Uterine Serous Carcinoma: Increased Familial Risk for Lynch-Associated Malignancies


Abstract

Serous uterine cancer is not a feature of any known hereditary cancer syndrome. This study evaluated familial risk of cancers for patients with serous uterine carcinoma, focusing on Lynch syndrome malignancies. Fifty serous or mixed serous endometrial carcinoma cases were prospectively enrolled. Pedigrees were developed for 29 probands and tumors were assessed for DNA mismatch repair (MMR) abnormalities. Standardized incidence ratios for cancers in relatives were estimated. A second-stage analysis was undertaken using data from Gynecologic Oncology Group (GOG)-210. Incidence data for cancers reported in relatives of 348 patients with serous and mixed epithelial and 624 patients with endometrioid carcinoma were compared. Nineteen of 29 (65.5%) patients in the single-institution series reported a Lynch-related cancer in relatives. Endometrial and ovarian cancers were significantly overrepresented and a high number of probands (6 of 29, 20.7%) reported pancreatic cancers. None of the probands’ tumors had DNA MMR abnormalities. There was no difference in endometrial or ovarian cancer incidence in relatives of serous and endometrioid cancer probands in the case–control study. Pancreatic cancers were, however, significantly more common in relatives of patients with serous cancer [OR, 2.39; 95% confidence interval (CI), 1.06–5.38]. We identified an excess of endometrial, ovarian, and pancreatic cancers in relatives of patients with serous cancer in a single-institution study. Follow-up studies suggest that only pancreatic cancers are overrepresented in relatives. DNA MMR defects in familial clustering of pancreatic and other Lynch-associated malignancies are unlikely. The excess of pancreatic cancers in relatives may reflect an as yet unidentified hereditary syndrome that includes uterine serous cancers.

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Introduction

Uterine serous carcinoma is an uncommon form of endometrial cancer, comprising less than 10% of uterine epithelial cancers. Patients can present with pure uterine papillary serous carcinoma (UPSC) or with mixed UPSC/other histology tumors. Despite its rarity, UPSC accounts for a disproportionate number of endometrial cancer deaths (estimated at ~40%; ref. 1). The poor outcomes for patients diagnosed with UPSC are attributable, in part, to a later stage at diagnosis and an increased risk for occult metastases in early-stage disease compared with the more common histologic type, endometrioid endometrial carcinoma (2–4). UPSC is more common among African-Americans than Caucasians, non-obese rather than obese women, and affects primarily postmenopausal women, whereas endometrial cancers have an increased incidence among perimenopausal women (5–9). Unlike endometrioid endometrial cancer, UPSC is not associated with an excess estrogen state and not surprisingly is associated with different molecular...
abnormalities than the more common endometrioid adenocarcinoma (10–15).

Serous-type uterine cancers are not a recognized feature of any currently defined hereditary cancer syndromes. Several studies have suggested an association between serous uterine cancer and breast cancer. Most studies assessing the link between breast cancer and UPS, however, have been focused on the proband and there have been no large-scale, in-depth family studies published to date. Although uterine cancer has been implicated in the hereditary breast and ovarian syndrome (16–22), an association between serous endometrial cancer and hereditary breast/ovarian syndrome has not been established.

Endometrial cancer may be the most common cancer in women with Lynch syndrome attributable to germline mutations in one of several DNA mismatch repair (MMR) genes. Patients with Lynch syndrome have a dramatically increased risk for colon and endometrial and a significantly increased risk for a number of other malignancies. The majority of patients with Lynch syndrome with uterine cancers have endometrioid endometrial cancers, although non-endometrioid histologies have been described for a small number of patients with Lynch syndrome (23).

The aim of this study was to evaluate familial risk for Lynch-associated cancers in patients diagnosed with serous uterine cancer and to assess DNA MMR status in the tumors of probands from family members affected with Lynch-associated malignancies.

