Malignancy in Systemic Lupus Erythematosus

Sasha Bernatsky

Department of Epidemiology and Biostatistics

McGill University, Montreal

September, 2001

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements of the degree of Master's of Science.

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ACKNOWLEDGEMENTS

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OBJECTIVES: 1.To estimate cancer incidence in systemic lupus erythematosus (SLE) as compared to the general population. 2. To estimate the sensitivity and specificity of methods of cancer ascertainment. 3. To determine the prevalence of malignancy risk factors in SLE. METHODS: 1. We determined the incidence of malignancy in the Montreal General Hospital (MGH) lupus cohort, through linkage with the Quebec tumor registry. Standardized incidence ratios (SIRs) were generated, using Quebec population rates. In addition, a meta-analysis was performed by pooling data from eight cohort studies of malignancy in SLE. 2.We administered a postal survey to cohort members to determine risk factors for cancer and self-report of cancer occurrence. For dead or lost-to-follow-up patients, data was abstracted from charts. We calculated the sensitivity and specificity of self-report and chart review for cancer ascertainment, compared to registry linkage results. 3. Using the data collected on self-report and chart review, we compared risk factor prevalence within the MGH cohort to that of the Quebec population. RESULTS: 1. Observed cancers in our cohort were greater than what would be expected; for all cancers, the SIR was 1.8 (95% Confidence Interval 1.2-2.6). The meta-analysis SIR (for all malignancies) was 1.67 (1.42-1.94). Postal survey and chart review methods demonstrated high specificity. Sensitivity was imperfect, but did not greatly effect estimation of the SIR estimate. 3. Our lupus cohort had a distinct profile of risk factors for malignancy compared to the general population; differences included more prevalent nulliparity, obesity, and use of hormone replacement therapy. CONCLUSIONS: The risk of malignancy in SLE patients is increased. Risk factor profiles could influence the incidence of certain malignancies in SLE.

OBJECTIFS: 1. Estimer l'incidence du cancer chez des patients atteints de lupus érythémateux systémique. 2. Estimer la sensibilité et la spécificité de méthodes d'identification de cas de cancer. 3. Déterminer la prévalence de facteurs de risque de cancer chez des patients atteints de lupus érythémateux systémique. MÉTHODES : 1. Nous avons déterminé l'incidence du cancer dans la cohorte clinique de patients atteints de lupus érythémateux systémique de l'hôpital général de Montréal (MGH) par un raccordement de dossiers avec ceux du Fichier des tumeurs du Québec. Des rapports standardisés d'incidence (SIR) ont été estimés, en utilisant les taux de la population générale du Québec comme base de comparaison. En outre, une méta-analyse a été exécutée en mettant en commun les données de huit études. 2. Nous avons distribué un questionnaire postal aux membres de la cohorte pour déterminer la présence de facteurs de risque de cancer et le diagnostic de cancer. Pour les patients décédés et ceux perdus au suivi, nous avons obtenu les données requises à partir des dossiers cliniques. Nous avons calculé la sensibilité et la spécificité de ces méthodes de détermination du diagnostic de cancer, comparant les résultats à ceux obtenus à partir du raccordement des fichiers. 3. Nous avons comparé la prévalence de facteurs de risque dans la cohorte du MGH à celle de la population du Québec.
RÉSULTATS : 1. Notre cohorte présente une augmentation de la fréquence du cancer par rapport à ce qui serait attendu; pour tous les cancers le SIR était de 1,8 (intervalle de confiance à 95% : 1,2-2,6). Le SIR provenant de la méta-analyse (pour tous les cancers) était de 1,67 (1,42-1,94). 2. Les méthodes postales de détermination du cancer ont démontré une spécificité élevée. Les sensibilités étaient par contre imparfaites. 3. Notre cohorte de patients présentait un profil distinct de facteurs de risque pour le cancer en comparaison avec la population générale; parmi les différences on notait une fréquence plus élevée de nulliparité, d'obésité, et d'utilisation d'homothérapie pour la ménopause. CONCLUSIONS : Le risque de cancer chez les patients atteints de lupus érythémateux systémique est augmenté par rapport à celui de la population générale. Le profil de facteurs de risque a pu influencer l'incidence de certains cancers chez ces patients.

I. Introduction

This thesis examines the association of cancer with systemic lupus erythematosus. In this introduction, I explain the rationale for studying this topic. Next, in chapter II, I provide a review of the literature. In chapter III, I examine the hypothesis that cancer risk is increased in persons with systemic lupus erythematosus, and present data generated from the Montreal General Hospital (MGH) lupus cohort. Chapter III discusses the results of a meta-analysis that I performed by combining estimates of the standardized incidence ratio (for malignancies in systemic lupus erythematosus) from studies published to date on this subject. Chapter IV presents data on the sensitivity and specificity of different methods of cancer ascertainment, which was collected during our study of the malignancy incidence in systemic lupus erythematosus. In Chapter V, I will present estimates of the prevalence of risk factors for malignancy within the Montreal General Hospital Lupus Cohort and compare these to the prevalence of those factors within the general population. As well as discussing the significance of the results for each chapter, I will provide a final discussion in chapter VI, and end with a summary and conclusions.

Rationale:

Systemic lupus erythematosus is an autoimmune condition that affects young women primarily. Its effects can be devastating, and prior to the 1950's, people survived only a few years after diagnosis. Since then, new treatments have allowed the preservation of life for decades (1). Now that persons with systemic lupus erythematosus are living longer, it is imperative that questions about long-term morbidity are addressed. Clinical research has moved towards determining factors that may adversely affect long-term outcome. Much concern has arisen regarding the risk of diseases such as atherosclerosis, osteoporosis, and cancer in lupus patients.

II. Literature Review

In this literature review, I will first examine existing data on the cancer risk in systemic lupus erythematosus, and whether the data suggests that the incidence of specific subtypes of malignancies are increased in systemic lupus erythematosus as compared to the general population. I will then review what is known about the sensitivity and specificity of different methods of cancer ascertainment. Following this, my literature review will focus on risk factors for malignancy, and I will present what is known to date about the prevalence of these factors in systemic lupus erythematosus.

i) Is Cancer Risk Increased in Systemic Lupus Erythematosus?

The association of cancer with autoimmune disease has been under investigation for several years. Since the 1970's, reports have appeared suggesting increased cancer risk in autoimmune diseases such as the inflammatory myopathies, Sjogren's syndrome, and systemic sclerosis (2-5). In systemic lupus erythematosus, the magnitude of cancer risk remains unknown, despite significant concern that the baseline immune system defects in systemic lupus erythematosus increase cancer susceptibility. Supporting this concern is the New Zealand Black (NZB) mouse model of systemic lupus erythematosus; these animals exhibit a marked predisposition to lymphoreticular malignancy (6). Genetic traits that may predispose both to malignancy and autoimmune disease are also under investigation in humans. For example, chronic lymphocytic leukemia, particularly the B cell type, has frequently been associated with immunologic abnormalities among B cell lymphocytic leukemia patients or their family members, including the development of systemic lupus erythematosus (7-11) .

There are several unresolved issues concerning cancer risk in systemic lupus erythematosus. The first question, and the point on which published research has focused thus far, is whether the estimated malignancy risk for lupus patients is actually increased compared to the general population. The earliest clinical evidence of an association of cancer with systemic lupus erythematosus came from case and case series reports (12-15). Since then, cohort studies (16-22) have produced some evidence

of increased cancer risk in systemic lupus erythematosus patients, although the conclusions have not been uniform (23-25).

Attempts to accurately estimate the cancer risk in systemic lupus erythematosus have most often been done with clinical cohorts (18-25). In a clinical cohort, the subjects have a definite diagnosis of systemic lupus erythematosus, either by American College of Rheumatology criteria (26) or by clinical judgment (generally, this would mean a patient has definite signs of lupus, such as classic kidney involvement, but doesn't fit exact American College of Rheumatology criteria . As systemic lupus erythematosus is a relatively rare condition (incidence has been estimated at 4.8 per 100,000 (1)) the size of these cohorts have been small, (ranging from 116 (25) to 724 (24)). In contrast, two authors (16; 17) have attempted to generate a much larger cohort, through assembling the names of individuals discharged from hospital with a diagnosis of systemic lupus erythematosus , and then linking these names to the national cancer registry. Though these cohorts were much larger in size than the clinical cohorts (for example, Mellamkjaer et al.'s cohort (16) included 1,585 subjects) the validity of the systemic lupus erythematosus diagnosis might be questionable, as this diagnosis was not necessarily made according to American College of Rheumatology criteria or confirmed by a sub-specialist. Also, even if the diagnoses of systemic lupus erythematosus were accurate, a cohort assembled in this fashion would select for a particular group of systemic lupus erythematosus patients (those that had been admitted to hospital), not the entire population of systemic lupus erythematosus patients.

Of all the above mentioned studies, six studies ascertained cancer incidence by linkage of lupus cohort and cancer registry data(16-20; 25); two through chart review [22][24]; one by patient interview (23); and one with a combination of chart review and patient self-report (21). As will be discussed later (see chapter V. The Sensitivity and Specificity of Postal Survey and Chart Review Methods Of Cancer Ascertainment), reliance solely on either self-report or chart review may introduce error.

Thus, limitations in these clinical series and cohort studies have been small sample size

(13-25), inclusion of a cohort not representative of the general systemic lupus erythematosus population (16;17), reliance solely on either self-report or chart review (21-24) without registry linkage, and absence of an appropriate age-adjusted population comparison group (13-15).

Considering only the results from clinical cohorts, there have been eight studies published (18-25). The authors of these studies calculated standardized incidence ratios (the ratio of observed to expected malignancies) and found standardized incidence ratios (SIRs) for malignancy in systemic lupus erythematosus from as low as 1.1 (95% CI 0.7-1.6) (24) to as high as 2.6 (1.5-4.4) (19). All studies were done with relatively small numbers of subjects, with resultant wide confidence intervals (Table 1). Given the estimates and their confidence intervals, the findings of all studies could be compatible with an increased risk of malignancy in lupus patients, although other explanations (i.e. differences in study design or study populations) for these results are also plausible.

Table 1: SIRs for overall malignancy in systemic lupus erythematosus

First Author	Ref.	Method of Cancer Ascertainment	N	SIR	95% CI
Cibere	18	Tumor Registry	297	1.59	1.1-2.3
Pettersson	19	Tumor Registry	205	2.6	1.5-4.4
Ramsey-Goldman	20	Tumor Registry	616	2.0	1.4-2.9
Nashi	21	Chart Review and Postal Survey	309	2.4	1.5-3.7
Sultan	22	Chart Review	276	1.2	0.55-2.1
Sweeney	23	Self-Report	219*	1.4	0.5-3.0
Abu-Shakra	24	Chart Review	724	1.1	0.7.1-1.6
Nived	25	Tumor Registry	116	1.5	0.8-2.6

* Cohort was updated in 1998 to total 412 persons with 1157 years of follow-up; the SIR estimate is unchanged although the confidence interval has narrowed (0.9, 2.2)(21).

Are Specific Types of Cancers Increased in systemic lupus erythematosus?

A refinement of the question "Is cancer incidence increased in systemic lupus?" is "Are specific subtypes of cancers increased in systemic lupus?" Several studies have suggested an increased risk of specific neoplasms; hematological malignancies have been implicated most often, although increased incidence rates of cervical, breast, and lung cancers have also been reported.

Hematological Malignancies:

Seven clinical cohort studies have suggested an increased incidence of hematologic malignancies, generally estimating that the risk for patients with systemic lupus erythematosus is increased several fold compared to the general population (18-22; 24; 25). Because the SIR estimates were often based on small numbers, the confidence intervals for these estimates are often wide. For example, Sultan et al. (22) reported a SIR of 17.42, but as this was based on a single case, the confidence interval was very large (0.5-100).

The most common type of hematologic malignancy occurring in systemic lupus erythematosus appears to be non-Hodgkin's lymphoma (NHL) (18-25).

Solid Tumors Among the clinical cohort studies published, several suggest increased cancer rates in systemic lupus erythematosus for specific types of solid cancers. The findings have by no means been uniform. Ramsey-Goldman et al. (20), who used cancer registry linkage in a clinical lupus cohort of women only, found an overall increased risk for cancer in systemic lupus erythematosus, with an increase in lung cancer in all women with systemic lupus erythematosus and an increased risk of breast cancer only in Caucasian women.

Pettersson et al. (19), who also used cancer registry linkage with a clinical cohort, reported an increased malignancy risk in persons with systemic lupus erythematosus as compared to the general population, with a standardized incidence ratio of 2.6. While their data suggested that lung, liver, and vulvar cancers were among the types of cancer increased in systemic lupus erythematosus, the majority of the increased risk was due to

an excess of hematological malignancies (which occurred 5 times more often than expected).

Nashi et al. (21) and Cibere et al. (18) both found an overall increased risk of cancer in systemic lupus erythematosus patients (most markedly for hematologic malignancies) with standardized incidence ratio estimates suggesting an increased risk of pancreatic, lung, breast, and ovarian malignancies, although the confidence intervals for these estimates did include one. Nived et al. (25), in a small cohort of only 116 patients, reported standard incidence ratios for total malignancies separately for men and women; both estimates were consistent with a possibly increased risk of cancer in systemic lupus erythematosus (2.24 for men, 1.02 for women) but with wide confidence intervals. The SIR for total malignancies in this cohort (men and women together) was 1.5, with 95% confidence interval 0.80 to 2.6.

