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Risk Factors for Developing Multiple Malignancies in Endometrial Cancer Patients

Stefano Uccella, MD, Stephen S. Cha, MS, L. Joseph Melton III, MD, Eric J. Bergstralh, MS, Lisa A. Boardman, MD, Gary L. Keeney, MD, Karl C. Podratz, MD, PhD, Fabio Francesco Ciancio, MD, and Andrea Mariani, MD

Division of Gynecologic Surgery (Drs Uccella, Podratz, and Mariani), the Division of Biomedical Statistics and Informatics (Messrs Cha and Bergstralh), the Division of Epidemiology (Dr Melton), the Division of Gastroenterology and Hepatology (Dr Boardman), and the Division of Anatomic Pathology (Dr Keeney), Mayo Clinic, Rochester, Minnesota; Mont de Marsan Hospital, Mont de Marsan, France (Dr Ciancio). Dr Uccella is now with Experimental Medicine and Oncology, University of Insubria, Varese, Italy.

Abstract

Objective—The purpose of this study was to investigate the clinical and pathologic characteristics of patients with endometrial cancer (EC) and associated breast, colorectal, or ovarian cancer and to define the risk of developing an associated malignancy during follow-up after EC treatment.

Methods/Materials—During a 13-year period, 1,028 women had a hysterectomy for EC at our institution and available clinical information. An associated malignancy was defined as diagnosis of another malignant disease before or at the time of operation for EC or during follow-up.

Results—Of these 1,028 patients, 208 (20%) had a history of another malignancy besides EC. Most frequent were carcinomas of the breast (10%), colon-rectum (3%), and ovary (4%). Patients with a family history of hereditary nonpolyposis colorectal cancer (HNPCC)-related cancers and presence of EC in the lower uterine segment (LUS) had a higher risk of developing colorectal cancer within 5 years after hysterectomy (2% and 6%, respectively). After multivariate analysis, only LUS involvement remained significantly associated with this risk. Patients with EC and associated ovarian cancer were more likely to be younger and have superficially invasive EC, family history of HNPCC-related tumors, and family history of breast or ovarian cancer. After multivariate analysis, only age younger than 50 years (odds ratio [OR], 4.27; 95% confidence interval [CI], 1.49–12.21) and family history of breast or ovarian cancer (OR, 3.95; 95% CI, 1.60–9.72) were significantly related to risk of having ovarian cancer associated with EC. No significant risk factors were identified for development of an associated breast cancer after EC.

Conclusions—Young age, family history of malignancy, and LUS involvement may indicate the need for more intensive preventive strategies for colorectal cancer as well as for evaluating the risk of synchronous ovarian cancer in EC patients.

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Reprints: Andrea Mariani, MD, Division of Gynecologic Surgery, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (mariani.andrea@mayo.edu).

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Keywords

breast cancer; colorectal cancer; endometrial cancer; multiple tumors; ovarian cancer

Introduction

Endometrial cancer (EC) is the most common malignancy of the female reproductive tract in the United States. During 2010, an estimated 43,470 new cases of EC were diagnosed and about 7,950 deaths occurred (1).

Patients with EC have been previously reported to have an excess of colorectal, ovarian, and breast cancers (2–6). Unfortunately, the available studies on this issue are limited either by small numbers of patients or lack of detail in description of patients' characteristics.

Generally accepted screening strategies have been developed for early detection of colorectal and breast cancer (7,8), but no effective screening exists for ovarian cancer. Identification of EC patients with a higher predisposition for developing subsequent colorectal or breast cancer would allow focused and more effective screening. Moreover, identification of EC patients at high risk of presenting synchronous ovarian cancer may be useful, especially for young women wishing to preserve fertility.

In the present paper, we describe the clinical and pathologic characteristics of patients with EC and associated colorectal, ovarian, and breast malignancies. We further investigate risk factors predictive of development of breast and colorectal cancer after hysterectomy for EC. Additionally, we identify variables that can predict the risk of having an associated ovarian cancer at the time of hysterectomy for EC. These observations can have important implications for evaluation and follow-up of women with EC.

Patients and Methods

With approval from the Mayo Clinic Institutional Review Board, we identified 1,109 patients whose EC was managed surgically at Mayo Clinic, Rochester, Minnesota, between 1984 and 1996. All patients had epithelial EC, and treatment included hysterectomy and removal of existing adnexal structures. Eighty-one patients were excluded because they had not authorized use of patient information in research studies (9) or follow-up information on associated malignancies was inadequate. The remaining 1,028 patients were the subjects of the current study.

