR SERVING SIZE S	M	L
MEATS, SOUPS, PASTA												
Hamburgers, cheeseburgers	○	○	○	○	○	○	○	○	1 medium or 4 oz.	○	○	○
Burritos or tacos with meat or beans	○	○	○	○	○	○	○	○	1 medium or 2 small	○	○	○
Beef roasts, steaks, sandwiches	○	○	○	○	○	○	○	○	4 ounces	○	○	○
Liver, including chicken livers	○	○	○	○	○	○	○	○	4 ounces	○	○	○
Pork, including chops, roasts	○	○	○	○	○	○	○	○	2 chops or 4 ounces	○	○	○
Fried chicken	○	○	○	○	○	○	○	○	2 small or 1 large pce.	○	○	○
Chicken or turkey (roasted or broiled, including on sandwiches)	○	○	○	○	○	○	○	○	2 small or 1 large pce.	○	○	○
Chicken stew or mixed dish with chicken	○	○	○	○	○	○	○	○	1 cup	○	○	○
Fried fish or fish sandwich	○	○	○	○	○	○	○	○	4 ounces or 1 sandwich	○	○	○
Tuna, tuna salad, tuna casserole	○	○	○	○	○	○	○	○	1/2 cup	○	○	○
Oysters	○	○	○	○	○	○	○	○	5 pieces, 1/4 cup or 3 oz.	○	○	○
Shell fish, (shrimp, crab, lobster, etc.)	○	○	○	○	○	○	○	○	5 pieces, 1/4 cup or 3 oz.	○	○	○
Other fish (broiled or baked)	○	○	○	○	○	○	○	○	2 pieces or 4 ounces	○	○	○
Beef or vegetable stew or pot pie with carrots and other vegetables	○	○	○	○	○	○	○	○	1 cup	○	○	○
Spaghetti, lasagna, other pasta with tomato sauce	○	○	○	○	○	○	○	○	1 1/2 cups	○	○	○
Cheese dishes without tomato sauce, like macaroni and cheese	○	○	○	○	○	○	○	○	1 cup	○	○	○
Pasta salad, other pasta without tomato sauce	○	○	○	○	○	○	○	○	3/4 cup	○	○	○
Pizza	○	○	○	○	○	○	○	○	2 slices	① slice	② slices	③ slices
Hot dogs	○	○	○	○	○	○	○	○	2 hot dogs	① dog	② dogs	③ dogs
Ham, bologna, other lunch meats (regular or made with turkey)	○	○	○	○	○	○	○	○	2 slices or 2 ounces	① slice	② slices	③ slices
Vegetable soups with carrots or tomatoes, such as vegetable beef or tomato soup	○	○	○	○	○	○	○	○	1 medium bowl	○ S	○ M	○ L
Lentil, pea and bean soups	○	○	○	○	○	○	○	○	1 medium bowl	○ S	○ M	○ L
Other soups, like chicken noodle, mushroom, cup-a-soup, ramen	○	○	○	○	○	○	○	○	1 medium bowl	○ S	○ M	○ L
	NEVER OR LESS THAN ONCE PER MONTH	1 PER MON.	2-3 PER MON.	1 PER WEEK	2 PER WEEK	3-4 PER WEEK	5-6 PER WEEK	EVERY DAY				

