Second Lymphomas and Other Malignant Neoplasms in Patients With Mycosis Fungoides and Sézary Syndrome

Evidence From Population-Based and Clinical Cohorts

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Objective: To assess risks for developing second malignancies in patients with mycosis fungoides or Sézary syndrome.

Design: Retrospective study of 2 cohorts.

Setting: Nine population-based US cancer registries that constitute the Surveillance, Epidemiology, and End Results Program (SEER-9), and Stanford University referral center cohort of patients with cutaneous lymphoma.

Patients: Patients with mycosis fungoides or Sézary syndrome from the SEER-9 registry diagnosed and followed up from 1984 through 2001 and from the Stanford University cohort diagnosed and followed up from 1973 through 2001.

Main Outcome Measures: Relative risk was estimated using the standardized incidence ratio (SIR). The expected cancer incidence for both cohorts was calculated using age-, sex-, race-, and calendar year–specific SEER-9 incidence rates for the general population. Non-melanoma skin cancers were excluded because these cancers are not routinely reported by the SEER database.

Results: In the SEER-9 cohort (n=1798), there were 197 second instances of cancer (SIR=1.32; 95% confidence interval [CI], 1.15-1.52) at all sites. Significantly elevated risk (P<.01) was observed for Hodgkin disease (6 cases; SIR=17.14; 95% CI, 6.25-37.26) and non-Hodgkin lymphoma (27 cases; SIR=5.08; 95% CI, 3.34-7.38). Elevated risk (P<.05) was also observed for melanoma (10 cases; SIR=2.60; 95% CI, 1.25-4.79), and urinary cancer (21 cases; SIR=1.74; 95% CI, 1.08-2.66). In the Stanford University cohort (n=429), there were 37 second instances of cancer (SIR=1.04; 95% CI, 0.76-1.44). Elevated risk (P<.01) was observed for Hodgkin disease (3 cases; SIR=27.27; 95% CI, 5.35-77.54). Elevated risk (P<.05) was also observed for biliary cancer (2 cases; SIR=11.76; 95% CI, 1.51-42.02).

Conclusion: Updated SEER (population based) and Stanford (clinic based) data confirm the generalizability of earlier findings of increased risk of lymphoma in patients with mycosis fungoides or Sézary syndrome.

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Mycosis fungoides (MF) is an extranodal, non-Hodgkin, cutaneous T-cell lymphoma first described in the literature in 1806.1-4 Classically, it is manifested as a flat patch or thin plaque and can progress to tumor and extracutaneous involvement.4,5 Sézary syndrome (SS) is the leukemic form of cutaneous T-cell lymphoma and is manifested with pruritic erythroderma, generalized lymphadenopathy, and circulating Sézary cells.3 In the new World Health Organization–European Organization for Research and Treatment of Cancer classification for cutaneous lymphomas, SS is described as an entity distinct6 from MF, although the diseases may have overlapping clinical features. Mycosis fungoides tends to be indolent in early stages, with intermediate to high risk of death in advanced stages. Although mortality rates for MF have been declining,7 studies have suggested that patients with MF are at higher risk for developing secondary primary cancers compared with the general population.8-12 In particular, studies have suggested evidence for increased risk of melanoma and other cutaneous malignancies.12 Kantor et al,11 using population-based data from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program for 1973 through 1983, did not
observe an increased incidence of cutaneous malignant neoplasm, but relative risk exceeding 1.5 was detected for lung cancer, colon cancer, and non-Hodgkin lymphoma (NHL). Previous studies of second instances of cancers in patients with MF or SS have shown conflicting results. With increasing prevalence of MF and SS, more detailed and precise studies are needed in larger population cohorts.13

