ONCOLOGY

Are endometrial polyps true cancer precursors?

Tamar Perri, MD; Kurosh Rahimi, MD; Agnihotram V. Ramanakumar, PhD; Karen Wou, MD; Dragana Pilavdzic, MD; Eduardo L. Franco, PhD; Walter H. Gotlieb, MD, PhD; Alex Ferenczy, MD

OBJECTIVE: The purpose of this study was to assess whether endometrial polyps (EMPs) represent cancer precursors.

STUDY DESIGN: Age standardized incidence ratios (SIRs) of histologically verified endometrial cancers (EmCas) were estimated in women with EMPs and in women with uterine leiomyomata, which is a condition that is unrelated to endometrial carcinogenesis. SIRs were calculated as the ratio of observed to expected EmCas based on age-specific incidence rates for female Montreal residents during the same period.

RESULTS: Of 1467 women with EMPs, 125 (8.5%) had EmCa. Of 1138 patients with uterine leiomyomata, 133 (11.7%) had EmCa. The SIRs of EmCa for women with EMPs (odds ratio, 8.0; 95% confidence interval, 6.6–9.5) were significantly lower than that in women with leiomyomata (odds ratio, 19.1; 95% confidence interval, 16.0–22.6). Abnormal uterine bleeding was the main reason for evaluating patients with EMP with or without associated EmCa.

CONCLUSION: The findings of higher EmCa incidence are consistent with enhanced detection opportunity rather than with the endometrial cancer precursor potential of EMPs.

Key words: cancer precursor, endometrial cancer, endometrial polyp, leiomyomata, uterine bleeding

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Endometrial polyps (EMPs) are localized exophytic overgrowths of endometrial mucosa. They have not been described in premenarcheal girls. Their incidence peaks in the fifth decade of life and gradually declines after menopause. The prevalence of EMPs in the general population has been estimated to range between 7.8% and 25%.[1-3] They are, by far, the most frequent endometrial disease in menopausal women. EMPs are often associated with bleeding; however, they may also be diagnosed incidentally in hysterectomy specimens or by screening or diagnostic endovaginal ultrasonography or hysteroscopy.

Traditional teaching has suggested that EMPs are cancer precursors.[4] The risk of EMPs that are associated with endometrial carcinoma (EmCa) increases with age, with the highest rate in patients >65 years in whom 32% of the polyps are associated with invasive or noninvasive malignancy.[5,6] The prevalence of malignant change in EMPs varies from 0.1-13%.[2,3,5-10] Despite these observations, there is no credible evidence that EMP per se is a true cancer precursor or simply represents focal mucosal outgrowth with similar biologic characteristics and behavior as nonpolyp-containing endometrium. It is also unclear whether the perceived high rate of EmCas in patients with EMPs is merely an incidental finding during the diagnostic workup of EMPs, because these patients seek medical attention because of bleeding and other symptoms and thus, are subjected to endometrial evaluations. The purpose of our study was to evaluate the prevalence of EmCa in a large number of patients with EMPs and to compare these findings with the expected EmCa occurrence in these patients using age-specific incidence rates for the Montreal population within the same period. We also aimed to evaluate whether cancer characteristics are different in patients with polyps, compared with cancers that are diagnosed in patients without polyps.

Patients and Methods

Internal review board approval was granted for the study by the Research and Ethics Committee of the Jewish General Hospital, which is an institution affiliated with McGill University in Montreal, Canada. All patients who were diagnosed consecutively with EMPs between the years of 2000 and 2007 were identified with the computerized database of the Department of Pathology in our institution (n = 1880). Clinical and demographic data were extracted from pathologic requisition forms that included age at diagnosis, reason for referral, menopausal status, use of hormone replacement therapy, tamoxifen therapy, presence of other cancers, and means of endometrial evaluation for histologic evaluation (eg, biopsy, curettage).

All histologic slides were reviewed independently by 2 experienced gynecologic pathologists. Discrepant cases were reviewed by a third pathologist who was blinded to the diagnoses of the first 2 pathologists. In situations of disagreement, the 3 pathologists reached a consensus

From the Division of Gynecologic Oncology, Department of Obstetrics and Gynecology (Drs Perri, Wou, Gotlieb, and Ferenczy), and the Department of Pathology (Drs Rahimi, Pilavdzic, and Ferenczy), Jewish General Hospital; the Division of Cancer Epidemiology, Departments of Oncology and Epidemiology (Drs Ramanakumar and Franco), McGill University, Montreal, Quebec, Canada.

Reprints: Alex Ferenczy, MD, Professor of Pathology and Obstetrics & Gynecology, Department of Pathology, Jewish General Hospital, 3755 Cote Sainte-Catherine Rd., Montreal, Quebec, Canada H3T 1E2. alex.ferenczy@mcgill.ca.