PLEASE DO NOT WRITE IN THIS AREA

TYPE OF FOOD	HOW OFTEN									HOW MUCH				
	NEVER OR LESS THAN ONCE PER MONTH	1 PER MON.	2-3 PER MON.	1 PER WEEK	2 PER WEEK	3-4 PER WEEK	5-6 PER WEEK	EVERY DAY	2+ PER DAY	MEDIUM SERVING	YOUR SERVING SIZE S	M	L	XL
BREADS, SNACKS, SPREADS (Please note that the categories for these columns are different.)														
Biscuits, muffins, (including fast foods)	○	○	○	○	○	○	○	○	○	1 medium piece	○ S	○ M	○ L	
Bagels, English muffins, hamburger buns	○	○	○	○	○	○	○	○	○	1 medium piece	○ 1/2	○ 1	○ 2	
White bread, French or Italian bread, including sandwiches	○	○	○	○	○	○	○	○	○	# slices **each time**	① slice	② slices	③ slices	
Dark bread, such as whole wheat, rye, pumpernickel	○	○	○	○	○	○	○	○	○	# slices **each time**	① slice	② slices	③ slices	
Corn bread, corn muffins	○	○	○	○	○	○	○	○	○	# pieces **each time**	① piece	② pieces	③ pieces	
Tortillas	○	○	○	○	○	○	○	○	○	# slices **each time**	① tort.	② 2 tort.	③ 3 tort.	④ 4 tort.
Snacks like nachos with cheese, potato skins with topping	○	○	○	○	○	○	○	○	○	1 medium serving	○ S	○ M	○ L	○ XL
Salty snacks, like potato chips, corn chips, popcorn, crackers	○	○	○	○	○	○	○	○	○	2 handfuls or 1 cup	○ S	○ M	○ L	○ XL
Peanuts, peanut butter	○	○	○	○	○	○	○	○	○	2 tablesp.	○ S	○ M	○ L	
Margarine on bread or rolls	○	○	○	○	○	○	○	○	○	2 pats	○ S	○ M	○ L	
Butter on bread or rolls	○	○	○	○	○	○	○	○	○	2 pats	○ S	○ M	○ L	
Rice, or dishes made with rice	○	○	○	○	○	○	○	○	○	3/4 cup	○ S	○ M	○ L	○ XL
SWEETS		1/ MON.		1/ WEEK				1/ DAY						
Ice cream (regular or lowfat)	○	○	○	○	○	○	○	○	○	1 scoop or 1/2 cup	○ S	○ M	○ L	○ XL
Doughnuts, pastry	○	○	○	○	○	○	○	○	○	1 piece	○ S	○ M	○ L	○ XL
Cookies or cake (regular or lowfat)	○	○	○	○	○	○	○	○	○	3-5 cookies	○ 1-2	○ 3-5	○ 6-7	○ 8+
Pumpkin pie, sweet potato pie	○	○	○	○	○	○	○	○	○	1 medium slice	○ S	○ M	○ L	
Other pies	○	○	○	○	○	○	○	○	○	1 medium slice	○ S	○ M	○ L	
Chocolate candy, candy bars	○	○	○	○	○	○	○	○	○	1 small bar or 1 oz.	○ S	○ M	○ L	
Other candy or jelly	○	○	○	○	○	○	○	○	○	3 pieces or 1 tblsp.	○ S	○ M	○ L	



TYPE OF FOOD	HOW OFTEN									HOW MUCH			
	NEVER OR LESS THAN ONCE PER MONTH	1-3 PER MON	1 PER WEEK	2-4 PER WEEK	5-6 PER WEEK	1 PER DAY	2-3 PER DAY	4 PER DAY	5+ PER DAY	MEDIUM SERVING	YOUR SERVING SIZE S	M	L
BEVERAGES (Please note that the categories for these columns are different.)													
Orange juice or grapefruit juice	○	○	○	○	○	○	○			6 oz. glass	○ 4 oz.	○ 6 oz.	○ 8 oz.
Apple juice, grape juice	○	○	○	○	○	○	○			6 oz. glass	○ 4 oz.	○ 6 oz.	○ 8 oz.
Whole milk (or chocolate whole milk), not including on cereal	○	○	○	○	○	○	○	○		8 oz. glass	○ 5 oz.	○ 8 oz.	○ 10 oz.
2% milk (or chocolate 2% milk), not including on cereal	○	○	○	○	○	○	○	○		8 oz. glass	○ 5 oz.	○ 8 oz.	○ 10 oz.
Skim milk, 1% milk, not including on cereal	○	○	○	○	○	○	○	○		8 oz. glass	○ 5 oz.	○ 8 oz.	○ 10 oz.
Kool-Aid, Hi-C, or other drinks with added vitamin C	○	○	○	○	○	○	○	○		8 oz. glass	○ 5 oz.	○ 8 oz.	○ 10 oz.
Snapple, Calistoga, sweetened bottled waters or iced teas	○	○	○	○	○	○	○	○		1 bottle	○ 8 oz.	○ 12 oz.	○ 16 oz.
Regular soft drinks (not diet soda)	○	○	○	○	○	○	○	○	○	12 oz. can or bottle	○ 8 oz.	○ 12 oz.	○ 16 oz.
Beer	○	○	○	○	○	○	○	○	○	12 oz. can or bottle	○ 8 oz.	○ 12 oz.	○ 16 oz.
Wine or wine coolers	○	○	○	○	○	○	○	○	○	1 medium glass	○ S	○ M	○ L
Liquor	○	○	○	○	○	○	○	○	○	1 shot	○ S	○ M	○ L
Coffee or tea	○	○	○	○	○	○	○	○	○	1 medium cup	○ S	○ M	○ L
Non-dairy creamer in coffee or tea	○	○	○	○	○	○	○	○	○	1 tablesp.	○ S	○ M	○ L
Cream (real) or Half-and-Half in coffee or tea	○	○	○	○	○	○	○	○	○	1 tablesp.	○ S	○ M	○ L
Milk in coffee or tea	○	○	○	○	○	○	○	○	○	1 tablesp.	○ S	○ M	○ L
Sugar or honey in coffee or tea or on cereal	○	○	○	○	○	○	○	○	○	2 teaspoons	○ S	○ M	○ L

