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Sex hormones and the risk of keratinocyte cancers among women in the United States: a population-based case-control study

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Abstract

Men are at a higher risk of developing both squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) than women, but there is emerging evidence that women may be experiencing greater increases in the incidence rates of these malignancies than men. One possible explanation is the expanding use of sex steroids among women, although only a few studies have examined this hypothesis. As part of a population-based, case-control study of women in New Hampshire, USA, we sought to evaluate the risk of SCC, BCC, and early-onset BCC in relation to exogenous and endogenous sex hormones. We found that oral contraceptive (OC) use was associated with an increased risk of SCC (OR = 1.4, 95% CI = 1.1–1.8) and BCC (OR = 1.4, 95% CI = 1.0–1.8), particularly high estrogen dose (>50mg) OC use. Hormone replacement therapy (HRT) use also related to SCC, with an elevated OR largely for progestin use (OR = 1.4, 95% CI = 1.1–1.8). Additionally, both OC use and combination HRT use were associated with more aggressive BCC subtypes. In contrast, menstrual and reproductive history did not appear to influence keratinocyte cancer risk in our data. Our findings provide evidence that use of sex steroids may enhance risk of KC.

Keywords

Keratinocyte cancer; sex hormones; oral contraception; hormone replacement therapy

Introduction

Keratinocyte cancers (KC), including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), are the leading invasive carcinomas among people of European descent both in the United States and worldwide.[1–4] In addition, population-based studies have observed increasing incidence rates of KCs in various parts of the world.[5–8] While death is rare[9,10], the large number of people affected by these cancers, along with high recurrence

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rates and incidence of second cancers[11], results in significant morbidity. Moreover, the necessary treatment consumes a large portion of total healthcare expenditure.[12, 13]

Men are at higher risk for developing KCs than women, even after controlling for ambient ultraviolet radiation (UVR) levels.[14] However, despite the higher overall incidence in men, there is evidence that the rate of increase may be higher among women than men.[5, 8, 15, 16] Potential mechanisms for gender-specific patterns of risk have not yet been studied extensively, although gendered patterns of behavior are traditionally thought to play a larger role than biological differences. Nonetheless, while sex-dependent steroids are known carcinogens for certain malignancies (e.g. breast, uterine, and prostate carcinoma)[17–19], relatively few studies have been conducted on keratinocyte cancers.[20–23] These studies have found varying risks of KC associated with hormone exposure; however, interpretation of these results has been challenging due to limited statistical power, variation in analyses by duration and timing of exposure, and lack of comprehensive investigation of different forms of hormone exposure in a single population and across both SCC and BCC. Therefore, we sought to elucidate the role of sex hormone-related factors in the occurrence of KCs in a large population-based case-control study of women in the US on whom detailed information was collected on oral contraceptive (OC) and hormone replacement therapy (HRT) use, along with menstrual and reproductive history.

Methods

Study population

The New Hampshire Skin Cancer Study has been described in detail elsewhere.[5, 24] Briefly, histologically confirmed cases of invasive newly diagnosed SCC, BCC, and early-onset BCC (≤ 50 years of age at time of diagnosis) among residents of New Hampshire aged 25–74 years old from July 1993–June 2009 were identified through a network of dermatology and dermatopathology practices in New Hampshire and surrounding regions.[25, 26] Cases were classified as either SCC or BCC according to the histology of the first diagnosed keratinocyte cancer during the study period. Early-onset BCC cases are a subset of BCC cases. Controls were chosen from either the Center for Medicare enrollment lists (for those ≥ 65 years old) or from driver's license records provided by the New Hampshire Department of Transportation (for those <65 years old), and frequency-matched to the age (25–34, 35–44, 45–54, 55–64, 65–69, and 70–74 years) and gender distribution of cases. Controls for SCC and BCC were identical for the period July 1993 to June 2003 of our study while the period July 2007 to June 2009 was limited to SCC and so controls from this phase are unique to the SCC analysis.

To be eligible, participants were required to be English-speaking and have a working telephone number. Cases and controls were interviewed concurrently, and interviewers were masked to the case-control status of study participants and study hypotheses. For cases, we requested the original diagnostic pathology materials, which underwent standardized histopathologic re-review by a study board certified dermatopathologist (AP) who documented the presence or absence of actinic keratosis and the level of solar elastosis (mild, moderate, severe) in the dermis adjacent to the tumor as described previously.[27] Of those eligible, 84% of cases and 73% of controls were interviewed. Only women were

selected for inclusion in this study. Informed consent was obtained as required by the Committee for the Protection of Human Subjects at Dartmouth College.

Detailed personal interviews were performed (usually at the participant's home) to ascertain information on sociodemographic characteristics (including level of education), hair and eye color, smoking status, skin sensitivity to the sun, history of sun burns, and time spent outdoors throughout their lifetime.[27] Medical history included use of oral contraceptives (OC) and hormone replacement therapy (HRT), and for positive responses, age at first and last use, duration of use, and specific type of medication used the longest. To aid in memory recall, pictures and names of common OC and HRT were provided. Reproductive and menstrual history questions included gravidity, parity, age of menarche, and age and type of menopause. Questions regarding OC and HRT use were first administered in October 1995, parity in July 1998, and age of menarche in July 2000. Body mass index (BMI) was calculated based on reported height and weight, variables that were first collected in July 1997.

