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Prediction of concurrent endometrial carcinoma in women with endometrial hyperplasia☆

Koji Matsuo [a,f,*,1], Amin A. Ramzan [a,1], Marc R. Gualtieri [b], Paulette Mhawech-Fauceglia [c], Hiroko Machida [a], Aida Moeini [a], Christina E. Dancz [d], Yutaka Ueda [e], Lynda D. Roman [a,f]

[a] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Los Angeles County Medical Center, University of Southern California, Los Angeles, CA, USA
[b] Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Los Angeles County Medical Center, University of Southern California, Los Angeles, CA, USA
[c] Department of Pathology, Los Angeles County Medical Center, University of Southern California, Los Angeles, CA, USA
[d] Female Pelvis Medicine Reconstructive Surgery, Department of Obstetrics Gynecology, Los Angeles County Medical Center, University of Southern California, Los Angeles, CA, USA
[e] Department of Obstetrics and Gynecology, Osaka University Graduate School of Medicine, Osaka, Japan
[f] Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA, USA

HIGHLIGHTS

- Older age, larger body habitus, diabetes mellitus, and complex hyperplasia with atypia were independent risk factors predicting concurrent endometrial cancer.
- Up to 45.5% of endometrial hyperplasia patients can harbor concurrent endometrial cancer if multiple risk factors are present.
- Hormonal treatment for endometrial hyperplasia may be beneficial among patients expressing 3 or more risk factors.

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ABSTRACT

Objective. Although a fraction of endometrial hyperplasia cases have concurrent endometrial carcinoma, patient characteristics associated with concurrent malignancy are not well described. The aim of our study was to identify predictive clinico-pathologic factors for concurrent endometrial carcinoma among patients with endometrial hyperplasia.

Methods. A case–control study was conducted to compare endometrial hyperplasia in both preoperative endometrial biopsy and hysterectomy specimens (n = 168) and endometrial carcinoma in hysterectomy specimen but endometrial hyperplasia in preoperative endometrial biopsy (n = 43). Clinico-pathologic factors were examined to identify independent risk factors of concurrent endometrial carcinoma in a multivariate logistic regression model.

Results. The most common histologic subtype in preoperative endometrial biopsy was complex hyperplasia with atypia [CAH] (n = 129) followed by complex hyperplasia without atypia (n = 58) and simple hyperplasia with or without atypia (n = 24). The majority of endometrial carcinomas were grade 1 (86.0%) and stage I (83.7%). In multivariate analysis, age 40–59 (odds ratio [OR] 3.07, p = 0.021), age ≥ 60 (OR 6.65, p = 0.005), BMI ≥ 35 kg/m^2 (OR 2.32, p = 0.029), diabetes mellitus (OR 2.51, p = 0.019), and CAH (OR 9.01, p = 0.042) were independent predictors of concurrent endometrial carcinoma. The risk of concurrent endometrial carcinoma rose dramatically with increasing number of risk factors identified in multivariate model (none 0%, 1 risk factor 7.0%, 2 risk factors 17.6%, 3 risk factors 35.8%, and 4 risk factors 45.5%, p < 0.001). Hormonal treatment was associated with decreased risk of concurrent endometrial cancer in those with ≥3 risk factors.

Conclusions. Older age, obesity, diabetes mellitus, and CAH are predictive of concurrent endometrial carcinoma in endometrial hyperplasia patients.

1. Introduction

Endometrial hyperplasia is a benign lesion that can precede or coexist with endometrial carcinoma. Cancer of the uterus is the most prevalent gynecologic malignancy in the United States, with 54,870 projected cases in 2015 [1]. The majority of endometrial carcinomas will be type I, which are hormonally sensitive and most commonly

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* Corresponding author at: Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Los Angeles County Medical Center, University of Southern California, 2020 Zonal Avenue, IRD 520, Los Angeles, CA 90033, USA.
E-mail address: koji.matsuo@med.usc.edu (K. Matsuo).

[1] Contributed equally to the work.

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have endometrioid histology. The rate of concurrent endometrial carcinoma in patients with untreated complex hyperplasia with atypia (CAH), the most severe category of the disease, is as high as 42.6% [2].

Endometrial hyperplasia is categorized using the World Health Organization (WHO) criteria based on the presence or absence of nuclear atypia and the degree of architectural crowding [3]. The standard of care for patients with atypical hyperplasia who are able and willing to undergo surgery, is hysterectomy [4]. Patients who desire future childbearing may choose to defer definitive management and opt for hormonal treatment of endometrial hyperplasia. The decision to forego surgical management is complicated by the lack of consensus regarding the non-surgical management of endometrial hyperplasia, and difficulty in identifying patients that are at increased risk of concurrent carcinoma.

Besides the presence of nuclear atypia, the characteristics that confer an increased risk of concurrent endometrial carcinoma in patients with endometrial hyperplasia are not well described. Identification of risk factors could allow better-informed counseling for patients considering non-surgical management of endometrial hyperplasia. It could also assist in the appropriate triage of patients desiring surgical management to a gynecologic oncologist, given that 1.2–2.1% of patients with CAH are estimated to have endometrial carcinoma with lymph node metastases [5]. The objective of this study was to identify clinico-pathologic factors for concurrent endometrial carcinoma in patients with endometrial hyperplasia.

