Skin cancer is the most common malignancy in the United States, with more than 1 million new diagnoses each year (1). Over the past 40 years, the incidence of both melanoma and nonmelanoma skin cancer has increased dramatically (1,2). Although the etiologies of nonmelanoma skin cancer (particularly basal cell and squamous cell carcinomas) and melanoma are not completely understood, sun exposure plays a critical role and is a primary risk factor (3,4).

Preclinical and clinical findings suggest that estrogen may be involved in the development of skin cancer. Estrogen receptors are present on skin keratinocytes (5), and in clinical trials, oral contraceptives and hormone therapy have been shown to decrease acne (6) and skin aging (7), respectively. Two case-control studies found an association between oral contraceptive use and an increased risk of nonmelanoma skin cancer (8,9). It has also been suspected that estrogen influences the risk of melanoma; however, two reviews suggest that the evidence linking hormone therapy to melanoma is weak (10,11). Moreover, melanoma incidence and survival differ by sex as women have a better prognosis than men (12,13), and the estrogen receptor is expressed in benign nevi, dysplastic nevi, and cutaneous melanomas (14). Although epidemiological studies of menopausal hormone therapy and the risk of melanoma have produced mixed findings, several studies reported that hormone use was associated with increased risk of melanoma (15–17). To our knowledge, no large randomized controlled trials have investigated the effects of hormone therapy on risk of skin cancer. We analyzed the incidence of nonmelanoma skin cancer and of melanoma in the large multiethnic Women’s Health Initiative (WHI) clinical trials of estrogen plus progestin (E + P) vs placebo and estrogen alone (E-alone) vs placebo.
**Participants and Methods**

**Study Design**

This study included postmenopausal women aged 50–79 years who were enrolled in the WHI hormone therapy trials (http://Clinicaltrials.gov identifier: NCT00000611) and recruited at 40 US clinical centers. In these studies, coronary heart disease and breast cancer were the primary monitored outcomes for benefit and harm, respectively. In an attempt to summarize important aspects of health benefits vs risks, a global index was defined as the earliest occurrence of coronary heart disease, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death (18). This global index was used to monitor the study for benefit or harm. The trials were not powered for the overall incidence of nonmelanoma skin cancer. Women were eligible for the WHI hormone therapy trials if they had no history of cancer, except nonmelanoma skin cancer and melanoma.

The WHI hormone therapy trials enrolled 27 347 women between 1993 and 1998; those with an intact uterus were enrolled in the E + P trial (N = 16 608) and those with a previous hysterectomy were enrolled in the E-alone trial (N = 10 739). Women were randomly assigned by use of a permuted block algorithm in a double-blind fashion to daily administration of either 0.625 mg of conjugated equine estrogen with 2.5 mg of medroxyprogesterone acetate (Prempro; Wyeth-Ayerst, Philadelphia, PA) or placebo in the E + P trial or, in the E-alone trial, to either 0.625 mg conjugated equine estrogen (Premarin; Wyeth-Ayerst) or placebo.

**Retention, Adherence, and Follow-up**

Study participants were contacted by telephone 6 weeks after random assignment to assess symptoms and reinforce adherence. Follow-up for clinical events occurred by telephone every 6 months, and annual in-clinic visits were required. At each semianual contact, a standardized self-administered questionnaire collected information on symptoms, safety concerns, and reports of changes in medical history, including any cancer diagnosis. Adherence to study interventions was assessed by weighing returned medication bottles at the annual visits and was predefined as taking 80% or more of study pills (active or placebo). Participants were followed for major outcomes, regardless of adherence to study interventions, until death or loss to follow-up. Over the course of the studies, 583 women (3.5%) in the E + P trial and 563 women (5.2%) in E-alone trial withdrew or were lost to follow-up (ie, had not provided outcomes information for >18 months).

The E + P trial was terminated at a mean follow-up of 5.6 years because the health risks, including increased incidence of coronary heart disease, stroke, pulmonary embolism, and breast cancer, exceeded the benefits of decreased incidence of colorectal cancer and hip fracture (18). The E-alone trial was terminated at 7.1 years of follow-up because of increased incidence of stroke and no suggestion of benefit regarding coronary heart disease (21). At the time each trial was terminated, 42% of E + P trial participants and 54% of E-alone trial participants had stopped taking study pills, whereas 6.2% of women assigned to active E + P trial pills and 10.7% of the placebo group had initiated hormone therapy through their own physicians, as had 5.7% of women assigned to active E-alone trial pills and 9.1% on placebo.

