Personal history of endometriosis and risk of cutaneous melanoma in a large prospective cohort of French women.

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Personal History of Endometriosis and Risk of Cutaneous Melanoma in a Large Prospective Cohort of French Women

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Background: An association between melanoma and endometriosis has been reported, but most findings relied on case-control studies or a limited number of melanoma cases, and therefore the available evidence is weak. Moreover, the effect of other benign gynecological diseases on melanoma risk is unknown.

Methods: We prospectively studied data from the Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale cohort, which includes 98 995 French women, insured by a national health scheme mostly covering teachers, aged 40 to 65 years at inclusion. Data on history of endometriosis and other benign gynecological diseases were regularly collected, starting in 1990. Relative risks and 95% confidence intervals were computed using Cox proportional hazards regression models.

Results: During 12 years of follow-up, 363 melanoma cases were ascertained among 91 965 subjects. A history of endometriosis (n=5949) was significantly associated with a higher risk of melanoma (relative risk, 1.62; 95% confidence interval, 1.15-2.29). There was also a significantly increased risk among women with a history of fibroma (n=24 375), compared with those who had no such history (relative risk, 1.33; 95% confidence interval, 1.06-1.67). A history of ovarian cyst, uterine polyp, breast adenoma/fibroadenoma, or breast fibrocystic disease was not significantly associated with risk.

Conclusions: These data provide the strongest evidence to date of a positive association between a history of endometriosis and melanoma risk. The association between fibroma and melanoma, which has not been previously described, warrants further investigation.

Previous research has suggested an unexpected association between melanoma and a history of endometriosis.[1-5] However, data from large prospective studies are scarce. Only 3 cohort studies are available,[1,6,7] but their analyses were based on a limited number of melanoma cases. Moreover, some were restricted to a population of infertile[1] and postmenopausal women,[7] and one of them is a retrospective study of women with endometriosis.[6] Because melanoma has been hypothesized to be related to female hormone levels,[8,9] and because endometriosis also involves hormonal factors,[10] a hormonal hypothesis may explain the link previously found between these 2 diseases. Other gynecological diseases, such as ovarian cyst, fibroma, uterine polyp, and benign breast diseases, may also involve hormonal alterations and thus have an effect on the risk of melanoma. However, previous studies did not investigate this issue. We sought to determine the potential effects of a personal history of endometriosis and some other benign gynecological diseases on the risk of cutaneous melanoma in the Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale (E3N) cohort.

METHODS

The E3N Cohort

The design of the prospective E3N has been detailed elsewhere.[11] Briefly, the cohort consists of 98 995 women living in France, aged 40 to 65 years at inclusion and insured by a national health insurance plan primarily covering teachers. The French National Commission for Computed Data and Individual Freedom gave its ethical approval for the study. Participants were enrolled from February 1, 1989, through November 30, 1991, after having replied to a baseline self-administered questionnaire and provided informed consent. Follow-up questionnaires were sent every 2 years thereafter and addressed medical events such as cancer and benign gynecological diseases and age at diagnosis. Information on potential confounders such as phototype factors and

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educational level was recorded at baseline. Data on body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) were available in each questionnaire. Age at menarche, duration of menstrual cycles, number of live births, and use of infertility treatment were collected in the first 2 questionnaires. Menopausal status and age at menopause were collected at baseline and updated in each follow-up questionnaire; use of oral contraceptives, oral progestagens, and hormone replacement therapy were also updated in each questionnaire and were first recorded in the second questionnaire.

Population for analysis and follow-up

Participants who reported a history of cancer other than basal cell carcinoma at baseline (n=5516), those who were lost to follow-up from baseline (n=1484), and those who reported to have never menstruated (n=30) were excluded. Person-years were computed from the date of the return of the first questionnaire to the date of the diagnosis of melanoma, the diagnosis of any other cancer, or the last questionnaire returned or July 4, 2002, whichever occurred first.

