Risk of subsequent melanoma after melanoma in situ and invasive melanoma: A population-based study from 1973 to 2011

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Background: Patients with melanoma in situ are at an increased risk of subsequent melanoma compared with the general population, but the risk of subsequent melanoma after initial melanoma in situ versus after initial invasive melanoma is not known.

Objective: We sought to compare the risk of subsequent melanoma in the cohort whose first cancer was melanoma in situ to the risk in the cohort whose first cancer was invasive melanoma.

Methods: In this cohort study, we identified individuals whose first cancer was either melanoma in situ or invasive melanoma from the Surveillance, Epidemiology, and End Results (SEER) program between 1973 and 2011 and used Cox proportional hazards models for comparison.

Results: Compared with the invasive melanoma cohort, the melanoma in situ cohort was more likely to develop subsequent melanoma of any stage after 2 years, subsequent invasive melanoma after 10 years, and subsequent melanoma in situ at all the time points ($P < .001$, $P = .003$, $P < .001$, respectively).

Limitations: Underreporting of melanomas, particularly melanoma in situ cases, and missing cases of subsequent melanomas as a result of patient migration from the SEER registry areas could affect results.

Conclusion: Given the increased long-term risk of subsequent melanoma in the melanoma in situ cohort, the patients with melanoma in situ diagnosis may benefit from a long-term surveillance for subsequent melanomas. (J Am Acad Dermatol 2015;72:794-800.)

Key words: invasive melanoma; melanoma; melanoma in situ; risk comparisons; Surveillance, Epidemiology, and End Results; subsequent melanoma.

Follow-up visits after treatment of primary cutaneous melanoma play an important role in early detection of subsequent primary, recurrent, or metastatic melanoma.[1,2] Almost all recurrent or metastatic melanomas are detected in fewer than 10 years after the initial melanoma diagnosis,[3-5] whereas long-term follow-up of patients with melanoma is beneficial in early detection of subsequent melanoma.[6-11] Evidence suggests that follow-up visits after a melanoma result in early diagnosis of subsequent melanoma and may reduce morbidity and mortality associated with the subsequent melanoma.[8,10,12] Patients with regular clinic

Abbreviations used:

CI:	confidence interval
HR:	hazard ratio
SEER:	Surveillance, Epidemiology, and End Results

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visits after the first melanoma diagnosis had a second melanoma that was thinner—hence with better prognosis—than the patients without regular follow-up schedule.[12] Studies showed that the subsequent primary melanoma detected at a follow-up visit were thinner than the first melanoma.[8,10]

The risk of subsequent melanoma after initial melanoma in situ or initial invasive melanoma is higher than the risk in the general population.[13-15] Patients with melanoma in situ have an overall better prognosis than those with invasive melanoma,[4,16] but the former group's subsequent melanoma risk compared with that of the latter group is not known. Although national/regional melanoma guidelines recommend regular follow-ups of patients with invasive melanoma for a number of years, necessity of regular follow-ups of patients treated for melanoma in situ is currently debatable. Some guidelines do not recommend additional follow-up after surgical excision of a melanoma in situ or do not address follow-up recommendations for patients with melanoma in situ.[1,2,17-21] The incidence of cutaneous melanoma in situ is rising in various countries.[22-29] Therefore, better characterization of subsequent melanoma risk in the patients with melanoma in situ would provide additional evidence for developing clinical surveillance plans that will be useful for the increasing patient population. This study compared the risk of subsequent melanoma in the population whose first primary cancer was melanoma in situ to the risk in the population whose first primary cancer was invasive melanoma.

CAPSULE SUMMARY

- Melanoma in situ increases the risk of subsequent melanoma, compared to the general population.
- After 2 years, patients with melanoma in situ were more likely to develop subsequent melanoma than those with invasive melanoma.
- These results support long-term surveillance for subsequent melanoma after melanoma in situ.

METHODS

Data source and selection criteria

Individuals whose first primary cancer was either in situ or invasive melanoma of the skin were identified in the Surveillance, Epidemiology, and End Results (SEER) 9 program from 1973 to 2011. SEER collects data on cancers, including melanoma, and SEER 9 started the data collection from 1973 to 1975 in 9 regions, which represents approximately 10% of the US population.[30] Melanoma of the skin was defined as cases that had the primary site coded as skin (C44.0-C49.0) and histology as melanoma (8720-8790) according to the *International Classification of Diseases for Oncology, Third Edition*. Only the individuals with the microscopically confirmed first melanoma diagnosis with known SEER summary stage were included in the study. Whether these individuals developed subsequent melanoma was identified from the SEER 9 database. Subsequent melanoma diagnosed within 2 months after the initial melanoma was excluded, because subsequent melanomas diagnosed within 2 months after the first melanoma were considered synchronous to the first one.[31,32] Our study was exempt from institutional review board oversight, because the SEER 9 database is accessible to the public and the subjects in the database are de-identified.

Study variables

Sex, race, birth year, and SEER registry were identified for each individual included in the analyses. SEER summary stage (in situ, localized, or regional/distant), based on a combined clinical and histologic assessment, were collected for both first and second melanomas.[33] Age at diagnosis and month and year of diagnosis were collected for both first and second melanomas, and the time duration from the first melanoma to the second melanoma was calculated. If no subsequent melanoma was developed, the time to follow-up was defined as the time from the first melanoma to death, loss to follow-up, or end of study.

Statistical analysis

The baseline characteristics (sex, birth year, age at first melanoma diagnosis, year of first melanoma diagnosis, and SEER registry) were compared by Wilcoxon rank sum tests between the melanoma in situ and the invasive localized melanoma cohorts and between the melanoma in situ and the invasive regional/distant melanoma cohorts. The incidence rate ratios of subsequent melanoma of any type, subsequent invasive melanoma, and subsequent melanoma in situ were calculated, comparing the melanoma in situ cohort with the invasive localized melanoma cohort or with the invasive regional/distant melanoma, separately. The risks of subsequent melanoma were compared between the melanoma in situ cohort (whose first primary cancer was melanoma in situ) and the invasive melanoma cohort (whose first primary cancer was invasive melanoma) with Cox proportional hazards regression models. The hazard ratios (HR) of the invasive melanoma