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Original Investigation

Outcomes After Diagnosis of Mycosis Fungoides and Sézary Syndrome Before 30 Years of Age
A Population-Based Study

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IMPORTANCE Mycosis fungoides and Sézary syndrome (MF/SS) are rare in children and young adults, and thus the incidence and outcomes in this patient population are not well studied.

OBJECTIVE To assess the incidence and outcomes of MF/SS in patients diagnosed before 30 years of age.

DESIGN, SETTING, AND PARTICIPANTS Retrospective study of 2 population-based cancer registries—the California Cancer Registry (n = 204) and 9 US cancer registries of the Surveillance, Epidemiology, and End Results program (SEER 9; n = 195)—for patients diagnosed with MF/SS before 30 years of age.

MAIN OUTCOMES AND MEASURES Overall survival was calculated by the Kaplan-Meier method. The risk of a second cancer was assessed by calculating the standard incidence ratio (SIR) comparing observed cancer incidence in patients with MF/SS with the expected incidence in the age-, sex-, and race-standardized general population.

RESULTS The incidence of MF/SS is rare before 30 years of age, with an incidence rate of 0.05 per 100 000 persons per year before age 20 years and 0.12 per 100 000 persons per year between ages 20 and 29 years in the California Cancer Registry. At 10 years, patients with MF/SS had an overall survival of 94.3% (95% CI, 89.6%-97.2%) in the California Cancer Registry and 88.9% (95% CI, 82.4%-93.2%) in SEER 9. In SEER 9, there was a significant excess risk of all types of second cancers combined (SIR, 3.40; 95% CI, 1.55-6.45), particularly lymphoma (SIR, 12.86; 95% CI, 2.65-37.59) and melanoma (SIR, 9.31; 95% CI, 8.75-33.62). In the California Cancer Registry, the SIR for risk of all types of second cancers was similar to that in SEER 9 (SIR, 3.45; 95% CI, 0.94-8.83), although not statistically significant.

CONCLUSIONS AND RELEVANCE Young patients with MF/SS have a favorable outcome, despite a strong suggestion of an increased risk of second primary cancers. Prolonged follow-up is warranted to definitively assess their risk of developing second cancers in a lifetime.

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Mycosis fungoides (MF) is an extranodal cutaneous lymphoma that accounts for approximately 1% to 2% of all non-Hodgkin lymphomas. It is a rare disease, with approximately 2000 new cases diagnosed in the United States annually.[1,2] Mycosis fungoides disproportionately affects the elderly, with a median age of presentation at 57 years, and is twice as likely to occur in men as in women.[1,2] The most important prognostic factor for MF is stage at diagnosis. Early-stage disease occurs in the skin only with varying extent and severity, whereas advanced-stage disease can involve lymph nodes, blood, and visceral organs. Sézary syndrome (SS) is an advanced-stage leukemic form of MF involving the blood, lymph nodes, and erythroderma. Early-stage MF is often indolent, with a median survival of more than 20 years, whereas advanced disease can be rapidly life-threatening, with a median survival of 5 years.[3-5] Most patients are diagnosed with early-stage disease and live for many years, highlighting the importance of survivorship issues in this patient population.

Mycosis fungoides and Sézary syndrome are incurable by standard therapy, with a possible exception for patients with the earliest stage, T1.[4] Patients experience repeated remission and relapse during the clinical course of the disease, thus requiring lifelong therapy. Studies on long-term survivors of adult MF/SS demonstrate an increased risk of second cancers compared with the general population.[6-10] It has been hypothesized that the immune dysregulation associated with MF/SS and/or long-term therapy contributes to the increased risk of second cancers reported in adult patients with MF/SS.[11-13]

Mycosis fungoides and Sézary syndrome are uncommon in children and young adults younger than 30 years and have distinct clinical features, such as a higher proportion of early-stage disease and superior disease-specific survival compared with older adults.[11,14-19] It is unknown whether these distinct clinical features translate into a different risk of second cancers in young patients with MF/SS. Therefore, this population-based study reports on the incidence, overall survival, and risk of second cancers in patients with MF/SS diagnosed before 30 years of age.