The purposes of this study were to assess increased risk for second malignant neoplasms in patients with MF or SS and to describe this second cancer profile in 2 distinct cohorts: a large, population-based series of patients with MF or SS (n = 1798) diagnosed from January 1984 through December 2001 compiled by the SEER-9 Program, and a clinical cohort of patients with MF or SS treated at Stanford University, Stanford, Calif, from January 1973 through December 2001 (n = 429). The Stanford group is part of a cohort recently used in a study for very long-term outcome in patients with MF or SS.14

PATIENTS AND DESIGN

SEER Cohort

The SEER-9 cohort consists of residents with cancer newly diagnosed from January 1984 through December 2001 from 9 SEER cancer registries: Atlanta, Ga; Connecticut; Detroit, Mich; Hawaii; Iowa; New Mexico; San Francisco–Oakland, Calif; Seattle–Puget Sound, Wash; and Utah.12 This period was chosen to avoid overlap with previously published data.11 Analysis was limited to patients with MF or SS (International Classification of Diseases—Oncology, Third Edition [ICD-O-3] morphology codes 9700–9701) as the first primary malignant neoplasm. Patients having second primary malignant cancers within 2 months of having MF or SS were excluded (72 patients). Only second primary malignant neoplasms were considered for this analysis. Keratinocyte carcinomas (basal and squamous cell carcinomas of the skin) are not routinely reported to the SEER program and, thus, are not included in this study. Second primary cancer sites were defined using the SEER site recode of ICD-O-3 site and histologic information.16 Relative risk was estimated with the standardized incidence ratio (SIR; the ratio of observed number of cancers divided by the expected number of cancers). The expected number of second cancers was generated by calculating person-years of follow-up and applying appropriate SEER-race. Based on the expected number of cancers calculated, 149 second cancers would be expected from SEER white patients, 31 black patients, and 7 patients of other race. Patients were followed up for a mean of 5.6 years, and the cohort was followed up for 10 069 person-years. Of the 197 patients in whom second cancers developed, mean latency time to development of a second cancer was 4.1 years (49 months). One hundred thirty-five were male and 62 were female. There were 159 white patients, 31 black patients, and 7 patients of other race. Based on the expected number of cancers calculated, 149 second cancers would be expected from SEER incidence data, yielding an overall SIR of 1.32 (95% CI, 1.15–1.52). Staging information for MF and SS was unavailable for patients in the SEER cohort. Statistical significant increased incidence of melanoma (10 cases; SIR=2.60; 95% CI, 1.25–4.79), urinary system cancers (21 cases; SIR=1.74; 95% CI, 1.08–2.66), Hodgkin disease (HD; 6 cases; SIR=17.14; 95% CI, 6.25–37.26), and NHL (27 cases; SIR=5.08; 95% CI, 3.34–7.38) was observed in the cohort (Table 1). Of these, HD and NHL were the only malignancies with significantly elevated risk using the more conservative P<.01 criterion.

Stanford Cohort

Between January 1973 and December 2001, 429 patients with MF or SS received a diagnosis and had their conditions managed at the Stanford University Multidisciplinary Cutaneous Lymphoma Clinic, Stanford, Calif. This is part of a cohort previously described by Kim et al.14 Institutional review board approval was obtained to use the Stanford University data for this research project. Patients having MF or SS diagnosed earlier than 6 months before treatment at the Stanford University clinic were excluded from the cohort to minimize treatment heterogeneity within the cohort. Patients having second primary cancers diagnosed within 2 months of diagnosis of MF or SS were excluded from the analysis. Race was reported by the patients or the investigator and was used to compare the demographic data for the Stanford cohort with those of the SEER population. Keratinocyte carcinomas were excluded from consideration. Occurrence of large-cell transformation of MF or lymphomatoid papulosis was not recorded as a second cancer. SIR was calculated using methods comparable to those described for the SEER cohort. Follow-up was reported as person-years starting from MF or SS diagnosis to development of the second neoplasm, death, last follow-up date, or the end of the observation period, whichever occurred first.

