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Endometriosis risk in relation to naevi, freckles and skin sensitivity to sun exposure: the French E3N cohort

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Background Endometriosis is an important women's health issue, however its aetiology remains unknown. An association between endometriosis and cutaneous melanoma was described, possibly explained through common genetic features. To further investigate this association, we assessed the link between phenotypic traits predisposing to melanoma and the risk of endometriosis.

Methods Using a case–control design, we analysed data from 97 215 women of the Etude Epidémiologique auprès de femmes de l'Education Nationale study, a cohort of 98 995 French women insured by a national health scheme mostly covering teachers, and aged 40–65 years at inclusion in 1990. Risk estimates were computed using unconditional logistic regression models.

Results After adjustment for potential confounding factors, there was a positive dose–effect relationship between risk of endometriosis (reported as surgically ascertained, $n = 4241$) and skin sensitivity to sun exposure [moderate: odds ratio (OR) 1.09, 95% confidence interval (CI) 0.99–1.19; high: OR 1.22; 95% CI 1.10–1.36; compared with none; $P_{trend} < 0.0001$], number of naevi (few: OR 1.19, 95% CI 1.05–1.35; many: OR 1.37, 95% CI 1.21–1.55; very many: OR 1.59, 95% CI 1.37–1.83; compared with none; $P_{trend} < 0.0001$) and number of freckles (few: OR 1.08, 95% CI 1.00–1.17; very many/many: OR 1.11, 95% CI 1.03–1.20; compared with none; $P_{trend} = 0.005$).

Conclusion This study is, to our knowledge, the first to report a positive dose–effect relationship between the risk of endometriosis and skin sensitivity to sun exposure, and number of naevi and freckles. These data suggest that endometriosis and melanoma may share some genetic features.

Keywords Case–control studies, endometriosis, genetics, hormones, melanoma, naevus, women's health

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Introduction

Endometriosis is a common condition with an estimated prevalence of 6–10% in women of childbearing age;[1,2] hence, it has been estimated to have considerable impacts in terms of public health and costs.[3] Conditions related to endometriosis include chronic pelvic pain,[1,2] infertility[4] and possibly severe diseases such as ovarian cancer.[5] Its aetiology is unknown although a number of theories involving genetic, immunological and environmental factors have been proposed.[2,6] In view of its frequency and health burden, a better understanding of the disease is requested.

We[7] and others[5,8–13] have previously reported an association between endometriosis and cutaneous melanoma. This finding is not yet understood, although likely explanations rely on shared hormonal or genetic features. Endometriosis has been associated with mutations occurring in some tumour suppressor gene loci[14–16] that have also been shown to be involved in melanoma aetiology,[17,18] which supports the research of common genetic features between these diseases. Phenotypic traits (i.e. hair colour, skin complexion, number of naevi and freckles and tanning ability) are determined mostly genetically and have been strongly associated with melanoma risk;[19–21] thus, an association between these traits and endometriosis risk could suggest the existence of common genetic characteristics between endometriosis and melanoma. Three studies suggested a relationship between endometriosis and red hair,[12,22,23] but the analyses did not take into account the effect of other characteristics associated with the red hair phenotype, such as freckling and skin sensitivity to the sun. Moreover, to date, no previous research has investigated the association between endometriosis and other phenotypic features. To further explore the association between endometriosis and melanoma, and to investigate the hypothesis of common genetic features between these diseases, we investigated the potential relationship between phenotypic factors and endometriosis in the Etude Epidémiologique auprès de femmes de l'Education Nationale (E3N) cohort.

Methods

Study population and data collection

E3N is a prospective cohort of 98 995 French women, aged 40–65 years at inclusion, and insured by a national health plan mostly covering teachers.[24] Subjects were enrolled in 1989–1991, after having returned an informed consent along with a baseline questionnaire on their lifestyle and medical history. Follow-up questionnaires were sent every 2 years thereafter. Each questionnaire asked participants whether endometriosis had been diagnosed, requesting information about age at diagnosis, type of treatment, and procedures that enabled diagnosis. The baseline questionnaire asked subjects to self-report their natural hair colour (red, blond, chestnut, brown or black), skin complexion (very fair, fair, medium, dark or very dark), number of naevi (very many, many, few or none) and skin sensitivity to sun exposure (high, moderate and none), which was defined as the skin's response if exposed to the sun for the first time in summer. Body mass index, menopausal age and histories of hysterectomy and cancer were available at inclusion and updated at each follow-up; data on hormonal treatments use were first recorded in the second questionnaire and subsequently updated. Women were considered postmenopausal if they reported 12 consecutive months of amenorrhea, bilateral oophorectomy, hormone replacement therapy (HRT) use or if they self-reported to be menopausal. Age at menarche, menstrual cycle length during mid-life (ages 25–40 years), parity and infertility treatment use were collected in the first two questionnaires. Body silhouettes at puberty, ages 20–25 years and ages 35–40 years were collected at baseline and were estimated using figure drawings ranking from 1 to 8, corresponding to increasing body size (from the leanest to the largest).[25,26]

