European Journal of Obstetrics & Gynecology and Reproductive Biology 238 (2019) 188–190

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Correspondence

Risk of unexpected uterine Cancer in women undergoing myomectomy: A population-based study

Dear Editor,

Up to 70% of American women develop uterine fibroids (benign smooth muscle tumors) by age 49 [1]. Myomectomy, surgical removal of fibroids while preserving the uterus, offers a treatment option for women who desire future fertility [1]. Although a common gynecologic procedure, myomectomy is not appropriate for patients with suspected or known cancer. Yet fibroids may present with similar symptoms as uterine sarcomas, and there is heightened concern about unrecognized uterine cancer since the U.S. Food and Drug Administration issued safety warnings against power morcellation of uterine tissues [2]. However, data on the risk of unexpected uterine cancer specifically for women undergoing myomectomy are limited, as prior research has centered on hysterectomies (surgical removal of the uterus). We addressed this important gap using a large population-based sample.

We identified adult women who underwent myomectomy from 10/1/2003-12/31/2013 using the New York Statewide Planning and Research Cooperative System database which encompassed all inpatient and outpatient discharges from civilian hospitals and ambulatory surgery centers throughout the state. These myomectomies were linked to the state cancer registry data via a personal identifier and date of birth to facilitate classification of occult uterine cancer. We excluded cases with an admitting diagnosis of any malignancy, endometrial hyperplasia, or non-gynecologic condition; a history of gynecologic cancer or endometrial hyperplasia (per cancer registry or discharge diagnoses within a 9-month look-back window); or a concomitant hysteroscopic procedure or polypectomy.

The primary outcome was occult uterine cancer, i.e., corpus uteri cancer diagnosed within 28 days after the index myomectomy based on International Classification of Diseases for Oncology site, behavior, and histology codes. We estimated the prevalence of occult uterine cancer and categorized major subtypes and histopathologic characteristics. Associations between patient characteristics and occult uterine cancer risk were assessed using multivariable regressions. P values <0.05 were considered statistically significant.

We found that among 34,526 women undergoing myomectomy, 36 had uterine cancer (0.10%, 95% confidence interval [CI]: 0.07-0.14%). This included 12 endometrial carcinomas (0.03%, 95% CI: 0.02-0.05%) and 24 uterine sarcomas (0.07%, 95% CI: 0.04-0.10%). Fourteen women (0.04%, 95% CI: 0.02-0.06%) had leiomyosarcoma, a major subtype of uterine sarcoma.

Occult uterine cancer risk varied by age, race/ethnicity, and comorbidities (Table 1). In particular, 1.44% of women age $\geq$60 years and 0.01% of women age 18–39 years had endometrial carcinoma (adjusted risk ratio [aRR] = 62.90, 95% CI: 6.02–657.23). Similarly, 0.36% and 0.06% of women age $\geq$60 and 18–39, respectively, had uterine sarcoma (aRR = 8.83, 95% CI: 1.25–62.34). Most uterine cancers were at localized stage.

Based on Current Procedural Terminology codes (available only in outpatient data), 3715 women underwent laparoscopic myomectomy where power morcellation was routinely performed. None of them had endometrial carcinoma, while 3 had uterine sarcoma (0.08%, 95% CI: 0.02-0.24%) (including 2 with leiomyosarcoma [0.05%, 95% CI: 0.01-0.19%]).

These estimates are lower than previous assessments of myomectomies (e.g., 0.19-0.29% for uterine sarcoma) which often relied on limited samples from selected institutions [3,4]. Despite the low risk, preoperative identification of uterine cancer is essential since myomectomy is inadequate for management of these patients and requires additional surgery for appropriate staging and cancer treatment (e.g., removal of the uterus). Moreover, disruption of the uterus in myomectomy (regardless of surgical route) and incidental morcellation in laparoscopic cases may aggravate cancer dissemination and worsen survival [5]. Nevertheless, screening strategies for uterine cancer are limited, especially for uterine sarcoma [5]. Supplementing biochemical/imaging screening with clinical risk factors may help identify high-risk patients. For instance, recognizing age as a strong risk factor, myomectomy should be used cautiously in older women who have completed childbearing.

Funding/Support

This project was supported by grant number R01HS024702from the Agency for Healthcare Research and Quality. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality. The New York State Cancer Registry was supported in part by the Centers for Disease Control and Prevention's National Program of Cancer Registries through cooperative agreement 5NU58DP006309 awarded to the New York State Department of Health.

Conference presentation

Preliminary results from this study were presented at the American College of Obstetricians and Gynecologists annual clinical and scientific meeting in Austin, TX, April 27–30, 2018.

https://doi.org/10.1016/j.ejogrb.2019.03.021

Table 1
Occult uterine cancer in women undergoing myomectomy for presumed benign indications in New York State, October 1, 2003-December 31, 2013.

