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Clinical and pathological characterization of endometrial cancer in young women: Identification of a cohort without classical risk factors

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ABSTRACT

Objective. Endometrial cancer (EC) is the most common gynecologic malignancy with known risk factors including excess estrogen and hereditary syndromes. The objective of this study was to determine the proportion of young women with EC that could be attributed to these factors and if, as we suspected, there is a third population of young women in which neither factor is identifiable. We were interested in comparing clinicopathologic characteristics and outcomes across subgroups in order to better inform treatment recommendations.

Methods. We performed a retrospective chart review of women age 15–49 diagnosed with EC or complex atypical hyperplasia. Demographic, clinicopathologic, treatment, fertility, and outcome parameters were analyzed.

Results. Of 719 women identified, 327 were fully evaluable. 57.5% fit the "High Estrogen" risk criteria. 8.25% met criteria for suspected Lynch syndrome. 34.25% classified as "Neither" had no classical risk factors identified. There were no statistical differences in age, gravidity, tumor grade, treatment selection and response to hormonal therapy. Age of menarche, stage, histology, and synchronous ovarian cancer differed significantly. Prevalence of synchronous ovarian cancer was 21.0% of "Neither", 23.1% of "Lynch", and 6.6% of "High Estrogen". For women who attempted pregnancy, 2/27 of "High Estrogen", 0/3 of "Lynch", and 2/16 of "Neither" achieved a live birth.

Conclusions. This study confirmed that a third population of young women with EC exist that lack classical risk factors and have distinct clinicopathologic parameters. No difference in success of conservative treatment or live births was noted in the small cohort in whom this treatment approach was attempted.

Introduction

Endometrial cancer is the most common gynecologic malignancy and the fourth most common cancer in women globally. In British Columbia there are over 600 new cases of endometrial cancer every year and approximately 14% of these arise in women under the age of 50 years, including approximately 5% under the age of 40 years [1–4]. Most endometrial cancers are low grade, early stage tumors, with good prognosis. Well-recognized risk factors for developing endometrial cancer fall under two main categories. The first category encompasses conditions of excess estrogen, including obesity, polycystic ovarian syndrome (PCOS), estrogen producing tumors, as well as exogenous exposure to unopposed estrogen therapy and tamoxifen [5–9]. The second risk category involves hereditary syndromes, most significantly Lynch syndrome. Lynch syndrome, or hereditary nonpolyposis colorectal cancer (HNPCC), is an autosomal dominant condition caused by a mutation in genes associated with DNA mismatch repair (MMR); most commonly *MLH1*, *MSH2*, *MSH6* and/or *PMS2* [10]. We have observed, however, that there are many young endometrial cancer patients that seem to be without either of these influencing features. What has prompted tumorigenesis in these individuals is unclear.

Complex atypical hyperplasia (CAH) is a pathologic diagnosis that describes an endometrial cancer precursor lesion of crowded glands, and atypical cells with no invasion. CAH is classically attributed to excess estrogen, and in young women is most commonly seen in association with obesity and PCOS [11,12]. It is also an established precursor lesion in endometrial cancers that develop in women with Lynch syndrome [13]. If untreated, the rate of progression from CAH to endometrial cancer is 29% [14]. Given the overlap between CAH and low-grade endometrial cancers, along with the similarities in management recommendations, we have included women with CAH in this study.

There are many considerations for young women with endometrial cancer or CAH that differ from the more common scenario of these pathologies arising in the post-menopausal cohort. Younger women may still be interested in fertility and seek a conservative approach with hormonal management rather than definitive surgery that would include hysterectomy. Gold standard staging for endometrial cancer includes removal of the uterus (including cervix), ovaries and fallopian

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tubes, washings +/− lymph node dissection [15]. Even if an individual is not interested in future fertility, preservation of hormonal function and thus preservation of her ovaries with the known benefits to cardiovascular, sexual, psychological, and bone health may be desired [16]. Women with CAH, or low grade and early stage cancer of endometrioid histology can be considered for treatment with progestin therapy [17–20]. Progestin type, dose, and treatment duration vary in both the literature and in clinical practice recommendations and there is no consensus on the ideal regimen [21,22]. A systematic review of women with CAH and grade 1 endometrial cancer (45 studies, 391 patients age 19-80) treated with a variety of conservative strategies (medroxyprogesterone acetate, megestrol acetate, levonorgestrel intrauterine system, intramuscular 17-hydroxyprogesterone, oral contraceptive pills, norethisterone, dihydrogesterone, and natural progesterone) alone or in combination revealed an average 53.2% complete response rate with no evidence of recurrence (follow up median time of 39 months) [18]. These studies do not address the additional risk of synchronous ovarian cancer in young women, estimated to be 2–19% [23–25]. Given the variations in study populations and methodologies across these studies, along with the lack of risk factor stratification, counseling women with respect to conservative treatment strategies remains challenging.

The main objective of the present study is to characterize our population of young women with endometrial cancer and determine the proportion of cases that could be attributed to 1) conditions of high estrogen or 2) suspected Lynch syndrome. We hypothesize that there is a third population of young women with endometrial cancer that seem to lack the traditional risk factors. The clinical and pathological characteristics of what we anticipate will be three subgroups of women < 50 years of age with endometrial cancer will be compared with respect to fertility and cancer-associated outcomes. Ultimately we hope that this will improve our understanding of this disease in young women and better inform decision making for both clinicians and patients.

