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## Utilization and Outcomes of Ovarian Conservation in Premenopausal Women With Endometrial Cancer

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### Abstract

**Objective**—To examine the trends in use and safety of ovarian conservation in young women with early-stage endometrial cancer undergoing hysterectomy.

**Methods**—We conducted a population-based analysis. The National Cancer Database (NCDB) was used to identify women <50 years of age with stage I endometrioid adenocarcinoma of the endometrium who underwent hysterectomy from 1998–2012. Patients were stratified based on whether they underwent oophorectomy or had ovarian conservation. Multivariable models were used to examine predictors of ovarian conservation and the association between ovarian conservation and survival.

**Results**—The cohort of 15,648 women included 1121 (7.2%) who had ovarian conservation and 14,527 (92.8%) who underwent oophorectomy. The rate of ovarian conservation was relatively stable from 6.9% (95% CI, 4.9–9.7%) in 1998 to 7.1% (95% CI, 5.8–8.7%) in 2012 (P=0.91). Ovarian conservation was more commonly performed in younger women, black women, those with low grade and earlier stage tumors, and in women treated at community hospitals. In a multivariable model, ovarian conservation was not independently associated with survival (HR=0.94; 95% CI, 0.65–1.37). Similarly, in a Kaplan-Meier analysis, there was no association between ovarian conservation and survival (P=0.19).

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**Conclusion**—Ovarian conservation does not adversely affect survival for women with early stage endometrial cancer. Despite the oncologic safety of ovarian conservation, the majority of young women with endometrial cancer still undergo oophorectomy at the time surgery.

## Introduction

Treatment for most women with localized endometrial cancer begins with hysterectomy in combination with bilateral salpingo-oophorectomy and possibly lymph node evaluation.<sup>1</sup> In young women, hysterectomy results in loss of fertility, while oophorectomy induces surgical menopause with the sequelae of estrogen deprivation.<sup>2</sup> This is particularly important as the outcome of early-stage endometrial cancer is excellent and most young women will be cured of the disease.

The potential benefits of ovarian preservation in the general population have now been well established.<sup>3–8</sup> A decision analysis of women undergoing hysterectomy for benign indications suggested that the benefits of ovarian conservation outweighed the risks until age 65.<sup>4</sup> Follow-up from the Nurses Health Study found that oophorectomy was associated with increased mortality in women <50 years of age who never used estrogen therapy.<sup>7</sup> Similarly, a large cohort study reported that oophorectomy before age 45 years was associated with an increased risk of cardiovascular and all-cause mortality.<sup>5,6</sup>

Despite the potential benefits of ovarian conservation, preservation of the ovaries in women undergoing hysterectomy for benign indications is highly variable.<sup>9,10</sup> For premenopausal women with endometrial cancer, the decision to perform oophorectomy at the time of hysterectomy is further complicated by the potential of the ovaries to harbor occult metastatic disease and provide estrogenic stimulation. To date, observational studies have suggested that ovarian conservation is safe in young women with early-stage endometrial cancer.<sup>11–17</sup>

Given the potential benefits of ovarian preservation in young women with endometrial cancer, we conducted a population-based analysis to examine the trends and oncologic safety of ovarian conservation in women <50 years of age.

## Materials and Methods

Patient level data from the National Cancer Data Base (NCDB) was used for analysis. NCDB is a nationwide registry developed by the American College of Surgeons and American Cancer Society.<sup>18,19</sup> We utilized the Participant Use Files from the NCDB. NCDB records all patients with newly diagnosed invasive tumors from over 1500 Commission on Cancer (CoC) affiliated hospitals from throughout the United States. The database includes information on patient demographics, tumor characteristics, treatment data, staging, and follow-up and survival.<sup>18,19</sup> Data are abstracted by trained cancer registrars, are audited regularly and have been utilized in a large number of outcomes studies.<sup>18</sup> The data did not contain patient identifiers and was deemed exempt by the Columbia University Institutional Review Board.

We selected women <50 years of age with stage I endometrioid adenocarcinomas of the endometrium. Tumors were classified as stage IA (tumor confined to the endometrium or <50% of the myometrium), IB (tumor with >50% myoinvasion) endometrioid or stage INOS if the depth of myoinvasion was not available. Patients with cervical involvement of spread beyond the uterus were excluded (stages II–IV). The cohort was limited to women who underwent hysterectomy between 1998 and 2012 with exclusion of patients who received preoperative radiotherapy. Patients were stratified based on performance of oophorectomy into two groups: ovarian conservation vs. oophorectomy.

