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ORIGINAL REPORT

Female Estrogen-Related Factors and Incidence of Basal Cell Carcinoma in a Nationwide US Cohort

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ABSTRACT

Purpose
UV radiation exposure is the primary risk factor for basal cell carcinoma (BCC), the most common human malignancy. Although the photosensitizing properties of estrogens have been recognized for decades, few studies have examined the relationship between reproductive factors or exogenous estrogen use and BCC.

Methods
Using data from the US Radiologic Technologists Study, a large, nationwide, prospective cohort, we assessed the relationship between reproductive factors, exogenous estrogen use, and first primary BCC while accounting for sun exposure, personal sun sensitivity, and lifestyle factors for geographically dispersed women exposed to a wide range of ambient UV radiation.

Results
Elevated risk of BCC was associated with late age at natural menopause (hazard ratio [HR] for ≥ 55 years *v* 50 to 54 years, 1.50; 95% CI, 1.04 to 2.17) and any use of menopausal hormone therapy (MHT; HR, 1.16; 95% CI, 1.03 to 1.30; *P* for trend for duration = .001). BCC risk was most increased among women reporting natural menopause who used MHT for 10 or more years versus women who never used MHT (HR, 1.97; 95% CI, 1.35 to 2.87). Risk of BCC was not associated with age at menarche, parity, age at first birth, infertility, use of diethylstilbestrol by participant's mother, age at hysterectomy, or use of oral contraceptives.

Conclusion
These analyses confirm a previous finding of increased risk of BCC associated with MHT. Novel findings of increased BCC risk associated with MHT in women experiencing natural menopause and for late age at natural menopause warrant further investigation. Users of MHT may constitute an additional high-risk group in need of more frequent skin cancer screening.

INTRODUCTION

Basal cell carcinoma (BCC), the most common human malignancy, is diagnosed in more than one million people in the United States annually, and incidence is increasing.[1] Despite having low mortality, BCC causes considerable morbidity and is responsible for substantial health care expenditures. It is widely accepted that the primary risk factor for BCC is exposure to UV radiation (UVR).[2] Photosensitizing agents, such as exogenous estrogens, are thought to reduce the minimal UVR dose needed to produce an erythemal response or reddening of the skin, increasing the risk of phototoxicity and, potentially, photocarcinogenesis.[3-9] Use of exogenous estrogens such as oral contraceptives (OCs) is common among women in the United States,[10] and despite increased cardiovascular and breast cancer risks related to menopausal hormone therapy (MHT),[11] MHT in lower doses continues to be an accepted remedy for menopausal symptoms.[12]

Although the photosensitizing properties of estrogens have been recognized for decades,[6,8] few epidemiologic studies have examined the relationship between exogenous estrogen use, female reproductive factors, and risk of BCC.[13-15] Studies examining the use of OCs and MHT have found an increased risk of BCC[14,15] or no association.[13,14] However, these studies have had limited length of follow-up,[13] considered all nonmelanoma skin cancer (NMSC) as a group,[13,15] or been set in locations with relatively low levels of UVR.[14,15] Few studies have examined reproductive factors, although they involve endogenous estrogen exposures and thus potentially

photosensitizing effects as well. Two studies examining parity in relation to BCC reported inconsistent findings.[15,16] However, both of these studies were conducted in northern European locations with low levels of ambient UVR and, thus, in populations with potentially reduced susceptibility to the photosensitizing properties of exogenous and endogenous estrogen. To our knowledge, no study has evaluated an extensive number of female reproductive factors in relation to risk of BCC.

The objective of this study is to assess the relationship between reproductive factors, exogenous estrogen use, and subsequent risk of first primary BCC using data from the US Radiologic Technologists (USRT) study. This is a large nationwide prospective cohort that has collected information on personal sun sensitivity characteristics, ambient sun exposure over the lifetime, and lifestyle factors in a population exposed to a wide range of ambient UVR.

METHODS

Overview

The USRT is an occupational cohort that comprises radiologic technologists who were certified by the American Registry of Radiological Technologists for at least 2 years from 1926 through 1982.[17] Detailed descriptions of the cohort and methods have been previously published.[17,18] Briefly, self-administered questionnaires were mailed to cohort members during the following three time periods: 1983 to 1989, 1994 to 1998, and 2003 to 2005. Informed consent was obtained to collect medical records. The USRT study has been annually approved by human subjects review boards at the University of Minnesota (Minneapolis, MN) and the National Cancer Institute (Bethesda, MD).

