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A case-control investigation of adenomyosis: impact of control group selection on risk factor strength

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Abstract

Objective—Using a medical-record abstraction-based case-control study with two control groups, we evaluated adenomyosis risk factors and investigated differences related to comparison group selection.

Materials and Methods—Medical records of all female 18-49 year old Group Health (GH) enrollees with ICD-9 code 617.0 were abstracted using a standard data collection form. Cases were enrollees diagnosed with adenomyosis (N=174) between April 1996 and September 2001. For comparison, medical records of two control groups were selected from the GH population: an age-matched sample of female enrollees (population-based controls N=149) and all female 18-49 year-old enrollees undergoing a hysterectomy (hysterectomy controls N=106) during the same time without adenomyosis. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using logistic regression, adjusted for identified covariates.

Results—Compared with normal and underweight women, overweight and obese women had increased adenomyosis risk using hysterectomy controls [OR (95% CI): 2.2 (1.0, 4.5) overweight; 2.2 (1.1, 4.3) obesity] and population controls [OR (95% CI): 2.1 (1.2, 4.0) overweight; 3.8 (2.0, 7.0) obesity]. Using population controls, women with at least one live birth were more likely to have adenomyosis than nulliparous women [OR (95% CI): 3.4 (1.9, 6.2)].

Conclusion—While some risk factors persisted in analyses using either control group, divergent results in relation to other risk factors for adenomyosis suggest that results of investigations of this disease may be affected by the choice of the comparison population.

Keywords

case-control study; population-based; hospital-based; adenomyosis; risk factors

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Introduction and background

Adenomyosis is a benign gynecological disorder characterized by the invasion of endometrial glands and stroma deep within the uterine myometrium.(Bird, McElin, & Manalo-Estrella, 1972; Ferenczy, 1998) It may be asymptomatic in up to one-third of cases, while symptoms, if present, can include severe and progressively increasing dysmenorrhea and menorrhagia. Other symptoms include excessive uterine bleeding, chronic pelvic pain and dyspareunia. Treatment of symptoms is primarily by hysterectomy. (Bird et al., 1972; Matalliotakis, Katsikis, & Panidis, 2005)

Most cases of adenomyosis are diagnosed by a pathologist through histologic examination of excised uterine myometrial tissue after hysterectomy. Other diagnostic methods include pelvic exam and surgical evaluation (laparoscopy and laparotomy) and biopsy. Diagnosis via these techniques is often inaccurate and as a result they are not commonly used. In recent years, diagnosis via magnetic resonance imaging or vaginal ultrasound has been explored; however, there is currently no consensus about non-surgical diagnostic criteria. As a result of historically poor preoperative diagnostic accuracy and the necessity for hysterectomy to confirm diagnosis, the prevalence of this condition in the general population is not known. The reported prevalence of adenomyosis among women who undergo hysterectomy has varied from 8% to 28% in studies conducted in Greece, Italy, Denmark, and the United States, and has been reported to be as high as 57% in Pakistan.(Bergholt, Eriksen, Berendt, Jacobsen, & Hertz, 2001; Chrysostomou et al., 1991; Curtis, Hillis, Marchbanks, & Peterson, 2002; McCausland, 1992; Parazzini et al., 1997; Shaikh & Khan, 1990; Vavilis et al., 1997; Vercellini et al., 1995; Vercellini et al., 2006) Variability in these estimates is partially due to differences in histological criteria used for diagnosis and may also be related to differences in the relative frequency of comorbidities that necessitate hysterectomy in different populations.(Bergholt et al., 2001)

Several epidemiologic studies have investigated risk factors for adenomyosis. The majority have aimed to sample all women with hysterectomies occurring during a given time period at one or more hospitals. In these case-control studies, cases usually are women with pathology-confirmed adenomyosis, and the remaining women with hysterectomy serve as the comparison population. The results of these studies have been highly variable for factors related to reproductive history. For example, cesarean delivery has been associated with increased, decreased and unchanged risk of adenomyosis.(Bergholt et al., 2001; Vavilis et al., 1997; Levgur, Abadi, & Tucker, 2000; Curtis et al., 2002; Panganamamula et al., 2004) The inconsistent findings in studies of this condition may be due in part to variations in comparison group selection. The current medical-record abstraction-based study provided an opportunity to assess risk factors for adenomyosis using both hysterectomy and population-based control groups and to evaluate issues related to this aspect of study design that might affect results and their interpretation.