Materials and Methods

Description of participants

We prospectively acquired tumor samples from hysterectomy specimens of patients being treated for suspected uterine cancer by the Division of Gynecologic Oncology at Washington University Medical Center (St. Louis, MO). All participants consented to molecular analysis and follow-up as part of the Washington University Medical Center Human Research Protection Office-approved protocol (93-0828). Fifty cases of uterine serous or mixed serous carcinomas were accrued to this protocol from January 2005 to December 2008. Participants consented to family history and tumor studies as part of the approved protocol. This series was unselected for family history information, age at diagnosis, or clinical features suggestive of an inherited susceptibility to cancer.

Probands were contacted and asked to participate in our study to obtain detailed family history data. Family history data were obtained at 2 different times. First, as part of their routine clinical care, participants completed a medical history questionnaire that included a single question about the health of first-degree relatives. These data, as well as information documented in the initial medical encounter, comprised the screening family history (24). A genetic counselor (S.A. Babb) later obtained a detailed, 3-generational pedigree from each proband, either face-to-face or over the telephone. The following data were obtained for all individuals in the pedigree: current age or age of death and history of cancer (including site, age at diagnosis, and city or hospital where treated). Medical record verification was sought. As standard practice, the genetic counselor requested the proband contact the identified relative, or if deceased, the closest living family member, to obtain permission to release their medical records. Medical records and/or death certificates were requested for confirmation of the cancer diagnosis. All records were reviewed independently by 2 gynecologic oncology fellows (N.T. Kizer and S.B. Dewdney) and a cancer research investigator (P.J. Goodfellow).

Microsatellite instability testing

Using the National Cancer Institute recommended microsatellite instability (MSI) markers (BAT25, BAT26, D7S250, D2S125, and D5S346), both tumor and normal DNA samples for each patient were analyzed for allelic shift using a multiplex fluorescence-based PCR assay. Amplified PCR products were then analyzed using capillary electrophoresis on an ABI 3130 Genetic Analyzer (Applied Biosystems), using the GeneMapper Analysis software provided by the manufacturer (Applied Biosystems). Tumors showing allelic shift at 2 or more markers were considered MSI-high; tumors showing allelic shift at only one marker were classified as MSI-low; and tumors with no allelic shift were classified as microsatellite stable (MSS).

Immunohistochemical staining

Immunohistochemistry (IHC) for the MMR gene products MLH1 (G168-15, 1:30; Pharmingen), MSH2 (FE11, 1:100; Oncogene Science), and MSH6 [G70220 (GenBank), 1:100; Transduction Laboratories] was conducted using formalin-fixed, paraffin-embedded sections as previously described (25). Tumors were categorized as positive or negative for MHL1, MSH2, and MSH6 expression (R.R. Broaddus).

Gynecologic Oncology Group methods

We sought to validate the findings of our institutional cohort through the analysis of family history data for patients with serous cancer enrolled in the Gynecologic Oncology Group-210 protocol (GOG-210). Briefly, this protocol is an ongoing collection of tissue samples for molecular and clinicopathologic analysis of endometrial cancer. The patients who participated in both the Washington University study and GOG-210 were cross-referenced and excluded from the GOG cohort, hence only to be included in the Washington University cohort for the purposes of this study.

The GOG-210 questionnaire contains a section inquiring about family history, which is completed by participants. The family history questionnaire section asked only about first-degree relatives; number of relatives (living and deceased), which relative(s) has a diagnosis of cancer, age of diagnosis, and type of cancer. We obtained these data and identified patients with first-degree relatives with cancer. Once a family was identified, a pedigree was created from the information provided on the
questionnaire. We analyzed both mixed (serous component) epithelial and pure serous histologic subtypes. The available data set included 245 pure serous histologies and 103 mixed (serous component) epithelial histologies. After an initial analysis of the GOG serous histology cases, we attempted to confirm our findings by comparing the GOG serous group with a matched endometrioid histology group. We obtained data from women with endometrioid histology tumors matched with the serous cases based on age, race, and stage (N = 624). These data were collected from 2003 to 2008.

