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Statin Use and Uterine Fibroid Risk in Hyperlipidemia Patients: A Nested Case-Control Study

Mostafa A. BORAHAY, MD, PhD[1,2,*], **Xiao FANG, MS**[3], **Jacques G. BAILLARGEON, PhD**[3], **Gokhan S. KILIC, MD**[1], **Darren F. BOEHNING, PhD**[2], and **Yong-Fang KUO, PhD**[3]

[1]Department of Obstetrics & Gynecology, The University of Texas Medical Branch at Galveston, TX

[2]Department of Biochemistry & Molecular Biology, The University of Texas Health Science Center at Houston, TX

[3]Department of Preventive Medicine & Community Health, The University of Texas Medical Branch at Galveston, TX

Abstract

Background—Statins are 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors primarily used for treatment of hyperlipidemia. Recently, they have been shown to inhibit proliferation of uterine fibroid cells and inhibit tumor growth in fibroid animal models.

Objectives—To examine the association between statin use and the risk of uterine fibroids and fibroid-related symptoms in a nationally representative sample of commercially insured women diagnosed with hyperlipidemia.

Study Design—We performed a nested case-control study of more than 190,000 women enrolled in one of the nation's largest commercial health insurance programs. From a cohort of females aged 18–65 years old diagnosed with hyperlipidemia between January 2004 and March 2011, we identified 47,713 cases (women diagnosed with uterine fibroids)143,139 controls (women without uterine fibroids) matched at a 1:3 ratio on event/index date (month and year) and age (± 1 year). We used conditional and unconditional logistic regression to calculate odds ratios (OR) and 95% confidence intervals (CI) for the risk of uterine fibroids and fibroid-related symptoms associated with prior use of statins.

Results—Exposure to statins within 2 years before the event/index date was associated with a decreased risk of uterine fibroids (OR of 0.85, 95% CI 0.83–0.87). In a separate sub-analysis

*Corresponding author: Department of Obstetrics & Gynecology, The University of Texas Medical Branch at Galveston, 301 University Boulevard, Galveston, TX 77555-0587. Phone: (409) 772-1574, maboraha@utmb.edu.

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restricted to cases, statin users had a lower likelihood of having menorrhagia (OR 0.88, 95% CI 0.84–0.91), anemia (OR 0.84, 95% CI 0.79–0.88), or pelvic pain (OR 0.85, 95% CI 0.81–0.91) and of undergoing myomectomy (OR 0.76, 95% CI 0.66–0.87) compared to nonusers.

Conclusion—The use of statins was associated with a lower risk of uterine fibroids and fibroid-related symptoms. Further studies, including randomized controlled trials, may be warranted.

Keywords

fibroids; leiomyoma; statins; menorrhagia; pelvic pain

INTRODUCTION

Uterine fibroids, also called myomas or leiomyomas, are the most common benign gynecologic tumors, with a lifetime incidence of approximately 70%.[1, 2] They are associated with multiple symptoms, including heavy uterine bleeding and pelvic pain. Currently used treatments include contraceptive steroids, gonadotropin-releasing hormone agonists (GnRHa), progesterone modulators, uterine artery embolization (UAE), magnetic resonance imaging-guided focused ultrasound surgery (MRgFUS), and radiofrequency ablation (RFA).[3–7] Even though many of these options may improve the symptoms, they possess significant side effects or other limitations. Surgery, whether removing the tumor (myomectomy) or uterus (hysterectomy), is indicated in many cases. In the United States alone, fibroids are associated with more than 200,000 hysterectomies,[8] with an estimated annual cost of $5.9–$34.4 billion.[9] Therefore, there is a need for a successful medical treatment for fibroids.

Statins are a drug family primarily used for hyperlipidemia. In addition to lowering cholesterol, statins have been observed to have antiproliferative effects against certain tumors,[10, 11] including breast,[12, 13] ovarian,[14, 15] leukemia,[16] prostate,[17] lung,[18] and colon cancer.[19] Recently, Liu and colleagues[20] published a meta-analysis of 14 studies, including 12,904 gynecologic cancer patients, and found that statins significantly decrease the incidence of ovarian cancer (RR 0.48 with 95% CI 0.28–0.8). In addition, Graaf and colleagues[21] analyzed records of a Dutch database and reported that statin use was associated with a 20% reduction of cancer incidence in general.

