Introduction

Endometrial cancer is the sixth most common neoplasm in women and the 14th most common type of cancer worldwide [1]. In the United States (U.S.), it is the most frequently occurring cancer of the female genital tract [2-4]. Endometrial cancer is independent of age and occurs in women of reproductive age to the elderly [5]. In the U.S., the incidence of endometrial cancer is rising, possibly due to the increase in the obesity and physical inactivity in the population [6, 7]. Fortunately, endometrial cancer is often identified at an early, localized, and treatable stage [2-4]. The most common type of endometrial cancer cell type is endometrioid adenocarcinoma, which is composed of malignant glandular epithelial elements (although an admixture of squamous metaplasia also occurs) [4, 8], followed by adenocan-thomas (benign squamous components), and adenosquamous carcinomas (malignant squamous components) [8]. Other uterine tumor cell types include papillary serous (5–10%), clear cell (1–4%), mucinous (1%), squamous cell (< 1%), mixed (10%), and undifferentiated [4].

Several factors influence the risk of developing endometrial cancer, including: drugs/therapies that affect hormone levels, such as birth control, the number of menstrual cycles over a lifetime, pregnancy, certain ovarian tumors, and polycystic ovarian syndrome [4, 6]. Obesity, age, diet, and exercise can influence the risk of endometrial cancer [9].

Treatment for endometrial cancer depends upon the type and stage of cancer. Standard treatment consists of primary hysterectomy and bilateral salpingo-oophorectomy. Removal of lymph nodes is contingent on histological factors (ie, subtype, tumor grade, involvement of the lymphovascular space), disease stage, patient characteristics (ie, age and comorbidities), and national and international guidelines [10]. Treatment may also involve radiation therapy, hormonal therapy, targeted therapy, and/or chemotherapy [3, 10].

Cancer survivors, including endometrial cancer survivors, have an increased risk of developing a second cancer compared with the general population [11]. One study found that compared with matched general population, the survivors of endometrial cancer had about three-fold higher risk of developing second cancer [11]. The increased risk may result from several factors including life-style, genetic

Summary

The aim of this study was to assess risk factors associated with developing second cancer in premenopausal and postmenopausal endometrial cancer survivors using data from the Surveillance, Epidemiology, and End Results (SEER) database. Multivariate analysis revealed that for both groups age was a risk factor for second cancer development. For premenopausal women, being white versus black, having endometrioid adenocarcinoma compared with other histological types increased the risk of developing a second cancer ($p$ values ≤ 0.018). For postmenopausal women, being Non-Spanish-Hispanic-Latino versus Spanish-Hispanic-Latino, having squamous cell carcinoma versus endometrioid adenocarcinoma, N0 compared with N1 nodes, M0 versus M1 metastasis, and no surgery or radiotherapy compared with surgery alone or surgery plus radiotherapy increased the likelihood of developing second cancer ($p$ values ≤ 0.012). The results of Cox proportional hazard analysis indicated that premenopausal and postmenopausal women with endometrial cancer who underwent surgery plus radiotherapy showed the greatest benefit with respect to cause-specific survival (adjusted HR 0.192, 95% CI: 0.135 to 0.274, and adjusted HR 0.206, 95% CI: 0.184 to 0.230, respectively). In summary, risk factors for second cancer in survivors of endometrial cancer differ between premenopausal and postmenopausal women, and suggests that the two groups of women should be managed differently.

Key words: Endometrial cancer; Premenopausal; Postmenopausal; Second primary cancer; Prognosis; Surveillance Epidemiology and End Results (SEER) Program.
susceptibility, and administration of radiation and chemotherapy [11, 12]. In a large U.S. Surveillance, Epidemiology and End Results (SEER)-based study, radiation therapy was associated with about 8% of second cancers. The other second cancers were proposed to be due to other factors, such as lifestyle and genetics [12].

The purpose of the current study was to assess the risk factors associated with developing second cancers among endometrial survivors, both premenopausal and postmenopausal, utilizing the SEER Program database.

### Materials and Methods

The data for the present study were derived from the SEER Program Research Data (1973-2013), National Cancer Institute (NCI), released April 2016. The SEER program provides information on cancer statistics, including survival and patient demographics, among the U.S. population. SEER collects data on cancer from a number of locations throughout the U.S. The population covered by SEER is comparable to the general U.S. population with regard to education and measures of poverty.