Definition of benign gynecological diseases

We considered benign gynecological diseases those that were reported as having been treated or detected via a specific diagnostic procedure. For all diseases, type of treatment included surgery, hormonal treatment, or other treatment. Endometriosis, ovarian cyst, fibroma, or uterine polyp was considered a positive exposure if any were reported to have been detected by laparoscopy, biopsy, hysterography, hysteroscopy, or ultrasonography, whereas detection methods for breast adenoma/fibroadenoma or breast fibrocystic disease included biopsy, mammography, or thermography. Ovarian cysts reported with endometriosis were not considered, to avoid potentially misdiagnosed ovarian endometriotic cyst cases. Overall, 8.9% of self-reported benign gynecological diseases were considered negative exposures and were included in the comparison group.

Statistical analysis

We used Cox proportional hazards regression models with age as the timescale to estimate the relative risks and 95% confidence intervals associated with a history of benign gynecological disease.We tested the proportional hazards hypothesis graphically by using log-log survivor plots and by adding an interaction term between each time-dependent variable and time in our model.We controlled for phototype factors, including hair color (blond, red, chestnut, brown, or dark), skin complexion (fair or dark), number of nevi (very many, many, few, or none), number of freckles (very many, many, few, or none), and skin sensitivity to sun exposure. Regarding the latter, we asked participants about their skin response if exposed to the sun for the first time in summer and recorded the answers as highly sensitive, moderately sensitive, and not sensitive. We further adjusted for BMI ($\leq$25 or >25), parity (nulliparous, 1 or 2, 3 or 4, or $\geq$5 children), use of oral contraceptives (ever or never), age at menarche (<13, 13 or 14, or $\geq$15 years), duration of menstrual cycles (irregular, $\leq$24, 25-31, or $\geq$32 days), and age at menopause (premenopausal, <48 years, 48-51 years, or $\geq$52 years). Data on history of benign gynecological diseases and BMI were analyzed as time-dependent variables. Missing data for age at diagnosis of benign gynecological disease were imputed to the age when the subject answered the questionnaire in which the corresponding disease was declared. Missing values in age at menopause were imputed to the median age at artificial menopause (47 years) or at natural menopause (51 years) in our cohort. Missing BMI values were imputed to the BMI provided in the closest questionnaire. For all other adjustment factors, we imputed missing values to the modal category. Two-sided maximum-likelihood tests were performed in all Cox models, with P<.05 being the threshold of statistical significance. All analyses were performed with SAS statistical software (version 9.1; SAS Institute Inc, Cary, North Carolina).

RESULTS

During follow-up, a total of 363 primary melanoma cases were ascertained among the 91 965 women included. Pathology reports were obtained for 97.8% of the melanoma cases, and the remaining 2.2% were confirmed by the subjects' physicians. The median follow-up time was 12.0 years.

As expected, women with melanoma were significantly more likely to have blond, red, or chestnut hair; fair skin; a high sensitivity to sun exposure; and a large number of nevi and freckles, although risks related to skin complexion and sensitivity were no longer statistically significant in the multivariate models (Table 1). Educational level and BMI were not significantly associated with melanoma.

A personal history of endometriosis or fibroma significantly increased the risk of melanoma in women (Table 2). After controlling for potentially confounding variables, the relative risk for women with a personal history of endometriosis was 1.62 (95% confidence interval, 1.15-2.29). A significantly increased risk of melanoma was also found among women with a personal history of fibroma, compared with women with no such history (relative risk, 1.33; 95% confidence interval, 1.06-1.67). A history of ovarian cyst, uterine polyp, breast adenoma/fibroadenoma, or breast fibrocystic disease was not significantly associated with melanoma. Results were not substantially modified, whether models were adjusted for all of the previously cited potential confounders (including phototype factors) or for the phototype factors only. Further adjustment for the use of infertility treatment, oral progestagens alone, or, in postmenopausal women, hormone replacement therapy did not affect our results. We found a significant association between endometriosis and red hair (*P*=.02). However, test results of an interaction between endometriosis and red hair on the risk of melanoma were not statistically significant.