Methods

Patients

This project was approved by the institutional review board of the Cancer Prevention Institute of California. We obtained data from the population-based California Cancer Registry (CCR) (www.ccrcal.org) and the National Cancer Institute's Surveillance, Epidemiology, and End Results program of 9 population-based cancer registries (SEER 9) in Atlanta, Georgia; Connecticut; Detroit, Michigan; Hawaii; Iowa; New Mexico; San Francisco–Oakland, California; Seattle–Puget Sound, Washington; and Utah (www.seer.cancer.gov). Of note, the 2 registries share a small patient population in the San Francisco–Oakland area. We identified 204 patients in the CCR with a first primary diagnosis of MF/SS (*International Classification of Diseases for Oncology, 3rd Edition* [*ICD-O-3*] histology codes 9700 and 9701) diagnosed before 30 years of age from January 1, 1988, through December 31, 2009. Similarly, we selected 195 patients fulfilling the same criteria in SEER 9 (www.seer.cancer.gov) from January 1, 1973, through December 31, 2009. For each patient, we obtained registry information routinely abstracted from the medical record at the time of diagnosis, including age, sex, race/ethnicity, and year of diagnosis. A second primary cancer was defined as a new diagnosis registered in the CCR or SEER 9 at least 2 months after the diagnosis of MF/SS. Registered second cancers were not included in the analysis if they had the same *ICD-O-3* code as MF/SS (9700 or 9701). In addition, we excluded registered second cancers that were coded as T-cell lymphoma, not otherwise specified (*ICD-O-3* code 9709), since these most likely represent large-cell transformation in patients with preexisting MF; fewer than 5 such cases were excluded by this criterion.

For patients in the CCR, we obtained a neighborhood measure of socioeconomic status based on patients' residential census tract at diagnosis. This measure is a previously described index that incorporates 2000 US census data on educational attainment, income, occupation, and housing costs.[20] Each patient was assigned to a neighborhood socioeconomic status quintile based on the socioeconomic status distribution across all census tracts in California.

Patient race/ethnicity, as reported in the CCR and SEER 9, was collected primarily through self-report, by assumption of hospital personnel, from death records, or from inference through the use of other information, including race of the parents, maiden name, surname, and birthplace.[21,22] We also obtained cancer registry information on vital status as of December 31, 2009 (SEER 9), or December 31, 2010 (CCR), through routine hospital follow-up and database linkages. As a measure of quality of care, we classified reporting hospitals in the CCR according to whether they were a National Cancer Institute–designated cancer center.

Statistical Analysis

We used SEER*Stat software[23] to compute incidence rates per 100 000 population and corresponding 95% CIs. Population estimates were developed by SEER based on US census projections. The risk of a second cancer was assessed by calculating in SEER*Stat the standard incidence ratio (SIR) to compare the observed cancer incidence in patients with MF/SS with the expected incidence in the general population, standardized by age, sex, and race/ethnicity. Statistical significance of the SIR was determined using the Poisson distribution to calculate 95% CIs, with $P < .05$ considered statistically significant. Survival estimates were analyzed using the Kaplan-Meier method in SAS version 9.3 (SAS Institute). Survival time was calculated from the time of diagnosis to lost to follow-up, the end of the observation period, or death by any cause, whichever came first. In accordance with CCR and SEER privacy and confidentiality guidelines, grouped data are not reported for fewer than 5 cases.

