

Cutaneous Melanoma in Postmenopausal Women after Nonmelanoma Skin Carcinoma

The Women's Health Initiative Observational Study

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BACKGROUND. An elevated risk for cutaneous melanoma has been reported in individuals with nonmelanoma skin carcinoma (NMSC), but to the authors' knowledge, this association has not been prospectively studied in a large, multiepidemiologic population of postmenopausal women.

METHODS. The association between NMSC and the incidence of cutaneous melanoma was assessed in the Women's Health Initiative Observational Study involving 67,030 non-Hispanic white postmenopausal women ages 50–79 years and who were free of prior other cancers at baseline. Cancer history, demographics, and previous and current risk exposures were determined by questionnaires at baseline and follow-up. Participants' reports of incident cutaneous melanoma collected annually were confirmed by physician review of medical records. Cox proportional hazards analyses were used to assess the relation of prior NMSC with incident cutaneous melanoma.

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RESULTS. In age-adjusted analysis, women with a history of NMSC but no other malignancy ($n = 5552$) were found to be 2.41 times more likely to develop cutaneous melanoma over a mean 6.5 years compared with women who had no history of NMSC (95% confidence interval [95% CI], 1.82–3.20). In a multivariate analysis, women with a history of NMSC and no other cancer history at baseline were 1.70 times more likely to develop cutaneous melanoma compared with women without NMSC (95% CI, 1.18–2.44).

CONCLUSION. The results of the current study provide evidence and further defines the magnitude of increased risk for cutaneous melanoma in postmenopausal non-Hispanic white women with a history of NMSC. *Cancer* 2006;106:654–63.

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An increased risk for malignant melanoma has been reported in association with a history of basal or squamous cell carcinoma of the skin (i.e., nonmelanoma skin carcinoma [NMSC]) in men and women.^{1–10} For example, death rates from melanoma in American men and women have been found to be 3.2–3.5 times higher in prospective mortality studies among those with NMSC compared with those without a history of NMSC.¹¹ Therefore, although NMSC by itself is a common and rarely fatal cancer that usually carries a clinically benign prognosis, it may portend the occurrence of the markedly less favorable malignancy of cutaneous melanoma.^{12,13}

Evidence in women of an association between NMSC and melanoma was observed cross-sectionally in the large, multiethnic, multigeographic population of U.S. postmenopausal women in the Observational Study of the Women's Health Initiative (WHI).¹⁴ In an age- and multivariate-adjusted analysis, women with a history of NMSC were 3.29 times (95% confidence interval [95% CI], 2.87–3.76) more likely to report having had cutaneous melanoma compared with women without a history of NMSC. However, this previous study was cross-sectional and could not establish a temporal correlation between NMSC and melanoma. Furthermore, the melanoma outcomes were self-reported and not confirmed by medical reports or records.

Previous studies investigating the occurrence of cutaneous melanoma in men and women with a history of NMSC have been limited by their small size, lack of a multigeographic cohort, absence of an NMSC-free comparison group, and an inability to address many important lifestyle and cancer risk factors and exposures (smoking, alcohol use, nutrition, sun exposure and skin type, latitude of residence, socioeconomic status, prior hormone therapy use, oral contraceptive use, family history, and medical surveillance), and other potentially confounding variables

such as body mass index (BMI), physical activity, supplement use, and diabetes.^{1–10,15}

In an effort to address limitations of the prior work, the current study was undertaken to prospectively ascertain the magnitude of risk for cutaneous melanoma occurrence in healthy postmenopausal women who report a history of NMSC, and to further examine and define factors that influence this association.

MATERIALS AND METHODS

Data were collected from the 93,676 community-dwelling, postmenopausal women enrolled between 1994 and 1998 in the WHI-Observational Study (WHI-OS) at 40 clinical centers distributed widely throughout the U.S. The overall study design of the WHI has been published previously.^{16–18} Human subjects review committees at each participating institution, the coordinating center at the Fred Hutchinson Cancer Research Center, and the National Institutes of Health, reviewed and approved the study. Informed consent was obtained from all participants. The current analysis incorporates demographics and information regarding cancer history, smoking, diabetes, diet (food frequency questionnaire), supplement use, exercise, health care, prior hormone use, anthropometric measures, family history of cancer, and sunlight exposure derived from responses on self-completed and interview questionnaires, and from certified clinic staff measurement documentation at the first screening clinic visit.

Weight and height were measured using a calibrated balance beam scale and a wall-mounted stadiometer, respectively. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Physical activity was calculated as the estimated total energy expended per week per kilogram and assigned a metabolic equivalent (MET) value expressed as MET hours per week (MET-hrs/wk).¹⁹ Data

regarding the effect of sunlight exposure on the skin and lifelong sun exposure history were collected from participant responses to questionnaires from the follow-up Year 4 questionnaires.

Geographic region was defined by location of the clinic that enrolled each participant. Clinics with a latitude $> 40^\circ$ north, between 35° and 40° north, or $< 35^\circ$ north were designated as falling in the northern, middle, or southern region, respectively.^{14,20} Data regarding lifelong location of residence were not collected.

At the time of study entry, each woman reported whether she had ever been diagnosed with a cancer other than NMSC, and if so, what specific type(s) of cancer. A woman who reported any cancer other than NMSC was coded as having a history of cancer. Information regarding the history of NMSC was collected separately. Nonmissing values for these 2 variables were available for 77,233 non-Hispanic white women. Of these women, 10,203 reported a history of a malignancy other than NMSC and were excluded from the current analyses. Therefore, there were 67,030 WHI-OS participants (5552 with prior NMSC and 61,478 with no prior NMSC) included in the current analyses.

