NOTE TO USERS

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Double Trouble:
Exploring the Link Between
Systemic Lupus Erythematosus
and Cancer

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PREFACE

Contributions of Authors

Submission guidelines stipulate that when co-authored papers are included in a thesis, the candidate must make an explicit statement as to who contributed to each work, and to what extent. I thus in this preface outline these details, for each of the five manuscripts included in my thesis.

MANUSCRIPT I: SYSTEMIC LUPUS ERYTHEMATOSUS AND CANCER

The initial draft of this review was written by Sasha Bernatsky, with the input of Drs. Clarke and Ramsey-Goldman. All three co-authors worked jointly on producing the final version of this paper.

MANUSCRIPT II: AN INTERNATIONAL COHORT STUDY OF MALIGNANCY IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

The study was proposed by members of the Systemic Lupus International Collaborating Clinics (SLICC) network (who appear as co-authors), including Drs. Clarke and Ramsey-Goldman, the two individuals who established the infrastructure necessary to collect the data. These two were joined by Dr. JF Boivin, Dr. L. Joseph, and Dr. R. Rajan in being responsible for the study design. Initial applications for operational grants were written by Drs. Clarke and Ramsey-Goldman, with the input of Drs Bernatsky, Boivin, Joseph, and Rajan. Sasha Bernatsky worked on all aspects of the data collection with the other collaborating co-authors. Data analyses were performed by Yvan St. Pierre and Sasha Bernatsky, with the supervision and assistance of Lawrence Joseph. Specifically, Yvan St. Pierre, statistician employed by Dr. Clarke, calculated the expected number of malignancies; Sasha Bernatsky and Yvan St. Pierre together determined the observed number of malignancies, and derived the SIRs and 95% CI. Sasha Bernatsky wrote the computer program to calculate the hierarchically modeled SIRs with the assistance of Dr. Joseph. The manuscript was written by Sasha Bernatsky, with the primary input of Drs. Clarke, Ramsey-Goldman, Boivin, Joseph, and. Rajan, and the additional input of the other collaborating co-authors.

MANUSCRIPT III: BREAST CANCER STAGE AT TIME OF DETECTION IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

This study was proposed by Sasha Bernatsky after discussions with her thesis committee, Drs. Clarke, Boivin, Joseph, and Rajan. Sasha obtained the population data on staging and performed the analyses. The manuscript was written by Sasha Bernatsky, with the primary input of Drs. Clarke, Ramsey-Goldman, Boivin, Joseph, and Rajan, and the additional input of the other collaborating co-authors.

MANUSCRIPT IV: NON-HODGKIN'S LYMPHOMA IN SYSTEMIC LUPUS ERYTHEMATOSUS

This study was proposed by Sasha Bernatsky after discussions with her thesis committee, Drs. Clarke, Boivin, Joseph, and Rajan. Sasha Bernatsky obtained the population data regarding demographics and survival in non-Hodgkin's lymphoma (NHL) cases that occurred in the general population, and performed the analyses. The manuscript was written by Sasha Bernatsky, with the primary input of Drs. Clarke, Ramsey-Goldman, Boivin, Joseph, and Rajan, and the additional input of the other collaborating co-authors.

MANUSCRIPT V: FACTORS ASSOCIATED WITH ABNORMAL PAP RESULTS IN SYSTEMIC LUPUS ERYTHEMATOSUS

This study was proposed by Sasha Bernatsky. Sasha Bernatsky compiled the data regarding the self-reported incidence of abnormal pap tests (as well as the relevant demographical, clinical, and other factors) from the contributing centres, and performed the analyses. The manuscript was written by Sasha Bernatsky, with the primary input of Drs. Clarke, Ramsey-Goldman, Boivin, Joseph, and Rajan, and the additional input of the other collaborating co-authors.

ABSTRACT:
Concern exists that individuals with systemic lupus erythematosus (SLE) have increased susceptibility to cancer compared with the general population. My thesis contains five chapters, each presenting a different perspective on the issue of cancer in SLE.

Although past literature has suggested an increased risk of cancer in SLE, conclusions from earlier studies were not uniform. I review this earlier data in the first chapter of my thesis.

The absence of adequate data regarding malignancy risk in SLE meant that a large, multicentre effort was needed. We have recently completed this multi-centre cohort study, comparing cancer risk in SLE relative to the general population. In the second chapter I present my analyses of these data, which confirm an increased risk of cancer in SLE. The risk is particularly evident for non-Hodgkin's lymphoma (NHL), where an almost four-fold increased risk is estimated.

A potential bias which has been invoked as a possible explanation for the associations between cancer and other chronic disease exposures has been variously called "misclassification", "detection" or "surveillance" bias. If this bias, related to a potential for greater scrutiny for cancer in SLE patients, does exist, one could expect that cancers in SLE patients are diagnosed at earlier stages than in the general population. I examine this in the third chapter, presenting my work that does not support the presence of "surveillance" bias in the results from the multi-centre SLE cohort study.

In the fourth chapter, I describe the demographic factors, subtypes, and survival of the NHL cases that arose in the multicentre SLE cohort sample. The data suggest that aggressive NHL subtypes and poor outcome are common in SLE.

Though the pathogenesis of cancer in SLE is unknown, one theory is that exposure to immunosuppressive medications is a factor. Although definitive evidence is not available, I present, in the final chapter, my findings within the Montreal General Hospital SLE cohort, where immunosuppressive exposure was associated with abnormalities on cervical cancer screening (Pap) tests.

In summary, our work demonstrates an increased risk of cancer in SLE; this is not likely due to surveillance bias. Immunosuppressive exposure may be associated with abnormal Pap tests; further work will determine whether immunosuppressives confer risk for other neoplastic events in SLE, particularly NHL.

RESUME
L'on croit que les individus souffrant de lupus érythémateux disséminé (LED) ont plus tendance à avoir un cancer que la population générale. Ma thèse comporte cinq chapitres traitant d'aspects différents de la question du cancer dans les cas de lupus.

Bien que la documentation existante suggère un risque accru de cancer dans les cas de lupus, les conclusions des études ne sont pas uniformes. Le premier chapitre de ma thèse porte sur la révision de ces données.

L'absence de données adéquates sur le risque de malignité dans les cas de LED indiquait le besoin d'une étude multicentrique d'envergure. Nous avons récemment terminé une étude de cohorte multicentrique visant à comparer le risque de cancer dans les cas de lupus à celui de la population générale. Dans le deuxième chapitre, je présente mon analyse de ces données confirmant un risque accru de cancer dans les cas de LED. Ce risque est particulièrement évident dans les cas de lymphomes non hodgkiniens (LNH) pour lesquels on estime q'il est quatre fois plus grand.

Comme explication possible de l'association entre le cancer et d'autres expositions à des maladies chroniques, l'on a évoqué la présence possible d'un biais appelé « de classification », « de détection » ou encore « de surveillance ». S'il y a effectivement un biais lié à une surveillance minutieuse du cancer dans les cas de LED, l'on pourrait s'attendre à ce que les cancers chez les patients souffrant de LED soient diagnostiqués à un stade moins avancé que chez la population générale. Je me suis penchée sur cette question dans le troisième chapitre, en présentant mon travail qui n'appuie pas la présence d'un biais de « surveillance » dans les résultats de l'étude de cohorte multicentrique de LED.

Dans le quatrième chapitre, je traite des caractéristiques démographiques, des sous-types et de la survie des cas de LNH survenus au sein de l'échantillon de la cohorte multicentrique de LED. Les données semblent indiquer que l'on retrouve plus souvent les formes agressives de LNH et une évolution défavorable de la maladie.

Bien que la pathogenèse des cancers dans les cas de LED soit inconnue, il y a une théorie voulant que l'exposition aux immunosuppresseurs constitue un facteur. Malgré l'absence de preuves concluantes, je présente dans le dernier chapitre les résultats que j'ai obtenus au sein de la cohorte de l'hôpital général de Montréal pour laquelle l'exposition aux immunosuppresseurs était liée à des résultats anormaux de dépistage du cancer cervical (Papanicolaou).

En résumé, notre travail démontre un risque accru de cancer dans les cas de LED qui ne serait apparemment pas dû à un biais de surveillance. L'exposition aux immunosuppresseurs pourrait être associée à des résultats anormaux des tests de Papanicolaou. D'autres recherches doivent être menées afin de déterminer si les immunosuppresseurs entraînent pour les gens souffrant de LED un risque d'autres néoplasies, en particulier les LNH.

1. Chapter One

1.1 Introduction

This thesis examines the association of cancer with systemic lupus erythematosus (SLE). SLE is the second most common autoimmune disorder to occur in women of childbearing age, with an annual incidence as high as 73 cases/million person-years, and a prevalence of 500/million population (1;2). Medical advances have improved survival in this often life-threatening disease, but morbidity remains considerable. For decades, concern has been mounting that individuals with SLE have an increased susceptibility to cancer. Recent data confirm that certain cancers, particularly hematological, occur more frequently in SLE than in the general population. Numerous pathogenic mechanisms are possible, but hypotheses remain largely speculative.

1.2 Objectives of this thesis

The first objective of my thesis work was to provide a comprehensive overview of past and present evidence regarding the association of cancer in SLE. My second objective was to determine if the incidence of cancer is greater in SLE compared to the general population. Then, since criticisms of previous studies of cancer in SLE included the possibility that "surveillance bias" explained the findings, a third objective was to investigate for the presence of this bias by determining whether cancers in SLE are diagnosed at earlier stages than in the general population. A fourth objective was to determine the demographic factors, subtypes, and survival of a cancer type (non-Hodgkin's lymphoma) in SLE. The fifth and final objective of my thesis work was to determine whether immunosuppressives are associated with neoplastic events (cervical dysplasia, according to self-reported abnormal Pap tests) in SLE.

There is still much work to be done, but I believe that my work has advanced, to an extent, the understanding of the association between SLE and cancer.

1.3 Thesis Overview

My thesis is a compilation of five manuscripts that are either published, in press, or submitted. These are organized into five chapters, corresponding to my five objectives. Each chapter contains an introductory or linking section preceding each manuscript. The first manuscript (which follows this introduction) is a comprehensive review entitled *Systemic Lupus Erythematosus and Cancer*. It is currently in press, in the journal Rheumatic Disease Clinics of North America. This review provides a synthesis of previously completed studies of cancer in SLE, touching also on some recent results of the research that will be presented in chapter two.

Chapter two contains a short preface, followed by the second manuscript (recently submitted to Lancet). The second manuscript is entitled *An International Cohort Study of Malignancy in Systemic Lupus Erythematosus*. This details the results of our recent cohort study estimating malignancy risk in SLE.

In chapter three, after a short bridging section, I present the third manuscript. This manuscript, published in Lupus, 2004, examines cancer stage at time of detection in SLE patients. In brief, the paper presents data that do not support the argument that "detection bias" accounts for reports of increased cancer risk in SLE.

The multi-site international cohort study that examined cancer risk in SLE found in particular a several fold increased risk of non-Hodgkin's lymphoma (NHL), consistent with other studies. In chapter four, I introduce and then present the fourth manuscript (*Non-Hodgkin's*

Lymphoma in Systemic Lupus Erythematosus). This manuscript is a description of the subtypes of NHL in the international multicentre SLE cohort, with a description of pertinent demographic factors (age, sex, and race) in the NHL cases. I also provide some preliminary work with respect to the stage and survival of the NHL cases that arise in SLE. This is important, particularly if the histological subtypes of NHL cancers that present in SLE vary from that expected in the general population.

Although the pathogenesis behind the increased risk of cancer in SLE is unknown, one theory is that exposure to immunosuppressive medications is a factor driving the phenomenon. Though definitive evidence is not available, I present, in the final chapter, the final manuscript describing the influence of immunosuppressive exposure on the odds of abnormal Pap test results occurring in women with SLE.

My thesis ends with a summary and conclusions. References for each manuscript are contained within the relevant chapter, and that any additional references are given at the very end of the thesis, after the acknowledgements.

1.4. First Manuscript:

Systemic Lupus Erythematosus and Cancer

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SYNOPSIS:
For decades, concern has been mounting that individuals with systemic lupus erythematosus (SLE) have increased susceptibility to cancer. Recent data confirm that certain cancers, particularly hematological, occur more frequently in SLE than in the general population. Numerous pathogenic mechanisms are possible, but hypotheses remain largely speculative. In particular, there are inadequate data on how cancer risk in SLE may be related to medication exposures. To evaluate the impact of medication exposures on cancer risk in SLE, cooperative efforts of SLICC and CaNIOS are currently in progress. This should provide much-needed insight into the pathogenesis of the association between cancer and SLE.

For decades, concern has been mounting that individuals with systemic lupus erythematosus (SLE) have increased susceptibility to cancer. The first clinical evidence of an association between cancer and SLE came from case and case series reports (1-3). Early cohort studies (4-10) produced various estimates of the cancer risk in SLE patients, and the conclusions have not been uniform (11-13). Given the estimates and their confidence intervals, the findings of all studies could be compatible with an increased risk of cancer in SLE compared with the general population. Recent efforts have confirmed this increased risk (14), as we will review.

A Review of Cancer Risk in SLE

Efforts to estimate cancer risk in SLE have most often been done with clinical cohorts (6-13), where subjects have a definite diagnosis of SLE, either by American College of Rheumatology (ACR) criteria (15) or by clinical judgment. As SLE is a relatively rare condition (16), the sizes of these cohorts have been relatively small, ranging from 116 (13) to 724 (12). Alternatively, attempts (5; 17) have been made to generate much larger national cohorts, through assembling the names of individuals with a hospital-discharge diagnosis of SLE, and then linking these names to the national cancer registry. These cohorts were much greater in size than the clinical cohorts (for example, Mellamkjaer et al.'s cohort (5) numbered 1,585 subjects, and Bjornadal's cohort was N= 5 715 (17)). These hospital-discharge studies may be biased, however, in that the subjects represent only a specific group of SLE patients (those admitted to hospital), and may not necessarily reflect the experience of the entire SLE population.

The parameter estimate presented in all cohort studies estimating cancer risk in SLE has been the standardized incidence ratios (SIR, ratio of observed to expected cancers). The SIR estimates (for cancer overall) in these studies ranged from as low as 1.1 (95% Confidence Interval [CI] 0.7-1.6) (12) to as high as 2.6 (95% CI 1.5-4.4) (7). All studies involved relatively small numbers of subjects, with resultant imprecise estimates, particularly for the clinical cohorts (Table 1).

