Risk of subsequent primary malignancies after dermatofibrosarcoma protuberans diagnosis: A national study

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Background: Patients frequently live many years after diagnosis of dermatofibrosarcoma protuberans (DFSP).

Objective: We sought to determine the risk of subsequent primary malignancy (SPM) after DFSP diagnosis.

Methods: Using the Surveillance, Epidemiology, and End Results database (1973-2008) for 3734 patients with DFSP, we compared the risk of developing 14 SPMs (12 most prevalent cancers in the United States plus other nonepithelial and soft tissue) relative to risk in the general population of same sex, race, and age and year of diagnosis.

Results: Patients given the diagnosis of DFSP had an overall increased risk of SPM (observed:expected [O:E], 1.20; 95% confidence intervals [CI], 1.04-1.39), with much of the overall increased risk attributable to increased risk of nonepithelial skin cancer (O:E, 9.94; 95% CI, 3.38-22.30). Specifically, female patients with DFSP were at increased risk of other nonepithelial skin cancer (O:E, 14.50; 95% CI, 3.46-38.98), melanoma (O:E, 2.59; 95% CI, 1.02-5.35), and breast cancer (O:E, 1.44; 95% CI, 1.00-2.00). Male patients were not at increased overall risk (O:E, 1.18; 95% CI, 0.96-1.44) of SPM or at increased risk of any specific malignancy ($P > .05$) adjusted for multiplicity of *t* tests.

Limitations: Surveillance bias may have led to increased rates and earlier detection of primary malignances in patients with DFSP compared with the general population. Individual data that may reveal shared environmental causes of DFSP and SPM were unavailable.

Conclusions: Patients with DFSP are at increased risk of a number of SPMs. (J Am Acad Dermatol 2013;68:790-6.)

Key words: dermatofibrosarcoma protuberans; second primary malignancy; skin cancer; subsequent primary malignancy; Surveillance, Epidemiology, and End Results.

Dermatofibrosarcoma protuberans (DFSP) is a skin cancer with an annual incidence of 4.2 per million people in the United States that, despite rates of metastasis to lymph nodes of less than 2%, can be locally destructive.[1,2] High rates of recurrence are commonly seen after surgical excision, which is first-line treatment for DFSP.[3-8] DFSP is identified histologically by a storiform pattern of monomorphic cells with spindle-shaped nuclei, and immunohistochemistry is often $CD34^+$. More than 90% of DFSP lesions contain a t(17;22) translocation that creates a fused platelet-derived

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growth factor (PDGF)β-collagen type 1 alpha 1 gene that constitutively produces collagen.[9]

With overall and cause-specific 15-year survival of 97.2% and 99.7%, respectively, patients with DFSP may live many years at risk of subsequent primary malignancy (SPM).[2] Literature discussion of malignancies associated with DFSP is limited to case studies. We describe the relative risk of SPM among patients with DFSP and describe the characteristics of this population using a large national database.

CAPSULE SUMMARY

- Given mean diagnosis age of 41 years and 15-year survival greater than 97%, patients with dermatofibrosarcoma protuberans live many years at risk of developing subsequent primary malignancies.
- Using the Surveillance, Epidemiology, and End Results database, we describe malignancies for which patients with dermatofibrosarcoma protuberans are at greatest risk relative than the general population.
- Understanding the malignancies patients with dermatofibrosarcoma protuberans are most likely to develop impacts monitoring by dermatologists and primary care physicians and can stimulate investigation of shared environmental causes and molecular pathways.

METHODS

Patients

Institutional review board approval was obtained from the University Hospitals Case Medical Center, Cleveland, OH. We used publicly available data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registries that enroll patients from the following regions (data collection start year): San Francisco-Oakland, CA (standard metropolitan statistical area), 1973; Connecticut, 1973; Detroit, MI (metropolitan), 1973; Hawaii, 1973; Iowa, 1973; New Mexico, 1973; Seattle, WA (Puget Sound), 1974; Utah, 1973; and Atlanta, GA (metropolitan), 1975.[10] SEER registries collect data on patient demographics, tumor characteristics (primary site, morphology, and stage at diagnosis), treatment, and vital status.

We included patients given the diagnosis of DFSP as their first cancer who lived at least 2 months beyond their diagnosis date. DFSP diagnosis was defined as code 8832/3 in the *International Classification of Diseases for Oncology, Third Edition*.[11] Autopsy cases and patients only given a diagnosis by death certificate were excluded. Patients were followed up from DFSP diagnosis until death, loss to follow-up, or study termination in 2008. Among these patients we calculated the incidence of subsequent (eg, second, third, fourth) primary malignancies. SEER collects only information on primary malignancies, so DFSP recurrences were not intentionally included. Only SPMs diagnosed at least 2 months after DFSP diagnosis were considered to avoid surveillance bias and temporal confusion with the primary tumor.

Statistical analysis

We used the Multiple Primary—Standardized Incidence Ratios feature in SEER*Stat, Version 7.0.5 and 7.1.0 (National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Cancer Statistics Branch, Rockville (MD); www.seer.cancer.gov/seerstat) to determine relative risk (observed:expected [O:E]) of patients with DFSP developing the 12 most common cancers plus other nonepithelial skin cancers and soft tissue cancers. Relative risk (O:E) was estimated by dividing the number of observed SPMs among patients with DFSP by the number of expected malignancies in general population of same sex, race, and age and year of diagnosis.

Significance was set at P less than .05, and Sidak correction was used to account for the multiplicity of t tests. The 95% confidence intervals (CI), also adjusted for multiplicity of t tests, were calculated assuming Poisson distribution in the observed group.

We also calculated excess absolute risk (EAR), which is the number of excess SPMs (beyond the expected amount), per 10,000 persons per year.

In addition, we stratified risk by sex and by latency of SPM diagnosis after DFSP diagnosis (2-11, 12-59, 60-119, and $\geq$120 months).

Sensitivity analyses of SPM risk were conducted after removing patients with possible DFSP recurrences to assess the potential bias of including these patients in the study population. Potential recurrence was defined as a subsequent DFSP in the same anatomic location independent of laterality (ie, left vs right).

We performed χ^2 tests using statistical software (SAS, Version 9.2, SAS Institute Inc, Cary, NC) to compare sex, age at DFSP diagnosis, anatomic location of DFSP lesion, race, and marital status between patients with DFSP given or not given the diagnosis of at least 1 SPM.

RESULTS

A total of 3749 patients with DFSP in the SEER database were given the diagnosis of DFSP as a first