Methods

Study design

The study population consisted of enrollees in Group Health Cooperative (GH), a mixed model health maintenance organization with over 500,000 enrollees in Western Washington State.(Saunders, Davis, & Stergachis, 2008) We reviewed and abstracted the medical records of all female, 18-49 year old enrollees diagnosed with International Classification of Disease 9th revision (ICD-9) code 617.0, uterine endometriosis, as part of a case-control study of endometriosis conducted between April 1, 1996 and September 30, 2001. Record review of all potential subjects with this diagnosis was conducted to separate women with endometriosis on the outside of the uterus (true endometriosis) from those with

adenomyosis. During this time period, all diagnoses were histologically confirmed using uterine tissue obtained via hysterectomy, and the resulting pathology reports were part of the record review. In total, 174 women with adenomyosis in the absence of endometriosis or gynecologic cancer were included as cases in the statistical analysis. The reference date was assigned as the day, month and year of the first visit in the work-up that led to the diagnosis of adenomyosis.

For comparison, the medical records of two control groups were selected from the GH population. Population-based controls (n=154) were randomly selected from 18-49 year old women without a history of hysterectomy who were enrolled in GH during the time the cases were diagnosed, frequency-matched to cases on age. The population controls were assigned reference dates to correspond with the distribution of case reference dates. A second control group consisted of all 18-49 year old women in the GH population undergoing a hysterectomy during the same time period but found not to have endometriosis, adenomyosis, or gynecologic cancer (n=122). These hysterectomy controls were assigned as a reference date the date of their first visit for symptoms leading to the hysterectomy or, if asymptomatic, the date of the pelvic exam that identified the need for hysterectomy. Individuals with a medical record history of endometriosis were excluded from the control groups (n=5 from population controls and 16 from hysterectomy controls), resulting in 149 population controls and 106 hysterectomy controls for analysis.

Data collection consisted of abstraction of comprehensive inpatient and outpatient medical records. These reports included operative notes, pathology reports, and discharge summaries. Information from these records was obtained for the time period up until the reference date, and included age, race, height, weight, smoking status, pregnancy history (including number of pregnancies, induced abortions, spontaneous abortions, live births and other pregnancy outcomes), history of abdominal or pelvic surgery, other disease history, menopausal status, and use of oral contraceptives or hormone therapy.

Statistical Methods

As an initial step, demographic and health characteristics abstracted from medical records were summarized for the case group and the two control groups. To evaluate risk factors for adenomyosis, adjusted ORs and corresponding 95% confidence intervals were calculated comparing cases to hysterectomy controls and to population-based controls separately using multivariable unconditional logistic regression. Race, body mass index (BMI, weight (kg) / height (m)²), history of smoking, gravidity, history of cesarean delivery, and history of uterine trauma were individually evaluated as potential risk factors for adenomyosis. BMI was calculated based on last recorded height and weight in the medical record prior to the following dates: adenomyosis diagnosis for the cases, hysterectomy for the hysterectomy controls and reference date for population-based controls. Uterine trauma was defined as a history of induced abortion and/or history of uterine surgery (dilation and curettage, cesarean delivery, myomectomy, or endometrial ablation) in the medical record. The potential risk factors for adenomyosis were explored as both continuous and categorical variables and in most cases were treated as dichotomous factors. These models, with the exception of the model evaluating gravidity, were adjusted for matching variables age and reference year, and parity, an *a priori* confounding factor. Since gravidity and parity are highly correlated, the ORs for gravidity and parity were adjusted for age and reference year only. Additionally, all the covariates listed above as potential risk factors for adenomyosis were separately evaluated as potential model-based confounding factors (using the criterion of a change of 10% or greater in the beta coefficient from the logistic regression model) of the association between adenomyosis and individual hypothesized risk factors.

Data analyses were performed using SAS software (SAS Version 9.1 for Windows; SAS Institute Inc., Cary, NC). The study protocol was reviewed and approved by the Institutional Review Boards at GH and University of Washington.