Women were mailed questionnaires annually to report any hospitalization and a wide variety of outcomes including cancers of any type. The average participant follow-up time was 6.54 years, with a maximum of 9.3 years as of February 29, 2004. Participants' reports of incident NMSC were recorded but were not confirmed by physician adjudication. Participants' reports of incident cutaneous malignant melanoma were confirmed by physician adjudicators after medical record review, including pathology reports, and coded as invasive, in situ, or borderline.²¹

Statistical Methods

The association between baseline descriptive characteristics and history of NMSC was examined using chi-squared tests. For all analyses, *P*-values < 0.05 were considered to be statistically significant.

The time of an incident melanoma event was defined to be the number of days from study enrollment to the first postenrollment diagnosis of melanoma. The follow-up time was censored at the time of the last documented follow-up contact or death. Comparisons of incident melanoma by NMSC status at baseline were presented as age-adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) from Cox proportional hazards analyses. The assumption of proportionality was tested by including an indicator for NMSC history and the product term between this indicator and follow-up time and using a likelihood ratio procedure to test for a zero coefficient for the product

term. The assumption was satisfied. The primary outcome in these analyses was cutaneous malignant melanoma, with secondary analyses assessing invasive and in situ melanoma separately. There were four borderline melanomas and four with unknown tumor behavior that were not assessed separately given the small numbers, but were included in the analyses of the total overall melanoma outcome.

Time-dependent Cox modeling was used to examine the effect of NMSC history combined with incident NMSC on incident melanoma. Multivariate adjusted Cox proportional hazards models using complete case data were used to assess the effect of NMSC history after adjustment for multiple risk factors. Interactions between NMSC history and baseline risk factors were examined by adding a product term between NMSC history and the given characteristic to a model that included both variables as main effects. *P*-values for assessing statistical significance were computed from likelihood ratio tests comparing models with and without the interaction term. Thirty-one subgroup comparisons were tested; fewer than two tests would be expected to be significant by chance alone. These subgroups included age; BMI (kg/m^2); diabetes; smoking; alcohol use; current healthcare provider; prior hormone therapy use; prior oral contraceptive use; geographic region; effect of sunlight exposure on skin; summer and other season sun exposure during childhood, adolescence, and 30s; months per year doing yardwork; cups of regular coffee drank; physical activity; dietary intake of fat, calcium, and vitamins D, C, and E; supplement use; family history of cancer; and nonsteroidal antiinflammatory medication use. Women with missing data for a given risk factor were excluded from analyses incorporating that risk factor. All analyses were performed using the SAS System for Windows, version 9.1 (SAS Institute, Inc., Cary, NC).

RESULTS

Baseline descriptive characteristics including various known cancer risk factors are shown in Table 1 according to NMSC history. Women with a history of NMSC and no other cancer were more likely to be older, more highly educated, and in a higher income bracket than their non-NMSC counterparts. Furthermore, they were more likely to have a current healthcare provider, to have had a medical visit in the past year, to engage in routine physical activity, be of a lower BMI, have lower dietary fat intake, drink less regular coffee, and take dietary supplements. They were more likely to have smoked in the past, to drink one or more alcoholic beverages per week, and to have used hormone therapy. Women with NMSC were less likely to have used oral contraceptives and more likely

to have a family history of cancer, most notably breast cancer and ovarian cancer. Women with a history of NMSC were more likely to live in the southern or middle latitudes of the U.S. They had a greater propensity to burn rather than tan upon exposure to sunlight, as well as report greater summer sun exposure in their childhood and teen years than their non-NMSC counterparts.

Overall, non-Hispanic white women who reported that they had NMSC on enrollment were 2.41 times more likely to develop melanoma of the skin over a mean follow-up period of 6.5 years compared with women of the same age who had not had NMSC (95% CI, 1.82–3.20) (Table 2).

Women with a prior history of NMSC or incident NMSC diagnosed during the follow-up period were included in the assessment of subsequent melanoma incidence in Table 3. The incidence of melanoma in these women was found to be 2.54 times that of women without NMSC (95% CI, 1.94–3.33) after age adjustment. Subanalyses for both of these groups demonstrated that the HR for in situ melanoma was greater than that for invasive melanoma; however, the 95% CIs for both invasive and in situ melanoma overlap, making a difference in the correlation between prior NMSC and invasive versus in situ melanoma impossible to detect.

Factors potentially related to the development of cutaneous melanoma such as the effect of sunlight exposure on the skin, lifetime sun exposure habits, and a family history of cancer, were examined separately by NMSC history and adjusted for age in the 67,030 women (Table 4). Women without prior NMSC were significantly more likely to develop melanoma if they experienced a burn rather than a tanning effect from exposure to sunlight, and if they reported summer sun exposure of greater than 2 hours per day in their 30s. However, among those women with a history of NMSC, melanoma risk estimates were somewhat similar, but did not reach statistical significance with regard to sunlight's effect on the skin nor with regard to summer sun exposure in their 30s. This may be due in part to the smaller sample size available for women with a prior history of NMSC. Sun exposure in childhood and the teen years did not appear to impart a change in risk for the development of melanoma in either the non-NMSC or NMSC groups. Having a family history of ovarian cancer increased the risk for melanoma among women with NMSC, but not among non-NMSC women. Although the effects of some of these baseline risk factors on cutaneous melanoma were different when examined separately by NMSC status, results of interaction testing yielded no statistical evidence of a difference in the effect of these or

any other baseline risk factors (31 risk factors total) on the association of NMSC with incidence of cutaneous melanoma (data not shown).

We further assessed the relation between a history of NMSC and the incidence of cutaneous melanoma using a multivariate analysis (Table 5). A woman with a history of NMSC and no history of any other cancer at baseline was 1.70 times (95% CI, 1.18–2.44) more likely to develop cutaneous melanoma after adjusting for age; socioeconomic level; education; smoking; alcohol use; cups per day of regular coffee; percentage of calories from fat; selenium and zinc intake from diet and supplements; history of diabetes; BMI; prior hormone therapy use; prior oral contraceptive use; current medical care provider; geographic region by latitude; sun exposure in childhood, adolescence, and 30s; and family history of any cancer. Similar to the age-adjusted model, the HRs and 95% CIs for invasive versus in situ melanoma overlap; therefore, no difference was detected with regard to the correlation between prior NMSC and invasive versus in situ melanoma in the multivariate-adjusted model.