Demographic data analyzed included age (<30, 30–34, 35–39, 40–44, 45–49 years), race (white, black, other or unknown), and insurance status (commercial, Medicare, Medicaid, uninsured, other and unknown). Comorbidity was estimated using the Deyo classification of the Charlson comorbidity score (0, 1, 2).<sup>20,21</sup> Tumor grade (1, 2, 3, unknown) was noted for each patient. Hospital characteristics analyzed included region and location (metropolitan, urban, rural). Hospitals were classified as academic/research cancer centers or community cancer centers based on the ACS CoC criteria.<sup>19</sup>

Frequency distributions between categorical variables were compared using  $\chi^2$  tests. Trends in ovarian conservation over time were analyzed using the Cochran-Armitage Trend Test. Rates of ovarian conservation are reported descriptively stratified by age, stage, and tumor grade with 95% confidence intervals.

The associations between the clinical and demographic characteristics and ovarian conservation were examined using multivariable random effects log-linear models with Poisson distribution to account for hospital-level clustering of patients. These models included all clinically relevant demographic, clinical, and oncologic variables. Results are reported as risk ratios (RR) with 95% confidence intervals (CI).

All-cause mortality was estimated as the number of months from the date of diagnosis until death from any cause. Patients alive at last follow-up were censored. Random effects Cox proportional hazards models that account for hospital clustering were developed to estimate the association between ovarian conservation and overall survival, while adjusting for other clinical, demographic, and tumor characteristics. Kaplan-Meier curves were developed to compare survival between women who underwent oophorectomy and those who had ovarian conservation. The log-rank test was used to compare the survival curves. All hypothesis tests were two-sided. A P-value of <0.05 was considered statistically significant. All analyses were conducted using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina).

## Results

A total of 15,648 women <50 years of age with stage I endometrial cancer were identified (Table 1). The cohort included 1121 (7.2%) women who had ovarian conservation and 14,527 (92.8%) women who underwent oophorectomy. The median follow-up time in the ovarian conservation group was 61.9 months (IQR, 32.5–92.0) and 61.0 months (IQR, 33.1–95.1) in the oophorectomy group. The rate of ovarian conservation was 6.9% (95% CI, 4.9–9.7%) in 1998 rose to a peak of 8.5% (95% CI, 6.8–10.5%) in 2002 and then declined

slightly and remained relatively stable at 7.1% (95% CI, 5.8–8.7%) in 2012 (Figure 1) (P=0.93).

Among women with stage IA neoplasms, ovarian conservation decreased with increasing grade from 8.3% (95% CI, 7.7–8.9%) for grade 1 neoplasms, to 5.0% (95% CI, 4.3–5.7%) for grade 2 tumors, and 4.7% (95% CI, 3.4–6.5%) for those with grade 3 carcinomas (Table 2). For each grade, ovarian conservation decreased with advancing age. For example, for women <30 years of age with stage IA, grade 1 tumors, ovarian conservation was utilized in 20.3% (95% CI, 15.7–25.9%) of women and decreased incrementally with age to 5.3% (95% CI, 4.6–6.0) in those age 45–49 years. Likewise, for stage IA, grade 3 tumors, ovarian conservation was used in 7.1% (95% CI, 1.3–31.5%) of those <30 years, 8.3% (95% CI, 4.1–16.2%) of women aged 35–39 years, and 3.9% (95% CI, 2.5–6.2%) of those age 45–49 years.

Ovarian conservation was more common in younger women; compared to women age 45–49 years, the risk ratio for ovarian conservation was 3.64 (95% CI, 2.82–4.69) in women <30 years of age and 2.54 (95% CI, 2.07–3.10) in those age 30–34 years (Table 1). Black women were more likely than white women to have ovarian conservation (RR=1.36; 95% CI, 1.11–1.67). Compared to patients treated at academic centers, women who underwent surgery at community centers were more likely to have ovarian conservation. Compared to women with stage IA neoplasms, those with IB neoplasms were less likely to have ovarian conservation (RR=0.76; 95% CI, 0.58–0.99). Similarly, ovarian conservation decreased with increasing tumor grade.

In a multivariable model, ovarian conservation was not independently associated with survival (HR=0.94; 95% CI, 0.65–1.37) (Table 3). Survival decreased with more advanced stage, higher tumor grade, and older age. Similarly, in a Kaplan-Meier analysis, there was no association between ovarian conservation and survival (P=0.19) (Figure 2, Table 4). Similar findings were noted when the analysis was limited to women with stage IA patients (data for stage IB not displayed given small number of women who had ovarian conservation).

## Discussion

Our findings suggest that ovarian conservation is safe for women with early stage endometrial cancer. Despite the oncologic safety of ovarian conservation, the majority of young women with endometrial cancer still undergo oophorectomy at the time of surgery. Age, stage, and tumor grade are important factors associated with the decision to offer ovarian conservation.