Statistical analysis

Standardized incidence ratios (SIR) were estimated for the retrospective Washington University School of Medicine cohort study focusing on first- and second-degree relatives. Probands were removed from the analyses for conservative cancer risk estimation. Lynch-related cancers were defined as colon, pancreas, ovary, endometrial, gastric, brain, upper urologic tract, and hepatobiliary cancers. The crude incidence rates of Lynch-related cancers overall and, for each type separately, were calculated as the total number of cases per unit of person-years at risk per 100,000 people. The person-year at-risk was defined as from birth to the earliest cancer diagnosis or death or the date of ascertainment during the lifetime exposure of individuals in the 29 kindreds. Age was divided into nineteen 5-year intervals following the Surveillance, Epidemiology, and End Results (SEER) database age categories, and the SEER’s age group-specific incidence rates were obtained using the SEER 17 regions 2000–2006 limited-use database (26) with adjustment for impact of Katrina by the SEER*Stat software (27). The SIRs of each cancer were calculated as the ratio of the total number of observed cases in our data to the expected number of cases on the basis of the age group–specific incidence rates from SEER (i.e., the sum of the product of the age group–specific person-years at-risk and the SEER age group–specific incidence rates). For the SIRs, we calculated the exact confidence intervals (CI) on the basis of Poisson distribution (28, 29) and the 95% CI on the basis of Boice–Monson method (30) and bootstrap 95% percentile CIs through 1,000 bootstrap sampling (31). The 2-sided P values for the SIRs were calculated on the basis of χ² tests.

To further identify any possible increased risk for cancers in the relatives of patients with serous uterine cancer, we matched each serous family by approximately 2 endometrial families of endometrioid histology in terms of age, race, and stage to conduct a case–control study. We compared 348 serous families and 624 endometrioid families (African-American matched 1:1 because of paucity of African-American endometrioid cases).

Given that the data were clustered in the family level and the matching case–control level, we analyzed the clustered data using a generalized estimating equation method. Various correlation structures were assessed and compared, all with similar results. ORs, accompanied with 95% CIs and P values on the Lynch-related cancer and each individual cancer type of interest were estimated.

Results

Cancer family histories for uterine serous cancer patients

Washington University cohort. Fifty women with serous endometrial cancers (N = 21) or mixed serous histology tumors (N = 29) consented to our ongoing molecular and family studies in the period from January 1, 2005, to December 31, 2008. Patient charts included cancer family histories for 44 (88%) of the women. Among those 44 probands, 10 (23%) reported a Lynch-related tumor in one or more first-degree relative(s).

Detailed family histories were developed for 29 subjects (58%). Among the 21 women for whom family histories were not obtained, 14 patients were deceased or in hospice at the time of the contact, 5 women declined to participate, and 2 failed to respond to written and phone requests to participate in the family history studies.

The demographic and clinicopathologic characteristics of the 29 probands are presented in Table 1. Fourteen of 29 patients had pure serous tumors and 15 had mixed epithelial histology tumors (serous plus other). Nineteen patients were Caucasian (67%) and 5 were African-American (17%). Nearly half (14 of 29) presented with stage III or IV disease at a median age of 67 years (range, 58–91 years). Similar data for the 21 probands for whom family histories were not obtained are presented in Supplementary Table S1.

Cancer family history data included information for 769 first- and second-degree relatives with a median family size of 24 (range, 10–52) and a gender ratio of 1:1.05 (male:female). Thirteen of the 29 probands reported one or more Lynch-related cancer in a first-degree relative. Of note, only 8 of those women had indicated that a relative had a Lynch-related cancer as part of the clinical family history screening intake. Of the 23 Lynch-related cancers in first-degree relatives, 8 were confirmed by medical records (3 colon, 1 serous