Results

Incidence Rates

Among all patients with MF/SS in the CCR, 204 were diagnosed before 30 years of age, representing 6.4% of all cases

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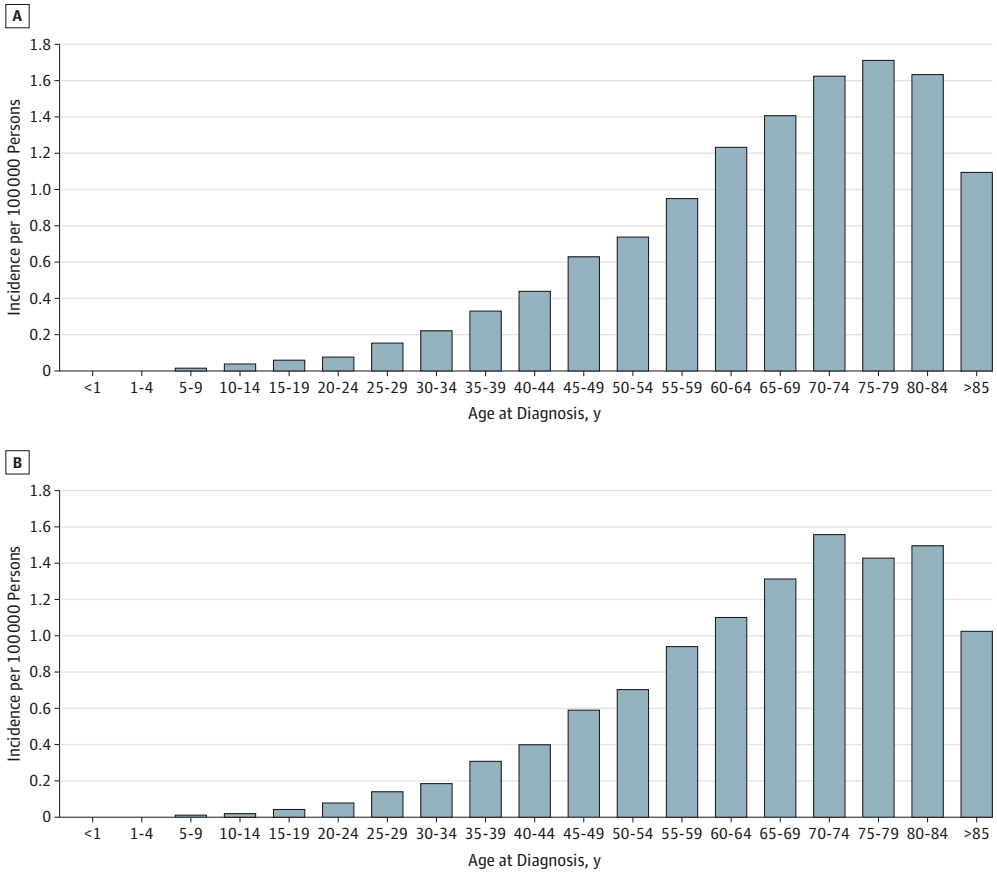
Figure 1. Age-Specific Incidence of Mycosis Fungoides



A, In the California Cancer Registry from 1988 through 2009. B, In the 9 Surveillance, Epidemiology, and End Results cancer registries from 1973 through 2009.

diagnosed in California from 1988 through 2009 (**Figure 1**A). The incidence rate of MF/SS was 0.05 per 100 000 persons per year before age 20 years and 0.12 per 100 000 persons per year between ages 20 and 29 years (**Table 1**). In this group of young patients, the annual incidence rate increased during the study period, with an annual percentage change of 6.0% (95% CI, 3.2%-8.9%; $P < .001$). Similar findings were noted in the 195 young patients with MF/SS identified from the SEER 9 cancer registries (Figure 1B). The annual percentage change of the incidence rate in this registry was stable from 1976 through 1992 (-1.0.%; 95% CI, −8.2% to 6.9%) and increased by 3.0% (95% CI, 0.6% to 5.4%) from 1994 through 2009 (the annual percentage change could not be computed in 1973, 1974, and 1993).

