Familial and hormonal risk factors for papillary serous uterine cancer

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Summary

Objectives: To identify genetic and non-genetic risk factors for papillary serous uterine cancer.

Methods: A case-control study was conducted. Case women with papillary serous uterine cancer were compared with two control groups: 1) women with endometrioid uterine cancer and 2) healthy women with no past history of cancer. Cases and controls were matched for age (within two years) and ethnic group. All study subjects completed a questionnaire addressing family history. The cases and healthy controls were assessed for factors associated with estrogen exposure.

Results: The risks of breast cancer (RR 1.84, CI 1.03-3.31) and of prostate cancer (RR 2.21, CI 0.77-6.37) were higher among the relatives of patients with papillary serous uterine cancer, than among relatives of those with endometrioid uterine cancer. Other significant risk factors included weight at 18 years ($p = 0.04$) and the use of estrogen replacement therapy ($p = 0.04$).

Conclusion: Relatives of women with papillary serous cancer of the uterus had an increased risk of breast and prostate cancer. Hormonal exposure also increases the risk for this cancer. These findings suggest that predisposing genetic factors, possibly related to hormone metabolism, may be common to the three forms of cancer.

Key words: Hormonal risk factors; Papillary serous uterine cancer.

Introduction

The most common histological form of uterine cancer is endometriod and tumors of serous papillary (UPSC) histology constitute only 10% of all cases. However, UPSC is more often fatal than is endometrioid cancer, and accounts for a disproportionate number of deaths. We recently reported a number of women with UPSC who had a family history of early-onset breast cancer. We found that eight of 56 unselected women with UPSC had a first-degree relative with breast cancer diagnosed under the age of 50. The present study was undertaken to quantify the relative risk of breast cancer in relatives of women with UPSC to investigate the possibility of a common genetic basis for UPSC and breast cancer.

Methods

Cases consisted of living women, diagnosed with UPSC by hysterectomy from January 1991 to December 1999, who were treated at the Regional Cancer Centres in Hamilton, London, Ottawa and Toronto. The health records department generated a list of patients with UPSC and the charts were reviewed. The patient's physician determined whether the patient was willing to be informed concerning the study. Subjects were excluded if they were deceased, their physician did not provide consent to contact the patient, if the patient did not speak English, or if she was not mentally competent. Study subjects were contacted between 1997 to 2000. On average, the patients were contacted 2.5 years following diagnosis (range 0 to 10 years).

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Two control groups were employed. The first control group consisted of women diagnosed with endometrioid uterine cancer by hysterectomy, identified from the Princess Margaret Hospital, University Health Network recruited from 1997-2000. An attempt was made to identify two endometrioid adenocarcinoma controls for each UPSC case. In addition, the endometrial cancer controls were matched for age of diagnosis (within 2 years).

A second control group consisted of healthy women who were recruited from the outpatient Healthwatch Clinic of the Sunnybrook and Women's College Health Sciences Center, from October 1999 to December 2000. This clinic offers a range of preventive services and offers screening examinations for women from the general population. Women were approached to participate in this study at the time of their clinic appointment. Women with a personal history of cancer and women who did not have an intact uterus were excluded. Cases and controls were matched for year of birth (within two years) and for ethnic group (i.e., white, black, Asian). An attempt was made to identify one healthy control for each UPSC case.

There were 560 healthy women and 325 women with endometrioid uterine cancer who were eligible to serve as controls. It was possible to find a matched healthy control for 57 of the papillary serous uterine cancer patients. It was possible to find two matched endometrial cancer controls for 69 papillary serous uterine cancer patients.

All study subjects underwent a 30-minute telephone interview addressing their family history of malignancy and their medical history. Questions related to their personal history of cancer, health factors, and reproductive and hormone use.

