Pigmentary traits, family history of melanoma and the risk of endometriosis: a cohort study of US women

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Background Endometriosis has been associated with a higher risk of cutaneous melanoma, but the mechanisms underlying this association are unknown. Some constitutional factors known to influence melanoma risk have been associated with endometriosis in some retrospective studies. However, prospective data are scarce, and more research is needed to confirm this potentially novel endometriosis risk profile.

Methods To investigate the relationships between pigmentary traits, family history of melanoma and endometriosis risk, we analysed data from the Nurses’ Health Study II, a cohort of 116,430 female US nurses aged 25–42 years at inclusion in 1989. Data were collected every 2 years with 20 years of follow-up for these analyses. We used Cox proportional hazards regression models to compute relative risks (RRs) and 95% confidence intervals (CIs).

Results During 1,212,499 woman-years of follow-up, 4,763 cases of laparoscopically-confirmed endometriosis were reported among premenopausal Caucasian women. Endometriosis risk was increased with presence of naevi on the lower legs (RR = 1.08, 95% CI = 1.02–1.14) and higher level of skin’s burning reaction to sun exposure in childhood/adolescence (‘burn with blisters’: RR = 1.20, 95% CI = 1.06–1.36) compared with ‘practically none’: $P_{\text{trend}} = 0.0006$ and family history of melanoma (RR = 1.13, 95% CI = 1.01–1.26).

Conclusion This assessment reports modest associations between several pigmentary traits, family history of melanoma and endometriosis risk, corroborating the results from previous retrospective studies. Our findings call for further research to better understand the mechanisms underlying these associations.

Keywords Endometriosis, epidemiology, melanoma, naevi, pigmentation, skin sensitivity to sun exposure
Introduction

Endometriosis manifests as the presence of endometrial tissue outside the uterus. The external implants respond to menstrual cycle hormones and ‘bleed’ as they would in the uterus, leading to adhesions, scarring and painful inflammation. Signs and symptoms of endometriosis include infertility, dysmenorrhoea, dyspareunia, dysuria and dyschezia. Unfortunately, there is delayed diagnosis, and treatment options are poor. A prevalence of 10% has been estimated in the general female population but, despite its frequent occurrence, substantial associated costs and considerable impact on quality of life, endometriosis aetiology remains largely unknown. The only known risk factors to date are those reflecting increased exposure to menstruation (i.e. earlier menarche, shorter menstrual cycles, nulliparity) and low body mass index (BMI).

An association between endometriosis and cutaneous melanoma has been reported but the mechanisms underlying this relation are unclear. Several constitutional factors known to be associated with melanoma (i.e. naevi, skin sensitivity to sun exposure, red hair, eye colour and family history of melanoma) have been associated with endometriosis risk in early and emerging retrospective studies. Red hair was also associated with endometriosis in a previous analysis from our group.

To confirm this potentially novel risk profile, further research is requested on these host factors in relation to endometriosis risk. Using data with 20 years of follow-up in the Nurses’ Health Study II (NHSII), we examined the relationships between several pigmented traits, family history of melanoma and the risk of laparoscopically-confirmed endometriosis.

Methods

Study population and data collection

The NHSII is a prospective cohort study involving 116,430 registered female US nurses, residing in one of 14 US states and aged 25–42 years at inclusion. Women were enrolled in 1989, when they started to complete biennial mailed questionnaires about their health, medical history and exposures to known or potential risk factors for several chronic diseases. Response rates have been consistently >90% throughout follow-up since inclusion. This research has been approved by the Institutional Review Boards of Brigham and Women’s Hospital and Harvard School of Public Health.

Case ascertainment and analytical definition

In 1993, women were asked if they had ‘ever had physician-diagnosed endometriosis’. If ‘yes’, they were asked to report the date of diagnosis and whether it had been confirmed by laparoscopy, the gold standard for endometriosis diagnosis. These questions were asked again in each subsequent questionnaire cycle.