DISCUSSION

This prospective study, which was undertaken in a large and clinically well-characterized sample of U.S. women, supports and further defines the magnitude of increased risk for cutaneous melanoma in non-Hispanic white postmenopausal women ages 50–79 years with a history of NMSC compared with those without NMSC. An increased risk for cutaneous melanoma was found in all age groups studied (ages 50–79 yrs), in women living in different latitudes of the U.S., for those with varying levels of lifelong sun exposure history and skin reactions to the sun, in those with both high and low BMI, in women who had used hormone therapy or taken dietary supplements and those who did not, in smokers and in never smokers, and in women with or without a family history of any cancer.

Previous studies of the subsequent occurrence of cutaneous melanoma after NMSC in U.S. women were unable to specifically address important potential confounding factors such as lifestyle variables, medical surveillance bias, sun exposure history, and nutrient intake, which may account for some or all of the association.^{1–10} In the current study, extensive data were available from the WHI-OS, including prior hormone therapy and oral contraceptive use, percent of dietary calories from fat, dietary supplement usage, level of physical activity, geographic region, sun exposure history, smoking and alcohol status, education, socioeconomic level, diabetes, and access to medical care.

TABLE 1
Baseline Characteristics of Non-Hispanic White WHI-OS Participants with and without NMSC History

| | NMSC ever | | | | Total | | P value ^a |
|-------------------------------------|-----------------|------|----------------|------|--------------|------|----------------------|
| | No (n = 61,478) | | Yes (n = 5552) | | (n = 67,030) | | |
| | No. | % | No. | % | No. | % | |
| Age at screening in yrs | | | | | | | < 0.001 |
| 50-59 | 19,793 | 32.2 | 1207 | 21.7 | 21,000 | 31.3 | |
| 60-69 | 27,301 | 44.4 | 2574 | 46.4 | 29,875 | 44.6 | |
| 70-79 | 14,384 | 23.4 | 1771 | 31.9 | 16,155 | 24.1 | |
| Education | | | | | | | < 0.001 |
| None-high school diploma/GED | 12,375 | 20.3 | 794 | 14.4 | 13,169 | 19.8 | |
| School after high school | 22,324 | 36.6 | 1906 | 34.5 | 24,230 | 36.4 | |
| College degree or higher | 26,328 | 43.1 | 2817 | 51.1 | 29,145 | 43.8 | |
| Family income | | | | | | | < 0.001 |
| < \$10,000 | 1658 | 2.9 | 125 | 2.4 | 1783 | 2.9 | |
| \$10,000-\$19,999 | 5968 | 10.4 | 468 | 9.1 | 6436 | 10.3 | |
| \$20,000-\$34,999 | 13,286 | 23.2 | 1150 | 22.4 | 14,436 | 23.2 | |
| \$35,000-\$49,999 | 11,728 | 20.5 | 1092 | 21.3 | 12,820 | 20.6 | |
| \$50,000-\$74,999 | 12,016 | 21.0 | 1063 | 20.7 | 13,079 | 21.0 | |
| ≥\$75,000 + | 12,538 | 21.9 | 1240 | 24.1 | 13,778 | 22.1 | |
| BMI in kg/m ² | | | | | | | < 0.001 |
| < 25 | 25,913 | 42.6 | 2638 | 48.0 | 28,551 | 43.1 | |
| 25-29 | 20,744 | 34.1 | 1826 | 33.2 | 22,570 | 34.1 | |
| ≥ 30 | 14,112 | 23.2 | 1030 | 18.7 | 15,142 | 22.9 | |
| Smoking | | | | | | | 0.12 |
| Never | 30,387 | 50.0 | 2699 | 49.1 | 33,086 | 49.9 | |
| Past | 26,787 | 44.1 | 2499 | 45.4 | 29,286 | 44.2 | |
| Current | 3570 | 5.9 | 302 | 5.5 | 3872 | 5.8 | |
| Alcohol use | | | | | | | < 0.001 |
| < 1 drink per week | 35,537 | 58.1 | 3026 | 54.7 | 38,563 | 57.8 | |
| 1 to > 7 drinks per week | 17,106 | 27.9 | 1634 | 29.5 | 18,740 | 28.1 | |
| ≥ 7drinks per week | 8560 | 14.0 | 870 | 15.7 | 9430 | 14.1 | |
| Cups of regular coffee/day | | | | | | | < 0.001 |
| None | 25,596 | 42.0 | 2518 | 45.7 | 28,114 | 42.3 | |
| 1 | 9173 | 15.1 | 869 | 15.8 | 10,042 | 15.1 | |
| 2-3 | 19,345 | 31.7 | 1620 | 29.4 | 20,965 | 31.6 | |
| 4-5 | 5372 | 8.8 | 408 | 7.4 | 5780 | 8.7 | |
| ≥ 6 | 1458 | 2.4 | 89 | 1.6 | 1547 | 2.3 | |
| Current health care provider | 58,165 | 95.4 | 5295 | 96.3 | 63,460 | 95.4 | 0.001 |
| Medical visit within the last year | 49,930 | 83.6 | 4611 | 85.6 | 54,541 | 83.8 | < 0.001 |
| Diabetes | 2592 | 4.2 | 239 | 4.3 | 2831 | 4.2 | 0.76 |
| Prior hormone therapy use | | | | | | | < 0.001 |
| None | 23,087 | 37.6 | 1924 | 34.7 | 25,011 | 37.3 | |
| Estrogen alone only | 18,885 | 30.7 | 1818 | 32.7 | 20,703 | 30.9 | |
| Estrogen plus progesterone only | 15,417 | 25.1 | 1370 | 24.7 | 16,787 | 25.0 | |
| Both | 4089 | 6.7 | 440 | 7.9 | 4529 | 6.8 | |
| Prior oral contraceptive use in yrs | | | | | | | 0.001 |
| Nonuser | 35,809 | 58.3 | 3361 | 60.5 | 39,170 | 58.5 | |
| < 5 | 14,371 | 23.4 | 1169 | 21.1 | 15,540 | 23.2 | |
| 5-10 | 5688 | 9.3 | 495 | 8.9 | 6183 | 9.2 | |
| ≥ 10 | 5592 | 9.1 | 527 | 9.5 | 6119 | 9.1 | |
| Geographic region by latitude | | | | | | | < 0.001 |
| Southern: < 35 degrees North | 16,774 | 27.3 | 1978 | 35.6 | 18,752 | 28.0 | |
| Middle: 35-40 degrees North | 17,115 | 27.8 | 1614 | 29.1 | 18,729 | 27.9 | |
| Northern: > 40 degrees North | 27,589 | 44.9 | 1960 | 35.3 | 29,549 | 44.1 | |
| Effect of sunlight exposure on skin | | | | | | | < 0.001 |
| No change in skin color | 3279 | 6.0 | 297 | 6.0 | 3576 | 6.0 | |
| Tans but does not burn | 16,732 | 30.8 | 1020 | 20.7 | 17,752 | 30.0 | |
| Burns, then tans | 13,957 | 25.7 | 1154 | 23.5 | 15,111 | 25.5 | |
| Burns, then tans a minimal amount | 14,458 | 26.6 | 1564 | 31.8 | 16,022 | 27.1 | |
| Burns but does not tan | 5877 | 10.8 | 881 | 17.9 | 6758 | 11.4 | |