Case definition and ascertainment

Endometriosis more generally occurs in women of reproductive age,[2] so to avoid the selection of late-occurring cases, we considered both prevalent cases (i.e. diagnosed before inclusion, reported retrospectively) ($n = 2569$) and incident cases (i.e. diagnosed after inclusion, reported prospectively) ($n = 1672$).

Since laparoscopic surgery is currently the standard procedure to establish a definitive diagnosis for endometriosis,[2] we restricted our analyses to cases reported as treated or diagnosed by laparoscopy/surgery. We carried out a validation study to ascertain self-reported endometriosis cases. A specific questionnaire was sent to 200 randomly selected women who reported endometriosis that had been surgically treated or diagnosed. Women were asked to confirm occurrence and date of diagnosis of endometriosis and to provide pathology or hospitalization reports, and the contact details of their physicians. A validation committee reviewed all documents. Among the 183 women who replied (92%), 75% (137 of 183) of the endometriosis cases were ascertained and the date of diagnosis was correctly reported in 82% of the validated cases (112 of 137). The self-reported diagnosis was incorrect in 17% of cases (31 of 183), and a clear conclusion could not be drawn in 8% of cases (15 of 183).

Population for analysis

Since pelvic endometriosis is rare in primary amenorrhea and before menarche, we excluded women who reported to have never menstruated ($n = 28$) and those who reported diagnosis before menarche ($n = 7$).

Data were not restricted to pre-menopausal women since several reports showed that endometriosis could occur after menopause, both in users and non-users of HRT.[27] In our cohort, 15% of cases were post-menopausal, and 84% of these had used HRT. Women who reported endometriosis but no treatment/diagnosis by a physician, and women who reported endometriosis that had been treated/diagnosed with any other procedure than surgery or laparoscopy were excluded from the analyses ($n = 1747$).

Statistical analyses

Statistical analyses were performed with SAS version 9.1. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using unconditional logistic regression models. The effect of phenotypic traits on endometriosis risk was first assessed in models adjusted for height (<160, 160–164 or ⩾165 cm), body mass index (<20, 20–24 or ⩾25 kg/m^2), age at menarche (<12, 12–13 or ⩾ 14 years), menstrual cycle length (irregular, ⩽24, 25–31 or ⩾32 days) and menopausal age (pre-menopausal, <48, 48–51 or ⩾52 years). Additional adjustment was performed for all phenotypic factors. Tests for linear trend were performed in models where each phenotypic trait was entered as an ordinal variable. Potential interactions between covariates were tested using likelihood ratio tests. We also performed homogeneity tests to compare risk estimates over strata.[28] Missing data in height or body mass index were imputed to the values provided in the closest questionnaire. For all other adjustment factors, missing values occurred in <5% of subjects and were imputed to the modal category.

Participants reported menopausal age and status with high levels of agreement (0.64 and 0.85, respectively),[29] and anthropometric measurements were valid in the cohort with high levels of correlation (0.80 and over).[26] Subjects were asked to self-report their age at menarche in 1990 and 1992. Among participants for whom data were available in both questionnaires ($n = 79\,282$), the correlation coefficient between responses was 0.92 ($P < 0.0001$), and the Kappa coefficient was 0.68 (P for symmetry <0.0001), which represents substantial agreement between the two measures.[30]

We investigated a potential effect modification by infertility status, using infertility treatment use as a proxy in stratified analyses. Indeed, some authors suggested a differential relationship between red hair and endometriosis risk according to infertility status.[22] Moreover, some difference in the proportion of asymptomatic cases may exist between fertile and infertile women since we only included endometriosis cases that were reported as surgically investigated/treated, and since endometriosis is a cause of infertility.

Results

Characteristics of the study population

A total of 4241 endometriosis cases were reported among the 97 215 women (Table 1). Women with endometriosis were younger and more likely to be tall, to have an early menarche, shorter menstrual cycles, to be pre-menopausal, and to have leaner silhouettes at puberty and at ages 20–25 years than women without endometriosis. There was no evidence of a difference according to body mass index or body silhouette at ages 35–40 years.

In our population, the proportion of women diagnosed with endometriosis was small before age 20 years, then gradually increased to peak by age 45–49 years and steeply decreased after age 50 years (Figure 1). Reported dates of diagnosis ranged between 1942 and 2003, with a peak between 1990 and 1994 (Figure 2).