Table 1. **Characteristics of study participants**

Characteristics	Incident cutaneous melanoma No. (%)		RR (95% CI)	
	Yes (n = 363)	No (n = 91,602)	Adjusted for Age	Multivariable[a]
Educational level				
< Bachelor's degree	238 (65.6)	60 009 (65.5)	1.00 (Reference)	1.00 (Reference)
≥ Bachelor's degree	125 (34.4)	31 593 (34.5)	1.02 (0.82-1.27)	0.94 (0.75-1.17)
BMI at baseline				
≤25	304 (83.7)	75 709 (82.6)	1.00 (Reference)	1.00 (Reference)
>25	59 (16.3)	15 893 (17.4)	0.93 (0.70-1.23)	0.92 (0.70-1.22)
Hair color				
Blond	64 (17.6)	9 172 (10.0)	3.07 (2.11-4.46)	2.38 (1.61-3.54)
Red	20 (5.5)	1 524 (1.7)	5.76 (3.42-9.70)	4.12 (2.36-7.20)
Chestnut	217 (59.8)	55 274 (60.3)	1.72 (1.26-2.36)	1.52 (1.10-2.09)
Brown	48 (13.2)	21 161 (23.1)	1.00 (Reference)	1.00 (Reference)
Dark	14 (3.9)	4 471 (4.9)	1.38 (0.76-2.51)	1.42 (0.78-2.59)
Skin complexion				
Dark	100 (27.5)	37 157 (40.6)	1.00 (Reference)	1.00 (Reference)
Fair	263 (72.4)	54 445 (59.4)	1.81 (1.44-2.28)	1.28 (0.97-1.69)
Skin sensitivity to sun exposure				
Highly sensitive	137 (37.7)	25 844 (28.2)	1.92 (1.42-2.61)	1.15 (0.81-1.64)
Moderately sensitive	167 (46.0)	44 779 (48.9)	1.34 (0.99-1.81)	1.00 (0.72-1.38)
Not sensitive	59 (16.3)	20 979 (22.9)	1.00 (Reference)	1.00 (Reference)
Number of nevi				
Very many	89 (24.5)	9 629 (10.5)	7.04 (3.92-12.65)	6.98 (3.88-12.56)
Many	181 (49.9)	39 759 (43.4)	3.38 (1.92-5.94)	3.37 (1.91-5.93)
Few	80 (22.0)	33 170 (36.2)	1.73 (0.96-3.11)	1.82 (1.10-3.27)
None	13 (3.6)	9 044 (9.9)	1.00 (Reference)	1.00 (Reference)
Number of freckles				
Very many	33 (9.1)	4 679 (5.1)	2.53 (1.71-3.73)	1.47 (0.97-2.22)
Many	140 (38.6)	26 360 (28.8)	1.88 (1.46-2.41)	1.54 (1.19-1.99)
Few	80 (22.0)	22 029 (24.0)	1.28 (0.96-1.71)	1.25 (0.93-1.67)
None	110 (30.3)	38 534 (42.1)	1.00 (Reference)	1.00 (Reference)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; RR, relative risk.

[a]Adjusted for all the covariates presented in the table

COMMENT

This large prospective study suggests a significant increase in the risk of cutaneous melanoma in women with a personal history of endometriosis or fibroma.