Statistical analyses

Using logistic regression analysis, we first calculated the age and skin type adjusted odds ratios (OR) and 95% confidence intervals (CI) for invasive SCC, BCC, and early-onset BCC by OC use and HRT as a dichotomous variable (ever versus never use). Ever OC use was defined as use for 3 months or longer. Those who reported never having used an OC or whose use was ≤ 3 months were classified as non-users. A similar definition was applied to HRT use, and these analyses were restricted to post-menopausal women. In addition to overall effects of OC use, we examined the years since last OC use (<25years, ≥25 years), duration of OC use (≤2 years, 3–6 years, ≥7 years), and for HRT use years since last use (current use, former use), and duration of use (<5 years, ≥5 years) with non-users as the reference group. These cutoffs were made to maintain consistency with our previous study, which performed a similar analysis. Models also included variables for OC use based on formulation (any estrogen or estrogen + progestin) and estrogen dose (<50mg or ≥ 50mg). To assess both latency and duration of OC use, we computed odds ratios for total duration of use (≤ 2 years, 3–6 years, ≥ 7 years) by time since last use (<25 years or ≥25 years). We used likelihood ratio tests to detect any interaction between oral contraceptive use and hormone replacement therapy.

To evaluate the possible effects of endogenous estrogens on KC risk, we examined age of menarche (<13 years old, 13–15 years old (referent), >15 years old), age of menopause (<40 years old, 40–54 years old (referent), ≥55 years old), type of menopause (surgical and natural (referent)), and parity both as a categorical variable (0 (referent), 1–2, 3–4, ≥5) and a continuous variable. Age at menarche and menopause were grouped according to ages that have historically been used in analyzing these reproductive factors in relation to cancer risk.[28] The duration of ovulation was calculated as the number of years between menarche and menopause for women who reached menopause without surgery or medication therapy.

To determine whether associations differed by characteristics of tumors based on pathology re-review of the original diagnostic tumor, we conducted a case-case analysis using unconditional logistic regression for subgroups of SCC and BCC by severity of solar

elastosis (severe vs. none-moderate), for SCC by the presence of actinic keratosis (present vs. absent), for BCC by histology (aggressive types including infiltrative, sclerosing, morpheaform, and micronodular vs. other), and for both types by anatomic site of the keratinocyte lesion.

In our models, we assessed the effects of potential confounding factors including skin reaction to first sun exposure (painful or blistering sunburn, tan or burn then tan), education level (less than college, college, graduate school), family history of KC, number of hours spent outdoors from 9 a.m. to 5 p.m. during the summer and recreationally, number of lifetime painful sunburns, and smoking status (never, former, current). Final models were then constructed using each hormone variable and confounders that changed the odds ratios (ORs) by more than 10% or were deemed clinically relevant (Maldonado G, 1993). In our analysis, we ultimately adjusted for reference age as a continuous variable and skin reaction following first sun exposure as a categorical variable (tan, mild burn then tan, peeling skin after a painful burn, blistering after a painful burn).

All statistical analyses were two-sided, and significance was assessed at the alpha=0.05 level. Analyses were conducted with the statistical software SAS version 9.4.

Results

Study population characteristics

Interviews containing questions of oral contraceptive use or hormone replacement use were administered to 570 SCC cases and 746 SCC controls, and 550 BCC cases and 633 BCC controls. Of these, oral contraceptive use or hormone replacement therapy were recorded as ever or never use by 558 (97.9%) SCC cases and 716 (96.0%) SCC controls, and 604 (95.4%) BCC cases, and 520 (94.5%) BCC controls (Table 1). The early-onset BCC subgroup included 362 cases and 246 controls of whom 347 (95.9%) and 228 (92.7%) had sex steroid use data.

Both SCC and BCC cases were more educated and had a lower BMI, but were similar to controls in terms of smoking status (Table 1). SCC cases were more likely to have red hair and blue or grey eyes and reported more sun exposure during recreation and summer months as well as more sensitive skin to solar exposure (Table 1). BCC cases were slightly more likely to have less sun exposure during recreation and summer but were also more likely to have red hair and blue or grey eyes (Table 1). Number of severe sunburns was higher in all KC case groups compared to controls (Table 1). Among cases, solar elastosis tended to be severe with 70% of the BCC cases, 60% of the SCC cases, and approximately 50% of early-onset BCC cases (Table 1).

Sex hormones and keratinocyte cancers

After adjustment for reference age and skin sensitivity to first solar exposure in the summer, we observed an elevated odds ratio of SCC (OR = 1.4, 95% CI = 1.1–1.8), BCC (OR = 1.4, 95% CI = 1.0–1.8) and early-onset BCC (OR 1.4, 95% CI = 0.9–2.1) in relation to OC use compared to non-use (Table 2). Longer durations of OC use (≥7 years) were associated with higher odds ratios of SCC (OR = 1.5, 95% CI = 1.1–2.0), BCC (OR = 1.5, 95% CI = 1.1–

