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Cancers, infections, and endocrine diseases in women with endometriosis

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Abstract

Objective—To assess the prevalence of patient-reported, physician-diagnosed comorbid conditions in women with endometriosis.

Design—Cross-sectional study of self-reported survey data.

Setting—Academic research.

Patient(s)—Four thousand three hundred thirty-one Endometriosis Association (EA) members reporting surgically diagnosed endometriosis.

Intervention(s)—None.

Main Outcome Measure(s)—Self-reported, physician-diagnosed infectious diseases, cancers, and endocrine diseases.

Result(s)—Nearly two-thirds of women reported one or more of the assessed conditions. Recurrent upper respiratory infections and recurrent vaginal infections were common and more likely in women responding to the EA survey. Melanoma was reported by 0.7% (n = 29), breast cancer by 0.4% (n = 16), and ovarian cancer by 0.2% (n = 10). While ovarian cancer and melanoma were significantly more common than in the general population, breast cancer was surprisingly less common. Addison's disease and Cushing's syndrome were rare (0.2% and 0.1%, respectively).

Conclusion(s)—Respondents reported a higher prevalence of recurrent upper respiratory or vaginal infections, melanoma, and ovarian cancer than the general population. These findings document other potential associations related to the immune system, which may help focus future research into this disease.

Keywords

Cancer; infectious disease; endocrine disease; endometriosis

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A higher prevalence of autoimmune diseases and chronic pain and fatigue states have previously been reported by women belonging to the Endometriosis Association who reported surgically diagnosed endometriosis (1). Immune response abnormalities and alterations as well as inflammation previously noted in women with endometriosis may (2,3) predispose them to have cancer and infections.

While studies assessing infections in women with endometriosis are lacking, research has suggested that endometriosis may increase the risk of ovarian cancer (4,5), particularly endometrioid and clear cell ovarian cancer (6,7). A diminished risk among those with tubal ligation and hysterectomy (8) suggests that cancer may be promoted by growth factors, cytokines, and inflammatory mediators, which gain access to the ovarian epithelium during retrograde menstruation. Further, dioxin and endocrine-disrupting environmental toxicants that modify the inflammatory process have been strongly associated with endometriosis (9). Other investigators have reported that women with endometriosis are at increased risk of melanoma (10,11) and non-Hodgkin's lymphoma (5,12). The relationship between endometriosis and breast cancer is less certain (4,10,13,14).

We hypothesized that women with surgically diagnosed endometriosis responding to the 1998 Endometriosis Association survey were more likely to report physician-diagnosed cancers, endocrine disease, and infections than women in the general population. We also determined the prevalence of other diseases reported in the survey including congenital birth defects and mitral valve prolapse.

MATERIALS AND METHODS

Data Source

In 1998, the Endometriosis Association (headquarters, Milwaukee, WI) surveyed approximately 10,000 of its female members in North America. The mailed questionnaire gathered self-reported information about the symptoms of endometriosis and general medical history. Questionnaires from 4745 respondents were entered into the Clinical Trials Database at the National Institutes of Child Health and Human Development in Bethesda, Maryland, and were available for analysis. Questionnaires were anonymized and deidentified to ensure confidentiality and were approved as exempt from Investigational Review Board reviews by the National Institutes of Health Office of Human Subjects Research and Committee on Human Research, George Washington University, Washington, DC.

Disease Prevalence in the Study

Data were restricted to women reporting a surgical diagnosis of endometriosis (n = 4331) and served as the denominator for all disease prevalence calculations. Demographic characteristics of race, education level, socioeconomic status, and age were tabulated.

Diseases were categorized as [1] cancers including breast, ovary, non-Hodgkin's lymphoma, and melanoma; [2] infectious diseases including recurrent upper respiratory or vaginal infections (each defined as one or more a year), candidiasis (defined as allergy/infection of the yeast Candida albicans), and Epstein-Barr virus infection (mononucleosis); [3] endocrine diseases including Addison's disease and Cushing's syndrome; and [4] other conditions including congenital birth defects and mitral valve prolapse. Women reported whether or not they had each condition and indicated physician diagnosis, age at diagnosis, and treatments prescribed that served to corroborate the diagnosis.