Abu-Shakra et al. (24), Sweeney et al. (23), and Sultan et al., (22) all reported standardized incidence ratio estimates for all cancers that were not greatly elevated compared to the general population (although an excess of non-Hodgkin's lymphoma was noted by Abu-Shakra et al. and Sultan et al.). However, there may have been incomplete ascertainment of cancer cases within the lupus cohort in these studies, as chart review or patient interview was used instead of linkage with cancer registries. Additionally, the small number of subjects in each study also meant that the confidence intervals for each of these estimates was wide, and did not exclude the possibility of a clinically important increased risk. In a similar fashion, each of these studies did in fact estimate an increased SIR for several different types of solid cancers; for example, Abu-Shakra et al. (24) estimated an SIR of 1.5 for lung cancers, and Sultan et al. (22) an SIR of 2.8 for breast cancer, although the confidence intervals included one. Thus, in these studies, both imprecise estimates and potentially incomplete cancer ascertainment may have prevented the authors from observing an increase in overall malignancies or in certain types of solid tumors. The point regarding potentially incomplete cancer ascertainment will be discussed further in the subchapter of the literature review entitled Cancer Ascertainment in Cohort Studies.

The findings of individual studies will be discussed further in the chapter on risk factor prevalence (Chapter VI). In general however, it is safe to say that the findings of the clinical cohort studies do not allow any summary conclusions regarding the direction or magnitude of risk in solid tumors. In chapter IV, I will present a meta-analysis which was designed in part to help address the uncertainty regarding the risk of solid tumors based on clinical cohort studies published to date.

ii) Cancer Ascertainment in Cohort Studies

As mentioned above, one possible explanation for the differences in findings between studies are variations in methods or design. In this chapter, I will discuss how different methods of cancer ascertainment may affect research results.

In comparing different methods of cancer ascertainment, one must be aware of practical limitations, the specificity and sensitivity of a given method of ascertainment, and the potential impact that different methods of ascertainment may have had on estimates obtained by other researchers.

The different methods to determine the occurrence of cancer (or for that matter, any clinical outcome) include questionnaires, interviews, diagnostic procedures, and data sources such as population tumor registries. Each has potential sources of error (27).

In epidemiological research, methods commonly used to determine cancer occurrence include:

1) Self-report, by questionnaires/interview of patient or proxy
2) Chart review
3) Tumor registry data linkage
4) Physician billing data
5) Additional information sources: hospital discharge summaries, pathology reports, and death certificates (tumor registries generally incorporate data from these sources)(28).

I will now discuss some aspects of self-report, chart review, and tumor registry linkage.

Self Report: It has been suspected that self-report may introduce inaccuracy (29-31), either because of under or over reporting by patients or proxies. The potential for bias in studies relying on self-report for cancer ascertainment includes imprecision in reporting tumor type (including confusion regarding primary tumors with metastases) and misunderstandings particularly in cases where pre-malignant lesions may be confused with actual cancers (such as in cervical neoplasms) and in lesions that are treated locally (such as skin cancers), where the status of an excised lesion may not be clear to a patient (30). And, obviously, this method is problematic for patients who have died or been lost to follow-up. Because case-fatality is non-negligible for cancer, several cases of cancer may be missed from self-report, due to patients who had died.

Estimates of the sensitivity of self-reported malignancy vary widely, likely due to differences in the population being sampled. The following review is of studies done in non-lupus populations, as studies of the sensitivity of self-report in cancer ascertainment have not been done in systemic lupus.

Schrijvers et al. compared the results of cancer ascertainment using a postal survey to tumor registry records (30). Data on self-reported cancer was obtained from a health interview postal questionnaire in1991 in the southeastern Netherlands. Surveys were mailed to 17,940 individuals, and over 70% responded. All responses (positive or negative for malignancy occurrence) were validated against records from the population-based cancer registry. Compared to the tumor registry data, the postal survey had a sensitivity of 0.55 (95% confidence interval 0.51,0.60) and a specificity of 0.99 (0.98, 1.0) for all cancer types. Of the 212 false negative cases, 46% were non-melanoma skin cancer. The failure to report cervical cancers and melanoma skin cancers was also frequent. Misclassification of cancer by the survey differed by age, sex, and education. Failure to self-report a malignancy was greater for men vs. women, older respondents (especially older than 65) vs. young respondents (especially those younger than 45), rural residents vs. urban residents, and respondents with a lower

educational level (10 years or less of education).

Bergmann et al. (29) found that self-report, compared to cancer registry data, had a sensitivity of 0.93 (0.92-0.94) in their cohort of over 65,000 American men and women, and a specificity of 0.99 (0.98-1.0). To calculate these parameters, a "true positive" was defined as a self-report of cancer by an individual registered in the cancer registry, regardless of whether the cancer site was correctly identified. (For exact matches, the sensitivity was 0.79, 95% CI 0.78,0.80). Because the subjects were participants in a cancer prevention study, they were likely not representatives of the general population, although the cohort was population-based and included a wide age range (39-96, mean 63).

Bergmann et al. found the sensitivity of self-report was slightly less among individuals aged 70 and older (0.76), compared to younger individuals (0.80), and the confidence interval for the difference was 0.02, 0.06. A lower sensitivity was found among those without a high school education (0.75) compared to those with (0.80; 95% CI for difference 0.03, 0.07) and among current smokers (0.75) compared to never smokers (0.80, 95% CI for difference 0.03, 0.07). A lower sensitivity was found for men (0.78, 0.76,0.80) than for women (0.80, 0.78, 0.82) although the confidence intervals overlap and the 95% CI for the difference includes zero. Sensitivity estimates for specific types of malignancies were particularly low for melanoma skin cancer and for leukemia and lymphoma.

A much lower sensitivity of self-report compared to cancer registry data has been found among the elderly (31). The sensitivity in a large sample of persons aged >75 was estimated to be 0.33. (95% CI 0.28, 0.39) and the specificity, 0.77 (0.68, 0.86). Prostate cancer was the type of malignancy most likely to be missed during self-report. The authors suggest that the low sensitivity of self-report for cancer in this population was likely related to cognitive or memory problems and attitudes towards health and disease (ex. failure to assimilate information about one's health; belief that the subject of cancer is taboo; etc.).

Chart review: Although cancer ascertainment based on a review of clinic or hospital records is widely relied upon (21; 22; 24) it may miss some cancers, since patients may be seen and diagnosed outside a given institution. The sensitivity and specificity of chart review obviously varies with completeness and accessibility of the charts, which varies considerably from center to center. For example, the percentage of medical records that could not be located in studies attempting to review medical records for cancer cases registered in the UK was 8 to 19% (32). A similar study in Saskatchewan was unable to locate 20% of the cancer patients' charts (33). The charts of deceased patients may be more likely to be unavailable (32; 33), as many institutions have a policy of destroying such charts after a period. One could postulate that the charts of individuals with multiple comorbidities (such as, for example, systemic lupus erythematosus and malignancy) might be the charts most likely to be missing or in use, limiting their availability for a chart review. Like self-report, cancer ascertainment by chart review is obviously a problem for lost to follow-up patients.

Tumor Registry Linkage: The sensitivity and specificity for cancer ascertainment using tumor registry linkage depends on the quality of the registry's data –whether or not entries are missing and whether the information (ex. tumor site, date of diagnosis) is accurate (30; 34; 35). This varies from one registry to another; as well, the completeness of most regional registries has improved over time.

Cancer misclassification can arise from a number of different sources, including errors in clinical or pathological diagnosis, which are more likely if the cancer has not been proven histologically or if the tumor has a pre-cancerous stage which can be confused with invasive cancer. Additionally, errors of classification may occur during the collection, interpretation, or coding of a cancer registry's data (27).

Though no method of cancer ascertainment is a 'gold standard', tumor registries are potentially the best available reference method, and they do allow a method of determining whether deceased or lost to follow up patients have had a malignancy

(provided the individual has not moved away from the region serviced by the registry). The usefulness of tumor registries relative to other means of cancer ascertainment depends on how complete the registry is- this depends on what methods are used for the registration of cancers and how compliant sources are (27; 28; 36). Means of cancer registry ascertainment include pathology reports, hospital discharges, death certificates, and (in the US, for example) physician billing information. Certain sources of error are well recognized. Some cases of noninvasive cancers, often treated in clinic or outpatient settings, (ex. some cervical and skin cancers) may not be captured by the tumor registry (27; 28).

Several studies of tumor registries in the UK have looked at the completeness of registration of malignancies. These have estimated the sensitivity of cancer ascertainment by a search of tumor registry records to be between 73 to 93% compared to the research registries maintained by a network of collaborating physicians (35-38). Of these, one (38) determined the specificity of the tumor registry for recording of malignancies, which was 93% compared to the research registries maintained by a network of collaborating physicians.

Potential for Bias:

Differential misclassification (misclassification occurring systematically in one group) and bias may result when different methods of outcome ascertainment are used for two groups under comparison. Non-differential misclassification may bias parameter estimates towards the null, but the effect of systematic misclassification may be unpredictable and potentially more serious (27).

A potential example of differential misclassification may be found in the research done by Sweeney et al. (23), who determined that the risk for cancer in a cohort of persons with lupus was only slightly increased compared to an sex and age matched population of individuals. Cancer rates for lupus patients were obtained from a postal survey, and cancer rates for individuals without lupus were obtained from the Pennsylvania Tumor Registry. The findings of Sweeney et al. were quite different from the findings of other

studies, in which tumor registry data had been used to ascertain cancer rates in both groups; these other studies suggested an up to two-fold increase in cancer risk for individuals with a diagnosis of lupus (18-20). One may hypothesize that the failure to demonstrate a greatly increased malignancy risk in systemic lupus erythematosus was in part due to differential misclassification (that is, systemic lupus erythematosus patients were potentially more likely to be misclassified than members of the general population, because cancer ascertainment among systemic lupus erythematosus patients was done by a ' less accurate' method). However, because the effect of systematic misclassification is difficult to predict in this situation, only speculation can occur in retrospect.

iii) Malignancy Risk Factor Prevalence in Systemic Lupus Erythematosus

Although several studies on cancer risk in systemic lupus erythematosus have been done, few have looked at how factors associated with malignancy may be influencing this risk. For example, little is known about the prevalence of risk factors for malignancy in Systemic lupus erythematosus and how this compares to non-lupus populations. Knowledge about these potential differences in malignancy risk factors will help in the interpretation of risk estimates, and suggest whether and how such estimates should be adjusted.

Potential Risk Factors for Carcinogenesis

a) Smoking: Tobacco use, particularly cigarette smoking, is an important cause of lung cancer (39). Cancers of the mouth, larynx, and pharynx are caused mainly by the smoking or chewing of tobacco, particularly in combination with the consumption of alcohol. Smoking is also a risk factor for cancers of the esophagus and pancreas. Bladder cancer is also associated with smoking, and cigarette smoking may account for between 17 and 45% of kidney cancer. (39)

b) Alcohol: An estimated 2 to 4% of all cancer cases are thought to be caused either directly or indirectly by alcohol (40). A strong association exists between alcohol use and cancers of the esophagus, pharynx, and mouth (41). Less consistent data link alcohol consumption and cancers of the liver, breast, and colon (42; 43). Overall, the risk appears to increase as the quantity and duration of alcohol consumption increases, with the risk starting at a consumption level of as little as 2 drinks a day.

For some cancers, such as mouth and esophageal, alcohol is thought to play a direct causal role. For others, such as liver and breast cancers, alcohol may act indirectly. Alcohol may initiate and promote oncogenes (44). Acetaldehyde, a product of alcohol metabolism, may impair the repair of DNA, increasing the chance that mutations will lead to cancer (45). Alcohol may act as a co-carcinogen by enhancing the carcinogenic effects of other chemicals, such as tobacco-related carcinogens (41). Alcoholism has been associated with suppression of the human immune system, theoretically increasing susceptibility to cancer (46).

An estimated 75% of esophageal cancers in the United States are attributable to chronic, excessive alcohol consumption (40). Nearly 50% of cancers of the mouth, pharynx, and larynx are associated with heavy drinking. Smokers who drink experience a 30-50 fold increased risk compared to non-smoking non-drinkers (41).

Excessive alcohol consumption has been linked to over a third (40) of cases of primary liver cancer. Chronic alcohol consumption has been associated with a small (about 10%) increase in a woman's risk of breast cancer (47-53) possibly by increasing estrogen levels in premenopausal women, which, in turn, may promote breast cancer. A small dose-dependent association between alcohol consumption and colorectal cancer has consistently been found (54; 55). A few studies have linked chronic heavy drinking with cancers of the stomach, pancreas, and lung. However, the association is consistently weak and the majority of studies have found no association (40).

c) Reproductive Factors that increase the amount of time a woman is exposed to estrogen increase breast cancer risk. Such factors include late age at first birth, nulliparity, early menarche and late age at menopause, the use of oral contraceptives, and post-menopausal hormone replacement with unopposed estrogens. Nulliparity is associated with ovarian cancer (39; 56) and low parity and a late age of menopause is associated with endometrial cancer (39;56).

It is now well accepted that hormone replacement with unopposed estrogen therapy (i.e. without progesterone) increases endometrial cancer risk (57; 58). Women who use postmenopausal estrogens for 10 years or more may face nearly double the normal risk of fatal ovarian cancer, as was found recently in a large (N=211,000) American study of postmenopausal women studied from 1982 to 1996 (59).