In March 1994, we conducted a validation study to assess the accuracy of self-reported endometriosis within the NHSII. A supplementary questionnaire was mailed to 200 women randomly selected from the 1766 cases who had then reported incident endometriosis diagnosis. Among those reporting laparoscopic confirmation and for whom records were received and reviewed (n = 105), a diagnosis of endometriosis was confirmed in 96.2%. However, among women without laparoscopic confirmation (n = 26), evidence of a clinical diagnosis was found in only 53.8% of the records. As part of this validation, requests for permission to review medical records were also sent to any woman who indicated hysterectomy during the time period of reported endometriosis diagnosis. A diagnosis of endometriosis at time of surgical procedure was confirmed in 79.6% (n = 144/181) of the records. However, endometriosis was the primary indication for hysterectomy in only 5.5% (n = 9/163) of women for whom an indication was available. Therefore, to reduce the magnitude of misclassification and prevent confounding by indication for hysterectomy, analyses of incident endometriosis were restricted to women who reported laparoscopic confirmation of their diagnosis.

Within this restricted case definition, the relation between endometriosis and infertility status is complex. At baseline, the prevalence of infertility (defined as attempting to become pregnant for >1 year without success) was greater among women with laparoscopic confirmation (20%) than among those who were clinically diagnosed without laparoscopic confirmation (4%), potentially resulting in over-sampling those with otherwise ‘asymptomatic’ disease. Because endometriosis with infertility may be indicative of asymptomatic disease secondary to other primary causes of infertility, the risk factors for endometriosis with infertility could differ from those for endometriosis without infertility. Hence, we looked at risk factors stratifying according to infertility history. Within this cohort, self-reported infertility was validated in a study of 100 randomly selected women who reported ovulatory infertility; 95% of self-reports were confirmed through medical record review.

Participants who reported endometriosis diagnosis before baseline were excluded from all analyses. Our analyses were also restricted to women who were premenopausal and had an intact uterus, since the occurrence of endometriosis is rare after menopause or hysterectomy. Women who reported a previous diagnosis of cancer (other than non-melanoma skin cancer) were also excluded, and since the studied pigmented traits are mainly driven by race, we restricted the analyses to Caucasian women. The total number of incident cases of laparoscopically-confirmed endometriosis for this analysis was 4763.
Exposure assessment
In 1989, we asked women to count the number of naevi on their lower legs (from knee to ankle on both legs), and to report their skin’s burning reaction during childhood/adolescence after ≥2h in the sun without sunscreen, once they had been exposed to the sun several times. Data on ancestry were collected at baseline, and those on race in the 2005 questionnaire. A combined variable was created for race from these two variables, allowing for multiple races and ‘other’ categories. Women reported their natural hair colour at age 18 years in the 1991 questionnaire and were asked if their first-degree relatives were ever diagnosed with cutaneous melanoma in the 1989, 1997 and 2005 questionnaires.

Assessment of covariates
We calculated BMI (kg/m²) at age 18 years from weight at age 18 years and current height that were reported at baseline. Age at menarche was collected in 1989, and current menstrual cycle length and pattern were assessed in 1993. A parity history (defined as the total number of pregnancies lasting ≥6 months) was collected at baseline and updated biennially. A history of oral contraceptive (OC) use since age 13 years was recorded at baseline, and information about subsequent use was updated biennially. Women who had used OCs for ≥2 months were classified as ever-users. A detailed cigarette smoking history was obtained at baseline and updated with each biennial questionnaire, allowing for adjustment for smoking status.

Statistical analysis
Data for these analyses were collected from September 1989 to June 2009 in the NHSII cohort. Because of a strong association between infertility and laparoscopic diagnosis of endometriosis, we analysed infertility as an effect modifier and stratified all analyses according to infertility history. We also checked that additional adjustment for infertility did not influence our findings. To further investigate the potential impact of infertility on the studied associations with endometriosis risk, we excluded all women with an infertility history at baseline or during follow-up in a sensitivity analysis. In that sub-analysis, we included only women who had an infertility evaluation, to equalize the possibility of secondary detection between cases and comparison subjects.