2.1) and early-onset BCC (OR = 1.6, 95% CI = 1.0–2.7) compared to shorter duration of use (≤2 years). The magnitude of the associations with SCC appeared stronger for women with a more remote history of OC use (<25 years, OR =1.0, 95% CI = 0.7–1.6; ≥25 years, OR = 2.1, 95% CI = 1.5–3.2) while for the association with BCC risk did not appear to differ by time since last exposure (<25 years, OR = 1.3, 95% CI = 1.0–1.8; ≥25 years, OR = 1.5, 95% CI =1.0–2.1). For SCC, an increasing trend in the odds ratios with duration of use was present among those who used OCs in the more distant past (≤2 years: OR = 1.7, 95% CI = 1.0–2.8, 3–6 years: OR = 2.6, 95% CI = 1.4–4.8, ≥7 years: OR = 3.0, 95% CI = 1.3 – 6.8; $p_{trend} < 0.06$). In contrast, for BCC, trends by duration of use were observed among more recent users (BCC, ≤2 years: OR = 1.4, 95% CI = 0.8–2.3, 3–6 years: OR = 1.3, 95% CI = 0.9–2.0, ≥7 years: OR = 1.7, 95% CI = 1.2 – 2.4; $p_{trend} < 0.96$. Early-onset BCC, ≤2 years: OR = 1.2, 95% CI = 0.7–2.2, 3–6 years: OR = 1.1, 95% CI = 0.7–1.9, ≥7 years: OR = 1.6, 95% CI = 1.0 – 2.6; $p_{trend} < 0.65$) (Supplemental Table 1). Women who used OC with ≥ 50mg of estrogen had somewhat higher odds ratios for SCC and early-onset BCC than those who used OC with lower estrogen doses (Table 2). There did not appear to be appreciable differences by combination versus sequential OC use (Table 2).

HRT use also was associated with increased risk of SCC (OR =1.4, 95% CI = 1.1–1.8). Both current and former HRT use was associated with an increased risk of SCC (current users: OR = 1.4, 95% CI = 1.1–1.8, former users: OR = 1.6, 95% CI = 1.0–2.5), and odds ratios increased with older age at first use ($p_{trend} <0.004$) (Table 2). Combined estrogen and progestin use was associated with a higher odds ratio than estrogen alone (Table 2).

We then examined the effects of OC use alone, HRT use alone, and combination OC and HRT use (Supplemental Table 2). SCC risk was highest among women who used both OC and HRT (OR = 1.9, 95% CI = 1.4 – 2.7) and slightly so for BCC (OR = 1.4, 95% CI = 1.0 – 2.1).

Neither age of menarche nor age of menopause was related to the risk of keratinocyte cancers (Table 2). With natural menopause as the referent group, bilateral oophorectomy was associated with a lower odds of SCC (OR = 0.6, 95% CI = 0.4–1.2) but with wide confidence intervals. Parity unrelated to risk of keratinocyte cancer (Table 2). Longer total duration of endogenous estrogen exposure was associated with a somewhat higher risk of SCC and BCC, but not statistically significantly so. Stratification by BMI did not indicate effect modification in KC associations with OC or HRT (Supplemental Table 3).

In our case-case analyses, OC use was related to SCCs and BCCs without histologic evidence of severe solar elastosis (Supplemental Table 4), and SCCs without evidence of actinic keratosis (Supplemental Table 5). In contrast, for HRT use there was a positive association with BCCs with severe elastosis compared to those with none to moderate elastosis (Supplemental Table 4), and SCCs with associated actinic keratosis (Supplemental Table 5). No clear patterns were observed by anatomic site (Supplemental Table 6). Notably, both OC and combination HRT users were more likely to have an aggressive BCC subtype (Table 3).

Discussion

In our population-based case-control study, we found an association between both oral contraceptive and hormone replacement therapy use and newly diagnosed SCC. Additionally, use of oral contraceptives related to newly diagnosed BCC, and both OC and HRT use were associated with aggressive BCC histology. No clear associations were observed for factors related to endogenous estrogens including timing of menarche, age or type of menopause, and parity.

There are relatively few prior cohort studies that have examined KC risk in relation to OC use. A large cohort study from the United Kingdom found no association between use of OCs and “nonmelanoma skin cancer” (presumably BCC and SCC combined).[29] While this study had the benefit of a large sample size (n=29,875 cases), the study population was aged between 25 and 39 years and therefore had only 83 KC events. Additionally, it relied on hospital referral codes rather than histologic diagnosis, leaving open the possibility of diagnostic misclassification and making BCC- and SCC-specific risk calculations impossible. Additionally, a Danish cohort study, found no OC-associated increased risk of SCC either overall or by duration or time since last use.[22] This study likewise had limited statistical power due to the small number of SCC cases (n=76). In a case-control analysis of pre-paid health plan data from California, the odds ratio for SCC associated with prior OC use was 2.4, but attenuated to 2.0 and was no longer statistically significant in the multivariate analysis.[20] In an earlier report, based on the first and second diagnosis periods of our study (1 July 1993 to 30 June 1995, and 1 July 1997 to 30 March 2000), we found an increased risk of SCC among women who had used OCs ≥25 years ago, with a trend in risk by duration of use.[21] We performed a similar analysis with two additional study phases, and our findings remain. Our observation that higher doses of estrogen in the early formulations of OC related to increased risk of SCC occurrence will need to be confirmed in future studies.

