Original Articles

Referral and ascertainment bias in patients with synchronous and metachronous endometrial malignancy*

A. Mariani[1], *M.D., Ph.D.*; S.S. Cha[2], *M.S.*; E.J. Bergstralh[2], *M.S.*; L.A. Boardman[3], *M.D.*; S.C. Dowdy[1], *M.D.*; G.L. Keeney[4], *M.D.*; K.C. Podratz[1], *M.D., Ph.D.*; L.J. Melton III[5,6], *M.D.*

[1]Department of Gynecologic Surgery, [2]Division of Biostatistics, [3]Division of Gastroenterology and Hepatology, [4]Division of Anatomic Pathology, [5]Division of Epidemiology, and [6]Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Mayo Clinic, Rochester, MN (USA)

Summary

The purpose of this study was to evaluate the frequency in patients with endometrial cancer of other malignancies and the influence of referral and ascertainment biases on these associations. Analysis of 1,028 local and referred patients who had a hysterectomy for endometrial cancer was based on residence at the time of diagnosis. Altogether, 208 patients had a history of another malignancy, most frequently breast, colon, and ovary. At the time of surgery for endometrial cancer, the prevalence of lymphoma and breast and ovarian cancers was greater than expected although the higher prevalence of lymphoma was limited to referred patients. During follow-up after hysterectomy, the incidence of lung cancer was lower than expected, whereas the incidence of lymphoma was higher. Breast, colorectal, and bladder cancers were more common than expected although this finding was limited to local patients. We concluded that results of epidemiologic studies from tertiary care centers may be misleading if they do not account for referral and ascertainment biases.

Key words: Ascertainment bias; Endometrial cancer; Epidemiology; Multiple malignancies; Referral bias.

Introduction

Endometrial cancer is the most common malignancy of the female reproductive tract in the United States [1]. Multiple primary cancers can occur in the same patient. Colon, ovarian, and breast cancers [2-6] have been reported previously to be the malignancies most commonly associated with endometrial cancer. Other associated malignancies are those arising in the bladder, small intestine, skin, and soft tissue [7]. However, these associations may be influenced by referral and ascertainment biases, which may be present in analyses of patients from tertiary care centers. In fact, there is a high likelihood that a greater proportion of patients with high-risk histologic features, in poor medical condition, or both are referred to tertiary care centers, resulting in an artificial increase in the number of patients with the above characteristics (referral bias). Patients with endometrial cancer who are referred to tertiary care centers are more likely to have advanced lesions, history of other malignancies, and more comorbid conditions than local patients [8]. Similarly, the rate of malignancies reported during follow-up is decreased among referred endometrial cancer patients [3]. This last finding demonstrated that less accurate follow-up, as may occur in patients who live far from tertiary care centers, may lead to ascertainment bias.

The aims of the present study were to evaluate the incidence and prevalence of other associated malignancies in a cohort of women with endometrial cancer and to assess the potential influence of referral and ascertainment biases on the above associations.

Patients and Methods

With approval by the Mayo Clinic Institutional Review Board, we identified 1,109 patients whose endometrial cancer was managed surgically at Mayo Clinic, Rochester, Minnesota, between 1984 and 1996. A portion of this cohort of patients has been described in detail in our previous analyses [9,10]. All patients had epithelial endometrial cancer, and their treatment included hysterectomy and removal of existing adnexal structures. Overall, 81 patients were excluded from the present analysis because they did not authorize use of their information for research [11], or follow-up information on associated malignancies was inadequate. The remaining 1,028 patients form the cohort of the current study.

As previously described [9], all hematoxylin-eosin–stained slides of the endometrial cancers were reviewed retrospectively to confirm the original diagnosis of adenocarcinoma and to determine histologic grade and subtype. Staging was also defined according to the International Federation of Gynecology and Obstetrics (FIGO) surgical staging system [12]. For patients who received treatment before 1988, stage was determined retrospectively on the basis of the surgical and pathologic assessments. Histologic classification was performed according to the World Health Organization classification [13]. Architectural grading was based on the degree of glandular differentiation in accordance with the FIGO guidelines [12].

The presence of other associated tumors was verified by histologic diagnosis in all patients undergoing surgery at Mayo Clinic, and the diagnosis was confirmed by pathology review. When

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patients had surgery outside Mayo Clinic, the diagnosis of an associated cancer was abstracted from the medical records of the other medical facilities or from letters from outside physicians.

