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Breast cancer in postmenopausal women after non-melanomatous skin cancer: the Women's Health Initiative observational study

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Abstract An increased risk of breast cancer has been reported in patients with non-melanomatous skin cancer (NMSC), but this association has not been studied in a large, multi-geographic population. We utilized data from the Women's Health Initiative observational study to assess whether history of NMSC is associated with breast cancer risk. This analysis included 70,246 postmenopausal White and Hispanic women aged 50–79, in which 4,247 breast cancer cases were identified over a mean (SD) of 11.3 (3.2) years. Baseline information was collected on demographics, medical history, sun exposure, and vitamin D intake. Cox proportional hazards regression was used to calculate hazard ratios (HRs) with 95 % confidence intervals (CIs). The relationship between NMSC and breast cancer was examined as a time-dependent exposure using updated information on NMSC gathered during follow-up visits. All statistical tests were two sided. There were 5,595 women diagnosed with NMSC at study entry. The annualized rate of breast cancer was 0.64 % among women with a history of NMSC and 0.55 % among women with no history of NMSC. The multivariable-adjusted HR for breast cancer among women with a history of NMSC versus no history of NMSC was 1.07 (95 % CI 0.95–1.20, $P = 0.27$). Further evaluation stratified by tumor characteristics showed an increased risk of lymph node-positive disease, HR = 1.30 (95 % CI 1.01–1.67, $P = 0.04$), and regional-stage disease, HR = 1.33 (95 % CI 1.05–1.70, $P = 0.02$), among women with NMSC. There was no significant overall association between NMSC and breast cancer; however, there was an increased risk of more advanced-stage breast cancer which needs further exploration.

Keywords Non-melanomatous skin cancer · Breast cancer · Women's Health Initiative · Cohort study · Cancer risk

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Introduction

In 2011, there were an estimated 226,870 new cases of invasive breast cancer and 39,510 deaths from breast cancer among women in the United States [1]. While breast cancer risk has been attributed to a number of genetic and environmental factors, breast cancer remains a disease of largely unknown etiology [2]. The identification of unrecognized risk and protective factors is crucial to our understanding of breast cancer etiology and to focus screening on women at higher risk.

Several studies have demonstrated that a history of non-melanomatous skin cancer (NMSC) is associated with increased risk of second primary cancers [3–16]. This

association is inversely related to age, suggesting that NMSC could be a predictor for inherited predisposition [12]. An association between NMSC and second malignancies may also be in part related to immunosuppression, given that renal transplant patients have higher rates of NMSC and other malignancies [17]. A prior Women's Health Initiative (WHI) analysis found that past history of NMSC was associated with a 2.3-fold greater chance of other prior cancers including breast cancer [3].

A link between NMSC and breast cancer may be in part due to genetic predisposition as there is an increased risk of basal cell carcinoma among families with *BRCA2* mutations [18]. It is hypothesized that sun exposure and UV radiation [19] may have anti-carcinogenic effects through increased production of vitamin D [20]. Another study from the WHI-OS found that women who spent an average of less than 30 min outside had a 20 % increased risk of breast cancer compared to women who spent an average of over 2 h outside, suggesting a possible protective effect of sun and vitamin D exposure [21]. Results from other studies also suggest that high serum vitamin D levels and/or sun exposure may be associated with a lower risk of breast cancer [20, 22–26]; however, this assertion has been disputed by others [15, 27].

While a relationship between NMSC and breast cancer risk has been suggested by others [3, 6, 10, 11, 15, 16], these findings have not been confirmed in a large multigeographic cohort. Moreover, other studies have failed to address the impact of important lifestyle factors associated with sun exposure. We used data from the WHI to assess whether history of NMSC is associated with breast cancer risk. To address the impact of exposure to vitamin D, we used various measures of lifetime sun exposure to serve as a proxy for the cutaneous production of vitamin D. We also estimated oral vitamin D intake from the WHI food frequency questionnaire (FFQ) [28]. A better understanding of the relationship between NMSC and breast cancer could provide insight as to whether vitamin D influences breast cancer risk.

Methods

Study population

The WHI includes an OS ($n = 93{,}676$) and three clinical trials (CT) ($n = 68{,}132$) described previously [29]. Recruitment was conducted between October 1, 1993 and December 31, 1998 at 40 clinical centers in the United States. Eligibility criteria included age 50–79 years, postmenopausal status, planning to remain in the area where they lived at recruitment, and having an estimated survival of at least 3 years [30, 31]. The current analysis is based on 70,246 White and Hispanic women who participated in the OS. We included white and Hispanic women because women who have fair skin have a higher risk for NMSC than darker-skinned women [32]. Follow-up was through September 30, 2010, for a mean (SD) follow-up of 11.3 (3.2) years.