ON AVERAGE, about how many times a year during the specified 5-year period, did you eat from take-out or other types of restaurants? Remember to think about all meals (breakfast, lunch, dinner or snacks).

RESTAURANT FOOD	AVERAGE NUMBER OF VISITS PER YEAR						
	NEVER	1-4 TIMES PER YEAR	5-11 TIMES PER YEAR	1-3 TIMES A MONTH	ONCE A WEEK	2-4 TIMES A WEEK	ALMOST EVERY DAY
Fried chicken	○	○	○	○	○	○	○
Burgers	○	○	○	○	○	○	○
Pizza	○	○	○	○	○	○	○
Chinese, Indian, Thai or other Asian food	○	○	○	○	○	○	○
Mexican food	○	○	○	○	○	○	○
Fried fish	○	○	○	○	○	○	○
Char broiled or BBQ'd meat	○	○	○	○	○	○	○

DO NOT WRITE IN THIS SHADED AREA

SUMMARY QUESTIONS	AVERAGE USE DURING THE 5 YEAR PERIOD								
	LESS THAN ONCE PER WEEK	1-2 PER WEEK	3-4 PER WEEK	5-6 PER WEEK	1 PER DAY	1 1/2 PER DAY	2 PER DAY	3 PER DAY	4+ PER DAY
a. How often did you usually use fat or oil in cooking?	○	○	○	○	○	○	○	○	○
b. About how many servings of vegetables did you usually eat, not counting salad or potatoes?	○	○	○	○	○	○	○	○	○
c. About how many servings of fruit did you usually eat, not counting juices?	○	○	○	○	○	○	○	○	○
d. About how many servings of cold cereal did you usually eat?	○	○	○	○	○	○	○	○	○
e. About how many glasses of milk (or chocolate milk) did you usually drink?	○	○	○	○	○	○	○	○	○

What kinds of fat did you *usually* use in cooking (to fry or stir-fry)? Mark the one or two you used most often.

○ Don't know ○ Pam or no oil ○ Lard, fatback, baconfat ○ Crisco shortening
○ Stick margarine ○ Soft tub margarine ○ Low calorie margarine
○ Butter ○ Olive oil or canola oil ○ Corn oil, vegetable oil

What kinds of fat did you *usually* add to vegetables, potatoes, etc.? Mark the one or two you used most often.

○ Don't add fat ○ Lard, fatback, baconfat ○ Crisco shortening
○ Stick margarine ○ Soft tub margarine ○ Low calorie margarine
○ Butter ○ Whipped butter ○ Olive oil

When you ate the following foods, how often did you eat a low-fat or non-fat version of that food?

Cheese	○ Always low-fat	○ Sometimes	○ Rarely low-fat
Ice cream or yogurt	○ Always low-fat	○ Sometimes	○ Rarely low-fat
Salad dressing	○ Always low-fat	○ Sometimes	○ Rarely low-fat
Cake or cookies	○ Always low-fat	○ Sometimes	○ Rarely low-fat

Again referring to the specified 5-year period:

How often did you add salt (add salt at the table) to your food?	○ Seldom	○ Sometimes	○ Often
How often did you eat the skin on chicken?	○ Seldom	○ Sometimes	○ Often
How often did you eat the fat on meat?	○ Seldom	○ Sometimes	○ Often
How did you like your meat cooked?	○ Rare	○ Medium	○ Well done

About how many times did you make major changes in your diet in order to lose weight or for some other reason, during the specified 5-year period?