We found an association between OC use and BCC, which was similar to the findings from the Danish cohort (n= 1,175 BCC cases), in which BCC risk was slightly increased overall and among past users, but not current users.[22] Both in our study and in the Danish study, higher doses of estrogen were associated with increased risk. Our findings further suggest that the association may be stronger for early-onset BCC, and BCCs with a more aggressive phenotype. While these need to be confirmed by other studies, our observations support the hypothesis that risk factors for early-onset BCC may differ from those of later-onset disease.[25, 30]

The published literature concerning HRT use and keratinocyte cancers is relatively scant. A retrospective analysis of the Women’s Health Initiative examined records of 27, 347 postmenopausal women with follow-up period of 6 years and found no relation with nonmelanoma skin cancers and HRT use.[31] This study relied on self-reported skin cancer diagnoses and hence lacked histologic information. In a Danish cohort, the reported relative risk was 1.35 for every 5 years of HRT exposure.[22] We found a similarly increased risk specific to SCC, which appeared to be independent of prior exogenous hormone exposure as the risk was unchanged when excluding those with prior OC use. Our findings raise the

possibility of a synergistic effect among those with HRT and OC use although we had limited statistical power to detect interactions. The risk for SCC was especially strong among those who used combined estrogen and progestin HRT, an effect previously described for other cancers including breast and possibly ovarian cancer.[32–36] Thus, the potential effects of HRT on KC occurrence warrant further investigation.

Estrogen receptors are present on the surface of keratinocytes and when activated induce proliferation.[37] Estrogen receptor activation further may alter the DNA repair capacity of keratinocytes leading to increased susceptibility to repeated environmental insults.[38, 39] Indeed, our earlier study provided evidence of a potential modifying role of altered DNA repair capacity, with findings of an interaction between OC-SCC risk by an XPD genotype.[21] Another potential mechanism in theory could be estrogen-induced photosensitization.[40–42] We found that degree of solar elastosis was more severe in BCC cases who had taken HRT. Solar elastosis is a marker of chronic UVR exposure and has been shown in a meta-analysis to be related to risk of BCC.[43] An association between OC or HRT exposure and aggressive subtypes of BCC has not previously been reported but if true, this would suggest that increased surveillance and early identification is important among women taking sex steroids.

Increased physiologic exposure to sex hormones as measured by number of years spent ovulating, age at first pregnancy, and number of pregnancies have been implicated in some cancers in women[44–49], although the effects on keratinocyte cancer are not well documented. A single study in the literature reported that a large number of deliveries (≥10) was associated with a reduced incidence of BCC in a Finnish population.[48] In addition, a meta-analysis found that women with a late age at first pregnancy were at increased risk of melanoma while having more than one child resulted in a lower risk.[50] We did not detect clear associations with parity, reproductive factors, or cumulative years spent menstruating. There was the suggestion of a trend toward increased risk among women with longer duration of ovulation, but we lacked statistical power to observe this trend among those ovulating longest. Future studies may be able to more clearly define a possible risk due to increased endogenous estrogen exposure.

As with all retrospective studies, an important limitation in our study is recall bias, which may have affected the reported history of OC and HRT use. We provided subjects with photo-aids in order to assist in recall of medications, however, timing and duration of use were solely based of subject recollection. Another limitation is that a large portion of our study population was older and these women were likely to have been exposed to different OC and/or HRT formulations than are currently available. For example, modern OC formulations have greatly reduced levels of estrogen and therefore current OC users may not experience the same risks we observed. Finally, only limited conclusions can be drawn from our study on risk differences by sex. While we studied the effects of sex-specific hormones, our study analyzed data according to subject reported sex, which could be affected by gender identification. This is most relevant to risk among OC users since these medications would be more likely to be used in those of female gender regardless of sex. Our findings with regard to HRT and reproductive factors would be less likely to be confounded by gender orientation.

In conclusion, we found additional support for the hypothesis that female sex steroids may contribute to the pathogenesis of KC in a population of US women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations

AK	actinic keratosis
BCC	basal cell carcinoma
BMI	body mass index
CI	confidence interval
HRT	hormone replacement therapy
KC	keratinocyte carcinoma
OC	oral contraceptives
OR	odds ratio
SCC	squamous cell carcinoma
UVR	ultraviolet radiation

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Novelty and Impact

We evaluated the risk of SCC, BCC, and early-onset BCC among a population of US women. Our data support an association between oral contraception (OC) and hormone replacement therapy (HRT) and KC. Risk was related to duration of exposure, years since last exposure, and the formulation and dose of OC and/or HRT therapy. We found a higher risk of aggressive BCC subtypes among women exposed to OCs or combined formulations of HRT.

Table 1

Selected characteristics of keratinocyte cancer cases and controls among women from the New Hampshire Skin Cancer Study

