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=5,949) 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.

Arch Intern Med. 2007;167(19):2061-0

Previous research has suggested an unexpected association between melanoma and a history of endometriosis. However, data from large prospective studies are scarce. Only 3 cohort studies are available, but their analyses were based on a limited number of melanoma cases. Moreover, some were restricted to a population of infertile and postmenopausal women, and one of them is a retrospective study of women with endometriosis. Because melanoma has been hypothesized to be related to female hormone levels, and because endometriosis also involves hormonal factors, 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 design of the prospective E3N has been detailed elsewhere. 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 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, hysteroscopy, hysteroscopy, or ultrasonography, whereas detection methods for breast adeno/ 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 (≤ 25 or > 25), parity (nulliparous, 1 or 2, 3 or 4, or ≥ 5 children), use of oral contraceptives (ever or never), age at menarche (< 13, 13 or 14, or ≥ 15 years), duration of menstrual cycles (irregular, ≤ 24, 25-31, or ≥ 32 days), and age at menopause (pre-menopausal, < 48 years, 48-51 years, or ≥ 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 91965 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 post-menopausal 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.

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.

Our findings are in substantial agreement with the conclusion of a recent review1 that suggested a possible association between endometriosis and melanoma. Endometriosis, a cause of infertility, is strongly related to nulliparity.2 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 study7 or in a Swedish historical cohort study of women with endometriosis6; 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 alumnae4 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,7 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 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 distin-
gestagens alone, which are often prescribed in France for cohort. These include oral contraceptives and pro-
lact detailed data on overall hormonal treatments in the for the studied gynecological conditions, we regularly col-
labable on the specific type of drug used as hormonal treatment
ng association between melanoma and treatment of be-
causes few symptoms; thus, some endometriosis cases may
garding endometriosis because it has a high incidence and
magnitude. Underreporting may also have occurred re-
cannot be totally discarded, it is unlikely to be of great
sance. Thus, although a potential bias toward the null
related to the risk of melanoma in our cohort. Moreover,
with gynecological diseases and thus to be potential
confounders; in addition, our results were stable after ad-
potential diseases. However, further adjustment for edu-
tional level did not affect our results. Data on sun expo-
ure and sunburn history were not available for analysis,
but these environmental factors are unlikely to be associ-
ed with gynecological diseases and thus to be potential
confounders; in addition, our results were stable after ad-
justment 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 as-
certained by pathology reports, and data on potentially confounding factors such as phototype factors, educa-
tional 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 his-
tory of endometriosis and cutaneous melanoma. Although a hormonal hypothesis cannot be excluded to ex-

### Table 2. Relative Risks for Cutaneous Melanoma in Relation to History of Benign Gynecological Diseases in the E3N Cohort, 1990-2002

<table>
<thead>
<tr>
<th>History</th>
<th>No. of Cases of Cutaneous Melanoma/No. of Subjects (n = 363/91965)</th>
<th>Person-Years (n = 1 007 319)</th>
<th>RR (95% CI) Adjusted for Age</th>
<th>Adjusted for Phototype Factors</th>
<th>Adjusted for All Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometriosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>36/5949</td>
<td>96 618</td>
<td>1.78 (1.26-2.51)</td>
<td>1.60 (1.13-2.25)</td>
<td>1.62 (1.15-2.29)</td>
</tr>
<tr>
<td>Ovarian cyst</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>54/12 420</td>
<td>248 379</td>
<td>1.22 (0.91-1.63)</td>
<td>1.18 (0.88-1.57)</td>
<td>1.20 (0.90-1.61)</td>
</tr>
<tr>
<td>Fibroma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>116/24 375</td>
<td>406 014</td>
<td>1.41 (1.13-1.76)</td>
<td>1.31 (1.05-1.64)</td>
<td>1.33 (1.08-1.67)</td>
</tr>
<tr>
<td>Uterine polyp</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>297/75 669</td>
<td>743 591</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Ever</td>
<td>66/16 296</td>
<td>263 728</td>
<td>1.17 (0.90-1.53)</td>
<td>1.12 (0.86-1.47)</td>
<td>1.13 (0.86-1.47)</td>
</tr>
<tr>
<td>Breast adenoma/fibroadenoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>327/84 985</td>
<td>884 303</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Ever</td>
<td>36/9380</td>
<td>123 016</td>
<td>1.47 (1.04-2.07)</td>
<td>1.38 (0.98-1.95)</td>
<td>1.37 (0.97-1.93)</td>
</tr>
<tr>
<td>Breast fibrocystic disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>24/3536</td>
<td>68 289</td>
<td>1.64 (1.04-2.57)</td>
<td>1.51 (0.96-2.37)</td>
<td>1.50 (0.96-2.36)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; E3N, Etude Epidemiologique auprès de Femmes de la Mutuelle Générale de l’Education Nationale; RR, relative risk.
aIncludes hair color, skin complexion, skin sensitivity to sun exposure, number of nevi, and number of freckles.
bIncludes phototype factors, body mass index, parity, use of oral contraceptives, age at menarche, duration of menstrual cycles, and age at menopause.
plain 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.

Accepted for Publication: June 11, 2007.

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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, 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.

Financial Disclosure: None reported.

Funding/Support: This study was supported by the French League Against Cancer, the European Community, the 3M Company, the Mutuelle Générale de l’Education Nationale, the Institut Gustave Roussy, the Institut National de la Santé et de la Recherche Médicale, and the Fondation de France (Ms Kvaskoff).

Role of the Sponsors: The funding sources had no involvement in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.

Additional Contributions: We thank all of the study cohort for their continued participation in the study and for providing data, and the practitioners for providing pathology reports. Rafika Chait, MSc, Marie Fangon, Lyan Hoang, MSc, and Maryvonne Niravorang, BSc, managed the data.

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