(continued)

TABLE 1
(Continued)

| | NMSC ever | | | | Total | | P value ^a |
|----------------------------------------------|-----------------|------|----------------|------|--------------|------|----------------------|
| | No (n = 61,478) | | Yes (n = 5552) | | (n = 67,030) | | |
| | No. | % | No. | % | No. | % | |
| Childhood summer sun exposure in hrs/day > 2 | 39,333 | 71.4 | 3674 | 72.8 | 43,007 | 71.5 | 0.04 |
| Teen summer sun exposure in hrs/day > 2 | 33,111 | 60.2 | 3147 | 62.4 | 36,258 | 60.3 | 0.002 |
| 30s summer sun exposure in hrs/day > 2 | 17,538 | 31.8 | 1654 | 32.9 | 19,192 | 31.9 | 0.14 |
| Mos/yr in the yard | | | | | | | < 0.001 |
| < 1 | 24,113 | 39.5 | 2197 | 39.9 | 26,310 | 39.5 | |
| 1-3 | 10,693 | 17.5 | 896 | 16.3 | 11,589 | 17.4 | |
| 4-6 | 11,751 | 19.3 | 981 | 17.8 | 12,732 | 19.1 | |
| 7-9 | 7080 | 11.6 | 658 | 11.9 | 7738 | 11.6 | |
| 10-12 | 7395 | 12.1 | 780 | 14.2 | 8175 | 12.3 | |
| Physical activity in MET, hrs/week | | | | | | | <0.001 |
| None | 7677 | 12.7 | 576 | 10.6 | 8253 | 12.6 | |
| > 0-7.4 | 16,414 | 27.3 | 1387 | 25.5 | 17,801 | 27.1 | |
| 7.5-17.4 | 18,015 | 29.9 | 1700 | 31.2 | 19,715 | 30.0 | |
| ≥ 17.5 | 18,124 | 30.1 | 1779 | 32.7 | 19,903 | 30.3 | |
| Percent of total calories from fat | | | | | | | < 0.001 |
| ≤ 30 | 28,472 | 47.7 | 2737 | 50.5 | 31,209 | 47.9 | |
| > 30-35 | 12,485 | 20.9 | 1142 | 21.1 | 13,627 | 20.9 | |
| > 35-40 | 9380 | 15.7 | 825 | 15.2 | 10,205 | 15.7 | |
| > 40 | 9380 | 15.7 | 721 | 13.3 | 10,101 | 15.5 | |
| Dietary selenium in μg | | | | | | | 0.09 |
| ≤ 71.3 | 19,037 | 31.9 | 1664 | 30.7 | 20,701 | 31.8 | |
| 71.4-101.6 | 20,578 | 34.5 | 1940 | 35.8 | 22,518 | 34.6 | |
| > 101.6 | 20,102 | 33.7 | 1821 | 33.6 | 21,923 | 33.7 | |
| Dietary zinc in mg | | | | | | | < 0.001 |
| ≤ 7.9 | 18,519 | 31.0 | 1521 | 28.0 | 20,040 | 30.8 | |
| 8.0-11.6 | 20,490 | 34.3 | 1959 | 36.1 | 22,449 | 34.5 | |
| > 11.6 | 20,708 | 34.7 | 1945 | 35.9 | 22,653 | 34.8 | |
| Supplement use (any) | 45,854 | 74.6 | 4415 | 79.5 | 50,269 | 75.0 | < 0.001 |
| Selenium | 24,772 | 40.3 | 2397 | 43.2 | 27,169 | 40.5 | < 0.001 |
| Zinc | 28,634 | 46.6 | 2826 | 50.9 | 31,460 | 46.9 | < 0.001 |
| Family history of any cancer | 39,780 | 67.2 | 3865 | 72.2 | 43,645 | 67.6 | < 0.001 |
| Breast cancer | 11,274 | 19.3 | 1146 | 21.8 | 12,420 | 19.5 | < 0.001 |
| Ovarian cancer | 622 | 1.3 | 69 | 1.6 | 691 | 1.3 | 0.10 |

WHI-OS: Women's Health Initiative-Observational Study; NMSC: nonmelanoma skin cancer; GED: general equivalency diploma; BMI: body mass index; E: estrogen; P: progesterone; MET: metabolic equivalent.

