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Endometriosis and the risk of skin cancer: a prospective cohort study

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Abstract

Purpose—Endometriosis has been associated with an increased risk of skin melanoma. However, associations with other skin cancer types and how they compare with melanoma are unclear. Our objective was to prospectively investigate the relationships between endometriosis and risk of non-melanoma and melanoma skin cancers.

Methods—E3N is a prospective cohort of 98,995 French women aged 40–65 years in 1990. Data on surgically-confirmed endometriosis and skin cancer diagnoses were collected every 2–3 years through self-report, with skin cancer cases confirmed through pathology reports. Hazard Ratios (HR) and 95% confidence intervals (CIs) were calculated using Cox regression models.

Results—Between 1990 and 2008, 535 melanoma, 247 squamous-cell carcinoma (SCC), and 1,712 basal-cell carcinoma (BCC) cases were ascertained. Endometriosis was associated with an increased overall risk of skin cancer (HR=1.28, 95% CI=1.05–1.55). When considering skin cancer type, endometriosis was associated with melanoma risk (HR=1.64, 95% CI=1.15–2.35), but

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not with SCC (HR=1.21, 95% CI=0.62–2.36) or BCC (HR=1.16, 95% CI=0.91–1.48) (non-melanoma skin cancers combined: HR=1.17, 95% CI=0.93–1.46), although no heterogeneity was detected across skin cancer types (Phomogeneity=0.13).

Conclusion—These data support an association between a personal history of endometriosis and the risk of skin cancer and suggest that the association is strongest for melanoma.

Keywords

cohort studies; cutaneous melanoma; endometriosis; skin cancer; epidemiology

Introduction

Endometriosis, a chronic hormone-dependent gynaecologic disease affecting approximately 10% of women (1–3), is defined by the presence of endometrial glands and stroma outside of the uterus (1). Women with endometriosis have been reported to be at higher risk for various chronic diseases, including several malignancies such as ovarian cancer, breast cancer, and melanoma skin cancer (4–6).

Skin cancers are among the most frequent neoplasms worldwide (7, 8) and consist of two major types, non-melanoma skin cancers (NMSCs), including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), and cutaneous melanoma, which is the least frequent type but has the highest metastatic potential. These cancer types share several risk factors, including fair skin complexion, sun exposure, and family history of skin cancer (9, 10). Previous research suggested an increased melanoma risk among women with a history of endometriosis (5). However, most studies collected data retrospectively or included small numbers of cases and thus could be prone to bias (11–16). Additionally, there has been limited research on the associations between endometriosis and NMSCs.

In the present analysis, we sought to prospectively examine the associations between endometriosis and the risk of the three main types of skin cancer in a large sample of women. To our knowledge, this is the largest and most complete analysis of endometriosis and skin cancer heterogeneity to date. This study extends our previous work on endometriosis in relation to melanoma (4) by i) additionally investigating NMSC risk and allowing comparisons between risks of NMSCs and melanoma, ii) investigating the association with melanoma with nine years of additional follow-up and accrual of melanoma cases, thereby allowing assessment of heterogeneity across melanoma subgroups, and iii) investigating potential mediators of these associations, which has never been addressed.

Materials and Methods

E3N (Etude Epidémiologique auprès de femmes de l’Education Nationale) is a prospective cohort study involving 98,995 French women born in 1925–1950 and insured by a national health plan primarily covering teachers. Women were enrolled in 1990 after having returned a self-administered questionnaire on their lifestyle and medical history along with informed consent. Follow-up questionnaires were sent every 2–3 years thereafter. The E3N cohort

received ethical approval from the French National Committee for Computerized Data and Individual Freedom (Comité National Informatique et Libertés, CNIL).

Endometriosis assessment

The 1992 questionnaire retrospectively asked participants whether they had ever been diagnosed with endometriosis. Additional information about age at diagnosis, type of treatment, and procedures that enabled diagnosis was also collected. Subsequent follow-up questionnaires prospectively collected this information. Because endometriosis occurs mostly in women of reproductive age, we considered both prevalent cases (i.e. diagnosed before the 1992 questionnaire, retrospectively reported) and incident cases (i.e. diagnosed after the 1992 questionnaire, prospectively reported). Compared with prevalent cases, incident cases were younger at inclusion and more likely to be parous and to have ever used hormonal treatments, while they had similar height, BMI at inclusion, body size at ages 20–25 years, age at menarche, and menstrual cycle length before age 17, as previously described (17).