STATISTICAL ANALYSIS

The 95% CIs were calculated using a binomial distribution. We used SAS statistical software (SAS Institute Inc, Cary, NC) for this analysis. Confidence intervals for quantiles of time to second malignant neoplasm were calculated with 3000 bootstrap iterations according to the method of Akritas15 as implemented by Harrell20 in the R computing environment.20,21

RESULTS

SEER COHORT

The mean age at diagnosis in the 1798 patients having MF and SS diagnosed and followed up from 1984 through 2001 was 59 years (age range, 10–88 years); 1081 patients were male and 717 were female. In this cohort, there were 1432 white patients, 266 black patients, and 100 patients of other race. Patients were followed up for a mean of 5.6 years, and the cohort was followed up for 10 069 person-years. Of the 197 patients in whom second cancers developed, mean latency time to development of a second cancer was 4.1 years (49 months). One hundred thirty-five were male and 62 were female. There were 159 white patients, 31 black patients, and 7 patients of other race. Based on the expected number of cancers calculated, 149 second cancers would be expected from SEER incidence data, yielding an overall SIR of 1.32 (95% CI, 1.15–1.52). Staging information for MF and SS was unavailable for patients in the SEER cohort. Statistical significant increased incidence of melanoma (10 cases; SIR=2.60; 95% CI, 1.25–4.79), urinary system cancers (21 cases; SIR=1.74; 95% CI, 1.08–2.66), Hodgkin disease (HD; 6 cases; SIR=17.14; 95% CI, 6.25–37.26), and NHL (27 cases; SIR=5.08; 95% CI, 3.34–7.38) was observed in the cohort (Table 1). Of these, HD and NHL were the only malignancies with significantly elevated risk using the more conservative P<.01 criterion.

STANFORD COHORT

The mean age at diagnosis in the 429 patients having MF or SS diagnosed and managed at the Stanford University clinic from 1973 through 2001 was 55 years (Table 2).
Patients were followed up for a mean of 7.8 years, with a total of 3341 person-years. Thirty-seven second cancers were observed, with an SIR of 1.04 (95% CI, 0.76-1.44). Significant increases in incidence were observed for HD (3 cases; SIR=27.27; 95% CI, 5.35-77.54) and biliary cancer (2 cases; SIR=11.76; 95% CI, 1.51-42.02) (Table 3). Of these, HD was the only malignant neoplasm with significantly elevated risk using the more conservative P/H11021 criterion. Incidence of HD and NHL considered as a single entity (all lymphomas) was also statistically elevated (7 cases; SIR=5.11; 95% CI, 2.06-10.40). Of the 4 patients having NHL, 2 had B-cell subtypes, 1 had natural killer T-cell lymphoma, and 1 had histiocytic gastric lymphoma. Of the 37 patients in whom second cancers developed, mean time to development of a second cancer was 4 years for all types, 6 years for HD, 1 year for NHL, and 9 years for biliary cancer. In this patient group, MF stage at diagnosis was IA in 14 patients, IB in 10 patients, IIA in 7 patients, IIB in 4 patients, and IIIB in 2 patients (Table 2). The life table estimate for second malignant neoplasm was observed in 1% of the population at 1 year (95% CI, 0.7-2.1), in 5% at 4.9 years (95% CI, 4.0-6.3), and in 10% at 8.6 years (95% CI, 5.8-12) (Figure). Cox regression analysis showed that there was no difference between stage at diagnosis of MF and time to onset of second malignant neoplasm.

**COMMENT**

Our study demonstrates that patients with MF and SS are at significantly increased risk of developing a second primary lymphoma, especially HD. This increased risk was consistent in both cohorts studied and confirms reports of at least 2 previous studies.8,11 Our analysis of data for patients in the SEER Program diagnosed between 1984 and 2001 demonstrated a different pattern of second cancer development when compared with the Stanford cohort. The Stanford cohort, but not the SEER cohort, had an increased risk of biliary cancer. Increased risk of melanoma and urinary cancer were seen in the SEER cohort.
but not in the Stanford cohort. Increased risk of biliary or urinary cancer has not been reported in previous studies and the clinical basis of these findings is unknown.