Sun exposure

We used clinic geographic location to estimate lifetime sun exposure. Clinics with a latitude >40° north were defined as northern and classified as the least sun exposed. Clinics between 35° and 40° north were defined as middle region with intermediate exposure and clinics <35° north were classified as southern with the most exposure. Other measures of sun exposure collected at year 4 included time spent outdoors during summer and non-summer months (childhood, teenage, thirties, and currently), use of a hat, use of sunscreen and the usual sun protection factor (SPF), number of years lived or worked on a farm, and number of months per year working outside. We also asked each individual to self-report the effect of sunlight on the skin as either: no change, tans with no burn, burns followed by tanning, burns then tans minimally, or burns with no tan.

Cancer diagnoses

Prior NMSC was reported on the baseline questionnaire. Women who had a history of cancer besides NMSC ($n = 10{,}743$) or who had unknown cancer history at baseline ($n = 636$) were excluded. Updates on breast cancer diagnoses were reported annually and were confirmed by trained physician adjudicators after review of medical records using the Surveillance Epidemiology and End Results (SEER) coding system. There were 4,288 centrally adjudicated and SEER coded cases (3,505 invasive and 783 in situ) and only women with a first diagnosis of breast cancer were included ($n = 4{,}247$).

Covariates

Table 1 lists the covariates collected on the WHI participants. Breast cancer risk was assessed by the Gail Model [33]. Current and previous use of menopausal hormones and oral contraceptives was ascertained by questionnaire including type, route of administration, quantity, and duration of use. Hormone users included those who used estrogen (with or without progestin) after menopause for at least 3 months. Participants were categorized based on type of hormones used (unopposed estrogen or estrogen + progesterone) and duration (none, <5, 5–10, and ≥10 years). Vitamin D intake from foods was assessed by self-administered FFQ [28]. Total vitamin D (from diet

Table 1 Baseline characteristics of WHI-OS participants with and without NMSC History

	No prior NMSC ($N = 64,651$)		Prior NMSC ($N = 5,595$)		Total ($N = 70,246$)		P value*
	N	%	*N*	%	*N*	%	
Age group at screening (years)							<0.0001
50–59	21,387	33.1	1,217	21.8	22,604	32.2	
60–69	28,512	44.1	2,594	46.4	31,106	44.3	
70–79	14,752	22.8	1,784	31.9	16,536	23.5	
Ethnicity							<0.0001
White	61,480	95.1	5,553	99.2	67,033	95.4	
Hispanic	3,171	4.9	42	0.8	3,213	4.6	
Education							<0.0001
≤HS diploma/GED	13,706	21.4	806	14.5	14,512	20.8	
School after HS	23,412	36.5	1,917	34.5	25,329	36.3	
College deg or higher	27,029	42.1	2,836	51.0	29,865	42.8	
Family income							<0.0001
<$10,000	2,132	3.6	128	2.5	2,260	3.5	
$10,000–$19,999	6,524	10.9	475	9.2	6,999	10.7	
$20,000–$34,999	13,924	23.2	1,165	22.5	15,089	23.2	
$35,000–$49,999	12,201	20.3	1,095	21.1	13,296	20.4	
$50,000–$74,999	12,367	20.6	1,070	20.7	13,437	20.6	
$75,000+	12,822	21.4	1,246	24.1	14,068	21.6	
Marital status							0.21
Never married	2,815	4.4	248	4.5	3,063	4.4	
Divorced/separated	9,373	14.6	781	14.0	10,154	14.5	
Widowed	10,515	16.3	966	17.3	11,481	16.4	
Presently married/living as married	41,688	64.7	3,574	64.2	45,262	64.7	
Body mass index (BMI), (kg/m^2)							<0.0001
<25	26,823	42.0	2,650	47.9	29,473	42.4	
25 to <30	21,954	34.4	1,844	33.3	23,798	34.3	
≥30	15,125	23.7	1,042	18.8	16,167	23.3	
History of diabetes	2,900	4.5	244	4.4	3,144	4.5	0.66
Smoking							0.02
Never smoked	32,363	50.7	2,724	49.2	35,087	50.6	
Past smoker	27,713	43.4	2,511	45.3	30,224	43.6	
Current smoker	3,777	5.9	304	5.5	4,081	5.9	
Alcohol use, drinks/week							<0.0001
Non/past drinker	17,216	26.8	1,324	23.8	18,540	26.5	
<1	20,718	32.2	1,732	31.1	22,450	32.1	
1+	26,373	41.0	2,514	45.1	28,887	41.3	
Current health care provider	60,782	94.8	5,335	96.3	66,117	94.9	<0.0001
Medical insurance	61,932	96.7	5,484	98.7	67,416	96.8	<0.0001
Last medical visit within 1 year	52,096	83.1	4,642	85.5	56,738	83.3	<0.0001
Mammogram recency							<0.0001
Never had a mammogram	1,937	3.1	93	1.7	2,030	3.0	
0–6 months	15,561	24.7	1,485	27.2	17,046	24.9	
>6 months–1 year	20,332	32.3	1,847	33.8	22,179	32.4	
>1–2 years	17,374	27.6	1,480	27.1	18,854	27.6	
>2 years	7,736	12.3	558	10.2	8,294	12.1	
Baseline NSAID use[a]	9,903	15.3	870	15.5	10,773	15.3	0.64