○ Never ○ 1 - 5 ○ 6 - 10 ○ More than 10 times

If you answered 1-5 or more times in the above question, did you make one of the following permanent dietary changes? Mark all that apply.

○ Became vegetarian ○ Lost weight permanently ○ Not applicable
○ Reduced red meat intake ○ Some other reason

With regard to these changes did your answers in the questionnaire reflect your diet as it was?

○ Before the changes ○ After the changes ○ In transition

During that period of time was your health

○ Excellent ○ Very Good ○ Good ○ Fair ○ Poor

THANK YOU VERY MUCH FOR TAKING THE TIME TO FILL OUT THIS QUESTIONNAIRE

Please take a moment to fill in any questions you may have skipped.

PLEASE DO NOT WRITE IN THIS AREA

0343

Appendix IV

Life Events Calendar

Saskatchewan Health

3475 Albert Street
Regina, SK S4S 6X6
Phone: (306) 787-4491
Fax: (306) 787-3237

The Saskatchewan Health - McGill University

Hormone Replacement Therapy and Colon Cancer Study

INSTRUCTIONS FOR LIFE EVENTS CALENDAR AND QUESTIONNAIRES

The following table of life events is a calendar we are asking you to complete ***before you complete the mailed questionnaire and respond to questions during the telephone interview.*** It will help you organise important events that have occurred in your life. By referring to these events as you complete the questionnaire and answer questions during the upcoming interview you will be better prepared to recall various past events and activities (diet, activity, use of medication and general health).

Beginning at age 20, write down the year in which an event occurred in the first column, and your age at the time of the event in the second column. List the places where you lived in the third column, and important **life events and state of health** in the fourth column (e.g. weddings, births, deaths, age when you started to menstruate, age when you stopped menstruating). In the fifth column, identify any years in which you took birth control pills and/or hormones to treat menopause.

In the sixth column, list all of your **education** and **jobs** held, along with your age at the time of starting and stopping these activities. For the **Food Questionnaire** and the **Activity Questionnaire,** we have specified a five-year period of time that we're interested in. While filling out the calendar it might help to keep this period of time in mind. Please think about whether your jobs during this time required activity that was sedentary (mainly sitting), light activity (mainly standing and some slow walking), moderate activity (continuous walking and carrying light loads of 5 to 10 lbs., light perspiration) or heavy activity (carrying loads of greater than 10 lbs., increased heart rate and heavy sweating). In the **Activity Questionnaire** we also ask about work that you did around your home.

Finally, in the last column, list all of the main leisure activities you engaged in, giving special attention to the period of time specified on the **Activity Questionnaire**. For exercise and sport activities, please think about the number of years you participated in these activities, and how often you engaged in them i.e. number of months per year, days per week and the amount of time in hours you spent at each session.

Please remember to include the following life events and activities in your outline:

- Education and jobs held*
- Any history of cancer in your immediate family members*
- Household, exercise and sports activities done during the specified period of time*
- Any doctors visits, tests or operations that you had to in order to check or treat your large intestine/bowel*

* These are questions about which you will be asked either in the mailed questionnaire or the telephone interview.

Using personal events such as weddings, births, deaths in the family and places lived in at different ages may help you to remember the above if you also use the calendar to record these items.

LIFE EVENTS CALENDAR

This is a shortened example of what a completed life events calendar might look like:

Year	Age	Where did you live?	Life Events	Hormone Use	Education and Job History	Main Physical Activities *
			(May include births, deaths, weddings, family cancer diagnosis, hospital stays, etc.)	(List use of birth control pills and any hormones taken during menopause)	(List when you did your education and/or all the jobs that you held)	
1960-62	20-22	*Saskatoon*			*College*	*Swimming*
1963	23	*Toronto*	*Get married*		*Start working as primary school teacher*	*Take up tennis*
1970	30	*Regina*	*First child is born*		*Stay at home mother*	*Housework/child care*
1973	33		*Second child is born*	*Start birth control pills*	*Stay at home mother*	*Same as above*
1984	44	*Regina*	*Father dies; mother diagnosed with colon cancer*	*Stop birth control pills; start estrogen replacement with progesterone*		*Start cross country skiing*
1992	52	*Calgary*	*Have first mammography*			*Build new garden*
1997	57		*First child is married*			