^a P values were derived from chi-square tests.

Because sunlight is considered the main environmental cause of both NMSC and cutaneous melanoma, and given the strong relationship in the U.S. of southern latitude residence and NMSC history, it is important to control for geographic latitude of residence and history of lifetime sun exposure.^{12,13,20,22-24} After adjusting for these confounding factors as well as others, the HR for the association between NMSC and melanoma development is reduced to 1.70. A change of this magnitude suggests that several of the covariates are related to both exposure and outcome.

Controlling for medical surveillance appears to be especially important given the univariate relation of current healthcare provider with NMSC (Table 1), and

the possibility that those who had NMSC would be more likely to undergo skin inspection by a physician on a regular basis, and therefore be diagnosed with cutaneous melanoma more readily. Although we did adjust for having a medical provider, our medical surveillance adjustment is limited due to a lack of information on the frequency or quality of skin examinations specifically. Furthermore, although invasive and in situ melanomas were diagnosed with similar frequency, we did not have pathologic information available for Breslow thickness; therefore, surveillance bias could not be eliminated based on pathologic diagnosis.²⁵

The current study relied entirely on self-report of

TABLE 2
Incidence (Annualized %) of Cutaneous Melanoma in Non-Hispanic White WHI-OS Participants for Participants with and without NMSC History

| | History of NMSC | | | | Adjusted HR | 95% CI | P value |
|----------------------------|-----------------|--------|-----------|--------|-------------|-----------|----------|
| | No | | Yes | | | | |
| | No. | % | No. | % | | | |
| Number enrolled | 61,478 | | 5552 | | | | |
| Mean follow-up in yrs (SD) | 6.5 (1.4) | | 6.5 (1.4) | | | | |
| Melanoma of the skin | 272 | (0.07) | 59 | (0.16) | 2.41 | 1.82-3.20 | < 0.0001 |
| Invasive | 153 | (0.04) | 29 | (0.08) | 2.15 | 1.44-3.21 | 0.0002 |
| In situ | 113 | (0.03) | 28 | (0.08) | 2.66 | 1.75-4.03 | < 0.0001 |

WHI-OS: Women's Health Initiative-Observational Study; NMSC: nonmelanoma skin cancer; HR: hazards ratio; 95% CI: 95% confidence interval; SD: standard deviation. The hazard ratios, 95% confidence intervals, and *P* values were derived from Cox proportional hazards analyses and were adjusted for age.

TABLE 3
Cutaneous Melanoma HRs for Non-Hispanic White WHI-OS Participants with a History of NMSC at Baseline or NMSC Prior to Melanoma during Follow-Up^a

| | Prior NMSC | | Adjusted HR | 95% CI | P value |
|----------------------|------------|-----|-------------|-----------|----------|
| | No | Yes | | | |
| Melanoma of the skin | 265 | 66 | 2.54 | 1.94-3.33 | < 0.0001 |
| Invasive | 150 | 32 | 2.22 | 1.51-3.25 | < 0.0001 |
| In situ | 110 | 31 | 2.78 | 1.86-4.15 | < 0.0001 |

HR: hazards ratio; WHI-OS: Women's Health Initiative-Observational Study; NMSC: nonmelanoma skin cancer; 95% CI: 95% confidence interval.

^a Prior nonmelanoma skin cancer (NMSC) includes a history of NMSC at baseline or incident NMSC occurring during follow-up prior to cutaneous melanoma. Hazard ratios, 95% confidence intervals, and *P* values were from Cox proportional hazards analyses and were adjusted for age.

NMSC overall, and could not differentiate whether a particular histologic subtype (i.e., squamous cell vs. basal cell) was differentially associated with melanoma. Furthermore, the validity of self-reported NMSC within the WHI-OS has not been assessed to our knowledge. However, recent studies suggest that self-reported NMSC has a high degree of accuracy.²⁶ For example, Ming et al.²⁶ found that patients correctly identified their overall NMSC status in 91.8% of cases, and Colditz et al.²⁷ reported from the Nurses Health Study that > 90% of self-reported cases of cancer of the skin were confirmed by histopathology reports. Therefore, although the current study relied only on self-report of NMSC, prior research strongly supports a high rate of agreement with actual diagnosis of NMSC.

The current study was limited to observations in postmenopausal non-Hispanic white women ages 50-79 years only, and furthermore excluded women with a prior history of any cancer other than NMSC.

Therefore, the magnitude of the association may be underestimated. Further assessment of the extent of the association for women age < 50 years, those of non-white and Hispanic ethnicities, premenopausal women, and men is warranted.

Epidemiologic findings support an association between fair skin, inability to tan, and the risk of both melanoma and NMSC.^{12,22,28,29} For whites in the U.S., the incidence of NMSC is associated with age and lifelong residence in areas with high levels of ambient ultraviolet B (UVB) radiation (i.e., lower latitude).^{12,13,22,30,31} Although chronic, cumulative, UV exposure appears to be the most important risk factor for developing NMSC overall, recent studies suggest that intermittent intense sun exposure early in life, leading to sunburn, may also be a risk factor for some basal cell carcinomas.^{23,30,32} Cutaneous melanoma is believed to be associated with intense intermittent sun exposure and sunburn. Yet the optimal relation between melanoma risk and the dose of sun exposure received is complex and appears to vary according to age, the dose received, and host characteristics.^{23,33,34} In the current study, women without a history of NMSC, but not those with such a history, were more likely to develop melanoma if they reported experiencing a burn rather than a tanning effect from exposure to sunlight and if they reported summer sun exposure greater than 2 hours per day in their 30s (Table 4). These findings support the concept that distinct, dual, gene-environment interactive pathways lead to cutaneous melanoma in NMSC and non-NMSC women.^{23,35} For example, researchers have found that BRAF mutations were more common in melanomas occurring on intermittently sun-exposed skin than on chronically sun-damaged skin.³⁶ There may be a molecular distinction between those individuals whose melanomas arise on chronic sun-ex-