Study Population

Our study population included female, white participants who completed both the second and third questionnaires and reported being cancer free at the time of the second questionnaire (N = 46,100). Follow-up continued from completion of the second questionnaire until the earlier of first primary cancer diagnosis, including NMSC, or completion of the third questionnaire.

Outcomes and Validation

Incident BCCs, defined as a first primary BCC diagnosis after the second questionnaire, were ascertained from the third questionnaire through self-report (n = 1,618). Medical records to confirm BCC diagnosis were obtained for 840 women (52%), of whom 809 (96%) were confirmed and 31 (4%) were denied. Because the confirmation rate for self-reported BCC diagnosis was high, women with nonvalidated BCCs (n = 778) were also included. During medical validation of reported cancers other than BCC, an additional 112 BCCs were identified and are included in the analyses, bringing the total number of patient cases to 1,730 women.

Exposure Assessment

Reproductive factors and exogenous estrogen use were ascertained on the second questionnaire (entry into the study population), which also collected information on smoking history, alcohol use, height, weight, physical activity, work history, skin complexion, eye color, hair color at age 20, Gaelic/Celtic ancestry, Hispanic ethnicity, marital status, dental x-rays in the last 4 years (as an indicator of health care access and utilization[19-22]), work history, age at menarche, parity, age at first birth, infertility, menopausal status, reason for menopause, age at menopause, mother's use of diethylstilbestrol, and medication use. The third questionnaire ascertained incident BCC, as well as information on education, work history, and residential location over the lifetime (for ages 0 to 12, 13 to 19, 20 to 39, 40 to 64, and ≥ 65 years).

Average annual lifetime ambient UVR exposure was derived by linking the geocoded residential locations reported by respondents to the Total Ozone Mapping Spectrometer database maintained by the National Aeronautics and Space Administration.[23] Cloud-adjusted daily ambient UV irradiance of 305 nm, which is part of the UVB spectrum and therefore related to the erythemal response of the skin,[24] is provided on a 1 degree latitude by 1 degree longitude grid corresponding to approximately 111 × 85 km (69 × 53 miles), respectively. Satellite-based annual estimates of UVR have varied little since the start of measurements in the late 1970s, except from small fluctuations as a result of the 11-year solar cycle[25]; thus, daily noon-time estimates were averaged over years 1982 to 1992.

Statistical Analysis

To evaluate the relationship between reproductive factors, estrogen use, and first primary BCC, Cox proportional hazards regression analyses were used to compute hazard ratios (HRs) and 95% CIs with age as the time scale, which adjusts for age in all models.[26] The following variables were considered potential confounders because they were significantly associated with both reproductive factors or estrogen use and BCC incidence, but not believed to be on the causal pathway: birth cohort; education; marital status; dental x-rays; body mass index (BMI); smoking history; alcohol consumption; physical activity; diuretic use (a photosensitizing medication); occupational radiation dose to head, neck, and arms; OC use (for reproductive factors and MHT models) and MHT use (for OC use); skin complexion; hair color; eye color; Celtic/Gaelic ancestry; Hispanic ethnicity; and average annual lifetime ambient UVR exposure. Our data do not contain a direct measure of skin cancer screening. To account for potential surveillance bias among users of MHT, we examined the following correlates of skin cancer screening: education, age, marital status, constitutional characteristics (hair color and skin complexion),[27-29] and dental x-rays because dental visits are associated with access and use of preventative care.[19-22] Missing values were coded as separate categories and included as indicator variables in the models. Potential confounders that changed the risk coefficients by at least 10% were included in the final models. Birth cohort (5-year groups), dental x-rays, and lifetime average annual ambient UVR exposure were included in all models for a priori reasons because they were considered in previous publications and are strong risk factors for BCC in this cohort. We examined whether mutual adjustment for reproductive factors and exogenous hormone use altered findings. Final models for exogenous hormones were adjusted for age, birth cohort (5-year groups), dental x-rays (nine, one to nine, or ≥ 10 x-rays in last 4 years), BMI category, alcohol use (none, one to two, three to six, or ≥ seven drinks per week), ever use of MHT (for OC models), Celtic/Gaelic heritage, and ambient UVR (continuous). Final models for reproductive factors were adjusted for age, birth cohort (5-year groups), BMI category, alcohol use (none, one to two, three to six, or ≥ seven drinks per week), MHT use (ever/never), Celtic/Gaelic heritage, and average annual lifetime ambient UVR (continuous).