In addition, studies have demonstrated that simvastatin and atorvastatin inhibit progression of certain benign steroid-dependent gynecologic disorders, such as endometriosis.[22–25] More recent reports demonstrated that simvastatin inhibits proliferation and induces calcium-dependent programmed cell death in fibroid cells.[26] It was also reported to inhibit tumor growth in a patient-derived xenograft mouse model.[27] However, no clinical or population-based studies have examined the association of statin use and the risk of uterine fibroids. The aim of this population-based study was to examine the hypothesis that statin use is associated with a lower risk of uterine fibroids and fibroid-related symptoms.

MATERIALS AND METHODS

Data source

This population-based study used administrative health data from Clinformatics™ DataMart (CDM) Database (OptumInsight, Eden Prairie, MN), a database of one of the nation's largest commercial health insurance programs. CDM data have been used to examine health services and drug utilization in numerous studies.[28–31] Persons enrolled in this insurance program may be included in either a fee-for-service plan or a managed care plan, which includes health maintenance organizations, preferred provider organizations, and exclusive provider organizations. For each of these plans, providers are required to submit complete claims to receive reimbursement.

We used a combination of outpatient, inpatient, and pharmacy claims data. The pharmacy database contains eligibility and claims information for medications from retail pharmacies through a member's pharmacy benefit. This study was approved by the institutional review board of The University of Texas Medical Branch at Galveston.

Overall study cohort

The overall study cohort included females aged 18 to 65 years who had continuous enrollment in CDM for at least 3 years and diagnoses of hyperlipidemia during the study period (January 1, 2004 through March 31, 2011). Hyperlipidemia was diagnosed using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis code (272.X). Appendix 1 includes a list of ICD-9-CM codes used in this study.

Because statins are commonly prescribed for hyperlipidemia, we restricted the overall study cohort to women with hyperlipidemia so that all cases and controls have a diagnosis of the potentially confounding condition, hyperlipidemia.

Cases

Within the overall study cohort, we identified cases who received first-time diagnoses of uterine fibroids, identified by ICD-9-CM code 218.X. We defined a first-time diagnosis as a patient with no uterine fibroid diagnosis in the previous 2 years (look back period). The date of uterine fibroid diagnosis served as the event date for all subsequent analyses.

Controls

From the overall study cohort, controls (women without diagnoses of uterine fibroids) were selected to match cases on event/index month and age (± 1 year) at a 3:1 ratio. The initial starting dates for controls were assigned to match the month and year of diagnosis of the cases (index date). We performed matching using a conventional methodology as previously described.[32]

Sociodemographic characteristics of the study population included age and region (Midwest, Northeast, South, and West). Elixhauser Comorbidity index[33] was generated based on claims within the year prior to the diagnosis/index date. This database did not include race/ethnicity data; therefore, we were unable to analyze these variables.

Statin use

Information on statin use was collected from the prescription data files of CDM. Patients were considered exposed to statins if they filled statin prescriptions within the 2 years before the event/index date. A statin prescription fill was assessed using the generic name (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin).

Statistical analysis

Descriptive statistics were used to assess the demographic and clinical variables in cases and controls. Conditional logistic regression was used to examine the risk of uterine fibroids in association with statin use, calculated as odds ratios (ORs) with 95% confidence intervals (CIs).

To adjust for geographic regions and unbalanced comorbidities, we added these variables in the conditional logistic regression to calculate adjusted odds ratios (aORs). To examine the robustness of results, we performed sensitivity analyses with statin prescriptions within the 90- and 30-day periods before the diagnosis/index date, based on the STROBE statement.[34] To examine the association among different age groups and different statins, we performed stratified analyses.

To examine the association of statin use and fibroid-related symptoms among the fibroid case group, we performed a separate exploratory subanalysis where we used unconditional logistic regression to further analyze the risk for menorrhagia, anemia, pelvic pain, myomectomies, and hysterectomies that occurred within 1 year following the diagnosis of uterine fibroids.

In this study, we used ICD-9-CM and Current Procedural Terminology (CPT) codes (Appendix 1). All analyses were performed using SAS, version 9.3 (SAS Institute Inc, Cary, NC). All statistical tests were 2-sided with $P < .05$ considered to be statistically significant.