Results

Clinical symptoms reported by adenomyosis cases were menorrhagia (59.3%), dysmenorrhea (33.1%), pelvic pain (19.8%) and dyspareunia (6.4%). Only 17.2% of cases reported no symptoms. The distributions of demographic characteristics among the case group, hysterectomy controls, and population-based controls are shown in Table 1. The mean ages of the cases, hysterectomy controls and population controls were 42.5, 39.1 and 41.4 years, respectively. Compared with the cases, a higher percent of hysterectomy controls were Caucasian (93.3% vs. 86.7%), whereas a lower percent of population controls were Caucasian (79.2%). The cases, hysterectomy controls and population controls had similar mean heights, 164.7, 165.8, and 164.5 centimeters, respectively. Cases were similar in weight to the hysterectomy controls and heavier than the population controls [mean weight in kilograms (sd): 82.4 (20.8), 80.0 (24.5), 74.1 (19.9), respectively].

Adjusted ORs comparing the adenomyosis cases to hysterectomy controls and population controls are presented in Table 2. In analyses using the population-based controls, overweight and obesity were strong risk factors for adenomyosis [odds ratio (OR) (95% confidence interval (CI)): 2.1 (1.2, 4.0) overweight; 3.8 (2.0, 7.0) obesity]. Using the hysterectomy controls, the results were similar for overweight but of a lesser magnitude for obesity [OR (95% CI): 2.2 (1.0, 4.5) overweight; 2.2 (1.1, 4.3) obesity].

Adjusting for age and reference year, women with at least one pregnancy were much more likely to have adenomyosis than nulligravid women [OR (95% CI): 5.4 (2.5, 11.8)] and women with at least one live birth were more likely to have adenomyosis compared with nulliparous women [OR (95% CI): 3.4 (1.9, 6.2)] when using the population-based controls. In contrast, in analyses using hysterectomy controls, adenomyosis risk was not associated with gravidity or parity.

After adjustment for age, reference year and parity, we found no associations between adenomyosis and history of cesarean delivery, uterine trauma or smoking using either control group. Because of the concern that the majority of the case group consisted of women with leiomyomas in addition to adenomyosis, in one analysis we restricted the case group to women with adenomyosis only (n=46). The risk estimates were slightly attenuated for obese BMI when comparing the case group to either hysterectomy [OR (95% CI): 2.0 (0.8, 5.4)] or population-based controls [OR (95% CI): 3.4 (1.3, 8.6)], while risk estimates for gravidity [OR (95% CI): hysterectomy controls 1.7 (0.4, 9.4); population-based controls 7.3 (1.7, 32.6)] and parity [OR (95% CI): hysterectomy controls 2.4 (0.7, 8.6); population-based controls 4.8 (1.6, 14.4)] increased.

Discussion

In this study, selected potential risk factors for adenomyosis were assessed using two distinct control populations: 1) women undergoing hysterectomy who were found not to have adenomyosis, endometriosis, or gynecologic cancer; and 2) a population-based sample of 18-49 year old female GH enrollees with no history of adenomyosis, endometriosis, or gynecologic cancer. For two of the risk factors we investigated, the results differed substantially depending on which control group we utilized.

Women undergoing hysterectomy for the treatment of chronic gynecologic conditions have almost always been used as controls in studies of adenomyosis. They enable the assessment

of predictors of adenomyosis within a subset of the population, specifically women with pelvic symptoms severe enough to warrant surgical evaluation and treatment. They may offer advantages of convenience, economy, and comparability with cases in terms of recall, and they have a documented absence of adenomyosis. However, selecting controls from proven non-cases does not ensure that this group is representative of the underlying population from which the cases arose; often symptoms associated with non-malignant uterine conditions (e.g. leiomyomas and prolapse) lead women to seek medical or surgical treatment. Hysterectomy-based controls may therefore have abnormal hormonal profiles due to an over-representation of co-existing hormonally-dependent gynecologic conditions. Thus, risk estimates for variables associated with high estrogen exposure (i.e. high waist: hip ratio and early onset of menstrual periods) would likely be falsely low using this type of control group. Additionally, because women who are willing to undergo a hysterectomy are more likely than women in the general population to have given birth (Koepsell, Weiss, Thompson, & Martin, 1980; Brett, Marsh, & Madans, 1997; Vessey, Villard-Mackintosh, McPherson, Coulter, & Yeates, 1992), case-control comparisons with hysterectomy control groups will result in low risk estimates for parity compared to those obtained with other control groups, as demonstrated in the current study. In prior case-control studies of adenomyosis, using as controls women who had undergone hysterectomy, ORs have ranged from 1.2-3.1 comparing women with one or more births to nulliparous women. (Vercellini et al., 1995; Parazzini et al., 1997; Levгур et al., 2000) This range of ORs is consistent with the OR of 1.6 reported in our study comparing women with any number of births to nulliparous women using hysterectomy controls. In contrast, using population-based controls, we reported an OR of 3.4 comparing women with any births to nulliparous women. The difference in magnitude of the ORs is likely due in part to the willingness of study subjects with hysterectomy to terminate their reproductive ability.