All hematoxylin-eosin–stained slides of the ECs were reviewed retrospectively by one of us (G.L.K.). Staging was defined according to the 1988 International Federation of Gynecology and Obstetrics surgical staging system (10). For patients who received treatment before 1988, stage was determined retrospectively on the basis of surgical and pathologic assessments. For the purpose of this analysis, we defined patients with lower uterine segment (LUS) involvement as those who had EC invading the LUS but not the endocervical canal. Patients who had tumor limited to the LUS and those with tumor located concomitantly also in other areas of the uterine corpus have been grouped for this analysis.

For distinguishing synchronous tumors of the ovary and endometrium from ovarian metastases, the criteria of Ulbright and Roth (11) were used. In brief, an ovarian tumor was considered metastatic from the endometrium if both of the following were true: there was an EC, and the ovarian cancer and EC had the same histologic subtype and grade. In addition to these criteria, a multinodular pattern of tumor dissemination on the ovary was considered a major criterion for defining metastasis. At least 2 of the following minor criteria defined

metastasis: small ovaries (<5 cm), bilateral involvement, deep myometrial invasion (>50%) of EC, lymphovascular invasion in the uterus, and tubal lumen involvement. All ECs with associated ovarian involvement had been reviewed by one of us (G.L.K.) and appropriately classified as synchronous primary or metastatic tumors.

The presence of other associated tumors was verified by histologic diagnosis in all patients who had surgery at Mayo Clinic; the diagnosis was confirmed by pathologist review (G.L.K.). When patients were treated outside Mayo Clinic for a second neoplasm, diagnosis of an associated cancer was usually abstracted from the medical records of other medical facilities. If the medical records reflected insufficient follow-up information about survival, recurrence, or presence of other malignancies, death certificates were obtained, and letters were sent or telephone calls were made to patients and family physicians.

Family history of cancer was defined as presence of at least 1 first-degree relative with any cancer. A similar definition was used for family history of hereditary nonpolyposis colorectal cancer (HNPCC)-related tumors, in accord with the literature (12). The following were considered HNPCC-related tumors: transitional cancers of the urinary tract, pancreas, colon, rectum, endometrium, ovary, small bowel, stomach, biliary tract, and brain; sebaceous gland adenomas; and keratoacanthomas (11). Family history had been collected retrospectively by review of forms completed by patients at the time of EC surgery.

We included in the definition of "other malignancy" all invasive cancers (ie, no in situ malignancies, except for in situ cancer of the urinary bladder), excluding basal and squamous cell carcinomas of the skin except when these occurred on the vulva. When a patient had multiple independent cancers (not recurrences) at the same site, diagnosed at different times (eg, 2 different breast cancers diagnosed 4 years apart), for the purpose of counting the overall number of associated cancers, only the first appearance of a malignancy at a certain anatomic site was included. Age at the time of EC surgery was analyzed as both a continuous variable and a categorical variable. Age of 50 years was used as an arbitrary cutoff for the categorical variable.

Patients who had an associated cancer at the time of or after EC were analyzed separately to identify predictive factors for development of the other malignancy. The mean $\pm$ SD of a continuous variable or frequency (percentage) of a categorical variable was determined. The Student *t* test, analysis of variance, or Pearson χ^2 test was performed to compare groups accordingly. The Fisher exact test was also used when appropriate. The log-rank test, Kaplan-Meier survival curves, and Cox proportional hazards model were used to predict development of breast and colorectal cancer within 5 years or over time after EC, respectively. Any *P* value less than .05 was considered statistically significant. All statistical analyses were performed using SAS version 9.1.3 software (SAS Institute Inc, Cary, North Carolina).

Results

The characteristics of the 1,028 patients with EC are summarized in Table 1.

Altogether, 242 (24%) of the 1,028 patients had a history of another malignancy. However, in 34 women, the prior malignancy was nonmelanoma skin cancer (ie, basal cell carcinoma or localized squamous cell carcinoma other than vulvar cancer), and they were consequently excluded. Therefore, 208 patients (20%) were categorized as having a history of associated malignancy. Most frequently associated with EC were carcinomas of the breast (n=98; 10%), colon-rectum (n=30; 3%), and ovary (n=36; 4%). However, after pathologist review of the 36 cases listed as double primary ovarian cancer and EC, 9 were categorized

according to published criteria (11) as ovarian metastases of endometrial origin. Therefore, 27 patients (3%) were ultimately listed as double tumors of the ovary and endometrium.