Laparoscopic surgery is considered the clinical gold-standard for endometriosis diagnosis (1); therefore, we restricted our analyses to women who reported endometriosis as diagnosed or treated by laparoscopy or surgery. We performed a validation study by sending a specific questionnaire to 200 randomly selected women who self-reported surgical treatment or diagnosis of endometriosis. We asked women to confirm their date of diagnosis and to provide pathology or hospitalization reports, and the contact details of their physicians. A validation committee reviewed all documents; a mention of the presence of endometriosis was sought, and the physicians of the women were contacted in case of dubious reports, until a definitive conclusion was made. Among the 183 women who replied (92%), 75% (137 of 183) were confirmed, and the date of diagnosis was correctly reported in 82% of the validated cases (112 of 137).

Assessment of covariates

In 1990, we collected data on education, and pigmentary factors such as hair colour (red, blond, light brown, dark brown, black), skin complexion (very fair, fair, medium, dark, very dark), numbers of naevi and of freckles (none, few, many, very many), and skin sensitivity to sun exposure (none, moderate, high) which was defined as the participants' skin response after exposure to the sun for the first time in the summer: "you would get sunburnt even if you used sunscreen" (high sensitivity), "you would probably get sunburnt if you did not use sunscreen" (moderate sensitivity), or "you would not or only mildly get sunburnt" (low sensitivity)." Family history of skin cancer in first degree relatives was collected in 2000. To estimate average levels of sun exposure, we linked data on county of birth and county of residence at inclusion (as reported at baseline) to a database from the Joint Research Centre of the European Commission containing mean daily ultraviolet radiation dose in French counties (18). Self-reported height and weight were available in each questionnaire, and a body surface area (BSA) was calculated according to the formula: BSA (m^2)=0.007184 x weight (kg)$^{0.425}$ x height (cm)$^{0.725}$ (19). Age at menarche was recorded in the 1990 and 1992 questionnaires. Data on parity, hysterectomy, and use of oral contraceptives (OCs) and premenopausal progestogens were collected in 1992 and were then updated at each follow-

up cycle. Body size at ages 20–25 years was collected in 1990, while menstrual cycle length during midlife was recorded in 1992.

Statistical analyses

Hazard Ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards regression models with age as the time scale. Primary models were adjusted for age and stratified on birth cohort in 5-year categories. Secondary models were additionally adjusted for education, pigmentary factors, and family history of skin cancer. To test the potential influence of sun exposure on the associations between endometriosis and skin cancer, further adjustment was performed for residential sun exposure in county of birth and at inclusion in a separate model. We used competing-risk models for stratified analyses according to tumour site or histological type (20), and we performed interaction tests to compare risk estimates between strata. Since endometriosis and melanoma have both been associated with height and body size (21–23) and age at menarche (24, 25), we tested the effect of additional adjustment for these factors. Using interaction tests, we tested potential effect modification of our findings by hysterectomy, OC use, premenopausal progestogens use, oophorectomy, menopausal status, and type of menopause (natural or surgical) for each skin cancer outcome. Lastly, we conceptualized some covariates that may be influenced either by endometriosis biology or endometriosis diagnosis as potential mediators: hysterectomy, oophorectomy, oral contraceptives, and progestogen use. Using the difference method (28), under the assumptions of no interaction between mediator and endometriosis and no unmeasured confounding variables, we calculated the proportion of associations accounted by mediating factors. This was done by comparing models adjusted for and not adjusted for potential mediators using mediation tools described by Lin et. al.(29–31).

In a separate sub-analysis, we examined associations between family history of skin cancer, residential UV exposure at birth and at cohort inclusion, and endometriosis risk. For this, we used a nested case-control design and analyzed endometriosis as the outcome using logistic regression modelling, as previously described (17). The models were adjusted for birth cohort, number of freckles, number of nevi, skin sensitivity to sun exposure, skin colour, hair colour. age at menarche, menstrual cycle length during midlife, parity, height, body size at ages 20–25 years, and quartiles of residential sun exposure in county of birth and at inclusion (for family history of skin cancer).