Phenotypic factors and endometriosis risk

In fully adjusted models, we observed dose–effect relationships between endometriosis risk and skin sensitivity to sun exposure (moderately sensitive: OR = 1.09, 95% CI = 0.99–1.19; highly sensitive: OR = 1.22, 95% CI = 1.10–1.36; compared with not sensitive; $P_{trend} < 0.0001$), number of naevi (few: OR = 1.19, 95% CI = 1.05–1.35; many: OR = 1.37, 95% CI = 1.21–1.55; very many: OR = 1.59, 95% CI = 1.37–1.83; compared with none; $P_{trend} < 0.0001$) and number of freckles (few: OR = 1.08, 95% CI = 1.00–1.17; very many/many: OR = 1.11, 95% CI = 1.03–1.20; compared with none; $P_{trend} = 0.0049$) (Table 2). Risk estimates remained stable in all adjustment models.

In models adjusted for hormonal factors, fair skin complexion was positively associated with endometriosis compared with medium complexion (OR = 1.10, 95% CI = 1.03–1.17, $P_{trend} = 0.0111$); however, after additional adjustment for the other phenotypic traits, skin colour was no longer associated with endometriosis. Hair colour was not associated with endometriosis risk in our study.

Further adjustment for parity (nulliparous, 1–2 or 3 or more children), infertility drugs use, oral progestagens, oral contraceptives (ever or never), or body silhouette at different ages (drawings 1, 2, 3, 4, 5 or more, or missing) did not substantially modify the findings. Our conclusions remained unchanged when restricting analyses to women with no history of hysterectomy, with no history of cancer (other than basal cell carcinoma) or pre-menopausal women, except for number of freckles, for which there was no more trend in non-hysterectomized and in pre-menopausal women (data not shown).

Stratified analysis

When stratifying analyses according to infertility treatment use, estimates were slightly higher in ever-users regarding skin sensitivity to sun exposure

Table 1 Characteristics of study participants, E3N cohort ($n = 97\,215$)

	History of endometriosis		
	Yes *n* (%) 4241 (100)	No *n* (%) 92 974 (100)	***P*-value[a]**
Year of birth			
1925–1930	244 (5.8)	9695 (10.4)	<0.0001
1931–1935	430 (10.1)	12 928 (13.9)	
1936–1940	808 (19.0)	18 902 (20.3)	
1941–1945	1224 (28.9)	22 739 (24.5)	
1946–1950	1535 (36.2)	28 710 (30.9)	
Body mass index at inclusion (kg/m^2)			
<20	765 (18.1)	16 913 (18.2)	0.4323
20–24	2750 (64.8)	59 484 (64.0)	
⩾25	726 (17.1)	16 577 (17.8)	
Height at inclusion (cm)			
<160	1230 (29.0)	31 301 (33.7)	<0.0001
160–164	1495 (35.2)	32 197 (34.6)	
⩾165	1516 (35.8)	29 476 (31.7)	
Age at menarche (years)			
<12	995 (23.5)	18 875 (20.3)	<0.0001
12–13	2813 (66.3)	63 713 (68.5)	
⩾14	433 (10.2)	10 386 (11.2)	
Menstrual cycle length during mid-life (ages 25–40 years)			
Irregular	254 (6.0)	5255 (5.7)	0.0451
⩽24 days	336 (7.9)	6456 (6.9)	
25–31 days	3382 (79.8)	75 604 (81.3)	
⩾32 days	269 (6.3)	5659 (6.1)	
Age at menopause (years)			
Pre-menopause	214 (5.1)	9019 (9.7)	<0.0001
<48	1233 (29.1)	15 554 (16.7)	
48–52	1834 (43.2)	40 545 (43.6)	
⩾52	960 (22.6)	27 846 (30.0)	
Body silhouette at puberty			
Drawing 1	991 (23.4)	19 715 (21.2)	0.0068
Drawing 2	1511 (35.6)	33 084 (35.6)	
Drawing 3	937 (22.1)	21 261 (22.9)	
Drawing 4	594 (14.0)	13 920 (15.0)	
Drawings 5 or more	208 (4.9)	4994 (5.3)	
Body silhouette at ages 20–25 years			
Drawing 1	477 (11.3)	9225 (9.9)	0.0005
Drawing 2	1906 (44.9)	40 756 (43.8)	
Drawing 3	1357 (32.0)	30 184 (32.5)	
Drawing 4	391 (9.2)	9958 (10.7)	
Drawings 5 or more	110 (2.6)	2851 (3.1)	
Body silhouette at ages 35–40 years			
Drawing 1	149 (3.5)	3428 (3.7)	0.1952
Drawing 2	1203 (28.4)	25 112 (27)	
Drawing 3	1889 (44.5)	41 265 (44.4)	
Drawing 4	740 (17.5)	17 112 (18.4)	
Drawings 5 or more	260 (6.1)	6057 (6.5)	

[a]Chi-square tests were performed to compare women with a history of endometriosis with women with no such history.