The limitations of previous studies have recently been surmounted by a multi-site international cohort study. It involves 23 centres from the Systemic Lupus International Collaborating Clinics [SLICC] and Canadian Network for Improved Outcomes in Systemic Lupus [CaNIOS] networks of lupus researchers (14) and draws from academic and community-based

practices to produce a study sample representative of the general SLE population. This study showed, for all cancers combined, an SIR estimate of 1.15 (95% CI 1.05, 1.27). This is consistent with earlier estimates, although vastly more precise than earlier studies. Thus, the data do support a small increased risk for SLE patients in cancer overall.

The next question of interest is then "Are specific types of cancers increased in SLE?". Several of the cohort studies of malignancy in SLE (mentioned above) have suggested an increased risk of particular cancer types; hematological malignancies (particularly non-Hodgkin's lymphoma, NHL) have been implicated most often. In addition, increased incidence rates of lung, hepatobiliary, and other kinds of non-hematological tumors have been variously suggested.

Hematological Malignancies:

Most of the data from earlier cohort studies strongly suggested an increased incidence of hematological malignancies, generally estimating that the risk for patients with SLE is increased several fold compared with the general population (6-9; 11-13). Because the SIR estimates were generally based on small numbers, the confidence intervals for these earlier estimates were almost always wide.

The results from the recent multi-centre international cohort study demonstrated almost a 4-fold increased risk for NHL in SLE (14).This is consistent with previous estimates, though the results from the multi-centre international effort are vastly more precise than previous studies using clinical cohorts (6-9; 11-13).

Non-Hodgkin's lymphoma includes a heterogeneous group of subtypes, including both indolent and more aggressive types (18). There is some suggestion that more aggressive NHL histological subtypes predominate in SLE (19;20). Preliminary data suggest a poorer prognosis in SLE patients that develop NHL compared with the general population (21). However, it is not known if this may be related to more aggressive presentation, delayed cancer diagnosis, decreased survival related to SLE or other co-morbidity, or other factors. There is some suggestion that some therapeutic measures, particularly radiation therapy, may be inappropriately withheld from SLE patients that develop cancer (22). Ongoing collaborative efforts of clinical research networks

SLICC and CaNIOS should provide much-needed insight into the patterns of presentation, prognosis, and etiology of NHL in SLE.

Other Tumors:

In contrast to hematological malignancy, the findings of cohort studies regarding other specific cancers types have not been uniform. In general, estimates from even the largest studies have yielded inconclusive results for most types of non-hematological tumors. However, for lung cancer, there are some fairly consistent results suggesting a slightly increased risk for SLE patients compared with the general population. The recent multi-site international cohort study showed this, with an SIR for lung cancer in SLE of 1.37 (95% CI 1.05, 1.76) (14). If this result is compared to earlier data, one can see that the SIR point estimates from five of the earlier clinical cohort studies (6;8;9;12;13) had suggested an increased risk of lung cancer (SIR estimates of 1.1 to 4). Ramsey-Goldman et al.'s results (8) produced the largest SIR; this was the only study of these five where the confidence interval did not include the null value (SIR 3.1, 95% CI 1.1, 10.2). In the two studies that examined cancer risk in hospital-discharge SLE cohorts, both showed a definitely increased risk of lung cancer, with SIR estimates of 1.73 (95% CI 1.25, 2.32) (17) and 1.9 (95% CI 1.1, 3.1) (5).

Another non-hematological cancer type where there seems to be some evidence for an increased risk in SLE is primary hepatobiliary cancer. The results of the large multi-centre cohort study supported this increased risk, with an SIR estimate of 2.60, (95% CI 1.25, 4.78) (14). Mellemkjaer, in a Danish hospital-discharge SLE cohort, found an increased risk of liver cancer (SIR 8.0, 95% CI 2.6, 18.6) (5). Bjornadal's estimate for primary liver cancer, using the same method of cohort assembly in Sweden, was 1.6 (0.93, 2.6) (17).

There is little that is definitive regarding other non-hematological cancers. Very interestingly, the recent multi-centre cohort study suggested that this sample over all had less occurrence of breast cancer than in the general population (SIR 0.76, 95% CI 0.60, 0.95) (14),. This is intriguing because there has been some suggestion (based on earlier clinical cohorts) of increased breast cancer risk in SLE, with a Chicago-based study published in 1998 which found increased occurrence of breast cancer in white women with SLE (SIR 2.9, 95% CI 1.4,6.4) (8). At least one

other study was supportive of this magnitude of risk, although the confidence limits included the null value (SIR 3.4, 95% CI: 0.9-8.7) (23).The SIR point estimates for breast cancer risk in several other cohorts (1.2 to 2.8) could be consistent with a small increased risk of breast cancer in SLE (7-11), but the confidence intervals for these estimates were quite wide, and included the possibility of a small protective effect. On the other hand, two clinical cohort studies whose SIR point estimate was below one (6; 12) also had wide confidence intervals, with upper limits that included the possibility of about a two-fold increased risk. One of the studies in a hospital-discharge SLE cohort provided evidence of a decreased risk of breast cancer in SLE (SIR 0.72, 95% CI 0.54, 0.95) (17) while the SIR point estimate of the other hospital-discharge cohort was 1.0 (95% CI 0.5, 1.7) (5). Thus, there appears to be some inhomogeneity of published results with respect to breast cancer in SLE

Because SLE is a disease predominantly of women, there is a natural interest in the incidence of cancers of the female genital tract (including vulvar and vaginal, invasive cervical, ovarian, and endometrial cancers). Even the international cohort study recorded only a few of these relatively rare events. In all but one of the published cohort studies (6; 9; 11; 12; 17) the SIR estimates for cervical neoplasms have been imprecise; Cibere et al. was the only study (6) that produced a clearly increased risk of cervical cancer (SIR 8.2, 95% CI 1.6, 23.8). Cibere et al was the only single-centre cohort study which included both in-situ and invasive cervical neoplasms; the other studies, including the international study, focused only on invasive lesions, hence finding fewer cervical cancers and less precise SIR estimates. Data do suggest that women with SLE have an increased prevalence of cervical dysplasia and atypia on Pap testing, compared with the general population (24-27).

With respect to ovarian malignancy, the results from the international multi-centre cohort study showed a trend suggesting decreased risk for ovarian cancer (SIR 0.62, 95% CI 0.28, 1.18). This protective effect for ovarian cancer was demonstrated in Bjornadal's cohort, assembled through hospital discharge (SIR 0.48, 95% CI 0.19, 0.99) (17) although for the category of "unspecified female cancer" the SIR was above 1 (2.70, 95% CI 1.09, 5.57) which raises the question as to whether some of these unspecified female cancers in SLE were ovarian

malignancies, hence explaining the low number of ovarian cancers recorded in their SLE sample. The results from the clinical cohort studies (7-12) have been variable and imprecise.

Endometrial cancer occurrence in clinical cohort studies of malignancy in SLE (6-8; 10-12) has been reported very rarely. The recent international cohort study estimated a decreased incidence of endometrial cancer in SLE (SIR 0.36, 95% CI 0.13, 0.78) (14).

The decreased risk of colorectal cancer seen in rheumatoid arthritis (RA) (28) and other rheumatic populations (29-31) has not been demonstrated in SLE. On the other hand, research in SLE has also not shown the same dramatic increased risk of bladder cancer as has been demonstrated in oral cyclophosphamide-treated vasculitis patients (32; 33).

To summarize, SLE patients are at particular risk for certain types of cancer, notably NHL, and likely lung, and hepatobiliary. Quite variable results have been found for other tumors; the relative inhomogeneity of published results might suggest a complex interplay of risk factors that differ across centres or calendar time.

Is Surveillance Bias a Concern?

There are strong reasons to believe that surveillance bias does not entirely explain the findings of an increased risk of malignancy in SLE. Breast cancer, a neoplasm amenable to screening, is not consistently increased in SLE cohort studies, in contrast to the striking increase in hematological cancers, where there is no formal screening strategy for early detection. Bias could still operate in that cancers may be uncovered sooner in a lupus patient (during a periodic clinic visit) than in the general population. This might create a "lead time" in diagnosis but not an increased cancer incidence, and thus would not bias the incidence rate or SIR, providing the follow-up time in the cohort under study is adequate.

Additionally, in a study of 1,193 women with SLE, the proportion of cancer cases presenting at a localized stage did not appear to differ from the general population, suggesting that increased scrutiny does not explain an observed increased risk of cancer in SLE (34). As well, recent data suggest that cancer mortality (not just incidence) is increased in SLE, which also argues for a true increased risk of cancer in SLE (35).

Etiology of Cancer Risk in SLE

Since the association between malignancy and SLE seems to be substantiated, what are the pathogenic pathways linking SLE and cancer? Possibilities include an increased prevalence of traditional "lifestyle" risk factors influencing cancer incidence, putative links between medication use and cancer in SLE, or potential interactions between medications and viral exposures. Also of interest are clinical characteristics, such as secondary Sjögren's or other overlap syndromes; geographical and race or ethnic factors; and intrinsic abnormalities of the immune system. Probably, different factors are of varying importance in different types of malignancies. For example, there is evidence of a common genetic predisposition to autoimmunity and hematological malignancy (36; 37), but it is unknown whether these genetic factors, or other forces, drive the risk of non-hematological cancers in SLE. Links between lung cancer and hepatobiliary cancer have been reported for other autoimmune disorders, including rheumatoid arthritis and systemic sclerosis (38; 39). Again, here it is not known what drives the observed associations; it may be the autoimmune state, or it may be other factors, such as medication exposures.

"Lifestyle" cancer risk factors in SLE: Smoking and obesity

Important "lifestyle" factors known to be associated with cancer development in the general population include smoking and obesity.

Tobacco use, particularly cigarette smoking, is an important cause of lung and other cancers (40). The prevalence of smoking in SLE has been estimated in several cohorts (41-45) but often, comparable figures for the population have not been presented. Several small studies have suggested (6) (45; 46) that the proportion of smokers in SLE is similar to that of the general population. However, in one study, among current smokers, the mean pack-years was higher in the SLE patients (47) than in the age and sex matched general population.

Obesity is associated with greater risk of endometrial, prostate, colorectal, gallbladder, and post-menopausal breast cancer (48-51). Obesity prevalence has been determined in SLE cohort studies (6; 42; 47), although a comparison with population figures has been provided only by two authors. In one cohort of SLE men and women, obesity prevalence was identical to population figures (6) (although a slightly higher value of body mass index for the definition of obesity was

used for the SLE population (52)). In another cohort study, with age adjusted for, SLE women had an increased prevalence of obesity compared with the general population (47).

The above factors seem unlikely to completely explain the association between increased cancer risk and SLE, particularly with respect to the association between SLE and NHL. Other putative determinants of an increased cancer risk in SLE include medication exposures, which are discussed below.

Medications and cancer in SLE

Although there are several case reports of malignancies associated with either azathioprine (53;54) or cyclophosphamide (55-57) in SLE, the striking association of azathioprine with lymphoreticular malignancies in the NZB/NZW mouse model of SLE (58) and in organ transplant recipients (59;60) (where cyclosporin also seems culpable) has not been clearly demonstrated in human SLE populations (61). There is also no convincing evidence that cancer occurrence is a common outcome after intravenous (IV) cyclophosphamide therapy in SLE (62-65). It must be noted that in these studies not only was the duration of follow up likely too short to adequately capture the cancer experience of these patients, but that the mean duration of exposure was also rather low, and might not reflect the experience of SLE patients treated as per the early (circa 1980's) National Institutes of Health (NIH) cyclophosphamide nephritis protocol (64). An increased risk of cervical dysplasia in SLE patients treated with cyclophosphamide has been noted, however. Also, there is evidence that at least some of the increased burden of cancer seen in rheumatoid arthritis and other rheumatic diseases is mediated by medication exposure (38; 66).

To date, no study has been designed to specifically evaluate the relative importance of alkylating agents and immunosuppressive drugs in SLE-related malignancies, although some of the low-powered cohort studies have attempted to look at the issue. Cibere (6) did not believe that use of immunosuppressive or cytotoxic agents was linked to the cancer cases in their cohort, as only two out of 27 (7%) SLE patients with cancer had been exposed to any of these agents. Other authors reported similar findings and drew the same conclusions (7; 8; 10-12). The moderately low rate of exposure to these agents, compounded by the relatively infrequent occurrence of

malignancy within observed cohorts, makes it difficult to establish the effect of these drug exposures on malignancy risk in SLE.

Although it has been observed that women with SLE have an increased prevalence of cervical dysplasia and atypia on Pap testing, compared with the general population of women (24-27), the determinants of this association are not clear. However, immunosuppressive medication exposure may be an etiologic factor (24-27), possibly related to the resultant decreased ability to clear human papilloma virus (HPV), which is a causative agent in cervical dysplasia.

In the multi-centre international cohort study of cancer incidence in SLE, the data showed an increased cancer risk (for all cancers combined, as well as for the hematological cancer group) even early in the course of SLE (14). This may suggest that cumulative drug exposure is not the primary cause of the association between cancer and SLE.

On the other hand, non-steroidal anti-inflammatories (NSAIDs) and aspirin have been suggested, in the general population, as a factor potentially protective against colorectal, breast, lung, and other tumors (67-69). Interestingly, recent evidence suggests that NSAIDs may not have as important an effect as aspirin (70). One might suspect that aspirin and NSAIDs might be used more in SLE than in the general population, and actually confer some protection against certain types of non-hematological tumors; there is some evidence to support a protective effect of aspirin against cancer development in SLE (23).

As stated earlier, research in SLE has not shown the same dramatic increased risk of bladder cancer as has been demonstrated in vasculitis patients treated with oral cyclophosphamide (32; 33). This may be due to the fact that SLE patients receive more moderate cyclophosphamide doses, usually by the IV route, which is believed to decrease the carcinogenic potential of this agent (at least in the bladder), although this is not definitively known.