Table 2. **Relative risks for cutaneous melanoma in relation to history of benign gynecological diseases in the E3N Cohort, 1990-2002**

History	No. of cases of cutaneous melanoma/No. of subjects (n=363/91 965)	Person-Years (1 007 319)	RR (95% CI)		
			Adjusted for Age	Adjusted for phototype factors[a]	Adjusted for all variables[b]
Endometriosis					
Never	327/86 016	910 701	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Ever	36/5 949	96 618	1.78 (1.26-2.51)	1.60 (1.13-2.25)	1.62 (1.15-2.29)
Ovarian cyst					
Never	309/79 545	758 940	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Ever	54/12 420	248 379	1.22 (0.91-1.63)	1.18 (0.88-1.57)	1.20 (0.90-1.61)
Fibroma					
Never	247/67 590	601 305	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Ever	116/24 375	406 014	1.41 (1.13-1.76)	1.31 (1.05-1.64)	1.33 (1.06-1.67)
Uterine polyp					
Never	297/75 669	743 591	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Ever	66/16 296	263 728	1.17 (0.90-1.53)	1.12 (0.86-1.47)	1.13 (0.86-1.47)
Breast adenoma/fibro-adenoma					
Never	327/84 985	884 303	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Ever	36/6 980	123 016	1.47 (1.04-2.07)	1.38 (0.98-1.95)	1.37 (0.97-1.93)
Breast fibrocystic disease					
Never	339/88 409	939 030	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Ever	24/3 556	68 289	1.64 (1.04-2.57)	1.51 (0.96-2.37)	1.50 (0.95-2.36)

Abbreviations: CI, confidence interval; E3N, Etude Epidémiologique auprès de Femmes de la Mutuelle Générale de l'Education Nationale; RR, relative risk.

a Includes hair color, skin complexion, skin sensitivity to sun exposure, number of nevi, and number of freckles.

b Includes phototype factors, body mass index, parity, use of oral contraceptives, age at menarche, duration of menstrual cycles, and age at menopause.

Our findings are in substantial agreement with the conclusion of a recent review[3] that suggested a possible association between endometriosis and melanoma. Endometriosis, a cause of infertility, is strongly related to nulliparity.[3] However, in our population, nulliparity was not related to the risk of melanoma, and results were stable after adjustment for parity or for use of infertility treatment. We were not able to test effect modification of parity or treatment for infertility because of the lack of power in the small subgroups.

No association between melanoma and endometriosis was found in a US cohort study[7] or in a Swedish historical cohort study of women with endometriosis[6]; however, those studies included limited numbers of melanoma cases (4 and 35, respectively). In contrast, a significantly increased risk among women with endometriosis was found in a retrospective cohort of infertile women (relative risk, 2.06; 95% confidence interval, 1.0-4.4, based on 42 melanoma cases).[1]

A single research group has found a significant positive association between melanoma and some disorders of the reproductive system, including endometriosis, in a prospective study of college alumnae[4] and no significant association between endometriosis and melanoma in a case-control study.[12] More recently, using updated data from their prospective study, the same group described a nonsignificant positive association between melanoma risk and endometriosis among red-haired women, but not among non–red-haired women, and a significant association between endometriosis and red hair,[5] as previously reported in the literature.[13] In our cohort, endometriosis was associated with red hair, but the test of an interaction between red hair and endometriosis on

the risk of melanoma was not statistically significant. Several authors have hypothesized susceptibility to endometriosis in red-haired women via altered coagulation or a deficient immune system.[5,13,14]

Some reproductive factors may be associated with both endometriosis and melanoma. Indeed, endometriosis has been shown to be associated with nulliparity and pauciparity,[10] and the risk of melanoma has previously been found to be reduced in women with higher parity and an earlier age at first birth.[8,15] Therefore, a hormonal pathway cannot be excluded. Another hypothesis is that endometriosis and melanoma may be related through genetic features because endometriosis is associated with an allelic imbalance in some tumor suppressor genes (p16Ink4, p53, and *PTEN*[phosphatase and tensin homolog]), loci[16-18] that have also been shown to be involved in melanoma.[19,20] Endometriosis and melanoma may thus share common etiological genetic aspects, and the results we observe may only be a reflection of correlated factors.