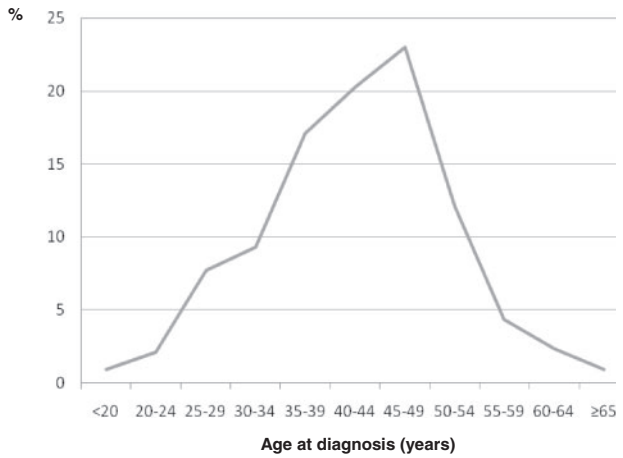

Figure 1 Distribution of age at diagnosis of endometriosis, E3N cohort ($n = 3871$). Values on age at diagnosis were missing in 370 subjects

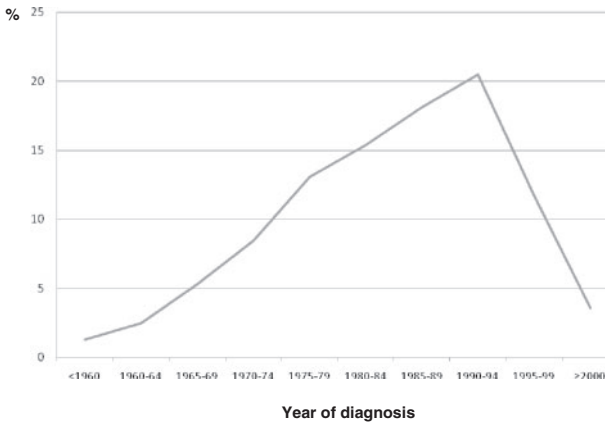

Figure 2 Distribution of year of diagnosis of endometriosis, E3N cohort ($n = 3871$). Values on age at diagnosis were missing in 370 subjects

(Table 3). There was no more trend for number of naevi in ever users. Interestingly, endometriosis risk increased with darkening of skin complexion in ever-users ($P_{trend} = 0.0039$), but not in never-users. There was evidence for heterogeneity in estimates for high and moderate skin sensitivity ($P = 0.0422$ and $P < 0.0001$), very fair and fair skin complexion ($P = 0.0023$ and $P < 0.0001$) and brown hair ($P = 0.0082$), but this did not modify our conclusions.

Sensitivity analyses

Calendar timing of diagnosis

We first repeated our analyses in prevalent and incident cases separately (Table 4). Estimates were slightly higher with the prevalent cases analysis, whereas they were slightly lower with the incident cases, in which there was less evidence of a trend for skin sensitivity to sun exposure and number of freckles. Findings were not substantially modified regarding other factors. Heterogeneity in estimates was detected for very many naevi, fair skin complexion and red hair colour according to prevalent/incident cases ($P = 0.0114$, $P < 0.0001$ and $P = 0.0252$), although this did not change our global conclusions.

Birth cohort

We then stratified our analyses according to birth cohort to test for the homogeneity of estimates according to year of birth (Table 5). Results were quite similar over the strata. There was evidence for heterogeneity for brown hair ($P = 0.0436$), which did not modify our findings.

Definition of cases

To assess a potential misclassification bias, we repeated analyses using several definitions of cases. First, when cases that were not reported as surgically confirmed were considered as non-cases instead of being excluded, our results were identical. Then, when we considered as cases all endometriosis cases reported to have been treated (surgical treatment, hormonal treatment, other treatment) or diagnosed by any procedure (laparoscopy, biopsy, hysterography, hysteroscopy or ultrasonography), our results were unchanged. Finally, when we considered all declared endometriosis as cases (whether they were reported to have been treated/diagnosed or not), estimates were slightly lower but our conclusions remained unmodified.

Discussion

The present study suggests positive dose–effect relationships between endometriosis risk and skin sensitivity to sun exposure, number of naevi and number of freckles. For the latter, results were less robust than for other traits, suggesting a potential spurious association.