The demographic characteristics of the young patients with MF/SS from the CCR are described in Table 1. Incidence rates of MF/SS increased with age group; 67.2% of patients younger than 30 years were diagnosed between ages 20 and 29 years, and the median age at diagnosis was 24 years. Males and females had the same incidence rate of MF/SS. Asians or Pacific Islanders and blacks had the highest incidence rates, followed by non-Hispanic whites and Hispanics. More than half of the young patients resided in the highest 2 neighborhood socioeconomic status quintiles. Notably, almost half of the cases were reported to the CCR by National Cancer Institute–designated cancer centers. The demographic characteristics of the 195 patients from SEER 9 cancer registries were similar to those of the patients from the CCR. The incidence rate was 0.03 per 100 000 persons per year before age 20 years and 0.10 per 100 000 persons per year between ages 20 and 29 years (**Table 2**). The incidence rate was highest among blacks and was similar for males and females (Table 2).

Overall Survival

Among the 204 patients from the CCR, 9 (4.4%) died after a median of 4.4 years following diagnosis. The most common cause of death was non-Hodgkin lymphoma (n < 5), and the second leading cause of death was infection, including human immunodeficiency virus (n < 5). With a median follow-up of 8.1 years (range, 0-23.1 years), patients in the CCR had a 5-year overall survival of 97.1% (95% CI, 93.0%-98.8%) and a 10-year overall survival of 94.3% (95% CI, 89.6%-97.2%) (**Figure 2**A). Among the 195 patients with MF/SS in the CCR alive at last follow-up, 82.6% had a follow-up date (ie, were verified as being alive) within 1 year of the study end date, and 89.2% had a follow-up date within 2 years.

In the SEER 9 cancer registries, 23 (11.8%) of the 195 patients died (Table 2) after a median of 5.3 years following di-

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Table 1. Demographics of Young Patients With Mycosis Fungoides and Sézary Syndrome in the California Cancer Registry, 1988 Through 2009[a]

Characteristic	No. (%)	Incidence Rate (95% CI)
Age, y		
0-9	11 (5.4)	. . .
10-19	56 (27.5)	0.05 (0.04-0.07)
20-29	137 (67.2)	0.12 (0.10-0.14)
Sex		
Male	101 (49.5)	0.06 (0.05-0.07)
Female	103 (50.5)	0.06 (0.05-0.08)
Race/ethnicity		
White, non-Hispanic	88 (43.1)	0.06 (0.05-0.08)
Black, non-Hispanic	21 (10.3)	0.08 (0.05-0.13)
Hispanic	46 (22.6)	0.03 (0.03-0.05)
Asian or Pacific Islander	32 (15.7)	0.08 (0.06-0.12)
Unknown	17 (8.3)	. . .
Year of diagnosis		
1988-1992	20 (9.8)	0.03 (0.02-0.04)
1993-1997	39 (19.1)	0.05 (0.04-0.07)
1998-2001	48 (23.5)	0.08 (0.06-0.10)
2002-2005	42 (20.6)	0.07 (0.05-0.09)
2006-2009	55 (27.0)	0.08 (0.06-0.11)
Neighborhood socioeconomic status, quintile		
1 (Lowest)	30 (14.7)	. . .
2	34 (16.7)	. . .
3	34 (16.7)	. . .
4	48 (23.5)	. . .
5 (Highest)	58 (28.4)	. . .
Case by NCI-designated cancer center		
No	112 (54.9)	. . .
Yes	92 (45.1)	. . .
Outcome		
Alive	195 (95.6)	. . .
Dead	9 (4.4)	. . .
% Overall survival, y		
5	. . .	97.1 (93.0-98.8)
10	. . .	94.3 (89.6-97.2)

Abbreviations: NCI, National Cancer Institute; ellipses, statistic could not be calculated.

[a] Rates are per 100 000 and age adjusted to the 2000 US standard population.