Potential confounders were tested for multiplicative interaction with reproductive factors and hormone use. We also conducted analyses to determine whether risk estimates differed for early-onset BCC (developed at age < 50 *y* ≥ 50 years) and for the subset of validated patients (n = 921). Hazard models satisfied the proportionality assumption. Statistical tests were two-sided, and *P* values were considered significant at the $\alpha = .05$ level. Analyses were conducted using SAS 9.3 software (SAS Institute, Cary, NC).

RESULTS

The study population included 46,100 female, white participants who were cancer free at baseline. Four percent of the eligible participants had an incident BCC (n = 1,730) during up to approximately 10 years of follow-up from completion of the second questionnaire to completion of the third questionnaire. Women with BCC were 2 years older at study entry and contributed an average of 3 fewer years of follow-up than women without BCC (Table 1). The proportions of participants with fair complexion, light eye and hair color, Celtic/Gaelic ancestry, and high lifetime ambient UVR exposure were higher for those who

Table 1. Distribution of Selected Characteristics of Women With and Without BCC Among 46,100 Women in the US Radiologic Technologists Study

Characteristic	% of Women	
	No BCC (n = 44,370)	BCC (n = 1,730)
Age at entry, years		
Mean	46.9	49.0
SD	8.1	9.3
Person-years at risk		
Mean	8.9	5.4
SD	1.6	2.7
Education		
Two-year radiologic technology program	48.7	48.4
College or graduate school	35.9	37.5
Missing	15.4	14.2
Marital status		
Never married	6.2	6.0
Married	77.2	77.8
Living together, not married	1.5	1.0
Divorced	10.6	10.6
Widowed	2.8	3.5
Separated	1.0	0.5
Missing	0.8	0.6
Smoking status		
Nonsmokers	57.2	56.7
Former	30.1	31.7
Current	12.1	11.0
Missing	0.6	0.6
Alcohol use, No. of drinks per week		
None	21.5	18.5
1-2	51.3	49.4
3-6	11.5	13.1
≥ 7	9.0	11.0
Missing	6.8	8.0
BMI, kg/m^2		
Underweight, < 18.5	1.6	1.9
Normal, 18.5-24.9	55.8	62.5
Overweight, 25-29.9	25.6	22.0
Obese, ≥ 30	15.0	11.5
Missing/unknown	2.0	2.1
Ever taken prescription diuretics regularly		
Yes	12.5	14.7
No	86.6	83.9
Missing/unknown	0.9	1.4
Complexion		
Fair	50.6	59.8
Medium	47.4	39.0
Dark	1.5	0.5
Missing/other	0.6	0.7
Eye color		
Blue/green/gray	44.7	52.0
Hazel	22.6	22.4
Brown	31.6	24.3
Missing/other	1.2	1.3
Natural hair color at age 20 years		
Red/blonde	21.7	29.5
Brown	75.4	68.2
Black	1.8	1.0
Missing/other	1.1	1.3
Celtic or Gaelic ancestry		
Yes	21.1	28.8
No	56.5	50.3
Don't know	19.9	18.3
Missing	2.5	2.6
Average lifetime annual solar UVR		
Quartile 1 (lowest)	25.2	20.8
Quartile 2	24.5	21.3
Quartile 3	23.5	24.7
Quartile 4 (highest)	24.3	30.4
Missing	2.6	2.8

Abbreviations: BCC, basal cell carcinoma; BMI, body mass index; SD, standard deviations; UVR, UV radiation.

developed BCC compared with those who did not, as previously reported in the overall cohort.[30] Participants with BCC were more likely to have a normal BMI versus being overweight or obese and were more likely to have ever taken prescription diuretics, a photosensitizing medication.