*Remember this **calendar is entirely optional and for your personal use only.** You do not have to fill it out but it will help you answer the questions that you will be asked at the time of your telephone interview. We will not be asking you about all of the details, but surveys have shown that in reviewing life events people start to remember more of their past. Please don't worry about areas of the calendar or years you leave blank.*

***You will only be asked to provide detailed activity information for a five- year period specified on your Activity Questionnaire.**

LIFE EVENTS CALENDAR

Please fill in all the important events in your life and personal history beginning at age 20. These reference points will be useful when answering the questions in the interview. You can fill in the calendar in whatever order is best for you.

Year	Age	Where did you live?	Life Events	Hormone Use	Education and Job History	Main Physical Activities
			(May include births, deaths, weddings, family cancer diagnosis, hospital stays, etc.)	(List use of birth control pills and hormones during menopause)	(List when you did your education and all the jobs that you held)	
	20					

Appendix V

Study Brochure and Letters For Recruitment

Appendix V

Saskatchewan Health

A Saskatchewan Health - McGill University Study

Lifestyle and Risk of Colon and Rectal Cancer in Women

SASKATCHEWAN CANCER AGENCY

Did you know that...

- ***colon and rectal cancers are the third cause of cancer death in women.***
- ***studies are being done to find out whether or not certain lifestyle factors such as diet, physical activity, and the use of some medications, prevent or cause colon and rectal cancers.***

Women need to get involved!

What is the Saskatchewan-McGill Lifestyle and Risk of Colon and Rectal Cancer in Women Study all about?

Researchers at **Saskatchewan Health**, the **Saskatchewan Cancer Agency** and **McGill University** are working together to study factors that may prevent colon and rectal cancer.

We are interested in whether or not diet, exercise and hormones like estrogen or Premarin are associated with colon and rectal cancer.

How can you help?

We need help from women:

- Who have or have had colon or rectal cancer.
- Who have never had colon or rectal cancer.
- Who have used hormones.
- Who have not used hormones.

How have women been selected for the study?

They have been selected using:

i) Information from the **Saskatchewan Prescription Drug Plan** about past use of hormones.

ii) Information from the records of the **Saskatchewan Cancer Agency** about colon and rectal cancer.

Information about past use of tests to detect colon and rectal cancers has also been collected from the **Saskatchewan Medical Services Plan** records.

The above information provided to the McGill University researchers DID NOT include your name and address. Only Saskatchewan Health and the Saskatchewan Cancer Agency know your name and address.

We are asking Saskatchewan women to help us in this study by agreeing to answer some questions over the telephone to provide us with more information. We are also asking women to respond to a mailed questionnaire that will take approximately one hour to complete.

A female Saskatchewan Health employee will conduct the telephone interview*. It will take about 30 minutes. In the mailed questionnaire and the interview you will be asked questions about such things as:

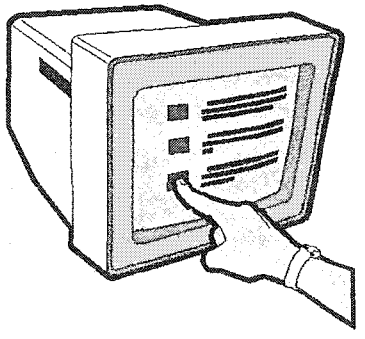
- use of Aspirin and other painkillers
- the number of children you have had
- use of the pill and other female hormones
- eating habits and physical activity
- whether any relatives have had colon and rectal cancer

** Long distance phone calls will be paid by us.*

Your decision to answer these questions is entirely up to you.

You do not have to participate in this study. If you decide to participate you may leave the study at any time, for any reason. Your decisions will not affect the health care that is available to you.

If you agree to participate, information you provide will be added to information collected from the **Saskatchewan Cancer Agency, Saskatchewan Prescription Drug Plan, and the Saskatchewan Medical Services Plan.** This will be done by **Saskatchewan Health**.



Nobody will be able to identify you by name when all the information is put together.