Table 2. Demographics of Young Patients With Mycosis Fungoides and Sézary Syndrome in 9 SEER Cancer Registries, 1973 Through 2009[a]

Characteristic	No. (%)	Incidence Rate (95% CI)
Age, y		
0-9	10 (5.1)	. . .
10-19	37 (19.0)	0.03 (0.02-0.04)
20-29	148 (75.9)	0.10 (0.09-0.12)
Sex		
Male	98 (50.3)	0.04 (0.04-0.05)
Female	97 (49.7)	0.05 (0.04-0.06)
Race[b]		
White	126 (64.6)	0.04 (0.03-0.04)
Black	49 (25.1)	0.09 (0.07-0.12)
Other	20 (10.3)	0.05 (0.03-0.07)
Year of diagnosis		
1973-1979	12 (6.2)	. . .
1980-1989	39 (20.0)	0.03 (0.02-0.04)
1990-1999	49 (25.1)	0.04 (0.03-0.06)
2000-2009	95 (48.7)	0.08 (0.06-0.10)
Outcome		
Alive	172 (88.2)	. . .
Dead	23 (11.8)	. . .
% Overall survival, y		
5	. . .	93.3 (88.2-96.3)
10	. . .	88.9 (82.4-93.2)

Abbreviations: SEER, Surveillance, Epidemiology, and End Results; ellipses, statistic could not be calculated.

[a] Rates are per 100 000 and age adjusted to the 2000 US standard population. Data for fewer than 5 cases were excluded, with details of the second primary cancer not recorded.

[b] n = 10 with unknown race.

agnosis. Again, the most common cause of death was non-Hodgkin lymphoma (n = 13), followed by infection, including human immunodeficiency virus (n < 5). With a median follow-up of 8.4 years (range, 0-36.5 years), patients in SEER 9 had a 5-year overall survival of 93.3% (95% CI, 88.2%-96.3%) and a 10-year overall survival of 88.9% (95% CI, 82.4%-93.2%) (Figure 2B). When SEER 9 analyses were limited to cases diagnosed between 1988 and 2009 (ie, the same years as the CCR analyses), SEER 9 patients had a 5-year overall survival of 95.3% (95% CI, 89.7%-97.9%) and a 10-year overall survival of 92.2% (95% CI, 84.4%-96.2%), survival estimates comparable to those of patients with MF/SS in the CCR. The percentage of patients who had a follow-up date within 1 and 2 years of the study end date was 90.1% and 94.2%, respectively.

Risk of Second Cancers

In the CCR, the age-, sex-, and race-standardized SIR of all second cancers was 3.45 (95% CI, 0.94-8.83) (**Table 3**). We also observed an increased risk of melanoma after diagnosis of MF/SS, with an SIR of 6.88 (95% CI, 0.17-38.32), although it was not statistically significant. While the risk of any second cancer was not statistically significantly elevated among young patients with MF/SS in the CCR, the SIR was similar in magnitude and statistically significantly elevated in the SEER 9 cancer registries (SIR, 3.40; 95% CI, 1.55-6.45). Furthermore, in the SEER 9 population, the risk of lymphoma (SIR, 12.86; 95% CI, 2.65-37.59) and melanoma (SIR, 9.31; 95% CI, 8.75-33.62) was significantly increased after the diagnosis of MF/SS in patients younger than 30 years. Although based on small numbers, the increased SIR for second cancers did not appear to be due to heightened medical surveillance after MF/SS diagnosis. Of the 9 patients with second primary tumors following MF/SS, the mean time to any second cancer diagnosis was 9 years (range, 1-28 years); the mean time to melanoma and second lymphoma diagnosis was 4 and 2 years, respectively. There was