**Determining Incident Cases of Skin Cancer**

Women were provided questionnaires at 6-month intervals to report any hospitalizations and other outcomes, including nonmelanoma skin cancer and melanomas. Incident cases of cutaneous malignant melanoma were confirmed by central review of medical records, including pathology reports, and coded as invasive, in situ, or unknown (22). Incident cases of nonmelanoma skin cancer were not adjudicated.

**Statistical Analysis**

Descriptive characteristics and potential risk factors for skin cancer, including race, body mass index (BMI), smoking status, regional solar radiation (based on the amount of sunlight reaching the clinic site as measured by the US Weather Bureau), total outdoor walking energy expenditure (metabolic equivalent tasks per week), nonsteroidal anti-inflammatory drug use, and history of skin cancer, were evaluated by treatment group within each trial. In post hoc analyses, incidences of nonmelanoma skin cancer and melanoma were compared between the two randomization arms.
groups within each trial by using hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) and Wald statistic P values from Cox proportional hazards models. We confirmed the proportionality assumption by running a proportional hazards model that modeled each outcome as a function of the interaction between the hormone therapy effect and the log survival time. We also verified the proportionality assumption graphically. Modeling analyses used time-to-event methods according to the intention-to-treat principle. Kaplan–Meier estimates were used to describe event rates over time. Potential differential effects across subgroups of risk factors for both nonmelanoma skin cancer and melanoma were tested by running proportional hazards models with the E + P or E-alone intervention, the categorical subgroup of interest, and their interaction. Hazard ratios for active hormone therapy treatment vs placebo within each subgroup are presented along with the P value for interaction. Sensitivity analyses were performed by restricting the analysis to participants who were adherent to the study interventions (ie, those who took ≥80% of study pills) during the trial. All P values are two-sided, and P values less than or equal to .05 were considered to be statistically significant.

For nonmelanoma skin cancer and melanoma, six predefined subgroup analyses were performed for each of the two trials as well as for combined hormone therapy trial results (ie, active E + P and E-alone groups vs combined placebo groups) to assess possible statistical interactions between active hormone therapy use and the following variables: 1) age (50–59, 60–69, or 70–79 years), 2) BMI (<25 or ≥25 kg/m²), 3) regional solar radiation (<375 or ≥375 langleys) based on the amount of sunlight reaching the clinic site as measured by the US Weather Bureau, 4) history of nonmelanoma skin cancer (yes, no), 5) smoking status (never, past, or current), and 6) ever use of nonsteroidal anti-inflammatory drug at study entry (baseline; yes or no). Cut points for age, BMI, and regional solar radiation were as previously defined in the WHI clinical trials. All statistical analyses were conducted using SAS (version 9.2; SAS Institute Inc, Cary, NC). All statistical tests were two-sided.

Results

Demographic Characteristics of Participants

Baseline demographic characteristics, medical history, health behaviors, and measures of sun exposure (regional solar radiation and outdoor walking) were generally balanced between randomization groups for each trial (Table 1). A minor difference in the history of cancer was seen between randomization groups in the E-alone trial (4.5% E-alone vs 5.7% placebo), and total outdoor walking energy expenditure differed by less than 2% between randomization groups in both trials.

Nonmelanoma Skin Cancer

Postmenopausal women were followed for a mean of 5.6 years in the E + P trial and 7.1 years in the E-alone trial. There was no effect of combined E + P or E-alone on the number of incident cases of self-reported nonmelanoma skin cancer (E + P vs placebo: 494 vs 486 cases, HR = 0.95, 95% CI = 0.83 to 1.07, P = .38; E-alone vs placebo: 406 vs 414 cases, HR = 1.03, 95% CI = 0.89 to 1.18, P = .73) (Figure 1, A and B). Because of the null findings in the each of the two trials, we combined the data from the E + P and E-alone trials to enhance the statistical power. Hormone therapy use had no effect on the incidence of nonmelanoma skin cancer in the combined analysis (HR = 0.98, 95% CI = 0.89 to 1.07, P = .65) (Table 2) nor did hormone therapy use affect the incidence of nonmelanoma skin cancer within any of the six predetermined subgroups (ie, age, BMI, regional solar radiation, history of nonmelanoma skin cancer, smoking status, or nonsteroidal anti-inflammatory drug use) Supplementary Tables 1 and 2, available online).