Previous studies reported on age at endometriosis diagnosis in women of reproductive age. Houston described a minimal incidence in adolescence with a steep increase with age reaching its peak around 40–44 years over the 1970s.[31] In contrast, Missmer reported a maximal incidence around 25–30 years over the 1990s with then a steep decrease with age.[32] These reports show that in the 1970s and before, endometriosis was usually diagnosed at later ages, and that in the 1990s, presumably with improvement of detection procedures and the introduction of laparoscopy as a reference diagnostic tool, age at diagnosis considerably decreased with then very few women being diagnosed in later life. Our data are consistent with these previous observations considering the period of diagnosis of our cases.

Little research has been conducted to date regarding the relationship between endometriosis and phenotypic factors. To our knowledge, no previous study

Table 2 OR and 95% CIs for endometriosis in relation to phenotypic factors in the E3N cohort ($n = 97\,215$)

	History of endometriosis				
	Yes (4241)	No (92 974)	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)	Adjusted OR[b] (95% CI)
Skin sensitivity to sun exposure					
Highly sensitive	1370	26 062	1.33 (1.22–1.45)	1.27 (1.16–1.39)	1.22 (1.10–1.36)
Moderately sensitive	2022	45 433	1.13 (1.04–1.22)	1.11 (1.02–1.20)	1.09 (0.99–1.19)
Not sensitive	849	21 479	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
			$P_{trend} < 0.0001$	$P_{trend} < 0.0001$	$P_{trend} < 0.0001$
Number of naevi					
Very many	582	9692	1.84 (1.59–2.12)	1.61 (1.39–1.85)	1.59 (1.37–1.83)
Many	1981	40 205	1.51 (1.33–1.70)	1.38 (1.22–1.56)	1.37 (1.21–1.55)
Few	1374	33 785	1.24 (1.10–1.41)	1.18 (1.04–1.34)	1.19 (1.05–1.35)
None	304	9292	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
			$P_{trend} < 0.0001$	$P_{trend} < 0.0001$	$P_{trend} < 0.0001$
Number of freckles					
Very many/many	1584	31 361	1.22 (1.13–1.30)	1.18 (1.10–1.27)	1.11 (1.03–1.20)
Few	1021	22 263	1.10 (1.02–1.20)	1.09 (1.01–1.18)	1.08 (1.00–1.17)
None	1636	39 350	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
			$P_{trend} < 0.0001$	$P_{trend} < 0.0001$	$P_{trend} = 0.0049$
Skin complexion					
Very fair	61	1123	1.27 (0.98–1.66)	1.21 (0.93–1.57)	1.01 (0.76–1.32)
Fair	2561	54 062	1.11 (1.04–1.19)	1.10 (1.03–1.17)	1.00 (0.92–1.08)
Medium	1547	36 288	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Dark/very dark	72	1501	1.13 (0.88–1.43)	1.15 (0.90–1.46)	1.16 (0.91–1.49)
			$P_{trend} = 0.0023$	$P_{trend} = 0.0111$	$P_{trend} = 0.6122$
Hair colour					
Red	83	1566	1.16 (0.93–1.46)	1.18 (0.89–1.40)	1.04 (0.82–1.31)
Blond	461	9265	1.09 (0.99–1.21)	1.08 (0.98–1.20)	1.05 (0.94–1.16)
Chestnut	2554	56 070	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Brown	917	21 525	0.94 (0.87–1.01)	0.93 (0.86–1.01)	0.96 (0.88–1.04)
Dark	226	4548	1.09 (0.95–1.25)	1.08 (0.94–1.25)	1.12 (0.97–1.30)

[a]Adjusted for age, height, body mass index, age at menarche, menstrual cycle length and age at menopause.
[b]Additionally adjusted for hair colour, skin complexion, skin sensitivity to the sun, number of naevi and number of freckles. Because of small numbers, we collapsed the 'dark' and 'very dark' categories of skin complexion as well as the 'very many' and 'many' categories of number of freckles.

investigated the link between endometriosis and cutaneous phenotypic characteristics. However, in two case–control studies, one research group reported a higher rate of self-reported endometriosis among dysplastic naevi cases,[33] and a positive association between laparoscopically confirmed endometriosis and dysplastic naevi in women aged $\leqslant 32$ years.[9] No information about number of dysplastic naevi was available, and a dose–response effect has not been tested.

Three studies reported a positive association between red hair and endometriosis, among college alumnae,[13] in a large prospective cohort where the association was limited to fertile women[22] and in a prospective study of infertile patients.[23] Our findings do not confirm this association, although the small proportion of red-haired women in our cohort may have restricted our ability to observe it. However, results from these studies were not adjusted for number of freckles and skin sensitivity to sun exposure, and associations with these features were not investigated. Indeed, these traits are strongly associated with red hair,[34] and we found an association between number of freckles or skin sensitivity to sun exposure and endometriosis in our study.

