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Excess of early onset multiple myeloma in endometrial cancer probands and their relatives suggests common susceptibility

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Abstract

Objective— Determine whether there is an association between uterine cancer and multiple myeloma.

Methods— Data on second malignancies were obtained for 368 uterine corpus cancer patients treated between 1992 and 2005. Detailed family histories were devised for 192 probands. Diagnoses of multiple myelomas, lymphomas and leukemias in family members were medical record verified. The frequency of multiple myeloma among uterine cancer patients was compared to the female age-adjusted incidence rate of multiple myeloma obtained from the SEER database. The crude rate of multiple myeloma (as well as Hodgkin's, non-Hodgkin's lymphomas and leukemias) among first-degree relatives of patients with uterine cancer was compared to the age-adjusted incidence rate of multiple myeloma in the general population. Descriptive statistics were used to evaluate disease and cohort characteristics. A *P* value less than 0.05 was considered statistically significant.

Results— Two of 368 uterine cancer patients were also diagnosed with multiple myeloma, both at age 50. The observed incidence of multiple myeloma in this cohort (543 per 100,000; 95% CI: 66 – 1962 per 100,000) represents a 120-fold increase based on predicted incidence (*P*=0.00014). The frequency of multiple myeloma in first-degree relatives was 2/1,351 (148 per 100,000; 95% CI: 14.8 – 533 per 100,000) which represents a 27-fold increase compared to the general population (*P*=0.0026). The frequencies of leukemias and lymphomas in these family members on the other hand were not significantly increased (*P*=0.152 and *P*=0.218).

Conclusion— This specific excess frequency of early onset multiple myeloma in endometrial cancer probands and their relatives suggests shared susceptibility.

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Article Précis. Endometrial cancer patients and their relatives have an excess of multiple myeloma suggesting common genetic or environmental risk factors.

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Keywords

Endometrial Cancer; Multiple Myeloma; Incidence; Susceptibility; Familial

Introduction

Endometrial cancer represents the most commonly diagnosed malignancy of the female reproductive tract in the United States. Approximately 40,880 new cases of cancer of the uterine corpus were diagnosed last year with a median age at diagnosis of 63 years [1]. The vast majority of endometrial cancers are sporadic, with an estimated 5–7% believed to be hereditary [2,3].

Multiple myeloma is a relatively uncommon malignancy that typically affects older individuals. The median age of diagnosis is 70 years of age. It is estimated that 15,980 new cases were diagnosed last year in the United States [1]. A small fraction of multiple myelomas are familial. Recent reports suggest this clustering is due to inherited factors and not to shared environmental exposures to substances such as pesticides and solvents [4,5].

The National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database reports age-adjusted incidence rates of 24.2 per 100,000 for endometrial cancer and 4.5 per 100,000 for females with multiple myeloma respectively [1].

As part of our ongoing studies to evaluate genetic and epigenetic factors associated with endometrial cancer heritability we noted what seems to be a disproportionately high frequency of multiple myeloma among patients with endometrial cancers and their relatives.

Materials and methods

Research subjects

The study population includes patients with uterine cancer treated by the Division of Gynecologic Oncology at Washington University Medical School between April 1992 and January 2005. In that period, our laboratory prospectively acquired 920 tumor specimens from patients with suspected uterine cancer. Uterine cancer diagnoses were histologically confirmed by experienced gynecologic pathologists at our institution. All participants in these studies consented to family history and molecular analyses as part of Washington University Medical Center Human Studies Committee approved protocols (HSC 93-0828).

The study cohort (n=368) represents the totality of patients with confirmed cancer of the uterine corpus for which data on second malignancies is available. Detailed familial history has been collected in 192 of these cases (52%). The family history data were obtained through face-to-face or telephone interviews by a genetic counselor (S.B.). Three-generation pedigrees were developed for these families and are updated periodically through follow-up interviews. Medical record confirmation was sought for all reported malignancies. The accuracy of cancer reporting by a subset of these probands and other family members has been previously reported by our group [6]. Diagnoses of multiple myelomas, lymphomas and leukemias were confirmed through verification of medical records in all cases (pathology and/or hospital and treatment reports). Only confirmed cases were included to assess disease frequencies. Individual and tumor characteristics for the uterine cancer cohort are presented in Table 1.

Statistical analysis

The frequency of multiple myeloma among patients with endometrial cancer was determined and compared to the age-adjusted incidence rate of multiple myeloma in females obtained from

the SEER database [1]. Similarly, the crude rate of multiple myeloma among first-degree relatives of patients with endometrial cancer was determined and compared to the SEER age-adjusted incidence rate of multiple myeloma in the general population [1].