General Population Data

Demographic data for the 1998 U.S. female population were obtained from the Census Bureau. Population disease prevalence estimates in the United States were from published literature and sources such as the Centers for Disease Control and Prevention and the National Center for Health Statistics. Cancer data for breast, ovary, non-Hodgkin's lymphoma, and melanoma were obtained from the National Cancer Institute's Surveillance, Epidemiology, and End Results database. Prevalences could be compared only if [1] the prevalence for females was reported and [2] a denominator could be determined. If available, population data were from 1998, when the Endometriosis Association survey was conducted. Age-specific data in the population were available for comparisons of breast cancer, ovarian cancer, non-Hodgkin's lymphoma, melanoma, and recurrent upper respiratory infections. Because of the heightened risk of melanoma among whites, and the overrepresentation of whites in our study, population age-specific rates from white females for melanoma were used.

Data Analysis

The prevalence of patient-reported, physician-diagnosed conditions was compared with estimates in the U.S. general female population. Two-sided, two-sample *Z*-tests were used to compare demographic characteristics and disease prevalences. One-sample *t*-tests were used to compare age at diagnosis of breast cancer, ovarian cancer, non-Hodgkin's lymphoma, and melanoma. Prevalence odds ratios (POR) and 95% confidence intervals (CI) were computed. Data were analyzed using SAS v9.1 (SAS Institute, Inc., Cary, NC) and PEPI v4.0 (Gahlinger & Abramson, 1993–2001, Sagebrush Press, Salt Lake City, UT).

Sensitivity Analysis

For all statistically significant differences, a sensitivity analysis was done to determine the threshold for overestimation and underestimation at which the observed statistically significant difference between the two groups would disappear. This enabled us to evaluate the potential impact of misclassification on the validity of the findings. Disease prevalence was assumed to be overreported in the study sample self-reporting physician diagnosis and underreported in the general population by 10%–90%.

RESULTS

Study Population

The sample was restricted to women reporting surgical diagnosis of endometriosis who were members of the Endometriosis Association (n = 4,331). Respondents were primarily white, with fewer than 6% blacks, Hispanics, Native Americans, Asians, and others (Table 1). Almost all (97.1%) women were of reproductive age, with a mean age of 36.2 years (range, 14–74 years). Most respondents were college educated and had a combined family annual income above $50,000 (Table 1). Compared with the general population, women in the study were more likely to be white ($P<.0001$), young ($P<.0001$), college-educated ($P<.0001$), and of a higher socioeconomic status ($P<.0001$).

Cancers, Infections, and Other Diseases

Overall, 2,859 (66.0%) women self-reporting surgical diagnosis of endometriosis also reported physician diagnosis of at least one other condition, of whom 80% reported conditions in only one category, 19% in two, and <1% in three, and none indicated all four categories.

Women in this study were substantially younger than the general population at the time of diagnosis of breast cancer (mean age 40.9 vs. 62.0 years, $P<.0001$), melanoma (mean age 32.2 vs. 54.0 years, $P<.0001$), ovarian cancer (mean age 39.4 vs. 64.0 years, $P=.0005$), and non-

Hodgkin's lymphoma (mean age 36.0 vs. 70.0 years, *P*=.04). Fifty-seven (1.32%) completing the survey reported specific cancers (Table 2), with melanoma in 29 (0.67%), breast cancer in 16 (0.37%), ovarian cancer in 10 (0.23%), and non-Hodgkin's lymphoma in 2 (0.05%). Ovarian cancer and melanoma were each significantly more common in the women in this study than in similarly aged women in the general population (ovarian cancer POR = 3.43; 95% CI, 1.74–6.54, *P*<.0001; melanoma POR = 3.81; 95% CI, 2.60–5.56, *P*<.0001). Breast cancer was significantly less common in women with endometriosis than in similarly aged women in the general population (POR = 0.54; 95% CI, 0.32–0.90, *P*=.016).