TABLE 4
Association of Various Risk Factors with Cutaneous Melanoma by History of NMSC^a

| | History of NMSC | | | | | |
|-------------------------------------|-----------------|-----------|---------|----------------|------------|---------|
| | No (n = 61,478) | | | Yes (n = 5552) | | |
| | HR | 95% CI | P value | HR | 95% CI | P value |
| Effect of sunlight exposure on skin | | | | | | |
| Tans but does not burn | 1.00 | | | 1.00 | | |
| No change in skin color | 0.71 | 0.32–1.58 | 0.40 | 1.18 | 0.24–5.88 | 0.84 |
| Burns, then tans | 1.51 | 1.04–2.20 | 0.03 | 1.80 | 0.67–4.83 | 0.24 |
| Burns, then tans a minimal amount | 2.04 | 1.44–2.89 | < 0.01 | 2.33 | 0.94–5.79 | 0.07 |
| Burns but does not tan | 2.25 | 1.48–3.42 | < 0.01 | 1.96 | 0.71–5.40 | 0.19 |
| 30 summer sun exposure > 2 hrs/day | 1.48 | 1.15–1.91 | < 0.01 | 1.19 | 0.68–2.09 | 0.54 |
| Family history of ovarian cancer | 0.72 | 0.18–2.89 | 0.64 | 4.26 | 1.32–13.75 | 0.02 |

NMSC: nonmelanoma skin cancer; HR: hazards ratio; 95% CI: 95% confidence interval.
^a Cox proportional hazards models examined the effect of each risk factor separately and were adjusted for age.

TABLE 5
Incidence (Annualized %) of Cutaneous Melanoma and Multivariate-Adjusted^a HRs in Non-Hispanic White WHI-OS Participants for a History of NMSC

| | History of NMSC | | | | HR | 95% CI | P value |
|----------|-----------------|------------|------|-----------|-------|--------|---------|
| | No | Yes | HR | 95% CI | | | |
| Melanoma | 203 (0.07%) | 36 (0.14%) | 1.70 | 1.18–2.44 | 0.004 | | |
| Invasive | 112 (0.04%) | 20 (0.08%) | 1.69 | 1.04–2.75 | 0.03 | | |
| In situ | 86 (0.03%) | 15 (0.06%) | 1.69 | 0.96–2.95 | 0.07 | | |

HR: hazards ratio; WHI-OS: Women’s Health Initiative–Observational Study; NMSC: nonmelanoma skin cancer; 95% CI: 95% confidence interval.
^a Cox proportional hazards models were adjusted for age; education; socioeconomic level (income); smoking; alcohol use; cups per day of regular coffee; percent calories from fat; selenium and zinc intake from diet and supplements; history of diabetes; body mass index (kg/m²); prior hormone therapy use; prior oral contraceptive use; current medical care provider; geographic region by latitude; sun exposure in childhood, adolescence, and 30s; and family history of cancer.

posed skin such as in many of those with NMSC, and those in whom melanoma develops on sun-protected, fair, or non-NMSC skin.

Previous investigations report findings in both animal and human models of common etiologic mechanisms for both NMSC and cutaneous melanoma that support the association observed in the current study. A qualitative impairment of the immune response, exemplified by the elevated production of type 2 cytokines, and the concomitant reduction in type 1 cytokines, have been reported in basal and squamous cell skin carcinomas and melanoma.^{12,37–41} A number of oncogenes and suppressor genes have been implicated in the genesis and progression of both NMSC and cutaneous melanoma. UV-induced reduction of DNA repair capacity, as well as early- and late-stage p53 suppressor gene mutations, have been docu-

mented to play a role in NMSC and cutaneous melanoma.^{42–50} Still another example of common etiologies regards the BRCA2 gene, which encodes a protein important in DNA repair. BRCA2 mutation carriers have an increased risk of breast and ovarian cancer, as well as melanoma.⁵¹ Interestingly, in the current study, women in the NMSC group were more likely to have a family history of breast or ovarian cancer compared with their non-NMSC counterparts. Furthermore, among women with NMSC a family history of ovarian cancer increased the risk for melanoma, whereas this was not observed among women in the non-NMSC group. These characteristics and findings in the women with NMSC may suggest that a BRCA2 gene is involved in the association of NMSC and melanoma.

Consequently, in NMSC and non-NMSC populations of women, different predisposing genes may interact with sun exposure and cause defective molecular signaling, and therefore influence the probability of melanoma development. If multiple molecular pathways to melanoma development are supported by other investigations, public health messages can be tailored to the population at risk.⁵²

It is estimated that over 1.3 million cases of NMSC are diagnosed yearly in the U.S., making it the most common (yet largely undocumented) cancer entity in the U.S.^{53,54} NMSCs are not routinely included in U.S. cancer registries. Furthermore, because NMSC usually carries a favorable prognosis, patients are unlikely to be questioned specifically regarding a history of NMSC during the course of a routine general physical examination. These factors hamper the ability to calculate the incidence and prevalence of NMSC accurately, as well as monitor trends and associations.

Cutaneous melanoma (invasive) was estimated to affect 59,580 Americans in 2005 (26,000 women), and account for 7770 deaths (2860 women). An additional 46,170 individuals will be affected with cutaneous melanoma in situ.^{29,55} Noted for its rapid rise in incidence, its high mortality rate in patients with advanced disease, and as a leading cause of lost productive years, melanoma is routinely included in U.S. cancer registries.^{29,53,56,57} Nevertheless, much of the registries' information does not include epidemiologic risk information, including documentation of NMSC. Efforts to reduce the incidence of cutaneous melanoma in individuals age > 50 years are focused on secondary, rather than primary prevention (i.e., screening persons at high risk).^{29,57,58} In the WHI-OS, 8% of the women enrolled reported a history of NMSC.¹⁴ In the current study, the annual incidence of melanoma in non-Hispanic white women with a history of NMSC was 160/100,000 versus 70/100,000 for women without a history of NMSC. The high prevalence of NMSC in non-Hispanic white postmenopausal women in the U.S., and its link to an increased risk of subsequent cutaneous melanoma as delineated in this study, is important not only for further defining melanoma risk in white postmenopausal women, but also for sensitizing the medical community to this risk and for developing new routines of follow-up and patient assessment by medical providers to promote the early detection of melanoma.