All SEER data are de-identified and analysis of the data does not require institutional review board (IRB) approval or informed consent by patients. The present authors obtained permission...
Patients diagnosed with endometrial carcinoma (ICD-O-3 site code C541) from 2004 to 2013 were included. The identified population was stratified into premenopausal (< 50 years of age) and postmenopausal (≥ 50 years of age) patients.

The primary endpoint was overall cancer-specific mortality, specifically from advance stage cancer (ie, Stages III and IV). This was determined from the data for cause-specific survival that indicated the person died due to their cancer. Overall cancer-specific mortality was calculated from the first day of diagnosis to the date of death, which was indicated as “vital status” in the SEER database.

The secondary endpoint was the incidence of a second primary malignancy that occurred after the initial diagnosis of endometrial cancer. All available second malignancies were extracted and grouped under functional system. The time interval from the initial endometrial diagnosis to the second neoplasm was also calculated.

Independent variables for comparison included patient demographics (age at diagnosis, marital status, race/ethnicity, NHIA Hispanic race), disease characteristics [histology, American Joint Committee on Cancer (AJCC) TNM classification system (6th edition)], and treatment modalities (no treatment performed, cancer-directed surgery, radiation therapy, and both surgery and radiation therapy).

Comparability between the two groups was tested using independent two sample t-test for continuous variables and Chi-square test/Fisher’s exact test for categorical variables. Continuous variables were represented as mean and standard deviation (SD) and categorical data were represented by number (n) and percentage (%). Kaplan-Meier method with log-rank test was used to compare cause-specific survival between the groups. Univariate logistic regression analysis was performed to analyze the odds ratio (OR) of significant factors associated with development of a second cancer. Variables having a p-value < 0.05 in the univariate analysis were selected and evaluated by multivariate regression model with stepwise selection. In addition, Cox proportional hazard regression was performed to analyze the hazard ratio (HR) of significant factors associated with cause-specific survival. All p values were two-sided and <0.05 were considered statistically significant. Statistical analyses were performed using the statistical software package SPSS version 22.

**Results**

A total of 93,953 women with primary endometrial cancer were identified in the SEER database during the period of 2004–2013. Of this cohort, 13,613 patients were premenopausal and 80,340 were postmenopausal (Table 1). In the overall study population, most women were white (82%), married (81%), and were non-Spanish-Hispanic-Latino (89%). The most frequent type of endometrial cancer was endometrioid carcinoma (90%). Overall, 1.1% of cancer cases were AJCC Stage 0, 71.6% were Stage I, 7.6% were Stage II, 13.3% were Stage III, and 6.5% were Stage IV. In addition, a total of 66.5% of patients with primary endometrial cancer had been treated with surgery.

Significant differences between premenopausal and postmenopausal women were observed between groups with respect to age, race, marital status, origin recode NHIA, type of histology, T stages, nodes, metastasis AJCC stages, and treatments (all p < 0.001) (Table 1).

A total of 12,294 patients died from endometrial cancer during the study period. A significant difference in cause-specific survival between premenopausal and postmenopausal women was observed (log-rank test, p < 0.001) (Figure 1). Premenopausal women had longer cause-specific survival than postmenopausal women. The one-, three-, and five-year cause-specific survival rates were 96.6%, 93.6%, and 92.4%, respectively, for premenopausal patients, and 93.0%, 85.9%, and 82.7% for postmenopausal women. Of these 93,953 patients, 6,590 (7.0%) had a second cancer between 2004 and 2013. Postmenopausal patients with endometrial cancer were 2.89-times more likely to develop breast cancer than premenopausal patients (data not shown). The results of univariate logistic regression analysis indicated the following factors were significantly associated with development of second cancer: age, race, type of histology, and treatments.