Although not all studies have found an increased risk of breast cancer in oral contraceptive users, several have (60-67). (Generally subjects were considered as exposed if the pills were taken for at least 6 months, and compared to "non-users".) The increased incidence of breast cancer among users of birth control pills was seen in young women (that is, cases of cancer occurring either before the age of 35, or before the age of 45); those who started the pill at a young age (<18) have been found to have a higher risk than those who start use later. A meta-analysis of 54 studies conducted in 25 countries that involved over 150,000 subjects found that current or recent users of birth control pills had a slightly elevated risk of developing breast cancer (68).

The use of combination oral contraceptive pills appears to reduce the risk of developing endometrial and ovarian cancer by 50% (69-71). This beneficial effect persists for at least 15 years after the discontinuation of the pill. Reduced ovulation may mediate this effect of oral contraceptives on gynecologic cancers. Oral contraceptives likely reduce endometrial cancer risk only when the estrogen content is balanced by progesterone in the same pill. There is some evidence that long-term use (5 or more years) of oral contraceptives may increase slightly the risk of cancer of the cervix (72; 73). However, because other risk factors (74) (early age at first intercourse, multiple sex partners,

infection with human papilloma virus [HPV]) may be different between women who use oral contraceptives and those who have never used them, the precise role of oral contraceptives in cervical cancer is unknown.

There is some evidence that oral contraceptives may increase the risk of malignant and nonmalignant hepatic tumors (75-77). However, the risk is difficult to evaluate because of different patterns of oral contraceptive use and because these tumors are rare outside the Orient.

A meta-analysis of 20 studies (including the United States Nurses' Health Study and the United Kingdom Royal College of General Practitioner oral contraceptive study) estimated an 18% reduction in colorectal cancer risk, an effect that appeared stronger for recent oral contraceptive use (78). The effect may result from reduced colonic bile acid concentration, growth inhibition of colon cancer cells, or reduced levels of Insulin-like Growth Factor-I (IGF-1 is a factor that may promote cancer).

Obese women are at greater risk of endometrial, ovarian and possibly breast cancer, while obese men have an increased risk of prostate cancer (79; 80). The increased incidence of these cancers among obese patients is likely hormonally linked. Obesity is associated with a number of endocrine abnormalities that may increase health risks and promote the development of central obesity. The changes in sex hormone levels associated with obesity (particularly the high levels of estrogen) may explain the increased risk of hormone-dependent cancers among obese patients.

Obese patients are also at increased risk of gastrointestinal cancers, such as colorectal and gallbladder cancer (81). The incidence of colorectal cancer shows a strong relationship with body mass index (BMI) (82). Dietary factors that promote weight gain, such as a high dietary fat content, may give rise to the high incidence of gastrointestinal cancers in obese patients.

Central obesity and body mass index >25 kg/m² have been linked to endometrial cancer (83). The relationship between breast cancer and obesity is less clear (83-85). Post-menopausal obese women are at higher risk than post-menopausal lean women (83) and increased risk is correlated with central obesity (84-86).

iv) The Prevalence of Factors Influencing Cancer Risk in Systemic Lupus Erythematosus: Social Habits, Reproductive Issues, and Obesity

Although data suggest that malignancy incidence is increased in Systemic lupus erythematosus (18-21; 23), the pathogenesis of this potentially increased risk is unknown. Multiple hypotheses exist, and one etiologic hypothesis is that certain cancer risk factors (such as obesity and nulliparity) are increased in persons with systemic lupus erythematosus. Little has been published concerning the prevalence in systemic lupus erythematosus of standard risk factors for malignancies; the prevalence profile could potentially influence the risk of malignancy in systemic lupus erythematosus.

The prevalence of smoking in systemic lupus erythematosus has been estimated in several cohorts (87-91) but often, comparable figures for the population have not been presented. Hardy et al. (91) in their case-control study, did determine that the prevalence of " never smokers" was 52% among lupus patients, and 58% among age and sex matched population controls. Though this suggested that a history of current or past smoking is greater among lupus patients than in the general population, in fact the confidence intervals for "never smokers" among lupus patients (0.46, 0.64) included the figure for the prevalence of " never smokers" among the controls. (The confidence intervals were not provided in Hardy et al.'s paper, but were calculated from the data they presented.) Similar findings have been reported by Cibere et al. (18). Bruce et al. (92) found that the proportion of current smokers in a cohort of 235 systemic lupus erythematosus patients was slightly lower (0.16) than that of an age and sex matched control population (0.20), although the confidence intervals of these two estimates overlap.

Patterns of alcohol consumption for members of lupus cohorts have been described (90; 93). McAlindon et al. (90) looked at alcohol use in a cohort of persons with systemic lupus erythematosus but did not provide a comparison with consumption in the general population. Hardy et al. (93) determined that systemic lupus erythematosus patients consumed less alcohol than controls in a case-control study of 150 patients and 300 age and sex matched population controls in the UK. In this study, the prevalence of consumption of more than 2 drinks of alcohol per day among persons with systemic lupus erythematosus was 0.39, (95 % confidence interval 0.30, 0.45) compared to the prevalence among the controls (0.58, 95% confidence interval 0.54, 0.62).

Regarding the prevalence of reproductive risk factors for malignancy, of the studies that have examined reproductive history in systemic lupus erythematosus (90; 94) most have only looked at reproductive issues among a portion of the entire female cohort (for example, pregnancy outcome only among women who have become pregnant-which does not allow the calculation of the prevalence of nulliparity within the entire cohort). One study (94) did determine the odds of being "never pregnant" in a cohort of 138 women and compared this to 276 age and sex matched population-based controls. (Never being pregnant is not quite synonymous with never having given birth, of course.) Although the actual prevalence of nulliparity in the two groups was not reported, the odds ratio for being " never pregnant" for women with lupus versus controls was 1.2. The 95 % confidence interval for this estimate (0.64, 2.2) included the possibility of no difference between groups as well as the possibilities that either group had the higher odds. In a review of reproductive factors among women with systemic lupus erythematosus compared to controls, Cooper et al. (95) stated that there was "no difference" with respect to parity among the two groups, although it was not mentioned whether average parity was the parameter calculated, versus the prevalence of nulliparity.

An additional question is whether those women with lupus who do have a family give birth to their first child at a later age (for example, because pregnancies are delayed until disease is stable, or because of recurrent pregnancy losses). This specific issue has

not been addressed by more than a few studies. One study of two groups of lupus patients and two groups of controls (96) stated that a difference in the mean age at first pregnancy was not found for any of the groups, although the actual mean ages were not stated in the article. The number of subjects was small, and thus it seems likely that the confidence intervals for the differences might have included the possibility of a significant difference (as well as the null value, which was possibly why the authors simply stated that a difference was not apparent.) The subjects were also likely not representative of the general population either of lupus or of controls, as they had been selected for the presence or absence of particular antibodies (Anti-Ro and Anti-La).

The prevalence of oral contraceptive use in women with systemic lupus erythematosus has been reported with population-based comparison figures (18) where the authors suggested that past or present oral contraceptive use among Saskatchewan women with systemic lupus erythematosus (13%) was "similar to the expected proportion of 17%"; the later figure was obtained from a population-based study in the United States. The confidence interval for the estimate of oral contraceptive use among the Saskatchewan systemic lupus erythematosus patients does include an upper bound of 17%, but the lower bound, 9.1%, suggests that a difference between the two groups in terms of oral contraceptive use can not be excluded. Julkunen et al. (97) estimated that the prevalence of past or present oral contraceptive use among women in their Finish lupus cohort was 6% (95% confidence interval 2% to 13%) which was lower than the age-matched population estimate of 18% (95% confidence interval 15% to 21%).

Obesity prevalence has been determined in cohort studies (18; 88), although a comparison with population figures has been provided only by Cibere et al., who reported that, in a cohort of systemic lupus erythematosus patients in Saskatchewan, obesity prevalence among men (35%) and women (27%) were identical to the obesity prevalence for men and women determined by the Canadian Heart Health Survey. (Cibere et al. used a slightly higher value of body mass index for the definition of obesity than the Canadian Heart Health Survey (98)).

The prevalence of hormone replacement therapy in post-menopausal systemic lupus erythematosus patients has been reported as 19% to 32% in small studies (99; 100). Cibere et al. (18) reported, in a larger cohort that included 160 women, that the prevalence of current hormone replacement use was 6%, although it is unclear how many of the 160 women were post-menopausal. Cibere et al. noted that this was similar to population prevalence for hormone replacement therapy (5%) although that figure was based on population figures for the United States. Cooper et al. (95) found that a history of past use of hormone replacement therapy was more prevalent among post-menopausal women with systemic lupus erythematosus than among controls, but this study examined hormone replacement use retrospectively and only up to the time of systemic lupus erythematosus diagnosis.

Non-steroidal anti-inflammatories (NSAIDs) have been recognized as a factor potentially protective against colorectal (and perhaps other) tumors (101). Cibere et al., in their report on malignancy in a cohort of systemic lupus erythematosus patients, found the prevalence of NSAID use (including both previous and current users) in the cohort was 22%. Although the authors did not provide a comparison with age and sex matched data for the general population (the cohort was drawn from Saskatchewan) a recent report estimated that the crude rate of NSAID use in this province is 13.4% (95% confidence intervals 13.39 to 13.41) (132).

Thus, many of the lifestyle factors, habits, and exposures that are believed to affect malignancy risk in the general population have been incompletely studied in systemic lupus erythematosus, with respect to the extent that the prevalence of these factors differ between systemic lupus erythematosus and general populations.

Though it is interesting to speculate that differences in the prevalence of these risk factors is operative in increasing malignancy risk in systemic lupus erythematosus, they may not be the only explanation. There is a lot of interest in abnormalities in the immune system that may themselves predispose to both cancer and autoimmune disease. To complete my literature review, I will touch on some of these potential links

between malignancy and autoimmunity and also address briefly the question of how medications used in systemic lupus erythematosus may affect cancer risk.

iv) Basic Science Evidence Suggesting Immunologic Links Between Autoimmunity and Malignancy

Evidence exists that the genetic predisposition to autoimmunity overlaps with genetic susceptibility for malignancy; some suspected links are certain alleles that allow aberrant B cell proliferation. Thus, malignancy, autoimmunity, or both, may result from genetically determined regulatory abnormalities in B cell proliferation and/or differentiation. There are several potential immunologic mechanisms that may contribute to this predisposition.

Similarities are present in the pathogenesis of systemic lupus erythematosus and certain malignancies, especially B cell lymphocytic leukemia, a disorder of aberrantly developed B lymphocytes. These cells can produce autoantibodies, sometimes resulting in autoimmune disease. Systemic lupus erythematosus is characterized by the production (by plasma cells, of B lymphocyte lineage) of antibodies directed against self-proteins (102). Dysregulated proliferation of B cells is also central to B cell lymphocytic leukemia. Interestingly, the surface markers in B cell lymphocytic leukemia in the NZW mouse model of systemic lupus erythematosus are similar to the surface markers found in human B cell lymphocytic leukemia cells (103). The structure of immunoglobulins produced in B cell lymphocytic leukemia suggests an antigen-driven pathogenesis (104), which is also likely operational in systemic lupus erythematosus. Thus, one could postulate that chronic stimulation of B cells by self-antigens in association with major histocompatibility complex (MHC) class II may favor neoplastic transformation of cells not only in B cell lymphocytic leukemia but in systemic lupus erythematosus patients that develop malignancies.

One genetic explanation for the link between autoimmunity and malignancy is a background MHC haplotype that predisposes to both disorders (105). In mice (the

NZW lupus model), different, but related MHC haplotypes predispose either to autoimmune disease or to hematological malignancy. (106). Humans with B cell lymphocytic leukemia often share major histocompatibility complex haplotypes with relatives who have autoimmune diseases (107).

One of the non-MHC genes may be the tumor necrosis factor (TNF) gene. TNF-α can trigger the growth of B cell lymphocytic cells, acting in synergy with the cytokine IL-2 to cause B cell proliferation (108). Serum TNF-alpha is increased in B cell lymphocytic leukemia patients (109). Polymorphisms of the TNF-alpha gene likely modulate the development of autoimmunity in the NZW mouse model of systemic lupus erythematosus (108).

Another unifying genetic factor that could act pathogenically in both autoimmunity and malignancy is Interleukon-10 (IL-10) gene dysregulation. IL-10 is a chemokine (chemical signal) produced in large amounts by B-lymphocytes and monocytes. It is responsible for autoantibody production (110), and an excess production of this factor may be what causes organ damage in systemic lupus erythematosus. A possible role of IL-10 excess has been postulated in lymphomas, since IL-10 genes are expressed in B-cell lymphomas. (110) The establishment of IL-10's role in tumor progression is yet to be determined.

Abnormal apoptosis (regulated cell death) is believed to be one of the mechanisms driving immune system imbalances in systemic lupus erythematosus (111). (Specifically, abnormalities in apoptosis may impair deletion of self-reactive lymphocytes and a failure of tolerance to self-antigens; alternatively, since apoptosis generates altered self-antigens; abnormal apoptosis in the periphery may create a potential for breaking self-tolerance.)

Apoptosis is also one of the mechanisms the immune system uses to eliminate cells with irreparable DNA damage (as may occur in cancer pathways initiated by radiation,

chemicals, or other exposures). Thus, abnormal apoptosis could potentially explain an association between systemic lupus erythematosus and cancer.