For distinguishing synchronous tumors of the ovary and endometrium from ovarian metastases, the criteria of Ulbright and Roth [14] were used. All endometrial cancers with associated ovarian involvement had been reviewed and appropriately classified as either synchronous primary or metastatic.

History of malignancy was defined as the diagnosis of another invasive malignant disease before or at the time of the operation, including also the immediate 30 days after the operation for endometrial cancer (prevalence) or during the subsequent follow-up (incidence). As previously described [9], if sufficient follow-up information about survival, recurrence, or presence of other malignancies was not available in the clinical records, death certificates were obtained, and letters were sent or telephone calls were made to patients and family physicians to obtain the information.

The expected number of other primary malignancies was estimated from Surveillance Epidemiology and End Results (SEER) data for the year 2000, using the age-adjusted rate of the female population [15]. The incidence and prevalence statistics were generated by the locally developed SAS "personyrs" procedure [16]. We determined the age-specific person-years of follow-up and compared expected to observed numbers of subsequent malignancies. For comparison with SEER data, the prevalence information was limited to the ten years before the endometrial cancer diagnosis. However, information about incidence was considered even beyond ten years after the diagnosis of endometrial cancer.

The standardized incidence ratio (SIR) and standardized prevalence ratio (SPR) were calculated according to the SEER statistics manual [15]. All the analyses were performed with SAS version 8 software (SAS Institute Inc, Cary, NC).

When we analyzed the incidence and prevalence of "all cancers" in the SEER database, we subtracted the rate of endometrial cancers. Moreover, according to the definition of "all cancers" in the SEER database [15], in our analysis we included in the definition of "other malignancy" all invasive cancers (i.e., no in situ malignancies, except for in situ cancer of the urinary bladder), excluding basal and squamous cell carcinomas of the skin (except when squamous cell carcinomas occurred on the vulva). Furthermore, for the analysis of incidence and prevalence of different tumors, we considered the following cancer sites altogether: colon together with rectum; kidney with renal pelvis; and lung with bronchus. For the definition of cancer of the urinary bladder, we included in situ carcinoma; for lymphoma, we grouped together both Hodgkin's and non-Hodgkin's lymphoma.

When a patient had multiple independent cancers (not recurrences) at the same site diagnosed at different time periods (for example, 2 different breast cancers diagnosed 4 years apart), for the purpose of the analysis of incidence and prevalence (and the count of the overall number of associated cancers), only the first appearance of the cancer at a given anatomic site was considered. For the evaluation of possible referral and ascertainment biases, we performed a stratified analysis subdividing the cohort by residency at initial diagnosis (i.e., coming from within or beyond a 50-mile radius from our institution), using residency information from the Mayo Clinic database. Constancy of the risk estimates from one geographic area to the next would be evidence for nearly complete ascertainment of subsequent malignancies throughout the study; but a decline from the level attained where follow-up is most reliable (i.e., locally) would suggest underascertainment among referred patients [3].

Results

Characteristics of the 1,028 patients with endometrial cancer are summarized in Table 1. The mean (SD) age at surgery for endometrial cancer was 64.7 (11.0) years (median, 65 years). Mean body mass index (BMI) was 30.3 (8.3) (median, 28.6).

Analysis of the referral pattern at the Mayo Clinic

Altogether, 218 patients (21%) were living within a 50-mile radius of our institution at the time of their surgery; 182 patients (18%) were living between 51 and 100 miles away; 197 (19%) were living between 101 and 200 miles away; and the residence area of 431 patients (42%) was beyond 200 miles from our institution (Table 1). Compared with the 218 patients living within a 50-mile radius, the 810 living beyond 50 miles did not differ significantly by age, stage of endometrial cancer, depth of myometrial invasion, histologic grade, or subtype.

Table 1. — *Characteristics of 1,028 patients at the time of diagnosis of epithelial endometrial cancer undergoing surgery at Mayo Clinic between 1984 and 1996*.

