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Original Article

Survival outcome in endometrial cancer patients according to hereditary predisposition

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ABSTRACT

Objective: A familial history of ovarian cancer/breast cancer is considered a significant prognostic factor for ovarian cancer. We investigated hereditary factors by examining the incidence of synchronous malignancy in patients with endometrial cancer, and assessed the prognostic role of heredity in endometrial cancer.

Methods: We retrospectively evaluated patients with endometrial cancer who underwent surgery from January 2001 to April 2011. A hereditary background in this study was defined as *double primary cancer*, that is, endometrial cancer accompanied by colon, ovarian, or breast cancer suggestive of Lynch syndrome, hereditary breast ovarian cancer syndrome, or Cowden syndrome, respectively.

Results: Among 282 patients with endometrial cancer in the study population, 20 patients (7.1%) had a hereditary predisposition: 10 patients (3.5%) had ovarian cancer, six patients (2.1%) had breast cancer, and four patients (1.4%) had colon cancer. Age and lower uterine segment involvement were not statistically different between the hereditary and nonhereditary groups. The majority of the women in the hereditary group presented with Stage I cancer; however, there were no significant differences in Stage I cancer between the hereditary group and the sporadic endometrial cancer group (85% and 77%, respectively, $p = 0.561$). The median follow-up period was 60 months. A 5-year overall survival rate was not different between the two groups (95% and 95%, respectively, $p = 0.659$). Among a subgroup of patients with Stage I endometrial cancer, the 5-year overall survival rate was lower in the endometrial cancer with a hereditary predisposition group compared with the sporadic endometrial cancer group (94% and 98%, respectively, $p = 0.027$).

Conclusion: Seven percent of the women with endometrial cancer in our study had other malignancies such as ovarian, colon, or breast cancer synchronously. Among a subgroup of patients with Stage I cancer in the endometrial cancer with a hereditary predisposition group, the 5-year overall survival rate was significantly lower (94%). This finding should be confirmed in a larger population.

Introduction

The incidence of endometrial cancer has been increasing over the past decade in Korea [1–3]. Among the many risk factors for endometrial cancer, including obesity, diabetes, late menopause, unopposed estrogen therapy, and nulliparity [4], inherited factors have also been suggested as important risk factors [5].

The occurrence of synchronous cancers is relatively uncommon, but it is important to detect them in clinical practice because a diagnosis of synchronous malignancy in the later stages affects clinical management and prognosis. In particular, double primary cancer with endometrial cancer is strongly associated with hereditary factors; for example, colon cancer and endometrial cancer, suggestive of Lynch syndrome [5], ovarian cancer and endometrial

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cancer, suggestive of Lynch syndrome and/or hereditary breast ovarian cancer syndrome [6], and breast cancer and endometrial cancer, suggestive of Cowden syndrome [7].

A familial history of ovarian cancer/breast cancer is considered a strong prognostic factor for ovarian cancer, and this might be explained by *BRCA*ness [8]. However, double primary cancer with endometrial cancer has not been well studied previously. Therefore, we investigated the prognostic role of heredity in endometrial cancer, a potentially autosomal dominant disease.

Materials and methods

A total of 282 patients were diagnosed with endometrial cancer by pathologic examination at the Department of Uterine Cancer at the National Cancer Center Korea between January 2000 and April 2011. This retrospective study was approved by the Institutional Review Board of the National Cancer Center (NCCNCS-12-597). A hereditary background in this study was defined as the existence of a primary cancer concurrent with endometrial cancer, that is, colon cancer and endometrial cancer, suggestive of Lynch syndrome, ovarian cancer and endometrial cancer, suggestive of Lynch syndrome and/or hereditary breast ovarian cancer syndrome, and breast cancer and endometrial cancer, suggestive of Cowden syndrome. The clinicopathological factors analyzed were age at the time of diagnosis, body mass index (BMI), parity, menstrual history, history of diabetes, tumor histology, tumor grade, the International Federation of Gynecology and Obstetrics stage, and involvement of the lower uterine segment.

In the cases of synchronous cancers of the endometrium and ovary, all surgical specimens were examined by gynecologic pathologists, according to the criteria described by Scully et al [9]. The pathological criteria for synchronous primary cancers of the endometrium and ovary were as follows: (1) histological dissimilarity of tumors; (2) no or only superficial myometrial invasion of endometrial tumor; (3) no vascular space invasion of endometrial tumor; (4) atypical endometrial hyperplasia additionally present; (5) absence of other evidence of spread of endometrial tumor; (6) unilateral ovarian tumor (80–90% of cases); (7) ovarian tumors located mainly in the parenchyma; (8) no vascular space invasion, surface implants, or predominant hilar location in the ovary; (9) absence of other evidence of the spread of ovarian tumor; and (10) presence of ovarian endometriosis [9]. In the cases of synchronous cancers of the endometrium and breast or endometrium and colon, the records of the patients with a preexisting diagnosis of breast or colon cancer were examined to determine whether the endometrial cancer was a concurrent disease or a metastatic one. It has been reported that the risk of tamoxifen-related endometrial cancer increases proportionally with the duration of tamoxifen use irrespective of menopausal status [10]. In the current study, endometrial cancer patients who used tamoxifen for 5 or more years (odds ratio, 2.4; 95% confidence interval, 1.8–3.0) were excluded [10].

