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History of uterine leiomyoma and risk of endometrial cancer in black women

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Abstract

Background—Previous studies have found an association between uterine leiomyomata (UL) and uterine malignancies. This relation has not been studied in black women, who are disproportionately affected by UL.

Methods—We investigated prospectively the association between self-reported physician-diagnosed UL and endometrial cancer in the Black Women's Health Study. During 1995–2013, 47,267 participants with intact uteri completed biennial health questionnaires. Reports of endometrial cancer were confirmed by pathology data from medical records and cancer registries. Cox regression was used to derive incidence rate ratios (IRR) and 95% confidence intervals (CI).

Results—There were 300 incident endometrial cancer cases during 689,546 person-years of follow-up. In multivariable models, UL history was associated with a 42% greater incidence of endometrial cancer compared with no such history (95% CI: 1.12–1.80). IRRs for cancer diagnosed 0–2, 3–9, and ≥10 years after UL diagnosis were 3.20 (95% CI: 2.06–4.98), 0.95 (95% CI: 0.60–1.52), and 1.35 (95% CI: 1.03–1.77), respectively. Stronger overall associations between UL history and endometrial cancer were observed for later stages at cancer diagnosis (IRR=2.25, 95% CI: 1.09–4.63) and type II/III cancers (IRR=3.13, 95% CI: 1.64–5.99).

Conclusions—In this large cohort of black women, a history of UL was positively associated with endometrial cancer, particularly type II/III tumors. The strongest association was observed for cancer diagnosed within two years of UL diagnosis, a finding that might be explained by greater surveillance of women with UL or misdiagnosis of cancer as UL. However, an association was also observed for cancer reported ≥10 years after UL diagnosis.

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Keywords

African Americans; uterine leiomyoma; endometrial cancer; prospective studies

Incidence rates for endometrial cancers are rising across all racial/ethnic groups in the United States, with the greatest annual percent increase observed among non-Hispanic black women.[1] After accounting for hysterectomy, black women have higher incidence rates of endometrial cancer than white women.[2–5] Black women are also more likely to be diagnosed with aggressive endometrial cancers (clear cell, serous, high-grade endometrioid, and malignant mixed Mullerian tumors) compared with non-Hispanic white women. For nearly every stage and subtype of endometrial cancer, mortality rates are significantly higher among black women than white women.[1]

Uterine leiomyomata (UL), benign tumors of the myometrium, are clinically-recognized in up to 40% of women[6] and are the primary indication for hysterectomy in the United States.[7,8] Compared with white women, black women have 2–3 times the incidence of UL, an earlier age at first diagnosis, and greater disease severity.[6,9] Only a handful of studies have assessed whether a history of UL predisposes women to uterine cancer. In case series, UL have been shown to be more common among women undergoing hysterectomy for endometrial carcinoma[10–14] and uterine sarcomas.[15] Two case-control studies found that women with UL had about a 2- to 3-fold increased risk of uterine malignancies[16,17] and a Danish registry-based cohort study found a positive association of UL with risk of uterine cancer, particularly sarcomas.[18] Given the recent trend toward nonsurgical management of UL in the United States,[7,19,20] and the larger proportion of UL-affected women opting for uterine-conserving therapies (e.g., myomectomy) instead of hysterectomy, additional data about whether UL predispose to endometrial cancer are needed.

The pathophysiology of UL depends on the biological activity of the endogenous sex steroid hormones—estrogens (estradiol, estrone, estriol) and progesterone[21–23]—as well as locally derived growth factors.[24–30] The hormone-dependent nature of UL is supported by the fact that they do not occur before menarche, they have an increased concentration of estrogen and progesterone receptors compared with normal myometrium,[31] and they shrink in volume with suppression of ovarian function.[32] Likewise, mitotic activity in endometrial cells is primarily regulated by sex steroid hormones, with proliferation stimulated by estrogen and inhibited by progesterone.[33] According to the unopposed estrogen hypothesis of uterine cancer etiology,[34] any factor that increases estrogen levels or decreases progesterone levels could plausibly increase cancer risk. Thus, if an estrogenic hormonal milieu promotes UL development and growth, and endometrial cancer is also influenced by estrogens, it seems plausible that a history of UL may serve as a marker of increased future risk of endometrial cancer.

To clarify the extent to which UL is a risk factor for endometrial cancer, we evaluated the association of history of diagnosed UL with incidence of endometrial cancer in a large prospective cohort study of U.S. black women. Data were stratified by age at UL diagnosis, histologic type, and stage at diagnosis of endometrial cancer.