				Uterine Sarcoma			
		Endometrial Carcinoma		All Uterine Sarcoma		Leiomyosarcoma	
Patient Characteristic	Sample Size	Prevalence n (%)	Adjusted RR[a] (95% CI)	Prevalence n (%)	Adjusted RR[a] (95% CI)	Prevalence n (%)	Adjusted RR[a] (95% CI)
Risk factor							
Age, in years							
18-39	21496	2 (0.01%)	Reference	12 (0.06%)	Reference	6 (0.03%)	Reference
40-49	11860	5 (0.04%)	4.24 (0.86-20.91)	10 (0.08%)	1.49 (0.65-3.43)	7 (0.06%)	2.04 (0.69-5.97)
50-59	893	1 (0.11%)	8.85 (0.90-87.22)	1 (0.11%)	2.16 (0.29-16.09)	1 (0.11%)	3.60 (0.51-25.45)
≥60	277	4 (1.44%)	**62.90 (6.02-657.23)**	1 (0.36%)	**8.83 (1.25-62.34)**	0 (0.00%)	
Race/ethnicity							
Non-Hispanic white	9625	2 (0.02%)	Reference	6 (0.06%)	Reference	4 (0.04%)	Reference
Non-Hispanic black	14712	3 (0.02%)	1.97 (0.24-16.12)	6 (0.04%)	0.70 (0.21-2.30)	4 (0.03%)	0.63 (0.15-2.69)
Hispanic	3571	1 (0.03%)	2.37 (0.20-27.85)	3 (0.08%)	1.46 (0.34-6.32)	1 (0.03%)	0.70 (0.08-6.25)
Other	4433	4 (0.09%)	**9.29 (1.66-52.03)**	8 (0.18%)	**3.18 (1.05-9.64)**	4 (0.09%)	2.25 (0.54-9.31)
Unknown	2185	2 (0.09%)	**8.94 (1.19-67.21)**	1 (0.05%)	0.80 (0.10-6.73)	1 (0.05%)	1.19 (0.13-10.64)
Admitting diagnosis							
Uterine fibroid	28866	6 (0.02%)	Reference	21 (0.07%)	Reference	13 (0.05%)	Reference
Not uterine fibroid[b]	5660	6 (0.11%)	1.77 (0.54-5.76)	3 (0.05%)	0.57 (0.19-1.75)	1 (0.02%)	0.34 (0.06-2.05)
Postmenopausal bleeding	17	1 (5.88%)	NA	1 (5.88%)	NA	0 (0.00%)	NA
Other menopausal disorders	93	0 (0.00%)		0 (0.00%)		0 (0.00%)	
Menstrual disorders	1537	0 (0.00%)		0 (0.00%)		0 (0.00%)	
Ovarian cyst/benig neoplasm of ovary	807	0 (0.00%)		0 (0.00%)		0 (0.00%)	
Endometriosis	296	0 (0.00%)		0 (0.00%)		0 (0.00%)	
Other female genital disorders	1418	2 (0.14%)		1 (0.07%)		0 (0.00%)	
Abdominal mass/pain	803	0 (0.00%)		1 (0.12%)		1 (0.12%)	
Other	689	3 (0.44%)		0 (0.00%)		0 (0.00%)	
History of other malignancy							
Yes	307	2 (0.65%)	3.02 (0.30-30.32)	0 (0.00%)	NA	0 (0.00%)	NA
No	34219	10 (0.03%)	Reference	24 (0.07%)		14 (0.04%)	
Number of benign comorbidities							
0	20761	4 (0.02%)	Reference	14 (0.07%)	Reference	6 (0.03%)	Reference
1	9472	2 (0.02%)	1.01 (0.20-5.15)	6 (0.06%)	0.97 (0.38-2.45)	6 (0.06%)	2.25 (0.77-6.56)
2	3036	2 (0.07%)	2.22 (0.32-15.21)	4 (0.13%)	1.43 (0.47-4.32)	2 (0.07%)	1.72 (0.34-8.65)
≥3	1257	4 (0.32%)	**6.26 (1.37-28.50)**	0 (0.00%)		0 (0.00%)	
Tumor characteristics							
Sample size		12		24		14	
Stage							
Localized		10 (83.3%)		14 (58.3%)		10 (71.4%)	
Regional		1 (8.3%)		3 (12.5%)		1 (7.1%)	
Distant		1 (8.3%)		3 (12.5%)		2 (14.3%)	
Unknown		0 (0.0%)		4 (16.7%)		1 (7.1%)	
Grade							
1		4 (33.3%)		3 (12.5%)		0 (0.00%)	
2		1 (8.3%)		3 (12.5%)		0 (0.00%)	
3		2 (16.7%)		4 (16.7%)		4 (28.6%)	
4		3 (25.0%)		4 (16.7%)		3 (21.4%)	
Unknown		2 (16.7%)		10 (41.7%)		7 (50.0%)	
Tumor size							
< 2 centimeters		2 (16.7%)		0 (0.0%)		0 (0.0%)	
2-5 centimeters		1 (8.3%)		6 (25.0%)		4 (28.6%)	
> 5 centimeters		2 (16.7%)		7 (29.2%)		6 (42.9%)	
Unknown		7 (58.3%)		11 (45.8%)		4 (28.6%)	
Subtype							
Adenocarcinoma		9 (75.0%)		NA		NA	
Adenosarcoma		2 (16.7%)		NA		NA	
Carcinosarcoma		1 (8.3%)		NA		NA	
Leiomyosarcoma		NA		14 (58.3%)		14 (100.0%)	
Low grade ESS		NA		6 (25.0%)		NA	
High grade ESS		NA		1 (4.2%)		NA	
Other		NA		3 (12.5%)		NA	