For all analyses, missing values were imputed to the modal category if occurring in <5% of observations, otherwise a missing category was created. Statistical analyses were performed with the SAS© software (version 9.3, SAS Institute Inc, Cary, North Carolina).

Population for analysis

From the original population, we excluded women who reported a cancer history at inclusion (n=5,140), those lost to follow-up from inclusion (n=2,085), with multiple skin cancers of different types (n=17), primary amenorrhea (n=27), or those missing age at menarche (n=1,397). We further excluded women whose age at endometriosis diagnosis was missing (n=816), those who reported endometriosis diagnosis before menarche (n=5) or after menopause (n=836), and those who reported untreated endometriosis or treatment/

diagnosis through any other procedure than surgery or laparoscopy (n=1,244). Our final sample for analysis consisted of 87,428 women. Woman-years were computed from the date of return of the first questionnaire to the date of diagnosis of skin cancer or any other cancer, date of last questionnaire returned, or date of end of follow-up (December 7th, 2011), whichever occurred first. For the sub-analysis of family history of skin cancer and residential UV exposure in relation to endometriosis risk, the study population consisted of 75,918 women, as previously described (17).

Results

Women with endometriosis were slightly younger and more highly educated than those without endometriosis; they were also more likely to report a large number of naevi and higher skin sensitivity, and to have lower residential sun exposure levels at birth and at inclusion compared to women without the disease (Table 1). However, women with or without endometriosis did not differ in hair colour, skin colour, and number of freckles.

During 1,338,729 woman-years of follow-up, 87,248 women reported a total of 535 melanomas, 1,712 BCCs, and 247 SCCs (median follow-up: 17.9 years). Skin cancer diagnoses could be confirmed by medical report for 95%, 92%, and 94% of melanoma, BCC, and SCC cases, respectively. A history of endometriosis (n=2,968) was found to be associated with an increased risk of all skin cancers combined in crude (HR=1.39, 95% CI=1.15–1.68) and multivariable adjusted models (HR=1.28, 95% CI=1.05–1.55) (Table 2). However, the association appeared stronger for melanoma skin cancer (HR=1.64, 95% CI=1.15–2.35) than for NMSC (HR=1.17, 95% CI=0.93–1.46), although with no statistically significant heterogeneity ($P_{homogeneity}$=0.13).

Among NMSCs, the association with endometriosis was of similar magnitude for BCC (HR=1.16, 95% CI=0.91–1.48) and SCC (HR=1.21, 95% CI=0.62–2.36). However, there was heterogeneity in results between melanoma and BCC ($P_{homogeneity}$=0.05), but not between melanoma and SCC ($P_{homogeneity}$=0.39). In sensitivity analyses, results for melanoma and NMSCs were not substantially modified after additional adjustment for height, BSA, or age at menarche, or treatments for endometriosis: hysterectomy, oophorectomy, or use of OCs or of premenopausal progestogens (data not shown).

In sensitivity analyses, we observed differences in the effect of endometriosis on NMSC ($P_{interaction}$=0.02) and BCC risks ($P_{interaction}$=0.01) according to premenopausal progestogens use, with the associations being restricted to the never-users group (Supplementary Table 1). We did not find effect modification by parity, menopausal status, oophorectomy, OC history, or type of menopause.

We found no difference in risk across anatomic sites of skin cancer (head or neck, trunk, upper limbs, lower limbs) ($P_{homogeneity}$=0.99) (Supplementary Table 2). When considering melanoma only, endometriosis appeared more strongly associated with trunk melanoma (HR=2.14, 95% CI: 0.99–4.65) than with other sites, although we detected no heterogeneity across body sites ($P_{homogeneity}$=0.79); of note, statistical power was limited by numbers per site for women with endometriosis (n_{group}=2–14). Among melanoma subtypes, there was a

statistically significant association in the superficial spreading melanoma/nodular melanoma group only (HR: 1.73, 95% CI: 1.13–2.64), although there was no statistically significant difference across subtypes ($P_{homogeneity}$=0.60) and low power in some subgroups. For BCC, no heterogeneity was found across anatomic subtypes ($P_{homogeneity}$=0.63).

In analyses investigating potential mediating factors, we detected no evidence of mediation by hormonal treatment use (OCs: $P_{mediation}$: 0.78; premenopausal progestogen: $P_{mediation}$: 0.33), hysterectomy ($P_{mediation}$: 0.45), or oophorectomy ($P_{mediation}$: 0.10).