RESULTS

We identified 47,713 cases with uterine fibroids and 143,139 age-matched controls, nested within a cohort of women who were diagnosed with hyperlipidemia from January 2006 to March 2011. First, we looked at the demographic and clinical characteristics of the study population (table 1). As expected, most of the cases were in the 40–48 (41.79%) and 50–59 (36.29%) age groups. In addition, most cases came from the southern geographic region (51.91%). We also assessed 31 comorbidities in both cases and controls using Elixhauser Comorbidity index.[33] Except for congestive heart failure, uncomplicated diabetes, paralysis, and pulmonary circulation disorders, comorbidities were not balanced between case and control groups. Therefore, we adjusted for these unbalanced comorbidities in subsequent analyses.

To examine the association of statin use and the risk of uterine fibroids, we used conditional logistic regression (table 2). We found that statin use within the 2 years before the event/index date was associated with a lower risk of uterine fibroids(OR 0.85, 95% CI 0.83–0.87). Our sample sizes provided at least 81% power to detect an odd ratio of 0.85 for using statin

among cases compared to controls. This calculation was based on a logistic regression model with a two-sided significance level of 0.05 and an estimated rate of statin use of 30% among patients with hyperlipidemia. The effect was almost unchanged after adjusting for geographic region and unbalanced comorbidities (adjusted OR, 0.87, 95% CI 0.85–0.89). Sensitivity analyses, which examine the association of statin use within the 30- and 90-day periods before the event/index date, also yielded protective effects (aOR 0.91, 95% CI 0.88–0.94 and aOR 0.89, 95% CI 0.87–0.91, respectively).

To examine the association at different age groups and across individual statins, we performed a stratified analysis (tables 3 and 4). We found that statin use was associated with a lower risk of uterine fibroids in all age groups, although the effect was not statistically significant in the 18–29 age group, possibly due to the smaller sample size. Similarly, we found that the 7 statins we examined were associated with a lower risk of uterine fibroid, although the association was not significant for fluvastatin and pitavastatin, possibly due to a small number of users (147 and 2, respectively).

To examine the association of statin use and fibroid-related symptoms and procedures in the 1 year after event date, we performed unconditional logistic regression among cases (table 5). We found that the fibroid-associated symptoms of menorrhagia, anemia, and pelvic pain were significantly lower among statin users compared to nonusers (ORs of 0.88, 95% CI 0.84–0.910; 0.84, 95% CI 0.79–0.88; and 0.85, 95% CI 0.81–0.91, respectively). In addition, statin use was associated with a lower risk of myomectomy (OR 0.76, 95% CI 0.66–0.87). However, statin use was not associated with a lower risk of hysterectomy (OR 1.09, 95% CI 1.02–1.15, and adjusted OR 1.049, 95% CI 0.99–1.11).

COMMENT

We found that statin use was associated with a lower risk of uterine fibroids and—in a separate analysis restricted to women with uterine fibroids—a lower incidence of menorrhagia, anemia, pelvic pain, and myomectomy. While this is the first population-based investigation of the association of statin use and the risk uterine fibroids, the findings are consistent with previous reports in cell culture and animal models.[26, 27]

The precise mechanism of action of statins on uterine fibroids in humans is not fully understood. Recent reports have demonstrated that simvastatin inhibits proliferation and induces programmed cell death in leiomyoma cell culture[26] and inhibits tumor growth in an animal model.[27] The mechanisms are thought to be mediated by the inhibition of growth factor signaling and activation of calcium-dependent apoptotic pathways.[26] However, it is possible that the mechanism of action of statins in patients may be different from that observed in cell culture or animal models.

The finding that statin use was associated with fewer symptoms in cases, such as menorrhagia, anemia, and pelvic pain, is clinically significant. Uterine fibroids are very common, and in many asymptomatic cases, no treatment is needed. Therefore, this beneficial association of statins on fibroid-related symptoms is promising. However, given the nature of this subanalysis (patients with both hyperlipidemia and uterine fibroids), future

more rigorous studies should be conducted on broader and more generalizable study samples.

