EJGO European Journal of Gynaecological Oncology

Original Research

Characteristics and prognostic factors among premenopausal versus postmenopausal patients with advanced endometrial cancer: a SEER-based analysis

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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 $\leq$ 0.018). For postmenopausal women, being Non-Spanish-Hispanic-Latino versus Spanish-Hispanic-Latino, having squamous cell carcinoma versus endometroid 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 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.

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 adenoacanthomas (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

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Published: 15 February 2020

Eur. J. Gynaecol. Oncol. - ISSN: 0392-2936
XLI , n. 1, 2020
doi: 10.31083/j.ejgo.2020.01.5172

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Table 1. — *Demographics and pathological features between premenopausal and postmenopausal victims of endometrial cancer (n=93,953).*

	Premenopausal women (n=13,613)	Postmenopausal women (n=80,340)	*p*-value
Age (years)	42.25±6.03	64.83±9.78	<0.001*
Race, n (%)[a]			<0.001*
White	10301 (76.6%)	66110 (82.9%)	
Black	1135 (8.4%)	7599 (9.5%)	
American Indian/Alaska Native	180 (1.3%)	463 (0.6%)	
Asian or Pacific Islander	1824 (13.6%)	5539 (6.9%)	
Marital status, n (%)[b]			<0.001*
Single	4503 (35.0%)	12699 (16.7%)	
Married	8378 (65.0%)	63348 (83.3%)	
Origin recode NHIA, n (%)			<0.001*
Non-Spanish-Hispanic-Latino	10752 (79.0%)	72776 (90.6%)	
Spanish-Hispanic-Latino	2861 (21.0%)	7564 (9.4%)	
Histology, n (%)			<0.001*
Endometrioid adenocarcinoma	12164 (89.4%)	72035 (89.7%)	
Clear cell adenocarcinoma	65 (0.5%)	1104 (1.4%)	
Squamous cell carcinoma	76 (0.6%)	241 (0.3%)	
Others	1308 (9.6%)	6960 (8.7%)	
T stage, n (%)[c]			<0.001*
T0	4 (0.0%)	20 (0.0%)	
Tis	254 (2.1%)	660 (0.9%)	
T1	9535 (77.8%)	55511 (75.1%)	
T2	1109 (9.1%)	7179 (9.7%)	
T3	1207 (9.9%)	9150 (12.4%)	
T4	141 (1.2%)	1370 (1.9%)	
Nodes, n (%)[d]			<0.001*
N0	11355 (92.9%)	66305 (90.0%)	
N1	874 (7.1%)	7357 (10.0%)	
Metastasis, n (%)[e]			<0.001*
M0	11856 (95.8%)	70330 (94.0%)	
M1	526 (4.2%)	4501 (6.0%)	
AJCC stage, n (%)			<0.001*
Stage 0	254 (2.1%)	660 (0.9%)	
Stage I	9128 (75.3%)	52194 (71.0%)	
Stage II	906 (7.5%)	5583 (7.6%)	
Stage III	1249 (10.3%)	10107 (13.7%)	
Stage IV	587 (4.8%)	5020 (6.8%)	
Treatment, n (%)[f]			<0.001*
No surgery nor radiotherapy	891 (6.7%)	4494 (5.7%)	
Surgery performed	10206 (76.7%)	53443 (68.0%)	
Radiotherapy performed	150 (1.1%)	1612 (2.1%)	
Surgery PLUS radiotherapy	2055 (15.4%)	19082 (24.3%)	

*[a] Unknown, n=802. [b] Missing value, n=5,025. [c] Not applicable/tumor cannot be evaluated, n=7,813. [d] Not applicable/nearby lymph nodes cannot be evaluated, n=8,062. [e] Not applicable/distant spread cannot be evaluated, n=6,740. [f] Missing value, n=2,020. * Indicates a significant difference among the groups, p < 0.05.*

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

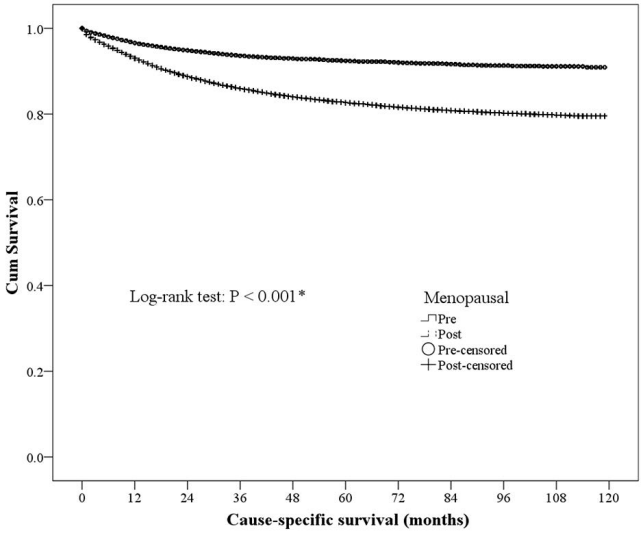

Figure 1. — Kaplan–Meier curves of cause-specific survival between premenopausal and postmenopausal women.

(16209-Nov2017) from the NCI to access the research data file in the SEER program.