Kantor et al\textsuperscript{11} reported an overall increase of second cancers in patients in the SEER cohort having MF or SS diagnosed from 1973 through 1983, specifically with increased risk of NHL, lung cancer, and colon cancer. Increased incidence of colon and lung cancers was not found in either the Stanford cohort or the updated SEER cohort during the same period investigated in our study. When we aggregated data from the SEER cohort for the 2 periods under study from 1973 through 2001 (N = 2232), equivalent to the study period in the Stanford cohort, we found significant increases in incidence of second cancers overall, as well as lung cancer, HD, and NHL. The increase in lung cancer was not found in the Stanford cohort, and the increase in biliary cancer was not found in the aggregated 1973-2001 SEER cohort. The consistently increased incidence of second lymphomas in 2 different cohorts during the same period supports the generalizability of this finding to other populations.

A major strength of this study is inclusion of data from both a population-based cohort and a clinical cohort. To our knowledge, this study constitutes the largest cohort of patients with MF or SS followed up for second cancers reported to date. While the SEER cohort has the greatest number of patients with MF or SS, our assessments were limited somewhat by the lack of detailed staging and treatment data for these patients. This deficit was ameliorated by examining the Stanford clinical cohort, for which treatment protocols were consistent, inasmuch as all patients were evaluated and treated by the same multidisciplinary cutaneous oncology group. The liability of studying a clinical cohort from a tertiary referral center such as Stanford University Medical Center may be referral bias or other nongeneralizability properties of the patient population. Stanford cohort patients were generally northern California residents, with a small proportion of patients traveling from other states or countries. To minimize treatment heterogeneity and referral bias in the Stanford cohort, we excluded any patients having MF or SS diagnosed more than 6 months before treatment at Stanford University Medical Center.

Our study of the SEER cohort has confirmed previous reports of an increased risk overall for development of second cancers; however, previous smaller studies reported different second cancer profiles from ours. Vakeva et al\textsuperscript{8} observed an increased incidence of lymphoma and lung cancers. Olsen et al\textsuperscript{22} found an overall increase in second cancers but without predominance of specific cancer type; however, this study differed from ours by including cancers diagnosed before MF diagnosis. Differences among the various studies can also be attributed to the various types of populations and treatments used at different institutions.

**Table 3. Standardized Incidence Ratio for Second Malignant Neoplasms After MF or SS Diagnosis in Stanford Cohort,\textsuperscript{*} 1973 Through 2001**

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Observed, No.</th>
<th>Expected, No.</th>
<th>SIR</th>
<th>95% Confidence Interval</th>
<th>P Value$^\dagger$</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites‡</td>
<td>37</td>
<td>35.61</td>
<td>1.04</td>
<td>0.76-1.44</td>
<td>.005</td>
</tr>
<tr>
<td>Biliary system</td>
<td>2</td>
<td>0.17</td>
<td>11.76</td>
<td>1.51-42.02</td>
<td>.005</td>
</tr>
<tr>
<td>Colon</td>
<td>5</td>
<td>4.84</td>
<td>1.03</td>
<td>0.34-2.39</td>
<td>.005</td>
</tr>
<tr>
<td>Lung</td>
<td>5</td>
<td>6.09</td>
<td>0.82</td>
<td>0.27-1.90</td>
<td>.005</td>
</tr>
<tr>
<td>Skin: Melanoma</td>
<td>1</td>
<td>0.92</td>
<td>1.09</td>
<td>0.05-5.99</td>
<td>.005</td>
</tr>
<tr>
<td>Bladder</td>
<td>0</td>
<td>2.07</td>
<td>0.00</td>
<td>0.00-1.78</td>
<td>.005</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>7</td>
<td>1.37</td>
<td>5.11</td>
<td>2.06-10.40</td>
<td>.005</td>
</tr>
<tr>
<td>Hodgkin disease</td>
<td>3</td>
<td>0.11</td>
<td>27.27</td>
<td>5.35-77.54</td>
<td>.005</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4</td>
<td>1.26</td>
<td>3.17</td>
<td>0.85-8.06</td>
<td>.005</td>
</tr>
</tbody>
</table>

Abbreviations: MF, mycosis fungoides; SIR, standardized incidence ratio (ie, the ratio of observed number of cancers divided by the expected number of cancers); SS, Sézary syndrome.