Characteristic	No. (%)[a]	Mean (SD)
Age at diagnosis (years)		64.7 (11.0)
Body mass index, diagnosis		30.3 (8.3)
Follow-up (months)[b]		74.1 (44.9)
Vital status at last follow-up		
Deceased	297 (30)	
Alive	708 (70)	
Missing information[c]	23	
Associated other tumors[d]		
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)	
Referral patterns, mi[e]		
≤ 50	218 (21)	
51-100	182 (18)	
101-200	197 (19)	
> 200	431 (42)	

[a] Percentage excludes missing patients.
[b] Months from diagnosis of endometrial cancer to last known.
[c] No available information after discharge from the hospital at the time of hysterectomy.
[d] Excluding skin cancers other than melanoma and in situ cancers other than bladder cancer. Some patients had multiple primary cancers.
[e] Distance in miles from Rochester, Minnesota.

Table 2. — *Prevalence of other cancers in women with endometrial cancer compared with the general population and stratified by residency (≤/> 50 mi from Rochester, Minnesota)*[a].

	All patients (N = 1,028)			≤ 50 mi (n = 218)			> 50 mi (n = 810)		
Cancer	O/E	SPR (95% CI)	*p* value	O/E	SPR (95% CI)	*p* value	O/E	SPR (95% CI)	*p* value
Breast	48/27.3	1.8 (1.3-2.3)	< .001	12/5.6	2.1 (1.1-3.7)	.007	36/21.7	1.7 (1.2-2.3)	.002
Colorectal	8/6.6	1.2 (0.5-2.4)	.60	1/1.4	0.7 (0.0-3.8)	.71	7/5.2	1.3 (0.5-2.8)	.42
Ovary	26/2.1	12.7 (8.3-18.6)	< .001	7/0.4	16.9 (6.8-34.9)	< .001	19/1.6	11.6 (7.0-18.1)	< .001
Lung	2/3.2	0.6 (0.1-2.2)	.50	0/0.6	0.0 (0.0-5.8)	.42	2/2.6	0.8 (0.1-2.8)	.72
Bladder	0/1.7	0.0 (0.0-2.1)	.19	0/0.4	0.0 (0.0-10.0)	.54	0/1.4	0.0 (0.0-2.7)	.24
Kidney	1/1.1	0.9 (0.0-5.2)	.95	1/0.2	4.6 (0.1-25.8)	.09	0/0.8	0.0 (1.5-4.3)	.36
Lymphoma	7/2.4	2.9 (1.2-6.1)	.003	0/0.5	0.0 (0.0-7.5)	.48	7/1.9	3.7 (1.5-7.7)	< .001
Melanoma	4/2.2	1.8 (0.5-4.6)	.24	1/0.5	2.1 (0.1-12.0)	.43	3/1.8	1.7 (0.3-4.9)	.36
Thyroid	1/1.1	0.9 (0.0-5.1)	.93	1/0.2	4.4 (0.1-24.7)	.10	0/0.9	0.0 (0.0-4.3)	.35

O/E, observed/expected; SPR, standardized prevalence ratio; CI, confidence interval.
[a] Shaded cells indicate significant values ($p < 0.05$). To compare our data with the SEER database (15), we included only patients from our series who had a diagnosis of another tumor either synchronous (including the immediate 30 days after hysterectomy) or during the previous ten years before hysterectomy (see note c of Table 1).

However, patients living within 50 miles of Mayo Clinic had a mean BMI of 30.1 (0.3) compared with 31.3 (0.6) for those living beyond 50 miles ($p < 0.05$).

Frequency of other tumors

In total, 242 patients (24%) had a history of another malignancy. In 34 patients, however, the additional malignancy was skin cancer other than melanoma (i.e., basal cell carcinoma or localized squamous cell carcinoma other than vulvar cancer). Because these 34 women would be considered as having no history of associated malignancy according to the SEER definition [15], they were excluded. Thus, 208 patients (20%) were categorized with a history of associated malignancy. Overall, 238 malignancies occurred in these 208 patients.

According to the pathology reports, the most frequent malignancies associated with endometrial cancer were carcinomas of the breast in 98 patients (10%), colon in 30 patients (3%), and ovary in 36 patients (4%). However, after the 36 patients listed as double primary ovarian and endometrial cancer were reviewed, nine were categorized as ovarian metastases of an endometrial tumor according to published criteria. Therefore, 27 patients (3%) were listed as double tumors of the ovary and endometrium.

Of the 73 patients who had breast cancer either before or at the time of the diagnosis of endometrial cancer, 20 (27%) had been (or still were) receiving tamoxifen treatment.

