**Hormonal and reproductive factors and incidence of basal cell carcinoma and squamous cell carcinoma in a large, prospective cohort**

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**Key words:** keratinocyte cancer; basal cell carcinoma; cutaneous squamous cell carcinoma; menopausal hormone therapy; oral contraceptive; parity; menarche; menopause

**abbreviations:**

BCC – basal cell carcinoma

SCC – squamous cell carcinoma

KC – keratinocyte cancer

OC – oral contraceptive

MHT – menopausal hormone therapy

HR – hazard ratio

Dear Editor,

Previous research suggests that hormonal factors might influence the development of keratinocyte cancers (KCs), but the evidence is inconsistent.[1](#_ENREF_1), [2](#_ENREF_2) A potential mechanism for an association is photosensitization via estrogen.[3](#_ENREF_3) We examined the association between hormonal and reproductive factors and subsequent risk of first histologically confirmed primary BCC or SCC in a large cohort of women that was well-characterized with respect to important potential confounding factors, as well as clinical factors that may inform about possible detection bias.

White women from the QSkin Sun and Health study[4](#_ENREF_4) with no past history of melanoma, excisions for skin cancer or more than 5 self-reported ablations for ‘sunspots or skin cancers’ were eligible for study (n=11,152). The latter criterion was stipulated to minimize potential bias caused by including women with prior disease in the analyses, since KCs can be ablated without a histologically confirmed diagnosis. Information on hormonal and reproductive factors was self-reported at baseline (2011). KC outcomes were identified from administrative medical claims data (Medicare - Australia’s universal health insurance scheme) to June 30, 2014 and exact diagnoses of BCC and SCC established through linkage with pathology records.[5](#_ENREF_5) We used Cox proportional hazards models to estimate the hazard ratios (HR) associated with OCs and MHT, age at menarche, menopausal status, age at menopause and parity and first histologically confirmed BCC/SCC, while taking account of the effects of age, sun exposure, phenotypic and lifestyle characteristics.

Selected characteristics of the study cohort, overall and amongst post-menopausal women, are provided in Supplementary Table 1. During a median follow-up of 3 years, 336 women developed one or more BCCs (mean age 55.0 years) and 85 women one or more SCCs (mean age 55.6 years). We found no association between OC use (ever/never; duration of use), parity, age at menarche or menopause and incidence of BCC or SCC (Tables I, II). Among post-menopausal women, ever (vs. never) use of MHT at baseline was associated with an increased risk of BCC (adjusted HR 1.46; 95%CI 1.07-1.97), but there was no dose-response with duration of use (*P* trend 0.2; Table I). MHT use was not associated with SCC (0.79; 0.45-1.38). We investigated detection bias as a possible explanation for the positive association between MHT use and BCC through analyses stratified by self-reported history of skin checks by a doctor, and number of Medicare claims for doctor consultations, biopsies and cryotherapy treatments during follow-up; we observed no material difference in the effect estimates according to these factors. The association between MHT use and BCC did not differ materially across strata of sun exposure variables (data not shown).

Our findings in relation to both OC and MHT use and BCC accord with findings from two other prospective studies, the USRT[1](#_ENREF_1) and the Danish Diet, Cancer and Health cohort,[2](#_ENREF_2) although a significant trend with duration of MHT use was observed in the USRT cohort. A limitation of our study was the relatively short follow up, and the analyses for SCC were constrained by sample size.

In summary, we did not observe an association between OC use or reproductive factors and incidence of BCC or SCC but found a modest positive association between ever use of MHT and BCC only. While we found no conclusive evidence of detection bias or confounding to explain the latter finding, in view of the lack of a dose-response relationship, we counsel cautious interpretation until further longitudinal studies have explored these associations.

**REFERENCES**

1. Cahoon EK, Kitahara CM, Ntowe E, Bowen EM, Doody MM, Alexander BH et al. Female Estrogen-Related Factors and Incidence of Basal Cell Carcinoma in a Nationwide US Cohort. J Clin Oncol 2015;33:4058-65.

2. Birch-Johansen F, Jensen A, Olesen AB, Christensen J, Tjonneland A , Kjaer SK. Does hormone replacement therapy and use of oral contraceptives increase the risk of non-melanoma skin cancer? Cancer Causes Control 2012;23:379-88.

3. Robinson SN, Zens MS, Perry AE, Spencer SK, Duell EJ , Karagas MR. Photosensitizing agents and the risk of non-melanoma skin cancer: a population-based case-control study. J Invest Dermatol 2013;133:1950-5.

