Cancer, infections, and endocrine disease in women with endometriosis

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Introduction

- Women with endometriosis
  - Higher prevalence of autoimmune disease, chronic pain and fatigue (Sinaii, 2002)
  - Abnormal immune response may predispose cancer and infection (Giudice, 2004; Bulum, 2009)
    - Risk of ov cancer↑ (endometrioid and clear cell)
    - Risk of melanoma and non-Hodgkin's lymphoma ↑
    - Risk of breast Ca → less certain
  - Dioxin and toxicants strongly associated with endometriosis. (Bruner-Tran, 2008)

Aim of the study

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

Materials and Methods

Data source

- 10,000 members of Endometriosis Association in 1998 → mailed questionnaire
- Respondents : 4745 women

Disease Prevalence in the study

- Women with surgically diagnosis of endometriosis → 4331 pts
- Analysis demographic characteristics
  - Race
  - Education level
  - Socioeconomic status
  - Age

Disease Prevalence in the study

- Diseases (4 categories)
  - Cancers
    - Breast, ov , non-Hodgkin's lymphoma, melanoma
  - Infectious diseases
    - Recurrent URI, vaginal infection, candidiasis , mononucleosis
  - Endocrine diseases
    - Addison's disease, Cushing's syndrome
  - Other conditions
    - Congenital birth defects, MVP
- Age at diagnosis, treatment

General population data

- Demographic data → from the Census Bureau
- Disease data → from CDC and National Center for Health Statistics
- Cancer data → from National Cancer Institute

Data analysis

- Two-sided, two-sample Z-tests → demographic characteristics and disease prevalences

- One-sample t-tests → age at diagnosis of cancer

Sensitivity analysis

- Determine the threshold for overestimation and underestimation at which the observed statistically significant difference between the two groups would disappear.
- Evaluate the potential impact of misclassification
- Assumed the disease prevalence
  - Overreported in the study and underreported in the general population by 10~90%.

Results

Demographic characteristics

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, y	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		6.8
31–35		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		12.5
Hispanic		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 f annual		
$0–24,99		4.0
$25,000–49,999		29.4
$50,000–74,999	1132 (27.9)	21.6
≥$75,000	1452 (35.7)	25.0

Mostly reproductive age

Mostly white

Mostly college educated and income > $50,000

[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.

Gemmill. Endometriosis, cancer and other diseases. Fertil Steril 2010.

Cancers, infections, and other diseases

- 2859 (66%) women with endometriosis + at least one other condition
  - 1 category : 80%
  - 2 categories : 19%
  - 3 categories : <1 %
  - All 4 categories : none

Cancers, infections, and other diseases

- Age of diagnosis of breast Ca, melanoma, ov Ca and non-Hodgkin's lymphoma → studied women younger than the general population

57 women reported specific cancer

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* value	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

- Ov Ca and melanoma were each significantly more common.
- Breast Ca was significantly less common .

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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

- Recurrent URI and vaginal infection were 7 and 3 times more common in women with endometriosis .
- Mononucleosis was less likely in women with endometriosis.
- Candidiasis was as likely in both population .

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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

- Endocrine diseases were extremely rare.
- MVP was very common and more than twice as likely as estimated in the general population .

Sensitivity analysis

- Prevalence of melanoma and recurrent URI → need high degree of misclassification to negate
- Prevalence of ov Ca and recurrent vaginal infection → need minimal to moderate misclassification to negate
- Prevalence of breast Ca → sensitivity analysis supported

Discussion

Ovarian Cancer vs endometriosis

- Increased risk in the study, esp the disease was diagnosed before 30y/o
  - Women with ov ca diagnosed after endometriosis had had cancer at a younger age (Melin et al.2006)

- Factors of transformation of endometriosis
  - Genetic mutation (Obata,1998; Baxter,2001; Baranova,1997; Martini,2002; Berchuck,2004)
  - Danazol : risk factor of ov ca → risk ↑3.2times (Cottreau,2003), use commonly in endometriosis. (Sinaii, 2007)

Ovarian Cancer vs endometriosis

- In our study : increased occurrence of ov Ca but low prevalence
  - Need moderate misclassification to negate by sensitivity analysis
    - Young age
    - Took OCPs and other hormones for endometriosis → lowered the risk of ov Ca. (Sinaii, 2007)
    - s/p oophorectomy and/or hysterectomy (Sinaii, 2007)

Melanoma vs Endometriosis

- Melanoma was more common in the study population than the general population.
- Increased relative risk of melanoma in women with primary infertility due to endometriosis. (Brinton, 2005)
- Increased incidence of dysplastic nevi (precursor lesion) in pts with endometriosis. (Hornstein,1997)

Breast Ca vs endometriosis

- Lack of an increased prevalence → may due to high rate of oophorectomy (32%).
- Incidence of breast cancer increases with age → younger population in this study .
- Other studies (Brinton, 1997; Weiss,1999; Moseson,1993)
  - Relation between endometriosis and breast cancer → inconclusive or no relationship.

Recurrent URI and vaginal infection

- Might be expected as other autoimmune diseases and immune abnormalities . (Sinaii, 2002; Giudice, 2004; Bulun, 2009)
- Self-reported data → may be possible mistakenly reported .
- Physician-diagnosed recurrent URI or vaginal infection are likely in this group of women (by sensitivity analysis).

Candidiasis vs endometriosis

- Lower prevalence in the study
  - May be due to narrow definition as “allergy and systemic infection with the yeast candida albicans”.

Mononucleosis vs endometriosis

- May be underreported: not familiar with or not be diagnosed by a physician.

Endocrine disease vs endometriosis

- The prevalence were extremely low, both P < 0.0001
  - The statistical significance occurred by chance

MVP vs endometriosis

- The higher prevalence is negated by minimal misclassification.
- May be diagnosed during evaluation for OP but not ascertained.

Advantages of the study design

- Large sample size _ 4331 pts
- Detail information collection
  - Age of diagnosis
  - Treatments
  - Responses
- Sensitivity analysis : assess the validity of the findings .
- Care methodological steps to minimize the likelihood of errors and biases.

Limitations of the study

- Conditions are self-reported
- Disease misclassification of endometriosis and other conditions
  - Overestimate in the study sample or underestimate in the general population .
- Selection bias
  - Respondents (47%) maybe different from non-respondents or other members.
  - More educated than the general population.

Conclusion

- Respondents to the Endometriosis Association survey were more likely to have recurrent URI and vaginal infections than the general population .

- Ov Ca and melanoma were statistically more common in the study population .

Conclusion

- The younger age of the study population and the low prevalence limit our ability to make inferences about these associations.

- These findings document other potential associations related to the immune system, which may help focus future research.

Thank you !!!