<table>
<thead>
<tr>
<th>Table 1. Clinical and demographic characteristics of 29 probands</th>
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<tbody>
<tr>
<td><strong>Characteristics</strong></td>
</tr>
<tr>
<td><strong>Histologies</strong></td>
</tr>
<tr>
<td>Mixed</td>
</tr>
<tr>
<td>Pure</td>
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<tr>
<td><strong>Stage</strong></td>
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<tr>
<td>I</td>
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<td>II</td>
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<tr>
<td>III</td>
</tr>
<tr>
<td>IV</td>
</tr>
<tr>
<td><strong>Race</strong></td>
</tr>
<tr>
<td>Caucasian</td>
</tr>
<tr>
<td>African-American</td>
</tr>
<tr>
<td>Hispanic</td>
</tr>
<tr>
<td>Native American</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Age, y, median (range)</strong></td>
</tr>
</tbody>
</table>
endometrioid, 2 pancreatic, and 2 transitional cell cancers). Thirteen additional Lynch cancers were reported in second-degree relatives of 8 probands (medical record verification for only 3 tumors, 1 colon, 1 hepatobiliary cancer, and 1 glioblastoma). The numbers and types of Lynch-related cancers in relatives are presented in Table 2. Median age of diagnosis of Lynch-related cancers was 65 years (ranging from 43 to 92 years). Several probands had family histories suggestive of Lynch syndrome and, notably, 4 probands reported pancreatic cancers in relatives (2 families each with 2 pancreatic cancers). Representative pedigrees suggestive of inherited cancer susceptibility are shown in Fig. 1 (all remaining pedigrees are shown in Supplementary Fig. S1).

We used cancer incidence and SIRs to determine whether Lynch-related cancers were over- or underrepresented in the relatives of the 29 serous endometrial cancer probands. These analyses suggested an excess of Lynch-related cancers overall, with overrepresentation of endometrial, ovarian, and pancreatic cancer and fewer than expected colon cancers (Table 3). Seven endometrial cancers were reported (2.6 expected) for an SIR of 2.69 (95% CI, 1.28–5.65; \( P = 0.006 \)) and 4 ovarian cancers were reported (1.5 expected) for an SIR of 2.68 (95% CI, 1.01–7.14; \( P = 0.04 \)). The 1.40 SIR for pancreatic and 0.63 SIR for colon cancers were not statistically significant (\( P = 0.40 \) and 0.13, respectively).

Follow-up studies: a case–control study of 972 endometrial cancer patients enrolled in the GOG-210 protocol

We evaluated the cancer family histories for 972 patients with endometrial cancer enrolled in the GOG-210 study in an effort to determine whether the excess of Lynch-related cancers seen in the Washington University School of Medicine endometrial cancer cohort was also seen in patients with serous cancer that are part of the large, multi-institution cohort. The data on cancers in relatives of the GOG-210 study population were reported by probands (no medical record verification and uncertain involvement of family members other than the proband in developing family histories) and were limited to first-degree relatives. Given that birth years and current ages of cancer-free children and siblings were not collected, it was not possible to estimate SIRs for Lynch-related cancers.

During the initial phase of GOG-210 accrual (September 22, 2003, to September 24, 2007), 3,738 patients were enrolled in the study. Among those, 317 cases had serous endometrial cancers and 240 had mixed histology epithelial cancers on the basis of the pathology reports provided by the individual GOG participating centers. Family cancer history data were available for 245 serous cancer cases and for 103 of the mixed histology cancers (limiting mixed histologies to those tumors that included a serous component), for a total of 348 probands. These 348 serous/mixed serous histology cases were age, race, and stage matched with endometrioid cancer cases enrolled during the same time period (controls) and the numbers and types of Lynch-related cancers in the 2 groups were compared. Caucasian patients were matched 2:1 (14 of the 281 matched 1:1) and African-Americans 1:1 (due to the relative paucity of African-American patients with endometrioid). Demographics, clinicopathologic features and family information for the GOG-210 cases and controls are presented in Supplementary Table S2. The median family size was 7 for both cases and controls and there was no difference in the sex ratio of relatives of the cases and controls.