	SCC controls N = 746	**SCC cases N = 570**	**BCC controls N = 550**	**BCC cases N = 633**	**Early-onset BCC controls[a] N = 246**	**Early-onset BCC cases N = 362**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Age (years)						
25–44	139 (18.6)	23 (4.0)	135 (24.5)	197 (31.1)	139 (56.5)	197 (54.4)
45–54	163 (21.8)	79 (13.9)	131 (23.8)	207 (32.7)	107 (43.5)	165 (45.6)
55–64	160 (21.4)	169 (29.6)	98 (17.8)	104 (16.4)		
65–69	150 (20.1)	144 (25.3)	98 (17.8)	59 (9.3)		
70–74	134 (18.0)	155 (27.2)	88 (16.0)	66 (10.4)		
Highest level of education[b]						
High school	313 (42.0)	205 (36.0)	242 (44.1)	186 (29.6)	66 (26.8)	74 (20.6)
College	293 (39.3)	230 (40.4)	212 (38.6)	289 (45.9)	133 (54.1)	191 (53.2)
Graduate or professional school	139 (18.7)	134 (23.6)	95 (17.3)	154 (24.5)	47 (19.1)	94 (26.2)
Cigarette smoking history[c]						
Never	333 (44.6)	235 (41.3)	263 (47.8)	334 (52.9)	121 (49.2)	199 (55.1)
Former	285 (38.2)	244 (42.9)	191 (34.7)	201 (31.9)	75 (30.5)	102 (28.3)
Current	128 (17.2)	90 (15.8)	96 (17.5)	96 (15.2)	50 (20.3)	60 (16.6)
Body Mass Index (kg/m2)[d]						
< 18.5 (underweight)	9 (1.5)	16 (3.2)	199 (49.1)	298 (60.1)	2 (0.9)	12 (3.9)
18.5 – 24.9 (normal)	281 (46.8)	234 (46.6)	7 (1.7)	13 (2.6)	117 (54.7)	195 (63.1)
25–29 (overweight)	157 (26.1)	151 (30.1)	110 (27.2)	112 (22.6)	53 (24.8)	64 (20.7)
≥ 30 (obese)	154 (25.6)	101 (20.1)	89 (22.0)	73 (14.7)	42 (19.6)	38 (12.3)
Number of Severe Sunburns[e]						
0–2	391 (58.7)	233 (44.9)	303 (59.9)	269 (46.1)	113 (48.9)	131 (39.6)
≥3	275 (41.3)	286 (55.1)	203 (40.1)	314 (53.9)	118 (51.1)	200 (60.4)
Hours recreational sun exposure in warm months 9am–5pm[f]						

	SCC controls N = 746	SCC cases N = 570	BCC controls N = 550	BCC cases N = 633	Early-onset BCC controls[a] N = 246	Early-onset BCC cases N = 362
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
T1 [0–7864 hours]	262 (39.8)	128 (24.6)	238 (47.4)	262 (43.9)	128 (55.4)	177 (51.3)
T2 [7865–11601 hours]	205 (31.1)	137 (26.3)	157 (31.3)	173 (29.0)	75 (32.5)	105 (30.4)
T3 [11602–44113 hours]	192 (29.1)	256 (49.1)	107 (21.3)	162 (27.1)	28 (12.1)	63 (18.3)
Hours total sun exposure in warm months 9am–5pm[g]						
T1 [0–11978 hours]	327 (49.8)	162 (31.4)	279 (55.8)	327 (55.3)	157 (68.3)	230 (67.4)
T2 [11979–19335 hours]	201 (30.6)	205 (39.7)	142 (28.4)	187 (31.6)	61 (26.5)	91 (26.7)
T3 [19336–48123 hours]	128 (19.5)	149 (28.9)	79 (15.8)	77 (13.0)	12 (5.2)	20 (5.9)
Sun sensitivity to first solar exposure[h]						
tan	89 (12.0)	42 (7.4)	54 (9.9)	48 (7.7)	20 (8.1)	24 (6.7)
mild burn then tan	316 (42.5)	244 (43.0)	222 (40.5)	249 (39.7)	116 (47.2)	146 (40.6)
burn then peel	260 (34.9)	223 (39.3)	207 (37.8)	282 (45.0)	93 (37.8)	160 (44.4)
burn then blister	79 (10.6)	59 (10.4)	65 (11.9)	48 (7.7)	17 (6.9)	30 (8.3)
Anatomic site of keratinocyte cancer						
Head and neck		238 (42.5)		365 (59.7)		208 (58.9)
Upper and lower limbs		231 (41.3)		69 (11.3)		40 (11.3)
Thorax and abdomen		91 (16.3)		177 (29.0)		105 (29.7)
Amount of Solar Elastoses						
Absent		2 (0.6)		5 (1.4)		2 (0.9)
Minimum		40 (11.5)		22 (6.4)		33 (15.6)
Moderate		96 (27.5)		76 (22.0)		71 (33.6)
Severe		211 (60.5)		243 (70.2)		105 (49.8)

[a] Early-onset BCC defined as age ≤ 50 at time of diagnosis

[b] Level of education is missing from 1 SCC case, 1 control, and 4 BCC cases (3 early-onset).

[c] Smoking status is missing from 1SCC case, 2 BCC cases (1 early-onset).

[d] Body mass index calculated from subject height and weight, variables that were collected starting July 1997.

[e] The number of severe, painful sunburns is missing from 80 SCC controls, 51 SCC cases, 44 BCC controls (8 early-onset) and 50 BCC cases (31 early-onset).

[f]Hours of recreational sun exposure during warm months between 9am and 5pm is missing from 87 SCC controls and 49 SCC cases, 48 BCC controls (8 early-onset) and 36 BCC cases (17 early-onset). Tertile cut points based on the hours of sun exposure in controls.

[g]Hours of total sun exposure in warm months between 9am and 5pm is missing from 90 SCC controls and 54 SCC cases, 50 BCC controls (9 early-onset) and 42 BCC cases (21 early-onset). Tertile cut points based on the hours sun exposure in controls.