Table 1 continued

	No prior NMSC ($N = 64,651$)		Prior NMSC ($N = 5,595$)		Total ($N = 70,246$)		P value*
	N	%	*N*	%	*N*	%	
Duration of prior unopposed estrogen use (year)							<0.0001
None	40,579	62.8	3,321	59.4	43,900	62.5	
<5	8,135	12.6	685	12.2	8,820	12.6	
5 to <10	4,853	7.5	414	7.4	5,267	7.5	
≥10	11,084	17.1	1,175	21.0	12,259	17.5	
Duration of prior estrogen + progesterone use (year)							<0.0001
None	44,455	68.8	3,777	67.5	48,232	68.7	
<5	9,760	15.1	780	13.9	10,540	15.0	
5 to <10	5,596	8.7	505	9.0	6,101	8.7	
≥10	4,839	7.5	533	9.5	5,372	7.6	
Duration of oral contraceptive use (years)							0.0003
Non-user	37,718	58.4	3,392	60.6	41,110	58.5	
<5	15,104	23.4	1,174	21.0	16,278	23.2	
5 to <10	5,979	9.3	498	8.9	6,477	9.2	
≥10	5,829	9.0	531	9.5	6,360	9.1	
Geographic region by latitude							<0.0001
Southern: <35 degrees N	19,034	29.4	2,008	35.9	21,042	30.0	
Middle: 35–40 degrees N	17,546	27.1	1,618	28.9	19,164	27.3	
Northern: >40 degrees N	28,071	43.4	1,969	35.2	30,040	42.8	
Skin reaction to sun							<0.0001
No change in skin color	3,614	6.4	303	6.1	3,917	6.4	
Tans but does not burn	17,753	31.4	1,029	20.8	18,782	30.5	
Burns, then tans	14,372	25.4	1,160	23.4	15,532	25.2	
Burns, then tans a minimal amount	14,750	26.1	1,572	31.8	16,322	26.5	
Burns but does not tan	6,077	10.7	886	17.9	6,963	11.3	
Spent >2 h outdoors during summer months							
Childhood	40,525	70.7	3,695	72.7	44,220	70.9	0.002
Teens	34,210	59.7	3,167	62.4	37,377	60.0	0.0002
Thirties	18,122	31.6	1,666	32.9	19,788	31.7	0.07
This year	11,082	19.3	865	17.1	11,947	19.1	0.0001
Spent >2 h outdoors during non-summer months							
Childhood	21,021	36.9	1,933	38.2	22,954	37.0	0.06
Teens	17,355	30.4	1,586	31.4	18,941	30.5	0.17
Thirties	9,755	17.1	945	18.7	10,700	17.2	0.004
This year	6,487	11.3	539	10.6	7,026	11.3	0.13
Use of hat when outdoors							
Teens	2,627	4.7	223	4.5	2,850	4.7	0.52
Thirties	9,870	17.4	995	19.9	10,865	17.6	<0.0001
This year	26,741	46.4	3,008	58.9	29,749	47.5	<0.0001
Usually use sunscreen outside	29,339	51.6	3,493	69.7	32,832	53.1	<0.0001
Usual sunscreen SPF							<0.0001
No sunscreen use	27,530	49.2	1,516	30.6	29,046	47.7	
2–14	2,816	5.0	176	3.6	2,992	4.9	
15–24	16,262	29.1	1,997	40.3	18,259	30.0	
≥25	9,367	16.7	1,268	25.6	10,635	17.5	
Years lived or worked on a farm							<0.0001