We found no significant associations for most reproductive factors and BCC incidence (Table 2). The exception was an increased risk of BCC in postmenopausal women who underwent natural menopause at a late age (age ≥ 55 *v* 50 to 54 years: HR, 1.50; 95% CI, 1.04 to 2.17; *P* for trend = .017) among the 7,533 women who reported natural menopause.

We found a significantly increased risk of BCC among ever-users of MHT in the total population (HR, 1.16; 95% CI, 1.03 to 1.30) but no association for OC use and BCC incidence (Table 3). History of hysterectomy significantly modified the relationship between MHT use and risk of BCC (*P* for interaction = .03) among the 17,522 postmenopausal women reporting either natural menopause or hysterectomy; thus, we also present analyses for MHT separately among the 7,533 women reporting natural menopause and among the 9,989 women reporting hysterectomy (Table 3). BCC risk was not significantly associated with ever use of MHT in women reporting hysterectomy (HR, 1.12; 95% CI, 0.99 to 1.40) but was increased among women reporting natural menopause (HR, 1.47; 95% CI, 1.16 to 1.86). BCC risk increased with duration of MHT use in the total cohort (*P* for trend = .001) and in women who underwent natural menopause (*P* for trend < .001) but not in women reporting hysterectomy (*P* for trend = .090). In the total population, higher risk of BCC was observed for women reporting use of both unopposed estrogen (HR, 1.17; 95% CI, 1.01 to 1.36) and estrogen/progestin combination therapies (HR, 1.14; 95% CI, 0.99 to 1.31) compared with never-users of MHT.

Sensitivity analyses restricted to patients with validated BCCs revealed similar increased BCC risks with MHT use and MHT duration of use. Risk estimates did not differ for early-onset (age < 50 years) versus late-onset (age ≥ 50 years) BCC with age at menarche, parity, age at first birth, infertility, diethylstilbestrol use in mother, and OC use (data not shown).

Table 2. Reproductive Factors and Risk of BCC Among 46,100 Women in the US Radiologic Technologists Study

Factor	No. of Women*	No. of Women With BCC*	HR†	95% CI	*P* for Trend‡
Age at menarche, years					
< 12	9,893	346	Ref		
12-13	26,875	999	1.00	0.88 to 1.13	
14-15	7,112	291	1.02	0.87 to 1.20	
≥ 16	1,599	75	1.16	0.90 to 1.51	.392
No. of live births					
Nulliparous	8,568	300	0.90	0.79 to 1.03	
1-2	24,185	901	Ref		
3-4	11,525	459	0.99	0.88 to 1.12	
≥ 4	1,162	51	0.87	0.64 to 1.17	.482
Age at first birth among parous women, years					
< 20	991	37	Ref		
20-24	14,176	544	1.13	0.80 to 1.58	
25-29	14,430	547	1.20	0.85 to 1.69	
≥ 30	6,905	269	1.24	0.87 to 1.77	.119
Tried becoming pregnant without success for 2 years					
No	38,236	1,445	Ref		
Yes	7,575	277	1.03	0.90 to 1.17	
Menopausal status at baseline					
Premenopausal	26,922	856	Ref		
Postmenopausal, natural menopause	7,533	353	0.93	0.77 to 1.12	
Postmenopausal, hysterectomy, two ovaries removed	4,622	214	1.01	0.83 to 1.24	
Postmenopausal, hysterectomy, one ovary removed	1,256	49	0.87	0.63 to 1.20	
Postmenopausal, hysterectomy, still has two ovaries	3,867	170	0.99	0.81 to 1.21	
Postmenopausal, hysterectomy, ovaries unknown	244	21	1.67	1.03 to 2.71	
Postmenopausal, other/unknown reasons for menopause	380	12	0.78	0.44 to 1.39	
Age at natural menopause, years§					
< 50	3,623	146	0.88	0.68 to 1.13	
50-54	3,091	154	Ref		
≥ 55	542	42	1.50	1.04 to 2.17	.017
Age at hysterectomy, years‖					
< 45	6,469	278	Ref		
45-49	1,356	62	1.02	0.77 to 1.35	
≥ 50	658	24	0.75	0.49 to 1.14	.290
Mother took DES					
No	36,951	1420	Ref		
Yes	786	30	1.10	0.76 to 1.60	