[h]Sun sensitivity to first solar exposure is missing from 2 SCC controls, 2 SCC cases; 6 BCC cases (2 early-onset).

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Table 2

Odds ratios (95% CI) of keratinocyte cancers in relation to oral contraceptive (OC) use, hormone replacement therapy (HRT) use, and reproductive factors

	SCC controls N = 746	**SCC cases N = 570**		**BCC controls N = 550**	**BCC cases N = 633**		**Early-onset BCC controls[a] N = 246**	**Early-onset BCC cases N = 362**	
	N (%)	**N (%)**	**OR (95% CI)[b]**	**N (%)**	**N (%)**	**OR (95% CI)**	**N (%)**	**N (%)**	**OR (95% CI)**
Oral contraception use[c]									
No	307 (43.2)	270 (48.6)	1.0 (ref)	236 (45.8)	200 (33.6)	1.0 (ref)	49 (21.5)	57 (16.6)	1.0 (ref)
Yes	404 (56.8)	286 (51.4)	1.4 (1.1–1.8)	279 (54.2)	396 (66.4)	1.4 (1.0–1.8)	179 (78.5)	287 (83.4)	1.4 (0.9–2.1)
Age at last OC use									
Non user	307 (45.0)	270 (49.3)	1.0 (ref)	236 (48.4)	200 (36.2)	1.0 (ref)	49 (24.1)	57 (18.8)	1.0 (ref)
< 29 yrs. old	173 (25.4)	100 (18.2)	1.3 (0.9–1.9)	120 (24.6)	168 (30.4)	1.3 (0.9–1.8)	97 (47.8)	144 (47.5)	1.3 (0.8–2.0)
>=29 yrs. old	202 (29.6)	178 (32.5)	1.4 (1.1–1.9)	132 (27.0)	185 (33.5)	1.4 (1.1–2.0)	57 (28.1)	102 (33.7)	1.5 (0.9–2.5)
Continuous			$p_{trend} < 0.018$			$p_{trend} < 0.019$			$p_{trend} < 0.091$
Duration of OC use									
Non user	307 (43.3)	270 (48.6)	1.0 (ref)	236 (46.0)	200 (33.6)	1.0 (ref)	49 (21.6)	57 (16.6)	1.0 (ref)
≤ 2 yrs.	60 (8.5)	35 (6.3)	1.0 (0.7–1.7)	41 (8.0)	64 (10.8)	1.6 (1.0–2.4)	22 (9.7)	44 (12.8)	1.7 (0.9–3.3)
3–6 yrs.	157 (22.1)	106 (19.1)	1.4 (1.0–2.0)	119 (23.2)	149 (25.0)	1.2 (0.8–1.6)	87 (38.3)	111 (32.4)	1.1 (0.7–1.8)
≥ 7 yrs.	185 (26.1)	144 (25.9)	1.5 (1.1–2.0)	117 (22.8)	182 (30.6)	1.5 (1.1–2.1)	69 (30.4)	131 (38.2)	1.6 (1.0–2.7)
Continuous			$p_{trend} < 0.030$			$p_{trend} < 0.052$			$p_{trend} < 0.047$
Years since last OC use									
Non user	307(52.6)	270(62.5)	1.0 (ref)	236 (46.2)	200(33.7)	1.0 (ref)	49 (21.7)	57 (16.6)	1.0 (ref)
< 25 yrs.	213(36.5)	77(17.8)	1.0(0.7–1.6)	211 (41.3)	308(51.9)	1.3 (1.0–1.8)	162 (71.7)	254 (74.1)	1.4 (0.9–2.1)
≥ 25 yrs.	64(11.0)	85(19.7)	2.1(1.5–3.2)	64 (12.5)	85(14.3)	1.5 (1.0–2.1)	15 (6.6)	32 (9.3)	1.7 (0.8–3.7)
Continuous			$p_{trend} < 0.020$			$p_{trend} < 0.150$			$p_{trend} < 0.895$
OC formulation									
Non user	307 (53.3)	270 (59.1)	1.0 (ref)	236 (55.0)	200 (39.9)	1.0 (ref)	49 (37.7)	57 (27.3)	1.0 (ref)
Estrogen dose ≤ 50mg	193 (38.6)	120 (30.8)	1.2 (0.9–1.6)	135 (36.4)	166 (45.4)	1.2 (0.8–1.6)	91 (65.0)	119 (67.6)	1.1 (0.7–1.8)
Estrogen dose > 50mg	211 (40.7)	166 (38.1)	1.5 (1.1–2.1)	144 (37.9)	230 (53.5)	1.5 (1.1–2.1)	88 (64.2)	168 (74.7)	1.7 (1.0–2.6)
Combination	266 (46.4)	186 (40.8)	1.5 (1.1–2.0)	193 (45.0)	296 (59.7)	1.5 (1.1–2.0)	136 (73.5)	230 (80.1)	1.5 (1.0–2.3)