The recent international cohort study estimated a decreased incidence of endometrial cancer, breast, and possibly ovarian cancer, in SLE (14). The relative inhomogeneity of published results might suggest a complex interplay of risk factors for breast cancer in SLE that differ across centres or calendar time. Possible risk factors for breast cancer in SLE in some populations might include exposure to alkylating agents (i.e. cyclophosphamide). Conversely, the use of aspirin (and

potentially NSAIDs) in some SLE patients may confer protection against the development of breast and other cancers (23). Also of interest are data suggesting that women who develop SLE enter menopause earlier than women without SLE (71). At the same time, because of clinical concern that exogenous estrogens may cause lupus flares (72), some samples of SLE women may be less likely to be maintained on hormone replacement therapy (HRT) than women in the general population. These factors (more aspirin use, or less endogenous/exogenous estrogen exposure) potentially could explain the overall decreased risk of breast cancer seen in the large international cohort study of cancer in SLE (14).

Endometrial cancer, like breast (and probably ovarian) cancer, is an estrogen-sensitive malignancy (73-75). As mentioned previously, it is possible that some female SLE study populations, being at risk for early ovarian failure (71; 76), overall tend to have less endogenous estrogen exposure than women without SLE (71). And, as also mentioned previously, in the past some clinicians avoided HRT in SLE (as it has been suspected of causing lupus flares (72)). These factors might also have mediated a decreased risk of endometrial (and possibly ovarian) cancer seen in the recent international multi-centre cohort study.

Although these hypotheses are interesting, in general, there are currently insufficient data on the role of medication exposures and cancer risk in SLE. It is on this basis that members of the SLICC and CaNIOS networks have initiated an extension of the multi-centre cohort study of cancer and SLE, in a case-cohort study, to determine how medication exposures affect the risk of cancer. The results of this work will shed much-needed light on the extent to which medications influence cancer incidence in SLE.

Potential interactions between medications and viral exposures

As well as potentially relevant exposures of immunosuppressive agents, one might also invoke viral exposures (77-80) or an interaction between immunosuppressive agents and viral exposures. It is possible that infectious exposures, particularly viruses such as the Epstein - Barr virus (EBV), may both trigger SLE (81) and create a predisposition to malignancy (82). Although this hypothesis is intriguing, EBV infection is not likely to entirely explain the increased risk of cancer in SLE, particularly with respect to the increased risk of NHL in SLE, as EBV infection is

not believed to play as primary a role in most types of NHL as it does in Hodgkin's lymphoma (83).

Use of immunosuppressive agents may predispose lupus patients to infection (or delay the clearance of infectious agents) and thus allow viral and other infectious triggers to initiate abnormal cell differentiation, conferring malignant potential. This may be true with respect to HPV and cervical dysplasia (84), and some work suggests that women with SLE have increased prevalence of HPV infection (85). Whether this is due to medication exposure or a baseline abnormality in the immunology of patients with SLE (86) is unknown. Some have suggested that the increased risk of heptobiliary cancers in SLE may be related to increased susceptibility for (or a decreased ability to clear) hepatic viral infections (5), but at present this is only a hypothesis.

Possible clinical characteristics important in SLE-related malignancy

One factor that has been postulated as a potential mediator of cancer incidence in SLE patients is the secondary occurrence of Sjögren's syndrome. Because of the striking association between "primary Sjögren's" and NHL (87), it has been proposed that secondary Sjögren's syndrome may explain some of the increased cancer risk in SLE (88;89) However, the few studies assessing the relationship (between secondary Sjögren's in SLE and cancer) have not definitively established this link . As well, the lymphoma types that arise in primary Sjögren's appear to be quite different from lymphomas that arise in other autoimmune conditions. In primary Sjögren's, marginal-cell lymphomas appear to dominate, whereas in RA (90), and possibly in SLE (19; 20), more aggressive types of lymphomas may predominate. This suggests more than one etiologic pathway in the occurrence of hematologic malignancies in autoimmune diseases.

Scleroderma can co-exist with SLE in over-lap syndromes (91), and there is evidence of a link with scleroderma and non-hematological tumors, including lung cancers (92; 93). Hepatobiliary cancer is strongly associated with autoimmune liver disease (ex. primary biliary cirrhosis (94)), which can co-exist in SLE (95). Thus, perhaps those SLE patients with specific overlap features may be the ones most likely to develop lung and hepatobiliary tumors. The unifying process may be that neoplasia arises as a consequence of inflammation or fibrosis in involved organs.

Geographical variations and race/ethnicity in cancer risk

There are, of course, important world-wide variations (96) in the baseline population cancer rates that are, in part, dependent not just on the country where one lives, but also on the racial or ethnic mix (since different race or ethnic groups have different baseline cancer risk (40; 96-98)). There has been some preliminary work within the multi-centre SLE cohort established by members of SLICC and CaNIOS, with respect to the effect of geographical factors and race/ethnicity on cancer incidence. For example, cohort members from North American countries were more likely to have a cancer than those from other countries (Odds ratio [OR] 2.0, 95% CI 1.5, 2.7) (99). This may represent a mix of effects, including clinical features, race/ethnicity, and differences in completeness of cancer registration (100-103).

Controlling for age, sex, SLE duration, and geographic location (that is, country and continent), Caucasian race in SLE was associated with the occurrence of cancer (OR 2.9, 95% CI 2.3, 3.8) (99). In terms of comparisons for specific cancer type, the possibility of an increased risk of cancer in Caucasian SLE subjects compared with subjects of all other races/ethnicities may be related more to non-hematological tumors such as breast cancer, than for hematological tumors such as NHL (8; 99).

Genetic factors and their place in the pathways between autoimmunity and NHL

The genetic abnormalities that may underlie the association between SLE and NHL are unknown. An important feature of NHL is the presence of chromosomal abnormalities (Table 2), such as translocations where an oncogene is juxtaposed next to a gene important in immune cell function (104). These chromosomal abnormalities are of interest in terms of being possible common pathways linking SLE and lymphoproliferative malignancies.

Recommendations for cancer screening SLE

With respect to what recommendations can be made to clinicians for suggested cancer screening of SLE patients, there is no evidence that any formal strategies be employed, aside from following age and specific recommendations for the general population (105). Caveats to this include the following suggestions for patients exposed to immunosuppressive agents: i) specific screening for cyclophosphamide-related bladder cancer; and, ii) recommendations for the

frequency of Pap testing in any women receiving immunosuppressive agents. These are discussed below.

Because hematuria may be the first manifestation of bladder cancer, it's been recommended that all patients treated with cyclophosphamide have a urinalysis every 3 to 6 months, even after cyclophosphamide therapy is discontinued (106). These recommendations stem from experience with the use of oral, not intravenous, cyclophosphamide in the rheumatic diseases; caution would, however, suggest the extension of these suggestions to patients receiving cyclophosphamide regardless of the route. The authors of the review in which these recommendations are found further suggest that patients with cyclophosphamide-induced cystitis should also undergo cytological examination of the urine every 6 to 12 months, and any atypia or dysplasia followed up with cystoscopic evaluation; they add that since urine cytology is relatively insensitive for detecting lower-grade malignant lesions, that routine cystoscopy every 1 or 2 years should be considered for all patients with cyclophosphamide-induced hematuria.

In addition to the above, it should be noted that recent guidelines published by the American College of Obstetricians and Gynecologists (ACOG) (107) recommend that all women receiving immunosuppressive agents should be screened at least annually for cervical cancer with Pap smears.

As a final point, it is noteworthy that Bruce et al. (45) found that physicians providing care for patients with SLE tended not to provide advice regarding cessation of smoking. Rectification of this would assist in limiting the damage done to persons with SLE, not only in coronary heart disease but presumably with respect to malignancies as well.

Summary

Recent data confirm that certain cancers, particularly hematological, occur more frequently in SLE than in the general population. Numerous pathogenic mechanisms are possible, but hypotheses remain largely speculative. In particular, there are inadequate data on how cancer risk in SLE may be related to medication exposures. To evaluate the impact of medication exposures on cancer risk in SLE, cooperative efforts of SLICC and CaNIOS are currently in

progress. This should provide much-needed insight into the pathogenesis of the association between cancer and SLE.

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Table 1: Standardized Incidence Ratios (SIR) of Overall Cancer Occurrence in Systemic Lupus Erythematosus (SLE) with 95% confidence intervals (CI)

Clinical Cohort studies				
First Author (City Centre)	**Country**	**Calendar Years**	**N**	**Total Cancer SIR (95% CI)**
Pettersson (7) (Helskinki)	Finland	1967-1987	205	2.6 (1.5, 4.4)
Ramsey-Goldman (8) (Illinois)	USA	1985-1995	616	2.0 (1.4, 2.9)
Cibere (6) (Saskatoon)	Canada	1985-1995	297	1.6 (1.1, 2.3)
Nived (13) (Lund)	Sweden	1981-1998	116	1.5 (0.8, 2.6)
Sweeney (11) (Pittsburgh)	USA	1981-1991	219	1.4 (0.5, 3.0)
Sultan (10) (London)	UK	1978-1999	276	1.2 (0.5, 2.1)
Abu Shakra (12) (Toronto)	Canada	1970-1994	724	1.1 (0.7, 1.6)
Hospital Discharge Database studies				
First Author (Ref)	**Country**	**Calendar Years**	**N**	**Total Cancer SIR (95% CI)**
Bjornadal (17) (Stockholm)	Sweden	1964-1995	5715	1.4 (1.3, 1.5)
Mellemkjaer (5) (Copenhagen)	Denmark	1977-1989	1585	1.3 (1.1, 1.6)

Table 2: Selected chromosomal abnormalities seen in specific subtypes of NHL

Molecular Events	Translocation	Oncogene Affected	Example of NHL Subtype
Apoptosis inhibition	t(14;18)(q32;q21)	*bcl-2*	Follicular
	t(1;14)(p22;q32)	*bcl-10*	Marginal zone MALT*
Lymphocyte proliferation	t(3;16)(q27;p11)	*bcl-6*	Diffuse large B cell
	t(8:14)(q24:q32)	*c-myc*	Burkitt's

* MALT=mucosal associated lymphoid tissue

2. Chapter Two

2.1 Introduction to Second Manuscript.

As was reviewed in the previous chapter, single-center cohort studies conducted in several countries over the past ten years have produced varying estimates of relative cancer risk in SLE, all with fairly wide confidence intervals. This led to some uncertainty regarding the interpretation of these results, and recognition of the need for a larger, multi-center effort.

The limitations of previous studies have recently largely been surmounted by a multi-site international cohort study that was initiated and coordinated by our research team. It involves 23 centers from two SLE research networks, the Systemic Lupus International Collaborating Clinics (SLICC) and the Canadian Network for Improved Outcomes in Systemic Lupus (CaNIOS). Altogether, the cohort includes almost 10,000 subjects (3). The multi-site international cohort study has drawn from academic and community-based practices to produce a study sample representative of the general SLE population. The results of this work are presented next (*An International Cohort Study of Cancer in Systemic Lupus Erythematosus*). This manuscript has recently been submitted to Lancet.

2.2. ManuscriptTwo:

An International Cohort Study of Cancer in Systemic Lupus Erythematosus (SLE)

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Background: Mounting evidence supports an association between Systemic Lupus Erythematosus (SLE) and malignancy, but earlier efforts were unable to quantify the association precisely. Our purpose therefore was to ascertain the incidence of cancer in SLE patients, compared to the general population.

Methods: We assembled a multi-site international cohort (23 centres) of subjects with a diagnosis of SLE. Subjects at each centre were linked to regional tumor registries to determine cancer occurrence. Standardized incidence ratios (SIR) were calculated as the ratio of observed to expected cancers. Cancers expected were determined by multiplying person-years in the cohort by the geographically matched age, sex, and calendar-year specific cancer rates, and summing over all person-years.

Findings: The 9,547 patients from 23 centres were observed for a total of 76,948 patient-years with an average follow up of 8 years. Within the observation interval, 431 cancers occurred. The data confirmed an increased risk of cancer in SLE. For all cancers combined, the SIR estimate was 1.15 (95% CI 1.05, 1.27), for all hematological malignancies, it was 2.75 (95% CI 2.13, 3.49), and for non-Hodgkin's lymphoma, it was 3.64 (95% CI 2.63, 4.93). The data also suggested an increased risk of lung (SIR 1.37, 95% CI 1.05, 1.76), and hepatobiliary (SIR 2.60, 95% CI 1.25, 4.78) cancers.

Interpretation: These results support an association between SLE and cancer, which is most evident for hematological malignancies, particularly lymphoma. It is not yet known whether this association is mediated by genetic factors or exogenous exposures.

Key words: Systemic Lupus Erythematosus, malignancy, cancer, lymphoma

Introduction

Systemic Lupus Erythematosus (SLE) is the second most common autoimmune disorder to occur in women of childbearing age. Although survival has improved, morbidity related to the disease and its treatment remains considerable. Mounting evidence supports an association between SLE and malignancy (1). Cohort studies (2-10) produced varying estimates of relative cancer risk in SLE, most with fairly wide confidence intervals. The standardized incidence ratios (SIR, quotient of observed to expected number of cancers) ranged from 1.1 (95% confidence interval [CI] 0.7, 1.6) (2) to 2.6 (95% CI 1.5, 4.4) (7) in these studies (Table 1). These efforts could not quantify precisely and accurately the association between SLE and malignancy, due to small study sizes and unrepresentative sampling. This led to recognition of the need for a larger, multi-centre cohort effort (11).

The Systemic Lupus International Collaborating Clinics (SLICC) (12) agreed in 1998 to prioritize this effort, working in conjunction with the centres from the Canadian Network for Improved Outcomes in Systemic Lupus (CaNIOS). We attempted to overcome previous limitations by assembling a multi-site international cohort, to compare the incidence of malignancy in SLE with that expected for an age, sex, and calendar-year matched geographically appropriate general population.

Methods:

The study was approved by the ethics review boards of all participating institutions, and the procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 1983.

Study subjects:

All patients with definite SLE according to American College of Rheumatology (ACR) (13; 14) or clinical criteria were eligible for inclusion. The study base encompassed 23 collaborating lupus centres in North America, Europe, Iceland, and Asia (Table 2). Patients included have been followed in either outpatient clinics and/or in the inpatient hospital setting. Although most investigators are based at tertiary academic centres, they actively encourage the enrollment of patients from community physicians.

Data Collection:

Data were collected on patient birth-date and sex, dates of lupus diagnosis and cohort entry, and date of death, if applicable. Observed cancers were determined by linkage of the study subjects with regional cancer registries (listed in the acknowledgements). Vital statistic linkages were performed for patients deceased or lost to follow-up, in the United States (US) cohorts with the National Death Index, and for the non-US cohorts with regional vital statistic registries. For three centres, ethical approval did not permit linkage of lost-to-follow up patients to vital status registries. Of the sample, these centres contributed only 515 subjects, very few of whom were lost to follow up, but to be conservative, we assumed that any lost to follow-up patients from these centres remained at risk until the end of the observation interval.