Similarly, the association of statin use with fewer myomectomies is clinically important. Myomectomies are typically performed in cases with enough symptoms to warrant removal of tumors. Therefore, we can reasonably assume that statin use was associated with a significant reduction of symptoms, and thus fewer procedures were warranted. However, our results did show a reduced risk of hysterectomies associated with statin use. A possible explanation is that hysterectomies can be performed for non-fibroid-related indications, such as pelvic organ prolapse and different cancers. Additional studies should further investigate this association.

The peak serum level of simvastatin for treatment of hypercholesterolemia is approximately 0.3μM.[35–37] Although the drug level at tumor tissue is unknown, it is expected to be even lower than the serum level due to the excessive deposition of extracellular matrix and the nature of tumor vascularity.[1, 38] Therefore, there may be room for even more effective targeted delivery technologies, eg, nanotechnology.[39–41]

There are several statins in clinical use. Although they share the same mechanism of action of inhibiting 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase enzyme, there differ in their chemical and pharmacologic properties. For example, some statins are categorized as lipophilic (e.g. simvastatin, lovastatin, atorvastatin) while others are considered hydrophilic (e.g. pravastatin, fluvastatin, rosuvastatin). These differences may affect their tissue distribution where hydrophilic ones are more hepatoselective (concentrated in the liver) due to a specific transporter mechanism.[42–44] The lipophilic group is available for both hepatic and extrahepatic (peripheral) tissue distribution, including uterine fibroid. In addition, statins significantly differ in their metabolism and their active metabolites.[42, 45] In our study, the 2 statins that were not associated with significant reduction in the risk of fibroids (fluvastatin and pitavastatin) were used by relatively small number of patients (147 and 2 respectively). Therefore, additional epidemiological, molecular and clinical studies are warranted to further examine differences among individual statins.

The findings of the current study may have been affected by some limitations. First, the diagnosis of uterine fibroids and fibroid-associated symptoms as menorrhagia and pelvic pain were made via ICD-9-CM codes, which are not always complete or accurate.[46, 47] In addition, diagnostic criteria for these symptoms may differ among different providers and organizations. Second, ICD-9-CM data does not provide information regarding how the diagnosis was made, whether by physical exam, imaging, or pathologic examination. Third, claims data does not provide information about the number, size, or location of the tumors and, therefore, the possible impact on the patient symptomatology. Fourth, statin use was evaluated through claims data indicating a filled prescription, and therefore actual intake of the medication cannot be verified. In addition, statins dispensed outside of this commercial insurance plan (e.g., from another insurance provider) were available in our database. Fifth, because the Clinformatics DataMart database does not include race/ethnicity data, we were unable to analyze the potential confounding effect of race. Previous studies show that African Americans have a higher risk for fibroid tumors. [48] and a lower rate of adherence to

statin therapy.[49] Given this direction of association, our inability to adjust for race has possibly biased our findings toward the null hypothesis, resulting in a more conservative effect estimate. It will be important, however, to examine the role of race and ethnicity on this association in further large database analyses. Sixth, reliance on claims data precluded assessment of a number of potential confounding factors such as family history, diet, alcohol use, and age at menarche. Seventh, many of the patients in the study cohort are expected to be taking other medications. Since we are not currently aware of specific commonly used medications that affect the incidence of uterine fibroids, it will be difficult to search and adjust for a randomly selected list of medications. However, this limitation can be addressed in future studies.

Despite these limitations, this study has several strengths. First, the idea of repurposing statins for uterine fibroids has advantages. For example, since statins are FDA approved and have been in use for several years, their safety profile is well-documented. Second, the large number of the study subjects significantly increases its power. Third, we followed the STROBE statement for strengthening the reporting of observational studies in epidemiology.[34] Fourth, we sought to minimize bias and confounding by nesting the case-control study in a hyperlipidemia cohort. If we only compared statin users vs nonusers in the general population, then hyperlipidemia can be a confounding factor since statin users will overwhelmingly have hyperlipidemia. Thus, by having cases and controls diagnosed with hyperlipidemia, we minimized this potential confounder. The potential drawback of this design is that the findings apply to hyperlipidemia patients. Again, randomized controlled trials of statins in a general population with uterine fibroids may be warranted to further address this question.