Woman-months at risk were calculated from entry into the cohort until independently confirmed death or cancer diagnosis (other than non-melanoma skin cancer), laparoscopically-confirmed endometriosis diagnosis, hysterectomy, menopause onset, or date of end of follow-up. Women who reported physician-diagnosed endometriosis with no laparoscopic confirmation were censored at the time of that report but were allowed to re-enter the analysis population with their interim person-time, if they reported laparoscopic confirmation on a subsequent questionnaire.

Incidence rates for each exposure category were computed as the number of incident cases divided by the person-time accumulated. Time-varying Cox proportional hazards models that treated age in months and stratifying by 2-year questionnaire cycle as the time scale were used to estimate multivariate relative risks (RRs) and to calculate 95% confidence intervals (CIs). We built three different adjustment models: Model 1 adjusted for current age and calendar time; Model 2 additionally adjusted for factors known to be associated with endometriosis (BMI at age 18 years, age at menarche, menstrual cycle length and pattern, parity, OC use and smoking status); and Model 3 further adjusted for other pigmentary traits. Tests for linear trend in ordinal categorical exposures were calculated by creating an ordinal variable in which the median value or midpoint of each category was assigned to all participants in that group. To evaluate whether the associations between the studied exposures and endometriosis varied by levels of specific risk factors, we conducted stratified analyses and calculated likelihood ratio tests, to compare the model with both the main effects and the interaction terms against the model with the main effects only.

Results
Over 1212499 person-years, a total of 4763 incident cases of laparoscopically-confirmed endometriosis were reported among the 94444 included women. Table 1 describes the characteristics of the study population. Women with a higher level of burning reaction to the sun during childhood/adolescence were more likely to have had an early menarche, to be nulliparous and to have ever been infertile, and they were less likely to have ever used OCs (Table 2).

Number of naevi on the lower legs was associated with a modest increase in endometriosis risk ($P_{\text{trend}}=0.02$) (Table 3). Given the similarity of magnitude of RRs across categories, it seems that presence of naevi (RR = 1.08, 95% CI = 1.02–1.14), rather than their number, was mostly driving the association. Skin’s burning reaction to sun exposure was associated with an increased endometriosis risk (‘burn with blisters’: RR = 1.20, 95% CI = 1.06–1.36, compared with none; $P_{\text{trend}}=0.0006$). Also, women reporting a family history of melanoma in their first-degree relatives had a slightly higher endometriosis risk (RR = 1.13, 95% CI = 1.01–1.26), whereas hair colour was not associated with risk.

In an analysis not restricted to Caucasian women ($n=102165$), we observed lower endometriosis risk in Black (RR = 0.61, 95% CI = 0.47–0.80) and Asian women (RR = 0.74, 95% CI = 0.58–0.94) as compared with White women, but no association in other groups (Table 4).
In all analyses, results were almost identical when additionally adjusted for infertility history (data not shown). Results were not substantially modified in a sensitivity analysis excluding all women with a history of infertility (at baseline or during follow-up).

Results were similar across subgroups when we stratified our analyses according to BMI (<25 / ≥25 kg/m²), parity (parous/nulliparous), smoking status (ever/never) or infertility (ever/never). However, red hair was differentially associated with endometriosis risk according to OC use, with an inverse association in never-users (RR = 0.56, 95% CI = 0.31–1.00), but a positive association in ever-users (RR = 1.20, 95% CI = 1.03–1.39; \(P_{\text{interaction}} = 0.009\)).

**Discussion**

In this cohort study, we observed modest associations between endometriosis risk and presence of naevi on the lower legs, higher level of skin’s burning reaction to sun exposure and family history of melanoma. Whereas natural hair colour was not associated with overall endometriosis risk, risk was increased in red-haired women who had ever used OCs and was decreased in red-haired women who never used OCs.