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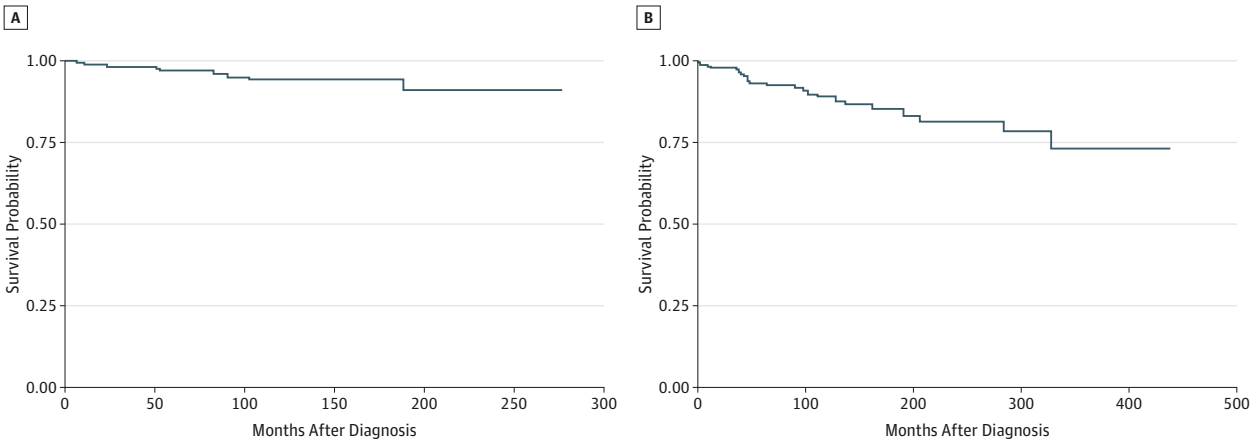
Figure 2. Overall Survival of Young Patients With Mycosis Fungoides and Sézary Syndrome



A, In the California Cancer Registry from 1988 through 2009. B, In the 9 Surveillance, Epidemiology, and End Results cancer registries from 1973 through 2009.

Table 3. Relative Risk of Second Cancers in Young Patients With Mycosis Fungoides and Sézary Syndrome in the California Cancer Registry and 9 SEER (SEER 9) Cancer Registries

	California Cancer Registry (1988 -2009)			SEER 9 Cancer Registries (1973-2009)		
Cancer Sites	Observed No.	Expected No.	Standardized, Incidence Ratio (95% CI)	Observed No.	Expected No.	Standardized, Incidence Ratio (95% CI)
All sites	<5	1.16	3.45 (0.94-8.83)	9	2.65	3.40 (1.55-6.45)
Lymphoma	<5	0.14	. . .	<5	0.23	12.86 (2.65-37.59)
Melanoma	<5	0.15	6.88 (0.17-38.32)	<5	0.21	9.31 (8.75-33.62)

Abbreviations: SEER, Surveillance, Epidemiology, and End Results; ellipses, statistic could not be calculated.

no indication of clustering of second primary tumors around the earlier years.

Discussion

Mycosis fungoides is the most common form of cutaneous lymphoma in childhood and adolescence, comprising 30% of all cases.[24] To our knowledge, our report is the largest study of patients diagnosed with MF/SS before 30 years of age and the first to investigate second cancers in this young patient population. Our study described several epidemiologic patterns in young patients with MF/SS that are different from those in adults. First, MF/SS has a much lower incidence rate in young persons than in older adults. This finding is consistent with the reported incidence rate of 0.29 per 100 000 persons per year in Kuwaiti patients diagnosed younger than 18 years.[25] In our study, patients with MF/SS diagnosed before 30 years of age constituted fewer than 7% of all cases during the study period, a proportion similar to the 2.7% to 5% reported from institutional studies with different age cutoffs from 16 to 30 years.[18,26-28] Second, we observed a different racial or ethnic pattern in young patients with MF/SS than previously reported in older patients. In particular, our data from the CCR showed a higher incidence rate in Asians or Pacific Islanders than in non-Hispanic whites, whereas whites have had higher rates among older adults.[2] Third, the male predominance noted in older patients[2,4,5,29] was not observed in the young patient population, consistent with previous studies.[2,11]

Although the natural history of MF/SS has been well described in adults, the data for young patients with MF/SS are scarce and variable. Some clinical series reported little disease progression and excellent survival,[18,26,28,30] while others attributed approximately 20% of deaths to MF/SS.[11,31-33] The variability in these reports may be a result of the small number of patients and short follow-up in many of these clinical series. Compared with previous reports,[11,14,18,24-28,30-32] our study had a larger number of patients and longer follow-up. Five-year overall survival was 97.0% in the CCR (1988-2009), 93.3% in SEER 9 (1973-2009), and 95.3% in SEER 9 (1988-2009), rates that are consistent with those previously reported from institutional studies.[18] The favorable survival may be a result of the disease characteristics of MF/SS in this age group. By comparison, in the largest institutional study to date, the 5-year overall survival rate of 58 young patients diagnosed with MF between 1958 and 1995 was 84%.[11] The difference in overall survival between this patient population and ours may be attributable largely to improvements in diagnosis and treatment over time. Previous studies have suggested that young patients tend to have early-stage disease, hypopigmentated lesions, and/or MF in association with lymphomatoid papulosis, all of which are associated with a favorable prognosis.[11,14,17,18,28,30,34,35] It should be recognized that the favorable prognosis of young patients with MF/SS may not be at-