For the assessment of risk by family history a historical cohort approach was used. The "exposed" group are the first-degree relatives of the UPSC cases and the "unexposed" group are the first-degree relatives of the controls. Both control groups

were used for the family history analysis. All first-degree relatives of the cases and controls were considered to be study subjects in this cohort analysis. The observed number of cases in the first-degree relatives were determined by review of the family pedigree. Person-years of exposure for first-degree relatives were accumulated from birth, until age of death, age at the time of interview of the proband, or until age at diagnosis of the cancer. Kaplan-Meier survival analysis was used for the calculation of the cumulative incidence of cancer in the first-degree relatives of the cases and controls. The log-rank test was used to assess statistical significance of differences in survival curves. The relative risk (RR) of cancer among first-degree relatives was estimated by the use of the Cox proportional hazards model. The point estimate and 95% confidence interval (CI) for the RR was calculated for all cancers as well as specifically for cancers of the endometrium, breast, colon, prostate and lung cancer.

Reproductive histories were compared between the UPSC cases and the matched healthy controls (Healthwatch attendees). For univariate matched comparisons, odds ratios were estimated by comparing the ratio of concordant and discordant pairs and McNemar's test was used to assess statistical significance. The paired t-test was used for comparing continuous variables in the univariate-matched analysis. A cut-off of 5% was chosen as significant. All p-values were two-tailed. The statistical program SPSS.10.0.7 was used.

Results

A total of 136 women were identified who were alive with the diagnosis of interest. Excluded were nine women whose physicians did provide consent for contact, one woman who was cognitively impaired, three who were unable to speak English, and 12 who we were unable to contact. Of the 111 women, 32 declined participation. The following information was collected for 79 women with papillary serous uterine cancer. Given that three women were adopted, they were not candidates for the genetic risk factor part of the study.

Both control groups were used to assess the effect of family history (Table 1). There were 23 cases of breast cancer reported among the 290 female first-degree relatives of the patients with papillary serous cancer (mean age of breast cancer diagnosis was 62.0 years) compared to 22 of 478 first-degree female relatives of the endometrioid cancer controls (mean age of breast cancer diagnosis 62.4 years) and 11 of 209 cases among first-degree relatives of healthy controls (mean age of breast cancer diagnosis 57.6 years). By the Cox proportional hazards method, the relative risk of breast cancer to age 70 was 1.84 for relatives of UPSC, compared to relatives with endometrioid cancer (p = 0.038) and was 1.49 for relatives of UPSC patients compared to relatives of healthy controls (p = 0 .278). There were 28 breast cancers that occurred in women under 50 years. By the Cox proportional hazards method, the relative risk of breast cancer to age 50 was 1.85 for relatives of UPSC, compared to relatives with endometrioid cancer (p = 0.153) and was 1.121 for relatives of UPSC patients compared to relatives of healthy controls (p = 0 .813).

One of the exclusion criteria in the control groups was a previous personal history of cancer. However, six women with UPSC had a previous diagnosis of breast cancer, a mean of 5.5 years (range 1-15 years) prior to the occurrence of papillary serous uterine cancer. One woman developed breast cancer two years after surgery for papillary serous uterine cancer. The five women with previous breast cancer had all received tamoxifen for a mean of 5 years (range 0.5-12 years). On average, UPSC was diagnosed 1.5 years after tamoxifen was stopped in these women (range 0-3 years). Re-analyzing the data after removing the five cases with previous breast cancer (and their matched controls) showed that first degree relatives of women with UPSC still had an increased risk of breast cancer when compared to those with endometrioid cancer (RR 1.73 95% CI 0.95-3.18) and healthy controls (RR 1.56 95% CI 0.74-3.32) however, the finding was no longer statistically significant (Table 2).

Given Sherman's [8] excellent work addressing the non-genetic factors between UPSC cases and endometrial

Table 1. — *Comparison of family history between patients with UPSC, endometrioid uterine cancer and women without cancer.*

	Patients with UPSC vs those with endometrial uterine cancer			Patients with UPSC vs healthy cases		
	RR	95% CI	p-value	RR	95%CI	p-value
Endometrial	0.882	0.301-2.580	0.818	3.517	0.411-30.114	0.221
Breast	1.842	1.027-3.306	0.038	1.485	0.724-3.047	0.278
Colon	1.276	0.603-2.698	0.522	0.998	0.408-2.443	0.997
Prostate	2.208	0.766-6.366	0.132	1.225	0.368-4.072	0.741
Lung	1.047	0.458-2.393	0.913	0.658	0.261-1.658	0.371
All Cancers	0.892	0.674-1.181	0.426	0.819	0.583-1.151	0.250