*\textsuperscript{n} = 429; person-years = 3341.

$^\dagger$P values are adjusted for multiple comparisons.

‡Also includes the following (number of cases): breast (7), prostate gland (4), sinuses (1), hepatic system (1), uterus (1), central nervous system (1), endocrine glands (1), and leukemia (1).
In the Stanford cohort, most of the second cancers occurred in patients with stage IA and IB disease. Kim et al. have described better prognosis and long-term outcomes in patients having cancers diagnosed at earlier stages. It is possible that more second cancers were observed in this subset of patients because they had better survival, leading to longer follow-up in the study. The mean time to development of second cancers in the Stanford cohort was 4 years. Follow-up in patients with stage IA to IIA disease ranged from 7.2 to 11.7 years compared with 2.3 to 5.8 years in patients with stage IIB to IVB disease.

While an increased risk of developing melanoma subsequent to diagnosis of MF or SS was observed in our SEER cohort, this has not been reported in previous cohort studies. Smaller case reports, however, have reported this relationship. These studies included cases in which melanoma was diagnosed either before or after MF, whereas other studies only considered second cancers diagnosed after MF diagnosis. Patients with MF are possibly at increased risk for melanoma as a result of the various topical treatments for MF; for example, an increased incidence of melanoma has been found in patients who receive oral methoxsalen (psoralen) and UV-A radiation therapy or other skin-damaging agents used to treat MF and SS. Because various institutions have different protocols for treating MF, it is likely that different treatment centers would note variable risk for development of melanoma in patients with MF. Previous studies have also found that there is a genetic mutation in both melanoma and MF in the p16 gene. Thus, further larger studies should continue to investigate the association between MF and SS, and melanoma.

It is uncertain why patients with MF and SS are at increased risk of developing secondary malignant neoplasms, especially lymphomas. It is possible that these secondary cancers are related to MF therapy. Alternatively, these patients may have a common underlying environmental factor or inherent predisposition to developing particular malignant neoplasms. Previous studies have shown that patients with advanced MF and SS have impaired T-cell immunity with altered cytokine profiles. Patients with SS can also have a deficiency in normal T cells that are similar to ranges found in patients with advanced AIDS. These immunologic alterations may predispose these patients to development of a secondary malignant neoplasm, particularly HD and NHL, both of which are known to occur with greater frequency in patients with AIDS.

In summary, this analysis of secondary malignant neoplasms in patients with MF or SS in 2 cohorts, one large, population based and the other smaller, clinic based, with uniform treatment, confirms earlier reports of increased incidence of second cancers, specifically lymphomas. The consistency of this finding in both cohorts supports the generalizability of this finding. We also suggest that the profile of second cancers diagnosed in patients having MF or SS may be evolving, although the cause for increased risk of second cancers is unclear and warrants further investigation.

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Author Contributions: Drs Huang and Kim had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Huang, Weinstock, Hoppe, and Kim. Acquisition of data: Huang, Hoppe, and Kim. Analysis and interpretation of data: Huang, Weinstock, Clarke, McMillan, and Kim. Drafting of the manuscript: Huang and Kim. Critical revision of the manuscript for important intellectual content: Huang, Weinstock, Clarke, McMillan, Hoppe, and Kim. Statistical analysis: Weinstock, Clarke, and McMillan. Obtained funding: Kim. Administrative, technical, and material support: Huang and Kim. Study supervision: Weinstock and Kim.

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REFERENCES