Endometriosis is a highly heritable disease with a complex aetiology, and several candidate susceptibility genes have been reported.[2,35,36] Among those, some tumour suppressor genes (*CDKN2A/p16^{Ink4}*, *TP53*,

Table 3 OR and 95% CIs for endometriosis in relation to phenotypic factors stratified by infertility treatment use, E3N cohort ($n = 97\,215$)

	Ever			Never			
	n (6785)	Cases (604)	OR[a] (95% CI)	*n* (90 430)	Cases (3637)	OR[a] (95% CI)	***P* for homogeneity**
Skin sensitivity to sun exposure							
Highly sensitive	2131	207	1.39 (1.06–1.83)	25 301	1163	1.19 (1.07–1.33)	0.0422
Moderately sensitive	3172	275	1.18(0.93–1.50)	44 283	1747	1.08 (0.98–1.19)	<0.0001
Not sensitive	1482	122	1 (Referent)	20 846	727	1 (Referent)	–
			$P_{trend} = 0.0156$			$P_{trend} = 0.0012$	
Number of naevi							
Very many	903	85	1.39 (0.92–2.10)	9371	497	1.6 (1.37–1.87)	0.2071
Many	3006	292	1.49 (1.04–2.15)	39 180	1689	1.35 (1.18–1.54)	0.3015
Few	2314	191	1.27 (0.87–1.84)	32 845	1183	1.17 (1.02–1.34)	0.4378
None	562	36	1 (Referent)	9034	268	1 (Referent)	–
			$P_{trend} = 0.0541$			$P_{trend} < 0.0001$	
Number of freckles							
Very many/many	2451	224	1.06 (0.87–1.30)	30 494	1360	1.12 (1.04–1.21)	0.3255
Few	1617	144	1.04 (0.83–1.30)	21 667	877	1.09 (1.00–1.19)	0.4585
None	2717	236	1 (Referent)	38 269	1400	1 (Referent)	–
			$P_{trend} = 0.5668$			$P_{trend} = 0.0048$	
Skin complexion							
Very fair	110	8	0.57 (0.27–1.24)	1074	53	1.09 (0.81–1.46)	0.0023
Fair	4063	349	0.76 (0.62–0.94)	55 560	2212	1.03 (0.95–1.12)	< 0.0001
Medium	2498	234	1 (Referent)	35 337	1313	1 (Referent)	–
Dark/very dark	114	13	1.32 (0.72–2.43)	1459	59	1.12 (0.85–1.47)	0.3379
			$P_{trend} = 0.0039$			$P_{trend} = 0.6051$	
Hair colour							
Red	144	14	1.07 (0.60–1.92)	1505	69	1.01 (0.79–1.31)	0.741
Blond	704	59	0.94 (0.70–1.26)	9022	402	1.06 (0.95–1.19)	0.1258
Chestnut	4081	373	1 (Referent)	54 543	2181	1 (Referent)	–
Brown	1502	123	0.83 (0.67–1.04)	20 940	794	0.98 (0.90–1.07)	0.0082
Dark	354	35	1.02 (0.69–1.49)	4420	191	1.13 (0.97–1.33)	0.299

[a]Adjusted for age, height, body mass index, age at menarche, menstrual cycle length, age at menopause, hair colour, skin complexion, skin sensitivity to the sun, number of naevi and number of freckles. Because of small numbers, we collapsed the 'dark' and 'very dark' categories of skin complexion as well as the 'very many' and 'many' categories of number of freckles.

PTEN)[14–16] have also been shown to be associated with melanoma.[17,18] In particular, naevi count has been associated with the *CDKN2A* region,[37,38] which is consistent with our data and may explain our findings. Also, some authors have hypothesized a possible linkage between endometriosis and melanoma via the *GALT* region (9p13),[9] which is close to the *CDKN2A* locus (9p21). Freckling, red hair and tanning ability are associated with *MC1R*, which is also involved in melanoma aetiology.[39] However, no report to date has related this gene to endometriosis.

Another potential explanation of our findings is via hormonal pathways. Naevi and freckles result from a multiplication of skin melanocytes, which is influenced by sex hormones including oestrogens,[40] and naevi development reaches a peak at puberty before a progressive decline with age.[41] Moreover, although hormonal therapy in melanoma patients yielded little response,[42] melanoma progression has been associated with the expression of both oestrogen receptors ERα and ERβ,[43,44] which suggests that melanoma itself may be influenced by oestrogens. On the other hand, although endometriosis symptoms are clearly oestrogen dependent,[2] it has not been clarified whether the aetiology of ectopic migration of endometrium tissue is hormone related. Therefore, common hormonal pathways between phenotypic features and endometriosis remain to be determined.