Recurrent upper respiratory infections were reported by 35% and recurrent vaginal infections by 29% of patients. Compared with the general population, these were 7 and 3 times more common in women with endometriosis than in the general female population, respectively (Table 2, *P*<.0001). Mononucleosis was surprisingly less likely in women with endometriosis than in those in the general population (Table 2, *P*<.0001), with candidiasis just as likely in both populations.

Endocrine diseases were extremely rare, with only 10 (0.23%) and four (0.09%) subjects reporting Addison's disease and Cushing's syndrome, respectively. Mitral valve prolapse was very common, reported in 15% of respondents, and more than twice as likely as estimated in the general population (POR = 2.74; 95% CI, 2.32–3.24, *P*<.0001). Congenital birth defects were not common.

Sensitivity Analysis

Sensitivity analyses indicated that a high degree of misclassification in both the study sample and the general population would be necessary to negate the higher prevalence of melanoma and recurrent upper respiratory infections in women with endometriosis (Table 2). By contrast, minimal to moderate (25%–50%) misclassification in cases of ovarian cancer and recurrent vaginal infections would eliminate the observed differences between populations. The small absolute number of women reporting Cushing's syndrome and Addison's disease made their higher likelihood less so. It is likely that recurrent upper respiratory infections and recurrent vaginal infections are significantly more common among women with endometriosis in this study. However, physician-diagnosed ovarian cancer and melanoma may be a valid association, even though a small number of women with endometriosis reported their diagnosis. The lower occurrence of breast cancer in the study sample was supported with the sensitivity analysis.

DISCUSSION

This group of 4331 surveyed Endometriosis Association members who reported surgically diagnosed endometriosis commonly reported other physician-diagnosed diseases. Of the infectious diseases, recurrent upper respiratory infections and recurrent vaginitis were more likely in the study population, but candidiasis and mononucleosis were not. The nature of these infections (bacterial, viral, fungal) is not known, and thus many women with recurrent vaginitis may have had vaginal candidiasis and therefore were unsure of the diagnosis. Melanoma and ovarian cancers were reported by about 30 and 10 women, respectively, but were more common in the study population than in similarly aged women in the general population. Addison's disease and Cushing's syndrome were rare but were more common in the survey respondents than in the general population. However, their low absolute numbers did not assure statistical significance. Mitral valve prolapse was common.

Studies have noted an increased risk of ovarian cancer with endometriosis, especially among patients with a long-standing history (>10 years) of the disease and diagnosis before age 30

(4,7,15,16). Melin et al. reported that those with ovarian cancer diagnosed after endometriosis had had cancer at a younger age when compared with the general population (5).

Molecular investigations on the transformation of endometriosis to ovarian cancer have attributed it to various genetic mutations (17–21). The androgenic agent, danazol, which is commonly used in treating endometriosis, has been shown to be an independent risk factor for ovarian cancer, with women who have ever used danazol having a 3.2 times increased risk of ovarian cancer compared with those who did not (22). We have noted that danazol use was common in this cohort of women (23). The potential role of endogenous or exogenous hormones in promoting the development of ovarian cancer continues to be explored.

Melanoma has been reported in those with subfertility, with an increased relative risk of melanoma among women with primary infertility due to endometriosis (12). An increased incidence of dysplastic nevi, a precursor lesion of melanoma, has been documented in patients with endometriosis (24).

While our study suggests an increased occurrence of ovarian cancer and melanoma, the low prevalence of ovarian cancer may be explained by the young age of the study population. While the relatively low prevalence of both and, in sensitivity analysis, the disappearance of increased ovarian cancer prevalence with moderate misclassification brings into question these findings, there are some characteristics of this population that may be responsible for this lower prevalence. The common treatments of oral contraceptives and other hormones for endometriosis, which are frequently used in this population (23), may have lowered the risk of ovarian cancer. In addition, half of the women reported oophorectomy and/or hysterectomy (20% oophorectomy, 18% hysterectomy, and 12% both) (23), possibly reducing the risk of ovarian cancer in these women who reported surgically diagnosed endometriosis.