All oncological treatments were performed in accordance with institutional guidelines, which were based on the National Comprehensive Cancer Network (NCCN) guideline and the Health Insurance Review and Assessment Service (HIRA) in Korea. All patients underwent total hysterectomy and pelvic lymph node dissection, with or without para-aortic lymph node dissection. Adjuvant pelvic radiation after complete surgical staging was performed in patients with potential adverse risk factors such as age, grade, lymphovascular invasion, tumor size, lower uterine involvement, and outer-third myometrial invasion [11–13].

Adjuvant chemotherapy was performed in patients with Stage IVb disease or concurrent ovarian cancer. However, the endometrial patients with concurrent ovarian cancer, which was stage Ia or Ib and Grade 1 tumor, were not performed adjuvant chemotherapy based on the NCCN guideline. We reviewed the medical records, such as the stages for each cancer, tumor markers, and imaging studies, to exclude the possibility of recurrence from colon or breast cancer. In this study, we excluded all patients who had uncertain recurrence from endometrial or colon/breast cancer.

Chi-square test and *t* tests were used to evaluate differences in patient and tumor characteristics between the sporadic and hereditary endometrial cancer groups including age at diagnosis, menopause, BMI, parity, diabetes, stage, tumor grade, endometrial cancer histology, and lower uterine segment involvement. Endometrial cancer-specific survival was used for analysis. Kaplan–Meier survival analyses were generated and compared by the log-rank test. A p value <0.05 was taken to be significant. All the analyses were performed using STATA 11.0 (STATACORP, College Station, TX, USA) and SPSS 21.0 (IBM-SPSS Inc., Chicago, IL, USA).

Results

The clinicopathological characteristics of endometrial cancer according to hereditary components are presented in Table 1. Among 282 patients with endometrial cancer in the study population, 20 patients (7.1%) had a hereditary predisposition: 10 patients (3.5%) had ovarian cancer, six patients (2.1%) had breast cancer, and four patients (1.4%) had colon cancer. The mean age of the total endometrial cancer patients at onset was 53.2 ± 12.1 years (range, 23–81 years). The mean age at diagnosis of endometrial cancer for the hereditary predisposition was not statistically different compared with the mean age at diagnosis for the sporadic endometrial cancer group (55 years and 53 years, respectively, $p = 0.791$). The percentage of patients diagnosed at an age younger than 50 years in the hereditary endometrial cancer group was 40%, and there were no significant differences in this percentage between the sporadic endometrial cancer group and the endometrial cancer with a hereditary predisposition group ($p = 0.428$). The BMI and incidence of diabetes were not significantly different between the sporadic endometrial cancer group and the endometrial cancer with a hereditary predisposition group ($p = 0.434$ and $p = 0.149$, respectively).

As shown in Table 2, both cancers were detected simultaneously in the majority of the synchronous cases (55%). All ovarian cancers were found concurrently with endometrial cancer. However, only one colorectal cancer was diagnosed concurrently with endometrial cancer. Apart from the simultaneous cases, the interval between the first and second tumor was <2 years in four cases, <3 years in one case, and <5 years in one case, and >5 years in three cases. Among the six patients who had breast cancer, two patients had taken tamoxifen for 26 months and 16 months, respectively, before the diagnosis of endometrial cancer. The interval from the last dose of tamoxifen to the diagnosis of endometrial cancer was 46.1 months and 1 month, respectively. BMI of two patients who had taken tamoxifen was 26.7 and 21.8 and there was no familial history of cancers.

The majority of the women in the hereditary predisposition group presented at Stage I. However, the proportion of patients who presented at Stage I was not statistically different between the group with a hereditary predisposition and the group with sporadic endometrial cancer (85% and 76%, respectively, $p = 0.561$). Tumor grade and histological type were not significantly different between the two groups ($p = 0.804$ and $p = 0.999$, respectively). Lower uterine segment involvement, a factor suggestive of hereditary endometrial cancer, was not different between the group with endometrial cancer and a hereditary predisposition and the group with sporadic endometrial cancer (15% and 11%, $p = 0.471$).

The median follow-up period was 60 months (range, 1–102 months). There were three cases of recurrence (15%); all patients