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.*

Table 2. — *The significant risk factors associated with developing second cancer in premenopausal and postmenopausal women with endometrial cancer.*

	Premenopausal women		Postmenopausal women	
	Adjusted odds ratio (95%CI)	*p*-value	Adjusted odds ratio (95%CI)	*p*-value
Age (years)	1.026 (1.012, 1.040)	<0.001*	1.014 (1.011, 1.018)	<0.001*
Marital status				
Married *vs.* single	—		1.047 (0.965, 1.135)	0.268
Race				
Black *vs.* white	0.681 (0.496, 0.935)	0.018*	0.966 (0.869, 1.074)	0.528
American Indian/Alaska Native *vs.* white	0.481 (0.197, 1.175)	0.108	1.302 (0.918, 1.848)	0.139
Asian or Pacific Islander *vs.* white	1.003 (0.810, 1.241)	0.981	0.916 (0.814, 1.031)	0.145
Origin recode NHIA, n (%)				
Spanish-Hispanic-Latino *vs.* non-Spanish-Hispanic-Latino	—		0.816 (0.732, 0.910)	<0.001*
Histology				
Clear cell adenocarcinoma *vs.* endometrioid adenocarcinoma	1.067 (0.385, 2.956)	0.901	1.046 (0.818, 1.337)	0.718
Squamous cell carcinoma *vs.* endometrioid adenocarcinoma	1.969 (0.884, 4.388)	0.097	1.862 (1.149, 3.016)	0.012*
Others *vs.* endometrioid adenocarcinoma	0.660 (0.489, 0.890)	0.007*	1.062 (0.918, 1.230)	0.418
Nodes				
N1 *vs.* N0	—		0.870 (0.781, 0.969)	0.011*
Metastasis				
M1 *vs.* M0	—		0.619 (0.521, 0.736)	<0.001*
Treatment				
Surgery performed *vs.* no surgery or radiotherapy	1.315 (0.913, 1.894)	0.142	1.628 (1.322, 2.004)	<0.001*
Radiotherapy performed *vs.* no surgery nor radiotherapy	1.348 (0.623, 2.916)	0.449	1.119 (0.813, 1.541)	0.491
Surgery PLUS radiotherapy *vs.* no surgery or radiotherapy	1.276 (0.852, 1.909)	0.237	1.704 (1.378, 2.107)	<0.001*

*— Not included in the multivariate analysis.*Indicates a significant factor, $p < 0.05$.*

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 ≤ 0.018). For postmenopausal women, being non-Spanish-Hispanic-Latino versus Spanish-Hispanic-Latino, having squamous cell carcinoma versus endometroid 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 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.

Only a few studies have evaluated the long-term outcomes, including the development of second cancer, in en-

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.*

	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
Histology				
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*
T stage				
T1 *vs.* T0	—		1.300 (0.578, 2.927)	0.526
T2 *vs.* T0	—		1.823 (0.809, 4.108)	0.148
T3 *vs.* T0	—		2.432 (1.084, 5.455)	0.031*
T4 *vs.* T0	—		3.042 (1.355, 6.832)	0.007*
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.*

dometrial cancer survivors [11-20]. However, none compared second cancer rate between premenopausal and postmenopausal survivors. Most have evaluated the impact of different therapies, particularly radiation therapy, on the risk of second cancer. Similar to the present findings, they found that type of therapy and age influences the risk of second cancer; consistently younger age was associated with increased likelihood of second cancer [11, 12, 18].

Wiltink *et al.* pooled data from two large studies in women with endometrial cancer (Post Operative Radiation Therapy in Endometrial Cancer [PORTEC-1 and PORTEC-2] to investigate the long-term probability of developing second cancer in this patient population [11]. The combined trials included 1,141 patients. All patients had a hysterectomy without lymphadenectomy and were randomized to receive external-beam radiation therapy or not. In the PORTEC-1 and PORTEC-2 studies, 27.5% and 11.0%, respectively developed second cancer. Patient age affected the likelihood of having second cancer; patients aged ≤ 60 years at diagnosis of primary cancer, in general, had a higher second cancer probability than those > 60 years of age (27.2% *vs.* 23.9%, respectively; $p = 0.01$). The risk of second cancer was 5.5-times higher for patients ≤ 60 years of age compared with matched general population. No difference between external-beam radiation or no radiation treatment groups in frequency of second cancer, regardless of age, was observed. The most common second cancers were skin, breast, gastrointestinal, and urogenital. In contrast, several other studies indicate that radiation therapy may increase the risk of second cancer in survivors of endometrial cancer [18-20]. In a randomized controlled trial of 586 patients with Stage I endometrial cancer an increased risk of second cancer was observed in patients treated with external-beam radiation therapy compared with vaginal brachytherapy (HR, 1.42; 95% CI, 1.01 to 2.00), and the risk was even greater for women < 60 years of age (HR, 2.02; 95% CI, 1.30 to 3.13) [18]. A retrospective cohort study using SEER data from 69,739 patients with endometrial cancer found patients treated with external-beam radiation therapy developed more second cancers compared with patients treated with radiotherapy ($p < 0.001$), particularly second colon, rectal, bladder, vaginal, and soft tissue cancers (p values ≤ 0.04) [19]. Patients treated with vaginal brachytherapy only showed an increased risk of second cancer of the urinary bladder ($p = 0.006$) [19]. Another SEER-based study evaluated the association between radiation therapy and second cancer in 90,502 patients with endometrial cancer [20]. They found that the relative risk for developing second cancer following radiation therapy was 1.25 (95% CI, 1.20 to 1.29), and

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.

Acknowledgements

The authors acknowledge the efforts of the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER database.

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