Variables found significant in univariate analysis were used for multivariate logistic regression. Multivariate analysis found that age (adjusted OR: 1.026, p < 0.001), race (black vs. white: adjusted OR: 0.681, p = 0.018), and type of histology (others vs. endometrioid adenocarcinoma: adjusted OR: 0.660, p = 0.007) were significantly associated with the likelihood of development of second cancer in premenopausal women (Table 2). For postmenopausal women, multivariate analysis found age (adjusted OR: 1.014, p < 0.001), origin recode NHIA in the SEER database (Spanish-Hispanic-Latino vs. Non-Spanish-Hispanic-Latino: adjusted OR: 0.816, p = 0.018), type of histology (squamous cell carcinoma vs. endometrioid adenocarcinoma: adjusted OR: 1.862, p = 0.012), nodes (N1 vs. N0: adjusted OR: 0.870, p = 0.011), metastasis (M1 vs. M0: adjusted OR: 0.619, p < 0.001), and treatments (surgery performed vs. no surgery or radiotherapy: adjusted OR: 1.628, p < 0.001; surgery PLUS radiotherapy vs. radiotherapy only: adjusted OR: 0.848, p = 0.042) were found significant.
no surgery nor radiotherapy; adjusted OR: 1.704, \( p < 0.001 \) were significantly associated with the likelihood that postmenopausal women developed second cancer (Table 2).

The present authors further determined the prognostic factors for cause-specific survival in patients with Stage III and IV endometrial cancer by premenopausal and postmenopausal women. Variables having a \( p \)-value < 0.05 in the univariate analysis were selected and evaluated by multivariate Cox proportional hazard regression models with stepwise selection. The results of multivariate analysis implied that premenopausal women with endometrial cancer who underwent surgery plus radiotherapy showed the most benefit with respect to cause-specific survival (adjusted HR 0.192; 95%CI: 0.135 to 0.274) after controlling for race, type of histology, nodes, and metastasis (Table 3). Similar to premenopausal women, after controlling for age, race, type of histology, T stage, nodes and metastasis, and patients who underwent surgery plus radiotherapy showed the greatest benefit for cause-specific survival (adjusted HR 0.206; 95%CI: 0.184 to 0.230).

**Discussion**

Endometrial cancer survivors have a risk of developing second cancer. The factors that influence this risk are not well understood. The aim of this study was to assess risk factors associated with developing second cancer in premenopausal and postmenopausal endometrial cancer survivors using data from the SEER database. The study found that premenopausal women had longer cause-specific survival than postmenopausal women, and that postmenopausal patients with endometrial cancer were almost three times more likely to develop breast cancer compared with premenopausal patients. Risk factors for second cancer differed between premenopausal and postmenopausal endometrial cancer survivors. Multivariate analysis found for both groups that age was a risk factor for second cancer development. The analysis found that for premenopausal women being white versus black and having endometrial cancer compared with other histological types, increased the risk of developing a second cancer (\( p \)-values \( \leq 0.018 \)). For postmenopausal women, being non-Spanish-Hispanic-Latino versus Spanish-Hispanic-Latino, having squamous cell carcinoma versus endometrioid adenocarcinoma, N0 compared with N1 nodes, M0 versus M1 metastasis, and no surgery or radiotherapy compared with surgery alone or surgery plus radiotherapy, increased the likelihood of developing second cancer (\( p \)-values \( \leq 0.012 \)). The results of Cox proportional hazard analysis indicated having surgery plus radiotherapy showed the greatest benefit with respect to cause-specific survival for both premenopausal and postmenopausal women with endometrial cancer (adjusted HR 0.192; 95%CI: 0.135 to 0.274; and adjusted HR 0.206; 95%CI: 0.184 to 0.230, respectively). The differences between premenopausal and postmenopausal survivors of endometrial cancer with respect to risk factors for development of second cancer suggests the two groups of women should be managed differently.
Table 3. — The result of Cox proportional hazard for the prognostic factors for CSS in patients with Stage III and IV endometrial cancer by premenopausal and postmenopausal women.

