Trends in the diagnosis and clinical features of melanoma in situ (MIS) in US men and women: A prospective, observational study

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Background: The incidence of melanoma in situ (MIS) is increasing, but little is known about its clinical and epidemiologic features.

Objective: We sought to determine trends in diagnosis and clinical features of MIS.

Methods: Incident cases of melanoma were collected prospectively from the Nurses' Health Study (1976-2010) and Health Professionals Follow-up Study (1986-2010).

Results: MIS incidence increased from 2 to 42 per 100,000 person-year among women, and from 11 to 73 per 100,000 person-year among men, exceeding the rate of increase of invasive melanomas. Melanoma mortality initially increased during the follow-up period then plateaued. Men were more likely than women to develop in situ melanomas on the upper half of the body ($P < .001$). Invasive melanomas were diagnosed at a younger age than MIS ($P < .001$), and were more likely to be found on the lower extremities than MIS ($P < .001$).

Limitations: This is a strictly descriptive study without examination into mechanisms.

Conclusion: We found epidemiologic and clinical differences for in situ and invasive melanomas, which support further examination into the variations in etiologic pathways. The lack of improvement in mortality despite the increase in detection of in situ relative to invasive lesions further highlights the need to improve invasive melanoma-specific clinical screening features. (J Am Acad Dermatol 2016;75:698-705.)

Key words: age; anatomic sites; epidemiology; gender; incidence; invasive malignant melanoma; lentigo maligna; melanoma; melanoma in situ; melanoma screening; occupational cohorts.

In situ melanomas, characterized by malignant melanocytes limited to the epidermis during a noninvasive radial growth phase, are believed to be a biologic precursor to invasive melanomas.[1] Over the past 30 years, multiple epidemiologic studies have shown that incidence of melanoma in situ (MIS) is increasing at a faster rate than invasive melanomas.[2-4] Despite the increase in detection of

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Conflicts of interest: None declared.

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preinvasive lesions, the distribution of invasive melanoma thickness and melanoma-associated mortality in the United States has not improved.[2,5-10] These epidemiologic observations have led some to conclude that the increase in MIS incidence may not be exclusively a result of earlier detection,[5] whereas others believe that the stabilization in mortality in the setting of increased incidence supports that screening efforts have been sufficient in preventing further rise in mortality.[2] Around the world, primary and secondary prevention efforts for melanoma have produced conflicting results. Although some groups have shown that screening was effective in increasing the proportion of thin tumors,[11-13] stabilizing the incidence of thick tumors,[14] and improving survival,[13,15] others have shown that the proportion of thick invasive malignant melanomas and fatal incidence has remained unaffected by screening efforts.[3,12,14,16-19]

Although understanding the clinical features of MIS over time will provide important information on the biologic properties of these tumors, understanding the epidemiologic trends of MIS over time will also provide important information on primary and secondary prevention of invasive melanomas. To our knowledge, in the United States, there are currently no large-scale studies evaluating the epidemiologic and clinical features of MIS. This is partially because epidemiologic studies on melanomas have been largely supported by national registries missing information on MIS.[2,20] This study circumvented this and other issues of other large national registries[21-24] by using information from 2 prospective cohorts of health care professionals with consistent follow-up and validated reporting[25,26]

CAPSULE SUMMARY

- The incidence of melanoma is increasing in the United States and around the world.
- The incidence of melanoma in situ is increasing at a faster rate than that of invasive melanoma.
- In situ and invasive melanomas demonstrate distinct epidemiologic and clinical features, suggesting divergent etiologic pathways of development.

METHODS

Data source

Nurses' Health Study (NHS) is an ongoing prospective cohort of 121,700 female registered nurses established in 1976. At enrollment, study participants were 30 to 55 years of age. No restrictions were made on the basis of ethnicity or race, however, the participants were 97% Caucasian, reflecting the ethnic background of women trained as registered nurses in 1976. Health Professionals Follow-up Study (HPFS) is an ongoing prospective cohort study, established in 1986 to complement the all-female NHS. HPFS is composed of 51,529 men in the health care professions, ages 40 to 75 years. Similarly, the participants were 97% Caucasian. This study was approved by the Institutional Review Board of Brigham and Women's Hospital. The participants' completion and return of the self-administered questionnaires were considered as informed consent.

Data ascertainment

Participants reported new cases of melanoma in each biennial cycle. Skin cancer confirmation was carried out routinely through review of primary pathological records. Melanoma pathology records were reviewed for tumor depth (in situ, Clark level, Breslow thickness), affected skin type (cutaneous, mucosal/oral, vulvar, or anal), pathological subtype (in situ not otherwise specified or nonlentigo maligna, lentigo maligna, superficial spreading, nodular, lentigo maligna melanoma, ocular, acral lentiginous, or invasive not otherwise specified), and affected anatomic site (head/neck, trunk, thigh/buttock, upper extremity, leg/ankle, knee/popliteal, anal/vulvar, ocular, or site unknown). Only pathologically confirmed cases were included as eligible outcomes.

Statistical analysis

The main analysis was based on 2656 cases with invasive (n = 1609, 1114 in NHS and 495 in HPFS) or in situ (n = 1047, 726 in NHS and 321 in HPFS) melanomas. We conducted several sets of statistical descriptions and comparisons for the epidemiologic and clinical features of invasive and in situ melanomas. First, we calculated the age-adjusted incidence of in situ and invasive melanomas and compared the ratio of in situ versus invasive melanomas during the follow-up in the women's (NHS, 1976-2010) and men's (HPFS, 1986-2010) cohort. Next, we calculated the age-adjusted incidence of in situ melanomas by subtypes. As lentigo maligna occurs on sun-damaged skin, we examined the trend in lentigo maligna to elucidate whether the increase in melanoma incidence can be attributed to cumulative sun exposure in the aging cohorts. We subsequently compared the distribution in anatomic sites of in situ and invasive melanomas in women and men. The χ^2 test or Fisher exact probability test was used to compare the distribution in anatomic sites between in situ and invasive melanomas, and