We observed ten lung tumors (< %). Overall, nine of the ten patients with lung cancer had a histologic diagnosis of adenocarcinoma, carcinoid, neuroendocrine, or small cell lung tumor. Only one patient had a diagnosis of squamous cell cancer (7 years before the diagnosis of endometrial cancer).

Of the five patients who developed bladder cancer after treatment for endometrial cancer, two had radiotherapy as part of their primary treatment for the uterine neoplasm.

Prevalence of other tumors associated with endometrial cancer

At the time of surgery for endometrial cancer, the prevalence of lymphoma (SPR = 2.9; $p = 0.003$), breast cancer (SPR = 1.8; $p < 0.001$), and ovarian cancer (SPR = 12.7; $p < 0.001$) was higher than expected for the general population (Table 2). All ovarian cancers had been diagnosed at the time of surgery for endometrial cancer. The higher prevalence of breast and ovarian cancers was confirmed both in local patients and referred patients, whereas the higher prevalence of lymphoma was observed only in referred patients (Table 2).

Incidence of other tumors associated with endometrial cancer

Median follow-up was 69 months after the diagnosis of endometrial cancer. During this period of follow-up, the incidence of lung cancer was significantly lower than expected (SIR = 0.4; $p < 0.05$), whereas the incidence of lymphoma was significantly higher (SIR = 2.4; $p = 0.008$) (Table 3).

Among the endometrial cancer patients living within a 50-mile radius, the incidence of breast (SIR = 1.9; $p < 0.05$), colorectal (SIR = 3.1; $p < 0.001$), and bladder (SIR = 5.4; $p = 0.001$) cancer and lymphoma (SIR = 4.7; $p < 0.001$) was significantly higher than that among the general US population. However, none of these risks were elevated among patients residing beyond the 50-mile radius (Table 3). The finding of a decreased incidence of lung cancer was consistent in all subgroups analyzed (i.e., within or beyond the 50-mile radius) ($p = 0.08$ after stratification for residence area within or beyond the 50-mile radius).

Discussion

Patients who have already had a malignancy present a high likelihood of having a second primary cancer diagnosed during their lifetime. The overall rate of other associated cancers in patients with endometrial cancer was 20% in our series. Similarly, the frequency of synchronous or metachronous tumors associated with corpus cancer has been previously reported to be between 10% and 23% [3, 6, 17-20]. However, these percentages are only crude rates. To determine a true figure of the epidemiology of multiple tumors, we described separately the prevalence and the incidence of different cancers, comparing the results with data for the general US population [15].

Table 3. — *Incidence of other cancers in women with endometrial cancer compared with the general population and stratified by residency (≤/> 50 mi from Rochester, Minnesota)*[a].

	All Patients (N = 1,028)			≤ 50 mi (n = 218)			> 50 mi (n = 810)		
Cancer	O/E	SIR (95% CI)	*p* value	O/E	SPR (95% CI)	*p* value	O/E	SIR (95% CI)	*p* value
Breast	25/24.9	1.0 (0.6-1.5)	.99	10/5.3	1.9 (0.9-3.5)	.04	15/19.6	0.8 (0.4-1.3)	.30
Colorectal	12/11.3	1.1 (0.5-1.8)	.84	8/2.6	3.1 (1.3-6.1)	< .001	4/8.7	0.5 (0.1-1.2)	.11
Ovary	1/3.2	0.3 (0.0-1.7)	.22	1/0.7	1.4 (0.0-8.0)	.71	0/2.5	0.0 (0.0-1.5)	.11
Lung	5/13.7	0.4 (0.1-0.8)	.02	0/2.9	0.0 (0.0-1.3)	.09	5/10.8	0.5 (0.1-1.1)	.08
Bladder	5/2.5	2.0 (0.6-4.6)	.12	3/0.6	5.4 (1.1-15.8)	.001	2/2.0	1.0 (0.1-3.7)	.98
Kidney	2/1.8	1.1 (0.1-4.1)	.85	1/0.4	2.6 (0.1-14.6)	.31	1/1.4	0.7 (0.0-4.0)	.75
Lymphoma	9/3.8	2.4 (1.1-4.5)	.008	4/0.8	4.7 (1.3-12.1)	< .001	5/3.0	1.7 (0.5-3.9)	.24
Melanoma	1/2.2	0.4 (0.0-2.5)	.42	0/0.5	0.0 (0.0-7.5)	.48	1/1.7	0.6 (0.0-3.2)	.59
Thyroid	1/0.8	1.2 (0.0-6.6)	.87	0/0.2	0.0 (0.0-19.7)	.67	1/0.7	1.5 (0.0-8.4)	.67

O/E, observed/expected; SIR, standardized incidence ratio; CI, confidence interval.
[a] Shaded cells indicate $p < .10$.