Abbreviations: BCC, basal cell carcinoma; DES, diethylstilbestrol; HR, hazard ratio; Ref, reference.
*Numbers may be inconsistent because of missing values.
†Models adjusted for age, birth cohort (5-year categories), baseline body mass index category (< 18.5, 18.5 to 24.9, 25 to 29.9, and ≥ 30 kg/m^2), alcohol consumption (none, one to two, three to six, and ≥ seven drinks per week), Celtic/Gaelic ancestry, and lifetime average annual ambient UV radiation (continuous).
‡Trend tests were conducted by modeling categorical values as ordinal.
§Restricted to 7,533 postmenopausal women reporting natural menopause without hysterectomy.
‖Restricted to 9,989 postmenopausal women reporting hysterectomy (includes 439 women who also reported natural menopause).

DISCUSSION

This is the first study to evaluate prospectively a broad range of reproductive factors and estrogen use in relation to BCC in a large nationwide US population with information on personal sun sensitivity characteristics, lifetime ambient UVR exposures based on location of residence, and reproductive, lifestyle, and anthropometric factors. We found late age at natural menopause and MHT use to be significantly associated with increased risk of BCC. Among women who experienced natural menopause, the use of MHT for 10 or more years was associated with almost twice the risk of BCC compared with never-users. This is the first study, to our knowledge, to show that the relationship between MHT use and BCC was limited to those with natural menopause. Use of OCs and other reproductive factors were not associated with risk of BCC in this cohort.

The findings from this study support previous research demonstrating an increased risk of BCC among users of photosensitizing medications, including MHT.[14,31,32] Birch-Johansen et al[14] observed an increased risk of BCC among ever-users of MHT (incidence rate ratio, 1.15; 95% CI, 1.07 to 1.37) in a cohort of 30,000 women in Denmark. Tang et al[13] found no relationship between MHT use and NMSC in the US Women's Health Initiative (WHI) clinical trial; however, unlike the reference group in our study, which was never exposed to MHT, WHI study participants were not excluded from random assignment if they had previously used MHT. In addition, follow-up for NMSC was limited to the period of intervention, approximately 6 to 7 years, whereas latency for BCC is estimated to be from 20 to 50 years.[33] In contrast, more than 20% of MHT users in our cohort reported a duration of MHT use of 10 or more years at baseline and were then observed for up to an additional 10 years. The increased

Table 3. Exogenous Estrogen Use and Risk of BCC Among 46,100 Women in the US Radiologic Technologists Study

Factor	No. of Women*	No. of Women With BCC*	HR†	95% CI	*P* for Trend‡
Total population§					
OC use					
Never-users	11,061	474	Ref		
Ever-users	34,823	1,247	1.00	0.88 to 1.13	
Duration of OC use in ever-users, years					
Never	11,061	474	Ref		
< 1	3,558	140	1.06	0.87 to 1.30	
1-2	6,458	248	1.11	0.94 to 1.31	
3-4	7,458	263	1.01	0.86 to 1.20	
5-9	10,132	342	0.92	0.79 to 1.08	
≥ 10	6,798	238	0.96	0.81 to 1.14	.235
MHT use					
Never-users	32,208	1,073	Ref		
Ever-users	13,581	651	1.16	1.03 to 1.30	
Past users	2,534	114	1.07	0.87 to 1.33	
Current users	10,705	518	1.17	1.03 to 1.33	
Duration of MHT use in ever-users, years					
Never	32,208	1,073	Ref		
< 1	2,598	92	0.94	0.75 to 1.17	
1-2	2,361	111	1.24	1.01 to 1.54	
3-4	2,156	100	1.20	0.96 to 1.50	
5-9	3,007	133	1.07	0.88 to 1.31	
≥ 10	2,986	192	1.37	1.14 to 1.65	.001
MHT type					
Never use	32,208	1,073	Ref		
Unopposed estrogen	5,582	277	1.17	1.01 to 1.36	
Estrogen/progestin	7,734	358	1.14	0.99 to 1.31	
MHT use in women with natural menopause‖					
MHT use					
Never-users	3,154	122	Ref		
Ever-users	4,347	230	1.47	1.16 to 1.86	
Past users	951	41	1.06	0.73 to 1.55	
Current users	3,305	180	1.61	1.25 to 2.07	
Duration of MHT use in ever-users, years					
Never	3,154	122	Ref		
< 1	940	30	0.89	0.58 to 1.36	
1-2	928	53	1.72	1.21 to 2.43	
3-4	816	44	1.59	1.10 to 2.30	
5-9	1,025	52	1.31	0.92 to 1.87	
≥ 10	520	41	1.97	1.35 to 2.87	<.001
MHT type					
Never use	3,154	122	Ref		
Unopposed estrogen	430	21	1.12	0.69 to 1.84	
Estrogen/progestin	3,858	203	1.52	1.19 to 1.94	
MHT use in women with hysterectomy¶					
MHT use					
Never-users	3,028	116	Ref		
Ever-users	6,924	336	1.12	0.89 to 1.40	
Past users	946	53	1.25	0.89 to 1.76	
Current users	5,843	278	1.10	0.87 to 1.39	
Duration of MHT use in ever-users, years					
Never	3,028	116	Ref		
< 1	811	32	0.96	0.64 to 1.45	
1-2	933	40	1.07	0.73 to 1.56	
3-4	1,027	41	1.01	0.69 to 1.47	
5-9	1,697	73	1.06	0.78 to 1.45	
≥ 10	2,293	142	1.29	0.98 to 1.70	.09
MHT type					
Never use	3,028	116	Ref		