Breast Cancer

Patients with EC and associated breast cancer were significantly older and had lower probability of nodal involvement compared with patients without breast cancer (Table 2). Conversely, no difference was found in terms of body mass index (BMI), EC stage, depth of myometrial invasion, EC histologic grade and subtype, family history of cancer, and presence of tumor in the LUS.

Of the 98 patients with associated breast cancer, 26 (3% of the overall 1,028 patients) had a diagnosis of breast tumor after primary surgery for EC. The median time between diagnosis of EC and subsequent diagnosis of breast carcinoma was 6 years (range, 0–15 years). The median follow-up of these 26 patients after EC diagnosis was 111 months (range, 19–211 months).

Considering the whole population of EC patients at the time of hysterectomy, we tested the following variables: age, BMI, stage, depth of myometrial invasion, histologic grade and subtype, lymph node status, family history of cancer, and invasion of the LUS. However, we did not find any predisposing condition that significantly predicted a higher risk of developing breast cancer following EC.

Colorectal Cancer

Among patients with available information, family history of HNPCC-related cancer and EC involving the LUS were significantly related to the risk of having associated colorectal cancer (Table 2). Considering the whole population of EC patients at the time of hysterectomy, we focused on the risk of developing colorectal cancer after surgery. Of the 30 patients with associated colorectal cancer, 14 (1% of the overall 1,028 patients) had a diagnosis of carcinoma of the colon-rectum at the time of or after primary surgery for EC. The median time between diagnosis of EC and subsequent diagnosis of colorectal cancer was 4 years (range, 0–14 years), and colorectal cancer developed in 10 of them within 5 years. The median follow-up of these 14 patients after diagnosis of EC was 76 months (range, 2–171 months).

We tested the risk of developing colorectal cancer after EC. Family history of HNPCC-related malignancy was related to this risk on univariate analysis: 0.6% of patients with no family history had colorectal cancer at 5 years, compared with 2% of patients with family history ($P=.04$). Also, presence of EC in the LUS was significantly associated with risk of developing colorectal cancer after hysterectomy. In fact, colorectal cancer developed in less than 1% of patients without tumor in the LUS at 5 years after hysterectomy compared with 6% of patients with tumor in the LUS ($P=.02$). Multivariate analysis selected LUS as the only significant variable predictive of development of colorectal cancer within 5 years after hysterectomy ($P=.02$; odds ratio [OR], 4.74; 95% confidence interval [CI], 1.25–18.0).

Ovarian Cancer

Overall, 26 of the 27 patients (96%) with double ovarian cancer and EC had synchronous tumors, discovered at the time of primary surgery. The remaining patient had a vaginal hysterectomy with adnexal preservation at the time of primary treatment for EC, and ovarian cancer was diagnosed 5 years later.

The 27 patients with double tumors of the ovary and endometrium did not differ significantly from those without associated ovarian cancer on the basis of BMI, stage, lymph

node invasion, histologic grade and subtype, family history of cancer, and tumor in the LUS. However, patients with associated ovarian cancer were more likely to be younger at the time of diagnosis of EC and have superficially invasive EC, family history of HNPCC-related tumors, and family history of breast or ovarian cancer (Table 2).

After multivariate analysis, only age younger than 50 years (OR, 4.27; 95% CI, 1.49–12.21) and family history of breast or ovarian cancer (OR, 3.95; 95% CI, 1.60–9.72) remained significantly related to the risk of having ovarian cancer associated with EC.

Considering the whole population of 1,028 patients, 3 of the 23 patients (13%) who were younger than 50 years and had at least 1 first-degree relative with HNPCC-related cancer had associated ovarian cancer compared with 20 of 841 other patients (2%) ($P=.001$) (164 patients had missing information on family history of HNPCC). Also, of the 11 patients who were younger than 50 years and had at least 1 first-degree relative with breast or ovarian cancer, 3 (27%) had associated ovarian cancer compared with 19 of 885 other patients (2%) ($P<.001$) (132 patients had missing information on family history of breast or ovarian cancer) (Table 3).