Analysis:

For each cancer type, we determined the ratio of the observed incidence of cancer with that expected (SIR). In secondary analyses, SIRs were estimated for subgroups according to sex, age group, and duration of SLE.

The expected numbers of cancers were calculated by multiplying person-years at risk in the cohort by the geographically appropriate age, sex, and calendar year-matched cancer rates. The person-years for each subject were determined by subtracting the later of two entry dates (the beginning of the cancer registry observation interval or the first visit to the respective lupus clinic) from the earliest of three exit dates (end date of cancer registry data or death). SIRs were obtained by dividing the observed number of cancers by the expected number, and 95% CIs were calculated using methods described (15) for Poisson parameters.

As SIRs for cancer may differ across centres, we also fit a hierarchical random effects model allowing centres to differ in their cancer rates, rather than assuming a single fixed rate across all centres. SIR estimation using this hierarchical modeling represents a compromise between the pooling of data across sites (our primary analysis, which assumes no variation in cancer experience from one centre to the next) versus independent estimates for each centre (the other extreme, which would preclude estimation of the SIR across all centres). We used the Gibbs sampler as implemented in WinBUGS 1.4 software to estimate the model parameters, with 95% credible intervals (16).

At the first level of our hierarchical model, the number of observed cancers within each centre i was assumed to follow a Poisson distribution, with mean $\theta_i = \lambda_i t_i$, where λ_i is the rate for centre i, and t_i is the total person-years at centre i. The second level of the model specifies a gamma distribution $\lambda_i \sim$gamma (α, β) for the centre mean. Diffuse prior distributions were used for the gamma priors, $\alpha \sim$exp (1) and $\beta \sim$gamma (0.1, 1) so that the data would dominate the posterior

distribution (17). A robustness check of variations in the prior parameters was also performed, as detailed in the results section.

Funding for this study was provided through operating grants from the National Cancer Institute of Canada, the Canadian Institutes of Health Research, the US Arthritis Foundation, Lupus Canada (Manitoba), and the Arthritis Society of Canada.

Results:

The 9,547 patients were observed for a total of 76,948 patient years (average follow up 8 years). The calendar period of observation was 1958-2000. Most (71%) of the patients entered into the observation interval within the first two years of their SLE diagnosis. As may be expected, given that SLE is a disease primarily of women, ninety percent of the subjects were female; demographics are presented in Table 3. In Scotland, patients were identified by hospital discharge data without having specific confirmation of SLE by ACR classification or known clinical confirmation by a relevant specialist. However, examination of the data at this site revealed that the cancer incidence and patterns were similar to the data from other centres. Sensitivity analyses with and without data from this site produced very similar SIRs, thus the data from all 23 sites were included for all analyses presented in this paper.

Within the observation interval, 431 cancers occurred. The data confirmed an increased risk of cancer in SLE particularly for specific subtypes. For all cancers combined, the SIR estimate was 1.15 (95% CI 1.05, 1.27), for all hematological malignancies, it was 2.75 (95% CI 2.13, 3.49), and for non-Hodgkin's lymphoma (NHL), it was 3.64 (95% CI 2.63, 4.93). The data also suggested

an increased risk of lung (SIR 1.37, 95% CI 1.05, 1.76), and hepatobiliary (SIR 2.60, 95% CI 1.25, 4.78) cancers. Further results concerning specific cancer types are given in Table 4.

The results of analyses of SIRs by sex, age, and SLE duration are provided in Table 5. The 95% CI for the SIR estimate for all cancer occurrence, in males, included the null value, as well as the possibility of an SIR below or above one. For hematological cancers, the confidence interval excluded the null value for both men and women. The results were consistent with similar relative risks for hematological malignancies for SLE patients of both sexes. For both all cancers combined, as well as for hematological malignancies only, the SIR estimates are highest early in SLE, particularly in the first year after diagnosis. However, the majority of the cancers did occur beyond the first year.

To address a potential surveillance or detection bias (18) or the possibility that some of the SLE cases represented paraneoplastic phenomena, we repeated the calculation of the SIRs, excluding all observed cancers for the first year of SLE duration. This led to an SIR estimate of 1.1 (1.0, 1.2) for all cancers, and 2.5 (1.9, 3.3) for hematological cancers.

The Bayesian hierarchical (random effects) model produced a point estimate for the total cancer SIR of 1.16 (95% CI 1.06, 1.27), similar to the primary analysis approach (in which data were pooled). This model used diffuse, non-informative prior distributions for the gamma priors; to investigate the robustness of the hierarchical modeling to changes in the prior distribution, we considered the literature regarding cancer rates in SLE (2-10), and substituted clinical prior values for the gamma prior distribution i.e. $\alpha \sim \exp(0.7)$ and $\beta \sim \text{gamma}(38, 2)$ for overall cancer rates.

The checks for robustness produced SIR and observed cancer rate estimates that were very stable, being unchanged within two decimal points for the SIR.

Discussion:

We have confirmed that certain cancers, particularly hematological, occur more frequently in SLE than in the general population. Ours is the first study where these results are clearly shown in a large representative sample of patients with clinically established SLE. Cohort patients represent the full spectrum of disease in terms of SLE severity, as indicated by data compiled from several of the sites (19). These study results are of importance to both the patient and physician; awareness of the association should guide appropriate follow up care, directed by clinical judgment.

Our work has overcome important limitations of previous studies related to sample size, completeness of ascertainment, and use of an appropriate comparison population. Our sample size was vastly larger than any other clinical cohort previously studied. Cancer occurrence within the subjects at each centre was determined systematically by linkage with the appropriate regional cancer registries; the same registries provided comparison population incidence rates.

We believe our estimates of the relative risk of cancer in SLE are conservative, since we assumed that any lost to follow-up patients who were not identified in the registry linkages (as having had a tumor or as having died) remained alive and at risk for a cancer up to the end of the observation interval at that centre. Some of these patients may have moved out of the area served by the registry (for example, moving to another country) and developed a cancer or died without documentation. With our conservative assumption, these persons would still contribute person-

time to the cohort, which would inflate the total number of person-years in the cohort. This would slightly inflate the denominator (expected cancers) for our SIR estimates, creating more conservative estimates.

Given that men comprise only about 10% of the total SLE population, we realize the limited precision of our estimates in men. However, our data represent the largest cohort of men with SLE ever assembled, and provide the first useful information on malignancy in a clinical cohort of men with SLE. Our estimates of relative risks for hematological malignancies were similar for SLE patients of both sexes.

Interestingly, the SIR point estimates suggest that the increased risk of cancer is highest early in the course of SLE, particularly in the first year after diagnosis. Could some of the cancers detected in the first year of follow-up be paraneoplastic presentations, masquerading as SLE? It seems unlikely, since the literature suggests that lupus-like paraneoplastic syndromes are rare (20). However, at least 2 of the ACR criteria for SLE (13; 14), positive anti-nuclear antibodies and cytopenias, are non-specific and could be seen in both SLE and hematological malignancies (21). Thus, we cannot rule out that the SLE diagnosis in some of the cancer cases that occurred within the first year were paraneoplastic phenomena.

This issue might be resolved if the ACR criteria for SLE persisted even after the malignancy was in remission. However, intermediate and high-grade NHL often leads to rapid demise (22), and thus whether the autoimmune disorder would have persisted beyond the active malignancy may never be established. We therefore also presented the SIRs excluding cancers diagnosed in the first year of SLE. Since the estimates change little, it seems unlikely that

association between cancer and SLE reflects a paraneoplastic process, alone. Furthermore, we note that the majority of the cancers in fact did occur beyond the first year.

The presence of elevated risk beyond the first year of SLE also suggests that our findings are not just due to the discovery of sub-clinical malignancies during the diagnostic work up (including laboratory and radiographic investigations) for SLE. Granted, cancer in SLE patients may be more likely to come to medical attention compared to individuals who do not have similar medical follow-up. Surveillance or detection bias (18) is a potential limitation when investigating cancer risk in persons with chronic disease. This is because cancer occurring in the general population can remain undetected during life and found only on necropsy, if at all, unless a diagnostic workup is provoked. In individuals with chronic disease, such as SLE, regular contact with physicians may mean more regular screening procedures (i.e. mammograms and Pap tests). The potential result is the early detection of small or early neoplasms that may never have surfaced clinically, which could inflate cancer incidence in the SLE cohort relative to the general population.

There are strong reasons to believe that this potential bias does not entirely explain our findings of an increased risk of malignancy in SLE. Breast cancer, a neoplasm amenable to screening, was not increased in our study, in contrast to the striking increase in hematological malignancies. Hematological malignancies seem unlikely to be subject to this bias as there is no formal screening strategy for early detection. Bias could still operate in that hematological malignancies may be uncovered sooner in a lupus patient (during a periodic clinic visit) than in the general population. This might create a "lead time" in diagnosis but not an increased malignancy

incidence, and thus would not bias the incidence rate or SIR, providing the follow-up time in the cohort study is adequate.

There are additional arguments against greater scrutiny for cancer in SLE patients as an explanation of our findings. In a study of 1,193 women with SLE, the stage distribution of diagnosed cancer cases did not differ from the general population, suggesting that increased scrutiny does not explain the results of our current study (23). As well, recent data indicate that cancer mortality (not just incidence) is increased in SLE, which also argues for a true increased risk of cancer in SLE (24).

Although our current work has persuasively shown a positive association between SLE and malignancy, it does not allow us to evaluate mechanisms of association. Numerous pathogenic mechanisms are possible. Intriguingly, evidence of genetic predispositions common to autoimmunity and hematological malignancies (25; 26) has implicated abnormalities in apoptosis (cell death regulation) (27) and other pathways.

Exogenous exposures may also mediate cancer risk. The potential impact of immunosuppressive medications on cancer risk (28-32) has created widespread concern for SLE patients and their physicians. However, our finding of increased cancer risk even early on in SLE (which is likely not to be related to cumulative treatment) suggests that drug exposure alone is not the sole cause of the association between malignancies and SLE. An increased risk of cancers (including hematological, lung and hepatobiliary tumors) has been shown in other autoimmune disorders, including rheumatoid arthritis and scleroderma (33)(34), but here also it is unknown to

what extent the association is due to the autoimmune condition itself, or to related exposures (such as medications).

We observed, in our sample, a decreased incidence of endometrial and possibly breast and ovarian cancer. Endometrial cancer occurrence in clinical cohort studies of malignancy in SLE (2; 4; 7-10) has been reported very rarely, and precise estimates of the effect have, to date, been unavailable. The estimates for breast and ovarian cancer risk in cohort studies of malignancy in SLE have also been quite variable, and generally imprecise.

It is known that both endogenous estrogen levels (35) and unopposed hormone replacement therapy (HRT) increase endometrial cancer (36; 37). It is possible that this in part contributed to our observed findings, for two reasons. First, women with SLE are at risk for premature ovarian failure (38), in part due to medication exposure (39), and in those cases endogenous estrogen exposure is arrested. Because of clinical concern that exogenous estrogens may cause lupus flares (40), it may be that the overall population of SLE women was, over the period we studied, less likely to be maintained on HRT than women in the general population. Of course, at different clinical centers, there is variability regarding prevalence of HRT use. The hypothesis that lower use of HRT in SLE patients mediates a decreased risk of endometrial cancer is perhaps further supported by our SIR point estimates suggesting decreased risk in SLE for ovarian and breast cancers, which are also estrogen-sensitive (41-44). We note, however, that some of our preliminary work indicates that factors (as yet unknown) other than HRT may be influencing breast cancer risk in SLE (45). The lack of homogeneity of the estimates of ovarian and breast

cancer risk in previously published single-centre SLE cohorts (2-10) might suggest a complex interplay of risk factors that differ across centres or calendar time.

In summary, our results confirm that certain cancers, particularly hematological, occur more frequently in SLE than in the general population. Numerous pathogenic mechanisms are possible, but hypotheses remain largely speculative. In particular, there are inadequate data on how cancer risk in SLE may be related medication exposures. To evaluate the impact of medication exposures on cancer risk in SLE, cooperative efforts of SLICC and CaNIOS are currently in progress. This should provide much-needed insight into the pathogenesis of the association between cancer and SLE.

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Table 1: Published studies on cancer occurrence in Systemic Lupus Erythematosus (SLE) with 95% confidence intervals (CI)

First Author (Ref)	Cancer Ascertainment	N	Total Cancer SIR (95% CI)	SIR Non-Hodgkin's Lymphoma (95% CI)	SIR Other Cancers (95% CI) †
Clinical Cohort studies					
Pettersson (7)	Tumor Registry	205	2.6 (1.5, 4.4)	44(12,111)	
Ramsey-Goldman(8)	Tumor Registry	616	2.0 (1.4, 2.9)	1.5 (0.02, 8.6)	Lung 3.1 (1.3, 7.9)
Cibere (4)	Tumor Registry	297	1.6 (1.1, 2.3)	7.0 (1.9, 18)	Cervical‡ 8.2 (1.6, 23.8)
Nived (6)	Tumor Registry	116	1.5 (0.8, 2.6)	12 (1.3, 42)	
Sweeney (10)	Self-Report	219*	1.4 (0.5, 3.0)	10 (0.13, 56)	
Sultan (9)	Chart Review	276	1.2 (0.5, 2.1)	No cases	
Abu Shakra (2)	Chart Review	724	1.1 (0.7, 1.6)	5.4 (1.1, 16)	
Hospital Discharge Database studies					
Bjornadal (3)	Tumor Registry	5715	1.4 (1.3, 1.5)	2.9 (2.0, 4.0)	Lung 2.7 (2.1, 3.4)
Mellemkjaer (5)	Tumor Registry	1585	1.3 (1.1, 1.6)	5.2 (2.2, 10)	Lung 1.9 (1.1, 3.1) Liver 8.0 (2.6, 18.6)

* 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) (1) †Where CI excluded null value for a specific cancer type ‡Included in-situ cervical neoplasms.