In additional sensitivity analyses, we found an association between family history of skin cancer and endometriosis risk (odds-ratio=1.49, 95% CI=1.16–1.92) (data not tabulated). We also found a decreased odds of endometriosis diagnosis in women with higher levels of residential sun exposure (≥ 2.69 kJ/m^2 compared to < 2.36) at birth (OR: 0.82, 95% CI: 0.74–0.91, p-value test for linear trend: 0.002) and at study baseline (OR: 0.81, 95% CI: 0.73–0.89, p-value test for linear trend: 0.002) (Supplementary Table 3).

Discussion

In this large prospective study, a personal history of endometriosis was associated with a higher skin cancer risk, which was primarily driven by the association with melanoma. For NMSCs, associations with endometriosis were restricted to BCC among never-users of premenopausal progestogens. We also found that women with a family history of skin cancer were at increased endometriosis risk.

Our findings confirm a positive association between endometriosis and melanoma that was reported in previous studies (4, 11, 12, 16, 32–34), including in E3N (4), in which we reported a 62% higher risk of melanoma among women with endometriosis with a 12-year follow-up. The present study expands upon this previous work with an additional nine years of follow-up. We were also able to investigate different anatomical sites and histological types of melanoma, which have been hypothesized to reflect distinct risk factors (35–37).

It is currently unclear whether the reported association between endometriosis and melanoma risk reflects common associated factors between the two diseases, such as shared environmental, genetic, or hormonal history, or if it reflects systemic changes to the hormonal or inflammatory milieu caused by endometriosis.

A common genetic basis for the two diseases has previously been suggested (4). Endometriosis risk has been associated with melanoma risk factors known to be of genetic origin: red hair (11, 13, 38, 39), freckling (27, 40), number of naevi (13, 14, 26, 27), skin sensitivity to sun exposure (26, 27, 40, 41), and eye colour (40, 42). This may suggest that endometriosis and melanoma share common genetic factors, possibly involving a pigmentation pathway. Also consistent with a common genetic aetiology is our observation of a higher endometriosis risk in women with family history of skin cancer, which corroborates the findings from a US prospective study (14).

In our analyses stratified by anatomic site of melanoma, endometriosis appeared to be most strongly associated with trunk tumours, although we had low power for this sub-analysis. If

these results are confirmed in future studies, this will be consistent with the "common genetic origin" hypothesis since melanomas on this location have been associated with naevus-associated gene polymorphisms (43, 44), *MC1R* (the red hair colour gene) status, and somatic *BRAF* mutations (45).

Shared environmental factors may also increase the risk of both diseases. The effect of naevi could indeed also reflect an effect of sun exposure, since number of naevi is associated with higher sun exposure levels (46). While a strong effect of sun exposure is recognized for melanoma (47), this factor has been little investigated in relation to endometriosis (40). In our study, high levels of residential UV exposure at birth and at study baseline were inversely associated with endometriosis diagnosis, consistent with a previous Italian study that suggested inverse associations between days of sun exposure per year, use of tanning creams, and endometriosis diagnosis (40). However, in our analysis, residential sun exposure did not substantially modify effect estimates after model adjustment (Table 2, multivariable model b). Other potentially shared environmental exposures include polychlorinated biphenyls and organochlorine compounds, which have recently been associated both with melanoma (48) and endometriosis (49, 50). Further studies of common environmental risk factors between endometriosis and melanoma will help shed light on their common etiologic background. Our mediation analysis did not support the hypothesis that the association between endometriosis and skin cancer could be attributed to potential treatments for endometriosis including surgery, oral contraceptives, or progestogens.

It has also been hypothesized that endometriosis and melanoma may share a common hormonal origin; however, although both diseases have been associated with hormonal factors (2, 24), a common hormonal pathway remains to be clarified. Alternatively, endometriosis may increase skin cancer risk by altering the immune response or inflammatory milieu of women with the disease (51–55).