Discussion

Development of multiple primary malignancies within the same individual has been described since the late 19th century (13). EC has been shown previously to be mainly associated with cancers of the ovary (3,5), colon-rectum (3,6,14), and breast (2,3,15). The first studies showing these associations reported that the proportion of EC patients in whom multiple primary malignancies develop is slightly more than 10% (4,6,15,16). These studies, however, recruited a small number of cases and were hospital based. The consequence was an underestimation of the real incidence of multiple malignancies in EC patients, probably because of a lack of information on patients managed at outside institutions. More recently, a large population-based study with estimated case ascertainment of more than 97% showed that the real incidence of other primaries in EC patients is approximately 22% (2). However, the limitation of this study is the absence of details about clinical and pathologic characteristics of the patients included. Thus, the information provided to the clinician relies on statistical considerations and does not specify how to individualize patients' management. A recent Canadian population-based study of 3,473 women found that the incidence of colorectal cancer after EC was higher than expected for the general population of women of the same age, yet the incidence of breast cancer was not increased (17). However, this study censored all cases of colon or breast cancer diagnosed before EC, thus probably underestimating the possible associations. This study also failed to provide clinical and pathologic details of the patients included.

Although our study is not population based, the percentage of patients in whom a second primary developed before, contemporarily with, or after diagnosis of EC (20%) is comparable to the previously quoted findings by Re et al (2) on the population of Orange County, California. This high ascertainment capability is probably attributable to accurate collection of follow-up data. The consequence is provision of reliable information that can be applied to clinical practice.

In our study, breast cancer developed in about 3% of EC patients at a mean of 6 years after hysterectomy, but we failed to identify any possible predictive factors to better focus preventive strategies.

We also observed that colorectal cancer developed in approximately 1% of patients with EC at a median time interval of 4 years after surgery for uterine cancer. In the present series,

LUS involvement at the time of hysterectomy for EC was the only independent predictive factor for development of colorectal cancer within 5 years. A recent study by Westin et al (18) showed that patients with EC confined to the LUS had 29% probability of being affected by Lynch syndrome (or at least a high suspicion of it) on the basis of tissue molecular assays. Although our definition of LUS was slightly different (we included patients with tumors involving not only the LUS but also the uterine corpus), our data provide clinical confirmation of the findings by Westin et al (18).

The differential diagnosis between metastasis and a synchronous primary in the case of contemporary endometrial and ovarian malignant processes is not always easy. All the histologic slides of our patients were reviewed by our pathologist (G.L.K.) to ensure better discrimination between metastases and primary ovarian tumors. In our series, patients with associated ovarian cancer were significantly younger and presented with earlier EC compared with the remaining EC patients. This finding is commonly reported in the literature (19). However, the characteristics of early-stage disease (ie, superficially invasive EC) are part of the criteria for differentiating a synchronous ovarian cancer from metastasis (11). Therefore, by definition, patients with synchronous ovarian cancer and EC usually have a diagnosis of early endometrial disease.

Interestingly, as ovarian cancer is part of the HNPCC syndrome, in our series, patients with synchronous ovarian cancer and EC were more likely (43% of them [10/23]) to have first-degree relatives with HNPCC-related cancers compared with the other EC patients. A recent study of patients younger than 45 years by Walsh et al (20) reported an alarmingly high incidence of synchronous ovarian tumors in young EC patients (especially those with low-grade or low-stage disease), but the association with family history was not described. In our series, diagnosis of EC in patients younger than 50 years with at least 1 first-degree relative with breast or ovarian cancer yielded 27% probability of having ovarian cancer associated with EC. Therefore, our study adds useful information to the literature for the appropriate management of the adnexa in young patients with a family history of breast or ovarian cancer, particularly those young women who request conservative treatment. We believe that in this group of high-risk patients, hysterectomy and bilateral salpingo-oophorectomy (or at least laparoscopic exploration of the abdomen) should be discussed.

Conclusions

In conclusion, our study shows that, when EC is diagnosed, histopathologic findings as well as the patient's personal and family history should be thoroughly investigated to identify conditions that increase the risk of associated malignancies. In particular, family history of breast or ovarian cancer and HNPCC-related tumors, as well as young age (<50 years) and tumor located in the LUS should be regarded as risk factors for concomitant or subsequent development of ovarian and colorectal cancer, thus prompting effective screening and implementation of diagnostic or preventive strategies to reduce morbidity and mortality from those conditions.