There are also growth and hormonal factors that may link malignancies and autoimmunity. Factors of interest are IGF2 (insulin-like growth factor 2, or its receptor ILGF2r), prolactin, and growth hormone. IGF2r acts as a tumor suppressor gene in both humans and mouse, and abnormalities in IGF2 levels or IGF2R function causes susceptibility to malignancy (112).

Prolactin, growth hormone, and IGF may all play roles in the immune system through modulation of lymphocyte growth, development, differentiation, and function (113). Growth hormone and prolactin also appear to partially regulate apoptosis (114). Thus, it has been suspected that abnormalities in one or more of these hormones or growth factors may contribute to the problem of autoimmunity. (In particular, it has been suggested that abnormally high levels of prolactin may play an aggravating role in systemic lupus erythematosus (115; 116).) Since these hormones have been implicated in oncogenesis (112), they could conceivably be the link between the association of autoimmunity with malignancy.

v) Other Factors: Infections, Sjögren's, and Immunosuppressive Drugs

Infectious Agents: Innate immune dysfunction may predispose to viral infection and confer malignant potential to cells. Similarly, use of immunosuppressive agents may predispose systemic lupus erythematosus patients to viral infection and thus allow these viral triggers to initiate abnormal cell differentiation. Patients with systemic lupus erythematosus have been reported to have a higher incidence of warts (117) for example. Venereal warts are caused by human papillomavirus (HPV), an agent also associated with cervical cancer (118). A predisposition to HPV infection potentially could explain some of the increased incidence of cervical atypia, which has been reported in systemic lupus erythematosus (119).

Sjögren's Disease/ Syndrome: It is known that patients with systemic lupus erythematosus may develop a 'sicca syndrome' (dry eyes and mouth) which is similar to the autoimmune condition known as primary Sjögren's disease. Because hemopoetic malignancies are increased in individuals with primary Sjögren's disease, one suspicion has been that the excess of hematologic malignancies seen in systemic lupus erythematosus was occurring in individuals who also had this syndrome. To date, very few of the systemic lupus erythematosus patients in which cancers have occurred had sicca symptoms or an 'overlap' diagnosis of Sjögren's disease (18-22) although the majority of studies have been done in cohorts where the prevalence of this syndrome in the cohort overall was unknown. Thus, it is difficult to estimate whether features of Sjögren's occurring secondarily in lupus patients is a risk factor for hematologic malignancies over and above the existence of lupus itself.

Immunosuppressive and Cytotoxic Drugs: The reason why cancers may occur more commonly in systemic lupus erythematosus patients compared with the general population is unknown, although some reports implicated immunosuppressive or cytotoxic drugs as a cause (117; 120-124). The incidence of lymphoreticular malignancy in the NZB/NZW mouse model of systemic lupus erythematosus is increased by treatment with the immunosuppressive agent, azathioprine (125). Immunosuppressive and cytotoxic therapies have also been mentioned in case reports of malignancies in systemic lupus erythematosus patients (122-126), including azathioprine (an immunosuppressive agent) (120; 122)and cyclophosphamide, (a cytotoxin which alkylates DNA) which has been associated with bladder cancer and leukemias (121;123;124).The International Agency on Research in Cancer considers alkylating agents such as cyclophosphamide as carcinogens (42).The striking effect of azathioprine in predisposing organ transplant recipients to early lymphoreticular malignancies has not seemed as apparent in systemic lupus erythematosus populations (122), (126). Though exposures to alkylating agents and immunosuppressive drugs may increase the risk of some cancers (especially lymphoma), a study of the relative importance of this in systemic lupus erythematosus compared to the general population is difficult to formulate, given the vary low incidence of exposure to these agents in the

general population. Cibere et al. (18) noted that 3% of the systemic lupus erythematosus patients in their cohort had received cyclophosphamide during their lupus treatment. In terms of use of immunosuppressive agents, 8.4% of patients had received azathioprine, and 2% had received methotrexate. The authors did not believe these agents were linked to the cases of cancer in their cohort, as only two individuals with cancer (out of 27 cancer cases) had been exposed to immunosuppressive agents. Although the low numbers of exposed individuals and the relatively infrequent occurrence of cancer within the cohort makes it difficult to say whether or to what degree these drug exposures may influence cancer risk, other authors have reported findings similar to Cibere et al. and have drawn the same conclusions (19;20;22-24).

Thus, it has not been proven that excess cancers in systemic lupus erythematosus are caused by treatment with immunosuppressive drugs and alkylating agents (18-20; 22; 24). Therefore, it is possible that an increased risk of malignancy in systemic lupus erythematosus is conferred either by a genetic susceptibility for autoimmunity, which predisposes also to cancer, or to overlapping etiologic factors.

III. Cancer Risk in a Cohort of Montreal Systemic Lupus Erythematosus Patients

To quantify the cancer experience of systemic lupus erythematosus patients followed in Montreal, we determined the incidence of malignancy in a cohort of over 300 patients. In this chapter, I describe the malignancy incidence in this cohort, which we determined by using cancer registry data. We compared this to the malignancy incidence in the Quebec population, using age and sex adjusted data from the Quebec tumor registry for the years 1984-97. We have additional data on cancer ascertainment by chart review and self-report in the same cohort, as well as information on potential risk factors for malignancies which was collected at the same time. These data will be presented in subsequent chapters (V and VI). Ethics board approval was secured for the collection and analysis of these data and informed consent was obtained from the patients or their proxies.

Setting and Subjects The participants were members of the Montreal General Hospital Lupus cohort. Each member has a clinical diagnosis of systemic lupus erythematosus confirmed by a sub-specialist (either a rheumatologist or immunologist). These patients fulfill the American College of Rheumatology (ACR) criteria for systemic lupus erythematosus (26). The calendar periods of observation spanned from 1977 to the present (which is, as of the time of the preparation of this manuscript, September 2001). For the purposes of this study, we limited the period of observation to 1984-1997, as this was the period during which the records of the Quebec tumor registry were believed to be most accurate. The cohort size is 325; of these, 16 persons were unable or unwilling to participate in our study of malignancy and thus the number studied was 309. The age and sex distribution of the subjects who did not participate was similar to that of the participants.

For each cohort member, entry occurred at the time he or she was first seen in the Montreal General Hospital lupus clinic. To determine the rate of occurrence of all cancers combined, we used the later of two entry dates: the start date of the cohort study (January 1st, 1984) or the date of the first visit to the respective lupus cohort. The end of the

observation interval for each patient was marked by the occurrence of the earliest of two exit dates: the closing date of the cohort study (December 31, 1997), the death of the patient. For site-specific cancer analyses, the observed and expected incidences for the cohort during the study interval were calculated using the earliest of three exit dates: the death of the patient, the date of the occurrence of the site-specific cancer of interest, or the end of the cohort study interval.

Data Collection For all study subjects, we obtained the following: date of birth, sex, date of lupus diagnosis, date of entry into lupus cohort, and vital status (with date of death, if applicable). The observation interval for each individual was calculated by subtracting the entry date from the exit date, as explained above.

The years between date of systemic lupus erythematosus diagnosis and date of cohort entry were not included in the observation interval. This is because, though our cohort is drawn from the general lupus population, there are some lupus patients who, perhaps because of early demise or mildness of disease, never enter into a clinical cohort. Thus, the observation interval for this small group is automatically censored and the incidence of cancers in these persons is not captured. If we had not similarly censored our cohort members during the period from time of systemic lupus erythematosus diagnosis to time of cohort entry, we might inaccurately estimate cancer incidence.

Patients who developed a malignancy contributed observation time for the calculation of that tumor-specific standardized incidence ratio only up to the time of the diagnosis of the malignancy. Thereafter, these individuals contributed observation time only for tumor-specific SIRs for malignancies that they had not experienced.

Tumor Registry Linkage Cancer cases were ascertained for the entire cohort through linkage with the Quebec tumor registry, a population registry. A list of the patients, with corresponding demographic information (name, sex, date of birth, and date of systemic lupus erythematosus diagnosis) was sent to the Quebec tumor registry to

determine malignancies that had occurred in patients during the observation interval. (This registry relies on hospital discharge information.) Along with information about observed malignancies, the cancer registry provided (on computer disc) age and sex specific population incidence rates for all malignancies for each year of the observation interval. (At the time of study completion these rates were available in print form up to and including 1996, and in electronic form for the years up to and including 1997.)

Statistical analysis: The Standardized Incidence Ratio (SIR) was calculated for total cancer occurrence by dividing the total observed number of cancers by the total number of cancers expected. The total expected number of cancers was obtained by multiplying each person-year at risk in the cohort by the appropriate age, sex, and calendar specific cancer rate (as provided by the Quebec tumor registry) for that person-year and summing over all person-years across all patients. Standardized incidence ratios for of cancers occurring in body systems (i.e. digestive organs, respiratory system, gynecologic, and hematologic systems) and for cancers (colorectal, lung, breast, ovarian, and endometrial malignancies, and lymphoma and leukemia) within those systems were calculated by dividing the observed number of malignancies (of the type of interest) by the expected number of malignancies (of that type).

Confidence intervals for the SIRs were calculated using methods described by Breslow and Day (127) for estimating a Poisson-distributed variable.

Cancer ascertainment and determination of vital status for patients lost to follow-up
Only those cancers diagnosed after the diagnosis of lupus were used in calculating incidence rates. As non-melanoma skin cancers and in-situ cervical carcinomas may be under-reported, they were not included in the primary analysis. Patients who had been lost to follow up (no contact for $\geq$12 months) were linked with the Quebec vital statistics database to determine their vital status. Lost to follow-up patients not appearing in the tumor registry or the vital statistics database were assumed to have survived cancer-free up to the end of the observation interval (December 31, 1997) and

this assumption was used to calculate the person years that these individuals contributed to the observation interval.

Results: The 309 patients observed between 1984 and up to the end of 1997 contributed a total of 2547 person years. The frequency distribution of demographic features is given in Table 2. The distribution of patient years by sex and over the observation interval is given in Table 3 .The subjects were over 90% female, with a mean age at diagnosis of 35 years (SD 15.0 years) and mean duration of follow-up of 8.24 years. Thirty nine patients had been lost to follow up (12.6%); linkage with the Quebec vital statistics database determined that 11 of these individuals had died-none of cancer.

Table 2: Description of cohort: Age, duration of systemic lupus erythematosus, and drug exposures

	Mean age at lupus diagnosis	Mean age at end of observation	Mean lupus duration at end of observation	Proportion exposed to	
				Cyclophosphamide	Azathioprine
	Years[SD]	Years[SD]	Years[SD]		
All Subjects	35 (15)	49 (15)	14 [9.0]	0.08	0.20
By Sex					
F	34 (14)	48 (15)	14 (9)	0.08	0.20
M	40 (19)	55 (19)	14 [8.8]	0.10	0.19

Table 3: Number of subjects and person-years by selected characteristics

	Entire cohort		Distribution of person years over the observation interval			Distribution of person years by age group			
	Number Of Subjects	Person-Years	84-88	89-93	94-97	<35	35-49	50-65	>65
All Subjects	309	2547	773	888	886	645	1020	556	326
By Sex									
F	279	2337	704	813	820	609	955	518	255
M	30	210	69	75	66	36	65	38	71

Cancer registry linkage indicated the occurrence of malignancies in 27 patients (all but one were women) during the period 1984-1997. Among these, two cancer cases were not included in the analysis because they had occurred prior to the patient's entry into the cohort (one Non-Hodgkin's lymphoma and one vulvar cancer). Excluding these, as well as four cases of cervical carcinoma in-situ (CIS) and one case of non-melanoma skin cancer, the number of individuals with cancers was 20 (which represents 6.5% of the cohort).

Of these individuals, two patients had more than one malignancy (one patient with a hematologic malignancy was later diagnosed with colon cancer; one patient with colon cancer was later recorded as having a brain neoplasm). The second malignancies have been included in the analyses, so that the total number of malignancies is 22.

Standardized Incidence Rates: Table 4 displays the Standardized Incidence Ratios (SIRs) for the lupus cohort, according to cancer site. Compared with the general population, a 1.8 fold increased risk (for all cancers combined) was observed in patients with systemic lupus erythematosus. The system-specific SIRs are consistent with increased risk of cancer in the lupus cohort for hematologic, breast, and gynecologic tumors. SIRs for specific anatomic sites are consistent with possibly increased risk of several solid tumors. However, the confidence intervals for these estimates are wide and in many cases include the null value (or even include the possibility of a decreased risk of that type of tumor). The risk was increased most for hematological malignancies (observed cases being 6 times that which was expected) with a confidence interval that clearly excludes the null value.

Table 4: Standardized† incidence rates (Observed: Expected) of cancer in the systemic lupus erythematosus cohort (by cancer type)

Cancer System Site or type	Number of Cancers (Occurring over 2547 patient-years)		Standardized Incidence Ratio (SIR)	95% Confidence Interval
	Observed	Expected		
Hematological††	6	0.93	6	2.2-13
NHL	4	0.45	8.9	2.4-23
HL	1	0.08	12.5	0.2-70
Leukemia	1	0.27	3.7	0.05-20
Breast	7	3.1	2.3	0.91-4.7
Respiratory†††	2	1.87	1.1	0.13-3.9
Lung	2	1.85	1.1	0.12-3.9
Gynecologic*	3	1.09	2.8	0.57-8.0
Ovary	2	0.40	5	0.56-18
Endometrial	1	0.55	1.8	0.05-10
Digestive**	3	2.49	1.20	0.24-3.5
Colon	2	1.01	1.98	0.22-7.2
Pancreas	1	0.3	3.3	0.04-19
Total Cancers¶	22	12.5¶	1.8	1.2-2.6

† Standardized to the Quebec population based on the distribution of person years in the systemic lupus erythematosus population, according to age, sex, and calendar year.