The lack of an increased prevalence of breast cancer in the study population may have been decreased by the high rate of oophorectomy (32%), which might offset the effect of the high rate of infertility (1) and hormone use (23). The lower prevalence may be expected in this younger population as incidence increases with age, with the highest rates in women over age 50. We do not know whether the members of this cohort would have developed breast cancer as they aged. Other studies assessing the relation between endometriosis and breast cancer have been inconclusive or have shown no relationship (4,13,14).

The higher prevalence of recurrent upper respiratory and vaginal infections might be expected as other autoimmune diseases have been reported by this group of women and immune abnormalities occur in women with endometriosis (1–3). Due to the self-reported nature of the data, it is possible that women mistakenly reported any recurrent or chronic vaginal complaint as vaginitis. Similarly, recurrent upper respiratory infections might indicate other recurrent respiratory problems like sinusitis or frequent colds. Nonetheless, physician-diagnosed recurrent upper respiratory or vaginal infections are likely in this group of women because, by sensitivity analyses, high degrees of misclassification would need to exist for these observed differences to disappear.

The lower prevalence of candidiasis may be due to its narrow definition as “allergy and systemic infection with the yeast Candida albicans,” a condition hypothesized to be common in women with endometriosis, that was used in the survey. The prevalence of women with mononucleosis may have been underreported because women may not have been familiar with the term “mononucleosis” or may have had the disease but not been diagnosed by a physician.

The prevalence of Cushing’s syndrome and Addison’s disease were extremely low, suggesting that their statistical significance occurred by chance.

The higher prevalence of mitral valve prolapse is negated with minimal misclassification. Perhaps women were diagnosed with mitral valve prolapse during evaluation for surgery, although whether diagnosis was made by echocardiogram was not ascertained.

While this study primarily involved white, young, educated, and more affluent women, the large sample size strengthened the study and provided statistical power. In addition, the survey collected information regarding diagnoses, including age and treatment, which were used to corroborate responses. The sensitivity analysis helped assess the validity of the findings.

There are, however, several limitations. First, conditions are self-reported, and it is not possible to confirm the diagnosis by laboratory tests or review of medical records. Although the analysis was restricted to women reporting a surgical diagnosis of endometriosis, disease misclassification for endometriosis was possible. Misclassification of other conditions may have occurred, leading to an overestimate of the true prevalence in the study sample or an underestimate in the general population. Selection bias may also exist, since the 47% of women who opted to complete the questionnaire may be different from nonrespondents or other members of the Endometriosis Association; in addition, they were more educated than the general population. It would be ideal to compare results from women with endometriosis with a similar group of women without endometriosis completing the same survey, but it might be difficult to administer to women without endometriosis since the survey was specifically designed to capture the health experiences of women with endometriosis.

Our study has many strengths, and careful methodological steps were taken to minimize the likelihood of errors and biases. While the limitations are less likely to affect the study's internal validity, the study findings can be generalized only to women with endometriosis similar to those who belong to the Endometriosis Association. In addition, women who join support groups may not be representative of the population of individuals with the disease.

In conclusion, our study describes the prevalence of several coexisting diseases suspected to be common in women with endometriosis. Respondents to the Endometriosis Association survey were more likely to have recurrent upper respiratory and vaginal infections than the general population. As others have reported, ovarian cancer and melanoma were statistically more common in the study population than in the general population. The younger age of the study population and the low prevalence limit our ability to make inferences about these associations. These findings support our previous observation that women in this study reporting pain and surgically diagnosed endometriosis also report a high prevalence of autoimmune diseases. This documents another potential association with the immune system, which may help focus future research into this disease.

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TABLE 1

Demographic characteristics of 4331 respondents reporting surgically diagnosed endometriosis compared with the general U.S. female population.