The results of the study will describe groups of people. No one person will be described.

Please read the enclosed consent form carefully and ***consider participating in this study.*** We believe the study will be of value to women in the future. We greatly appreciate your help.

Should you have any future questions about this study, please contact **Dr. MaryRose Stang** by mail or call collect during regular business hours.

Saskatchewan Health

3475 Albert Street
Regina, SK S4S 6X6
Phone: (306) 787-4491
Fax: (306) 787-3237

Participants may also contact the **Office of Research Services** at the University of Saskatchewan at (306) 966-4053 with regard to the rights of research subjects, and related concerns.

«First_Name» «Last_Name»
«Address»
«City» «Pr» «Postal_Cd»

Dear MRS. «Last_Name»:

Researchers at **Saskatchewan Health**, **Saskatchewan Cancer Agency** and **McGill University** are working together to study the effect of lifestyle and female hormones on the occurrence or prevention of colon cancer in postmenopausal women.

The enclosed pamphlet **Hormone Replacement Therapy and Colon Cancer Study** describes the study and the type of information we need from you. You are one of 1,200 women invited to participate in this study. The more women who participate, the better the study will be. Every person is important.

Please read the enclosed material carefully. ***If you agree to participate, please sign the consent form and return it in the envelope provided.*** *Please indicate the day of the week and the time of day that would be most convenient for you to be interviewed. Keep one copy of the consent form for your records.*

A diet and physical activity questionnaire will be mailed to you. We will also mail you a **Life Events Calendar** along with instructions for its completion. *The calendar will be for your use only.* Its purpose is to help you prepare for the telephone interview because many of the questions are about the past. After we have received a signed consent form, you will be contacted for the interview.

If you decide not to participate, please return the unsigned consent forms so we can remove your name from our list and you will not be contacted again. If you want more information or have any questions, please call me in Regina at (collect if long distance).

Sincerely,

MaryRose Stang

August 13, 1999

«First_Name» «Last_Name»
«Address»
«City» «Pr» «Postal_Cd»

Dear MRS. «Last_Name»:

We have received your signed consent form agreeing to participate in our **Hormone Replacement Therapy and Colon Cancer Study.** We would like to thank you for helping us with this very important research.

Please find enclosed the diet and activity questionnaires that we would like you to complete at home. They ask questions about your diet and activities in the past. To help you recall these past events I am including a **Life Events Calendar**. Use it only if you want to. It may help you remember your activities and habits so that you can answer the questions in the questionnaires and the interview more easily. Do not return this calendar to us. Keep it handy for the telephone interview.

Please fill out the questionnaires and return them to me in the enclosed stamped and addressed envelope. A researcher from Saskatchewan Health will be calling you in the next few weeks for the telephone interview. She will ask you questions about reproductive and family colon cancer history, past hormone use, and Aspirin use. If you have questions about the diet and activity questionnaires please feel free to ask the interviewer when she calls.

You may also call me with any questions you may have at (call collect if long distance). Thank you again for your help.

Sincerely,

MaryRose Stang

<Date>

«First_Name» «Last_Name»
«Address»
«City» «Pr» «Postal_Cd»

Dear MRS. «Last_Name»:

A couple of weeks ago, you were mailed information describing **The Hormone Replacement Therapy and Colon Cancer Study.** We have not received a response from you. If your consent form is in the mail, thank you. If not, we would like to ask you again to consider helping us with this very important research. **Please note that we are interested in women who have not used hormones or had colon cancer, as well as those who have.**

Please find enclosed another copy of the pamphlet and consent form that was sent before. In addition, we are sending you two questionnaires and a **Life-Events Calendar**. One questionnaire is about diet and the other is about physical activity. The Life-Events Calendar is included to help you complete the questionnaires and get ready for the telephone interview but it is entirely optional.

If you would like to take part in this study please sign the consent form and send it back in the small white addressed envelope as soon as possible. Send us the completed questionnaires in the large envelope after you have been interviewed. If you have any problems completing them the interviewer will be able to help you. Remember to tell us the day of the week and the time of day that you would like to be called for the telephone interview. ***Do not return the Life-Events Calendar*** and please have it handy for the interview.

If you decide not to participate please return the unsigned consent form and blank questionnaires. We will then remove your name from our list and not contact you again. If you need more information or have any questions, please call me in Regina at (call collect if long distance).