Table 1 continued

	No prior NMSC ($N = 64,651$)		Prior NMSC ($N = 5,595$)		Total ($N = 70,246$)		P value*
	N	%	N	%	N	%	
Never worked on a farm	47,574	74.1	4,228	76.2	51,802	74.2	
<5	4,239	6.6	398	7.2	4,637	6.6	
5–19	9,867	15.4	744	13.4	10,611	15.2	
≥20	2,556	4.0	177	3.2	2,733	3.9	
Months per year spent working in the yard							<0.0001
<1	25,721	40.2	2,215	39.9	27,936	40.1	
1–3	11,218	17.5	901	16.2	12,119	17.4	
4–6	12,079	18.9	988	17.8	13,067	18.8	
7–9	7,287	11.4	661	11.9	7,948	11.4	
10–12	7,731	12.1	788	14.2	8,519	12.2	
Total expenditure from physical activity, METs							<0.0001
None	8,281	13.1	581	10.6	8,862	12.9	
>0–7.4	17,437	27.6	1,402	25.6	18,839	27.4	
7.5–17.4	18,729	29.6	1,715	31.3	20,444	29.7	
≥17.5	18,802	29.7	1,785	32.6	20,587	30.0	
Percent energy from fat							<0.0001
≤30	33,350	53.3	3,076	56.2	36,426	53.5	
>30–35	11,967	19.1	1,042	19.0	13,009	19.1	
>35–40	9,195	14.7	754	13.8	9,949	14.6	
>40	8,100	12.9	600	11.0	8,700	12.8	
Total vitamin D intake, (IU/day)[b]							<0.0001
<200	21,202	33.9	1,572	28.7	22,774	33.4	
200 to <400	11,305	18.1	958	17.5	12,263	18.0	
400 to <600	16,367	26.1	1,531	28.0	17,898	26.3	
≥600	13,738	21.9	1,411	25.8	15,149	22.3	
Family history of breast cancer (female)	11,633	18.9	1,156	21.8	12,789	19.2	<0.0001
Family history of ovarian cancer	1,552	2.6	149	2.9	1,701	2.6	0.22
Gail 5 year risk							<0.0001
<1.25	16,583	25.7	867	15.5	17,450	24.8	
1.25–1.74	21,780	33.7	1,854	33.1	23,634	33.6	
≥1.75	26,288	40.7	2,874	51.4	29,162	41.5	

* P values are from Chi square tests of independence

[a] Includes ibuprofen and prescription NSAID use

[b] Total vitamin D intake includes vitamin D from diet and supplements

and supplements) was categorized into quartiles of less than 200, 200 to <400, 400 to <600, and 600 IU/day or greater. Weight and height were recorded using a calibrated balance beam scale and a wall-mounted stadiometer. Body mass index was calculated as weight in kilograms divided by height squared in meters (kg/m^2). Physical activity was recorded as the total energy expended per week per kg (kcal/week/kg) [34]. The percent of energy intake from fat was categorized as less than 30, 30–35, 35–40 %, or greater than 40 %.

Statistical analysis

Characteristics of women at baseline with and without a prior history of NMSC were compared by Chi square tests. Annualized breast cancer risks were calculated as the percentage of women with an event divided by total follow-up time in years by history of prior NMSC. Subgroup analyses were performed for women with invasive versus in situ disease and by clinical features including lymph node status, tumor grade, stage, histology, and ER/PR status.

Cox proportional hazards analyses were used to assess associations between history of NMSC and breast cancer risk. Age-, ethnicity-, and mammography-adjusted (recency and time dependent) and multivariable-adjusted models were developed, where covariates were selected based on known associations seen in previous studies. The multivariable model was adjusted for linear age, ethnicity, education, smoking, alcohol use, physical activity, BMI, type and duration of hormone use, current health care provider, mammography history, geographic location, percent energy from fat, multivitamin use, sun exposure, and Gail 5-year risk. To evaluate the effects of NMSC which occurred after study entry, time-dependent models were run using updated information on NMSC gathered during follow-up. Comparisons of invasive and in situ breast cancer risk by age, ethnicity, BMI, region, sun exposure, and vitamin D intake were based on Cox models incorporating an interaction term between the corresponding risk factor and history of NMSC at baseline. Given that sixteen tests of interaction were examined, approximately 1 test could be significant at the alpha = 0.05 level by chance alone.

Results

There were 5,595 women with a past history of NMSC among 70,246 White and Hispanic women in the WHI-OS included in this analysis. Table 1 shows the baseline characteristics of the cohort stratified by prior history of NMSC. Many of the differences were statistically significant because of the large sample size. Women with a history of NMSC were more likely to be older; white; have a lower BMI; have a history of tobacco use; use more alcohol; be greater consumers of medical care as evident by a current health provider, medical insurance, and recency of medical visits; and also have had more exposure to the sun during their lives.