Demographic	Study population[a] n (%)	General U.S. female population,[b] %
Age, years[c]:	n = 4188	n = 138,218,000
<15	2 (0.1)	20.5
15–20	55 (1.3)	6.7
21–25	307 (7.3)	6.3
25–30	702 (16.8)	6.8
31–35	982 (23.4)	7.4
35–40	1004 (24.0)	8.2
41–45	738 (17.6)	8.0
46–50	282 (6.7)	7.0
>50	116 (2.8)	29.4
Race/ethnicity[c]:	n = 3919	
White	3700 (94.4)	72.2
Black	75 (1.9)	12.5
Hispanic	74 (1.9)	10.9
Native American	14 (0.4)	0.7
Asian	39 (1.0)	3.7
Other	17 (0.4)	Not available
Education level[c]:	n = 4247	
Did not complete high school	22 (0.5)	21.7
High school graduate	296 (7.0)	32.9
Some college	828 (19.5)	18.6
College graduate	1810 (42.6)	14.1
Postgraduate degree	1168 (27.5)	5.5
Other	123 (2.9)	7.2
Combined family annual income[c]:	n = 4063	
$0–24,999	377 (9.3)	24.0
$25,000–49,999	1102 (27.1)	29.4
$50,000–74,999	1132 (27.9)	21.6
≥$75,000	1452 (35.7)	25.0

[a] Women with surgically diagnosed endometriosis completing the Endometriosis Association survey in 1998.

[b] General U.S. female population data (1998) from the U.S. Census Bureau.

[c] $P<.05$ compared with the general U.S. female population.

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TABLE 2

Prevalence of cancers, infectious diseases, endocrine diseases, and other reported conditions among women with endometriosis completing the Endometriosis Association survey compared to estimates in the U.S. general female population.

	Women with endometriosis, n (%)	Prevalence among women with endometriosis (per 1000)	Estimated prevalence in the general U.S. female population (per 1000)	Prevalence odds ratio	95% CI	*P*	Sensitivity analysis threshold[a]
Cancers (25):							
Melanoma	29 (0.67)	6.70	1.76	3.81	2.60, 5.56	<0.0001	>25/>75
Breast	16 (0.37)	3.69	6.82	0.54	0.32, 0.90	0.016	>90 / >90
Ovary	10 (0.23)	2.31	0.67	3.43	1.74, 6.54	<0.0001	25 / 50
Non-Hodgkin's lymphoma	2 (0.05)	0.46	0.55	0.84	0.14, 3.37	NS	*b*
Infectious diseases:							
Recurrent upper respiratory infections (26)	1523 (35.17)	351.65	70.14	7.19	6.73, 7.68	<0.0001	>50 / >50
Candidiasis (27)	1372 (37.65)	376.51	374.88	1.01	0.87, 1.16	NS	*b*
Recurrent vaginal infections (28)	1267 (29.25)	292.54	100.00	3.72	3.48, 3.98	<0.0001	50 / 50
History of mononucleosis (29)	596 (13.76)	137.61	900.00	0.02	—	<0.0001	>90 / >90
Endocrine diseases:							
Addison's disease (30)[c]	10 (0.23)	2.31	0.09	—	—	<0.0001	*b*
Cushing's syndrome (28)[c]	4 (0.09)	0.92	0.00	—	—	<0.0001	*b*
Other diseases:							
Mitral valve prolapse (31)	632 (14.59)	184.36	76.19	2.74	2.32, 3.24	<0.0001	25 / 50
Congenital birth defects (26)	118 (2.72)	27.25	30.00	0.91	0.75, 1.09	NS	*b*

Note NS = not significant.

[a] Sensitivity analysis threshold is the amount of misclassification required to negate statistically significant differences found between populations. Assumed were an overestimation in prevalence in the study sample (%) and an underestimation in the general population prevalence (%).

[b] Not applicable because statistically nonsignificant at the observed crude level or comparison with the general population could not be done.

[c] The prevalence in the general population was extremely low for meaningful POR and 95% CI calculations.

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