	SCC controls N = 746	SCC cases N = 570		BCC controls N = 550	BCC cases N = 633		Early-onset BCC controls[a] N = 246	Early-onset BCC cases N = 362	
	N (%)	N (%)	OR (95% CI)[b]	N (%)	N (%)	OR (95% CI)	N (%)	N (%)	OR (95% CI)
Sequential	182 (37.2)	141 (34.3)	1.5 (1.1–2.1)	124 (34.4)	197 (49.6)	1.5 (1.0–2.1)	81 (62.3)	152 (72.7)	1.6 (1.0–2.6)
Hormone replacement therapy use[c, d]									
No	310 (58.7)	254 (49.7)	1.0 (ref)	207 (60.3)	194 (58.1)	1.0 (ref)			
Yes	218 (41.3)	257 (50.3)	1.4 (1.1–1.8)	136 (39.7)	140 (41.9)	1.0 (0.8–1.4)			
Exclusive estrogen	146 (32.0)	155 (37.9)	1.2 (0.9–1.6)	88 (29.8)	95 (32.9)	1.1 (0.8–1.6)			
Estrogen + progestin	45 (12.7)	73 (22.3)	2.1 (1.4–3.2)	29 (12.3)	32 (14.2)	1.0 (0.5–1.7)			
Age at first HRT use									
Non user	310 (58.7)	254 (49.9)	1.0 (ref)	207 (60.3)	194 (58.1)	1.0 (ref)			
< 48 yrs. old	108 (20.5)	111 (21.8)	1.3 (0.9–1.7)	61 (17.8)	60 (18.0)	0.9 (0.6–1.4)			
≥ 48yrs.old	110 (20.8)	144 (28.3)	1.5 (1.1–2.0)	75 (21.9)	80 (24.0)	1.1 (0.8–1.6)			
Continuous			$p_{trend} < 0.004$			$p_{trend} < 0.690$			
Duration of HRT use									
Never User	310 (58.9)	254 (50.3)	1.0 (ref)	207 (60.7)	194 (58.6)	1.0 (ref)			
> 0– ≤ 5 yrs.	83 (15.8)	71 (14.1)	1.1 (0.7–1.5)	55 (16.1)	57 (17.2)	0.9 (0.6–1.4)			
> 5 yrs.	133 (25.3)	180 (35.6)	1.6 (1.2–2.1)	79 (23.2)	80 (24.2)	1.1 (0.8–1.6)			
Continuous			$p_{trend} < 0.057$			$p_{trend} < 0.566$			
Years since last HRT use									
Non User	310 (60.5)	254 (50.7)	1.0 (ref)	207 (63.1)	194 (59.5)	1.0 (ref)			
Current User	163 (31.8)	190 (37.9)	1.4 (1.1–1.8)	89 (27.1)	103 (31.6)	1.2 (0.8–1.7)			
Former (≥1yr)	39 (7.6)	57 (11.4)	1.6 (1.0–2.5)	32 (9.8)	29 (8.9)	1.0 (0.6–1.7)			
Continuous			$p_{trend} < 0.771$			$p_{trend} < 0.696$			
Age at menarche[e]									
<13 yrs. old	178 (43.3)	120 (41.4)	1.0 (0.7–1.4)	104 (47.9)	112 (43.2)	0.8 (0.5–1.2)	78 (51.0)	103 (45.2)	0.8 (0.5–1.2)
13–15 yrs. old	206 (50.1)	155 (53.4)	1.0 (ref)	100 (46.1)	130 (50.2)	1.0 (ref)	68 (44.4)	112 (49.1)	1.0 (ref)
>15 yrs. old	27 (6.6)	15 (5.2)	0.9 (0.4–1.8)	13 (6.0)	17 (6.6)	1.2 (0.5–2.6)	7 (4.6)	13 (5.7)	1.2 (0.4–3.2)
Continuous			$p_{trend} < 0.346$			$p_{trend} < 0.128$			$p_{trend} < 0.382$