Our findings regarding naevi and skin’s reaction to sun exposure confirm those reported in the French E3N cohort and a recent Italian case-control study. The latter reported an increased endometriosis risk in women with >15 vs ≤15 naevi (odds ratio = 1.45, 95% CI = 0.74–2.87). The inclusion of benign gynaecological diseases (particularly fibroids) in the control group may have diluted the naevus-endometriosis association in that study, since naevi have also been associated with fibroids. Our results on skin’s reaction to sun exposure also confirm those reported in the French and Italian studies.
Table 3 Relative risks and 95% confidence intervals for host factors in relation to endometriosis risk, NHSII cohort 1989–2009 \(^{194 666}\)

<table>
<thead>
<tr>
<th>Number of moles on lower legs</th>
<th>Cases</th>
<th>Person-years</th>
<th>Model 1 RR(^a) (95% CI)</th>
<th>Model 2 RR(^b) (95% CI)</th>
<th>Model 3 RR(^c) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None ((n = 45 410))</td>
<td>2201</td>
<td>581 141</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>1–2</td>
<td>17 137</td>
<td>880</td>
<td>1.07 (0.98–1.15)</td>
<td>1.07 (0.98–1.15)</td>
<td>1.06 (0.98–1.15)</td>
</tr>
<tr>
<td>3–5</td>
<td>9 200</td>
<td>480</td>
<td>1.08 (0.98–1.19)</td>
<td>1.08 (0.97–1.19)</td>
<td>1.08 (0.97–1.19)</td>
</tr>
<tr>
<td>6–9</td>
<td>6 175</td>
<td>327</td>
<td>1.09 (0.97–1.22)</td>
<td>1.09 (0.97–1.22)</td>
<td>1.09 (0.97–1.22)</td>
</tr>
<tr>
<td>≥10</td>
<td>13 371</td>
<td>728</td>
<td>1.12 (1.03–1.22)</td>
<td>1.09 (1.00–1.19)</td>
<td>1.09 (1.00–1.19)</td>
</tr>
<tr>
<td>(P_{\text{trend}})</td>
<td>0.004</td>
<td></td>
<td></td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>None ((n = 45 883))</td>
<td>2415</td>
<td>588 224</td>
<td>1.09 (1.03–1.15)</td>
<td>1.08 (1.02–1.14)</td>
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</tr>
<tr>
<td>≥1</td>
<td>45 883</td>
<td>2415</td>
<td>1.09 (1.03–1.15)</td>
<td>1.08 (1.02–1.14)</td>
<td>1.08 (1.02–1.14)</td>
</tr>
</tbody>
</table>

Skin’s burning reaction to sun exposure during childhood/adolescence

| Practically none \((n = 13 439)\) | 668  | 171 190     | 1.00 (Reference)           | 1.00 (Reference)          | 1.00 (Reference)          |
| Some redness only \((n = 35 160)\) | 17 191| 454 870     | 0.96 (0.88–1.05)           | 0.97 (0.89–1.06)          | 0.97 (0.88–1.06)          |
| Burn \((n = 23 090)\)              | 1114 | 299 299     | 0.95 (0.86–1.04)           | 0.95 (0.86–1.04)          | 0.94 (0.85–1.03)          |
| Painful burn \((n = 15 979)\)      | 869  | 202 984     | 1.09 (0.99–1.21)           | 1.10 (0.99–1.21)          | 1.09 (0.98–1.20)          |
| Burn with blisters \((n = 6801)\)  | 385  | 82 047      | 1.20 (1.06–1.37)           | 1.20 (1.06–1.36)          | 1.18 (1.04–1.35)          |
| \(P_{\text{trend}}\)             | 0.004 |              | 0.0006                     | 0.002                     | 0.002                     |

Hair colour

| Black \((n = 11 48)\)             | 57   | 14 431      | 1.02 (0.78–1.33)           | 0.98 (0.75–1.28)          | 1.00 (0.76–1.30)          |
| Dark brown \((n = 31 964)\)       | 15 88 | 416 841     | 0.98 (0.91–1.05)           | 0.98 (0.91–1.05)          | 0.99 (0.92–1.06)          |
| Light brown \((n = 33 182)\)      | 17 16 | 434 171     | 1.01 (Reference)           | 1.00 (Reference)          | 1.00 (Reference)          |
| Blonde \((n = 13 884)\)           | 760  | 185 371     | 1.03 (0.94–1.12)           | 1.02 (0.94–1.11)          | 1.01 (0.93–1.10)          |
| Red \((n = 33 01)\)               | 189  | 42 802      | 1.12 (0.96–1.30)           | 1.12 (0.96–1.30)          | 1.06 (0.90–1.23)          |
| Non-red \((n = 80 178)\)          | 421  | 10 50 815   | 1.00 (Reference)           | 1.00 (Reference)          | 1.00 (Reference)          |
| Red \((n = 33 01)\)               | 189  | 42 802      | 1.12 (0.97–1.30)           | 1.12 (0.97–1.30)          | 1.06 (0.91–1.23)          |