We also obtained “control” frequencies of other non-HNPCC associated hematologic malignancies (i.e. Hodgkin’s and non-Hodgkin’s lymphomas and leukemias) in our cohort and compared those to the population reference age-adjusted rates obtained from the SEER database [1]. SEER rates and demographic patterns for these malignancies appear similar to reported statistics for the State of Missouri [1,7].

Descriptive statistics were used to evaluate disease and cohort characteristics. The point estimates for the events of interest and their 95% confidence intervals [95% CI] were calculated. We assumed that the distribution for these events (cancer incidence rates) follow a Poisson distribution. The probabilities for the observed data given their true expected values were calculated and 95% confidence intervals were also provided. A *P* value less than 0.05 was considered statistically significant.

Results

Multiple myeloma in endometrial cancer probands

Two endometrial cancer probands also had multiple myeloma (2/368). One Caucasian patient (Case 1) was diagnosed with stage IA grade 2 endometrioid endometrial adenocarcinoma at age 46 and multiple myeloma at age 50. The proband reported colorectal cancer at age 44 in her brother and breast cancer (ages 60 and 48) in her maternal grandmother and aunt respectively. The pedigree for this case is presented in Figure 1.

The second case (Case 2), was identified in an African American patient diagnosed with multiple myeloma at age 50. This patient subsequently presented with post-menopausal bleeding at age 52 and at that time was diagnosed with a stage IA grade 1 endometrioid endometrial cancer. We are currently pursuing a cancer family history for this proband.

The observed frequency of double primaries in this cohort (2/368 or 543 per 100,000; 95% CI: 66-1962 per 100,000) represents a 120-fold increase from the expected occurrence of multiple myeloma in the general population based on SEER data on age-adjusted incidence rate of multiple myeloma for females (*P* = 0.00014) [1].

Multiple myeloma in relatives of endometrial cancer probands

Detailed pedigrees were available for 192 families. The total number of first-degree relatives was 1,366 individuals. Children younger than 10 years of age (N=15) were considered non-informative for malignancies and therefore excluded from the calculations. There were no cases of childhood hematologic malignancies among these children. Data were obtained for 378 parents, 567 siblings and 406 children. In 6 families, data for one parent were not available. Two cases of multiple myeloma occurred in 1,351 first-degree relatives of patients with endometrial cancer. One was the mother of the proband who was diagnosed with multiple myeloma at age 52 (Family 1). The second case also occurred in the mother of the proband who was diagnosed with multiple myeloma at age 59 (Family 2). Detailed pedigrees for these families are presented in Figure 1. The frequency of multiple myeloma among this group of first-degree relatives (2/1,351 or 148 per 100,000; 95% CI: 14.8 – 533 per 100,000) represents a 27-fold increase compared to the age-adjusted incidence rates of 5.5 per 100,000 in the general population (*P* = 0.0026) [1].

It is worth mentioning that two additional cases of multiple myeloma were reported among more distant relatives of these 192 probands. Multiple myeloma was reported in a maternal

half-uncle of one proband and in a maternal uncle of another proband. In both instances the reported multiple myeloma family members died at age 70.

We also assessed the frequencies of other confirmed hematologic malignancies (e.g. leukemias and Hodgkin's/non-Hodgkin's lymphoma) among this group of first-degree relatives. We identified one case of leukemia and one case of Hodgkin's lymphoma. The observed frequencies for leukemias and lymphomas (1/1,351 or 74 per 100,000 each; 95% CI: 7.4 – 414 per 100,000) represent a more modest increase (6-fold and 3-fold, respectively). However, these rates were not significantly different from age-adjusted incidence rates for these malignancies in the general population (12.2 and 21.8 per 100,000 respectively, $P = 0.152$ and $P = 0.218$) [1].

Discussion

Familial aggregation of malignancies has long been recognized. This is likely due to shared environmental and genetic factors. The overall frequency of cancers among first-degree relatives of cancer patients has been shown to exceed that of the general population [8]. Synchronous and metachronous malignancies (double primaries) are a hallmark of inherited cancer susceptibility. As part of our ongoing studies to assess genetic factors contributing to endometrial malignancies, we have evaluated patterns of malignancies in families of patients with endometrial cancer [9].

Here we describe what appears to be a disproportionately high frequency of multiple myeloma among endometrial cancer patients and their first-degree relatives. Compared to the age-adjusted incidence rate for multiple myeloma in the general female population, our observed frequency for multiple myeloma in this uterine cancer cohort represents a 120-fold increase ($P = 0.00014$). The fold increase described is based on SEER data for myeloma in females and is intended only as a crude estimate. The data were not queried for myeloma in patients with histologically confirmed uterine endometrial cancers.

Misclassification of malignancies in the SEER database could lead to imprecision in estimating cancer incidences. Although we currently have data on second malignancies for only 368 out of 920 cases, the minimal estimated frequency of multiple myeloma in our entire tumor bank cohort (2/920 or 217 per 100,000) would also represent a considerable 48-fold increase.