A total of 317 Lynch-related cancers were reported in the 313 relatives of the 2 groups. Among the serous cases, there were 47 reported colorectal cancers, 17 uterine, 15 pancreatic, 12 ovarian, 10 stomach, and 10 brain cancers. The reported cancers in relatives of the controls included 90 colorectal, 39 uterine, 11 pancreatic, 14 ovarian, 20 stom- ach, and 8 brain cancers (Table 4). When the number of reported Lynch-related cancers among at-risk family members was compared for the serous cancer probands (cases) and matched endometrioid probands (controls), there was no difference in the number of Lynch-associated cancers in relatives (OR, 1.08; 95% CI, 0.85–1.38; \( P = 0.50 \)). There were fewer endometrial and colon cancers reported in relatives of the serous cancer probands than endometrioid cancer probands (OR, 0.75; 95% CI, 0.40–1.43; and OR, 0.91; 95% CI, 0.64–1.31, respectively) but the differences were not statistically significant. Ovarian and pancreatic cancers on the other hand were more common in the relatives of the serous cancer probands than endometrioid cancer probands. The excess of ovarian cancers was not statistically significant (OR, 1.49; 95% CI, 0.67–3.33). Pancreatic cancers were, however, significantly overrepresented in the relatives of the serous cancer probands with an OR of 2.39 (95% CI, 1.06–5.38; \( P = 0.03 \); Table 4).

MMR status of the probands’ endometrial cancers

Tumor and matched normal DNA was available for 26 of the 29 probands from the Washington University cohort. The MMR status of the 26 tumors was determined by PCR amplification of all 3 MMR genes (MLH1, MSH2, and MSH6) and sequencing of exons 3 and 7 of the MLH1 gene. The data are shown in Table 3. We found hypermethylation of the MLH1 gene in 3 of 26 tumors (12%, 95% CI, 0.21–0.51) and in none of the 4 tumors from patients from whom no matched normal DNA was available (95% CI, 0.00–0.33). These data were consistent with the hypothesis that the tumors in only a small proportion of patients with Lynch-related endometrial cancer would be attributed to hypermethylation of the promoter region of the MLH1 gene. The threshold for determining a true or false positive was set at \( \alpha = 0.05 \) (2-sided).

Table 2. Characteristics and Lynch-related cancers reported in first- and second-degree relatives

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median family size (range)</td>
<td>24 (10–52)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>375</td>
</tr>
<tr>
<td>Female</td>
<td>392</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
</tr>
<tr>
<td>First-degree relatives</td>
<td>222</td>
</tr>
<tr>
<td>Second-degree relatives</td>
<td>547</td>
</tr>
<tr>
<td>Lynch-related cancer</td>
<td>36</td>
</tr>
<tr>
<td>Colon</td>
<td>12</td>
</tr>
<tr>
<td>Uterine</td>
<td>7</td>
</tr>
<tr>
<td>Ovarian</td>
<td>4</td>
</tr>
<tr>
<td>Gastric</td>
<td>2</td>
</tr>
<tr>
<td>Transitional cell/other</td>
<td>5</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>6</td>
</tr>
<tr>
<td>Median age of diagnosis (range)</td>
<td>65 (43–92)</td>
</tr>
</tbody>
</table>
Figure 1. Representative 3-generation pedigrees for serous cancer probands suggestive of inherited cancer susceptibility. A, Lynch syndrome–like families. B, pancreatic cancer–prone families. +++, MLH1, MSH2, and MSH6 expressed; IHC, immunohistochemical assessment for MLH1, MSH2, and MSH6 expression; MSS, tumor microsatellite stable; nd, no data/not done.
along with formalin-fixed tumor specimens for 18 (62%) probands. None of the tumors had DNA mismatch abnormalities based on MSI testing and/or IHC (MLH1, MSH2, and MSH6). All 26 tumors investigated were MSS and 18 of 18 tumors evaluated expressed all 3 MMR proteins. Representative MSI and immunohistochemical analyses are presented in Supplementary Fig. S2.