Table 2: Participating Centres: International Cohort Study of Malignancy in Systemic Lupus Erythematosus (SLE)

Centre	N	Cohort assembly	Inclusion criteria
NORTH AMERICA			
Calgary, AB	522	Patients enrolled from regional physician network*	ACR SLE criteria§
Halifax, NS	109	Consecutive patients enrolled at first clinic visit*	ACR SLE criteria
London, ON	90	Unselected patients followed from first clinic visit †	ACR SLE criteria§
Montreal, PQ: Hopital Maisonneuve-Rosemont	120	Assembled using hospital discharge and clinic records †	ACR SLE criteria§
Montreal General Hospital	309	Consecutive patients enrolled at first clinic visit*	ACR SLE criteria
Notre-Dame Hospital	120	Unselected patients followed from first clinic visit‡	ACR SLE criteria
Saskatoon, SK	306	Consecutive patients enrolled at first clinic visit*	ACR SLE criteria§
Toronto, ON	873	Consecutive patients enrolled at first clinic visit*	ACR SLE criteria§
Vancouver, BC	81	Unselected patients followed from first clinic visit†	ACR SLE criteria§
Winnipeg, MB	158	Unselected patients followed from first clinic visit†	ACR SLE criteria§
Baltimore, MD	453	Unselected patients followed from first clinic visit‡	ACR SLE criteria§
Birmingham, AL	166	Inception cohort (subset consenting to cancer linkage)*	ACR SLE criteria
Chapel Hill, NC	223	Unselected patients followed from first clinic visit‡	ACR SLE criteria§
Chicago, IL	469	Unselected patients followed from first clinic visit‡	ACR SLE criteria
New York, NY: Albert Einstein University	240	Unselected patients followed from first clinic visit †	ACR SLE criteria§
State University-Brooklyn	957	Consecutive patients enrolled at first clinic visit*	ACR SLE criteria§
Pittsburgh, PA	1050	University of Pittsburgh /regional rheumatologists‡	ACR SLE criteria§
UNITED KINGDOM			
Birmingham, England	439	Unselected patients followed from first clinic visit*	ACR SLE criteria
London, England	273	Unselected patients followed from first clinic visit*	ACR SLE criteria§
Lanarkshire, Scotland	1937	Assembled using hospital discharge registry†	SLE discharge diagnosis‖
OTHER CENTRES			
Lund, Sweden	114	Inception cohort, enrollment at SLE diagnosis*	ACR SLE criteria
Reykjavik, Iceland	221	Unselected patients enrolled in national registry‡	ACR SLE criteria
Seoul, Korea	317	Unselected patients followed from first clinic visit‡	ACR SLE criteria§
TOTAL	9547		

The number of subjects at each centre corresponds to the number of patients present during the time in which cancer registry data were available.

* Prospective assembly †Retrospective assembly ‡Retrospective and prospective assembly

§ At least 95% of cohort members have 4 American College of Rheumatology (ACR) diagnostic criteria for SLE (13,14); patients with a clinical diagnosis of SLE but fewer than 4 ACR criteria are not excluded. ‖Any hospital discharge diagnosis of SLE, primary or non-primary. Cohort entry date is 1st discharge with SLE diagnosis.

Table 3: Demographics of cohort: Sex, age, and SLE duration

a. Sex	
Female (%)	N=8,607 (90%)

b. Patient-years of observation, according to age-group (All subjects were >16)

Age (years)	Person-years
<40	33,001.2
40-59	30,976.2
60+	12,970.7

b. Patient-years of observation, according to SLE duration

SLE duration (years)	Person-years
<1	5,424.1
1-4	21,612.9
5-9	21,930.9
10-19	21,399.5
20+	6,580.7

Table 4:Cancers observed and expected, with standardized incidence ratio(SIR)s *

a. Total Cancers

Malignancy	Observed	Expected	SIR	95% CI[†]
Total	431	373.3	1.15	1.05,1.27

b. Hematological Cancers

Malignancy	Observed	Expected	SIR	95% CI
All	67	24.4	2.75	2.13, 3.49
NHL[‡]	42	11.5	3.64	2.63, 4.93
HL[§]	5	2.1	2.36	0.75, 5.51
Leukemia	7	3.7	1.89	0.76, 3.88

c. Reproductive Cancers

Malignancy	Observed	Expected	SIR	95% CI
Breast	73	96.1	0.76	0.60, 0.95
Ovary	9	14.5	0.62	0.28, 1.18
Cervix[‖]	14	11.1	1.26	0.69, 2.11
Vagina	2	0.4	4.91	0.49, 17.69
Vulva	2	1.3	1.60	0.16, 5.76
Uterus	6	16.9	0.36	0.13, 0.78

d. Other Cancers

Malignancy	Observed	Expected	SIR	95% CI
Lung	62	45.3	1.37	1.05, 1.76
Hepatobiliary	10	3.8	2.60	1.25, 4.78
Pancreas	7	7.6	0.93	0.37, 1.91
Gastric	9	8.4	1.07	0.49, 2.03
Colorectal	40	39.5	1.01	0.72, 1.38
Thyroid	9	6.2	1.45	0.66, 2.76
Bladder	13	10.5	1.23	0.66, 2.11
Prostate	8	11.1	0.72	0.31, 1.43
Melanoma	9	9.3	0.97	0.44, 1.84

*Data shown are for 23 participating sites in North America, Europe, Iceland, and Asia. Total number of patients = 9, 547 (76,948 patient years). Calendar period 1958-2000. As well as the categories presented, the total included the following: 21 non-melanoma skin, 18 primary unknown, 15 head and neck, 12 kidney, 7 central nervous system, 5 esophagus, 5 connective tissue, 3 larynx or mediastinum, 2 small intestine, 2 other female genitourinary, 1 adrenal gland). [†]95% confidence intervals were produced using the Poisson distribution. [‡]NHL=non-Hodgkin's lymphoma [§]HL=Hodgkin's lymphoma. [‖]Cervical category includes invasive cancers; the only cancer registry data which include both invasive and in-situ cervical neoplasms are data from the Saskatchewan Cancer Centre.

Table 5: Cancers observed and expected, and standardized incidence ratios (SIRs) according to sex, age, and SLE duration

a. Total cancers				
Sex	**Observed**	**Expected**	**SIR**	**95% CI**
F	370	316.5	1.17	1.05, 1.29
M	61	56.8	1.07	0.82, 1.38
Age (years)	**Observed**	**Expected**	**SIR**	**95% CI**
<40	46	34.2	1.35	0.99, 1.79
40-59	178	147.9	1.20	1.03, 1.39
60+	207	191.2	1.08	0.94, 1.24
SLE Duration (years)	**Observed**	**Expected**	**SIR**	**95% CI**
<1	54	22.1	2.44	1.84, 3.19
1-4	116	88.7	1.31	1.08, 1.57
5-9	102	100.6	1.01	0.83, 1.23
10-19	108	114.4	0.94	0.77, 1.14
20+	51	47.5	1.07	0.80, 1.41
c. Hematological Cancers				
Sex	**Observed**	**Expected**	**SIR**	**95% CI**
Female	53	20.2	2.62	1.96, 3.43
Male	14	4.2	3.34	1.84, 5.61
Age (years)	**Observed**	**Expected**	**SIR**	**95% CI**
<40	10	3.3	3.00	1.44, 5.52
40-59	29	8.4	3.46	2.31, 4.96
60+	28	12.7	2.21	1.47, 3.19
SLE Duration (years)	**Observed**	**Expected**	**SIR**	**95% CI**
<1	9	1.4	6.38	2.91, 12.13
1-4	25	5.7	4.36	2.83, 6.44
5-9	14	6.6	2.13	1.17, 3.57
10-19	15	7.5	1.99	1.11, 3.28
20+	4	3.1	1.28	0.35, 3.26

AUTHOR CREDIT SECTION:

All of the authors have provided final approval of the submitted version of this article. In addition, the authors have declared the following in terms of authorship credit:

S. Bernatsky: Substantial contributions to acquisition, analysis and interpretation of data; drafting and revising the article.

J-F. Boivin: Substantial contributions to conception and design of the study and interpretation of data; revising the article critically for important intellectual content.

L. Joseph: Substantial contributions to conception and design of the study and analysis and interpretation of data; revising the article critically for important intellectual content.

R. Rajan: Substantial contributions to interpretation of data; revising the article critically for important intellectual content.

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Y. St. Pierre: Substantial contributions to conception and design of the study and analysis of data; drafting and revising the article.

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3. Chapter Three

3.1 Preface to Manuscript Three

Prior to accepting study results, one must be satisfied that major biases or confounding have been considered as potential explanations for the findings (4). The next chapter of this thesis considers one particular source of bias which has been invoked as a potential explanation for the associations between cancer and other chronic disease exposures, which has been variously called "misclassification", "detection" or "surveillance" bias (5-13).

Having one disease may increase one's chances of being subject to investigations that may reveal a cancer (5-12;14). This can lead to a potential "misclassification" bias (15), which must be considered when assessing an association between cancer and another disease state. For example, cancers in SLE patients, who tend to have regular, rigorous medical follow-up, may be more likely to be brought to medical attention, compared to cancers in individuals who do not have a chronic illness. This is because regular medical follow-up may mean more regular screening procedures (ex. mammograms and Pap tests). The resultant bias may be considered "misclassification" in that corresponding subclinical cancers occurring in the general population can remain undetected during life and found only on necropsy, if at all, unless a diagnostic workup is provoked. Consequently, the detection of small or early neoplasms in SLE patients, that may never have surfaced clinically, could have inflated cancer incidence in the SLE cohort relative to the general population. I thus felt that it was important to make some effort to determine if this bias was present.

If this greater scrutiny for cancer in SLE patients did exist, one could expect that cancers in SLE patients are diagnosed at earlier stages than in the general population. Most of the tumor registries that we relied on for cancer ascertainment were not able to provide data on cancer staging for the SLE or the general population. The Pennsylvania Cancer Registry was one exception. Thus, I determined the frequency distribution of cancer stages for the cases that arose in the SLE cohort subjects from the University of Pittsburgh. I then compared this to general population data for Pennsylvania. Since cancer types where screening is available are most likely to be associated with detection bias in studies, I examined breast cancer cases

specifically, as an example of a malignancy that would be likely to show a detection bias in this setting. This was, I felt, also a good choice because the absolute number of cancer cases would be relatively high (compared to rarer cancers, such as haematological malignancies). The result of this work is a paper (published in Lupus, 2004), which follow next. In brief, the paper presents data that do not support the argument that "detection bias" accounts for reports of increased cancer risk in SLE.

3.2. Manuscript Three:
Breast Cancer Stage at Time of Detection in Women with Systemic Lupus Erythematosus (SLE)

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Summary:
Mounting evidence suggests an increased cancer risk in several autoimmune diseases, including systemic lupus erythematosus (SLE). However, greater scrutiny for cancer in subjects with chronic disease (compared to the general population) might explain this apparent association. If so, one would expect cancers in SLE to be diagnosed at earlier stages than in the general population. This might be particularly evident in cancers where screening is available, such as breast cancer. We linked the University of Pittsburgh lupus cohort with the Pennsylvania Cancer Incidence Registry to determine the frequency distribution for stage at diagnosis of invasive breast cancers in the SLE subjects. Data on staging of cancers occurring in the general population of Pennsylvania were obtained from The US Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute. A lower percentage of women with SLE presented with localized breast cancer (9 of the 16, 56.2%) compared to the general population of women (63.5%). Although not definitive, this evidence suggests that cancers in SLE are not necessarily diagnosed at earlier stages than in the general population.

Keywords: systemic lupus erythematosus, malignancy, detection bias, cancer stage

Introduction

Mounting evidence supports the presence of a modest increased cancer risk in various autoimmune rheumatic diseases, including systemic lupus erythematosus (SLE) (1-4). However, a potential limitation of studies examining the association between two disease states is that malignancies occurring in the general population may be subject to "misclassification bias". Specifically, greater scrutiny for cancer in a chronic disease could potentially explain in part the observation of increased cancer risk compared to the general population. The term "misclassification" can be used to describe this phenomenon (the "misclassification" relating to subclinical, undetected cancer cases in the general population) although the term "detection bias" has also been widely used (5).

This bias could arise if in patients with chronic rheumatic diseases (such as SLE), cancers may be more likely to be brought to medical attention (because these individuals regularly see physicians), than cancers in individuals who do not have systematic medical follow-up. In the case of malignancies amenable to screening, such as breast cancer, regular contact with physicians may mean more frequent screening procedures (i.e. mammograms). Small or early neoplasms detected by screening could inflate the incidence of malignancy relative to the general population. If this greater scrutiny in SLE does exist, one might expect cancers in SLE patients to be diagnosed at earlier stages than in the general population.

Cancer types where screening is available are most likely to be associated with detection bias in studies. As well as examining the stages at presentation of all cancers, we examined breast

cancer cases specifically, as an example of a malignancy that would be likely to show a detection bias, since screening is available.

Materials and Methods

The University of Pittsburgh lupus cohort enrolled consecutive patients with American College of Rheumatology (6) (7) or clinical criteria for SLE at the time when they presented for their first clinic visit. The occurrence (and stage at diagnosis) of invasive cancer cases in this cohort was determined by linkage with the Pennsylvania Cancer Incidence Registry. Data on staging of cancers occurring in the general population of Pennsylvania were obtained from The US Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute. A descriptive analysis of the percentages of invasive cancer cases that were staged as local, regional, or distant at the time of diagnosis was performed in the SLE patients. Percentages of invasive breast cancer cases that were staged as local, regional, or distant at the time of diagnosis were determined for the SLE patients, and this was compared to the general population data. We calculated 95 % confidence intervals (CI) for percentages and differences using the Wilson procedure with a correction for continuity (8; 9).

The SEER program uses the Summary Staging classification, categorizing invasive cancers as localized, regionalized spread, distant spread, or unknown (Table 1). Noninvasive cancers ("in-situ" lesions) are generally excluded in cancer registry rates, and were not considered here.

Results

The SLE cohort numbered 1327 in total, and 1291 of these were present in the cohort during the period from Jan. 1, 1985 to Dec. 31, 2001. Among these 1291 persons, 1193 (92.4%) were

women. 81.3% of the subjects were Caucasian, with the remainder of African American (16.3 %) or other origin (Asian, Native American, Mexican/Mexican American, Puerto Rican, Indian, or other). The mean age at the time of SLE diagnosis for the subjects was 35.1 (standard deviation 14.0) years. In the cohort, 62 invasive cancers were recorded during the follow up period (1985-2001); 56 of these occurred in women.