Whether taken together or analyzed separately, we found no association between endometriosis and NMSC risk in our cohort. However, this association was not statistically significantly different from that with melanoma risk, which was consistent across analyses. Thus, we may have lacked statistical power to detect an association, especially for SCC (n=247). To our knowledge, only three previous studies investigated the association between endometriosis and NMSC risk. An early US case-control study reported a non-statistically significant positive association (OR:1.46, 95% CI=0.34–6.31, n=84 cases) (12). Additionally, two Swedish historical cohort studies reported standardized incidence ratios of 0.89 (95% CI=0.4–1.8, based on 7 observed NMSC cases) (15) and 1.05 (95% CI=0.82–1.31, based on 75 observed NMSC cases) (34) for NMSC in women with a hospital discharge of endometriosis. However, no individual assessments were available for BCC and SCC. If confirmed in future research, differences in the association between endometriosis and skin cancer risk across cancer types (non-melanoma and melanoma) may be due to differences in disease aetiology. Indeed, differences among skin cancer types have been reported for age of onset and body site distribution, and for the associations with patterns of sun exposure, nevi, and familial risk (56, 57). More research should contribute to unravel the potentially differential associations between endometriosis and various skin cancer types.

In our study, associations between endometriosis and risks of NMSCs and BCC were strongest among never users of premenopausal progestogens. The mechanisms underlying these differential associations are not clear. Progestogens are largely used in France (58) and are prescribed as treatment for endometriosis symptoms; therefore, a stronger association in the ever-user group would be expected. However, the relationships were strongest among women who had not used progestogens. This result may indicate that the severity or stage of endometriosis may modify risk. Unfortunately, we were not able to check this hypothesis as data in our cohort did not include stage or type of endometriosis; this should be investigated in future studies to better understand these associations. Nevertheless, since there was no differential association according to other treatments for endometriosis that may also represent markers of disease severity and modify risk (i.e. hysterectomy, oophorectomy, OC use), we cannot rule out the possibility of chance findings given the number of tests that were performed.

Some limitations should be considered in the interpretation of our findings. In our study, endometriosis was based on self-report, which may have induced misclassification; however, restricting the analysis to endometriosis cases reported to have been treated or diagnosed by surgery or laparoscopy is likely to have substantially decreased this bias, as supported by the high confirmation rate of endometriosis in our validation study. While we cannot rule out some non-differential misclassification of endometriosis diagnoses, this would most likely result in attenuation of our effect estimates towards the null. In addition, we did not collect data on endometriosis staging, type, and severity of endometriosis, which may represent important disease heterogeneity.

Despite these limitations, our study has several strengths, including the large sample size, the prospective design with collection of endometriosis data prior to skin cancer diagnosis, and the long duration of follow-up (21 years) of the E3N cohort. Almost all skin cancer cases were ascertained through pathology reports, which enabled us to perform stratified analyses according to anatomical site and histological subtype of the tumours. However, we had limited power among some melanoma histological types and tumour locations to detect statistically significant associations (statistical power ranged from 0.36 to 0.65). Moreover, findings were adjusted for several main established skin cancer risk factors (i.e. pigmentary characteristics, residential sun exposure, education), although behavioural sun exposure was not available. However, although the role of behavioural sun exposure in skin cancer risk has been well established in ecologic studies (47), analytical epidemiologic studies typically fail to show robust associations; therefore, we speculate that adjustment for this factor would have had little effect on our findings. In addition, our results were not modified after adjustment for residential sun exposure at birth and at inclusion.

In conclusion, in the largest and most comprehensive analysis of endometriosis and skin cancer to date, our data support an association between a personal history of endometriosis and skin cancer risk and suggest that the association is most robust for cutaneous melanoma. Because it is still unclear whether common associated factors between the two diseases or systemic changes caused by endometriosis explain the observed associations between endometriosis and melanoma, further research is needed to elucidate common pathways between these two diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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ABBREVIATIONS

BCC	Basal Cell Carcinoma
BSA	Body Surface Area
CI	Confidence Interval
GWAS	Genome-Wide Association Study
HR	Hazard Ratio
NMSC	Non-Melanoma Skin Cancer
OC	Oral Contraceptive
OR	Odds-Ratio
SCC	Squamous Cell Carcinoma

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Table 1

Characteristics of study participants, E3N cohort (n=87,428)