| Characteristic                        | Premenopausal women | Postmenopausal women |
|---------------------------------------|---------------------|----------------------|
|                                      | Adjusted hazard ratio (95%CI) | p-value | Adjusted hazard ratio (95%CI) | p-value |
| Age (years)                           | —                   | 1.027 (1.024, 1.030) | <0.001* |
| Marital status                        |                     |                      |        |
| Married vs. single                    | 0.958 (0.787, 1.168) | 0.673                |         |
| Race                                  |                     |                      |        |
| Black vs. white                       | 1.684 (1.272, 2.230) | <0.001*              | 1.479 (1.371, 1.594) | <0.001* |
| American Indian/Alaska Native vs. white| 1.214 (0.495, 2.973) | 0.672                | 1.384 (0.940, 2.036) | 0.099   |
| Asian or Pacific Islander vs. white   | 0.885 (0.668, 1.174) | 0.397                | 0.941 (0.840, 1.053) | 0.290   |
| Race                                  |                     |                      |        |
| Clear cell adenocarcinoma vs. endometrioid adenocarcinoma | 1.521 (0.807, 2.868) | 0.195                | 1.246 (1.085, 1.431) | 0.002*  |
| Squamous cell carcinoma vs. endometrioid adenocarcinoma | 0.965 (0.492, 1.893) | 0.918                | 1.442 (0.999, 2.082) | 0.050   |
| Others vs. endometrioid adenocarcinoma | 1.766 (1.322,2.358) | <0.001*              | 1.798 (1.657, 1.952) | <0.001* |
| Histology                             |                     |                      |        |
| T stage                               |                     |                      |        |
| T1 vs. T0                             |                     |                      |        |
| T2 vs. T0                             | 1.300 (0.578, 2.927) | 0.526                |         |
| T3 vs. T0                             | 1.823 (0.809, 4.108) | 0.148                |         |
| T4 vs. T0                             | 2.432 (1.084, 5.455) | 0.031*               |         |
| Nodes                                 |                     |                      |        |
| N1 vs. N0                             | 1.567 (1.289, 1.906) | <0.001*              | 1.540 (1.450, 1.635) | <0.001* |
| Metastasis                            |                     |                      |        |
| M1 vs. M0                             | 4.100 (3.334, 5.042) | <0.001*              | 2.526 (2.369, 2.693) | <0.001* |
| Treatment                             |                     |                      |        |
| Surgery performed vs. no surgery nor radiotherapy | 0.274 (0.199, 0.377) | <0.001*              | 0.299 (0.271, 0.330) | <0.001* |
| Radiotherapy performed vs. no surgery nor radiotherapy | 1.068 (0.710, 1.609) | 0.751                | 0.688 (0.598, 0.791) | <0.001* |
| Surgery PLUS radiotherapy vs. no surgery nor radiotherapy | 0.192 (0.135, 0.274) | <0.001*              | 0.206 (0.184, 0.230) | <0.001* |
| Second cancer                         |                     |                      |        |
| Yes vs. no                            | 0.730 (0.502, 1.061) | 0.099                | 0.622 (0.547,0.708) | <0.001* |

—Not included in the multivariate analysis. *Indicates a significant factor, p < 0.05.
an increased risk was found in the radiation field and after a long latency period (>10 years) [20].

The study has several limitations that should be considered when interpreting the results. The main limitation of the SEER data, like any observational study of treatment effects, is the lack of treatment randomization which may confound the results. In addition, the SEER database does not give information on smoking and other treatments, including chemotherapy and hormonal therapy for endometrial cancer. Hence, it is not possible to evaluate how these factors may impact second cancer development and also the present findings, consequently, may not entirely reflect that of the real-world setting. The SEER database included information through 2013, therefore, it is unclear if more recent changes in treatment of endometrial cancer may affect outcomes.

In summary, this study found that risk factors for second cancer in survivors of endometrial cancer differ between premenopausal and postmenopausal women, and suggests that the two groups of women should be managed differently.

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References

[1] World Health Organization, International Agency for Research on Cancer: GLOBOCAN 2012: Estimated cancer incidence, mortality, and prevalence worldwide in 2012. Population fact sheets. 2012. Available at: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx.

[2] Baden L.R., Bensinger W., Angarone M., Casper C., Dubberke E.R., Freifeld A.G., et al.: “National Comprehensive Cancer Network clinical practice guidelines in oncology: Prevention and treatment of cancer related infections, version 1.2012 2012”. Available at: http://www.nccn.orgprofessionals/physician_gls/pdf/infections.pdf.

[3] American Cancer Society: “Uterine (endometrial) cancer: detailed guide”. Available at: http://www.cancer.org/cancer/endometrialcancer/detailedguide/endometrial-cancer-detailed-guide-toc.

[4] “Uterine cancer treatment—health professional version (PDQ)”. Available at: https://www.cancer.gov/types/uterine/hp/endometrial-treatment-pdq.

[5] Zeng X.Z., Lavoue V., Lau S., Press J.Z., Abitbol J., Gotlieb R., How J., et al.: “Outcome of robotic surgery for endometrial cancer as a function of patient age”. Int. J. Gynecol. Cancer, 2015, 25, 637.