Sincerely,

MaryRose Stang

Appendix VI

Reprint of CMAJ Research Letter

Appendix

L02-040

SUBJECT: **Canadian Medical Association Journal**
***CMAJ* 22 January 2002; 166(2) pp 187-188**
Use of postmenopausal estrogen replacement therapy from 1981-1997

Dear Ms. Csizmadi:

Thank you for your correspondence dated 19 February 2002 requesting permission to photocopy the article as published in the *Canadian Medical Association Journal* for your thesis submission. I am pleased to confirm that the Canadian Medical Association (CMA), as copyright holder, grants you permission to reproduce this material as requested **(maximum 10 copies)**. As a courtesy, we also suggest that you seek permission from the author(s) directly. Please credit the original publication of the material as follows:

"Use of postmenopausal estrogen replacement therapy from 1981 to 1997"— Reprinted from, *CMAJ* 22 January 2002; 166(2) Page(s) 187-188 by permission of the publisher, © 2002 Canadian Medical Association

If you require further information or assistance, please do not hesitate to contact the undersigned.

Sincerely,

Janis Murrey

Research letter

Use of postmenopausal estrogen replacement therapy from 1981 to 1997

Ilona Csizmadi, Andrea Benedetti, Jean-François Boivin, James A. Hanley, Jean-Paul Collet

During the past 2 decades the health risks and benefits of estrogen replacement therapy (ERT) have been the focus of intensive research and scientific debate. Recommendations for its use by asymptomatic postmenopausal women are nevertheless still limited by many questions that remain unanswered.[1] Despite the uncertainty surrounding the overall impact of ERT on health, US data indicate that the prevalence of hormone use has been steadily increasing since the 1980s.[2] Longitudinal population-based data describing ERT use by postmenopausal women in Canada are lacking. We therefore examined the trends in the prevalence of estrogen use by peri- and postmenopausal women in Saskatchewan from 1981 to 1997.

We used Saskatchewan Health's computerized prescription drug plan database as the source of drug-dispensing information.[3] Women living in the province between 1981 and 1997 were selected from Saskatchewan Health records to participate in 2 population-based case–control studies,[4,5] and the control subjects formed a cohort of peri- and postmenopausal women for this analysis. At the time of sampling, the women were 45 years of age or older, did not have a diagnosis of cancer (except for non-melanoma skin cancer and cancer of the cervix in situ), were registered with Saskatchewan Health for at least 5 years and were eligible for out-patient prescription drug plan benefits.

The study was approved by the Research Ethics Committee of the Jewish General Hospital, the University Advisory Committee on Ethics in Human Experimentation of the University of Saskatchewan and the Data Access Review Committee of Saskatchewan Health. All patient identifiers in the data released by Saskatchewan Health were removed, and the data were limited to the variables required for the analysis.

The type, strength and quantities of estrogen dispensed to study subjects between 1976 and 1997 were compiled by Saskatchewan Health. For each woman in the study, estrogen dispensing data were available for at least 5 years beginning in 1976, or later if she had immigrated to the province at a later date, and were terminated at death, emigration from the province or the end of the case–control study, whichever came first.

The age-standardized prevalence rates of estrogen use were calculated for 1981, 1984, 1989, 1994 and 1997 using direct standardization. Saskatchewan census data from 1996 were used to provide the standard age distribution of women 45 years of age and older.[6] The age-specific proportions of women who had been dispensed at least one prescription of estrogen were also calculated for each of the 5 calendar years listed above.

The age-standardized prevalence of estrogen use increased substantially over time, from 5.1% in 1981, to 5.3% in 1984, 7.7% in 1989, 13.1% in 1994 and 15.4% in 1997. Increases in age-specific proportions of women re-