††Hematological: ICD 9 codes 200-208 [Lymphoma, leukemia, myeloma, lympho/reticulosarcomas]

††† Respiratory :ICD 9 codes 162-163 [Trachea, bronchus, lung, and pleura]

* Does not include cervical cancers. Includes ICD 9 codes 179/182 [Uterus] and 183-184[Ovary, adnexae, vagina, and female genital organs not otherwise specified]

** Digestive: ICD 9 codes 150-159 [Esophagus, stomach, intestine, colon, rectum, anus, liver, gallbladder, pancreas, peritoneum, and digestive not otherwise specified]

¶ Does not include cervical or non-melanoma skin cancers

Discussion

We have estimated that malignancies in individuals with systemic lupus erythematosus occur 1.8 times more commonly than expected. The percentage of patients who developed a cancer over the period of observation was 6.5 %, which is consistent with previous studies (18-25) showing the frequency of cancer in systemic lupus erythematosus patients to be between 2.7% (23) and 11.2% (25).

As well, we observed a striking increase in the risk for hematological cancers, the majority of which were non-Hodgkin's lymphoma. An increased risk for hematological malignancies has been observed in several recent studies (19-22, 23-25), with most estimates having wide confidence intervals, consistent with the small number of subjects in each. Although our confidence interval for the SIR estimate for hematologic malignancies is wide (2.2-13), both lower and upper limits suggest a clinically significant increased risk.

Although this study addressed some of the weaknesses of previous cohort studies, some limitations remain. An important weakness is the relatively small sample size (and subsequently, there were too few events among the occurrence of solid tumors to precisely estimate how often they occur in systemic lupus erythematosus). Linked to this, possibly, is the interval over which patients were observed, which may not have been long enough to obtain an estimation of cancer risk for lupus patients beyond a certain time (i.e. 10-15 years, which was the maximum length of the observation period for the majority of the subjects). Even though the period over which patients were enrolled and followed spanned several decades, and the mean follow-up time for patients was as long or longer compared to that of other cohort studies in this population (18-24), because cancer occurrence in general increases with age, the experience of systemic lupus erythematosus patients (particularly those who have had systemic lupus erythematosus for decades and lived well past middle age) likely still needs to be clarified.

Although sub-analyses could have been performed, according to age group and duration of disease, the even smaller numbers in individual groups would not allow precise estimates of the standardized incidence ratios. These limitations will only be addressed with the study of an adequately large cohort (consisting of at least 5,000 individuals); this in fact is the goal of a multi-centre project in which I will be participating.

An additional limitation is our inability to estimate rates of skin and cervical malignancies, because of the likelihood of incomplete ascertainment of these malignancies (both within the cohort and within the population). Overcoming this obstacle is difficult, as even the most complete cancer registries admit to incomplete ascertainment of these malignancies.

Another potential for bias exists for any study examining the prevalence of a second disease state (here, cancer) in a "patient population" (here, the lupus cohort) when the comparison group is the "general population". This potential for bias relates to the possibility for differential misclassification among members of the general population, due to lower scrutiny or use of screening tests in patient populations compared to the a non-patient population. That is, it may be more likely that some cases of cancer are missed in a member of the "general population" than in a lupus cohort member. However, there are no formal screening techniques for hematologic malignancies, for which (apparently) lupus patients are most likely at increased risk. In contrast, breast cancer, a neoplasm amenable to screening, are not so dramatically increased in lupus patients compared to the general population.

By linking the lupus cohort databases with only regional registries, cancers diagnosed in patients who are no longer residents of the region may not be captured. If anything, this would lead to a conservative estimate of the malignancy incidence in the lupus cohort.

IV) Cancer Risk in Systemic Lupus Erythematosus: A Meta-analysis

Although some researchers have offered very different conclusions regarding the risk of cancer in systemic lupus erythematosus, one could argue that all of the clinical cohort studies done to date lack precision in their estimates of cancer risk in systemic lupus erythematosus. Thus, all are potentially compatible with an increased risk of cancer in systemic lupus erythematosus. The purpose of this meta-analysis was to gain further insight into the question of increased cancer risk in systemic lupus erythematosus, with respect to the incidence of both total cancers and specific types of cancers.

Methods: A computerized search of medical journal articles from 1965 to the present (August 2001) was performed using MEDLINE, with keywords "malignancy (or) cancer (or) neoplasm" (and) "systemic lupus erythematosus (or) lupus (or) SLE". In addition, the supplement sections of four rheumatology journals (American College of Rheumatology, Journal of Rheumatology, Scandinavian Journal of Rheumatology, and Lupus) for the years 1998-2001 were searched by hand for abstracts. Articles or abstracts were retained for inclusion in the meta-analysis if they fulfilled the following criteria: the study was a cohort design, the patients had definite systemic lupus erythematosus either by American college of Rheumatology criteria (26) or clinical diagnosis, and the cohort had been assembled from the general systemic lupus erythematosus population (not, for example, from hospitalized patients only). One abstract was excluded because the findings were published later in full (22); this journal article was then included in the meta-analysis. This resulted in a total of eight studies of cancer occurrence in systemic lupus erythematosus that were suitable for pooling in the meta-analysis. One study was in abstract form (21); the others were journal articles. These studies were: Pettersson et al. in 1992 (19), Sweeney et al. in 1995 (23), Abu-Shakra et al. in 1996 (24), Ramsey-Goldman et al. in 1998 (20), Sultan et al. in 2000 (22), Nashi et al. in 2000 (21), Cibere et al. in 2001 (18) and Nived et al. in 2001 (25).

We assumed a fixed effects model, since the clinic settings, inclusion and exclusion criteria, and populations studied were believed to be similar across the studies. A

pooled data approach was used, which treats the data as if they all came from a single study (128).

The observed numbers of cancers from each study were added to obtain the total number of observed cancers. In cases of second malignancies occurring within the same individual during the observation interval of a study, the majority of studies included these in the total number of observed cancers. Thus, they were included in the total. The total expected number of cancers was obtained by adding the total expected number of cancers from each study, since this figure was available for all studies. The standardized incidence ratio (SIR) was calculated for total cancer occurrence by dividing the total observed number of cancers by the total number of cancers expected.

Confidence intervals for the SIRs were calculated using methods described by Breslow and Day (127). Exact 95% confidence limits were obtained by multiplying the observed number of cancers by the appropriate numbers from a table of confidence limit factors for estimating a Poisson-distributed variable (129) then taking the upper and lower limits of the observed number of cancers, and dividing each by the expected number of malignancies. For values (of observed cancers) not presented in the table of confidence limit factors, approximate 95% confidence limits were obtained using the formula of Rothman and Boice (130).

To explore subtypes of malignancies, SIRs were calculated for hematological malignancies and solid tumors, including breast cancer, lung cancer, and cancers of the gastrointestinal tract. SIRs were also generated for the following specific hematological malignancies: non-Hodgkin's lymphoma, Hodgkin's lymphoma, and leukemia.

We obtained the number of cases of types of cancer by adding the expected numbers of cancers in that subgroup as reported in each study; however, not all studies reported expected cancers for all cancer types. (In general most studies did not provide expected numbers for cancers that none of their cohort members experienced.) To estimate the number of cancers expected for specific cancer types, in each case where the authors

did not present these figures, we multiplied the contribution of person-years from that study by the age and sex specific expected incidence rate for the cancer type for members of the Montreal General Hospital cohort, from data provided by the Quebec tumor registry. In doing so, we assumed that the age-sex distributions of the person-years in these studies were the same as the age-sex distribution of the Montreal General Hospital cohort.

Results: The number of patients, person-years, and malignancies from each of the eight studies are presented in Table 5. The number of subjects was 2762; the cancer incidence in total was 164 cases in 23696 person years. Table 6 presents the cases by cancer type.

Table 5: Number of patients, person-years, and malignancies from each of the eight studies included in the meta-analysis

First Author	Subjects	Person years	Average follow up (years)	Observed cases	Expected cases
Sweeney	219	1157	5.28	6	4.42
Abu-Shakra*	724	7233	9.99	35	33
Ramsey-Goldman	616	4051	6.58	30	15
Sultan **	276	1695	6.14	11	8.6
Nashi†	309	2547	8.22	27	13.2
Pettersson	205	2340	11.41	15	5.7
Nived	116	1086	9.4	13	8.69
Cibere	297	3587	12	27	15
Total	2762	23696		164	93.4

*One vulvar malignancy, 6 cervical CIS, and 4 non-melanoma skin cancers that occurred in the Abu-Shakra cohort but were not included in their calculation of SIR (because of lack of population data) was included for this meta-analysis.

**One non-melanoma skin cancers which occurred in Sultan's cohort but which not used for their analysis, (because of lack of population data) were included in the meta-analysis

†In the data presented here, the figures for the Nashi study represent not the original numbers published in the abstract but the corrected numbers that were determined after the link with the tumor registry. Also, 4 cervical cancers and one non-melanoma skin cancers which occurred in Nashi's cohort but which not used for their analysis were included in the meta-analysis.

Table 6: Frequencies of types of cancer included in the meta-analysis

Malignancy	Number	Percent
Non-Hodgkin's Lymphoma	23	14
Hodgkin's Lymphoma	2	1
Leukemia	3	2
Other hematological	4	2
Breast	32	20
Lung	16	10
GI (colorectal & rectosigmoid)	9	6
Pancreas	4	2
Gastric	3	2
Hepatic/Gallbladder	4	2
Ovary	5	3
Cervix	20	12
Endometrial	3	2
Vulvar/Vaginal	4	2
Bladder	2	1
Prostate	5	3
Kidney	2	1
Thyroid	3	2
Brain	3	2
Unknown primary	1	1
Oropharyngeal	1	1
Non-melanoma Skin	11	7
Melanoma	2	1
Other	2	1
Total	164	100

The standardized incidence ratio estimates are presented in Table 7. For all cancers combined, the standardized incidence ratio was 1.67 (95% confidence interval 1.42-1.94). If we exclude non-melanoma skin and in-situ cervical carcinomas (which may be under-reported by any standard means of cancer ascertainment) from both observed and expected malignancies, the number of observed malignancies is 133, the expected is 83, for a SIR of 1.60, with a 95% confidence interval of 1.23, 2.86.

The SIR estimate for all hematological malignancies together was 4.2 (2.85, 5.87). Of the subtypes of hematologic malignancies, the highest risk was for non-Hodgkin's lymphoma, with a SIR estimate of 9.3 (5.93,14). This was the only type of hematologic malignancy for which the confidence interval did not include the null value.

Increased risk of solid tumors was suggested for cervical cancer (SIR 4.2, confidence interval 2.5, 6.4), for vaginal and vulvar cancers (SIR 11, 95% CI 2.9, 28), for hepatobiliary cancers (SIR 4.2, 95% CI 1.3, 9.7), and for breast cancer (SIR 1.3, 95% CI 1.0, 1.9). For several other cancers, the confidence intervals included both the possibilities of an increased risk and of a reduced risk among systemic lupus erythematosus patients for these specific malignancies.

Discussion of results: The SIR estimates for malignancy risk in systemic lupus erythematosus from these studies are consistent with an overall increased risk of developing cancer. Pooled results suggest at least a 60% increase in malignancies in individuals with systemic lupus erythematosus compared to the general population. The risk is most dramatic for hematological malignancies but is apparent also for certain solid tumors such as breast and cervical cancers, hepatobiliary cancers, and neoplasms of the vulva and vagina. The risk for other types of solid tumors, such as colorectal cancer, remains uncertain.