Over all, 36 of the 62 cancers (58.1%) were localized, 12 (19.3%) had regional spread, and 9 (14.5%) had distant spread at time of diagnosis. In the remaining five cancer cases (8.1% of the total), the stage was unknown. With respect to the 56 cancers diagnosed in women only, 33 (58.9%) were localized, and an equal number (9, or 16.1%) had regional and distant spread time of diagnosis; 5 (8.9% of the total) were unstaged.

Considering breast cancers only, a lower number of women with SLE presented with localized disease (9 of the 16, 56.2%) compared to the general population of women (Table 2). Breast cancer risk in SLE may be particularly important for those of Caucasian race (10) and indeed all of the cancers in the SLE population occurred in Caucasian women. Race is itself an important factor with respect to the stage at which breast cancer is detected in North American women (11). We thus compared the frequency distribution of the breast cancers that occurred in the SLE subjects (who were all Caucasian) to Pennsylvanian SEER population figures for Caucasian women alone. Again, the point estimate for the percentage of the SLE patients presenting with early, localized cancers was lower than the population point estimate (63.5%). The 95% confidence interval for the difference between the proportions (7.3%) was fairly wide and did include the null value (-15.8%, 32.9%).

The mean age of the 16 SLE subjects at the time of breast cancer diagnosis was 55.0 years (standard deviation 11.8 years, range 34-71) and their median age at the time of breast cancer diagnosis was 58.5 years. Applying the age-specific Pennsylvania population figures for breast cancer stage (unadjusted for race) to the age-distribution of the SLE breast cancer cases, the expected proportion of localized breast cancers in the SLE cohort should be 64.9%. Thus the observed proportion of localized breast cancers in the SLE cohort (56.2%) was lower than expected after this age-adjustment (64.9%), although the 95% CI for a difference between the observed and expected percentages is very wide and includes the null value (-21.6%, 41.6%).

Discussion

Mounting evidence supports an association between SLE and malignancy. Single-centre clinical cohort studies have produced varying estimates of relative cancer risk in SLE, all with fairly wide confidence intervals (1). This led to some uncertainty regarding their interpretation, and recognition of the need for a larger, multi-centre cohort effort (12). However, even with these limitations, a recurrent finding was the suggestion that SLE patients are at particular risk for certain types of cancer, notably lymphoma. An increased risk of breast cancer has been reported in several SLE cohort studies (10; 13), and in a meta-analysis (14) although this is not a uniform finding across all SLE cohorts.

Very recently, a landmark international cohort study of cancer in SLE has provided credible confirmation of the association between malignancy and SLE The study base for this cohort encompassed 23 collaborating lupus centers in North America, Europe and Asia. Preliminary data (15) confirm an increased risk of malignancy in SLE, particularly for specific subtypes of

hematological malignancies. The data suggest about a 3-fold increased risk of lymphoma in SLE. Risk estimates from this preliminary data were not precise enough to comment definitively about most solid tumors, including breast cancer, however. Final study results should be available in the coming year.

Factors influencing the development of solid tumors in SLE may include medications (alkylating agents and immunosuppressive drugs), other environmental exposures, or genetic influences predisposing to both autoimmune diseases and cancer. Alternatively, immune system pathology (i.e. in apoptosis and cell proliferation) may play a role in the emergence of neoplasms following the development of SLE. Important traditional breast cancer risk factors, such as nulliparity, may be increased in SLE (16). Recently, the experience of breast cancer in a combined SLE cohort was examined by adjusting for specific risk factors, such as reproductive and family history (17) and the results suggested that the risk of breast cancer in SLE is not completely explained by these factors. Exposure to exogenous estrogens also may not explain the phenomenon entirely (18).

There is some preliminary evidence that some SLE patient populations have differences in estrogen receptors or metabolism that may amplify endogenous estrogenic effects (19; 20). Differences in genetic polymorphisms in estrogen receptors or metabolism (related to variations in ethnic distributions) might explain why an elevated risk of breast cancer has not been clearly demonstrated in all SLE populations under study.

In summary, our evidence suggests that cancers in SLE are not necessarily diagnosed at earlier stages than in the general population, at least with respect to breast cancer, which is a malignancy

for which screening exists. These data do not support the argument that "detection bias" accounts for reports of increased cancer risk in SLE.

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Table 1: Summary Stage definitions of the US Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute

Localized: Confined to the primary organ of origin.
Regional extension: Direct extension to adjacent organs/structures or spread to regional lymph nodes.
Distant: Spread to body parts remote from the primary tumor.
Unknown: Insufficient information to assign stage (Ex. absence of thorough diagnostic work-up; ambiguous/contradictory data)

Table 2: Frequency distributions for breast cancers in the University of Pittsburgh lupus cohort

Cancers in the SLE cohort N (%) [a]

Category	N	Localized	Regional	Distant	Unknown stage
Breast cancers[b]	16	9 (56.2%)	5 (31.2%)	1(6.2%)	1(6.2%)

SEER General Population Data for Pennsylvania [c]

Category	N	Localized	Regional	Distant	Unknown stage
Breast cancers	9,791	6,124(62.5%)	2,778(28.4%)	521(5.3%)	368(3.8%)
Caucasian women breast cancers	8,853	5,619 (63.5%)	2462(27.8%)	464 (5.3%)	308(3.5%)

[a] Cancers occurring over the period 1985-2001
[b] All breast cancers occurred in Caucasian women
[c] SEER=Surveillance, Epidemiology, and End Results; figures presented are for the year 2000

4. Chapter Four

4. 1 Preface to Manuscript Four

Though the results presented in chapter three are not definitive, they are reassuring, as they do not suggest the presence of a strong "misclassification" or "detection" bias in *An International Cohort Study of Cancer in Systemic Lupus Erythematosus* (chapter two). With this in mind, I felt I could proceed to examine further the finding that SLE patients are at particularly high risk for NHL.

To date, little is known regarding the relative frequency of subtypes of the NHL cases that occur in SLE. Since etiologic factors differ according to the histological subtype, determining subtype predominance in SLE would be a very important step in exploring pathogenic mechanisms for the association of NHL and SLE. Manuscript IV (*Non-Hodgkin's Lymphoma in Systemic Lupus Erythematosus*) has been recently submitted. The article provides a summary of the demographic characteristics of the NHL cases that arose in this SLE cohort, and a description of the subtypes of these NHL cases, as well as information about the stage and survival of the NHL cases that arose in this SLE sample.

4.2. Manuscript Four:

Non-Hodgkin's Lymphoma in Systemic Lupus Erythematosus

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ABSTRACT:
Recent evidence supports an association between systemic lupus erythematosus (SLE) and non-Hodgkin's lymphoma (NHL). **Objectives:** To describe demographic factors, subtypes, and survival of NHL cases which arise in SLE. **Methods:** We have assembled a multi-site cohort of 9,547 subjects with definite SLE. Subjects at each centre were linked to regional tumor registries to determine cancer incidence. For the NHL cases ascertained, descriptive statistics were calculated, and NHL subtype frequency was determined, as well as median survival time. **Results:** 42 cases of NHL occurred in the SLE patients during the 76,948 patient-years of observation. The median age at time of NHL diagnosis for SLE patients was 57 years. The proportion of females among the SLE patients who developed NHL was 86.0%, reflecting the female predominance of the cohort. In the SLE patients, aggressive histological subtypes appeared to predominate, with the most commonly identified NHL subtype being diffuse large B cell (N=10, out of 20 cases where histological subtype was available). Across all subtypes, the median survival time after NHL diagnosis was 2.1 years. **Conclusions:** These data suggest aggressive pathology and relatively poor prognosis in SLE patients that develop NHL. However, other possible reasons for the observed data include delayed cancer diagnosis or decreased survival related to SLE comorbidity. Ongoing work should provide further insight into the patterns of presentation, prognosis, and etiology of NHL in SLE.

In the past three decades, there has been an accumulation of data regarding an increased risk of lymphoma, particularly non-Hodgkin's lymphoma (NHL) in systemic lupus erythematosus (SLE) (1-3). The reasons for this increased risk are not known. Also unknown is whether particular histological subtypes are predominant among the cases of NHL that develop in SLE.

In the general population, NHL risk is determined by various factors, including age, sex, race, among others (4-6). In general, more aggressive lymphoma types have been associated with immunosuppressed states (7). As well, the relatively aggressive diffuse large B-cell lymphoma subtype appears to dominate the NHL lymphomas that develop in rheumatoid arthritis (RA), an autoimmune disease which, like SLE, is also associated with an increased risk of NHL (8). In contrast, in primary Sjögren's syndrome, yet another autoimmune disease associated with NHL, the commonest lymphoid neoplasias are low grade (indolent), marginal-zone lymphoma related to mucosa-associated lymphoid tissue (MALT) (9).

It is unfortunate that little is known regarding the relative frequency of subtypes of the NHL that occur in SLE, because determining subtype predominance in SLE would be a very important step in exploring pathogenic mechanisms for the association of NHL and SLE. This has not been possible to date because of the small absolute number of NHL cases in single-centre studies.

We have recently completed a multi-site international cohort study that examined cancer risk in SLE. We found that the age, sex, and calendar year adjusted standardized incidence ratio (SIR) for NHL was 3.6 (95% CI 2.6, 4.9) (1), which was consistent with the magnitude of risk seen in other studies, although other study estimates were less precise, due to smaller sample size. The objectives of the current paper are to report the subtype distribution of NHL in this SLE cohort, and to describe pertinent demographic factors (age, sex, race, and SLE duration at the time of NHL diagnosis) in SLE subjects who develop NHL. We also provide some preliminary work with respect to the stage and survival of the NHL cases that arise in SLE.

Materials and Methods

We have assembled a multi-site international cohort study involving 23 centres; ten in Canada, seven in the US, three in the UK (England and Scotland), one in Sweden, one in Iceland, and one in Seoul, Korea (1). All patients with definite SLE according to American College of Rheumatology (ACR) or clinical criteria were eligible for inclusion. Patients included have been followed in either outpatient clinics and/or in the inpatient hospital setting.

Data were available on patient birth date and sex, dates of SLE diagnosis and cohort entry, and vital status. Non-Hodgkin's lymphoma cases were ascertained by linkage of the study subjects with regional cancer registries. The observation interval for each subject was determined by subtracting the later of two entry dates (the beginning of the cancer registry observation interval or the first visit to the respective SLE clinic) from the earlier of two exit dates (end date of tumor registry data or death). The calendar time spanned 1958-2000.

We calculated descriptive statistics concerning demographics (age, sex, and race) for all NHL cases that occurred within the observation interval, as well as the duration of SLE at the time of NHL diagnosis. We ascertained the frequency of histological subtypes and tumor stage, where known, for the subjects in our sample. As well as determining the median and mean survival times after NHL diagnosis, we calculated the Kaplan Meier estimate for the 5-year survival probability.

Results:

In total, 9,547 SLE patients have been observed for a total of 76,948 patient years (1). Forty-two cases of NHL occurred during the observation interval.

Overall, the mean age at the time of diagnosis of the NHL in our SLE sample was 55.5 (standard deviation, SD 15.1) years and the median age was 57 years (interquartile range=18). The proportion of females among the NHL cases was 86.0%. The majority of the SLE subjects who developed NHL were Caucasian (N=20); the remainder were black (N=5), other (one native North

American, one Asian) or unknown (N=15). The average duration of SLE at the time of diagnosis of the NHL was 6.7 years (SD 5.8, median 4.0 years, interquartile range=8).

For 21 of the NHL cases found on tumor registry linkage, the subtype was not specified. The most common NHL type among the remaining 21 cases was diffuse large B-cell (N=11, 52.4% percent of the cases of known subtype) with the remainder being small lymphocytic (N=4, 19.0%), follicular (N=3, 14.3%), and one each of Burkitt's, peripheral T cell, and MALT lymphoma. The demographics of the patients who developed NHL, according to the subgroups, is given in Table 1. In only 14 of the NHLs was information available on staging. Of these 14, five were localized disease, and the remainder were advanced (two being regionally spread, and the others widespread) stage.

In our sample, 22 of the cases had died after a median of 1.6 years after the diagnosis of lymphoma. The remaining subjects had survived to a median of 2.1 years. Altogether, the median survival time after NHL diagnosis was 2.1 years. The median survival times according to known subtypes are given in Table 2. For cancers of unknown subtype, the median survival time was 2.1 years (interquartile range, 5.4). After diagnosis of NHL, the Kaplan Meier estimate for the probability of survival to 5 years in our sample of SLE patients was 46.8% (95% confidence interval 19.6, 73.9%).

Discussion:

In the general population, NHL is more common in males (7), and indeed the percent of males among our SLE cohort subjects who developed NHL (14.0%) was slightly higher than the percentage of males in the entire cohort (10%) (1). The incidence of NHL is also highest among Caucasians (7); this was possibly reflected in our population since the proportion of Caucasians among the NHL cases (74.1% of all cases where race was known) was slightly higher than the proportion of Caucasians in the entire cohort (just under 70%) (10).

"Anticipation" is the term applied to describe the phenomena whereby individuals who have strong genetic determinants of cancer present with malignancies at an earlier age than the norm (11). For the general population, the median age at the time of NHL diagnosis is 60 to 65 years (7). The slightly lower (57 years) median age at time of cancer diagnosis for the cases of NHL in patients with SLE may be due to an overall younger age distribution of SLE subjects compared to the general population. Thus, one cannot necessarily interpret our findings as suggestive of a genetic basis for an association between NHL and SLE. Potential explanations for the association between NHL and SLE may include intrinsic events (i.e. uncontrolled lymphocyte proliferation) or extrinsic factors (i.e. immunosuppression).

Non-Hodgkin's lymphoma can be divided into two general prognostic groups: the indolent lymphomas and the more aggressive (intermediate or high grade) lymphomas (7). Of the 21 NHL of known type experienced by the SLE patients during the observation interval, only nine were probably indolent (four small lymphocytic, three follicular, one peripheral T-Cell lymphoma, one MALT) with the remaining being more aggressive (diffuse large B-cell and Burkitt's) lymphoma.