METHODS

Data source

The present investigation uses data from the Black Women's Health Study (BWHS), an ongoing prospective cohort study initiated in 1995.[35] A total of 59,001 self-identified Black women aged 21–69 were recruited from the subscription list of *Essence* magazine and from Black professional organizations. At baseline, data were collected via self-administered postal questionnaire on demographic, lifestyle and behavioral factors; reproductive and medical history; and use of medications. Participants completed follow-up questionnaires every two years to update outcome, exposure, and covariate data. Follow-up of the baseline cohort is complete for 87% of potential person-years through 2013.

Exclusions

In the present analysis, women were excluded at baseline if they reported a history of uterine cancer (N=340) or hysterectomy (N=10,659), reported UL without the year of diagnosis (N=288), or if they did not return a questionnaire subsequent to the baseline questionnaire (N=447). The analytic sample comprised the remaining 46,967 women who were followed for incident endometrial cancer from 1995 through 2013.

Outcome

Participants reported new diagnoses of "uterine cancer" on biennial follow-up questionnaires from 1997 through 2013. The 1995 and 2011 questionnaires did not ask specifically about uterine cancer but asked participants to report any "other serious illness." Cases were also identified through state cancer registry records and death certificate data provided via the National Death Index (NDI), with 13 cases identified via death certificate alone. In total, there were 367 potential incident cases. We obtained medical records, cancer registry data, or death certificate data for 249 potential cases. All but 18 were confirmed as either endometrial cancer (n=213) or uterine sarcoma (n=18). Because the confirmation rate was high, we accepted the remaining potential cases as cases of incident endometrial cancer. Thus, there were a total of 300 cases of endometrial cancer (213 confirmed and 87 unconfirmed) available for study. Data on histologic subtype (classified as shown in Supplemental Table 1) and stage at endometrial cancer diagnosis were available for 160 and 141 confirmed cases, respectively.

Exposure

Assessment of uterine leiomyomata—On the 1995 (baseline) questionnaire, participants reported whether they had ever been diagnosed with "fibroids in womb" and their age at initial diagnosis in the following categories: <30, 30–39, 40–49, ≥50 years. In 1997, participants reported whether they had *first* been diagnosed with UL in the following intervals: "before March 1995" and "since March 1, 1995." On subsequent follow-up questionnaires, participants reported whether they had been diagnosed with "fibroids in womb" in the previous two-year interval, the calendar year in which they were first diagnosed, and whether their diagnosis was confirmed by "pelvic exam" and/or by "ultrasound/hysterectomy." On the 2003, 2005, 2007, 2009, and 2011 follow-up

questionnaires, we changed “hysterectomy” to “surgery (e.g., hysterectomy)” to capture women who may have had other surgical procedures (e.g., myomectomy) and we divided “ultrasound” and “surgery” into two questions.

We assessed the accuracy of self-reported UL in a random sample of 248 cases diagnosed by ultrasound or surgery. Cases were mailed supplemental surveys and were asked for permission to review their medical records. We obtained medical records from 127 of the 128 women who gave us permission and confirmed the self-report in 122 (96%). Among the 188 (76%) cases who completed the supplemental survey, 71% reported UL-related symptoms prior to being diagnosed with the condition, with menorrhagia (53%) and pelvic pain (46%) being the most common. Over 87% reported their condition came to clinical attention because they sought treatment for symptoms or a tumor was palpable at the time of a routine pelvic exam. There were no appreciable differences between cases who did and did not release their medical records with respect to established risk factors for UL.[36]

Covariates

At baseline, participants reported data on reproductive history (age at menarche, age at menopause, parity), height, body weight, menopausal status, oral contraceptive use, female hormone use, alcohol use, smoking status, state of residence, breastfeeding, vigorous physical activity, marital status, education, physician-diagnosed diabetes, and household income. Energy intake was calculated from food frequency questionnaires administered in 1995 and 2001.[37,38] Body mass index (BMI) was defined as weight (kg)/height $(m)^2$. Data on reproductive history, exogenous hormone use, and body weight were updated on biennial questionnaires. In a validation study among 115 BWHS participants residing in the Washington, D.C. area, correlation coefficients between self-reported and technician-measured height and weight were 0.93 and 0.97, respectively.[39]