Acknowledgments

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Abbreviations

BMI	body mass index
CI	confidence interval

EC	endometrial cancer
HNPCC	hereditary nonpolyposis colorectal cancer
LUS	lower uterine segment
OR	odds ratio

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Table 1

Characteristics of 1,028 Patients at the Time of Diagnosis of Epithelial Endometrial Cancer Treated Between 1984 and 1996

Characteristics	No. (%) ^a	Mean±SD
Age at diagnosis, y		64.7±11.0
BMI at diagnosis		30.3±8.3
Follow-up, mo ^b		74.1±44.9
Vital status at last follow-up		
Deceased	297 (30)	
Alive	708 (70)	
Missing information	23	
Associated other tumors ^c		
Yes	208 (20)	
No	820 (80)	
Stage		
I	706 (69)	
II, III, IV	322 (31)	
Depth of myometrial invasion		
50%	773 (76)	
>50%	246 (24)	
Missing information	9	
Histologic grade		
1	430 (42)	
2	346 (34)	
3	250 (24)	
Missing information	2	
Histologic subtype		
Endometrioid	911 (89)	
Nonendometrioid	117 (11)	
Positive lymph nodes ^d		
Yes	103 (18)	
No	476 (82)	
Unknown (no lymphadenectomy)	449	
Family history of any cancer ^e		
Yes	574 (57)	
No	425 (43)	
Missing information	29	
Family history of HNPCC-related cancer ^f		
Yes	204 (24)	
No	660 (76)	
Missing information	164	

Characteristics	No. (%) ^a	Mean±SD
Family history of breast or ovarian cancer ^e		
Yes	117 (13)	
No	779 (87)	
Missing information	132	
Tumor invading the LUS ^g		
Yes	75 (7)	
No	953 (93)	

Abbreviations: BMI, body mass index; HNPCC, hereditary nonpolyposis colon cancer; LUS, lower uterine segment.

^a Percentages exclude missing patients.

^b From diagnosis of endometrial cancer to last known follow-up.

^c Excluding skin cancers other than melanoma and in situ cancers other than bladder cancer. Some patients had multiple previous primary cancers.

^d Pelvic and/or para-aortic.

^e At least 1 first-degree relative with cancer.

^f At least 1 first-degree relative with HNPCC-related tumor (ie, transitional cancers of the urinary tract, pancreas, colon, rectum, endometrium, ovary, small bowel, stomach, biliary tract, and brain; sebaceous gland adenomas; and keratoacanthomas).

^g Without invasion of the cervix.

Table 2Characteristics of Endometrial Cancer Patients With Associated Breast, Colorectal, or Ovarian Cancer^a

Site of Associated Cancer	Characteristics Significantly ($P<.05$) Associated With Double Tumors	Patients With Associated Cancer	Patients Without Associated Cancer	<i>P</i> Value
Breast	Age ^b	67.7±1.1 y	64.4±0.4 y	.004
	Positive lymph nodes	4%	11%	.02
Colon-rectum	FH-HNPCC	54%	23%	<.001
	EC in LUS ^c	17%	7%	.045
Ovary	Age ^b	56.3 y	64.9 y	<.001
	Myometrial invasion >50%	4%	25%	.005
	FH-HNPCC	43%	23%	.02
	FH-Br/Ov	36%	12%	.003

Abbreviations: EC, endometrial cancer; FH-HNPCC, family history of hereditary nonpolyposis colorectal cancer (ie, at least 1 first-degree relative with HNPCC-related tumor [transitional cancers of the urinary tract, pancreas, colon, rectum, endometrium, ovary, small bowel, stomach, biliary tract, and brain; sebaceous gland adenomas; and keratoacanthomas]); FH-Br/Ov, family history of breast or ovarian cancer (ie, at least 1 first-degree relative with ovarian cancer, breast cancer, or both); LUS, lower uterine segment.

^a Associated tumors (breast, colorectal, ovarian) reported in this table occurred either before, at the time of, or after diagnosis of EC.

^b At the time of diagnosis of EC.

^c Without invasion of the cervix.

Table 3

Risk of Having Ovarian Cancer at the Time of Hysterectomy for Endometrial Cancer According to Age and Family History of Breast or Ovarian Cancer^a

Age <50 y	FH-Br/Ov	Ovarian Cancer, % ^b
Yes	No	6 (4/68)
Yes	Yes	27 (3/11)
No	No	1 (10/711)
No	Yes	5 (5/106)

Abbreviation: FH-Br/Ov, family history of breast or ovarian cancer.

^aData on FH-Br/Ov were missing for 132 patients.

^bNumber of ovarian cancers/total number of patients. Five of the 27 patients had missing information on FH-Br/Ov.