(continued on following page)

Table 3. Exogenous Estrogen Use and Risk of BCC Among 46,100 Women in the US Radiologic Technologists Study (continued)

Factor	No. of Women*	No. of Women With BCC*	HR†	95% CI	*P* for Trend‡
Unopposed estrogen	4,614	237	1.17	0.92 to 1.48	
Estrogen/progestin	2,176	93	1.02	0.76 to 1.36	
MHT ever used by number of ovaries removed					
No ovaries removed					
Never	1,984	69	Ref		
Ever	1,873	99	1.28	0.89 to 1.84	
One ovary removed					
Never	547	21	Ref		
Ever	705	28	1.14	0.59 to 2.18	
Two ovaries removed					
Never	424	19	Ref		
Ever	4,179	195	1.08	0.66 to 1.77	

Abbreviations: BBC, basal cell carcinoma; HR, hazard ratio; MHT, menopausal hormone therapy; OC, oral contraceptive.
*Numbers may be inconsistent because of missing values.
†OC models are adjusted for age, birth cohort (5-year groups), baseline body mass index category (< 18.5, 18.5 to 24.9, 25 to 29.9, and ≥ 30 kg/m^2), alcohol consumption (none, one to two, three to six, and ≥ seven drinks per week), MHT use (ever/never), Celtic/Gaelic heritage, and lifetime average annual ambient UV radiation (continuous). MHT models are adjusted for age, birth cohort (5-year groups), dental x-rays in last 4 years (none, one to nine, and ≥ 10 x-rays), Celtic/Gaelic ancestry, and lifetime average annual ambient UV radiation (continuous).
‡Trend tests were conducted by modeling categorical values as ordinal.
§The total population includes 46,100 pre- and postmenopausal women.
‖Restricted to 7,533 postmenopausal women reporting natural menopause without hysterectomy.
¶Restricted to 9,989 postmenopausal women reporting hysterectomy (includes 439 women who also reported natural menopause).

risk of BCC was highest in the longest MHT duration group. Finally, the WHI study evaluated NMSC as a group, whereas we examine BCCs separately. NMSC is a heterogeneous category including BCC and squamous cell carcinoma. Differences between BCC and squamous cell carcinoma have been found for effect modification of UVR with other risk factors, suggesting the possibility of differences for the photosensitizing effects of estrogens as well.[34]