Family history of melanoma

| No \((n = 63 467)\)               | 33 52 | 870 415     | 1.00 (Reference)           | 1.00 (Reference)          | 1.00 (Reference)          |
| Yes \((n = 61 14)\)              | 364  | 84 533      | 1.11 (0.99–1.23)           | 1.13 (1.01–1.26)          | 1.12 (1.00–1.25)          |

\(^a\)Adjusted for current age (continuous months) and calendar time (2-year questionnaire period)

\(^b\)Additionally adjusted for BMI at age 18 years (<18.5, 18.5–22.4, 22.5–24.9, 25–29.9, 30.0–34.9, 35.0–39.9 or ≥40 kg/m\(^2\)), age at menarche (<11, 12–13 or ≥14 years), menstrual cycle length (<21, 21–25, 26–31, 32–39 or ≥40 days), menstrual cycle pattern (regular, usually irregular, always irregular, no menses), parity (nulliparous or 1, 2, 3 or ≥4 pregnancies lasting ≥6 months), oral contraceptive use (never, past or current use), and smoking status (never, past or current smoking)

\(^c\)Additionally adjusted for childhood skin’s reaction to sun exposure, number of moles on leg and natural hair colour, when appropriate.
Red hair was associated with endometriosis in three previous reports,\textsuperscript{12,13,16} including a study with 10 years of follow-up in the NHSII cohort.\textsuperscript{16} In that study, we had reported an increased endometriosis risk in red-haired women who had never been infertile (RR = 1.3) but a decreased risk in infertile red-haired women (RR = 0.4; \(P_{\text{interaction}} = 0.03\)).\textsuperscript{16} Although our present analysis with 20 years of follow-up in the NHSII does not confirm a differential association according to infertility history, we report effect modification by OC use. The association in ever-users of OCs (the largest group) is in the same direction as for the whole cohort population, whereas it is in the opposite direction in never-users. We have no a priori hypothesis to explain this differential association. However, since OC use reduces pelvic pain symptoms, OC use in endometriosis patients may reflect most severe pain. On the other hand, evidence suggests that red-haired women may be more sensitive to pain,\textsuperscript{21} which is consistent with our results of higher risk both in ever OC-users and infertile women. Of note is that there are two differences between our previous reports and the present analysis: (i) women with a history of infertility were systematically censored before\textsuperscript{16} but censored in a sensitivity analysis only here; (ii) race was previously derived from self-reported ancestry at baseline\textsuperscript{18} whereas here it combines information between ancestry reported in 1989 and race reported in 2005.

Other pigmentary traits have been described to associate with endometriosis. Higher freckling density was associated with higher endometriosis risk in the French\textsuperscript{14} and the Italian\textsuperscript{15} studies. In the latter, light eye colour was also related to endometriosis risk (OR = 1.95 for green/blue vs brown/black). Unfortunately, no data on freckling or eye colour were available in the NHSII, and we could thus not test these associations.

We also observed an association between family history of melanoma and endometriosis risk, which was observed in one previous study where a higher rate of family history of melanoma was found among endometriosis cases (28.6%) than in controls (10.0%) (\(P < 0.04\)).\textsuperscript{11} Women with a family history of melanoma are more likely to be diagnosed with melanoma,\textsuperscript{9,22} and thus this association could reflect a relation between endometriosis and melanoma diagnosis. Alternatively, our finding could be driven by fairer pigmentation in those with a family history of melanoma; however, our results were almost identical after adjustment for pigmentary traits.