Melanoma

There was no effect of combined E + P or E-alone on the number of incident cases of melanoma after a mean follow-up of 5.6 and 7.1 years in the respective trials (E + P vs placebo: 29 vs 28 cases, HR = 0.96, 95% CI = 0.57 to 1.61, P = .86; E-alone vs placebo: 17 vs 21 cases, HR = 0.85, 95% CI = 0.45 to 1.61, P = .61) (Table 2). Because there was no evidence that the results differed between trials, we combined the melanoma data for the E + P and E-alone trials to assess active hormone therapy use vs placebo (Table 2, Figure 1, C). Hormone therapy use had no effect on the incidence of melanoma in the combined analysis (HR = 0.92, 95% CI = 0.61 to 1.37) nor did hormone therapy use affect the incidence of melanoma within any of the six predetermined subgroups (Supplementary Table 3, available online). In a sensitivity analysis that was restricted to participants who were adherent to the study interventions (ie, those who took 80% or more of study pills) during the trial, there was no effect of hormone therapy use on the incidence of melanoma or nonmelanoma skin cancer (data not shown). Of the 95 incident cases of melanoma, 50 were invasive and 45 were in situ. We found no statistically significant differences in subtypes of melanomas (invasive vs in situ) between women randomly assigned to E-alone vs placebo, E + P vs placebo, or any hormone therapy vs placebo.