Data Analysis

Participants contributed person-time from baseline until the reported diagnosis of endometrial cancer or one of the following censoring events: reported diagnosis of a non-epithelial type of uterine cancer (e.g., leiomyosarcoma), hysterectomy, loss-to-follow-up, death, or the end of follow-up (2013), whichever came first. We calculated incidence rates and rate ratios (IRR) for all categories of exposure compared with the reference category. We classified women with a history of UL according to their age at first UL diagnosis and their time since first UL diagnosis, with cutpoints based on the distribution of cases within the cohort. Cox proportional hazards regression models,[40] stratified by age and questionnaire cycle, were used to calculate adjusted IRRs and 95% confidence intervals (CI). The Andersen-Gill data structure [41] was used to accommodate time-varying covariates. Departures from proportional hazards were assessed by comparing models with and without interaction terms between exposures and each of the time scales (age and questionnaire cycle) using the likelihood ratio test.

We controlled for covariates that were established risk factors for endometrial cancer and associated with UL in our cohort, including education (<11, 12, 13–15,16,≥17 years), marital status (single, married/living together, widowed/divorced/separated), age at

menarche (<11, 11, 12–13, ≥14 years), parity (parous/nulliparous), menopausal status (premenopausal, postmenopausal), oral contraceptive use (never, former, current), use of estrogen-only female hormone supplements (never, former, current), use of estrogen plus progesterone female hormone supplements (never, former, current), smoking status (never, former, current), body mass index (<25, 25–29, 30–34, ≥35 kg/m^2), and vigorous physical activity (0, 1–4, ≥5 hours/week). Further adjustment for income, age at first birth, age at last birth, pack-years of smoking, alcohol consumption, geographic region of residence, and energy intake had little effect on point estimates for the associations and were not included in the final multivariable models.

We stratified by menopausal status (premenopausal vs. postmenopausal), age (<55 vs. ≥55 years), histologic subtype of endometrial cancer (type I vs. type II/III), and stage at endometrial cancer diagnosis (1 vs. ≥2). We also stratified by BMI (normal weight, overweight, and obese) because UL may be more difficult to diagnose in obese women using standard (i.e., transabdominal) ultrasound methods.[42] The Fine and Grey subdistribution approach for competing risks analysis[43] was employed in secondary analyses to address the impact of hysterectomy on the IRR. This competing risks analysis provides estimates of the IRR in the presence of the rate of hysterectomy observed in these data, while the Cox model results estimate the IRR as it would have been if hysterectomy were not allowed.

RESULTS

Women with a history of diagnosed UL tended to be older at baseline, married or partnered, and ever users of oral contraceptives (Table 1). There were small differences in other baseline characteristics by UL diagnosis history. Women with an early diagnosis of UL tended to have lower educational attainment.

There were 300 incident endometrial cancer cases (median age at diagnosis: 56 years, interquartile range: 48–63 years) during 689,546 person-years of follow-up (Table 2). In multivariable models, history of UL was associated with a 42% increased incidence of endometrial cancer compared with no history (95% CI: 1.12–1.80). Associations were slightly stronger for women diagnosed with UL at earlier ages, ranging from 1.33 for age at diagnosis ≥40 to 1.60 for age at diagnosis <30. The strongest associations were observed among women with more recent UL diagnoses: IRRs for time since UL diagnosis of <2, 3–9, and ≥10 years were 3.20 (95% CI: 2.06–4.98), 0.95 (95% CI: 0.60–1.52), and 1.35 (95% CI: 1.03–1.77), respectively.

In analyses of the 141 cases for whom data on stage at diagnosis was available, associations were stronger for stage ≥2 (IRR=2.25, 95% CI: 1.09–4.63) than for stage 1 (IRR=1.11, 95% CI: 0.75–1.64 (Table 3). In analyses of the 157 cases that could be classified by type, associations were stronger for type II/III (IRR=3.13, 95% CI: 1.64–5.99) than for type I endometrial cancers (IRR=1.12, 95% CI: 0.78–1.59) (Table 4). Results did not differ appreciably between type II and type III cases, but there were small numbers of cases in each subgroup (Supplemental Table 2). Results were similar across levels of BMI, menopausal status, and age (data not shown). The IRR for history of UL in relation to

uterine sarcoma was 3.18 (95% CI: 1.07–9.44), based on 18 cases (12 exposed cases), with most cancers diagnosed more than 2 years since UL diagnosis (data not shown).