The diffuse large B-cell subtype makes up about 30% of all NHLs in the general population (7), and represented more than half of the NHL lymphomas of known cell type in our sample (a difference of 22.4%, 95 percent confidence interval 2.2, 41.8%). A limitation of our estimate is, of course, the fact that we did not have clear information about tumor subtype for several of the cases. However, the median survival time of the cases of unknown subtype was 2.1 years, which would certainly also be in keeping with the more aggressive kinds of NHL. However, since diffuse large B-cell lymphomas may arise from precursor lesions (such as follicular lymphomas) (12), it is possible that some of the diffuse large B-cell lymphomas seen in the SLE sample arose from a previously unrecognized more indolent pathology. That is, perhaps indolent lymphomas are less likely to be appreciated in patients with SLE, because symptoms of the malignancy might be incorrectly attributed to the underlying connective tissue disease.

Only one of the SLE subjects observed during the study interval developed a recorded case of MALT lymphoma. This is of interest, since some authors have questioned whether an increased risk of NHL in SLE might be related to overlap with Sjögren's syndrome. Since a low grade marginal-zone lymphoma related to mucosa-associated lymphoid tissue is the commonest lymphoid neoplasia in Sjögren's syndrome (9), it appears unlikely that identical pathologic processes are occurring in the cancer cases that develop in Sjögren's syndrome and SLE.

The genetic abnormalities that may underlie the association between SLE and NHL are unknown. An important feature of NHLs is the presence of chromosomal abnormalities (Table 3), such as translocations where an oncogene is juxtaposed next to a gene important in immune cell function (7). These chromosomal abnormalities are of interest in terms of being possible common pathways linking SLE and lymphoproliferative malignancies. Specifically, the oncogenic factors implicated may also be responsible for the pathogenesis of SLE, where uncontrolled lymphocyte proliferation also occurs.

Our current study was limited in that we were unable to comment about specific translocations arising in the NHL cases that arose in our subjects. For the present, a reasonable hypothesis is that uncontrolled lymphocyte activity in the setting of active SLE leads to chromosomal translocations that allow malignant transformation (13). However, the effect of immunosuppressive agents and viral exposures (such as the Epstein-Barr virus, EBV) are also of interest. These factors are currently under study.

In general, with current treatment, the median 5 year survival for the NHLs that arise in the general population exceeds 5 years (14); this rate has been relatively stable for the past three decades, which is when the NHL cases in our cohort occurred. The median survival for indolent NHL types is estimated at 8-10 years. Twenty-three of our 42 cases had died after a median of 1.2 year. The remaining subjects had survived to a median of 2.1 years. This suggests that SLE patients who develop NHL do not fare as well as most patients with NHL. This is particularly

interesting given that the majority of the NHL cases in our sample were young, Caucasian, and women, which are traditionally indicators of good prognosis.

Obviously, if more aggressive tumor types (such as diffuse large B-cell NHL) or late stage of presentation are more common in SLE, these might lead to a lower than expected survival. Also of interest is preliminary data suggesting that some therapeutic measures, particularly radiation therapy, may be inappropriately withheld from SLE patients who develop cancer (15). However, other possible reasons for our observed data include delayed cancer diagnosis or decreased survival related to SLE comorbidity. Regarding the first consideration, delayed diagnosis may occur if symptoms of malignancy (fever, lymphadenopathy, weight loss) are wrongly attributed to SLE. To avoid this, physicians who treat SLE patients must be vigilant when persistent symptoms of this type occur, so that malignancy is appropriately considered and investigated.

In summary, the data we present in this paper represent the most comprehensive assessment to date of NHL cases within a large SLE cohort. These data suggest more aggressive pathology in SLE patients that develop NHL compared to the general population. Ongoing work should provide much-needed insight into the etiology of NHL in SLE.

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Table 1: Demographics of NHL development for cases where subtype known (N=22)

Histological subtype	N (%)*	Median age, years (Interquartile range)	Sex: N (%) Female	Race: N (%) Caucasian
Diffuse large cell	11 (52.4)	51.0 (19)	9(81.8%)	7(63.6%)**
Small lymphocytic	4 (19.0)	60.0 (31)	4	4
Follicular	3 (14.3)	66.0 (13.0)	3	3
Burkitt's	1 (4.8)	(-) (age 23)	1	0***
MALT**	1 (4.8)	(-) (age 44)	1	1
Peripheral T-cell	1 (4.8)	(-) (age 23)	1	1

* Percent of cases of known subtypes (N=22).
**Three subjects were black, one was native North American.
***Case was Asian.
****MALT=mucosal associated lymphoid tissue.

Table 2: Median survival time for SLE patients after NHL development for cases where subtype known (N=22).

	N	Number (%) deceased	Median survival times, years (Interquartile range)
Diffuse large cell	11	9(82%)	1.0 (2.8)
Small lymphocytic	4	3 (75%)	3.1 (5.1)
Follicular	3	1(33%)	5.2 (1.1)
Burkitt's	1	0	
MALT*	1	0	
Peripheral T-cell	1	0	

*MALT=mucosal associated lymphoid tissue

Table 3 Selected chromosomal abnormalities seen in specific subtypes of NHL as reported in the literature

Translocation	Associated Histology	Oncogene Affected	Molecular Events	Comments
t(3;16)(q27;p11)	Diffuse large B cell (DLBC)	*bcl-6*	Lymphocyte proliferation	16-35% of DLBC and ≤13% of follicular NHL have *bcl-6* translocation. 15% of DLBC have *bcl-1* translocation. Mutations of the p53 suppressor gene may also be seen in DLBCL (especially those that transformed from FL).
t(14;18)(q32;q21)	Follicular (FL)	*bcl-2*	Apoptosis inhibition	80-90% of FL, and 6-30% of DLBC have *bcl-2* translocation. (These DLBC may represent transformation from FL.)
t(8:14)(q24:q32)	Burkitt's	*c-myc*	Lymphocyte proliferation	Translocation of t(8:14) and others involving *c-myc* present to a lesser extent in DLBC (~10%).
t(1;14)(p22;q32)	Marginal zone (MALT*)	*bcl-10*	Apoptosis inhibition	Another translocation, t(15;16) (p21,q21) in ~25% of MALT

* MALT=mucosal associated lymphoid tissue

5. Chapter Five

5.1 Preface to Manuscript Five

Recent evidence supports an association between SLE and cancer, and the association observed is unlikely due completely to bias. Among potential explanations for the observed increased risk, a favored hypothesis is that the increased susceptibility to cancer in SLE patients is caused by exposures to medication, specifically to immunosuppressive therapy and alkylating agents. However, due to power and design issues, no studies to date have been able to test this hypothesis. Because of this, we have proposed to overcome these deficiencies by using the multi-centre cohort study of cancer in SLE as the study base for a case-cohort study to determine whether immunosuppressive agents do influence cancer risk in SLE. This work has received operating grant funding from the Canadian Institutes for Health Research (CIHR) and the National Institutes of Health (NIH).

The preliminary results of this effort (to determine the influence of immunosuppressives on cancer incidence in SLE) will not be available for at least a year. However, a related research question, which is of interest, is the influence of immunosuppressives on the occurrence of cervical dysplasia in women with SLE. Cervical dysplasia, a precursor to cervical cancer, may be more common in SLE than in women in the general population. However, the factors associated with abnormal pap tests results in SLE have not been well studied. Thus, I present (in the following section, Manuscript V), an analysis of the factors associated with occurrence of an abnormal pap test in women with SLE, including the influence of immunosuppressive exposure. This work is in press in the journal *Rheumatology*.

5.2. Manuscript Five:
Factors Associated with Abnormal Pap Results in Systemic Lupus Erythematosus (SLE)

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(Key index terms: systemic lupus erythematosus, cervical dysplasia, Pap test)

ABSTRACT

Previous studies have suggested that women with SLE are at greater risk for cervical dysplasia than are women in the general population. However, the factors associated with abnormal Pap test results in SLE have not been well studied. **Objective:** To determine the factors associated with lifetime occurrence of an abnormal Pap test in women with SLE, and to determine the influence of immunosuppressive exposure on the odds of abnormal Pap test results occurring after SLE diagnosis. **Methods**: Data were pooled from SLE cohorts from three centers. Self-report data were available on smoking, reproductive history, use of oral contraceptives (OC), history of sexually transmitted diseases (STDs), and whether the subjects had had cervical dysplasia on Pap testing. Logistic regression was used to examine the effect of these variables on the lifetime odds of cervical dysplasia. We then generated the adjusted odds ratio (OR) for the effect of immunosuppressive exposure on cervical dysplasia occurring after SLE diagnosis.
Results: History of STDs and use of OCs were positively associated with reports of cervical dysplasia in adjusted analyses. The ORs for the effect of immunosuppressives on abnormal Pap test occurrence (adjusted for race, age, smoking, nulliparity, history of STDs, and OC use) after SLE diagnosis was 1.6 (95% CI 1.0, 2.7). **Conclusions:** History of STDs and use of OCs were associated with abnormal Pap reports in this SLE sample. Immunosuppressive exposure may confer further risk to women with SLE.

Recent work has suggested that women with SLE have an increased prevalence of cervical dysplasia and atypia on Pap testing, compared to the general population of women (1-4) but the determinants of this association are not clear. We recently estimated the prevalence (in an SLE sample) of several factors which are associated, in the general population, with risk of cervical dysplasia and neoplasia (5). However, we did not examine whether these factors, in women with SLE, influence cervical dysplasia as they do in the general population. As well as knowing whether (and to what extent) these traditional factors do play a role in cervical dyplasia in SLE, it is also important to know whether additional factors, such as exposure to immunosuppressive medication (3), might further influence the risk. Previous studies that have examined immunosuppressive medication exposure as a putative causative factor for cervical dysplasia in SLE (1-4) were limited because of small numbers of patients and an inability to control for the risk factors traditionally associated with cervical cancer in the general population.
Our objectives were, therefore, to determine the factors associated with lifetime occurrence of an abnormal Pap test in women with SLE, and to determine the influence of immunosuppressive exposure on the odds of abnormal Pap test results occurring after SLE diagnosis.

Patients and Methods:
The study sample consisted of patients from the SLE clinic cohorts at three centres, the Montreal General Hospital, the Feinberg School of Medicine at Northwestern University in Chicago, and the University of Birmingham Medical School. Consecutive patients with American College of Rheumatology criteria for SLE (6; 7) were enrolled in these clinic cohorts at the time when they presented for their first clinic visit. The total number of female subjects in the combined cohort was 1,015. Institutional review board approval was obtained at the respective sites.

Information on self-reported abnormal Pap tests, and on factors traditionally associated with cervical dysplasia (smoking, reproductive history, use of oral contraceptives (OC)), were obtained. Human papilloma virus (HPV) is an infectious agent sexually transmitted to the endocervix and is an important factor in cervical dysplasia and neoplasia in women (8). As a surrogate for the

presence of HPV (and because other sexually transmitted diseases (STDs) are possibly associated with cervical dysplasia (9; 10)) we also collected information on past history of STDs. Data on all of these factors were obtained from a patient self-report survey. For patients who had died or been lost to follow up, data were obtained from information in the clinical database or medical records. This was also done for 23 living Montreal patients who consented to participate but who did not wish to complete a survey.

Information about demographics (age, race) and exposure to immunosuppressive agents was collected from clinic-based records. For our analyses, we considered exposure to immunosuppressive agents as a dichotomous variable reflecting ever exposure to the agents most commonly used in SLE (11-13) during this time period (cyclophosphamide, azathioprine, and methotrexate).

Descriptive statistics were calculated for the subjects. We developed logistic regression models examining the importance of our covariates (age, race, smoking, nulliparity, OC use, history of STDs) with respect to the lifetime occurrence of an abnormal Pap test in our sample. We then generated the odds ratio (OR) for the effect of immunosuppressive exposure on abnormal Pap test results occurring after SLE diagnosis, adjusting for the demographic factors and the other covariates shown to be important in the first set of analyses.

Results:

The median age of the subjects at time of SLE diagnosis was 32.0 (SD 14.5) years. At the time of this study, the median age of the subjects was 42.0 years (SD 14.5), and the median duration of SLE was 9.0 years (SD 7.5). In terms of race, 73.4% of the subjects were Caucasian, 17.3% were black, and the remainder were of other ethnic origin.

The number of subjects with an abnormal Pap report was 134 (13.3%). Over half of these (74) had occurred after date of SLE diagnosis. For the 74 subjects who reported an abnormal Pap test

after the SLE diagnosis, the mean SLE duration at the time of the abnormal test was 12.1 years (SD 7.9). The mean age of the subjects at the time of the abnormal Pap test was 40.4 years (SD 13.0).

Table 1 presents the distribution of risk factors in the sample. Table 2 presents the unadjusted and adjusted ORs and 95% confidence intervals (CI) for the exposures of interest. History of STDs and use of OCs were associated with lifetime odds of abnormal Pap reports in the univariate analyses. The adjusted analyses (which took into account concomitantly the effects of STD history, OC use, nulliparity, smoking, and also age, race, and centre) produced similar estimates. These analyses did not include immunosuppressive exposure as the outcome represented lifetime history of abnormal Pap reports, including the time before a patient developed SLE.

The percent of the cohort that had been exposed to immunosuppressives at any time since their SLE diagnosis was 41.3%. The unadjusted OR for the effect of immunosuppressive exposure on abnormal Pap test results occurring after SLE diagnosis was 1.2 (95% CI 0.73, 1.9). The OR for the effect of immunosuppressive exposure on abnormal Pap test results occurring after SLE diagnosis, when adjusted for STD history, OC use, nulliparity, smoking, age, race, and centre, was 1.6 (95% CI 1.0, 2.7).

Discussion

Previous work has suggested an association between SLE and cervical dysplasia (1-4) but the determinants of this association are not clear. The four studies that have previously examined immunosuppressive medication exposure as a putative causative factor for cervical dysplasia in SLE were of small numbers of patients. Although these studies were unable to generate strong conclusions because of their limited sample size, in each there were trends towards more cases of dysplasia in patients exposed to immunosuppressives (cyclophosphamide, methotrexate, and

azathioprine). Ours is the first attempt to examine the effect of a multitude of factors on the risk (both lifetime and after SLE diagnosis) of cervical dysplasia.

Our previous work had suggested that SLE patients may have a distinct prevalence profile for cancer risk factors with respect to several factors influencing the risk of cervical dysplasia and neoplasia, compared to the general population (5). However, the profile of these factors (less use of OCs and more nulliparity) that we found would tend to decrease the risk of cervical dysplasia and cancer. Other factors, such as exposure to immunosuppressive medication (3) appear to increase the risk.