4. Olsen CM, Green AC, Neale RE, Webb PM, Cicero RA, Jackman LM et al. Cohort profile: the QSkin Sun and Health Study. Int J Epidemiol 2012;41:929-i.

5. Thompson BS, Olsen CM, Subramaniam P, Neale RE , Whiteman DC. Medicare claims data reliably identify treatments for basal cell carcinoma and squamous cell carcinoma: a prospective cohort study. Aust N Z J Public Health 2016;40:154-8.

**Table I.** Hormonal and reproductive factors and risk of BCC among 11,152 women in the QSkin study cohort.

Table continued

| **Variables** | **Number of women without BCC** (n=10,650)**N (%)a** | **Number of women with BCC** (n=336)**N (%)a** | **Adjustedb HR (95%CI)** | ***P* trenda** |
| --- | --- | --- | --- | --- |
| **Age at menarche**  |  |  |  |  |
|  ≤12 | 3947 (37.2) | 129 (38.7) | 1.00 (Ref) |  |
|  13 | 3184 (30.0) | 94 (28.2) | 0.84 (0.63-1.11) |  |
|  14 | 1939 (18.3) | 63 (18.9) | 0.96 (0.70-1.30) |  |
|  15+ | 1538 (14.5) | 47 (14.1) | 0.91 (0.65-1.29) | 0.7 |
| **Parity**  |  |  |  |  |
|  0 | 1347 (12.8) | 40 (12.0) | 1.00 (Ref) |  |
|  1-2 | 5219 (49.5) | 145 (43.7) | 0.93 (0.65-1.32) |  |
|  3+ | 3989 (37.8) | 147 (44.3) | 1.15 (0.80-1.64) | 0.4 |
| **Menopausal status at baseline**  |  |  |  |  |
|  Pre-menopausal | 4265 (40.2) | 122 (36.5) | 1.00 (Ref) |  |
|  Post-menopausal | 6358 (59.9) | 212 (63.5) | 0.90 (0.64-1.28) |  |
| **OC use (ever never)**  |  |  |  |  |
|  No | 1271 (12.0) | 41 (12.3) | 1.00 (Ref) |  |
|  Yes | 9336 (88.0) | 293 (87.7) | 1.06 (0.73-1.54) |  |
| **Duration of OC use (months)**  |  |  |  |  |
|  0-6 | 1271 (12.2) | 41 (12.6) | 1.00 (Ref) |  |
|  7-60 | 2486 (23.8) | 82 (25.2) | 1.11 (0.73-1.68) |  |
|  61-120 | 2401 (23.0) | 73 (22.5) | 1.02 (0.66-1.56) |  |
|  121-240 | 2841 (27.2) | 95 (29.2) | 1.12 (0.74-1.69) |  |
|  241+ | 1437 (13.8) | 34 (10.5) | 0.83 (0.51-1.37) | 0.9 |
| ***POST-MENOPAUSAL WOMEN ONLY:*** |  |  |  |  |
| **Age at menopause**  |  |  |  |  |
|  ≤46 | 1526 (26.4) | 46 (23.1) | 1.00 (Ref) |  |
|  47-50 | 2024 (35.0) | 69 (34.7) | 1.07 (0.72-1.57) |  |
|  51-52 | 894 (15.4) | 34 (17.1) | 1.27 (0.81-2.00) |  |
|  53+ | 1346 (23.3) | 50 (25.1) | 1.05 (0.69-1.62) | 0.9 |
| **MHT use (ever never)**  |  |  |  |  |
|  No | 4079 (65.4) | 114 (55.1) | 1.00 (Ref) |  |
|  Yes | 2162 (34.6) | 93 (44.9) | 1.46 (1.07-1.97) |  |
| **Duration of MHT use (months)**  |  |  |  |  |
|  0-6 | 4079 (66.2) | 114 (56.7) | 1.00 (Ref) |  |
|  7-26 | 548 (8.9) | 24 (11.9) | 1.52 (0.96-2.43) |  |
|  27-60 | 589 (9.6) | 24 (11.4) | 1.38 (0.87-2.21) |  |
|  61-120 | 513 (8.3) | 21 (10.5) | 1.25 (0.73-2.15) |  |
|  121+ | 436 (7.1) | 19 (9.5) | 1.58 (0.93-2.69) | 0.2 |
| ***MHT use by type of menopause*** |  |  |  |  |
| **Natural menopause - MHT use (ever/never)** |  |  |  |  |
|  No | 2926 (75.4) | 85 (67.5) | 1.00 (Ref) |  |
|  Yes | 955 (24.6) | 41 (32.5) | 1.52 (1.01-2.29) |  |
| **Hysterectomy – MHT use (ever/never)** |  |  |  |  |
|  No | 820 (49.7) | 21 (38.9) | 1.00 (Ref) |  |
|  Yes | 831 (50.3) | 33 (66.1) | 1.26 (0.68-2.33) |  |
|  |  |  |  |  |

**a** Numbers may not sum to total due to missing data; *P* trend is based on the continuous variable

b Age at menarche adjusted for age, skin phototype (tanning), freckling on face at age 21, moles at age 21, skin checks by a doctor in the past 3 years and smoking status.