To our knowledge, this study is the first to report an association between melanoma and a history of fibroma. Some reported fibromas might be misdiagnosed cases of adenomyomas because these 2 diseases were not clearly distinguished at the time women responded to the questionnaires.[21-23] However, although adenomyosis is a form of endometriosis of the uterine wall, its characteristics are quite different from those of pelvic endometriosis,[24] and no association with melanoma has been reported so far. Further studies are needed to investigate this issue.

Because information on gynecological diseases relied on self-report, our findings may be influenced by a misclassification bias. We did not consider gynecological disease cases that were not reported as treated or ascertained, which likely appreciably decreased a potential overreporting bias. To address this issue, we performed a sensitivity analysis, considering all gynecological disease cases as positive exposures (ie, including those not reported as treated or detected by a specific diagnostic procedure). Relative risks and statistical significances were not substantially modified, except for breast fibrocystic disease, for which relative risk reached statistical significance. Thus, although a potential bias toward the null cannot be totally discarded, it is unlikely to be of great magnitude. Underreporting may also have occurred regarding endometriosis because it has a high incidence and causes few symptoms; thus, some endometriosis cases may have been misclassified in the unexposed group, which most likely resulted in underestimation of our findings.

The relationships we observed may reflect an underlying association between melanoma and treatment of benign gynecological diseases. Although data were not available on the specific type of drug used as hormonal treatment for the studied gynecological conditions, we regularly collect detailed data on overall hormonal treatments in the cohort. These include oral contraceptives and progestagens alone, which are often prescribed in France for treatment of endometriosis or other benign gynecological diseases. However, any use of these treatments was unrelated to the risk of melanoma in our cohort. Moreover, relative risks for melanoma were not substantially modified after adjustment for the use of these exogenous hormones. Therefore, our data do not strongly support the hypothesis that an underlying relation to hormonal treatment explains most of the associations we observed.

Subjects in our cohort were mainly female teachers with high levels of education and socioeconomic status. They were thus more likely than the general population to have visited their physicians and to have been examined for potential diseases. However, further adjustment for educational level did not affect our results. Data on sun exposure and sunburn history were not available for analysis, but these environmental factors are unlikely to be associated with gynecological diseases and thus to be potential confounders; in addition, our results were stable after adjustment for phototype factors. Finally, our results might have resulted from unknown residual confounders.

Despite these limitations, our study has several strengths. The E3N cohort included a large number of women who were prospectively followed up for 12 years, with detailed and regularly updated information about gynecological diseases. Most melanoma cases were ascertained by pathology reports, and data on potentially confounding factors such as phototype factors, educational level, and BMI were collected at baseline, before the diagnosis of melanoma.

In conclusion, our findings constitute the strongest evidence to date of an association between a personal history of endometriosis and cutaneous melanoma. Although a hormonal hypothesis cannot be excluded to explain this finding, our results may reflect correlated genetic risk factors between these 2 diseases. Endometriosis is an important women's health issue worldwide. Because this disease appears to be a risk indicator for cutaneous melanoma, gynecologists may play a role in melanoma prevention by alerting patients with endometriosis of

their higher susceptibility to the disease. Our finding of a relationship between a personal history of fibroma and melanoma warrants further investigation.

Author Contributions: Ms Kvaskoff had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Kvaskoff, Boutron-Ruault, and Clavel-Chapelon. *Acquisition of data:* Clavel-Chapelon. *Analysis and interpretation of data:* Kvaskoff, Mesrine, Fournier, Boutron-Ruault, and Clavel-Chapelon. *Drafting of the manuscript:* Kvaskoff. *Critical revision of the manuscript for important intellectual content:* Kvaskoff, Mesrine, Fournier, Boutron-Ruault, and Clavel-Chapelon. *Statistical analysis:* Kvaskoff and Fournier. *Obtained funding:* Kvaskoff, Boutron-Ruault, and Clavel-Chapelon. *Administrative, technical, and material support:* Clavel-Chapelon. *Study supervision:* Mesrine and Clavel-Chapelon.

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