Tumor tissues from 9 serous cancer and 3 mixed serous/other histologic type tumors from probands in the GOG-210 study who reported pancreatic or both colon and pancreatic cancers in first-degree relatives were also assessed for DMMR abnormalities by IHC. All 12 serous or mixed serous histology cancers expressed MLH1, MSH2, and MSH6. IHC was also conducted for 8 of the endometrioid endometrial cancer probands who reported pancreatic (4) or pancreatic and colon (3) or pancreatic and endometrial (1) cancers in first-degree relatives. All tumors expressed all 3 MMR proteins (5 tested for MSI and were negative). The pedigrees MSI and immunohistochemical results for the GOG-210 probands from the case–control study results are provided in Supplementary Fig. S3.

Discussion

We identified a significant excess of ovarian and endometrial cancers in relatives of patients with endometrial cancer with pure serous and mixed serous tumors based on detailed 3-generation family history data and medical record confirmation of malignancies in a single-institution cohort. Pancreatic cancers were also overrepresented in relatives, but the observed excess was not statistically significant. The excess of Lynch syndrome–related malignancies in relatives was unexpected given that serous endometrial cancers are uncommon in Lynch syndrome (carriers of MSH2, MSH6, MLH1, or PMS2 mutations; ref. 32). Early-onset serous uterine cancers have, however, been reported in MSH2 mutation carriers (23). The absence of tumor MSI and normal immunohistochemical findings make Lynch syndrome very unlikely, as does the late age of onset of uterine cancer in the probands studied. Only family 2401 had clinical testing for Lynch syndrome mutations (MSH2, MLH1, and MSH6) and no abnormality was identified. Regardless, the SIRs for uterine and ovarian cancers estimated for the 29 families from our institution suggest genetic risk for these cancers.

Table 3. Incidence and SIRs of cancers

<table>
<thead>
<tr>
<th>Tumor site</th>
<th>No. of cases</th>
<th>Crude incidence rate per 100,000 people (95% CI)</th>
<th>Expected cases</th>
<th>SIR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lynch-related cancer</td>
<td>36</td>
<td>83.84 (59.10–111.44)</td>
<td>30.10</td>
<td>1.20 (0.86–1.66)</td>
<td>0.28</td>
</tr>
<tr>
<td>Colon</td>
<td>12</td>
<td>27.88 (13.70–44.96)</td>
<td>18.48</td>
<td>0.66 (0.37–1.14)</td>
<td>0.13</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>6</td>
<td>13.90 (4.57–25.72)</td>
<td>4.29</td>
<td>1.40 (0.63–3.11)</td>
<td>0.40</td>
</tr>
<tr>
<td>Endometrial</td>
<td>7</td>
<td>31.08 (9.28–54.81)</td>
<td>2.60</td>
<td>2.69 (1.28–5.65)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ovarian</td>
<td>4</td>
<td>17.7 (4.29–38.09)</td>
<td>1.49</td>
<td>2.68 (1.01–7.14)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Calculated for lifetime exposure.

* SIR Boice-Monson 95% CI.

* Compared with SEER population.

Table 4. Lynch-associated cancers reported in first-degree relatives of the GOG-210 study population

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Case (serous)</th>
<th>Controls (endometrioid)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Lynch-related cancers</td>
<td>123</td>
<td>194</td>
<td>1.08 (0.85–1.38)</td>
<td>0.50</td>
</tr>
<tr>
<td>Colorectal</td>
<td>47 (20/27)</td>
<td>90 (41/49)</td>
<td>0.91 (0.63–1.31)</td>
<td>0.62</td>
</tr>
<tr>
<td>Endometrial</td>
<td>17 (8/17)</td>
<td>39 (0/39)</td>
<td>0.75 (0.40–1.43)</td>
<td>0.39</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>15 (8/7)</td>
<td>11 (7/4)</td>
<td>2.39 (1.06–5.38)</td>
<td>0.03</td>
</tr>
<tr>
<td>Ovarian</td>
<td>12 (0/12)</td>
<td>14 (0/14)</td>
<td>1.49 (0.67–3.33)</td>
<td>0.33</td>
</tr>
<tr>
<td>Other</td>
<td>32</td>
<td>40</td>
<td>nd</td>
<td>nd</td>
</tr>
</tbody>
</table>

NOTE: Numbers of Lynch-related cancers by category in serous and endometrioid are provided. ORs and an estimating equation (GEE) analysis.