At this point, further research is warranted. First, we need to further understand the pharmacokinetics of statins and how much of the drug reaches fibroid tumors. This knowledge will help improve tumor targeting so that higher drug levels in tumor tissues are obtained while minimizing systemic exposure. Candidate drug delivery technologies include medicated intrauterine devices and adoption of nanotechnology. Second, further translational studies are needed to understand the action mechanism of statins in uterine fibroids, which may lead to the development of newer drugs that are more effective. Third, investigating the effects of statins on gynecologic symptoms, such as menorrhagia and pelvic pain, independent of fibroid diagnosis is intriguing. Finally, prospective studies, particularly randomized clinical trials, will help further examine the effects of statins on fibroid size, symptoms, and quality of life.

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Appendix 1: ICD-9-CM and CPT codes used in the study

Condition/Procedure	ICD-9-CM Code	CPT Code
Hyperlipidemia	272.X	
Uterine Fibroids	218.X	
Menorrhagia	626.X, 627.0, 627.1	
Anemia	280.0, 280.8, 280.9, 281.9, 285.X	
Pelvic Pain	625.9	
Myomectomy	682.9	58140, 58145, 58146, 58545, 58546, 58551, 58561
Hysterectomy		58150, 58152, 58180, 58260, 58262, 58263, 58267, 58270, 58275, 58280, 58290, 58291, 58292, 58293, 58294, 58541, 58542, 58543, 58544, 58550, 58552, 58553, 58554, 58570, 58571, 58572, 58573

Table 1

Demographic Characteristics of the Study Population

Characteristics	Fibroid Cases	Controls[a]	*P* Value
All Subjects — no.	47713	143139	
Age — no. (%), yr			.9999
18–29	414 (0.87)	1242 (0.87)	
30–39	5355 (11.24)	16065 (11.22)	
40–49	19940 (41.79)	59820 (41.79)	
50–59	17315 (36.29)	51945 (36.29)	
60–65	4689 (9.83)	14067 (9.83)	
Mean ± SD	48.74 ± 7.82	48.74 ± 7.82	
Geographic region — no. (%)			< .001
Northeast	8197 (17.18)	16173 (11.30)	
Midwest	8590 (18.00)	34470 (24.08)	
South	24768 (51.91)	72834 (50.88)	
West	6135 (12.86)	19627 (13.71)	
Unknown	23 (0.05)	35 (0.02)	
Comorbidities — no. (%)			
AIDS/HIV	112 (0.23)	177 (0.12)	<.001
Alcohol Abuse	229 (0.48)	833 (0.58)	.010
Blood Loss Anemia	1095 (2.29)	878 (0.61)	<.001
Cardiac Arrhythmia	2890 (6.06)	7067 (4.94)	<.001
Chronic Pulmonary Disease	5757 (12.07)	16734 (11.69)	.028
Coagulopathy	604 (1.27)	1356 (0.95)	<.001
Congestive Heart Failure	701 (1.47)	1980 (1.38)	.167
Deficiency Anemia	4314 (9.04)	6060 (4.23)	<.001
Depression	6623 (13.88)	22033 (15.39)	<.001
Diabetes Complicated	1309 (2.74)	4435 (3.10)	< .001
Diabetes Uncomplicated	7672 (16.08)	23356 (16.32)	.223
Drug Abuse	153 (0.32)	649 (0.45)	.001
Fluid and Electrolyte Disorders	2051 (4.30)	5466 (3.82)	<.001
Hypertension Complicated	1580 (3.31)	3822 (2.67)	<.001
Hypertension Uncomplicated	19888 (41.68)	55788 (38.97)	<.001
Hypothyroidism	10782 (22.60)	30367 (21.22)	<. 001
Liver Disease	2650 (5.55)	4893 (3.42)	<.001
Lymphoma	179 (0.38)	434 (0.30)	.016
Metastatic Cancer	341 (0.71)	534 (0.37)	<.001
Obesity	5011 (10.50)	12582 (8.79)	<.001
Other Neurological Disorders	772 (1.62)	2664 (1.86)	<. 001
Paralysis	106 (0.22)	345 (0.24)	.462