Discussion

To our knowledge, these are the first data on hormone therapy use and the risk of skin cancer from a randomized double-blind trial. In the WHI hormone therapy trials, neither E + P nor E-alone affected the incidence of nonmelanoma skin cancer or melanoma in postmenopausal women. The findings with regard to melanoma incidence are consistent with the preponderance of data from observational studies [as reviewed in (10,11)]. Of 14 observational studies that examined the association between hormone therapy and melanoma (15–17,23–33), only three (15–17) reported that hormone therapy use was statistically significantly associated with a higher incidence of melanoma. Findings from these three reports may have been confounded because of the lack of detailed information on sun exposure and constitutional risk factors such as skin color, and even among the 14 studies, the results were inconsistent (15). Because melanoma is associated with sunburn in childhood or teenage years (34), hormone exposure in early life may have a stronger effect on skin cancer development than exposures after menopause.
| Characteristic                                      | E + P trial | Placebo (N = 8102) | E-alone trial | Placebo (N = 5429) |
|----------------------------------------------------|-------------|---------------------|--------------|-------------------|
| **Age, y**                                         |             |                     |              |                   |
| 50–59                                              | 2837 (33.4) | 2683 (33.1)         | 1639 (30.9)  | 1674 (30.8)       |
| 60–69                                              | 3854 (45.3) | 3655 (45.1)         | 2386 (44.9)  | 2465 (45.4)       |
| 70–79                                              | 1815 (21.3) | 1764 (21.8)         | 1285 (24.2)  | 1290 (23.8)       |
| **Race/ethnicity**                                 |             |                     |              |                   |
| White                                              | 7141 (84.0) | 6805 (84.0)         | 4009 (75.5)  | 4075 (75.1)       |
| Black                                              | 548 (6.4)   | 574 (7.1)           | 781 (14.7)   | 835 (15.4)        |
| Hispanic                                           | 471 (5.5)   | 415 (5.1)           | 319 (6.0)    | 332 (6.1)         |
| American Indian                                    | 25 (0.3)    | 30 (0.4)            | 41 (0.8)     | 34 (0.6)          |
| Asian or Pacific Islander                          | 194 (2.3)   | 169 (2.1)           | 96 (1.6)     | 78 (1.4)          |
| Unknown                                            | 127 (1.5)   | 109 (1.3)           | 74 (1.4)     | 75 (1.4)          |
| **Education level**                                |             |                     |              |                   |
| Less than high school diploma or GED               | 2090 (25.7) | 2148 (26.5)         | 1769 (33.3)  | 1707 (31.4)       |
| Some school after high school                     | 3357 (39.5) | 3060 (37.8)         | 2271 (42.8)  | 2351 (43.3)       |
| College degree or higher                          | 2915 (34.3) | 2839 (35.0)         | 1217 (22.9)  | 1327 (24.4)       |
| **Body mass index, kg/m²**                         |             |                     |              |                   |
| <25                                                | 2579 (30.3) | 2479 (30.6)         | 1110 (20.9)  | 1096 (20.2)       |
| 25 to <30                                          | 2992 (35.2) | 2835 (35.0)         | 1798 (33.9)  | 1915 (35.3)       |
| ≥30                                                | 2899 (34.1) | 2737 (33.8)         | 2375 (44.7)  | 2385 (43.9)       |
| **Smoking status**                                 |             |                     |              |                   |
| Never                                              | 4178 (49.1) | 3999 (49.4)         | 2723 (51.3)  | 2705 (49.8)       |
| Past                                               | 3362 (39.5) | 3157 (37.8)         | 1986 (37.4)  | 2090 (38.5)       |
| Current                                            | 880 (10.3)  | 838 (10.3)          | 542 (10.2)   | 571 (10.5)        |
| **NSAID use (ever)**                               |             |                     |              |                   |
| Yes                                                | 2853 (33.5) | 2767 (34.2)         | 1881 (35.4)  | 1945 (35.8)       |
| No                                                 | 5653 (66.5) | 5335 (65.8)         | 3429 (64.6)  | 3484 (64.2)       |
| **Total vitamin D intake, IU†**                    |             |                     |              |                   |
| <200                                               | 3320 (39.0) | 3164 (39.1)         | 2379 (44.8)  | 2350 (43.3)       |
| 200 to <400                                        | 1608 (18.9) | 1547 (19.1)         | 885 (16.7)   | 937 (17.3)        |
| 400 to <600                                        | 1875 (22.0) | 1775 (21.9)         | 1083 (20.4)  | 1161 (21.4)       |
| ≥600                                               | 1414 (16.6) | 1347 (16.6)         | 731 (13.8)   | 727 (13.4)        |
| **Regional solar radiation, langleys‡**            |             |                     |              |                   |
| 300–325                                            | 2517 (29.6) | 2370 (29.3)         | 1458 (27.5)  | 1501 (27.6)       |
| 350                                                | 2000 (23.5) | 1927 (23.8)         | 1118 (21.1)  | 1129 (20.8)       |
| 375–380                                            | 965 (11.3)  | 905 (11.2)          | 640 (12.1)   | 662 (12.2)        |
| 400–430                                            | 1334 (15.7) | 1258 (15.5)         | 966 (18.2)   | 991 (18.3)        |
| 475–500                                            | 1690 (19.9) | 1641 (20.3)         | 1123 (21.1)  | 1142 (21.0)       |
| **Total outdoor walking energy expenditure, METs/wk**|             |                     |              |                   |
| 0                                                  | 2705 (31.8) | 2670 (33.0)         | 1951 (36.7)  | 1897 (34.9)       |
| ≤3.5                                               | 1585 (18.6) | 1573 (19.4)         | 1078 (20.3)  | 1064 (19.6)       |
| 3.6–7.0                                            | 1515 (17.8) | 1476 (18.2)         | 901 (17.0)   | 913 (16.8)        |
| >7.0                                               | 1866 (21.9) | 1877 (23.2)         | 950 (17.9)   | 1031 (19.0)       |
| **History of cancer§**                             |             |                     |              |                   |
| Yes                                                | 167 (2.0)   | 158 (2.0)           | 241 (4.5)    | 308 (6.7)         |
| No                                                 | 8339 (98.0) | 7944 (98.0)         | 5069 (95.5)  | 5121 (94.3)       |
| **History of melanoma skin cancer**                |             |                     |              |                   |
| Yes                                                | 11 (0.1)    | 10 (0.1)            | 6 (0.1)      | 10 (0.2)          |
| No                                                 | 8496 (99.9) | 8092 (99.9)         | 5304 (99.9)  | 5419 (99.8)       |
| **History of nonmelanoma skin cancer**             |             |                     |              |                   |
| Yes                                                | 491 (5.8)   | 456 (5.6)           | 257 (4.8)    | 290 (6.3)         |
| No                                                 | 8015 (94.2) | 7646 (94.4)         | 5053 (95.2)  | 5137 (94.7)       |
| **Hormone therapy use**                            |             |                     |              |                   |
| Never used                                         | 6277 (73.8) | 6022 (74.3)         | 2769 (52.1)  | 2769 (51.0)       |
| Past user                                          | 1671 (19.6) | 1587 (19.6)         | 1871 (35.2)  | 1947 (35.9)       |
| Current user                                       | 554 (6.5)   | 490 (6.0)           | 669 (12.6)   | 709 (13.1)        |
| **Dietary modification intervention assignment**   |             |                     |              |                   |
| Not randomly assigned                              | 6077 (71.4) | 5873 (72.5)         | 3656 (68.9)  | 3691 (68.0)       |
| Intervention                                       | 972 (11.4)  | 925 (11.4)          | 615 (11.6)   | 670 (12.3)        |
| Comparison                                         | 1457 (17.1) | 1304 (16.1)         | 1039 (19.6)  | 1068 (19.7)       |

(Table continues)
Although endogenous estrogens have been reported to modulate the growth of basal and squamous cell carcinomas in mouse models of skin cancer (35), we are unaware of any previous clinical studies that have examined the association between hormone therapy and nonmelanoma skin cancer.