Table 2 shows the risk of breast cancer by tumor characteristics and history of NMSC. Women with a history of NMSC had a higher risk of subsequent breast cancer (both invasive and in situ together) compared to those without NMSC (64 cases per 1,000 per year vs. 55 cases per 1,000 per year). This difference was statistically significant in the age-, ethnicity-, and mammography-adjusted model

Table 2 Incidence (annualized %) and hazard ratios (HRs) for breast cancer in WHI-OS Participants by tumor characteristics and history of NMSC

	No prior NMSC ($N = 64,651$)		Prior NMSC ($N = 5,595$)		Age/ethnicity adjusted[a]			Multivariate adjusted[b]		
	N	(%)	*N*	(%)	HR	(95 % CI)	*P* value	HR	(95 % CI)	*P* value
Total breast cancer	3,856	(0.55)	391	(0.64)	1.13	(1.01, 1.25)	0.03	1.07	(0.95, 1.20)	0.27
Invasive breast cancer	3,186	(0.45)	319	(0.52)	1.11	(0.99, 1.24)	0.08	1.04	(0.91, 1.18)	0.60
Positive lymph nodes	704	(0.10)	81	(0.13)	1.31	(1.04, 1.65)	0.02	1.30	(1.01, 1.67)	0.04
No positive lymph nodes	2,112	(0.30)	201	(0.33)	1.06	(0.91, 1.22)	0.45	0.98	(0.84, 1.16)	0.84
Well differentiated grade	817	(0.12)	80	(0.13)	1.08	(0.86, 1.36)	0.51	0.97	(0.75, 1.26)	0.82
Moderately differentiated grade	1,290	(0.18)	139	(0.23)	1.18	(0.99, 1.41)	0.06	1.07	(0.88, 1.30)	0.49
Poorly differentiated/anaplastic grade	776	(0.11)	66	(0.11)	0.96	(0.75, 1.23)	0.74	0.96	(0.73, 1.28)	0.79
Localized stage	2,356	(0.33)	228	(0.37)	1.06	(0.93, 1.22)	0.37	0.96	(0.82, 1.12)	0.61
Regional stage	729	(0.10)	85	(0.14)	1.32	(1.06, 1.66)	0.02	1.33	(1.05, 1.70)	0.02
Ductal histology	2,352	(0.33)	243	(0.40)	1.15	(1.01, 1.31)	0.04	1.07	(0.92, 1.24)	0.37
Lobular histology	336	(0.05)	34	(0.06)	1.07	(0.76, 1.52)	0.69	0.95	(0.64, 1.40)	0.78
Ductal and lobular histology	463	(0.07)	40	(0.07)	0.94	(0.68, 1.31)	0.73	0.96	(0.68, 1.36)	0.81
ER positive	2,495	(0.35)	262	(0.43)	1.15	(1.02, 1.31)	0.03	1.09	(0.95, 1.25)	0.24
ER negative	436	(0.06)	34	(0.06)	0.90	(0.64, 1.28)	0.56	0.81	(0.54, 1.22)	0.31
PR positive	2,089	(0.29)	218	(0.36)	1.15	(1.00, 1.32)	0.05	1.10	(0.94, 1.28)	0.23
PR negative	799	(0.11)	69	(0.11)	0.97	(0.76, 1.24)	0.83	0.83	(0.62, 1.10)	0.19
In situ breast cancer	707	(0.10)	76	(0.12)	1.21	(0.95, 1.53)	0.12	1.19	(0.93, 1.54)	0.17

[a] Hazard ratios, 95 % confidence intervals (CIs), and *P* values are from Cox proportional hazards models adjusted for age, ethnicity, and time-dependent use of mammography during the study

[b] Hazard ratios, 95 % confidence intervals (CIs), and *P* values are from Cox proportional hazards models adjusted for age; ethnicity; education; smoking; alcohol use; physical activity; body mass index; prior unopposed estrogen use and duration; prior estrogen + progesterone use and duration; current healthcare provider; recency of mammography; time-dependent use of mammography during the study; geographic region; percent energy from fat; multivitamin use; childhood, teenage, thirties, and current sun exposure; and Gail 5-year risk of breast cancer

Table 3 Incidence (annualized %) and hazard ratios (HRs) for breast cancer in WHI-OS participants by time-dependent NMSC