REFERENCES

1. Frisch M, Melbye M. New primary cancers after squamous cell skin cancer. *Am J Epidemiol.* 1995;141:916–922.
2. Frisch M, Hjalgrim H, Olsen JH, Melbye M. Risk for subsequent cancer after diagnosis of basal-cell carcinoma. A population-based, epidemiologic study. *Ann Intern Med.* 1996;125:815–821.
3. Marghoob AA, Slade J, Salopek TG, Kopf AW, Bart RS, Rigel DS. Basal cell and squamous cell carcinomas are important risk factors for cutaneous melanoma. Screening implications. *Cancer.* 1995;75:707–714.
4. Wassberg C, Thorn M, Yuen J, Ringborg U, Hakulinen T. Second primary cancers in patients with squamous cell carcinoma of the skin: a population-based study in Sweden. *Int J Cancer.* 1999;80:511–515.
5. Levi F, La Vecchia C, Te VC, Randimbison L, Erler G. Incidence of invasive cancers following basal cell skin cancer. *Am J Epidemiol.* 1998;147:722–726.
6. Levi F, Randimbison L, La Vecchia C, Erler G, Te VC. Incidence of invasive cancers following squamous cell skin cancer. *Am J Epidemiol.* 1997;146:734–739.
7. Lindelof B, Sigurgeirsson B, Wallberg P, Eklund G. Occurrence of other malignancies in 1973 patients with basal cell carcinoma. *J Am Acad Dermatol.* 1991;25:245–248.
8. Milan T, Pukkala E, Verkasalo PK, et al. Subsequent primary cancers after basal cell carcinoma: a nationwide study in Finland from 1953 to 1995. *Int J Cancer.* 2000;87:283–288.
9. Friedman GD, Tekawa IS. Association of basal cell skin cancer with other cancers (United States). *Cancer Causes Control.* 2000;11:891–897.
10. Efrid JT, Friedman GD, Habel L, Tekawa IS, Nelson LM. Risk of subsequent cancer following invasive or in situ squamous cell skin cancer. *Ann Epidemiol.* 2002;12:469–475.
11. Kahn HS, Tatham LM, Patel AV, Thun MJ, Heath CW Jr. Increased cancer mortality following a history of nonmelanoma skin cancer. *JAMA.* 1998;280:910–912.
12. Alam M, Ratner D. Cutaneous squamous-cell carcinoma. *N Engl J Med.* 2001;344:975–983.
13. Strom SS, Yamamura Y. Epidemiology of nonmelanoma skin cancer. *Clin Plast Surg.* 1997;24:627–636.
14. Rosenberg CA, Greenland P, Khandekar J, Loar A, Ascensao J, Lopez AM. Association of nonmelanoma skin cancer with second malignancy. The Women's Health Initiative Observational Study. *Cancer.* 2004;100:130–138.
15. Schottenfeld D. Basal-cell carcinoma of the skin: a harbinger of cutaneous and noncutaneous multiple primary cancer [editorial]. *Ann Intern Med.* 1996;125:852–854.
16. [no authors listed]. Design of Women's Health Initiative clinical trial and observation. The Women's Health Initiative Study Group. *Control Clin Trials.* 1998;19:61–109.
17. Langer RD, White E, Lewis CE, Kotchen JM, Hendrix SL, Trevisan M. The Women's Health Initiative Observational Study: baseline characteristics of participants and reliability of baseline measures. *Ann Epidemiol.* 2003;13:S107–S121.
18. Anderson GL, Manson J, Wallace R, et al. Implementation of the Women's Health Initiative Study Design. *Ann Epidemiol.* 2003;13:S5–S17.
19. McTiernan A, Kooperberg C, White E, et al. Recreational activity and the risk of breast cancer in postmenopausal women: the Women's Health Initiative Cohort Study. *JAMA.* 2003;290:1331–1378.
20. Scotto J, Fears TR, Kraemer KH, Fraumeni JF. Nonmelanoma skin cancer. In: Schottenfeld D, Fraumeni JF Jr., editors. *Cancer epidemiology and prevention*, 2nd ed. New York: Oxford University Press, 1996:1313–1330.
21. Curb JD, McTiernan A, Heckbert SR, et al. Outcomes ascertainment and adjudication methods in the Women's Health Initiative. *Ann Epidemiol.* 2003;13:S122–S128.
22. Preston DS, Stern RS. Nonmelanoma cancers of the skin. *N Engl J Med.* 1992;327:2:1649–1662.
23. Rosso S, Zanetti R, Pippione M, Sancho-Garnier H. Parallel risk assessment of melanoma and basal cell carcinoma: skin characteristics and sun exposure. *Melanoma Res.* 1998;8:573–583.
24. Dubin N, Pasternak BS, Moseson M. Simultaneous assessment of risk factors for malignant melanoma and non-melanoma skin lesions, with emphasis on sun exposure and related variables. *Int J Epidemiol.* 1990;19:811–819.
25. Balch CM, Soong S, Thompson JI. The natural history of melanoma and factors predicting outcome. In: Thompson JF, Morton DL, Kroon BB, editors. *Textbook of melanoma*. New York: Martin Dunitz, 2004:181–198.
26. Ming ME, Levy RM, Hoffstad OH, Filip J, Gimotty P, Margolis DJ. Validity of patient self-reported history of skin cancer. *Arch Dermatol.* 2004;140:730–735.
27. Colditz GA, Martin P, Stampfer MJ, et al. Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. *Am J Epidemiol.* 1986;123:894–900.
28. Gilchrist BA, Eller MS, Geller AC, Yaar M. The pathogenesis of melanoma induced by ultraviolet radiation. *N Engl J Med.* 1999;340:1341–1348.