One caveat is that we have assumed a " fixed effects" model. Perhaps it is reasonable to believe that the factors influencing cancer risk, and their subsequent effects, were very

Table 7: Total number of cancers observed and expected, with Standardized Incidence Ratios

MALIGNANCY	OBSERVED	EXPECTED	SIR	95% Confidence Interval
HEMATOLOGICAL	32	7.69	4.2	2.85,5.87
NON-HODGKIN'S	23	2.46	9.3	5.93,14.0
HODGKIN'S	2	0.71	2.8	0.32,10.2
LEUKEMIA	3	2.27	1.3	0.27,3.9
BREAST	32	23.75	1.3	1,1.9
OVARY	5	3.42	1.5	0.47,3.4
CERVIX	20	4.80	4.2	2.5,6.4
VAGINAL/VULVAR	4	0.37	11	2.9,28
UTERUS	3	4.80	0.6	0.13,2
LUNG	16	10.54	1.5	0.87,2.5
PANCREAS	4	1.72	2.3	0.63,6.0
HEPATOBILIARY	5	1.20	4.2	1.3,9.7
GASTRIC	3	2.32	1.3	0.26,3.8
COLORECTAL	9	10.14	0.9	0.41,1.7
BLADDER	2	2.66	0.8	0.08,2.7
OROPHARYNGEAL	1	0.66	1.5	0.02,8.4
THYROID	3	0.93	3.2	0.65,9.4
BRAIN	2	1.28	1.6	0.18,5.6
PRIMARY UKNOWN	1	2.41	0.4	0.01,2.3
PROSTATE	5	4.41	1.1	0.37,2.6
KIDNEY	2	1.68	1.2	0.13,4.3
NON-MELANOMA SKIN	11	10.59	1.0	0.52,1.9
MELANOMA	2	1.59	1.3	0.14,4.5
TOTAL	164	98.39	1.67	1.42,1.94
Total minus skin and cervical in-situ cancers	133	83.00	1.60	1.23,2.86

similar between cohorts. For example, the assembly of the cohorts was similar in that they were all clinic based and included only patients with a definite diagnosis of systemic lupus erythematosus, and did not enforce additional clinical inclusion or exclusion criteria, thus ensuring that the cohorts all likely represented similar populations. All cohorts were primarily women, all were from industrialized countries in North America or the United Kingdom, and most cohorts were overseen by specialists who were members of the same lupus research networks. The patients would be likely to have been similarly exposed, in terms of diet, lifestyle, and environmental factors, as well as to have received similar medical treatment for systemic lupus erythematosus. Of course, some differences in these exposures might be anticipated; to determine whether important differences exist, extensive data would need to be collected from patients in cohorts from these countries, with respect to exposures of interest. Although this information is not available for all cohorts included in the meta-analysis, we are currently collecting such data on a number of lupus cohorts from several countries, and analysis of these data might determine the validity of the assumption that similar exposures occur across the cohorts.

Of course, many influential factors, including genetic predispositions to malignancy and autoimmunity (currently too poorly elucidated to be studied in this context) may be factors that invalidate a "fixed effects" model and suggest that a "random effects" model might be more appropriate. However, the studies that were included in the meta-analysis were from countries with primarily Caucasian populations, and thus some elements of the genetic makeup may also be similar among cohorts.

Given that there may have been some invalidity in a fixed effects model (i.e. we did not account both for random variability of the studies and for study variation in true effect rates) we may have produced inappropriately narrow confidence intervals. If we had used a hierarchical random effects model, and incorporated some aspect of the variability between study results due to differences between studies in terms of cohorts make-up or study design, we would likely have produced wider confidence intervals. Given the clearly increased SIR estimate for hematological malignancies, particularly

non-Hodgkin's lymphoma, this would not likely have much affected our conclusions for these cancer types. However, it very well may have removed any ability to speculate on the true nature of cancer risk with respect to certain solid tumors (for example, breast cancers) where a slight increase in the width of the confidence interval would have meant the inclusion of both the null value and a potentially decreased risk of that tumor.

In addition, we must point out that some of the malignancies (for example, cervical and vulvar cancers) recorded in these patient populations may be more likely to be brought to medical attention (because these women regularly see physicians), than they would be in women who are not systematically followed in the medical system. This and other potential sources of bias are further discussed in the Concluding Discussion chapter.

V) The Sensitivity and Specificity of Postal Survey and Chart Review Methods of Cancer Ascertainment in a Clinical Cohort of Persons with Systemic Lupus Erythematosus

The first object of the work presented below was to determine the sensitivity and specificity of postal survey and chart review in determining malignancy occurrence in a population of individuals with systemic lupus erythematosus. Although it is evident that no method of outcome ascertainment is perfect, for the purpose of calculating the sensitivity and specificity of the postal survey and chart review methods, we used the results of the linkage with the Quebec tumor registry as our ' best available reference' standard.

As a second objective, we simultaneously determined the sensitivity and specificity of all three methods of cancer ascertainment using a Bayesian methodology. In this approach, none of the methods was defined as the 'best available reference'. The methodological principles are outlined below.

Methods: The study population consisted of patients followed in the Montreal General Hospital Lupus Clinic (N=325) during the period 1984-1997. For patients who had died (N=79) or been lost to follow up (N=38) during this period a chart review was undertaken (completed by a physician) to determine malignancy occurrence. The patients who were still alive and in follow-up were invited to complete a postal survey on malignancy occurrence. Of those who did not wish to complete the survey (N=39), 23 agreed to a chart review. Thus, 309 patients were included in the study. All participants were then linked to the Quebec tumor registry to determine the existence of malignancies. To calculate sensitivity and specificity of postal survey and chart review (when considering the tumor registry as the best available reference), attempts were made to verify that, in all cases of discrepancies between the tumor registry and the chart review or postal survey, the tumor registry data was correct through review of all medical records and by requesting the tumor registry to confirm the correctness of their entries.

As indicated earlier, in this first approach the above parameters (sensitivity and specificity) were calculated considering the tumor registry data as the standard. Though the tumor registry is probably the best available method of ascertaining cancer, it is not truly a "gold standard" as there is some chance (currently unknown) that a case may be misclassified within the tumor registry (i.e. a true case may not appear when it should, or a non-case may appear when not actually a case). However another approach could be to use the information from all three methods of cancer ascertainment in a Bayesian analysis, without considering any one of the three methods as a gold standard. This was our second approach, and it allowed the estimation of the sensitivity, specificity, and positive and negative predictive values for all three methods of cancer ascertainment (Bayesian analyses make use of Baye's theorem to combine prior information about a parameter with the information provided by one's new data. The result is the creation of a 'posterior distribution' for the parameter estimate.).

To do this second analysis, we used computer software written in the S-Plus language to estimate the marginal Bayesian posterior distributions by Gibbs sampling. This process uses iteration to determine marginal posterior probabilities that otherwise can't be estimated (128). In order to complete this exercise, a physician reviewed the charts of patients who had completed a postal survey. We thus had, on a subset of patients (those still alive and in follow-up at the time of the postal survey) data on cancer occurrence using all three methods. Uniform prior distributions were used for all unknown parameters (ex. the sensitivity of the tumor registry data was an unknown parameter). In a Bayesian analysis, the prior distribution represents 'prior knowledge' of the parameter; a uniform prior means we begin without depending on prior information about that parameter.

Results:

Table 8 presents estimates of the sensitivity and specificity of postal survey and chart review methods, using the tumor registry as the "best available reference".

For the 169 patients who had completed the postal survey, 10 cancers were identified by tumor registry linkage as having occurred during the observation interval. Eight of these were identified on postal survey, thus the sensitivity (compared to tumor registry) of the postal survey for malignancy occurrence was 80% (95% confidence interval 44%, 97%). Of these 10 malignancies, 2 were cervical carcinoma in-situ (CIS). These lesions are often excluded from consideration during analysis of cancer incidence in cohort studies, as neither self-report, chart-review, nor registry linkage is believed to completely capture the incidence of this malignancy. (The same is likely true of skin cancers, particularly non-melanoma skin cancers.) Excluding the one skin and two CIS lesions which were among the 10 cancers recorded in the registry, the sensitivity of self-report was 100% (95% confidence interval 65%, 100%) compared to tumor registry data (Table 8).

Considering the tumor registry method as the best available reference, the specificity of postal survey was 98% (95% confidence interval 94%, 99%). This was due to the reporting of one ovarian "cancer" that on review turned out to be a benign lesion; and to the reporting of 2 cervical CIS cancers and 2 skin cancers (reported as melanoma), none of which were reported in the tumor registry and none of which were supported by pathologic reports in the patient's chart.

One second primary was also found in the registry for an individual who had reported a cancerous GI polyp, which was confirmed on linkage with the registry; however, the individual was also registered as having a primary brain tumor, although she had not reported this. (Second cancers were not included in calculation of the sensitivity and specificity parameters, as it was suspected that having multiple cancers may be a source of bias i.e. persons with second malignancies may be systematically more or less likely to have the second malignancy reported.)

In comparing chart review to tumor registry data, it was determined that chart review (N=140) correctly identified 13 of 15 malignancies recorded in the tumor registry, for a sensitivity of 87% (95% confidence interval 60%, 98%). Excluding 2 cervical

malignancies, the sensitivity of chart review was 85% (95% confidence interval 55%, 98%). The 2 malignancies that had not been detected on chart review were hematological malignancies in patients who had become lost to follow up, and had been diagnosed with malignancies in other institutions.

Considering the tumor registry data as our "best available reference", the specificity of chart review for the detection of malignancy was 99.2% (95% confidence interval 94%, 99.8%); a skin lesion initially recorded as malignant on chart review was not found on the registry linkage and was confirmed benign on a second review of the chart.

In addition, one chart review had resulted in the recording of a GI tumor, which was confirmed on registry linkage; however, the same individual was also registered with a second primary, a hematological malignancy, which had been missed on the initial chart review, although a repeat review of the medical records did confirm the second malignancy also.

Table 8: Comparison of methods of cancer ascertainment (postal survey and chart review) in the MGH lupus cohort (using tumor registry data as the reference standard)

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Postal Survey All Cancers	0.80 (0.44, 0.97)	0.975 (0.94, 0.99)	0.67 (0.359, 0.901)	0.987 (0.954, 0.998)
Chart Review All Cancers	0.87 (0.60, 0.98)	0.992 (0.94, 0.998)	0.87 (0.60, 0.98)	0.984 (0.944, 0.998)
Postal Survey Excluding cervical & skin	1.0 (0.65,1.0)	0.994 (0.94, 0.998)	0.89 (0.47, 1.0)	1.00 (0.977, 1.00)
Chart Review Excluding cervical & skin	0.85 (0.55, 0.98)	1.00 (0.98, 1.00)	1.0 (0.75,1.0)	0.984 (0.944, 0.998)

In cases of discrepancies between the tumor registry and either the chart review or postal survey, all medical records were reviewed and the tumor registry was requested to confirm correctness of their entries. These efforts verified in each case of a discrepancy that the tumor registry was most likely correct.

In addition, the patients were linked to the Quebec mortality database. As a check for any cases of cancer that may have been missed in the tumor registry, the cause of death was determined for each deceased patient in the cohort. In no case was cancer the cause of death where it had not already been a case of cancer known to the tumor registry.

Predictors for Cancer Misclassification:

Several studies (29-31) have found misclassification of cancer by survey methods differed by age, sex, and education . With respect to our cohort, the mean number of years of schooling was slightly lower in the misclassified group, but the difference was less than a year and the confidence interval included the null value. Similarly, though the misclassified group was younger than the rest of the cohort, the confidence interval for the difference in ages included the null value of zero (Table 9).

Table 9: Comparison between misclassified subjects and remainder of cohort who completed postal survey, mean age and education

	Misclassified Group(N=6)	Remainder of cohort N=163	Difference
Mean Age (CI)	42.1(36.5, 47.7)	46.5(44.6, 48.1)	5.2 (-0.70, 11.2)
Mean Years of Education (CI)	12.8 (11.1, 14.5)	13.0 (12.6, 13.4)	0.15 (-1.6. 1.9)

It was difficult to evaluate whether sex was a predictor of being misclassified. The misclassified subjects were all female; however, the properly classified subjects were over 92% women (because the majority of systemic lupus erythematosus patients are women). With such a small number of misclassified subjects, even if half of the misclassified subjects had been male, the confidence interval for the difference in proportion that was male would have included the null value. Thus, the importance of sex as a predictor of misclassification can not be commented upon with any certainty.

Effect on SIR

One might have expected that calculation of the SIR using data from the tumor registry linkage would have increased the parameter estimate as compared to the calculation based on self-report and chart review. In fact the SIR using the combined methods of self report and chart review was 2.4; using the data from the tumor registry linkage the value was 1.8. This occurred because, although additional cancers were detected by tumor registry linkage, one of the cancers reported on survey (ovarian) was later considered to be a false report, as this malignancy was not found in the tumor registry, and on further inquiry it was determined that the ovarian lesion was in fact a benign lesion. Two other cases that had been included on the basis of chart review or self-report were excluded after the tumor registry linkage, because the precise date of the malignancy was determined to be before the entry into the cohort. In addition, by linking the patients that had been lost to follow up to the tumor registry, as well as to the Quebec mortality database, we extended the number of years of follow up to

include this period for which those lost to follow up had remained alive and cancer free. (Previously, the observation interval for lost to follow up patients ended at the time of their last clinic visit.) The resultant increase in the number of years of observation increased the number of expected malignancies to 12.5, with the resulting decrease in the SIR estimate to 22/12.5=1.8. This of course required the assumption that patients had not moved elsewhere and died or been diagnosed with cancer, and is thus a conservative estimate for the SIR.

Calculation of the Sensitivity and Specificity of Each Method using Bayesian Methodology

The above parameters (sensitivity and specificity) were calculated considering tumor registry as the gold standard. Although it is the best available method of ascertaining cancer, there is some chance (currently unknown) of misclassification of a case within the tumor registry. As such a second exercise made use of the data we had collected from all three methods of cancer ascertainment to estimate the sensitivity and specificity of all three methods. This method does not require that any of the three sources of information are assumed to be a gold standard.

Table 10 presents the sensitivity, specificity, and predictive values for each method of cancer ascertainment. Using the Bayesian approach, the estimates of sensitivity of the tumor registry for a cancer occurrence in the cohort is 0.93 (95% confidence interval 0.72, 0.99) when including cervical and skin cancers, which are malignancies that even the best of registries find difficult to register with accuracy. The estimate produced for the sensitivity of chart review was similar. When cervical cancers and skin cancers are excluded, the sensitivity of self-report becomes similar to the sensitivity of chart review and tumor registry (the estimate for self-report is actually highest, by a fraction, although the confidence intervals for these estimates overlap).