	Time-dependent NMSC[a]		Age/ethnicity adjusted[b]			Multivariate adjusted[c]		
	No ($N = 56{,}332$) Cases	Yes ($N = 13{,}620$) Cases	HR	(95 % CI)	*P* value	HR	(95 % CI)	*P* value
Breast cancer	3,569	678	1.06	(0.98, 1.16)	0.15	1.03	(0.94, 1.13)	0.57
Invasive	2,956	549	1.04	(0.95, 1.14)	0.42	1.00	(0.90, 1.10)	0.96
In situ	648	135	1.15	(0.95, 1.39)	0.16	1.11	(0.91, 1.36)	0.31

[a] Includes prevalence of NMSC at baseline, as well as incident NMSC prior to incident breast cancer

[b] Hazard ratios, 95 % confidence intervals (CIs), and *P* values are from Cox proportional hazards models adjusted for age, ethnicity, and time-dependent use of mammography during the study, examining the time-dependent association of NMSC prior to breast cancer

[c] Hazard ratios, 95 % confidence intervals (CIs) and *P* values are from Cox proportional hazards models adjusted for age; ethnicity; education; smoking; alcohol use; physical activity; body mass index; prior unopposed estrogen use and duration; prior estrogen +progesterone use and duration; current healthcare provider; recency of mammography; time-dependent use of mammography during the study; geographic region; percent energy from fat; multivitamin use; childhood, teenage, thirties, and current sun exposure; and Gail 5-year risk of breast cancer, examining the time-dependent association of NMSC prior to breast cancer

(hazard ratio HR 1.13, 95 % confidence interval CI, 1.01–1.25); however, in the multivariable-adjusted model, the difference was no longer significant (HR 1.07, 95 % CI 0.95–1.20). When stratified by tumor characteristics, prior history of NMSC was associated with an increased risk of lymph node-positive disease (HR 1.30, CI 1.01–1.67) as well as regional-stage disease (HR 1.33, 95 % CI 1.05–1.70); however, there were no other significant findings based on breast cancer subtypes.

Table 3 shows the time-dependent analysis taking into account women who reported diagnoses of NMSC after baseline. In these models, there was no overall significant relationship between NMSC and breast cancer risk. There was also no significant relationship between history of NMSC and the development of either invasive breast cancer or in situ breast cancer by age group, ethnicity, geographical region, BMI category, sun exposure by age, and total vitamin D intake (Tables 4, 5). There was an increased risk of invasive breast cancer associated with history of NMSC among Hispanic women compared to Whites (*P* value for interaction = 0.03); however, these findings were based on only five Hispanic women with a history of both NMSC and breast cancer.

Discussion

In our analysis, we found no overall significant association between NMSC and breast cancer risk; however, our results revealed an increased risk of more advanced breast cancer with a significantly increased risk of both lymph node-positive and regional-stage disease. In subset analysis, we also found a significantly increased risk of breast cancer among Hispanic women with history of NMSC; however, these results were based on small numbers. There have been seven studies that reported an increased risk of breast cancer associated with history of NMSC [3, 6, 10, 11, 15, 16, 35]; however, six other studies showed null results [4, 9, 12–14, 36]. Limitations in the previous studies include small sample size [13, 36] and the lack of adjustment for vitamin D and sun exposure [4, 6, 10, 11, 14]. We attempted to adjust for exposure to sun and vitamin D by using several measures of sun exposure and vitamin D intake from dietary and supplement sources. We also adjusted for variables that could influence access to health care including doctor appointments and mammography history. To our knowledge, no other study has evaluated the relationship between NMSC and breast cancer tumor characteristics.

There have been a number of studies that have looked at whether sun exposure as mediated by vitamin D is protective against the development of cancer [15, 20–25, 27]. In an evaluation of geographic variation in cancer risk, Tuohimaa et al. [26] found that the risk of second primary malignancies after NMSC was lower in countries with higher sun exposure for most cancers evaluated, except for cancer of the lip, mouth, and Hodgkin's lymphoma. Others have shown that history of NMSC is correlated with an increased risk of second primary cancers [3–6, 8–16, 35, 37].