Parity adjusted for age, skin color, freckling on face at age 21, moles at age 21 and smoking status.

Menopausal status at baseline adjusted for age, skin color, freckling on face at age 21, moles at age 21, skin checks by a doctor in the past 3 years and smoking status.

Age at menopause adjusted for age, skin phototype (tanning) and moles at age 21, skin checks by a doctor in the past 3 years and smoking status.

OC use adjusted for age, skin color, freckling on face at age 21, moles at age 21, number of sunburns as a child, skin checks by a doctor in the past 3 years and smoking status.

MHT use adjusted for age, eye color, moles at age 21, sunburns as a teenager/youth, skin checks by a doctor in the past 3 years and smoking status.

**Table II.** Hormonal and reproductive factors and risk of SCC among 11,152 women in the QSkin study cohort.

Table continued

| **Variables** | **Number of women without SCC** (n=10,901)**N (%)a** | **Number of women with SCC** (n=85)**N (%)a** | **Adjustedb HR (95%CI)** | ***P* trenda** |
| --- | --- | --- | --- | --- |
| **Age at menarche**  |  |  |  |  |
|  ≤12 | 4037 (37.2) | 39 (45.9) | 1.00 (Ref) |  |
|  13 | 3258 (30.0) | 20 (23.5) | 0.63 (0.37-1.10) |  |
|  14 | 1985 (18.3) | 17 (20.0) | 0.82 (0.46-1.47) |  |
|  15+ | 1576 (14.5) | 9 (10.6) | 0.53 (0.25-1.14) | 0.2 |
| **Parity**  |  |  |  |  |
|  0 | 1381 (12.8) | 6 (7.3) | 1.00 (Ref) |  |
|  1-2 | 5320 (49.2) | 44 (53.7) | 1.63 (0.69-3.85) |  |
|  3+ | 4104 (38.0) | 32 (39.0) | 1.50 (0.62-3.61) | 0.4 |
| **Menopausal status at baseline**  |  |  |  |  |
|  Pre-menopausal | 4371 (40.2) | 16 (18.8) | 1.00 (Ref) |  |
|  Post-menopausal | 6501 (59.8) | 69 (81.2) | 1.26 (0.58-2. 72) |  |
| **OC use (ever never)**  |  |  |  |  |
|  No | 1302 (12.0) | 10 (11.8) | 1.00 (Ref) |  |
|  Yes | 9550 (88.0) | 75 (88.2) | 1.78 (0.81-3.91) |  |
| **Duration of OC use (months)**  |  |  |  |  |
|  0-6 | 1302 (12.2) | 10 (11.9) | 1.00 (Ref) |  |
|  7-60 | 2545 (23.8) | 23 (27.4) | 1.89 (0.81-4.45) |  |
|  61-120 | 2454 (23.0) | 20 (23.8) | 1.89 (0.79-4.53) |  |
|  121-240 | 2913 (27.3) | 23 (27.4) | 1.75 (0.73-4.20) |  |
|  241+ | 1463 (13.7) | 8 (9.5) | 1.43 (0.51-4.00) | 0.8 |
| ***POST-MENOPAUSAL WOMEN ONLY:*** |  |  |  |  |
| **Age at menopause**  |  |  |  |  |
|  ≤46 | 1559 (26.3) | 13 (21.7) | 1.00 (Ref) |  |
|  47-50 | 2068 (34.9) | 25 (41.7) | 1.43 (0.73-2.83) |  |
|  51-52 | 921 (15.5) | 7 (11.7) | 0.84 (0.32-2.23) |  |
|  53+ | 1381 (23.3) | 15 (25.0) | 1.26 (0.59-2.69) | 0.4 |
| **MHT use (ever never)**  |  |  |  |  |
|  No | 4150 (65.1) | 43 (62.3) | 1.00 (Ref) |  |
|  Yes | 2229 (34.9) | 26 (37.7) | 0.79 (0.45-1.38) |  |
| **Duration of MHT use (months)**  |  |  |  |  |
|  0-6 | 4150 (65.9) | 43 (62.3) | 1.00 (Ref) |  |
|  7-26 | 562 (8.9) | 10 (14.5) | 1.18 (0.52-2.65) |  |
|  27-60 | 606 (9.6) | 6 (8.7) | 0.89 (0.38-2.13) |  |
|  61+ | 979 (15.6) | 10 (14.5) | 0.62 (0.27-1.42) | 0.6 |
| ***MHT use by type of menopause*** |  |  |  |  |
| **Natural menopause - MHT use (ever/never)** |  |  |  |  |
|  No | 2976 (75.1) | 35 (79.6) | 1.00 (Ref) |  |
|  Yes | 987 (24.9) | 9 (20.4) | 0.78 (0.43-1.40) |  |
| **Hysterectomy – MHT use (ever/never)** |  |  |  |  |
|  No | 834 (49.5) | 7 (36.8) | 1.00 (Ref) |  |
|  Yes | 852 (50.5) | 12 (62.3) | 1.02 (0.34-3.04) |  |
|  |  |  |  |  |