Women with a history of UL diagnosis had 6,122 hysterectomies over 258,224 person-years of follow-up, compared with 2,282 hysterectomies over 431,322 person-years among undiagnosed women. In analyses treating hysterectomy as a competing risk (Supplemental Table 3), we obtained an IRR of 1.23 for the overall association between UL history and incidence of endometrial cancer (95% CI: 0.97–1.57).

DISCUSSION

In this large prospective study of U.S. black women, a history of UL was associated with a 40% increased risk of endometrial cancer. Part of the overall association might be explained by diagnostic bias (e.g., incidental detection of UL at the time of a work-up for endometrial cancer) or a diagnostic error (e.g., physician initially misdiagnosing cancer as UL), as evidenced by the stronger association seen for cases diagnosed soon after the UL diagnosis. Nevertheless, a positive association was also observed for cases diagnosed with cancer 10 or more years after the UL diagnosis. The positive association appeared to be limited to Type II and III cancers.

Most studies of the association between UL and endometrial cancer incidence have been descriptive.[10–15] The lack of control group in case series is problematic because UL are highly prevalent asymptomatic tumors. Recall bias is a limitation in some case-control studies but not in prospective studies, where UL diagnoses can be ascertained before the diagnosis of cancer. In a Danish registry-based cohort study, Brinton et al.[18] found that UL diagnoses were associated with an increased risk of uterine cancers, particularly uterine sarcomas. However, the authors speculated that the association between UL and sarcoma risk could be explained by misdiagnosis of the initial tumor because they observed a high risk of endometrial cancer <1 year after UL diagnosis.[18] Because endometrial bleeding is a symptom of both UL and uterine cancer, it is possible that some uterine cancers are initially misdiagnosed as UL. In the present cohort study, the finding of a stronger association of UL with endometrial cancer diagnosed at stage 2 or greater is consistent with this possibility. To rule out bias due to misdiagnosis of cancer as UL or incidental detection of UL at the time of cancer diagnosis, regular pelvic imaging and endometrial sampling would be needed on a large cohort of women over an extended period of time. Although such a study could accurately differentiate between benign and malignant tumors prospectively in time, it would not be ethical or feasible to undertake.

Type II and type III endometrial cancer subtypes tend to be rarer and more aggressive than type I endometrial cancers, and their occurrence is substantially higher among black than white women.[1,44,45] In addition, far less is known about their etiology. In a 2013 report from the Gynecologic Oncology Group trial, which included 2,244 type I endometrial cancers and 581 type II endometrial cancers from 62 U.S. institutions, type II endometrial cancer was positively associated with multiparity and smoking, and inversely associated with obesity. In contrast, no such associations were found for low grade type I endometrial cancer. These findings implied a hormone dependence for type I but not type II endometrial cancer.

However, a subsequent 2013 pooled analysis of 24 epidemiologic studies with 14,069 endometrial cancer cases (12,853 type I and 854 type II) found that type I and II cancers shared many of the same hormonal risk factors,[46] including parity, oral contraceptive use, cigarette smoking, age at menarche, and diabetes, with the exception of obesity, which was more strongly associated with type I cancers. The present study suggests that UL history is a stronger determinant of type II (and type III) endometrial cancers than type I endometrial cancers.

The mechanism by which UL could be associated with a higher risk of type II/III endometrial cancers than type 1 cancers is unclear. Studies of genetic alterations in UL have identified two distinct pathways of tumorigenesis.[47–49] The more common pathway, estimated to account for ~70% of UL, is characterized by point mutations in the MED12 gene, while the other pathway (~20% of UL) is characterized by chromosomal rearrangements resulting in the expression of the *HMGA2* gene.[50] HMGA2, a protein that regulates chromatin remodeling and gene transcription,[51] is overexpressed in numerous benign and malignant tumors.[51] A recent study found HMGA2 overexpression in 91% uterine serous carcinomas but only 37% of stage 3 endometrioid tumors.[52] Another study found overexpression in 63% endometrial carcinosarcomas, but only 3% of stage 1 or 2 endometrioid carcinomas.[48] It is possible that expression of HMGA2 in malignant uterine tumors is driven by the same mechanism as in UL. The extent to which an estrogenic hormonal milieu mediates the association between UL and type II/ III cancers is uncertain.