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diagnosis using a multiheaded microscope. Cases without adjacent endometrium to EMPs and polyp mimics (such as polypoid carcinoma, hyperplasia or cyclic endometrium, basalis and lower uterine segment endometrium) were excluded (n = 413). Cases with poor hematoxylin-eosin staining were recut and restained (n = 31). The number of histologic slides with or without cancer and polyp size (greatest diameter measured with calibrated microscopic fields) was recorded. Polyps were histologically classified: 1, benign: functional or atrophic; 2, hyperplastic: simple hyperplasia without atypia, complex hyperplasia without atypia or both, or endometrial intraepithelial neoplasia (EIN)/atypical hyperplasia; and 3, cancerous. Cancer cases were classified in the following manner: 1, EMP with primary cancer (cancer confined exclusively to EMP; adjacent endometrium devoid of cancer); 2, EMP with synchronous or simultaneous cancer (cancer in EMP and adjacent endometrium); and 3, noncancerous EMP with cancer only in adjacent endometrium. The adjacent endometrium was classified as proliferative, secretory, menstrual, atrophic, disordered persistent proliferative, nonatypical and atypical hyperplasia, or invasive adenocarcinoma.

EmCas and, if appropriate, sarcomas were classified histologically according to accepted nomenclature.[4] Cancer cases were graded and surgically staged according to Fédération Internationale de Gynécologie et d'Obstétrique (FIGO; 1988). All EmCa cases without EMP that had been diagnosed between the years of 2000 and 2007 were identified with the Pathology Department's computerized data base. The histologic slides were reviewed by 1 of the pathologists (A.F.) to ensure the absence of EMP in these specimens. Age at diagnosis, tumor grade, and surgical stage were recorded.

The observed rate of associated malignancy in patients with EMPs was stratified by 5-year age groups and compared with the equivalent expected incidence of EmCa, with the assumption that cancer risk in these patients was the same as that of Montreal women of the same age and period of cancer diagnosis. Annual age-specific rates were obtained from the Quebec population-based cancer registry for the years of 2001-2005. Because incidence rates of cancer fluctuate over time, we used 2 sets of estimates: 1 estimate that assumed that our patients experienced the lowest incidence rates of EmCa reported in the cancer registry for female residents of Montreal ("conservative") and 1 estimate that assumed the highest rates recorded during the same period ("liberal").

As a secondary objective, we examined the extent of overdetection of EmCa in EMP cases that resulted from the aforementioned analysis with an analysis that was based on another uterine disease that may also prompt an incidental discovery of EmCa. Therefore, we repeated the same exercise for all patients who were found with uterine leiomyomata on pathologic investigation at our institution between the years of 2000 and 2007. As for EMP cases, these were retrieved from the same computerized database of the Department of Pathology and reviewed as described earlier.

We used Wilcoxon's rank sum test to compare means for interval-scaled variables and χ^2 tests for categoric or ordinal variables. The significance of trends for ordinal categories between groups was tested with the Cochran-Mantel-Haenszel method. To examine EmCa occurrence among women with EMPs and leiomyomata, we calculated age standardized incidence ratios (SIRs) and 95% CIs. Expected numbers were calculated based on the cumulative rates that were derived from the annual age-specific incidence rates of endometrial cancer for Montreal from 2001-2005 and cumulative age-defined person-time denominators for the 2 patient groups, EMPs, and leiomyomata. SIRs indicate how much more common EmCa was in each of the patient subsets (EMPs and leiomyomata) than in female Montreal residents of the same age.

RESULTS

Table 1 shows the clinical characteristics of the 1467 patients with EMP with and without cancer and the initial diagnostic methods that were used. The mean number of histologic slides ranged from 3 (endometrial biopsy specimens) to 12 (hysterectomy specimens). EMPs ranged from 2-5 cm (mean 1.8 cm) in the largest diameter. Consensus agreement by 2 pathologists was achieved in 1366 cases (93.1%), and 3-way consensus reading was carried out in the remaining 101 cases. Women with cancerous EMPs, whether primary or simultaneous (synchronous), were older ($P < .0001$) than those women without associated cancer; the majority of occurrences were in postmenopausal women after the age of 55 years. Abnormal bleeding was the most common reason for referral in both groups but was significantly more common in cancer-associated EMPs ($P = .003$). We detected endometrial malignancy in 125 cases (8.5%) in which EMPs were found on pathologic examination. Primary and synchronous cancerous EMPs accounted for 0.89% and 4.57% of all EMPs, respectively; 3.07% EMPs were noncancerous polyps with cancer in the adjacent endometrium.

Table 2 shows the histologic types of EMPs without and with carcinoma. There was a significant difference in distributions of histologic categories between the 2 groups ($P < .0001$). The majority of noncancerous EMPs were of the functional/atrophic type (71.2%). Among the hyperplastic polyps, simple hyperplasia without atypia dominated. Endometrial intraepithelial neoplasia/atypical hyperplasia occurred in only 55 of the 1386 evaluable EMPs (4.0%). Only 2 of 44 evaluable patients with cancer and polyps (4.5%) were of the functional type, and both were synchronous. The endometrium adjacent to the EMP without associated cancer was mainly of the nonhyperplastic, proliferative, secretory, or atrophic type (91%). In the 125 cases of both primary and simultaneous cancerous polyps, the adjacent noncancerous endometrium was mainly atrophic.

Table 3 shows the FIGO surgical stages, grades, and histologic types of endometrial cancers with and without EMP and leiomyomata uteri. During the same time period, 195 endometrial cancers were diagnosed in our hospital without associated EMPs or leiomyomata. Of 1138 patients who were found to have