Methods

After Institutional Review Board (IRB) approval, institutional databases (Vancouver General Hospital and BC Cancer Agency) were used to identify women diagnosed with CAH and endometrial cancer from January 1, 1997 to March 31, 2014. Inclusion criteria included age between 15 and 49 years at the time of specimen collection and a final diagnosis of CAH or endometrial cancer with all stages, grades, and histologic subtypes considered. Exclusion criteria included an alternate predisposing genetic condition (1), end-stage renal disease (1), or insufficient clinical data to categorize patients into risk factor groupings (281). The search terms "endometrial or uterine carcinoma" and "complex atypical hyperplasia and endometrial or uterine" were used, with resultant pathology reports manually evaluated to ensure that each final diagnosis was within our inclusion criteria. All pathology reports were initially generated by or later reviewed by a gynecologic oncology-specialized pathologist.

Information regarding patient age, body mass index, medical history, gynecological history, fertility concerns, co-morbid conditions, family history, treatment options, and follow-up assessments were abstracted from the medical records of these women. Pathology reports and laboratory studies were used to obtain information on histological subtype, grade, stage, and mismatch repair screening. Stages were reviewed and updated for each patient as needed to ensure that staging criteria followed the International Federation of Gynecology and Obstetrics guidelines (FIGO 2009) [26].

Information from the retrospective chart review was used to divide patients into three groups. Patients were placed in the "High Estrogen" group if they had body-mass-index (BMI) > 30 kg/m^2, clinical annotation of obese on medical charting at diagnosis, diagnosis of Polycystic Ovarian Syndrome (PCOS), and/or a past history of tamoxifen or post-menopausal hormone therapy, and did not fit the criteria for the Lynch syndrome group. Patients were placed into the suspected Lynch syndrome ("Lynch") group when Amsterdam II criteria for Lynch syndrome was met, Lynch syndrome was genetically confirmed through genome sequencing, or when immunohistochemistry (IHC) for mismatch repair (MMR) protein MSH2 was abnormal in the pathology specimen and genetic testing was not performed (e.g. suspected or confirmed Lynch II syndrome). The latter group was included in a previous study analyzing the sensitivity of abnormal MMR proteins by IHC showing that abnormal MSH2 on IHC was 94% sensitive for predicting a germline MSH2 deletion [27]. We did not include patients with abnormal MMR IHC for MLH1/PMS2 (loss) as the majority of these cases have MLH1 promoter hypermethylation and represent somatic/epigenetic inactivation of MLH1 and are unlikely to have a germline mutation in MLH1. When criteria for the former two grouping were not met (no identifiable exposure to high estrogen and no suspicion of Lynch syndrome) patients were placed into the "Neither" category. Statistical analysis without multiple testing correction was performed to compare clinicopathologic features and outcomes across groups.

Results

A total of 610 women between the ages of 15 and 49 were identified as being diagnosed with endometrial cancer or CAH between January 1997 and March 2014. Of these, 281 were excluded from the study due to insufficient clinical data available during chart review. One patient was excluded due to a diagnosis of Cowden syndrome and one with end-stage renal disease who underwent renal transplantation. This yielded 327 women within our cohort that were subsequently divided into three groups based upon their perceived risk factors for endometrial cancer. The "High Estrogen" group included women with risk factors for endometrial cancer related to high estrogen states: obesity (n = 173), PCOS (n = 49), tamoxifen therapy (n = 7), and post-menopausal hormone replacement therapy (n = 1) [5–9]. This group comprised 57.5% (188 of 327) of our study population. The "Lynch" group encompassed 8.3% (27 or 327) of our study population. Patients were placed into the "Lynch" group when Lynch syndrome was genetically confirmed through genome sequencing (n = 16), when Amsterdam II criteria for Lynch syndrome was met (n = 8), or when immunohistochemistry (IHC) for MMR protein MSH2 was abnormal and genetic testing was not performed (n = 3). The remaining 34.2% (112 of 327) of women in this cohort were classified within the "Neither" group.

The clinical characteristics of women in the three groupings were compared (Table 1). Calculation of the median BMI for the "High Estrogen" group excluded instances where BMI was deemed inaccurate due to patient weight exceeding the maximum scale value of 180 kg. Patient with an unknown BMI refers to instances where BMI was unknown but clinical records at the time of physical examination denote an obese (n = 29) or morbidly obese (n = 10) body habitus. Within the "High Estrogen" group, 3% had a normal BMI (<25 kg/m^2) and 6% were overweight (BMI 25–<30 kg/m^2) and represent women with a clinical diagnosis of PCOS or who had been treated with Tamoxifen therapy. The majority of women within the "Lynch" category had a BMI <30 kg/m^2 (86%). All women within the "Neither" grouping had a BMI <30 kg/m^2 as this was part of the definition of this grouping. Of the "High Estrogen" group, 3.7% had a concurrent diagnosis of Type 2 Diabetes Mellitus, compared to 1.8% in the "Neither" group and 0% in the "Lynch" group. The number of pregnancies prior to diagnosis was independent of the assigned subgroups (*p-value 0.26*); we do not find any evidence to suggest that there are more nulliparous women in the high estrogen group (*p-value 0.1*). Early age of menarche is another known risk factor for endometrial cancer [28]. A chi-squared test for trend suggests that there is an association between age at menarche and the "High Estrogen" group when compared with the other two groups (*p-value 0.01*).

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