The present study is the first to examine UL and endometrial cancer in black women. The prospective design rules out the possibility that incidental detection of UL at the time of endometrial cancer surgery caused a spurious association. Low loss-to-follow-up, high positive predictive value of self-reported UL, use of medical records and registry data to classify endometrial cancer by stage and histologic subtype, and control for a wide range of potential confounders are also strengths. The analysis was also able to account for competing risks due to higher rates of hysterectomy among women with UL, and the results were similar but of reduced magnitude due to the higher rate of hysterectomy among women with UL history.

The median age at cancer diagnosis in our cohort (56 years) was younger than that based on national SEER data (62 years).[53] The relatively high prevalence of hysterectomy in our cohort may explain the lower median age at endometrial cancer diagnosis of BWHS cases. The vast majority of women in the BWHS were not systematically screened with ultrasound or other pelvic imaging techniques to detect the presence of UL. Thus, under-diagnosis of UL was likely. Although incidental detection of UL at surgery for endometrial cancer is unlikely, increased gynecologic surveillance among women with UL may increase detection of subclinical endometrial cancer or expedite eventual cancer diagnosis. Women with bleeding from endometrial cancer can have menometrorrhagia or heavy bleeding that extends beyond their usual flow duration, through the entire menstrual cycle. Such women may present clinically with symptoms more typical of UL and not the intermenstrual bleeding classically seen with endometrial cancer. Performing an office endometrial biopsy during a bleeding episode can result in collection of mostly liquid blood, not endometrial

curettings, and thus a diagnosis of endometrial cancer can be missed. The extent to which misdiagnosis occurred in our study is unclear

In summary, the present cohort study of black women found that a history of UL was positively associated with endometrial cancer, particularly type II/III tumors. The strongest association was observed for cancer diagnosed within two years of UL diagnosis, a finding that might be explained by greater surveillance of women with UL or initial misdiagnosis of cancer as UL. However, an association was also observed for cancer diagnosed 10 or more years after the UL. It is still possible that some of the UL diagnoses were actually early endometrial cancers, which were not diagnosed until years later. Our finding of an association between UL history and increased risk of late-stage cancers lends support to this hypothesis. Therefore, despite the additional epidemiologic data contributed by this report, it remains difficult to determine whether there is a causal association between UL and incidence of endometrial cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

BWHS	Black Women's Health Study
CI	confidence interval
IRR	incidence rate ratio
UL	uterine leiomyomata

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Table 1

Baseline characteristics according to ever diagnosis and early diagnosis of uterine leiomyomata in the Black Women's Health Study[a]

	Uterine leiomyomata		
	No (n=36,135)	**Yes (n=11,132)**	**Age at diagnosis <30 (n=3,856)**
Age, mean years (SD)	36.4 (9.8)	37.2 (9.3)	36.7 (9.3)
Body Mass Index, mean kg/m^2 (SD)	27.7 (6.8)	28.0 (6.5)	27.9 (6.5)
>12 years of education, %	83.3	87.1	58.4
Single, %	39.4	35.4	35.2
Age at menarche, mean years (SD)	12.4 (1.6)	12.1 (1.6)	12.1 (1.6)
Nulliparous, %	38.8	39.3	38.1
Ever smoker, %	32.5	32.4	33.3
Vigorous physical activity, ≥5 hours/week, %	13.8	13.5	13.7
Ever use of oral contraceptives, %	84.8	88.7	89.0
Natural menopause, %	9.4	8.8	9.2
Ever use of estrogen-only menopausal female hormones, %	1.3	1.8	2.0
Ever use of estrogen and progesterone menopausal female hormones, %	3.3	3.7	3.9

SD=standard deviation

[a] All characteristics (with the exception of age and proportion of women having experienced natural menopause) are standardized to the age distribution of the cohort in 1995.

Table 2

Association of endometrial cancer risk and timing of uterine leiomyomata diagnosis, 1995–2013