Characteristics	Fibroid Cases	Controls[a]	*P* Value
Peptic Disease Excluding Bleeding	351 (0.74)	752 (0.53)	<. 001
Peripheral Vascular Disorders	1164 (2.44)	2876 (2.01)	<.001
Psychoses	220 (0.46)	829 (0.58)	.003
Pulmonary Circulation Disorders	306 (0.64)	833 (0.58)	.145
Renal Failure	536 (1.12)	1789 (1.25)	.029
Rheumatoid Arthritis/Collagen	2093 (4.39)	5550 (3.88)	<.001
Solid Tumor without Metastasis	2630 (5.51)	5078 (3.55)	<.001
Valvular Disease	3051 (6.39)	6986 (4.88)	<.001
Weight Loss	803 (1.68)	1934 (1.35)	<.001
Statin Use — no. (%)			<.001
Yes	13498 (28.29)	45155 (31.55)	
No	34215 (71.71)	97984 (68.45)	

[a]We matched 3 controls for each case based on age and being in the database at the time of the index diagnosis.

Table 2

Crude and Adjusted Associations between Statin Use and the Risk of Uterine Fibroids in the Study Population

Statin Use	*No. of Subjects (%)*		Unadjusted	Adjusted[a]
	Fibroid Cases	Controls	Odds Ratio (95% CI)[b]	Odds Ratio (95% CI)
Yes	13498 (28.29)	45155 (31.55)	0.848	0.869
No	34215 (71.71)	97984 (68.45)	(0.828–0.868)	(0.848–0.890)

[a] Analyses were adjusted for geographic region and unbalanced comorbidity.

[b] CI denotes confidence interval.

Table 3

Association of Statins with the Risk of Uterine Fibroids Stratified by Age

Age group	Unadjusted		Adjusted[a]	
	Odds Ratio (95% CI)[b]		Odds Ratio (95% CI)	
18–29	0.986	(0.621–1.566)	1.047	(0.643–1.704)
30–39	0.889	(0.810–0.977)	0.861	(0.779–0.951)
40–49	0.854	(0.822–0.887)	0.877	(0.843–0.913)
50–59	0.826	(0.797–0.856)	0.860	(0.829–0.893)
60–65	0.882	(0.825–0.942)	0.896	(0.837–0.959)

[a] Analyses were adjusted for geographic region and unbalanced comorbidity.

[b] CI denotes confidence interval.

Table 4

Association of Different Statins with the Risk of Uterine Fibroids

Statin Type[b]	Usage among Cases (%)	Unadjusted		Adjusted[a]	
		Odds Ratio (95% CI)[c]		Odds Ratio (95% CI)	
Atorvastatin	5661 (11.86)	0.904	(0.876–0.934)	0.916	(0.887–0.947)
Fluvastatin	147 (0.31)	1.005	(0.833–1.211)	0.992	(0.820–1.199)
Lovastatin	1132 (2.37)	0.879	(0.822–0.940)	0.921	(0.860–0.986)
Pitavastatin	2 (0.00)	0.462	(0.104–2.045)	0.494	(0.110–2.223)
Pravastatin	1327 (2.78)	0.888	(0.834–0.945)	0.898	(0.843–0.957)
Rosuvastatin	2063 (4.32)	0.871	(0.828–0.916)	0.864	(0.821–0.910)
Simvastatin	4884 (10.24)	0.856	(0.827–0.886)	0.892	(0.862–0.924)

[a] Analyses were adjusted for geographic region and unbalanced comorbidity.

[b] Some patients took more than one statin type and are included in multiple groups

[c] CI denotes confidence interval.

Table 5

Association of Statins with the Risk of Menorrhagia, Anemia, Pelvic Pain, Myomectomy, and Hysterectomy

Symptoms and Procedures	Number among Cases (%)	Unadjusted		Adjusted[a]	
		Odds Ratio (95% CI)[b]		Odds Ratio (95% CI)	
Menorrhagia	18528 (38.83)	0.875	(0.839–0.911)	0.893	(0.856–0.932)
Anemia	9692 (20.31)	0.843	(0.793–0.878)	0.781	(0.739–0.826)
Pelvic Pain	7187 (15.06)	0.854	(0.807–0.905)	0.856	(0.808–0.908)
Myomectomy	1212 (2.54)	0.757	(0.661–0.866)	0.803	(0.699–0.921)
Hysterectomy	6430 (13.48)	1.085	(1.024–1.149)	1.049	(0.989–1.113)

[a] Analyses were adjusted for geographic region and unbalanced comorbidity.

[b] CI denotes confidence interval.