Strengths of our study include the much larger sample size of an unselected group of women with SLE from several centres. As well, we performed adjusted analyses to quantify the risk associated with immunosuppressive exposure, which has not been done before.

We chose a questionnaire design in order to obtain information on covariates of interest, including STDs. Actual review of the Pap smear results of all of the subjects would not have been feasible for logistic reasons (including both cost and the fact that older specimens would not have been available). We do acknowledge that self-report of the frequency of abnormal Pap results is not perfect (a recent study found that 11% of women in a general population survey incorrectly stated that their last Pap test was normal (14)). Of course, self-report may be more accurate in our sample (which includes women with a chronic disease who are regularly followed by a physician). For example, we recently compared, in our Montreal lupus patients, the agreement between the self-report of cancers (all types) versus cancer registry records (15), and found a higher sensitivity of self-report compared to what has been published in the general population (16).

However, we would be remiss if we did not consider the possibility of information bias in our sample. One might expect there to be imperfect self-report (i.e. underreporting) of history of

STDs, for example, either because of recall error or hesitancy to admit to the fact. There may also have been some error introduced with respect to the data obtained from chart review on both exposure and outcome in the case of deceased or lost to follow up patients. The question is whether this occurs non-differentially, or if it might occur differentially among women with a history of abnormal Pap tests. Whether women who have had an abnormal Pap test might be more likely to recall a history of symptomatic STDs is not known. However, many STDs are asymptomatic in women, and these infections would be more likely to be picked up in women who engage in regular contact with a gynecologist for cervical screening. Thus, some of the association between STDs and abnormal Pap tests which we found may reflect this bias. However, there remains strong biologic plausibility (i.e. the association in the literature between certain STDs and cervical dysplasia) for the association that we demonstrated in terms of its direction and magnitude. Also, we note that for the self-report items examined, the direction and magnitude of the effects of these factors on history of abnormal Pap tests seems consistent with the literature in terms of their effects on cervical dysplasia.

Use of immunosuppressive agents may predispose lupus patients to infection (or delay the clearance of infectious agents) and thus allow viral and other infectious triggers to initiate abnormal cell differentiation, conferring malignant potential. Though HPV is the infectious agent most associated with cervical dysplasia and cancer (8), chlamydia has also been potentially implicated (9; 10). Recent work has suggested that women with SLE have increased prevalence of HPV infection (17). Whether this is due to medication exposure or a baseline abnormality in the immunology of patients with SLE (18) is unknown.

Recent guidelines published by the American College of Obstetricians and Gynecologists (ACOG) (19) suggest that yearly cytology screening should be performed in women younger than 30, and that older women who have had 3 consecutive cytologies negative for intraepithelial lesions or malignancy may be screened every 2-3 years. However, because HPV infection and cervical dysplasia occur more frequently in HIV-infected women (20), the current

recommendations are that all HIV-infected women should be screened at least annually for cervical cancer with Pap smears. The ACOG extend this recommendation as well to women receiving immunosuppressive agents, which would include many women with SLE.

What is not clear is whether all women with SLE, regardless of exposure history, should be followed this closely (i.e. at least annually). Though our research does not address this issue, previous publications suggest high rates of cervical dysplasia even in women with SLE who are not on immunosuppressive medications (2). Alternatively, the risk factors that we found to be associated with a history of lifetime abnormal Pap smear reports in our subjects (OC use and history of STDs) could serve as markers for those SLE patients likely to have a higher baseline risk of cervical dysplasia, irregardless of immunosuppressive medication use. Unfortunately, the rheumatologist overseeing the care of the SLE patient long-term may not be aware of these history items, thus the high-risk patients may not be evident from that perspective.

In summary, although abnormal Pap test results in SLE appear in part to be influenced by the same factors that are important in the general population, immunosuppressive exposure may confer further risk. Annual cytology screening should be performed in all SLE patients exposed to immunosuppressive agents, and prudence may suggest that all women with SLE follow this recommendation.

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Table 1: Covariate data for subjects in the combined lupus cohort (N=1,015)*

Factor	N (%)
Sexually transmitted disease**	122 (12.0%)
Oral contraceptive (Ever use)	440 (46.9%)
Nulliparous	421(41.4%)
Tobacco use (Ever smoked)	318 (31.4%)
Hormone Replacement (Ever exposure)	138 (14.4%)

* Combined cohort includes subjects from the Montreal General Hospital (N=266), The Feinberg School of Medicine Northwestern University Chicago (N=302) and the University of Birmingham (N=447). Missing data in 54 for hormone replacement use, 77 for oral contraceptive use, and 13 for tobacco use.

**Includes self-reported history of syphilis, gonorrhea, chlamydia, herpes simplex, and venereal warts in the Montreal and Chicago patients, and of herpes simplex in Birmingham.

Table 2: Logistic regression analyses for the combined lupus cohort (1,015 subjects): Odds ratios (OR) of ever having an abnormal Pap smear report (134 cases), according covariate factor

Factor	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Sexually transmitted disease**	2.8 (1.8, 4.4)	2.5 (1.6,4.1)
Oral contraceptive (Ever use)	3.3 (2.2, 4.9)	2.9 (1.9,4.4)
Nulliparous	0.9 (0.6, 1.3)	0.98 (0.65, 1.54)
Tobacco use (Ever smoked)	1.0 (0.67, 1.3)	0.86 (0.5, 1.3)

*Adjustment for all covariates listed in table, as well as for age, race, and centre.
**Includes self-reported history of syphilis, gonorrhea, chlamydia, herpes simplex, and venereal warts in the Montreal and Chicago patients, and of herpes simplex in Birmingham.

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6. Summary and Conclusions

The chapters presented in this thesis can be considered as small parts of a large puzzle. The first manuscript, *Systemic Lupus Erythematosus and Cancer*, provided an overview of both early and more recent data concerning cancer and SLE. Next, in the second manuscript, *An International Cohort Study of Malignancy in SLE*, I presented in detail the findings from our recent work estimating cancer risk in SLE. In the third manuscript (*Cancer Stage at Time of Detection in SLE*), I demonstrated no convincing evidence of a "stage shift" that would support the presence of a bias related to increased surveillance for cancer among SLE patients. Then, in the fourth manuscript, I described demographic factors, subtypes, and survival of the NHL cases that arise in SLE. Finally, in the fifth manuscript, I determined that immunosuppressive exposure may be associated with abnormal Pap reports in women with SLE.

The overall conclusions include the following. Cancer risk is increased in SLE, particularly with respect to NHL. The NHL cases that occur in SLE may tend to be of the more aggressive types, as is sometimes seen in other immunosuppressed populations who develop NHL. Although we do not have at present data on the link between NHL risk and immunosuppressant medication exposure in SLE, my work did suggest a link between the neoplastic precursor to cervical cancer and immunosuppressive exposure.

Still to be tested rigourously is the hypothesis that the increased susceptibility to NHL and other cancers in SLE patients is caused by medication exposures, specifically to immunosuppressive therapy and alkylating agents. We have recently proposed to bridge this knowledge gap by using the multi-centre cohort study of cancer in SLE as the base for a case-cohort study to determine whether immunosuppressive agents do affect NHL risk in SLE. We will also be examining the effect of these agents on other cancers that people with SLE appear to be at increased risk for, such as lung and hepatobiliary cancers. This work has received funding by CIHR and NIH operating grants, and the results of this effort will no doubt shed further light on the etiology of the association between cancer and SLE.

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Appendix: Methodological Details of *An International Cohort Study of Malignancy in SLE*

SETTING AND SUBJECTS

Subjects

We identified approximately 10,000 patients with definite SLE through 23 collaborating centers in North America, the UK, Europe and Asia.

Cancer Definition

Only cancers recorded after the diagnosis of lupus and after entry into the lupus registry were included. Second cancers that occurred within this interval and that did not represent an extension, metastasis, or recurrence (as defined by the International Agency for Research on Cancer) were included.

Cancer Ascertainment, Tumor Registries, and Vital Status Databases

All lupus registry participants were eligible for inclusion. We obtained data on: birthdate, gender, race, date of lupus diagnosis (when ACR criteria were first fulfilled), date of entry into lupus cohort, and date and cause of death, if applicable. The Montreal site oversaw all study activities and was directly responsible for ensuring data collection at all Canadian and non-US sites; the Chicago site was directly responsible for ensuring data collection at all US sites.

Each site's data were linked to their corresponding regional cancer registry. Most regional registries include only cancers diagnosed in the area, but some incorporate cancer incidence data on residents if their diagnosis was made out of state. By linking the SLE cohort databases with only regional registries, cancers diagnosed in patients who are no longer residents of the region will usually not be captured. Therefore, we have chosen an approach which may lead to a conservative estimate of the malignancy incidence in the SLE cohort.

We attempted to minimize this limitation in the US cohorts by tracking patients through the National Death Index (NDI) and elsewhere, through national vital status databases which indicate date and cause of death. The NDI provides a centralized computerized index of state vital statistics data from all states from 1979 onward. Patients who did not appear in either the regional tumor registry or vital status database were assumed to be alive and without a malignancy until the end of the tumor registry/vital statistics database observation interval. With this

approach, we may underestimate malignancies occurring outside a patient's region if they do not result in death. In some cases where no national vital status database exists, we will not only underestimate malignancies that do not result in death, but may even underestimate malignancies resulting in death as we must rely on regional tumor and vital status data. Reliance on regional vital status data will also likely result in underestimation of deaths (as some patients will likely die outside the boundaries covered by the regional database) and hence the construction of inappropriately long observation intervals for some patients. Our assumptions should therefore lead to conservative estimates of malignancy risk, implying that if an increased risk is observed, it is of substantial importance. (Note that a sensitivity analysis where we used the date of the last clinic visit as the end date for the observation interval led to no dramatic change in our SIR estimates.)

Data Management

Each site entered the required patient data into a computer-based program (e.g. Medlog, Access, or Paradox) allowing data transfer into ASCII files or standard software packages. The data sets were then linked to their respective regional cancer registries and the NDI (US sites only) and regional and national (where available) vital status databases (for non-US sites). These different data sources were merged on the basis of site-specific patient ID numbers using standard spreadsheet (e.g. Excel, Quattro Pro) or statistical software (e.g. SAS, STATA). Additional files were then generated summarizing regional cancer incidence rates, stratified by age and gender, in the general population, covering, where possible, the full calendar time of each specific SLE cohort study interval. Each US site then forwarded their data to Chicago for review and assignment of unique study ID numbers prior to sending the data to Montreal. All other sites sent their data directly to Montreal. There, data sets from all sites were formatted in STATA files and appended into a single file to facilitate observed and expected incidence calculations.

STATISTICAL ANALYSIS

To determine if SLE confers an increased risk of malignancy, SIRs were calculated for malignancies overall and for site-specific malignancies. The SIR represents the quotient of the

observed number of malignancies in the SLE cohort divided by the expected number from a geographically appropriate age, sex, and calendar-matched general population.

Observed Cancers

For each site, we determined the occurrence of individual cancers as described above. In general, tumor registries are assembled in a similar fashion. Calculation of the expected incidence rate in this way assumes that the risk factors in the SLE and general populations are comparable except for the presence of SLE in the study population. Adjustment for any potential difference in risk factor prevalence is methodologically difficult and beyond the scope of this proposal. Our primary objective was to determine if the relative risk of malignancy is increased in SLE; attribution of an increased risk to SLE itself, its therapy, or associated factors is not our focus. We also recognize that registry participants may move outside their initial region of residence during the observation interval and that using a comparison population from their initial region of residence may not be perfectly correct. However, we believe that movement in the cohorts is not frequent and when patients move, most likely move to a region where the difference in cancer incidence from their original region is small. We believe these factors will contribute to make the effect of movement negligible.

Cancers Expected

The **expected cancers** were calculated by multiplying each person-year at risk in the cohort by the geographically appropriate age, sex, calendar (and were applicable, race)-specific cancer rates for that person-year and summing over all person-years across all patients.

Person-years of Observation

The person-years at risk for each cohort participant were calculated as follows: we first subtracted the latter of two entry dates (the beginning of the cancer registry observation interval or the first visit to the respective lupus clinic) from the earlier of 2 exit dates (end of tumor registry data or death). This calculation provides the person-years at risk for each subject. The study intervals for each patient vary due to different entry and end dates. Calendar years were tracked for each person-year for each patient. Similarly, the observed incidence for site-specific cancers

represents the quotient of the total number of site-specific cancers observed and person-years at risk.

Because of our method of data collection, some patient observation intervals may be inappropriately long. Patients who are no longer residents of the area encompassed by the regional tumor registry/vital status databases may be incorrectly assumed to be alive and without a malignancy until the end of the database, but have, in actuality, developed a malignancy or died elsewhere. Our approach serves to increase the observation interval for the general population and hence, which may increase the expected number of cancers without increasing the observed number of cancers, making our incidence estimates conservative.

Years lupus patients are alive, but before they enter the cohort are termed immortal patient years, and are not included in the observation interval. This is because, although the cohort is drawn from the general lupus population, there are some lupus patients who, perhaps because of early death or very mild disease, never enter a clinical SLE cohort. Thus, the observation interval for these patients is automatically censored and the incidence of cancers in these patients is never captured. Our study cohort must therefore also be similarly censored for this period of time between SLE diagnosis to cohort entry. Otherwise, we might inaccurately estimate cancer incidence in the general population of SLE patients by including patient years in the observation interval over which most cohort patients were alive and well, whereas those patients who were potentially too unwell to enter the cohort were excluded from the observation interval.

Person-years at risk are calculated in the same way as patients having no previous cancer for patients who have developed: 1) a cancer prior to lupus diagnosis or 2) in the interval after SLE diagnosis but prior to SLE cohort entry.

Standardized Incidence Ratios

To ascertain if SLE confers an increased malignancy risk, SIRs for overall and site-specific cancers were calculated as the observed number of malignancies divided by the expected number of malignancies, and 95% CI were calculated using the Poisson distribution. An overall SIR was calculated for the multi-centre cohort; participating centres who contributed more person-years

count more in the final estimates. SIRs were also categorized according to age group and lupus duration.

As SIRs for cancer may differ across sites, we also fit a hierarchical random effects model which allows centers to differ in cancer experience while still providing overall estimates of the SIR for each center as well as overall estimates across all centers. Hierarchical models provide a compromise between simple pooling of data at one extreme and individual estimates at the other extreme.