The observed excess of multiple myeloma in endometrial cancer probands and their relatives could reflect common genetic or environmental factors, or may be a spurious observation. Several lines of evidence support the case for a genetic basis in this association.

The 27-fold increase of multiple myelomas in first-degree relatives of patients with endometrial cancer is striking ($P = 0.0026$). When the frequency of other hematologic malignancies in this group is considered, the fold excess for multiple myeloma is even more noteworthy. Like multiple myeloma, other hematologic malignancies are not known to be associated with hereditary cancer syndromes involving endometrial carcinomas. The observed 3- to 6-fold excess frequency for leukemias and lymphomas was not statistically significant. The overrepresentation of multiple myeloma compared to leukemias and lymphomas therefore suggests shared susceptibility is specific to multiple myeloma. Alternately, if environmental effects were to explain the excess of multiple myeloma, such factors would appear to influence myeloma risk specifically. Early onset disease is another feature of genetic susceptibility. The median age at diagnosis of multiple myeloma in these endometrial cancer probands and their first-degree relatives was 51 years. This is 19 years younger than the reported median age at diagnosis for this malignancy [1].

The excess of myelomas we observed in relatives of endometrial cancer patients could in part be attributable to a bias in ascertainment of cancer-prone families. Endometrial cancer patients with family members with cancers might be more inclined to provide family history data than those women with no or limited cancer family histories. The fact there was no excess of hematologic malignancies other than myeloma, however, makes a myeloma cancer history bias seen unlikely. Few studies have evaluated the association of multiple myeloma with other malignancies. Lynch and colleagues have recently presented observational data for 39 families with multiple cases of multiple myeloma [5]. Medical record confirmation of cancer diagnoses was not uniformly done. They reported a single case of uterine cancer (presumed to be endometrial) in a 50 year old sister of a multiple myeloma patient. In a study of familial clustering of ovarian cancer, there was a significant excess of both endometrial cancer and myeloma [10]. However, there have been no reports of association of myeloma in endometrial cancer families.

Todoí Parra and colleagues analyzed the frequency and site of secondary malignancies in 210 patients with multiple myeloma [11]. They found two cases of endometrial cancer. Assuming a 50% female representation, this yields a frequency of double primaries of 1,905 per 100,000 in their cohort. If we take into account an age-adjusted incidence rate of 14.3 per 100,000 for cancer of the uterine corpus in Spain [12], theirs would represent a 133-fold increase in the expected frequency of endometrial cancer.

It is unclear what common factor or factors might contribute to risk for multiple myeloma and endometrial cancer. A number of inherited mutations have been described in multiple myeloma patients and their relatives. For example, there is evidence for an increased risk of multiple myeloma in the relatives of BRCA1 and BRCA2 germline mutation carriers [13]. Additionally, a germline mutation in the CDKN2A (p16) was reported in a case of multiple myeloma identified in a familial melanoma family, suggesting that this gene might be associated with an increased susceptibility not only to melanoma and pancreatic cancer but also to multiple myeloma [14]. Defective DNA mismatch repair and PTEN mutation have been implicated in the progression of multiple myeloma [15,16].

Our data clearly indicate that there is an increased risk for multiple myeloma among patients with endometrial cancer and their first-degree relatives. The excess of multiple myeloma and early onset of this disease suggest inherited susceptibility. This observed association between multiple myeloma and endometrial cancer must, however, be confirmed in larger population-based studies. Analysis of candidate susceptibility genes in high risk families and patients with synchronous or metachronous multiple myeloma and endometrial cancer might point to genes and pathways that contribute to the development of these cancers.

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Figure 1.

Pedigrees for endometrial cancer probands and family members diagnosed with multiple myeloma. Family history data are unavailable for one patient (Case 2) with double primary endometrial cancer (diagnosed at age 52) and multiple myeloma (diagnosed at age 50).

Table 1**Patient Demographics and Disease Characteristics**

Age (years)		62.8 ± 11.6*
Factor		N (%)
Race	Caucasian	326 (88.6%)
	African American	41 (11.1%)
	Asian	1 (0.3%)
Histology	Endometrioid	339 (92.1%)
	Papillary Serous	2 (0.5%)
	Clear cell	9 (2.4%)
	Carcinosarcoma	5 (1.4%)
	Mixed	12 (3.3%)
	Leiomyosarcoma	1 (0.3%)
Grade	1	194 (52.7%)
	2	114 (31.0%)
	3	60 (16.3%)
Stage	I	273 (74.2%)
	II	25 (6.8%)
	III	54 (14.7%)
	IV	11 (3.0%)
	Unstaged	5 (1.4%)

* Age expressed as mean ± standard deviation