Abbreviation: nd, not determined.
The 2.69 SIR for endometrial cancer (95% CI, 1.28–5.65) is considerably lower than the 4.1 SIR (95% CI, 2.9–5.6) reported by Lindor and colleagues (33) for Amsterdam I criteria, MMR gene mutation–positive Lynch families. The SIR for ovarian cancer in our study (2.68; 95% CI, 1.01–7.14) is higher than for Lynch families (2.0; 95% CI, 1.3–3.2; ref. 33). The SIRs for our study and Lindor and colleagues (33), however, have overlapping CIs and overall the SIRs are very similar. It is noteworthy that we did not observe an excess of colon cancer (SIR, 0.65; 95% CI, 0.37–1.14) characteristic of Lynch syndrome. Lynch-related malignancies in the families we investigated could reflect some as yet unidentified genetic susceptibility, shared environmental risk factor, or simply chance occurrence. Site-specific endometrial cancer susceptibility, distinct from Lynch syndrome, has been described (34–36), and it is possible that some of the excess endometrial cancers reported in these families are attributable to this sort of genetic risk. BRCA1/2 mutation carriers may also have increased risk for endometrial cancer. There is a recent report that endometrioid endometrial cancers may be more common in relatives of BRCA1 carriers (37). Given the fact that our probands had serous rather than endometrioid histology cancer, it seems very unlikely that any excess of uterine cancers is due to BRCA1 mutation.

The number of pancreatic cancers reported in relatives of serous endometrial cancer probands was greater than expected (SIR, 1.4), but the excess was not statistically significant (95% CI, 0.63–3.11; P = 0.4). The SIR for pancreatic cancers in the 29 families is nonetheless similar to what was reported for Amsterdam I criteria, Lynch syndrome kindreds in a previous study (SIR, 1.7; 95% CI, 0.7–2.8; ref. 33). Given the small number of families studied, it is not possible to exclude a small but clinically significant risk for pancreatic cancer in relatives of patients with serous uterine cancer.

Our follow-up analysis of the cancer family histories for women enrolled in the GOG-210 study did not reveal an excess of endometrial and ovarian cancers in the serous group compared with the endometrioid control group. Because we did not calculate SIRs for the GOG-210 case and control populations, it is not possible to comment on whether there was an excess of these cancers in first-degree relatives compared with the general population. The GOG-210 family history data collected did not include the birth years or current ages of parents, siblings, and children. Estimating those would allow for a crude estimate of the incidence of Lynch-associated cancers. It is possible that both the cases (serous and mixed serous histologies) and control group (endometrioid tumors) have increased number of ovarian and endometrial cancers in relatives compared with the general population. We have previously reported that recall and accuracy of reporting for gynecologic cancers among endometrial cancer probands is poor (24). We do not believe that even a crude estimate of incidence for ovarian and endometrial cancers in relatives would be of value without extensive medical record verification. We note that in our case–control study, we believe that there would be shared risk factors for endometrioid and serous/mixed serous endometrial cancers. The fact that both histologic subtypes are present in a substantial fraction of all endometrial cancers speaks to the possibility of a common etiology.