	Women with a history of endometriosis (n=2,967)		Women with no history of endometriosis (n=84,461)	
	n	%	n	%
Birth cohort				
<1930	92	3.1	6535	7.7
1930–1934	204	6.9	10,846	12.8
1935–1939	459	15.5	15,899	18.8
1940–1944	787	26.5	20,314	24.1
≥1945	1425	48.0	30,867	36.6
Education (years)				
<12	314	10.6	11,311	13.4
12–14	1578	53.2	43,943	52.0
≥15	1075	36.2	29,207	34.6
Hair colour				
Red	57	1.9	1399	1.7
Blond	326	11.0	8435	10.0
Light brown	1761	59.3	50,885	60.2
Dark brown	661	22.3	19,621	23.2
Black	162	5.5	4121	4.9
Skin colour				
Very fair	44	1.5	983	1.2
Fair	1787	60.2	48,998	58.0
Medium	1089	36.7	33,131	39.2
Brown/Dark	47	1.6	1349	1.6
Number of naevi				
Very many	437	14.7	8766	10.4
Many	1392	46.9	36,349	43.0
Few	943	31.8	30,845	36.5
None	195	6.6	8501	10.1
Number of freckles				
Very many	159	5.4	4298	5.1
Many	953	32.1	24,232	28.7
Few	720	24.3	20,389	24.1
None	1135	38.2	35,542	42.1
Skin sensitivity to sun exposure				
Highly sensitive	956	32.2	23,712	28.1
Moderately sensitive	1428	48.1	41,235	48.8
Not sensitive	583	19.7	19,514	23.1
Family history of skin cancer				
No	2604	87.8	71,448	84.6

	Women with a history of endometriosis (n=2,967)		Women with no history of endometriosis (n=84,461)	
	n	%	n	%
Yes	74	2.5	1333	1.6
Missing	289	9.7	11,680	13.8
Residential sun exposure in county of birth (kJ/m^2)				
<2.36	690	23.3	18,190	21.5
2.36–2.49	822	27.7	22,519	26.7
2.50–2.69	728	24.5	18,830	22.3
≥2.70	539	18.2	17,892	21.2
Missing	188	6.3	7030	8.3
Residential sun exposure in county of residence at inclusion (kJ/m^2)				
<2.36	683	23.0	18,244	21.6
2.36–2.49	1009	34.0	26,263	31.1
2.50–2.69	688	23.2	18,492	21.9
≥2.70	587	19.8	21,462	25.4

E3N: Etude Epidémiologique auprès de femmes de l’Education Nationale

Table 2

Hazard Ratios (HRs) and 95% confidence intervals (CIs) for risk of skin cancers in relation to personal history of endometriosis, E3N cohort 1990–2008 (n=87,428)

Personal history of endometriosis	n	Cases	Age-adjusted HR (95% CI)	Multivariable HR[a] (95% CI)	Multivariable HR[b] (95% CI)
All skin cancers (n=2,494)					
No	84,461	2385	1.00	1.00	1.00
Yes	2967	109	1.39 (1.15–1.68)	1.28 (1.06–1.56)	1.28 (1.05–1.55)
Melanoma (n=535)					
No	84,461	503	1.00	1.00	1.00
Yes	2967	32	1.85 (1.30–2.65)	1.66 (1.16–2.37)	1.64 (1.15–2.35)
Non-melanoma skin cancers (n=1,959)					
No	84,461	1882	1.00	1.00	1.00
Yes	2967	77	1.26 (1.00–1.58)	1.17 (0.93–1.47)	1.17 (0.93–1.46)
Basal Cell Carcinoma (n=1,712)					
No	84,461	1644	1.00	1.00	1.00
Yes	2967	68	1.25 (0.98–1.60)	1.17 (0.92–1.49)	1.16 (0.91–1.48)
Squamous Cell Carcinoma (n=247)					
No	84,461	238	1.00	1.00	1.00
Yes	2967	9	1.28 (0.66–2.49)	1.21 (0.62–2.36)	1.21 (0.62–2.36)

CI: Confidence Interval; E3N: Etude Epidémiologique auprès de femmes de l'Education Nationale; HR: Hazard Ratio

[a]Stratified on birth cohort and adjusted for age, education, hair colour, skin complexion, number of naevi, freckling, skin sensitivity to sun exposure, and family history of skin cancer

[b]Additionally adjusted for quartiles of residential sun exposure in county of birth and at baseline