29. Tsao H, Atkins MB, Sober AJ. Management of cutaneous melanoma. *N Engl J Med*. 2004;351:998–1012.
30. Gloster HM Jr., Brodland DG. The epidemiology of skin cancer. *Dermatol Surg*. 1996;22:217–226.
31. Scotto J, Fraumeni JF. Solar irradiation. In: Schottenfeld D, Fraumeni JF Jr., editors. *Cancer epidemiology and prevention*, 2nd ed. New York: Oxford University Press, 1996:355–372.
32. Lang PG, Maize JC. Basal cell carcinoma. In: Rigel DS, Friedman RJ, Dzubow LM, Reintgen DS, Bystryjn JC, Marks R, editors. *Cancer of the skin*. Philadelphia: Elsevier Saunders, 2005:101–132.
33. Armstrong B. Epidemiology of cutaneous melanoma and current trends. In: Thompson JF, Morton DL, Kroon BB, editors. *Textbook of melanoma*. New York: Martin Dunitz, 2004:65–80.
34. Palmer JS, Duffy DL, Box NF, et al. Melanocortin-1 receptor polymorphisms and risk of melanoma: is the association explained solely by pigmentation phenotypes? *Am J Genet*. 2000;66:176–186.
35. Rivers JK. Is there more than one road to melanoma? *Lancet*. 2004;363:728–730.
36. Maldonado JL, Fridlyand J, Patel H, et al. Determinants of BRAF mutations in primary melanomas. *J Natl Cancer Inst*. 2003;95:1878–1890.
37. Grossman D, Leffell DJ. The molecular basis of nonmelanoma skin cancer: new understanding. *Arch Dermatol*. 1997;133:1263–1270.
38. Clerici M, Shearer GM, Clerici E. Cytokine dysregulation in invasive cervical carcinoma and other human neoplasias: time to consider the TH1/TH2 paradigm [review]. *J Natl Cancer Inst*. 1998;90:261–263.
39. Kripke ML. Effects of UV radiation on tumor immunity. *J Natl Cancer Inst*. 1990;82:1392–1396.
40. Kripke ML. Ultraviolet radiation and immunobiology: something new under the sun. *Cancer Res*. 1994;54:6102–6105.
41. Morison WL. Effects of ultraviolet radiation on the immune system in humans. *Photochem Photobiol*. 1989;50:515–524.
42. Wei Q, Matanoski GM, Farmer ER, Hedayati MA, Grossman L. DNA repair and aging in basal cell carcinoma. A molecular epidemiology study. *Proc Natl Acad Sci U S A*. 1993;90:1614–1618.
43. Wei Q, Lee JE, Gershenwald JE, et al. Repair of UV light-induced DNA damage and risk of cutaneous malignant melanoma. *J Natl Cancer Inst*. 2003;95:308–315.
44. Brash DE, Rudolph JA, Simon JA, et al. A role for sunlight in skin cancer: UV-induced p53 mutations in squamous cell carcinoma. *Proc Natl Acad Sci U S A*. 1991;88:10124–10128.
45. Hill LL, Ouhtit A, Loughlin SM, Kripke ML, Ananthaswamy HN, Owen-Schaub LB. Fas ligand: a sensor for DNA damage critical in skin cancer etiology. *Science*. 1999;285:898–900.
46. Ziegler A, Leffell DJ, Kunala S, et al. Mutation hot spots to sunlight in the p53 gene of nonmelanoma skin cancers. *Proc Natl Acad Sci U S A*. 1993;90:4216–4220.
47. Ziegler A, Jonason AS, Leffell DJ, et al. Sunburn and p53 in the onset of skin cancer. *Nature*. 1994;372:773–776.
48. Rizos H, Becker TM, Holland EA. Cell cycle regulation in the melanocyte. In: Thompson JF, Morton DL, Kroon BB, editors. *Textbook of melanoma*. New York: Martin Dunitz, 2004:18–24.
49. Brewster AM, Alberg AJ, Strickland PT, Hoffman SC, Helzlsouer K. XPD polymorphism and risk of subsequent cancer in individuals with nonmelanoma skin cancer. *Cancer Epidemiol Biomarker Prev*. 2004;13:1271–1275.
50. Merlino G. The weakest link? *Nature*. 2005;436:33–35.
51. The Breast Cancer Linkage Consortium. Cancer risks in BRCA2 mutation carriers. *J Natl Cancer Inst*. 1999;91:1310–1316.
52. Carlson JA, Slominski A, Linette GP, Mihm MC, Ross JS. Biomarkers in melanoma: predisposition, screening and diagnosis [review]. *Expert Rev Mol Diagn*. 2003;3:163–184.
53. Geller AC, Annas GD. Epidemiology of melanoma and non-melanoma skin cancer. *Semin Oncol Nursing*. 2003;19:2–11.
54. American Cancer Society. *Cancer Facts and Figures 2004*. Atlanta: American Cancer Society, 2004. Available at URL: http://www.cancer.org/downloads/STT/CAFF_finalPWSecured.pdf [accessed July 1, 2004].
55. Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. *CA Cancer J Clin*. 2005;55:10–30.
56. Albert VA, Koh HK, Geller AC, Miller DR, Prout MN, Lew RA. Years of potential life lost: another indicator of the impact of cutaneous malignant melanoma on society. *J Am Acad Dermatol*. 1990;23:308–310.
57. Tucker MA, Goldstein AM. Melanoma etiology: where are we? *Oncogene*. 2003;22:3042–3052.
58. Abbasi NR, Shaw HM, Rigel DS, et al. Early diagnosis of cutaneous melanoma. *JAMA*. 2004;292:2771–2776.