**a** Numbers may not sum to total due to missing data; *P* trend is based on the continuous variable

b Age at menarche adjusted for age, skin phototype (tanning), freckling on face at age 21, moles at age 21 and smoking status.

Parity adjusted for age, skin color, freckling on face at age 21, moles at age 21 and smoking status.

Menopausal status at baseline adjusted for age, skin color, freckling on face at age 21, moles at age 21 and smoking status.

Age at menopause adjusted for age, skin phototype (tanning) and moles at age 21 and smoking status.

OC use adjusted for age, skin color, freckling on face at age 21, moles at age 21, number of sunburns as a child and smoking status.

MHT use adjusted for age, eye color, moles at age 21, sunburns as a teenager/youth and smoking status.

**Supplementary Table I.** Distribution of selected characteristics of 11,152 women in the QSkin study cohort, and stratified by MHT use.

|  |  | **Post-menopausal Women** (n=6686)\* |  |
| --- | --- | --- | --- |
| **Variables** | **All women** (n=11,152) | **MHT use** (n=2296) | **No MHT use** (n=4267) | **Chi-Square*****P* value** |
| **N (%)a** | **N (%)a** | **N (%)a** |
| **Age at entry (Mean, SD)** | 53.7 (8.1) | 60.7 (5.8) | 57.6 (6.1) | <0.001b |
| **Age group** |  |  |  |  |
| 40-49 | 4137 (37.1) | 90 (3.9) | 422 (9.9) |  |
| 50-59 | 4180 (37.5) | 932 (40.6) | 2342 (54.9) |  |
| 60-69 | 2835 (25.4) | 1274 (55.5) | 1503 (35.2) | <0.001 |
| **Further Education** |  |  |  |  |
| No school certificate | 785 (7.4) | 246 (11.5) | 382 (9.5) |  |
| School certificate | 1792 (17.0) | 484 (22.7) | 826 (20.5) |  |
| Higher school certificate | 2369 (22.4) | 459 (21.5) | 948 (23.6) |  |
| Trade/certificate/diploma | 2749 (26.0) | 485 (22.7) | 996 (24.8) |  |
| University degree | 2873 (27.2) | 462 (21.6) | 871 (21.7) | 0.009 |
| **Skin color** |  |  |  |  |
| Fair | 6076 (54.8) | 1231 (54.2) | 2169 (51.2) |  |
| Medium | 4184 (37.8) | 874 (38.5) | 1727 (40.7) |  |
| Olive/dark | 819 (7.4) | 167 (7.4) | 344 (8.1) | 0. 1 |
| **Eye color** |  |  |  |  |
| Blue | 3836 (34.8) | 795 (35.1) | 1426 (33.9) |  |
| Green | 1744 (15.8) | 339 (15.0) | 659 (15.7) |  |
| Hazel | 2805 (25.5) | 609 (26.9) | 1055 (25.1) |  |
| Brown | 2627 (23.9) | 523 (23.1) | 1061 (25.3) | 0.1 |
| **Hair color** |  |  |  |  |
| Blonde  | 1738 (15.7) | 329 (14.4) | 623 (14.7) |  |
| Red/auburn | 457 (4.1) | 95 (4.2) | 163 (3.8) |  |
| Light brown | 4332 (39.1) | 874 (38.3) | 1659 (39.1) |  |
| Dark brown | 4185 (37.7) | 883 (38.7) | 1624 (38.3) | Table continued |
| Black | 382 (3.4) | 100 (4.4) | 172 (4.1) | 0.9 |
| **Skin type** |  |  |  |  |
| *Skin reaction to 30 minutes midday sun* |  |  |  |  |