Selection of controls who are representative of the underlying population in terms of exposure of interest is a foundation of population-based case-control studies, and offers the advantage of a comparison group that is representative of the population giving rise to cases. In our evaluation of BMI, the increase in risk associated with obesity using hysterectomy controls (OR 2.2) was lower than the risk observed using population-based controls (OR 3.8). A limited number of previous investigations have evaluated BMI as a risk factor of adenomyosis. In the California Teachers Study (CTS), Templeman and colleagues utilized statewide hospital discharge records to identify cases of surgically-diagnosed adenomyosis over eight years of follow-up and reported adjusted ORs for adenomyosis of 1.3 [95% CI: 1.1, 1.5] for overweight women compared with normal weight women and 1.4 [95% CI: 1.1, 1.6] for obese women compared with normal weight women. (Templeman et al., 2008) These ORs are lower than the ORs associated with increasing BMI reported for either hysterectomy or population controls in the current study. The CTS study most closely resembles our population-based control analysis rather than the hysterectomy control analysis, since the comparison population has not undergone screening, hysterectomy or otherwise, for adenomyosis. (Templeman et al., 2008)

Although advantageous in many study contexts, a population-based control group has potential limitations in studies of adenomyosis. Population-based controls will not be 100% disease free because they are unlikely to have had surgical evaluation to rule out the presence of adenomyosis. However, undiagnosed symptomatic adenomyosis is present only to a small degree in a population control group, making it unlikely that study results are affected appreciably by the inadvertent inclusion of these women as controls. Population-based controls also may be unwilling to undergo evaluation or hysterectomy if they had adenomyosis, making a portion of the population not comparable to the cases, all of whom were willing to undergo a hysterectomy. In interview-based studies of this disease, restricting population-based controls to women stating they would be willing to undergo

hysterectomy if diagnosed with adenomyosis or another gynecologic morbidity may improve the validity of the risk estimates using this type of control group.

In the current study, utilization of medical record abstraction provided us with the opportunity to objectively evaluate adenomyosis risk factors using two distinctly constituted control groups, with prospectively recorded exposures and confounders, there are several limitations to this approach. A limited number of variables were available in the medical record and this may have affected our ability to comprehensively control for confounding. Additionally, reproductive history assessment may not have been complete for all study participants and the timing of height and weight measurements may not have been consistent in all participants.

In sum, as demonstrated by our findings, the results of studies of risk factors for adenomyosis are likely to be affected by the choice of the comparison population, with any single comparator providing a potentially inaccurate or incomplete picture of risk. While neither control group provides definitive risk estimates, population-based controls may be preferable to hysterectomy controls when evaluating steroid hormone-related risk factors or lifestyle factors, such as BMI, given that women undergoing a hysterectomy often have comorbidities that may influence their hormonal profiles and body weight. (Dickersin & Lemaire, 2000) In contrast, hysterectomy controls may be a better comparison group choice when evaluating risk factors associated with a willingness to undergo a hysterectomy, such as parity. For other important risk factors for which the existence and direction of potential bias is more uncertain, the size of associations using hysterectomy controls and population-based controls may represent a realistic range of adenomyosis risk estimates. As researchers we can improve the comparability of future adenomyosis studies by clearly identifying the source population and case definition criteria, and by minimizing the under-ascertainment of cases as much as possible. Additionally, we can select the control group based on the primary research question and exercise caution when reporting results for exposures that may not be accurately interpretable given case and control definition decisions.

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Table 1

Demographic characteristics of the study population stratified by case/control status, Puget Sound Area, Washington, 1996-2001.