Table 4 OR and 95% CIs for endometriosis in relation to phenotypic factors in the E3N cohort, in prevalent and incident cases ($n = 97\,215$)

	Prevalent cases ($n = 2569$)[a]	Incident cases ($n = 1672$)[b]	
	Adjusted OR[c] (95% CI)	Adjusted OR[c] (95% CI)	*P* for homogeneity
Skin sensitivity to sun exposure			
Highly sensitive	1.26 (1.11–1.43)	1.17 (1.00–1.37)	0.1501
Moderately sensitive	1.09 (0.97–1.22)	1.08 (0.94–1.24)	0.8441
Not sensitive	1.00 (Referent)	1.00 (Referent)	–
	$P_{trend} = 0.0003$	$P_{trend} = 0.0586$	
Number of naevi			
Very many	1.71 (1.42–2.05)	1.41 (1.12–1.78)	0.0114
Many	1.40 (1.19–1.63)	1.32 (1.08–1.61)	0.3749
Few	1.24 (1.05–1.45)	1.11 (0.90–1.36)	0.1028
None	1.00 (Referent)	1.00 (Referent)	–
	$P_{trend} < 0.0001$	$P_{trend} < 0.0001$	
Number of freckles			
Very many/many	1.11 (1.01–1.22)	1.11 (0.99–1.25)	0.9625
Few	1.11 (1.00–1.23)	1.04 (0.92–1.18)	0.1479
None	1.00 (Referent)	1.00 (Referent)	–
	$P_{trend} = 0.0272$	$P_{trend} = 0.0712$	
Skin complexion			
Very fair	1.05 (0.75–1.47)	0.91 (0.57–1.45)	0.3237
Fair	0.93 (0.84–1.03)	1.10 (0.98–1.25)	<0.0001
Medium	1.00 (Referent)	1.00 (Referent)	–
Dark/very dark	1.20 (0.89–1.63)	1.09 (0.72–1.64)	0.4519
	$P_{trend} = 0.1295$	$P_{trend} = 0.2844$	
Hair colour			
Red	1.14 (0.86–1.52)	0.87 (0.58–1.29)	0.0252
Blond	1.05 (0.92–1.20)	1.04 (0.89–1.22)	0.9754
Chestnut	1.00 (Referent)	1.00 (Referent)	–
Brown	0.92 (0.83–1.02)	1.02 (0.90–1.15)	0.6974
Dark	1.13 (0.94–1.36)	1.11 (0.88–1.40)	0.7746

[a]Analysis performed in 94 946 women (1672 incident cases were excluded).
[b]Analysis performed in 95 543 women (2569 prevalent cases were excluded).
[c]Adjusted for age, height, body mass index, age at menarche, menstrual cycle length and age at menopause, hair colour, skin complexion, skin sensitivity to the sun, number of naevi and number of freckles. Because of small numbers, we collapsed the 'dark' and 'very dark' categories of skin complexion as well as the 'very many' and 'many' categories of number of freckles.

Strengths of this study include the large sample size of the E3N cohort, detailed and regularly updated information on endometriosis and detailed data on phenotypic factors. To our knowledge, our study is the first to assess the association between skin characteristics and endometriosis, and the first to examine the link with hair colour while taking into account the effect of other phenotypic factors, such as freckling and skin sensitivity to sun exposure.

There were several limitations in our study. Endometriosis was self-reported by the participants and was not ascertained by medical reports; a misclassification bias may thus have occurred. Also, a majority of cases were reported retrospectively, which could lead to recall bias. However, restricting our case definition to women who reported endometriosis as treated/diagnosed by surgery or laparoscopy is likely to have substantially decreased misclassification, and our validation study has shown a satisfactory confirmation rate of endometriosis cases. Diagnosis through laparoscopy could also reflect a selection of severe cases; however, previous reports do not support this hypothesis.[32] Risk estimates were slightly lower when restricting to incident cases, but our findings remained regarding number of naevi and skin sensitivity.