Exposure	Cases	Person- Years	Crude Rate [a]	IRR [b]	95% CI	IRR [c]	95% CI
History of UL							
No	140	431,322	32.5	1.00	Referent	1.00	Referent
Yes	160	258,224	62.0	1.36	1.08, 1.72	1.42	1.12, 1.80
Age at UL diagnosis (years)							
<30	30	62,894	47.7	1.55	1.04, 2.30	1.60	1.08, 2.39
30–39	59	116,643	50.6	1.39	1.02, 1.89	1.44	1.06, 1.97
≥40	71	78,686	90.2	1.26	0.94, 1.70	1.33	0.99, 1.80
Years since UL diagnosis							
0–2	25	36,989	67.6	3.15	2.03, 4.87	3.20	2.06, 4.98
Age at UL <40	6	19,340	31.0	2.65	1.09, 6.45	2.77	1.13, 6.74
Age at UL ≥40	19	17,649	107.7	3.32	2.02, 5.46	3.35	2.03, 5.53
3–9	21	71,857	29.2	0.94	0.59, 1.49	0.95	0.60, 1.52
Age at UL <40	7	41,803	16.7	1.27	0.56, 2.85	1.29	0.57, 2.91
Age at UL ≥40	14	30,054	46.6	0.82	0.47, 1.44	0.83	0.48, 1.46
≥10	100	125,467	79.7	1.28	0.98, 1.67	1.35	1.03, 1.77
Age at UL <40	69	101,320	68.1	1.35	1.00, 1.81	1.40	1.04, 1.89
Age at UL ≥40	31	24,147	128.4	1.09	0.72, 1.64	1.18	0.79, 1.78

UL=uterine leiomyomata, IRR=incidence rate ratio, CI=confidence interval.

[a] Per 100,000 person-years

[b] Adjusted for age and calendar time

[c] Additionally adjusted for education, marital status, age at menarche, parity, menopausal status, oral contraceptive use, female hormones, smoking history, vigorous physical activity, and body mass index.

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Table 3

Association between uterine leiomyomata and endometrial cancer, by stage at endometrial cancer diagnosis 1995–2013

	Stage 1 cancers				Stage 2–4 cancers			
Exposure	**Cases**	**Crude rate[a]**	**IRR[b]**	**95% CI**	**Cases**	**Crude rate[a]**	**IRR[b]**	**95% CI**
History of UL								
No	51	11.8	1.00	Referent	12	2.8	1.00	Referent
Yes	55	21.3	1.11	0.75, 1.64	23	8.9	2.25	1.09, 4.63
Age at UL diagnosis (years)								
<30	9	14.3	1.22	0.60, 2.50	6	9.5	4.48	1.62, 12.34
30–39	20	17.2	1.15	0.68, 1.94	7	6.0	2.12	0.81, 5.53
≥40	26	33.1	1.05	0.64, 1.71	10	12.7	1.79	0.75, 4.27
Years since UL diagnosis								
0–2	12	32.4	3.85	2.00, 7.42	4	10.8	10.64	3.09, 36.63
3–9	6	8.4	0.58	0.24, 1.36	1	1.4	0.59	0.07, 4.72
≥0	32	25.5	0.99	0.63, 1.57	16	12.8	2.23	1.02, 4.87

UL=uterine leiomyomata, IRR=incidence rate ratio, CI=confidence interval.

[a] Per 100,000 person-years

[b] Adjusted for age, calendar time, education, marital status, age at menarche, parity, menopausal status, oral contraceptive use, female hormones, smoking history, vigorous physical activity, and body mass index.

Table 4

Association between uterine leiomyomata and endometrial cancer, by histological subtype, 1995–2013

	Type I cancers				Type II and III cancers			
Exposure	**Cases**	**Crude rate[1]**	**Age- Adjusted IRR[2]**	**95% CI**	**Cases**	**Crude rate[1]**	**Age- Adjusted IRR[2]**	**95% CI**
History of UL								
No	63	14.6	1.00	Ref.	14	3.3	1.00	Ref.
Yes	46	26.3	1.12	0.78, 1.59	37	14.3	3.13	1.64, 5.99
Age at UL diagnosis (years)								
<30	10	15.9	1.08	0.55, 2.12	7	11.1	4.90	1.91, 12.57
30–39	24	20.6	1.09	0.68, 1.77	10	8.6	2.71	1.16, 6.29
≥40	34	43.3	1.15	0.74, 1.76	20	25.4	3.00	1.47, 6.10
Years since UL diagnosis								
0–2	13	35.2	3.87	2.07, 7.21	5	13.5	11.11	3.71, 33.27
3–9	9	12.5	0.75	0.37, 1.52	2	2.8	1.12	0.25, 5.09
≥10	37	29.5	0.90	0.60, 1.37	28	22.3	3.29	1.68, 6.46

UL=uterine leiomyomata, IRR=incidence rate ratio, CI=confidence interval.

[1] Per 100,000 person-years

[2] Adjusted for age and calendar time

[3] Additionally adjusted for education, marital status, age at menarche, parity, menopausal status, oral contraceptive use, use of estrogen-only and estrogen+progesterone female hormones, smoking history, vigorous physical activity, and body mass index.