| No burns | 1009 (9.1) | 283 (12.4) | 444 (10.5) |  |
| Burns a little | 4934 (44.5) | 1055 (46.3) | 2026 (47.8) |  |
| Burns moderately | 3710 (33.5) | 690 (30.3) | 1325 (31.2) |  |
| Burns badly | 1436 (13.0) | 252 (11.1) | 446 (10.5) | 0.1 |
| *Skin reaction to several weeks in sun* |  |  |  |  |
| No tan | 529 (4.8) | 103 (4.5) | 181 (4.3) |  |
| Tan lightly | 2145 (19.4) | 398 (17.5) | 772 (18.2) |  |
| Tan moderately | 5757 (51.9) | 1206 (53.0) | 2237 (52.8) |  |
| Tan deeply | 2657 (24.0) | 570 (25.0) | 1050 (24.8) | 0.9 |
| **Freckles at age 21 years (face)** |  |  |  |  |
| None | 4997 (45.0) | 1193 (52.2) | 2182 (51.4) |  |
| A few | 3750 (33.8) | 732 (32.0) | 1313 (30.9) |  |
| Some | 1774 (16.0) | 293 (12.8) | 559 (13.6) |  |
| Many | 583 (5.3) | 67 (2.9) | 175 (4.1) | 0.1 |
| **Moles at age 21 (whole body)** |  |  |  |  |
| None | 2588 (23.8) | 704 (31.5) | 1175 (28.3) |  |
| A few | 6241 (57.3) | 12257 (54.8) | 2342 (56.4) |  |
| Some | 1691 (15.5) | 278 (12.4) | 541 (13.0) |  |
| Many | 369 (3.4) | 30 (1.3) | 97 (2.3) | 0.004 |
| **Sunburns as a child** |  |  |  |  |
| Never | 2804 (27.6) | 620 (30.4) | 1191 (31.1) |  |
| 1-5 | 4665 (46.0) | 948 (46.6) | 1758 (45.9) |  |
| 6-10 | 1483 (14.6) | 261 (12.8) | 499 (13.0) |  |
| 11-20 | 784 (7.7) | 138 (6.8) | 249 (6.5) |  |
| 21-50 | 276 (2.7) | 41 (2.0) | 93 (2.4) |  |
| 50+ | 133 (1.3) | 28 (1.4) | 44 (1.2) | 0.8Table continued |
| **Lifetime sunbed use** |  |  |  |  |
| Never | 9219 (83.1) | 1990 (87.2) | 3701 (87.2) |  |
| 1-5 | 1168 (10.5) | 191 (8.4) | 348 (8.2) |  |
| 6-10 | 302 (2.7) | 40 (1.8) | 84 (2.0) |  |
| 11-20 | 206 (1.9) | 34 (1.5) | 61 (1.4) |  |
| 21-50 | 142 (1.3) | 17 (0.8) | 34 (0.8) |  |
| 50+ | 60 (0.5) | 8 (0.4) | 17 (0.4) | 0.98 |
| **Total lifetime sun exposure** |  |  |  |  |
| Q1 | 3634 (37.6) | 559 (29.4) | 1176 (32.8) |  |
| Q2 | 6579 (30.5) | 525 (27.6) | 1047 (29.2) |  |
| Q3 | 2095 (21.7) | 491 (25.8) | 898 (25.1) |  |
| Q4 | 990 (10.2) | 328 (17.2) | 462 (12.9) | <0.001 |
| **Skin checks by a Doctor (past 3 years)** |  |  |  |  |
| None | 4065 (37.5) | 791 (36.0) | 1696 (41.3) |  |
| 1 | 3797 (35.1) | 756 (34.4) | 1375 (33.5) |  |
| 2-5 | 2850 (26.3) | 618 (28.1) | 985 (24.0) |  |
| 6+ | 122 (1.1) | 31 ( 1.4) | 51 ( 1.2) | <0.001 |
| **Smoking status at baseline** |  |  |  |  |
| Non-Smoker | 6573 (59.1) | 1273 (55.5) | 2511 (59.0) |  |
| Ex-Smoker | 3525 (31.7) | 845 (36.9) | 1307 (30.7) |  |
| Current smoker | 1001 (9.2) | 175 (7.6) | 436 (10.3) | <0.001 |

**a** Numbers may not sum to total due to missing data \*MHT use missing for n=123 women

**b\***P value for significant difference between MHT user and non-users using the Ryan-Einot-Gabriel-Welsch multiple range test