Phenotypic characteristics were also based on self-report instead of objective assessment by

Table 5 OR and 95% CIs for endometriosis in relation to phenotypic factors in the E3N cohort, according to birth cohort ($n = 97\,215$)

	In women born between 1925 and 1940 ($n = 43\,007$)	**In women born between 1941 and 1950 ($n = 54\,208$)**	
	Adjusted OR[a] (95% CI)	Adjusted OR[a] (95% CI)	***P* for homogeneity**
Skin sensitivity to sun exposure			
Highly sensitive	1.27 (1.08–1.50)	1.22 (1.07–1.39)	0.4309
Moderately sensitive	1.10 (0.95–1.27)	1.09 (0.97–1.22)	0.8906
Not sensitive	1.00 (Referent)	1.00 (Referent)	–
	$P_{trend} = 0.0037$	$P_{trend} = 0.0019$	
Number of naevi			
Very many	1.54 (1.22–1.95)	1.67 (1.38–2.03)	0.3048
Many	1.38 (1.15–1.64)	1.43 (1.20–1.70)	0.5759
Few	1.22 (1.02–1.45)	1.20 (1.00–1.44)	0.8788
None	1.00 (Referent)	1.00 (Referent)	–
	$P_{trend} < 0.0001$	$P_{trend} < 0.0001$	
Number of freckles			
Very many/many	1.12 (0.99–1.27)	1.11 (1.01–1.22)	0.7516
Few	1.14 (1.00–1.31)	1.05 (0.95–1.16)	0.0507
None	1.00 (Referent)	1.00 (Referent)	–
	$P_{trend} = 0.0553$	$P_{trend} = 0.0267$	
Skin complexion			
Very fair	0.98 (0.59–1.64)	1.03 (0.74–1.42)	0.7731
Fair	0.95 (0.84–1.08)	1.01 (0.92–1.12)	0.1022
Medium	1.00 (Referent)	1.00 (Referent)	–
Dark/very dark	1.05 (0.70–1.56)	1.23 (0.90–1.68)	0.2108
	$P_{trend} = 0.4522$	$P_{trend} = 0.9415$	
Hair colour			
Red	1.01 (0.67–1.52)	1.05 (0.79–1.39)	0.7713
Blond	1.11 (0.94–1.32)	1.01 (0.89–1.15)	0.0823
Chestnut	1.00 (Referent)	1.00 (Referent)	–
Brown	1.02 (0.89–1.16)	0.93 (0.84–1.03)	0.0436
Dark	1.23 (0.97–1.57)	1.08 (0.90–1.29)	0.0857

[a]Adjusted for age, height, body mass index, age at menarche, menstrual cycle length and age at menopause, hair colour, skin complexion, skin sensitivity to the sun, number of naevi and number of freckles. Because of small numbers, we collapsed the 'dark' and 'very dark' categories of skin complexion as well as the 'very many' and 'many' categories of number of freckles.

dermatologists. This could generate misclassification. However, since such as bias is unlikely to be differential between endometriosis cases and non-cases, misclassification would tend to reduce the associations. We were unable to test the repeatability of dermatologic characteristics in our study; however, others have generally shown high levels of agreement for phenotypic measures,[45] although assessment of number of naevi was reported with moderate agreement.[45–47]

In our study, covariates were reported retrospectively and are thus subject to recall bias. However, the potential confounders that we included in the analyses have proved quite accurate in repeatability analyses.[26,29] Also, current body mass index was collected at baseline and is therefore imprecise in prevalent cases, which could explain the lack of association between endometriosis and body mass index in our study. However, our results were identical after further adjustment for body silhouette at younger ages.

Our study is, together with the Nurses' Health Study II,[22] the only cohort with a validation study of endometriosis cases. In the latter, 89% of self-reported cases with a history of laparoscopy were confirmed as true cases, but study subjects were health professionals, and in a young age range. Our proportion of 75% of confirmed cases is consistent with the high proportion of educated women in our cohort.

Although this constitutes a selected population as compared with the general French population, there is no biological reason that our results on the association between endometriosis and skin phenotype do not apply to all women. However, we cannot completely rule out a spurious association due to unknown residual confounders.

Conclusion

The present findings further support a positive association between endometriosis and melanoma, and suggest that these diseases may share some genetic features. These findings need to be replicated, and warrant further exploration in genetic studies, which should investigate a potential linkage between endometriosis and the *MC1R* locus, as well as further explore a linkage between endometriosis and the *CDKN2A* region. Allelic imbalances occurring in close genes involved in both diseases are another potential area of research. If our findings are further confirmed, these phenotypic traits might contribute to the understanding of endometriosis.

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KEY MESSAGES

- An association between endometriosis and cutaneous melanoma was previously described, possibly explained through common genetic features.
- Phenotypic traits are mostly determined genetically and have been strongly associated with the risk of melanoma; therefore, an association between these traits and the risk of endometriosis could suggest the existence of common genetic characteristics between endometriosis and melanoma.
- Our data showed a positive dose–response relationship between risk of endometriosis and skin sensitivity to sun exposure, number of naevi and number of freckles, and this is the first study to report these associations.
- These findings further support an association between endometriosis and cutaneous melanoma and suggest that these diseases may share some genetic features.

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