Our findings of increased risk of BCC associated with late age at natural menopause and use of MHT are consistent with the hypothesis that exposure to endogenous and exogenous estrogens is photocarcinogenic. The menopausal transition is characterized by reduced levels of endogenous estrogen production by the ovaries so that a late age at menopause suggests a higher lifetime cumulative exposure to estrogen.[35] In contrast to surgical menopause, which is associated with an immediate and dramatic drop in estrogen levels, women undergoing natural menopause may be exposed to a nontrivial amount of total and unopposed estrogen during the menopausal transition.[35] We found the highest risk of BCC for MHT use among women who experienced natural menopause and reported a duration of use of 10 or more years (HR, 1.97; 95% CI, 1.35 to 2.87; *P* for trend < .001). In this group, the combination of endogenous and exogenous estrogens may have increased the cumulative estrogen exposure (and, thus, the cumulative phototoxic effects). Phototoxic reactions occur when, in a dose-dependent manner, a compound able to absorb UVR within the skin causes damage to skin cell membranes or DNA.[36] Consistent with this hypothesis, women who experienced menopause due to hysterectomy but had no ovaries removed had a (nonsignificantly) higher risk of BCC associated with MHT use (HR, 1.28; 95% CI, 0.89 to 1.84) than women who had both ovaries removed (HR, 1.08; 95% CI, 0.66 to 1.77).

Our findings of no association between OC use and BCC are consistent with findings from the studies by Birch-Johansen et al[14] and Vessey et al[15]; however, the latter study did not adjust for lifestyle factors and examined all NMSCs as a group. In contrast to our findings for MHT, null findings for OC use may reflect low susceptibility to photosensitizing medications during young adulthood or the lower usual doses typically prescribed. For OCs, the estrogen level of ethinyl estradiol may range from 20 to 50 μg.[37] For MHT, prescribed doses of conjugated equine estrogen range from 500 to 2,000 μg, but a typical dose may be approximately 625 μg, which was the dose administered in the WHI clinical trial.[38] Thus, without regard to the different compounds and formulations, MHT users may be exposed to more than 10 times the estrogen dose of OC users.

The majority of reproductive factors were not associated with risk of BCC in our cohort. A study in the United Kingdom found no relationship between parity and all NMSCs as a group,[15] whereas a reduced risk for NMSC was observed with 10 or more pregnancies in a registry-based study of Finnish women.[16] Unlike our study, both of these northern European studies were set in areas of relatively low UVR exposure. Although estrogen levels are increased during pregnancy, they are reduced dramatically during breastfeeding. Unfortunately, data on breastfeeding were not collected in these studies or in our study, so we are not able to easily interpret the null associations between BCC and parity.

To our knowledge, this is the first study to evaluate prospectively a broad range of reproductive factors and use of exogenous estrogens in relation to BCC in a large population with information on lifetime ambient UVR exposures based on residential history, personal sun sensitivity characteristics, and lifestyle, anthropometric, and other potential risk factors. The nationwide distribution of the cohort from all US states and territories ensures a wide range in UVR exposures. More than 1,700 incident BCCs were reported and, consistent with other studies,[39] were confirmed with a 96% positive predictive value. In addition, BCC risks in the validated group were similar to those in the combined group of confirmed and unconfirmed BCCs.

Data on reproductive history and use of exogenous estrogens were self-reported, but as medical workers, these women may be able to more accurately report their medical histories than women in the general US population. We did not have information on specific doses of MHT or OC or on OC formulations, although less than 1% of women have been estimated to use progestin-only OCs. We cannot rule out the possibility of detection bias because there is no direct way to know whether MHT users were more likely than nonusers to be screened for skin cancer. However, when we adjusted for indicators for health care utilization and previously reported predictors of skin cancer screening (eg, education, age, marital status, constitutional characteristics, and number of dental x-rays), the results were essentially unchanged. USRT participants are health care workers who are likely to have high overall health care utilization patterns with potentially less variability than the general population. Our UVR exposure metric was based on lifetime residential location, which is likely recalled accurately, but did not account for time spent outdoors or sun-protective behaviors. It is possible that these UVR factors may differ among women who use MHT or OCs and for women with some reproductive factors such as parity.

In summary, in this large nationwide cohort study, late age at natural menopause and MHT use were significantly associated with increased risk of BCC. The relationship of MHT use and BCC was particularly evident in women with natural menopause. Users of photosensitizing medications such as MHT may constitute an additional high-risk group in need of more frequent skin cancer screening. Because, to our knowledge, this the first comprehensive examination of BCC risk with reproductive factors and exogenous estrogen use, our findings need to be replicated in other cohorts before strong conclusions can be drawn. Future studies could collect more detailed information on medication use, ask participants about photosensitivity reactions, and collect biomarkers of female sex hormones in relation to risk of BCC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Female Estrogen-Related Factors and Incidence of Basal Cell Carcinoma in a Nationwide US Cohort

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