Table 10 Bayesian estimates of sensitivity, specificity, and predictive values for each method of cancer ascertainment (no assumption that any method is the best reference)

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Postal Survey -All Cancers	0.74 (0.50, 0.91)	0.98 (0.95,0.99)	0.73 (0.47,0.92)	0.98 (0.96, 0.99)
Chart Review -All Cancers	0.93 (0.72,0.99)	0.99 (0.98, 1.0)	0.92 (0.72, 0.99)	0.99 (0.98,1.0)
Tumor Registry -All Cancers	0.93 (0.72, 0.99)	0.98 (0.98, 1.0)	0.93 (0.72, 0.99)	0.99 (0.98,1.0)
Postal Survey -Excluding cervical & skin	0.0.92 (0.69,0.99)	0.99 (0.97,1.0)	0.81 (0.54,0.97)	1.0 (0.98, 1.0)
Chart Review -Excluding cervical & skin	0.91 (0.67,0.99)	0.99 (0.98,1.0)	0.91 (0.66,0.99)	0.99 (0.98,1.0)
Tumor Registry -Excluding cervical & skin	0.91 (0.67,0.99)	0.99 (0.98,1.0)	0.91 (0.66,0.99)	0.99 (0.98,1.0)

Thus, in this patient population, the postal survey method of cancer ascertainment had a high specificity. A number of cervical and skin cancers were not reported. Chart review was also a specific means of cancer ascertainment, but using this method, several malignancies were not detected. This discrepancy was noted even after excluding cervical and skin cancers, which are often poorly documented. The low number of observed events limits the precision of the parameters produced, however. Given our findings, it is difficult to determine in retrospect the extent and direction of bias possibly introduced by differing methods of cancer ascertainment used in other published studies of malignancy in systemic lupus erythematosus.

VI) The Prevalence of Factors Influencing Cancer Risk in Women with Systemic Lupus Erythematosus: Social Habits, Reproductive Factors, and Obesity

Recognizing a paucity of data on the issue, we set out to determine the prevalence of malignancy risk factors in systemic lupus erythematosus. The study population was the Montreal General Hospital (MGH) Lupus Clinic cohort, which consists of patients with a clinical diagnosis of systemic lupus erythematosus who are followed in the MGH Lupus Clinic. This cohort was described in chapter III, entitled Cancer Risk in a Cohort of Montreal Systemic Lupus Erythematosus Patients. Consecutive patients are enrolled in the cohort at the time of diagnosis, and for our survey we studied all individuals that had been entered into the cohort up to and including 1998.

Methods: We administered a postal survey of risk factors for lung and aerodigestive (smoking, alcohol use) and breast and gynecologic cancers (nulliparity, age at birth of first child, use of oral contraceptives and hormone replacement therapy). For patients who had died (N=78) or been lost to follow up (N=39) as well as those still alive and in follow up, but who did not wish to complete a questionnaire (N=23) data was abstracted from the clinic database or medical records. Information about NSAID use (a potentially protective factor) was collected at the same time. Obesity prevalence for the cohort was determined using each patient's last recorded weight in the clinic database. (It should be noted that these risk factors were determined at the time of that the postal survey was administered or the chart review done. These time points were generally some time-months or even years- after the time of lupus diagnosis.) Risk factor prevalence for women within the cohort was compared to that of the general population, using age and sex adjusted data collected on Quebec women during the 1996-97 National Health Population Survey (131).

The National Population Health Survey collects cross-sectional as well as longitudinal data, using Statistic Canada's Labour Force Survey sampling frame to draw a sample of approximately 20,000 households. In each household, some limited information is

collected on all household members and one person in each household is randomly selected for an in-depth interview. It includes demographic information as well as data on topics such as smoking, alcohol consumption, and use of medications. The first cycle was in 1994-95, the second in 1996-97, and the third in 1998-99. The most recent cycle for which electronic data files were available in a format suitable for analyzing and subsetting data (via the Sherlock Co-operative Data Access System for Quebec Libraries) was 1996-97. This allowed us to retrieve data by sex and age (by 5-year age groupings) for the Quebec adult population. The same age categories were used to group the Montreal General Hospital lupus cohort members, so that prevalence rates for the risk factors could be standardized by age group.

As the National Health Population Survey has a single question on the use of analgesics which combines NSAIDs and other analgesics, we did not use these data for our comparison but used instead a figure for NSAID use in a Canadian study that evaluated the prevalence of NSAID use and its complications (132). This figure is not age or sex adjusted.

For both the National Health Population Survey and the data collection for the lupus cohort, the risk factor of smoking was defined as having ever smoked regularly (i.e. on a daily or weekly basis). This therefore included both current smokers and reformed smokers in the same category of "ever smokers". Similarly, for both the National Health Population Survey and the data collection for the lupus cohort, alcohol use exposure was dichotomized as the consumption of greater than two (versus two or less) glasses of alcohol per day. Also, the number of pack-years (i.e. the cumulative total of number of packs per day times the number of years smoking at that rate) was determined for members of both the general population and the lupus cohort (the value included both current and reformed smokers).

For both the National Health Population Survey and the data collection for the lupus cohort, current use of oral contraceptives was determined only for women aged 50 or less, as women over the age of 50 were unlikely to require contraception. In a like

fashion, to determine the prevalence hormone replacement use, we considered only women who were older than 30, as the majority of women younger than this would not be menopausal.

Results: Table 11 presents the results of the prevalence estimates for each risk factor, both for the MGH cohort and the general population. Compared to the general population, the following differences were noted: the lupus population had a lower prevalence of current use of oral contraceptives, and a greater prevalence of obesity, nulliparity and hormone replacement use. Positive history of smoking (past or current) was similar between the two groups; however, the average number of pack-years was greater in the lupus cohort compared to the general population.

Table 11: Prevalence of risk factors for malignancy in the Montreal General Hospital (MGH) lupus cohort and the Quebec population

Risk Factor	**MGH Cohort**	**Quebec Population**		**Predicted Effect**
	Prevalence (95%CI)	Prevalence (95%CI)	Difference (95% CI)	Lupus cohort cancer risk
Smoking (ever)	0.514 (0.464,0.564)	0.562 (0.526,0.598)	-0.05 (-0.11,0.01)	
Oral contraceptives (Current) Women<50	0.0408 (0.00163,0.0800)	0.101 (0.0785,0.124)	-0.0602 (-0.02,-0.11)	Endometrial ↑, Ovarian ↑
HRT (Current) Women>30	0.255 (0.175,0.335)	0.147 (0.119,0.174)	0.108 (0.0232, 0.193)	Endometrial ↑ (Possibly Breast↑)
Nulliparity: Women>50	0.257 (0.23,0.29)	0.0822 (0.0784,0.0860)	0.18 (0.10, 0.27)	Breast, Endometrial ↑ Cervical ↓
EtOH (>2drinks/d)	0.0370 (0.0133,0.0607)	0.0241 (0.0217,0.0265)	0.0129 (0.0, 0.0367)	
Obesity (BMI>27.3)	0.297 (0.234,3.60)	0.224 (0.221,0.227)	0.073 (0.01,0.14)	Breast ↑ Endometrial ↑
NSAID use	0.19 (0.14,0.24)	0.218 (0.165-0.247)	-0.03 (-0.11, +0.04)	
	Means (95%CI)	**Means (95%CI)**	Difference (95%CI)	
Age at first birth (Parous women)	24.7 (23.9,25.4)	25.0 (24.7,25.3)	0.300 (-0.487,1.09)	
Pack-years (includes current and reformed smokers)	16.35 (13.68,19.02)	13.34 (12.34,14.34)	3.01 (0.159, 5.86)	Lung, Aerodigestive, Breast, Colorectal ↑

Discussion of results:

Smoking: The prevalence of "ever smokers" (persons who were currently regular smokers or who had been in the past) appeared to be similar between members of the cohort and the general population. However, among current smokers, the mean pack-years was higher in the systemic lupus erythematosus patients. There are several ways this could be interpreted. Hardy et al. (93) found that the odds ratio for smoking (prior to the onset of systemic lupus erythematosus) was increased among systemic lupus erythematosus patients compared with controls (odds ratio 1.95 (95% CI 1.14, 3.31)). For our results to be consistent with this, it might be that, for a non-smoker of a given age, the odds of becoming a smoker are less after being diagnosed with systemic lupus erythematosus. This might bring the prevalence of "ever smokers" within the cohort to very near that of the general population, and this might be expected, given that after being diagnosed with systemic lupus erythematosus, the increased contact with the medical system might discourage the initiation of unhealthy habits. Those persons with systemic lupus erythematosus who do not quit may be the heavier smokers.

The prevalence of current smokers in the cohort is 0.471 (95% CI 0.402, 0.539). It is noteworthy that Bruce et al. (91) found that physicians providing care for patients with systemic lupus erythematosus tended not to provide advice regarding cessation of smoking. Rectification of this would assist in limiting the damage done to persons with systemic lupus erythematosus, not only in coronary heart disease but presumably with respect to malignancies as well.

Having said this, if the high number of average pack-years of smoking among systemic lupus erythematosus patients contributed to an increased malignancy risk, one might expect more of a pronounced effect on rates of lung cancer. For lung cancer, of the clinical cohort studies published, five (18; 20; 21; 24; 25) suggest increased risk (SIR estimates of 1.1 to 4). Ramsey-Goldman et al.'s results (20) produced the largest SIR, and the confidence interval does not include the null value (95% CI 1.1, 10.2) but the confidence intervals for the estimates for the other 4 studies include the null value. In the 3 other clinical cohort studies, no events were observed.

With respect to other cancers associated with smoking, there is no convincing evidence of a tendency for increased risk in systemic lupus erythematosus. Ramsey-Goldman et al.'s results (20) do suggest an increased risk (SIR estimate 2, 0.03, 12) for gastric cancer, and for bladder cancer (1.5, 95% CI 0.02, 8). Events were few and the confidence intervals wide. Only two clinical cohorts reported any renal cancers (24; 25) but, given the relative infrequency of this malignancy in the general population, the SIR estimates are elevated (2.6 and 5.3) although with wide confidence intervals that include the null value of one, or even the possibility of a decreased risk of this cancer. An increased risk of pancreatic cancer in systemic lupus erythematosus was suggested in the cohort study of Abu, Shakra et al. (24), whose study produced evidence of an increased SIR for pancreatic malignancies (13, 1.4, 45) as did Pettersson et al. (3.7, 95% CI 0.05, 21) (19). Increased risks of mouth, larynx, and pharynx cancers have not been noted in clinical cohorts of systemic lupus erythematosus.

Alcohol: We did not find evidence that systemic lupus erythematosus patients were more likely to consume >2 drinks of alcohol a day, compared to the rest of the Quebec population. Of course, it is possible we may have found different results if we had chosen a different measure of exposure. (For example, with some evidence existing that the risk starts at a consumption level of as little as 2 drinks a day, we could have looked for a difference between systemic lupus erythematosus patients and the general population with respect to >1 drink per day.) We chose the measure of exposure as we did because that was how the risk factor questionnaire data were recorded; there is no a priori reason to suspect we would have found a great difference in the prevalence of alcohol consumption even if we had used a different measure for exposure. And, a heightened rate of malignancies most strongly associated with alcohol use (esophagus, pharynx, and mouth) has not been noted in systemic lupus erythematosus. Ramsey-Goldman et al.'s results (20) are consistent with an increased risk (SIR estimate 3.32, 95% CI 0.04, 18) of hepatic malignancy, although the confidence interval is wide, since this estimate is based on a single event.

Reproductive Factors that increase the amount of time a woman is exposed to estrogen increase breast cancer risk. Such factors include late age at first birth, nulliparity, early menarche and late age at menopause, the use of oral contraceptives at young ages and unopposed estrogens. Characteristics of women with endometrial carcinoma are obesity, low parity, and a late age of menopause (39). Nulliparity is associated with ovarian cancer (39; 56) and low parity and a late age of menopause are associated with endometrial cancer (39;56) .

The lupus cohort had a distinct prevalence profile for cancer risk factors with respect to reproductive issues, compared to the general population of age-matched women. The differences may have arisen for a variety of reasons. The higher number (compared to the general population) of women with systemic lupus erythematosus who were nulliparous may have resulted from infertility (which may be caused by treatment with cyclophosphamide) or from early pregnancy loss (which may be associated with antiphospholipid antibodies in systemic lupus erythematosus) or even from concern that a pregnancy may lead to a flare of lupus (133). On the other hand, the lower use of oral contraceptives among women with systemic lupus erythematosus may be because these women are less sexually active, or may be due to an avoidance of these agents, given that oral contraceptives with high estrogen content may precipitate a venous or arterial thrombosis or a lupus flare (97; 134).

These differences in reproductive issues could influence the incidence of certain malignancies in systemic lupus erythematosus. However, because some of the factors appear to be acting in different directions, it is difficult to estimate the overall effect. For example, nulliparity may influence the risk of breast cancer (tending to increase the risk) but the decreased use of oral contraceptives might lower breast cancer risk. Of the 7 clinical cohort studies published, 5 produced a SIR for breast cancer suggesting increased risk (1.2 to 2.8) (19-23) but the confidence intervals were all wide, including the null value. The two studies whose results did not produce a SIR estimate suggestive of an increased risk of breast cancer (18; 24) also had wide confidence intervals, and the upper limits included the possibility of a SIR as high as 1.79.