Garland and Garland suggested that breast cancer mortality was inversely proportional to the intensity of local sunlight, and hypothesized that vitamin D levels may play a role in this mortality reduction [22, 24]. Millen et al. [21] found that women who spent an average of less than 30 min outside had a 20 % increased breast cancer risk compared to women who spent an average of over 2 h outside, suggesting that vitamin D may have a protective effect. In our analysis, NMSC was not associated with a reduced risk of breast cancer. In fact, our results indicated that NMSC correlated with an increased risk of more advanced disease, countering the hypothesis that increased

Table 4 Incidence (annualized %) of invasive breast cancer by baseline risk factors and history of NMSC

	History of NMSC				HR (95 % CI)[a]	*P* value for interaction[b]
	No ($N = 64,651$)		Yes ($N = 5,595$)			
	N	(%)	*N*	(%)		
Age at screening (years)						0.22
50–59	974	(0.39)	61	(0.42)	1.00 (0.76, 1.32)	
60–69	1,483	(0.47)	157	(0.54)	1.12 (0.93, 1.34)	
70–79	729	(0.49)	101	(0.56)	0.95 (0.74, 1.22)	
Ethnicity						0.03
White	3,108	(0.46)	314	(0.51)	1.03 (0.90, 1.17)	
Hispanic	78	(0.26)	5	(1.31)	5.90 (1.64, 21.27)	
Body mass index (BMI), (kg/m^2)						0.22
<25	1,298	(0.43)	141	(0.47)	0.99 (0.81, 1.20)	
25 to <30	1,057	(0.44)	122	(0.60)	1.23 (1.00, 1.52)	
≥30	795	(0.50)	52	(0.48)	0.81 (0.59, 1.11)	
Geographical region by latitude						0.10
Southern: < 35 degrees N	886	(0.44)	106	(0.50)	1.00 (0.80, 1.25)	
Middle: 35–40 degrees N	917	(0.46)	117	(0.64)	1.25 (1.01, 1.55)	
Northern: >40 degrees N	1,383	(0.44)	96	(0.44)	0.88 (0.70, 1.11)	
Childhood sun exposure						0.51
Low	810	(0.44)	80	(0.53)	1.05 (0.82, 1.35)	
Moderate	1,085	(0.46)	104	(0.50)	0.93 (0.75, 1.16)	
High	1,049	(0.45)	118	(0.55)	1.12 (0.91, 1.38)	
Teenage sun exposure						0.19
Low	1,144	(0.45)	103	(0.49)	0.99 (0.80, 1.23)	
Moderate	955	(0.46)	94	(0.49)	0.93 (0.74, 1.17)	
High	831	(0.45)	105	(0.62)	1.23 (0.98, 1.53)	
Thirties sun exposure						0.61
Low	2,025	(0.47)	208	(0.55)	1.06 (0.91, 1.24)	
Moderate	500	(0.43)	43	(0.44)	0.90 (0.64, 1.27)	
High	416	(0.42)	52	(0.53)	1.08 (0.78, 1.50)	
Total vitamin D intake, (IU/day)[c]						0.23
<200	996	(0.43)	96	(0.56)	1.13 (0.89, 1.43)	
200 to <400	559	(0.45)	50	(0.47)	1.11 (0.82, 1.50)	
400 to <600	843	(0.47)	80	(0.47)	0.88 (0.68, 1.14)	
≥600	711	(0.47)	83	(0.54)	1.04 (0.81, 1.33)	

[a] Hazard ratios and 95 % confidence intervals (CIs) are from Cox proportional hazards analyses adjusted for age; ethnicity; education; smoking; alcohol use; physical activity; body mass index; prior unopposed estrogen use and duration; prior estrogen + progesterone use and duration; current healthcare provider; recency of mammography; geographic region; percent energy from fat; multivitamin use; childhood, teenage, thirties, and current sun exposure; and Gail 5-year risk of breast cancer

[b] *P* values for interaction are computed from likelihood ratio tests, comparing models with and without an interaction term for the corresponding covariate and history of NMSC

[c] Total vitamin D intake includes vitamin D from diet and supplements

vitamin D resulting from higher levels of sun exposure (manifested by a prior history of NMSC) may be protective. Our results are consistent with other studies in the literature suggesting a correlation between NMSC and increased breast cancer risk [3–6, 8–16, 35, 37]. While there are other studies showing no relationship between NMSC and breast cancer risk, some of these studies are limited by small sample size and lack of adjustment for vitamin D status [4, 13, 14, 36]. Further research will be needed to clarify this question.