Table 2. — *Comparison of family history between patients with UPSC but no personal history of breast cancer to patients with endometrioid uterine cancer and healthy controls.*

	Patients with UPSC vs those with endometrial uterine cancer			Patients with UPSC vs healthy controls		
	RR	95% CI	p-value	RR	95%CI	p-value
Breast	1.734	0.946-3.176	0.071	1.563	0.736-3.321	0.241

Table 3. — *Comparison of patient characteristics in UPSC cases and healthy controls.*

Iter	Number of matched pairs	Cases with UPSC	Healthy controls	P-value
Year of birth	57	1930.5±7.2	1930.6±7.2	0.51
Height	57	63.9±2.3"	63.6±2.1"	0.50
Current weight	56	155.5±25.3 lb	152.6±27.0 lb	0.63
Weight at 18 years	53	123.8±16.2 lb	117±13.9 lb	0.04
Change in weight	52	32.3±27.0 lb	35.3±23.6 lb	0.59
BMI	56	26.7±5.3 kg/m^2	26.5±3.9 kg/m^2	0.83
Menarche	54	13±1.4 yr	13±1.3 yr	0.95
Cycle length	50	28.1±2.7 days	27.8±1.8 days	0.48
Total births	57	2.5±1.9	2.6±1.5	0.65
Total live births	57	2.5±1.9	2.6±1.5	0.69
Total stillbirths	57	0	0.002±0.13	0.32
Abortions	57	0.007±0.32	0.005±0.23	0.74
Miscarriage	57	0.28±0.65	0.46±1.02	0.26
Nulliparous	57	21%	9%	0.12
Breast feeding (in months)	56	8.4±14.3 mos	5.1±8.3 mos	0.16
Oral contraceptive	54	0.81±2.68 yr	1.76±4.41 yr	0.20
Menopause	55	50.2±4.0 yr	49.2±5.1 yr	0.30
HRT	54	2.6±5.4 yr	2.2±5.2 yr	0.64
ERT	53	2.1±5.1 yr	0.5±2.0 yr	0.04
E+P	54	0.4±1.6 yr	1.6±4.8	0.11
Prog only	52	0.0009±0.001 yr	0.0005±0.0006 yr	0.74
Smokers		7.7 yrs	9.0 yr	0.80
Ever smoked	57	33%	33%	1.00

cancer controls, we confined our study to a comparison of UPSC cases and healthy controls (Table 2). No differences were found between the two groups in terms of gravidity, age of menarche, current height, weight or smoking. The papillary serous uterine cancer patients reported a greater mean weight at age 18 than the controls (123.8 ± 16.2 kg versus 117 ± 13.9 kg; p = 0.04). At the age of 18, 48.2% of cases and 33.3% of the controls weighed more than 60kg (unmatched odds ratio = 1.86; p = 0.11). The differences in weight at the age of diagnosis or at other ages were not significant.

Cases reported exposure to estrogen replacement therapy (i.e. without progesterone) for a longer mean duration than the controls (2.1 ± 5.1 years versus 0.5 (2 years, p = 0.04). In total, 20% of the cases and 9% of the healthy controls reported a history of estrogen replacement therapy.

Discussion

Papillary serous uterine cancer is similar to cancer of the ovary and fallopian tube in terms of its histologic appearance, pattern of metastatic spread and poor survival. Case reports describe familial aggregations of papillary serous uterine cancers and other serous gynecologic cancers [5, 6]. In a previous study, we observed several early-onset breast cancers in the families of unselected cases. However, we genotyped 56 women with UPSC and found no BRCA1 or BRCA2 mutation [7]. This observation prompted us to conduct a case-control study, to estimate the relative risk of breast cancer in these relatives. We compared the rate of various cancers in the families of women with UPSC and those of women without cancer, and with endometrioid adenocarcinoma of the uterus. We observed that the risk of breast cancer was higher in the families of women with papillary serous cancer of the uterus than in of the families of women with the more common endometrioid form.