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tributable to age, since age had no effect on MF prognosis after adjustment for stage of disease in previous reports.[11,18,36] Specifically, Crowley and colleagues[11] showed that patients with T2 and T3 stage disease have similar outcomes regardless of age, and Wain et al[18] demonstrated that older patients with stage 1A disease do equally well as young patients with stage 1A disease.

Previous reports have not established whether young patients with MF/SS have an increased risk of second cancers, as has been found in older adults.[6,7,10] A review of the literature revealed 3 cases of second cancers (2 Hodgkin lymphomas and 1 Merkel cell carcinoma) in 221 young patients with MF/SS.[18,32] In our study, analyses from the CCR and SEER 9 registries yielded similar results, showing an increased risk of second cancers overall in young patients with MF/SS. The excess risk was statistically significant only in SEER 9, possibly due to the longer follow-up time, but the SIR point estimates were nearly identical. The excess risk came, in part, from melanoma, a finding that has been observed in some previous studies.[37,38] The increased risk of second primary melanoma may result from the long-term use of light therapy rather than the biology of MF/SS. To ensure accurate assessment of the risk of second primary lymphoma, registered second cancers were not included in the analysis if they were MF/SS or T-cell lymphoma, not otherwise specified (n < 5), since T-cell lymphomas likely represented large-cell transformation in patients with preexisting MF/SS. Based on our inclusion and exclusion criteria for second primary cancers, there were no lymphomas of T-cell lineage in the second cancer analysis. It should also be noted that large-cell transformation is quite rare in this young patient population because most young patients with MF/SS have early-stage disease and do not progress to advanced-stage disease.[11,14,17-19,25,39] Although an increased risk of lymphoma has not been reported previously in young patients with MF/SS, it has been documented in the adult MF/SS population.[6,7,10] Overall, our findings suggest that patients diagnosed with MF/SS before 30 years of age may experience an increased risk of second cancers; thus, long-term monitoring is warranted.

Our results should be interpreted in light of the strengths and limitations of the study. The strength of the study lies in its population-based nature, which allows us to analyze a relatively large number of patients while minimizing the potential selection bias of single-institutional studies. This aspect is particularly valuable given the rarity of the disease. However, population-based cancer registry databases have limitations, such as the lack of uniform diagnostic expertise, which may affect the accuracy of the diagnosis, especially for rare diseases such as MF/SS. In addition, the small number of second cancers prevented us from reporting detailed analyses, for example, by histologic subtype, stage, and outcome of the second tumor.

Conclusions

In summary, we analyzed the incidence, outcome, and second cancer risk of MF/SS diagnosed before 30 years of age in the population-based CCR and SEER 9 cancer registries. We found that the incidence rates were much lower in this young population than that in older patients, and demographic patterns differ between the two age groups.[40] However, like older adults, young patients with MF/SS appear to be at an elevated risk of second cancers, particularly melanoma and lymphoma. Despite this risk, young patients with MF/SS in general have a favorable outcome. Continual monitoring of young patients over time can help to determine whether this excess risk persists throughout life and is due to increased medical surveillance, long-term treatment, or underlying disease processes.

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Author Contributions: Drs Ai and Chang 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: Ai, Keegan, Press, Kim.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Ai, Keegan, Press, Pincus.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Keegan, Yang, Pincus.
Administrative, technical, or material support: Ai, Press.
Study supervision: Ai, Press, Kim, Chang.

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