The strengths of this study include the randomization and double-blind design of the two trials, the large ethnically diverse study population, the length of follow-up in the trials, the large number of nonmelanoma skin cancer cases, and the central adjudication of the melanoma cases. This study has several limitations. First, the small
Table 2. Nonmelanoma skin cancer and melanoma events by trial and overall*  

| Event          | Number of cases (annualized %) | E + P (N = 8506) | Placebo (N = 8102) | HR (95% CI) | Pt |
|----------------|--------------------------------|------------------|-------------------|-------------|----|
| **NMSC**       |                                 |                  |                   |             |    |
| Melanoma       | 29 (0.06)                       | 28 (0.06)        | 0.96 (0.57 to 1.61) | .86         |    |
| Any HT         | 17 (0.05)                       | 21 (0.05)        | 0.85 (0.45 to 1.61) | .61         |    |
| Any HT         | 900 (1.08)                      | 900 (1.11)       | 0.98 (0.89 to 1.07) | .65         |    |
| Melanoma       | 46 (0.05)                       | 49 (0.06)        | 0.92 (0.61 to 1.37) | .67         |    |

* CI = confidence interval; E-alone = estrogen alone; E+P = estrogen plus progestin; HT = hormone therapy; HR = hazard ratio; * NMSC = nonmelanoma skin cancer.
† Two-sided (from Cox proportional hazards model).

number of melanoma cases precluded analyses stratified by anatomical location (eg, sun-exposed vs non–sun-exposed body sites) or type of tumor (invasive vs in situ). Second, there is a possibility of chance findings due to the nature of post hoc analyses. Third, the low rate of adherence to study medication, albeit higher than that observed in clinical practice (20), could have potentially attenuated the hormone effect estimates; however, a sensitivity analysis that was restricted to women who were adherent to treatment did not show an effect of hormone therapy on the risk of skin cancer. Fourth, major risk factors for skin cancer (ie, individual sun exposure, history of sunburns, number of nevi, family history of skin cancer, and skin type) were not collected in these WHI trials. However, the 40 WHI clinical centers were geographically diverse, which may serve as a proxy of sun exposure in our analyses (36). In addition, the lack of major differences in characteristics between randomization groups (Table 1) and skin cancer risk factors are likely to be balanced between the groups. Fifth, because follow-up time was limited to the period of the intervention, it is possible that any potential effects of hormone therapy on skin cancer incidence will take more than 6–7 years to become evident. Sixth, the nonmelanoma skin cancer outcome was based on self-report. However, studies assessing the validity of self-reports of skin cancer have found that they are highly correlated with pathology review (>90% correlation) (37,38). Finally, because information on the type of nonmelanoma skin cancer was not collected, we could not determine if there were differential effects of hormone therapy on the risks of basal cell vs squamous cell carcinoma.

In these trials of 27,347 postmenopausal women, we found no association between hormone therapy use and skin cancer. Although this cohort was followed for approximately 6 years, we cannot rule out a delayed effect of hormone therapy on risk of skin cancer. Given that the WHI continues to monitor most of the participants for additional outcomes even though the intervention has ended (39), in a future study, we plan to examine the effect of hormone therapy with 11 years of follow-up. In conclusion, the use of estrogen therapy, alone or in combination with a progestin, did not influence the incidence of nonmelanoma skin cancer or of melanoma in postmenopausal women.

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**Affiliations of authors:** Stanford School of Medicine, Stanford University, Stanford, CA (JYT, KMS, EK, MLS); Keck School of Medicine, University of Southern California, Los Angeles, CA (KMS); Los Angeles Biomedical Research Institute, Harbor-University of California Los Angeles Medical Center, Torrance, CA (RTC); Department of Dermatology, Roswell Park Cancer Institute and School of Medicine and Biomedical Sciences, State University of New York at Buffalo, Buffalo, NY (NCZ); Department of Social and Preventive Medicine, State University of New York at Buffalo, Buffalo, NY, (JW-W), Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis, TN (FT); Baylor College of Medicine, Houston, TX (MLA); WHI Clinical Coordinating Center, Fred Hutchinson Cancer Research Center, Seattle, WA (UCL).