It is not clear why NMSC is associated with breast cancer in Hispanic women only. As stated above, these results are based on small numbers and will need to be replicated in other studies. In our prior analysis of prevalent NMSC and

Table 5 Incidence (annualized %) of in situ breast cancer by baseline risk factors and history of NMSC

	History of NMSC				HR (95 % CI)[a]	*P* value for interaction[b]
	No ($N = 64,651$)		Yes ($N = 5,595$)			
	N	(%)	N	(%)		
Age at screening (years)						0.21
50–59	239	(0.10)	20	(0.14)	1.22 (0.74, 2.01)	
60–69	347	(0.11)	27	(0.09)	0.88 (0.59, 1.32)	
70–79	121	(0.08)	29	(0.16)	1.80 (1.14, 2.83)	
Ethnicity						–
White	687	(0.10)	76	(0.13)	1.20 (0.93, 1.55)	
Hispanic	20	(0.07)	0	(0.00)	–	
Body mass index (BMI), (kg/m^2)						0.69
<25	328	(0.11)	36	(0.12)	1.08 (0.75, 1.56)	
25 to <30	231	(0.10)	24	(0.12)	1.22 (0.77, 1.95)	
≥30	141	(0.09)	16	(0.15)	1.54 (0.89, 2.66)	
Geographical region by latitude						0.06
Southern: <35 degrees N	201	(0.10)	22	(0.10)	0.91 (0.54, 1.53)	
Middle: 35–40 degrees N	213	(0.11)	21	(0.12)	0.97 (0.61, 1.57)	
Northern: >40 degrees N	293	(0.09)	33	(0.15)	1.68 (1.16, 2.43)	
Childhood sun exposure						0.42
Low	181	(0.10)	19	(0.13)	1.05 (0.62, 1.76)	
Moderate	244	(0.10)	32	(0.16)	1.45 (0.99, 2.13)	
High	233	(0.10)	22	(0.10)	1.02 (0.64, 1.62)	
Teenage sun exposure						0.81
Low	260	(0.10)	30	(0.14)	1.27 (0.85, 1.90)	
Moderate	216	(0.10)	24	(0.13)	1.21 (0.79, 1.86)	
High	181	(0.10)	19	(0.11)	1.07 (0.64, 1.80)	
Thirties sun exposure						0.28
Low	453	(0.11)	44	(0.12)	1.03 (0.74, 1.43)	
Moderate	122	(0.10)	16	(0.17)	1.62 (0.95, 2.76)	
High	81	(0.08)	13	(0.13)	1.53 (0.80, 2.93)	
Total vitamin D intake, (IU/day)[c]						0.95
<200	200	(0.09)	20	(0.12)	1.23 (0.74, 2.03)	
200 to <400	129	(0.10)	15	(0.14)	1.42 (0.81, 2.51)	
400 to <600	183	(0.10)	21	(0.12)	1.06 (0.65, 1.72)	
≥600	176	(0.12)	19	(0.12)	1.14 (0.70, 1.87)	

[a] Hazard ratios and 95 % confidence intervals (CIs) are from Cox proportional hazards analyses adjusted for age; ethnicity; education; smoking; alcohol use; physical activity; body mass index; prior unopposed estrogen use and duration; prior estrogen + progesterone use and duration; current healthcare provider; recency of mammography; geographic region; percent energy from fat; multivitamin use; childhood, teenage, thirties, and current sun exposure; and Gail 5-year risk of breast cancer

[b] *P* values for interaction are computed from likelihood ratio tests, comparing models with and without an interaction term for the corresponding covariate and history of NMSC

[c] Total vitamin D intake includes vitamin D from diet and supplements

cancer risk in the WHI, NMSC was uncommon among Hispanic and African American women (0.8 and 0.3 % respectively); however, African American women with NMSC were significantly more likely to develop a 2nd primary cancer, with an increased risk of breast cancer of 1.31 (95 % CI, 1.21–1.44) [3]. This may be because among non-white individuals, NMSC is fairly rare due to enhanced melanin production. Therefore, if they do develop NMSC, their DNA repair system may be altered, leading to a higher risk for 2nd primary cancers. It is also possible that the non-white individuals who develop NMSC are more diligently screened for other cancers.

Limitations of our study include the fact that NMSC was not an adjudicated WHI outcome; however, a prior study of

organ transplant recipients found that patients correctly self-reported their skin cancer as NMSC 92 % of the time [38]. Another possible source of error is selection bias in that individuals with NMSC receive more regular medical care and are consequently more likely to be diagnosed with breast cancer. However, we accounted for this by adjusting for provider visits and screening. It is also unclear whether oral intake of vitamin D accurately reflects active vitamin D concentrations [39]. Lastly, we were limited to observations of postmenopausal women and information on age at NMSC was not ascertained. A previous study reported that the association between NMSC and risk of subsequent malignancy was greater for individuals diagnosed at a younger age [12].

This analysis offered the opportunity to investigate the association between NMSC and breast cancer in a large multi-geographic cohort and to address important lifestyle and cancer-related risk factors. The relationship between NMSC and advanced breast cancer is consistent with other studies in the literature and may have implications for screening.

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