[6] Amanat F., Moerman P., Neven P., Timmerman D., Van Limbergen E., Vergote I.: “Endometrial cancer”. Lancet, 2005, 366, 491.

[7] Nevadansky N.S., Van Aarsdale A., Strickler H.D., Moa del A., Kaur G., Levitt J., et al.: “Obesity and age at diagnosis of endometrial cancer”. Obstet. Gynecol., 2014, 124, 300.

[8] Plataniotis G., Castiglione M., Group E.G.W.: “Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up”. Ann. Oncol., 2010, 21, v41.

[9] Beavis A.L., Smith A.J., Fader A.N.: “Lifestyle changes and the risk of developing endometrial and ovarian cancers: opportunities for prevention and management”. Int. J. Womens Health, 2016, 8, 151.

[10] Morice P., Leary A., Creutzberg C., Abu-Rustum N., Darai E.: “Endometrial cancer”. Lancet, 2016, 387, 1094.

[11] Wiltink L.M., Nout R.A., Fiocco M., Moershочек-Kranenbarg E., Jürgenliemk-Schulz I.M., Jøsne J.J., et al.: “No Increased Risk of Second Cancer After Radiotherapy in Patients Treated for Rectal or Endometrial Cancer in the Randomized TME, PORTEC-1, and PORTEC-2 Trials”. J. Clin. Oncol., 2015, 33, 1640.

[12] Berrington de Gonzalez A., Curtis R.E., Kay S.F., Gilbert E., Lamart S., Berg C.D., et al.: “Proportion of second cancers attributable to radiotherapy treatment in adults: a cohort study in the US SEER cancer registrars”. Lancet Oncol., 2011, 12, 353.

[13] Herrera F.G., Cruz O.S., Achari C., Bourhis J., Oszakich M.: “Long-term outcome and late side effects in endometrial cancer patients treated with surgery and postoperative radiation therapy”. Ann. Surg. Oncol., 2014, 21, 2390.

[14] Martin-Dunlap T.M., Wachtel M.S., Margenthaler J.A.: “Outcomes for patients who are diagnosed with breast and endometrial cancer”. Oncol. Lett., 2013, 6, 1103.

[15] Mell L.K., Carmona R., Gulaya S., Lu T., Wu J., Saenz C.C., Vaida F.: “Cause-specific effects of radiotherapy and lymphadenectomy in stage I-II endometrial cancer: a population-based study”. J. Natl. Cancer Inst., 2013, 105, 1656.

[16] Zwahlen D.R., Ruben J.D., Jones P., Gagliardi F., Millar J.L., Schneider U.: “Effect of intensity-modulated pelvic radiotherapy on second cancer risk in the postoperative treatment of endometrial and cervical cancer”. Int. J. Radiat. Oncol. Biol. Phys., 2009, 74, 539.

[17] de Boer S.M., Nout R.A., Jürgenliemk-Schulz I.M., Jøsne J.J., Lutgens L.C., van der Steen-Banasik E.M., et al.: “Long-Term Impact of Endometrial Cancer Diagnosis and Treatment on Health-Related Quality of Life and Cancer Survivorship: Results From the Randomized PORTEC-2 Trial”. Int. J. Radiat. Oncol. Biol. Phys., 2015, 93, 797.

[18] Onsrud M., Cvancarova M., Hellebust T.P., Tropé C.G., Kristensen G.B., Lindemann K.: “Long-term outcomes after pelvic radiation for early-stage endometrial cancer”. J. Clin. Oncol., 2013, 31, 3951.

[19] Brown A.P., Neeley E.S., Werner T., Soisson A.P., Burt R.W., Gaffney D.K.: “A population-based study of subsequent primary malignancies after endometrial cancer: genetic, environmental, and treatment-related associations”. Int. J. Radiat. Oncol. Biol. Phys., 2010, 78, 127.

[20] Kumar S., Shah J.P., Bryant C.S., Awonuga A.O., Imudia A.N., Ruterbusch J.J., et al.: “Second neoplasms in survivors of endometrial cancer: impact of radiation therapy”. Gynecol. Oncol., 2009, 113, 233.

Corresponding Authors:

XUEQING WANG, Ph.D.
Department of Obstetrics and Gynecology of Beijing Jishuitan Hospital, The Fourth Teaching Hospital of Beijing Medical College, NO 31, Xinjiekou east street, Xicheng district, Beijing (China)
e-mail: xueqingwang@eduusbm.com