CI, confidence interval; ESS, endometrial stromal sarcoma; NA, not applicable; RR = risk ratio.
[a] Adjusted RR was estimated based on multivariable Poisson regression models. The dependent variable was occult endometrial carcinoma, occult uterine sarcoma, and occult leiomyosarcoma, respectively, in each model. The explanatory variables included age category, race/ethnicity, admitting diagnosis, history of other malignancy, and number of benign comorbidities (in categories).
[b] Admitting diagnosis that was not uterine fibroids was combined into one category in multivariable regression analysis.

Conflicts of interest disclosures

This project was mostly completed while Dr. Desai was a full-time faculty member at Yale University. Dr. Desai is currently an employee of CooperSurgical Inc. with an adjunct appointment with Yale University. Dr. Wright has served as a consultant for Tesaro and Clovis Oncology. Dr. Gross has received research funding from 21st Century Oncology and Pfizer, as well as funding to support new models of sharing clinical trial data from Johnson & Johnson and travel funding from Flatiron, Inc. The other authors had no conflict of interest to declare.

Acknowledgement

We would like to thank colleagues at the New York Statewide Planning and Research Cooperative System (SPARCS) for their assistance with data acquisition. We also thank Ms. Lindsey M. Hutchison at the New York State Cancer Registry for her valuable advice and assistance with data management.

References

[1] Hartmann KE, Fonnesbeck C, Surawicz T, Krishnaswami S, Andrews JC, Wilson JE, et al. Management of uterine fibroids. Comparative Effectiveness Review No. 195. Rockville, MD: Agency for Healthcare Research and Quality; 2017, doi: http://dx.doi.org/10.23970/AHRQEPCCER195 AHRQ Publication No. 17(18)-EHC028-EF. https://effectivehealthcare.ahrq.gov/topics/uterine-fibroids/research-2017.

[2] U.S. Food and Drug Administration. FDA updated assessment of the use of laparoscopic power morcellators to treat uterine fibroids. MD: Silver Spring; 2017 Available at: https://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/SurgeryandLifeSupport/UCM584539.pdf. Accessed August 14, 2018.

[3] Bean EM, Cutner A, Holland T, Vashisht A, Jurkovic D, Saridogan E. Laparoscopic myomectomy: A single-center retrospective review of 514 patients. J Minim Invasive Gynecol 2017;24(3):485–93.

[4] Brohl AS, Li L, Andikyan V, Običan SG, Cioffi A, Hao K, et al. Age-stratified risk of unexpected uterine sarcoma following surgery for presumed benign leiomyoma. Oncologist 2015;20(4):433–9.

[5] Sizzi O, Manganaro L, Rossetti A, Saldari M, Florio G, Loddo A, et al. Assessing the risk of laparoscopic morcellation of occult uterine sarcomas during hysterectomy and myomectomy: Literature review and the ISGE recommendations. Eur J Obstet Gynecol Reprod Biol. 2018;220:30–8.

Vrunda B. Desai[a,b,*]
[a]*Department of Obstetrics, Gynecology and Reproductive Sciences, Yale School of Medicine, New Haven, CT, United States*

[b]*CooperSurgical Inc., Trumbull, CT, United States*

Jason D. Wright
Department of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, New York, NY, United States

Cary P. Gross[a,b]
[a]*Department of Internal Medicine, Yale School of Medicine, New Haven, CT, United States*

[b]*Yale Cancer Outcomes, Public Policy and Effectiveness Research Center, New Haven, CT, United States*

Haiqun Lin
Department of Biostatistics, Yale School of Public Health, New Haven, CT, United States

Francis P. Boscoe
New York State Cancer Registry, New York State Department of Health, Albany, NY, United States

Peter E. Schwartz
Department of Obstetrics, Gynecology and Reproductive Sciences, Yale School of Medicine, New Haven, CT, United States

Xiao Xu[a,b]
[a]*Department of Obstetrics, Gynecology and Reproductive Sciences, Yale School of Medicine, New Haven, CT, United States*

[b]*Yale Cancer Outcomes, Public Policy and Effectiveness Research Center, New Haven, CT, United States*

* Corresponding author at: Department of Obstetrics, Gynecology and Reproductive Sciences, Yale School of Medicine, 310 Cedar Street, FMB 339, New Haven, CT 06520, United States.
E-mail address: vrunda.desai@yale.edu (V. Desai).

Received 20 December 2018