2. Patients and methods

2.1. Eligibility

After Institutional Review Board (IRB) approval was obtained at the University of Southern California, an institutional surgical pathology database was utilized to identify cases. For the case group representing endometrial hyperplasia with concurrent carcinoma, the diagnostic code "endometrial cancer" was used to identify patients with the diagnosis of primary endometrial cancer in a hysterectomy specimen between March 2003 and March 2014. Among those identified cases, the results of the endometrial biopsies performed antecedent to the hysterectomy were reviewed. Eligibility criteria for the study were: women with a diagnosis of endometrial hyperplasia in an endometrial biopsy specimen who subsequently underwent hysterectomy for treatment. Exclusion criteria were those without endometrial hyperplasia in a preoperative endometrial biopsy (normal endometrium, atrophic endometrium, or endometrial cancer) and those with no endometrial biopsy prior to hysterectomy. For the control group representing endometrial hyperplasia without concurrent carcinoma, the diagnostic code "endometrial hyperplasia" was used to identify patients that had a diagnosis of any type of endometrial hyperplasia in a hysterectomy specimen during the same study period. The same eligibility and exclusion criteria were applied for the control group. The STROBE guidelines were consulted for reporting in a case–control study [6]. Some cases of the study population were within the context of our previous studies [7–11].

2.2. Clinical information

Among eligible cases, medical records were examined to abstract the following information: (i) patient demographics at the time of endometrial hyperplasia diagnosis, (ii) treatment patterns for endometrial hyperplasia, and (iii) histology results for endometrial biopsies and hysterectomy. Patient demographics included age, ethnicity, body mass index (BMI), pregnancy history, and presence of medical comorbidities (hypertension, diabetes mellitus, and hypercholesterolemia). Methods of endometrial sampling was also abstracted (pipelle, dilation and curettage, or vacuum aspiration with Vabra). Treatment patterns included whether there was hormonal treatment between endometrial hyperplasia diagnosis and hysterectomy. Among those who received treatment, the hormonal agent was recorded. In addition, the time interval between the initial endometrial hyperplasia diagnosis and the date of hysterectomy was abstracted. Histology results included type of endometrial hyperplasia in the initial endometrial biopsy. These were classified into: CAH, complex hyperplasia without atypia (CH), simple hyperplasia with atypia (SAH), and simple hyperplasia (SH). Among patients that were diagnosed with endometrial cancer on the hysterectomy specimen, histologic subtype, grade, cancer stage, depth of myometrial tumor invasion, and presence of lymphovascular space invasion were abstracted. In addition, survival outcomes (presence of disease recurrence or death due to endometrial cancer) were examined. Cancer stage was re-classified based on the International Federation of Gynecology and Obstetrics (FIGO) 2009 system [12].

2.3. Statistical analysis

The primary objective of this study was to identify independent risk factors for the presence of concurrent endometrial cancer in hysterectomy specimens among patients with endometrial biopsy-proven endometrial hyperplasia. Continuous variables were examined for normality by the Kolmogorov–Smirnov test expressed with mean (±SD) or median (range) as appropriate. Statistical significance of continuous variables was examined by the Student *t*-test or the Mann–Whitney *U*-test as appropriate. For continuous variables, clinically relevant age cutoff (<40, 40–59, and ≥60), mean value for BMI (<35 *versus* ≥35 kg/m^2), and median for time interval between endometrial biopsy and hysterectomy (<105 *versus* ≥105 days) were used for the cutoff values. Pearson's correlation coefficient value was determined among the continuous variables. Categorical or ordinal variables were expressed with number (%), and statistical significance was examined by chi-square test or the Fisher exact test as appropriate.

A binary logistic regression model for multivariate analysis was used to determine independent risk factors for concurrent endometrial cancer in a population of women with biopsy-proven endometrial hyperplasia. All variables with significance at $p < 0.10$ in univariate analysis were considered as candidates in the final model. This relatively liberal cutoff of the p-value was chosen due to the small sample size that may have a risk of type II error with a lower cutoff. These included age (<40 *versus* 40–59 *versus* ≥60), BMI (<35 *versus* ≥35 kg/m^2), diabetes mellitus (yes *versus* no), hypertension (yes *versus* no), hypercholesterolemia (yes *versus* no), any hormonal treatment for endometrial hyperplasia (yes *versus* no), time interval between endometrial biopsy and hysterectomy (<105 *versus* ≥105 days), and endometrial hyperplasia type (SH/SAH *versus* CH *versus* CAH). Then, a conditional backward method was used to determine the independently significant covariates in the final model given the degree of freedom in this sample size, expressed with odds ratio (OR) and 95% confidence interval (CI). Covariates entered in the final model were age, BMI, diabetes mellitus, and endometrial hyperplasia type. All statistical tests were two-tailed, and *P* value of less than 0.05 was considered as statistically significant. Statistical Package of Social Science (SPSS, Inc., version 12.0, Chicago, IL) was used for statistical analysis.

3. Results

There were 194 hysterectomy specimens with a preoperative diagnosis of endometrial hyperplasia identified during the study period. Of those, 20 cases lacking an endometrial biopsy prior to hysterectomy and 9 cases without endometrial hyperplasia on endometrial biopsy, were excluded. The remaining 168 cases had endometrial hyperplasia on endometrial biopsy that was subsequently treated with hysterectomy. There were 674 cases of primary endometrial cancer that underwent hysterectomy during the study period. Of those endometrial cancer cases, 43 hysterectomies were performed for the preoperative indication of endometrial hyperplasia. Taken together, 211 cases of