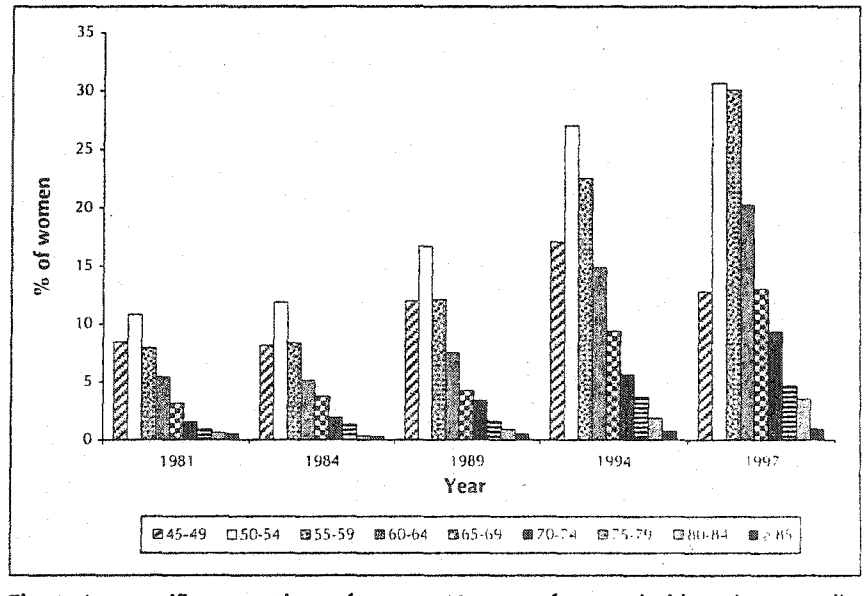


Fig. 1: Age-specific proportions of women 45 years of age and older who were dispensed at least one prescription of estrogen during 1981, 1984, 1989, 1994 and 1997.

ceiving at least one prescription of estrogen for the years 1981 (n = 28 261), 1984 (n = 29 594), 1989 (n = 29 708), 1994 (n = 27 240) and 1997 (n = 8836) are shown in Fig. 1. The highest prevalence of ERT use occurred among women 50 to 54 years of age and ranged from 10.8% [95% confidence interval [CI] 9.8–11.8] in 1981 to 30.6% [95% CI 24.7–36.5] in 1997. An increase in estrogen use over time, however, was apparent in all age groups, even in women over 65 years of age.

Our data demonstrate that important increases have occurred in the prevalence of estrogen use during the study period. As expected, peak estrogen use occurred consistently among women between the ages of 50 and 54 years, coinciding with the onset of menopausal symptoms for most women. With the exception of the prevention of osteoporotic bone fractures,[7] the role of ERT in the prevention of various chronic diseases has yet to be clearly defined. Results from the Heart and Estrogen/Progestin Replacement,[8] and the Estrogen Replacement and Atherosclerosis[9] studies have challenged the hypothesis that ERT reduces the risk of coronary artery disease in women with existing heart disease. Whether these findings affect women's decision-making with regard to the use of hormone replacement therapy will be of interest to clinicians.

This article has been peer reviewed.

Ms. Benedetti and Drs. Boivin, Hanley and Collet are with the Department of Epidemiology and Biostatistics, McGill University, Montreal, Que. Ms. Benedetti and Drs. Boivin and Collet are also with the Centre for Clinical Epidemiology and Community Studies, Sir Mortimer B. Davis–Jewish General Hospital, Montreal, Que. At the time of the study, Ms. Csizmadi was with the Department of Epidemiology and Biostatistics, McGill University, and the Centre for Clinical Epidemiology and Community Studies, Sir Mortimer B. Davis–Jewish General Hospital. She is currently with the Division of Epidemiology, Alberta Cancer Board, Calgary, Alta.

Competing interests: None declared.

Contributors: Ms. Csizmadi initiated the study, reviewed the pertinent literature, planned the design and data analysis, interpreted the results, drafted the initial manuscript and revised the final paper. Ms. Benedetti was responsible for data management and computer programming and contributed to the revising of the paper. Drs. Boivin, Hanley and Collet contributed to the study design and data analysis and to the revising of the paper.

Acknowledgements: Support for this work was provided by the National Cancer Institute (R01 CA78698-02), National Institutes of Health, United States. This study is based in part on data provided by the Saskatchewan Department of Health. The interpretation and conclusions contained herein do not necessarily represent those of the Government of Saskatchewan or the Saskatchewan Department of Health.

At the time of the study, Ms. Csizmadi was the recipient of a Doctoral Fellowship Award and Dr. Collet a Research Scientist Award from the Fonds de la Recherche en Santé du Québec.

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Appendix VII

Ethics Approval