We observed that the prevalence of breast and ovarian cancers in patients with endometrial malignancy was higher than that in the general population (Table 2). This is probably due to shared risk factors [3, 5] or to familial clustering [7], and it agrees with previously reported findings [3, 7]. However, an interesting observation of this study, not reported in the previous analysis from Mayo Clinic [3], was the significantly lower incidence of lung cancer in patients with endometrial tumors than in the general US population (Table 3). Our new observation might be explained by the fact that some of the "lung cancers" may have been diagnosed as "lung recurrences" in our series. Alternatively, we must emphasize that patients with lung cancer have different epidemiologic characteristics than those with endometrial cancer [21]. In fact, smoking, which is the most important risk factor for lung cancer, has been previously reported to be negatively associated with endometrial cancer [22]. In accord with the above observations, we reported that most lung cancers in our series were adenocarcinomas or other types different from the squamous lung malignancy and not related to smoking. This finding is also consistent with the fact that, in North America, the incidence of adenocarcinoma of the lung now exceeds that of squamous cell cancer [23].

The higher incidence of colon and bladder cancers (Table 3) may be explained by a genetic predisposition, like the familial hereditary nonpolyposis colorectal cancer-related syndrome [2]. In a minority of patients, the postoperative administration of radiotherapy [24] may have contributed to the higher incidence of bladder cancer (Table 3). However, our data are insufficient to support or reject this hypothesis.

It is possible that the patients managed in a particular institution and included in a certain study may not be representative of all patients with endometrial cancer. In fact, epidemiologic analyses from tertiary care institutions that do not account for possible differences between referred and local patients may lead to inaccurate results [3,8]. For the above reasons, in the present study we planned to analyze the association of other malignancies with endometrial cancer, stratifying for residence area. The 50-mile radius, which we used for defining local patients, permitted us to focus on a stable cohort, including patients who tend to return to Mayo Clinic for subsequent treatment. This area excluded the Minneapolis-St. Paul metropolitan statistical area, which includes patients more likely to be referred to other metropolitan hospitals for postoperative management.

In our patients, when stratified for residence area, we observed significant variations in incidence and prevalence of the associated malignancies (Tables 2 and 3). These findings may be simple artifacts, due to the relatively low numbers observed in the stratified subgroups. Alternatively, referral bias may explain the finding that the observed higher prevalence of lymphoma was limited to referred patients (Table 2). In fact, it is possible that patients were more likely to be referred to our hospital if they had a history that was "complicated" by the presence of lymphoma. Similarly, the higher incidences of breast, colorectal, and bladder cancers and lymphoma observed only in local patients and not in referred patients may be attributable to ascertainment bias (Table 3). Moreover, it is possible that the follow-up information was less accurate in patients living far from Mayo Clinic than it was in those living nearby.

Compared with the general US population, endometrial cancer patients present a higher likelihood of developing various malignancies during their lifetime (i.e., breast, ovarian, colorectal, and bladder cancers and lymphoma). Moreover, due to different epidemiologic risk factors, patients with endometrial cancer present a low risk of developing lung cancer. Our stratified analysis allowed us to characterize separately local and referred patients, and some significant differences were observed. Thus, results of epidemiologic studies from tertiary care centers must be interpreted with caution and can be misleading if they do not account for referral and ascertainment biases. In particular, for the analysis of cancer associations, ascertainment bias may artificially decrease the incidence of patients with double tumors in referred patients. Conversely, referral bias may artificially increase the prevalence of double tumors in patients who are attended at tertiary care centers.

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Address reprint requests to:
A. MARIANI, M.D., P.h.D.
Department of Gynecologic Surgery
Mayo Clinic, 200 First Street SW
Rochester, MN 55905 (USA)
e-mail: mariani.andrea@mayo.edu.