	Cases	Hysterectomy controls	Population Controls
	N=174	N=106	N=149
	n[*] (%)	n[*] (%)	n[*] (%)
Age [mean (std dev) <i>range</i>]	42.5 (4.9) 24-49	39.1 (6.3) 21-49	41.4 (5.4) 20-49
20-24	1 (0.6)	2 (1.9)	1 (0.7)
25-29	3 (1.7)	4 (3.8)	3 (2.0)
30-34	5 (2.9)	23 (21.7)	6 (4.0)
35-39	35 (20.1)	21 (19.8)	29 (19.5)
40-44	60 (34.5)	30 (28.3)	51 (34.2)
45-49	70 (40.2)	26 (24.5)	59 (39.6)
Race [†]			
Caucasian	143 (86.7)	97 (93.3)	114 (79.2)
African American	10 (6.1)	0 (0.0)	9 (6.2)
Asian American	6 (3.6)	4 (3.9)	14 (9.7)
Other	6 (3.6)	3 (2.8)	7 (4.9)
Height (cm) [mean (std dev) <i>range</i>]	164.7 (6.9) 149-181	165.8 (7.4) 144-186	164.5 (6.8) 149-178
Weight (kg) [mean (std dev) <i>range</i>] [‡]	82.4 (20.8) 45-158	80.0 (24.5) 41-164	74.1 (19.9) 42-141
Menopausal status			
Premenopausal	149 (88.2)	95 (89.6)	133 (91.1)
Postmenopausal	20 (11.8)	11 (10.4)	13 (8.9)

* Cell counts may not sum to column total because of missing data.

[†] P-value ≤ 0 .05 from logistic regression model comparing hysterectomy controls and population-based controls adjusting for age and reference year.

[‡] P-value ≤ 0 .05 from logistic regression model comparing cases and population-based controls adjusting for age and reference year.

Age-, reference year-, and parity-adjusted odds ratios (OR) and 95% confidence intervals (CI) comparing adenomyosis cases to hysterectomy controls and population controls, Puget Sound Area, Washington, 1996-2001.

Table 2

Risk factor	Cases	Hysterectomy controls		Population Controls			
	N=174 n* (%)	N=106 n* (%)	OR	95% CI	N=149 n* (%)	OR	95% CI
BMI							
Normal or below (<25 kg/m ²)	35 (22.1)	36 (40.0)	1.0	reference	61 (46.7)	1.0	reference
Overweight (25-29.9 kg/m ²)	51 (32.3)	24 (26.7)	2.2	1.0, 4.5	37 (28.2)	2.1	1.2, 4.0
Obese (≥ 30 kg/m ²)	72 (45.6)	30 (33.3)	2.2	1.1, 4.3	33 (25.1)	3.8	2.1, 7.0
Smoking							
Ever	29 (16.9)	26 (25.7)	0.8	0.4, 1.6	29 (20.0)	0.9	0.5, 1.6
Never	143 (83.1)	75 (74.3)	1.0	reference	116 (80.0)	1.0	reference
Gravidity (any past pregnancies) [†]							
Gravid	164 (94.8)	98 (92.5)	1.6	0.5, 4.6	109 (76.2)	5.4	2.5, 11.8
Nulligravid	9 (5.2)	8 (7.6)	1.0	reference	34 (23.8)	1.0	reference
Parity (any live births) [†]							
Parous	154 (88.5)	90 (84.9)	1.6	0.7, 3.6	99 (68.8)	3.4	1.9, 6.2
Nulliparous	20 (11.5)	16 (15.1)	1.0	reference	45 (31.2)	1.0	reference
History of cesarean-delivery							
Yes	25 (15.3)	18 (17.8)	0.9	0.4, 1.8	19 (17.3)	0.9	0.4, 1.7
No	138 (84.7)	83 (82.2)	1.0	reference	91 (82.7)	1.0	reference
History of uterine trauma							
Yes	54 (31.0)	45 (42.5)	0.6	0.3, 1.0	42 (28.2)	1.1	0.7, 1.8
No	118 (67.8)	61 (57.6)	1.0	reference	102 (68.5)	1.0	reference

* Cell counts may not sum to column total because of missing data.

[†] Models adjusted for age and reference year only (gravidity and parity are highly correlated).