Lower use of oral contraceptives might increase risk of colorectal cancer, although NSAID use could theoretically counteract a heightened potential for colorectal malignancies in systemic lupus erythematosus patients, as they are more likely than the general population to use non-steroidal medications. With respect to published data on colorectal cancers in systemic lupus erythematosus, in 2 clinical cohorts (22; 24) several events occurred, with SIR estimates greater than one (between 1.5 and 4.3) but in each case the confidence intervals include the null value or even the possibility of a decreased risk. One study found an SIR of one (20), two studies (19; 23) did not observe any colorectal malignancies, and three studies (18; 21; 25) found an SIR estimate less than one, with a wide confidence interval as each was based on a single event.

Decreased use of oral contraceptives and increased nulliparity would both tend to decrease the risk of cervical cancer, although various factors, including imperfect accuracy of cancer ascertainment for cervical neoplasia and the presence of other risk factors for cervical dysplasia, such as exposure to drugs like cyclophosphamide (117) might make such an association difficult to recognize. In fact, an increased risk of cervical atypia (i.e. pre-cancerous cervical lesions) has been reported in systemic lupus erythematosus (119) and an increased incidence of cervical cancers have been suggested in both clinical series and cohort studies (18; 24). Logistically, there are difficulties in establishing exactly what the risk may be. Several authors have not included cervical cancers in calculation of the observed and expected malignancies, as patients with these malignancies, in early stages, may undergo local treatment in outpatient clinics, and thus may not be recorded in hospital records or tumor registries (21). However, even given the fact that some cervical cancers within the cohort may not be detected in a linkage with the tumor registry, calculation of the SIRs from data from the published clinical cohort studies yields interesting results. In five out of the eight published clinical cohort studies (18; 19; 21; 22; 24) the number of events of cervical neoplasms (including in-situ lesions) that cohort members experienced is consistent with an increased risk for cervical cancers (SIR estimates range from 1.45 to

2.36) but all but the estimate in the Cibere et al. study (18) have wide confidence intervals, including the null value. (This study was based in Saskatchewan, where the regional cancer registry has been shown to be accurate even for cervical cancers (18; 33).) Pettersson (19) reported one cervical cancer in his cohort study, which would estimate the SIR to be less than one (0.29) but with a 95% confidence interval that included an increased risk (0.004, 1.59). Two other cohort studies (23,25) did not report any cervical cancers; one (23) specifically stated that cervical cancers were not included in the report because of concerns that cases would be misclassified.

One interesting finding in our study is the increased number of women with systemic lupus erythematosus who are on hormone replacement therapy compared to the general population. There are multiple reasons why this would be so. First, women in the general population are likely not in contact with physicians as often as systemic lupus erythematosus patients are, and thus may be less likely to discuss hormone replacement with their physicians. In addition, rheumatologists are aware of the increased risk in systemic lupus erythematosus for osteoporosis, and may offer their post-menopausal patients hormonal replacement for this reason. (Although HRT contains estrogen, the dose is low and some feel that it is not likely to cause flares of disease in lupus, although the issue is being studied currently (100).)

It is now well accepted that hormone replacement (particularly when not given with progesterone) increases endometrial cancer risk, and convincing evidence has recently suggested that the risk of fatal ovarian cancer is also increased. For this reason, one would expect that systemic lupus erythematosus patients might be at greater risk for both of these malignancies. Since oral contraceptive use protects against these malignancies, the tendency of women with systemic lupus erythematosus not to use oral contraceptives might further increase this risk. Interestingly, there have been suggestions of increased ovarian malignancy; the results from two studies (21; 23) suggested a 2 fold increased risk in systemic lupus erythematosus patients, but the SIR estimates were wide (including values less than one for the lower bound and double-digit SIRs for the upper bound). Abu-Shakra (24) et al. recorded only one event, with a

SIR estimate of less than one (0.88) but with a wide confidence interval (0.01-4.90). The other studies (19; 20; 22) did not report any ovarian malignancies in their clinical cohorts.

For two studies SIR estimates of 1.27 (24) and 1.96 (19) would suggest an increased risk of endometrial cancer for systemic lupus erythematosus patients, although the confidence intervals are wide and include the null value. No other clinical cohort studies reported occurrences of endometrial cancers.

We did not establish that a clinically significant difference in mean age at first birth exists among parous women with systemic lupus erythematosus compared to the population. We estimated that the mean age at first birth was just a few months younger for women with lupus, although the confidence interval included zero or the possibility that the mean age at first birth for women with lupus was a few months older than the general population. Overall, this argues against a clinically significant difference in mean age at first birth for women with systemic lupus erythematosus. Thus, among the reproductive factors that could potentially play a role in increasing risk of reproductive malignancies, age at first birth appears much less likely to be a factor than the other factors described above.

Obesity: Our findings indicating an increased prevalence of obesity in our cohort compared to members of the general population is consistent with existing literature suggesting that individuals with systemic lupus erythematosus may be at great risk of obesity (88).

Since obese women are at greater risk of endometrial and possibly other cancers, this factor could potentiate other factors (increased use of hormone replacement therapy and decreased use of oral contraceptives) that favor endometrial and other cancers.

Thus, the lupus cohort had a distinct prevalence profile for cancer risk factors compared to the general population. This could influence the incidence of certain malignancies in systemic lupus erythematosus.

The incomplete knowledge of risk factors for other cancers, such as hematological malignancies, leaves ample room for other pathogenic explanations of an increased risk of malignancy in systemic lupus erythematosus.

VII. CONCLUDING DISCUSSION

The subchapters presented in this thesis can be considered as small parts of a large puzzle. First, the findings presented in chapter III, Cancer Risk in a Cohort of Systemic Lupus Erythematosus Patients) are in keeping with the hypothesis that malignancy risk is increased in systemic lupus erythematosus. Although this study addressed some of the weaknesses of previous cohort studies, some limitations remain. An important weakness is the small sample size (and subsequently, there were too few events among the occurrence of solid tumors to precisely estimate how often they occur in systemic lupus erythematosus).

The findings from the meta-analysis, presented in chapter IV substantiate an increased risk of malignancy in systemic lupus erythematosus, and provide a fairly precise estimate of the risk overall and with respect to hematological malignancies. One caveat, however, is that we have assumed a " fixed effects" model, which may or may not be ideal. In addition, even with the pooling of data, the number of events was too small for most types of solid malignancies to obtain precise estimates of the SIR.

Regarding the results of both chapters III and IV, some of the malignancies occurring in the general population may be subject to misclassification bias. That is, cancers in lupus patients may be more likely to be brought to medical attention (because these individuals regularly see physicians), than they would be in individuals who are not systematically followed in the medical system. In the case of both breast and cervical cancers, women who have regular contact with physicians may have more regular screening procedures (i.e. mammograms and pap tests). Conceivably, small or early neoplasms may be detected by screening that may never have surfaced clinically; this could inflate the incidence of cancer in the cohort. However, the most striking occurrence of increased risk of hematological cancers seems unlikely to be subject to this bias, as there is no formal screening mechanism. (Of course, bias could still

operate, as during the course of the periodic clinic visits, history, physical exam, and routine lab tests may uncover a hematological malignancy sooner in a lupus patient than in someone in the general population. This might be more likely to create an increase in "lead time" but not overall malignancy incidence, and thus may not actually bias the incidence rate or SIR, providing the follow-up is sufficiently long.)

Regarding the findings of chapter V, The Sensitivity and Specificity of Postal Survey and Chart Review Methods of Cancer Ascertainment, we found that some malignancies were missed both on self-report and by chart review. However, our estimates of the sensitivity of these methods of cancer ascertainment are somewhat higher than some other studies (30; 31). This may reflect the fact that individuals with systemic lupus erythematosus have regular medical follow-up. Specifically with respect to the relatively high estimate we obtained for the sensitivity of self-report of malignancies, systemic lupus erythematosus patients may be more knowledgeable than the general population about their health history (and be more comfortable disclosing this information). Thus, these parameter estimates are not necessarily generalizable to non-lupus populations, although the same factors (periodic follow-up and a high level of knowledge) would likely be operational for groups of individuals with other chronic illnesses that are being surveyed for cancer incidence. It should be noted also that the confidence intervals of our estimates are wide and the lower estimates of sensitivity for methods of cancer ascertainment obtained by other studies are contained within these bounds.

With respect to the findings in chapter VI, The Prevalence of Factors Influencing Cancer Risk in Systemic Lupus Erythematosus, we believe we have presented the most thorough assessment to date of risk factor prevalence for malignancies within a cohort of individuals with systemic lupus erythematosus, at least with respect to social habits, reproductive issues, and obesity. However, it is also known that exposures to alkylating agents and immunosuppressive drugs increase the risk of some cancers. We did not include this as a risk factor because a population comparison is difficult to formulate,

given the very low incidence of exposure to these agents in the population. However, we were able to make a comparison between the prevalence of a potentially protective factor, NSAID use, within a lupus cohort and the general population.

Also, we did not present an assessment of dietary factors believed to be associated with cancer because this would have required the collection of detailed information that would be of questionable value if obtained retrospectively. As well, there is no consensus currently as to how best to isolate components of the diet history with respect to individual factors of interest (beta-carotene, fibre, etc.) and analyze them. The complexity involved thus makes consideration of dietary factors somewhat prohibitive in a study such as ours. If future studies of lupus cohorts are able to generate precise estimates of the solid tumors that are believed to be influenced strongly by dietary factors (such as GI tumors) and these estimates indicate an increased incidence of these tumors, then further study on dietary factors in systemic lupus erythematosus may be warranted.

VIII. FINAL CONCLUSIONS AND SUMMARY

The risk of malignancy in systemic lupus erythematosus patients appears to be increased compared to that of the general population. The increased risk is due in part to a strikingly elevated incidence of hematological malignancies in individuals with systemic lupus erythematosus. Risk factor profiles could influence the incidence of certain malignancies in systemic lupus erythematosus, although the incomplete knowledge of risk factors for other cancers, such as hematological malignancies, leaves ample room for other explanations of an increased risk of malignancy in systemic lupus erythematosus. All the same, attempts should be made to minimize the impact of known risk factors for malignancy that seem to be of high prevalence in systemic lupus erythematosus (such as obesity).

As we now have further evidence of an elevated risk of malignancy in systemic lupus erythematosus, this study will be followed by a case-control project in which information on risk factors for the development of cancer will be examined in a larger number of individuals. Future basic research is necessary to evaluate potential genetic and environmental risk factors.

For the present, patients with systemic lupus erythematosus, and their physicians, should follow standard policies for screening of malignancies, such as cervical cancers and breast cancers, as is advocated for the general population. In addition, physicians treating patients with systemic lupus erythematosus should be alert to any changes that suggest a possible malignancy (for example, the new development of persistent lymphadenopathy, which may suggest lymphoma) and arrange appropriate investigations without delay.

Acknowledgments.

The following individuals have provided assistance in the collection, analysis, and presentation of the data that appears in this thesis:

1. Dr. A. Clarke, Dr. JF Boivin, Dr. L. Joseph, and Dr. R. Rajan were responsible for the study design of the Montreal lupus cohort study on cancer incidence. These individuals formed my Thesis Committee and provided on-going assistance and direction in terms of formulating the additional projects on sensitivity and specificity of different methods of cancer ascertainment and malignancy risk factor prevalence. They also provided considerable editorial advice. Dr. Clarke and Dr. Boivin functioned as co-supervisors.

2. In addition, Dr. L. Joseph provided considerable assistance with statistical aspects of all work done in this thesis. Dr. Joseph wrote the S-plus software program that was used to estimate cancer prevalence and sensitivity and specificity using all three methods of cancer ascertainment.

3. The design of the meta-analysis was based on previous work of Dr. Boivin in another cohort of non-lupus patients.

4. The original study to provide a refined estimate of the incidence of malignancy in systemic lupus erythematosus was proposed by Dr. A. Clarke, who set in place much of the infrastructure necessary to collect the data, specifically by arranging for the questionnaire administration and chart review of MGH Lupus Clinic patients. Dr. A. Moore and Dr. P. Fortin assisted with this. Dr. Clarke also arranged for the tumor registry and mortality database linkage, in conjunction with Dr. R. Rajan.

5. The Quebec tumor registry and the Quebec mortality database are acknowledged for data provided; Mr. M. Beaupre of the Quebec tumor registry was instrumental in the performance of the linkage. Mr. Beaupre also answered questions relating to technical aspects of the linkage and reviewed the registry records where there were discrepancies between registry data and cancer ascertainment by the other methods.

6. Tina Panaritis, Popi Panaritis, and Diane Ferland of the Division of Clinical Epidemiology provided additional research assistance. Dr. E. Nashi and David Prichal assisted with chart review.

7. Calculation of SIRs for different methods of cancer ascertainment (Chart review/ Survey VS. Tumor Registry data) for the MGH cohort was performed by Yvan St. Pierre, who also did the calculation of most of the population risk factor figures.

8. The questionnaire for determination of risk factors for malignancies was provided by Dr. R. Ramsey-Goldman. Dr. Andrew Moore did the majority of the work in terms of initial collection and review of the questionnaire information.

9. The Arthritis Society and the Singer Family Lupus Research Fund provided operational funds for the collection of data and registry linkage ; the Division of Clinical Epidemiology at the Montreal General Hospital provided postgraduate fellowship funding.

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