	SCC controls N = 746	SCC cases N = 570		BCC controls N = 550	BCC cases N = 633		Early-onset BCC controls[a] N = 246	Early-onset BCC cases N = 362	
	N (%)	N (%)	OR (95% CI)[b]	N (%)	N (%)	OR (95% CI)	N (%)	N (%)	OR (95% CI)
Menopause type[f]									
Non surgical or medication induced	329 (46.4)	329 (59.3)	1.0 (ref)	208 (40.5)	197 (33.2)	1.0 (ref)	35 (15.6)	48 (14.1)	1.0 (ref)
All surgical types	182 (25.7)	162 (29.2)	0.9 (0.7–1.1)	121 (23.6)	121 (20.4)	1.0 (0.8–1.4)	23 (10.3)	40 (11.8)	1.3 (0.7–2.5)
Bilateral oophorectomy	30 (4.2)	20 (3.6)	0.6 (0.4–1.2)	21 (4.1)	21 (3.5)	1.1 (0.6–2.1)	3 (1.3)	4 (1.2)	1.0 (0.2–4.6)
Unilateral oophorectomy	91 (12.8)	87 (15.7)	0.9 (0.7–1.3)	57 (11.1)	57 (9.6)	1.1 (0.7–1.7)	10 (4.5)	15 (4.4)	1.2 (0.5–2.9)
Hysterectomy	56 (7.9)	50 (9.0)	0.9 (0.6–1.3)	40 (7.8)	41 (6.9)	1.0 (0.6–1.6)	9 (4.0)	21 (6.2)	1.7 (0.7–4.1)
Age at natural menopause									
<40 yrs.old	14 (4.4)	11(3.4)	0.9 (0.4–2.0)	12 (6.0)	5 (2.6)	0.4 (0.1–1.2)	0 (0)	0 (0)	**
40–54 yrs. old	255 (79.4)	249 (77.6)	1.0 (ref)	159 (79.1)	166 (84.7)	1.0 (ref)	32 (91.4)	47(97.9)	1.0 (ref)
≥ 55 yrs. old	52 (16.2)	61 (19.0)	1.1 (0.7–1.6)	30 (14.9)	25 (12.8)	0.9 (0.5–1.6)	0 (0)	0 (0)	**
Continuous			$p_{trend} < 0.768$			$p_{trend} < 0.595$			**
Age at surgical menopause									
<40 yrs.old	16 (53.3)	10 (50.0)	0.8 (0.2–2.7)	11 (52.4)	14 (66.7)	1.9 (0.5–7.9)	0 (0)	0 (0)	**
40–54 yrs. old	13 (43.3)	10 (50.0)	1.0 (ref)	10 (47.6)	7 (33.3)	1.0 (ref)	3 (100.0)	4 (100.0)	1.0 (ref)
≥ 55 yrs. old			**			**	0 (0)	0 (0)	**
Continuous			$p_{trend} < 0.331$			$p_{trend} < 0.707$			**
Parity[g]									
0	71 (11.8)	53 (10.6)	1.0 (ref)	49 (12.1)	73 (14.9)	1.0 (ref)	34 (17.0)	50 (16.4)	1.0 (ref)
1–2	291 (48.3)	221 (44.1)	1.0 (0.6–1.5)	203 (50.0)	256 (52.2)	0.8 (0.6–1.3)	123 (61.5)	184 (60.3)	1.0 (0.6–1.7)
3–4	185 (30.7)	177 (35.3)	0.8 (0.5–1.3)	115 (28.3)	139 (28.4)	0.9 (0.6–1.5)	37 (18.5)	64 (21.0)	1.2 (0.6–2.1)
≥ 5	55 (9.1)	50 (10.0)	0.7 (0.4–1.2)	39 (9.6)	22 (4.5)	0.5 (0.3–1.0)	6 (3.0)	7 (2.3)	0.7 (0.2–2.4)
Continuous			$p_{trend} < 0.252$			$p_{trend} < 0.199$			$p_{trend} < 0.906$
Duration of ovulation[h]									
≤ 29 years	19 (11.0)	11 (7.3)	1.0 (ref)	10 (16.1)	6 (10.9)	1.0 (ref)	4 (14.3)	4 (10.8)	1.0 (ref)
> 29–35 years	49 (28.3)	34 (22.5)	1.3 (0.5–3.2)	19 (30.6)	16 (29.1)	1.1 (0.3–3.8)	11 (39.3)	12 (32.4)	1.1 (0.2–6.3)
> 35–39 years	59 (34.1)	63 (41.7)	1.8 (0.7–4.1)	21 (33.9)	26 (47.3)	2.2 (0.6–7.6)	13 (46.4)	18 (48.6)	2.0 (0.3–12.5)

	SCC controls N = 746	SCC cases N = 570		BCC controls N = 550	BCC cases N = 633		Early-onset BCC controls[a] N = 246	Early-onset BCC cases N = 362	
	N (%)	N (%)	OR (95% CI)[b]	N (%)	N (%)	OR (95% CI)	N (%)	N (%)	OR (95% CI)
> 39 years	46 (26.6)	43 (28.5)	1.5 (0.6–3.7)	12 (19.4)	7 (12.7)	1.5 (0.3–6.8)	0 (0.0)	3 (8.1)	**
Continuous			$p_{trend} < 0.270$			$p_{trend} < 0.581$			$p_{trend} < 0.103$

[a] Early-onset BCC defined as age ≤ 50 at time of diagnosis.

[b] Odds ratios and 95% confidence intervals adjusted for reference age and skin sensitivity to first solar exposure.

[c] Oral contraceptive use and hormone replacement therapy questions were administered beginning on the 5th of October, 1995.

[d] Hormone replacement therapies are restricted to those women who have begun menopause.

[e] Age of menarche was administered beginning on the 1st of July 2000.

[f] Menopause induced by medication, or non-surgical therapies were excluded from this analysis.

[g] Gravidity and parity questions were administered beginning on the 1st of July 1998.

[h] Endogenous estrogen exposure was calculated as the number of years between menarche and menopause in women who had reached menopause without surgery or medication therapy.

Table 3

Case-case odds ratios (95% CI) of basal cell carcinoma (BCC) in relation to oral contraceptive and hormone replacement therapy use by subgroups according to histology

	BCC cases		
	Non-aggressive histology N (%)	Aggressive histology N (%)	OR (95% CI)[a]
Oral contraceptive use			
Non user	449 (38.5)	5 (16.7)	1.0 (ref)
Any user	717 (61.5)	25 (83.3)	3.3 (1.3–8.8)
Hormone replacement therapy			
Non user	821 (69.9)	20 (66.7)	1.0 (ref)
Any user	354 (30.1)	10 (33.3)	1.2 (0.5–2.6)
Any estrogen	306 (27.2)	9 (31.0)	1.2 (0.5–2.7)
Exclusive estrogen	230 (21.9)	3 (13.0)	0.5 (0.2–1.9)
Estrogen + progestin	76 (8.5)	6 (23.1)	3.3 (1.3–8.5)

[a]Odds ratios and 95% confidence intervals adjusted for reference age and skin sensitivity to first solar exposure.