Pancreatic cancers were reported more often in the relatives of the serous cancer cases from the GOG-210 population than for endometrioid controls’ families, consistent with a shared risk for pancreatic and serous-type uterine cancer. A Swedish Family-Cancer Database study of 21,000 pancreatic cancers revealed a slight increase in the number of pancreatic cancers among sons of women with endometrial cancer (38). The study by Hemminki and Li (38) did not stratify uterine cancers by histologic subtype. In addition to Lynch syndrome, pancreatic cancer is associated with mutation in BRCA1 and BRCA2 (39–42, PALB2 (43), and CDKN2 (44). There are conflicting reports on the role that inherited mutation in BRCA1 and BRCA2 play in risk for serous endometrial cancers. Some studies have revealed frequent germ line mutations in patients with serous cancer whereas others have not. The effects of population stratification and tamoxifen therapy for breast cancer complicate interpretation of findings for individual studies and for the data as a whole (21, 45–47). The early-onset breast cancer in the daughter of proband 1972, her father’s pancreatic cancer, along with the hematopoietic neoplasms in her siblings (Fig. 1B) is highly suggested of a BRCA defect. Clinical testing for BRCA1/2 mutation was not conducted in this family (only 1 family tested and was negative). Research testing for BRCA1/2 defects could shed light on the role of the genes play in familial risk for serous carcinoma of the uterus, particularly given the link between BRCA1 mutation and pancreatic cancer (39–42, 48).

Our analysis of detailed 3-generation family histories for patients with uterine serous/mixed serous histology tumor is limited by the relatively small sample size. Uterine serous cancer is an uncommon malignancy with a poor prognosis. There is often a short interval from diagnosis to death, making collection of family history data even more difficult in what is a comparatively older population. We recognize the possibility that our study may be biased to include women and families who are aware of their familial risk for cancers and motivated to enroll in a cancer research study; however, eligibility for this study was simply a diagnosis of endometrial cancer, with serous or mixed serous histology. Finally, as in all family studies, recall bias is another limitation. To confirm records, all family history was obtained directly from the proband, and subsequently validated by medical records when available.

The Washington University serous cancer cohort and the GOG-210 serous cancer cases were similar overall with respect to racial makeup, age, and stage at diagnosis. The Washington University cohort, however, had a higher proportion of serous mixed histologies (58%) than the cases from the GOG-210 study (30%). This difference could reflect differences in how institutions report mixed histotype uterine neoplasms, with the possibility that some serous cases with minor endometrioid or other histotype
components would not be described as such in the pathology report (underreporting for non-serous components). Alternatively, tumors that are primarily endometrioid but with minor serous components could be described as endometroid. Pathologic review for the GOG-210 population is ongoing, with planned completion for all subjects enrolled in the period from September 22, 2003, to September 24, 2007, by January 2012. Our efforts to validate findings from our single-institution series in the GOG-210 case-control study were complicated by the fact that we did not have a cancer-free control population. As noted, without such a study group, it is impossible to say definitively whether serous and endometrioid patients with endometrial cancer have increased familial risk for ovarian and endometrial cancers. The 2 groups did not differ with respect to these cancers in relatives. Pancreatic cancers were on the other hand more common in relatives of serous cancer cases.

The excess of Lynch syndrome cancers (specifically uterine, ovarian, and pancreatic) in relatives of patients with serous endometrial cancer may reflect an as yet unidentified hereditary syndrome that includes uterine serous cancers. Exome or whole genome sequencing for probands could reveal mutations in candidate genes and/or pathways, some of which may be clinically relevant. Therapies that are tailored to key genetic abnormalities offer promise for better treatments for this deadly form of uterine cancer. The recent discovery of clinical benefit for PARP inhibitors in patients with germ line defects in double-strand break repair (49, 50) is but one example of gene-based advances in the treatment of malignancies. Large-scale genomic efforts to better understand the genetic and epigenetic changes important in uterine serous carcinoma such as the Endometrial Cancer TCGA project are not focused on germ line factors. Family-based studies of serous cancers of the uterus are likely to yield important insights into the key genetic factors involved in tumor initiation.

Disclosure of Potential Conflicts of Interest

S.B. Lele is a consultant/advisory board member for Genentech. No potential conflicts of interests were disclosed by other authors.

References


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Cancer Prevention Research

Uterine Serous Carcinoma: Increased Familial Risk for Lynch-Associated Malignancies

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