Taken together, our findings and those from previous studies suggest that fair pigmentation and family history of melanoma (and thus a high-risk profile for skin cancers) may increase endometriosis risk, although the magnitude of effects was more modest in our study compared with previous reports. These associations may be explained through at least three potential mechanisms.

First, since pigmentary traits are determined mostly genetically,\textsuperscript{23,32} associations between host factors and endometriosis risk may reflect an underlying genetic relation. Several variants of naevus\textsuperscript{23,24,27} and pigmentation\textsuperscript{11} genes have been associated with melanoma risk, and may be additionally associated with endometriosis risk. However, to our knowledge, no previous study specifically explored pigmentation-, naevus- or melanoma-associated genes in relation to endometriosis risk. Further investigation into the genetics of endometriosis may help elucidate whether genetic markers from these pathways have an influence on endometriosis.

Second, skin expresses estrogen receptors\textsuperscript{32} and estrogens have been shown to stimulate melanogenesis,\textsuperscript{33,34} which suggests an influence of sex hormones on skin pigmentation. Since endometriosis is a
hormone-dependent disease, a hormonal pathway may also potentially explain these associations.

Third, our findings may reflect an underlying association between pigmentary traits and environmental exposures independently associated with endometriosis. Higher urinary concentrations of benzophenone-type ultraviolet (UV) filters have been associated with higher endometriosis risk. This could suggest a direct association between endometriosis risk and these chemicals, known to have endocrine-disruptive effects. Alternatively, it could reflect an underlying association with sun-sensitive skin types and/or sun exposure. Women with sun-sensitive skin may be more likely to use sunscreen, consistent with our finding of a higher burning level of skin in women with endometriosis. Moreover, those who intentionally seek sun exposure may also use more sunscreen, and thus the sunscreen-endometriosis association could suggest an association between endometriosis and sun exposure. Further, since naevus propensity is also associated with sun exposure, the relation between naevi and endometriosis may additionally reflect a relation between sun exposure and endometriosis risk. However, the sole study exploring sun exposure and sunscreen use in relation to endometriosis reported a decreased number of days per year of sun exposure in endometriosis patients, although other sun exposure measures were unrelated to risk, and endometriosis cases were less likely than controls to use sunscreen. Thus, more research is needed in this area in order to elucidate these questions.

As previously observed in our and other studies, endometriosis was less common among Black compared with White women in this analysis. Asian women were reported to be at increased endometriosis risk compared with other races; however, we observed decreased endometriosis incidence in Asian compared with White women. The mechanisms underlying these racial disparities are unknown and need to be researched further. Interestingly however, the lower endometriosis incidence in Black and Asian women could be partly related to the association between endometriosis and light pigmentation phenotypes. Cutaneous melanoma and other skin cancers are indeed also less common in Asian or African populations.

The large sample size and cohort design of the NHSII offer a unique opportunity to clarify the relations between pigmentation, family history of melanoma and endometriosis risk, taking into account potential confounders of these associations. However, the large sample size of our cohort made it possible to detect very small associations, and considering the modest magnitude of our findings, we cannot rule out residual confounding by unmeasured factors. Also, our cohort did not include data on other pigmentary traits that were investigated in other studies, several of those being specifically designed to investigate the relations between pigmentary traits, family history of melanoma and endometriosis risk. Since endometriosis diagnosis and host factors were self-reported, there is potential for outcome and exposure misclassification. Regarding the outcome, our validation study showed that endometriosis diagnosis could be confirmed in 96.2% of women who reported laparoscopically-confirmed endometriosis. Thus, a small proportion of cases may be misclassified, but this is unlikely to have a strong impact on our findings. The studied exposures were collected once in the NHSII, and thus we could not measure reproducibility of these factors. However, others have generally shown high levels of agreement for pigmentary factors, although assessment of number of naevi was reported with moderate agreement. Nevertheless, potential misclassification in pigmentary traits is unlikely to be differential between endometriosis cases and non-cases, thus mostly resulting in underestimation of the associations.

In conclusion, our data support the increasing evidence suggesting that fair pigmentation, naevus propensity and family history of melanoma may be associated with endometriosis risk. Further research is needed to clarify these relationships and confirm this potentially novel risk profile for endometriosis.

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