Previous studies have shown that that there is an increased risk of various cancers in first-degree relatives of women with endometrioid cancer. The CASH study, involving 455 women with endometrioid uterine cancer and 3,216 controls, showed a 3-fold increase in the risk of endometrial cancer in first-degree relatives (odds ratio 2.8, 95% CI 1.9-4.2) [9, 10].

It is important to consider past tamoxifen use in the interpretation of our findings. Several authors have implicated tamoxifen in the development of aggressive types of uterine cancers [11, 12] and of papillary serous cancer of the uterus in particular. Magriples [1] and Silva [2] were the first to suggest that there is a higher than expected proportion of papillary serous uterine cancer among tamoxifen users who develop uterine cancer (OR of 4.5 and 6.6). Recently, Bergman and colleagues [11] describe a nationwide case-control study from the Netherlands of 309 women with endometrial cancer after breast cancer. They showed that tamoxifen use in women diagnosed with breast cancer is associated with an increased risk of uterine cancer (RR 1.5, CI 1.1-2.0), particularly worse histologies like mixed mesodermal tumors ($p < 0.02$), and poorer 3-year survival (p = 0.02). Interestingly, in their study there was no association of tamoxifen use with the clear cell and papillary serous cancer group. There are five (4.8%) cases in the 110 tamoxifen users compared to ten (5.8%) cases in 199 non-tamoxifen users. Narod and colleagues [12] described the histologic features of the endometrial tumors in 148 women with breast and endometrial cancer. Tamoxifen was associated with more aggressive histologic types (e.g. papillary serous and malignant mixed mesodermal cancer) (p = 0.0002) and with high-grade disease (p = 0.05).

Initially, there was an increase in breast cancer risk in the relatives of women with UPSC that was not limited to those with a history of tamoxifen use (and a personal history of breast cancer). Among women with no past history of breast cancer (and no tamoxifen use) a non-significant trend toward increased familial risk of breast cancer was seen. There was no difference in the risk of

Table 4. — *Risk that a family member has breast cancer in the healthy control group compared to population breast cancer rates.*

	Relative Risk	95% confidence intervals
Breast cancer < 55 yrs	1.6	0.6-3.2
Breast cancer = 55 yrs	0.6	0.2-1.6

family history of breast cancer between papillary serous cancer of the uterus and healthy controls. It may be that our control group is not representative of the population. To address this, we compared our control group to population breast cancer rates and validated our suspicions (Table 4). Indeed, our control group appears to have a higher risk for breast cancer suggesting that younger women who attend the Healthwatch clinic may do so specifically for the benefit of screening. Given that papillary serous cancer of the uterus is a disease of older women it is unlikely that this bias played a significant role.

Sherman [8] conducted a multi-institution case-control study assessing estrogen exposure in 328 women with endometrioid uterine cancer as compared to 26 women with papillary serous cancers of the uterus. Women with endometrioid uterine cancer had the strongest association with estrogen exposure; risk factors included a BMI of 29 of higher, use of estrogen alone replacement therapy, menarche before age 12 years and high parity. These observations are consistent with the hypothesis that endometrioid adenocarcinoma is attributable to estrogen exposure. In Sherman's study, use of exogenous estrogens and obesity were not associated with a statistically significant increased risk of developing serous carcinoma. They concluded that this may be related to the small sample size and would require confirmation in larger series.

Our finding of excess body weight at age 18 and exposure to unopposed estrogen replacement therapy supports the hypothesis that estrogens may have a role in the pathogenesis of UPSC. Endogenous estrogens rise either from increased production of androstenedione or peripheral conversion of this hormone to estrone. The extraglandular aromatization of androstenedione to estrone is increased in obese women. The development of endometrioid uterine cancer appears to be related to the duration of unopposed estrogen stimulation and degree of obesity. Our finding of increased body weight at age 18 is consistent with the hypothesis of duration of exposure.

In conclusion, we demonstrate that the increased risk of breast cancer in the relatives of women with papillary serous as compared to those with endometrioid uterine cancer was not statistically significant when controlled for personal history of breast cancer (RR 1.74, 0.95-3.18). We showed a significant difference in the weight at age 18 years and use of estrogen replacement therapy between women with UPSC and healthy controls. There appears to be a relationship between estrogen exposure and the development of papillary serous uterine cancer.

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