There is a growing body of literature supporting the oncologic safety of ovarian conservation in young women with endometrial cancer.<sup>11–17</sup> In a cohort of women <45 years of age derived from the Surveillance, Epidemiology, and End Results database, ovarian conservation did not negatively affect survival.<sup>13</sup> Similarly, the Korean Gynecologic Oncology group has demonstrated that among women with stage I–II endometrial cancer, ovarian conservation has no effect on either recurrence rates or survival.<sup>14</sup> Our current analysis included over 1100 women who had ovarian preservation and in accord with prior

work, found that conservation of the ovaries for women with stage I tumors did not influence survival.

The reticence to consider ovarian preservation for premenopausal women with endometrial cancer stems from a number of theoretic concerns.<sup>22</sup> Perhaps most importantly, the ovaries may be the site of spread of metastatic endometrial cancer or harbor a concurrent primary ovarian tumor. One analysis of 102 women with endometrial cancer found coexisting ovarian tumors in 25% of women. The majority of the neoplasms (88%) were synchronous primary tumors while the remaining 12% were thought to be metastases.<sup>23</sup> More recent studies have reported a lower rate of ovarian involvement and suggested that the majority of women with ovarian disease have grossly visible ovarian lesions or extrauterine disease.<sup>11,12</sup>

In addition to the possibility of occult metastatic disease, there is concern that ovarian-derived estrogen may stimulate occult endometrial cancer cells. However, studies to date have not found an increase in recurrence rates with ovarian preservation. A study of 495 women with endometrial cancer noted a recurrence rate of 2.3% in patients who had ovarian preservation compared to 2.5% after salpingo-oophorectomy.<sup>14</sup> Likewise, among women who have undergone surgery for endometrial cancer, exogenous hormonal replacement therapy has not been shown to increase recurrence risk or alter prognosis. A prospective study of hormone replacement therapy undertaken by the Gynecologic Oncology Group found no increased risk with exogenous estrogen administration.<sup>24</sup>

While our study benefits from inclusion of a large cohort of young women with endometrial cancer, we acknowledge a number of limitations. First, we lack data on prior surgical history and cannot exclude the possibility that some women had undergone oophorectomy previously. However, given the young age of the women included, it is unlikely that many women would have undergone bilateral oophorectomy prior to the index procedure (hysterectomy). Second, as with any observational study, a number of unmeasured confounders may have influenced the allocation of treatment. We lack data on family history, the presence of inherited genetic abnormalities such as Lynch syndrome, body mass index, and the gross appearance of the ovaries at the time of operation. All of these factors likely affect the choice to perform oophorectomy, and our findings should be interpreted in the context of these and other factors that influence the risk of ovarian neoplasms. Third, while our study included a large number of women, there were a relatively small number of patients with deep myoinvasion and high tumor grade.

Despite multiple observational studies, we noted that the rate of ovarian conservation has changed little over the last decade. There are likely a number of factors contributing to the slow dissemination of ovarian conservation including patient and provider perceptions of increased risk, lack of awareness of the available data, and hesitancy to change established practices.<sup>25,26</sup> However, despite the recognized limitations of observational data, it is unlikely that a randomized controlled trial of oophorectomy versus ovarian conservation would ever be performed. For women undergoing hysterectomy for benign indications, ovarian conservation has now been suggested as a quality metric.<sup>10</sup>

In the context of prior work, our data suggests that ovarian preservation is a reasonable option in some young women with endometrial cancer. For premenopausal women, the risks of long-term estrogen deprivation may outweigh the oncologic benefits of oophorectomy. Individualized risk assessment may help both patients and providers weigh the risks and benefits of oophorectomy. As the prognosis is excellent for the majority of women with early stage endometrial cancer, treatment paradigms that focus on long-term health benefits and well-being are clearly needed.

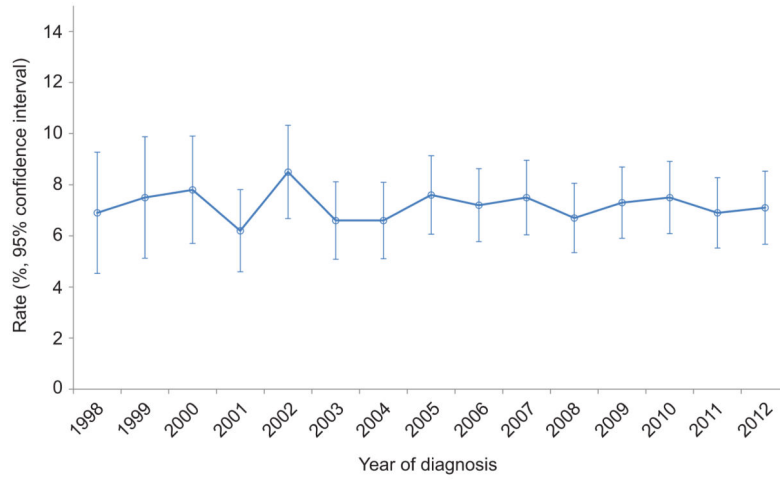
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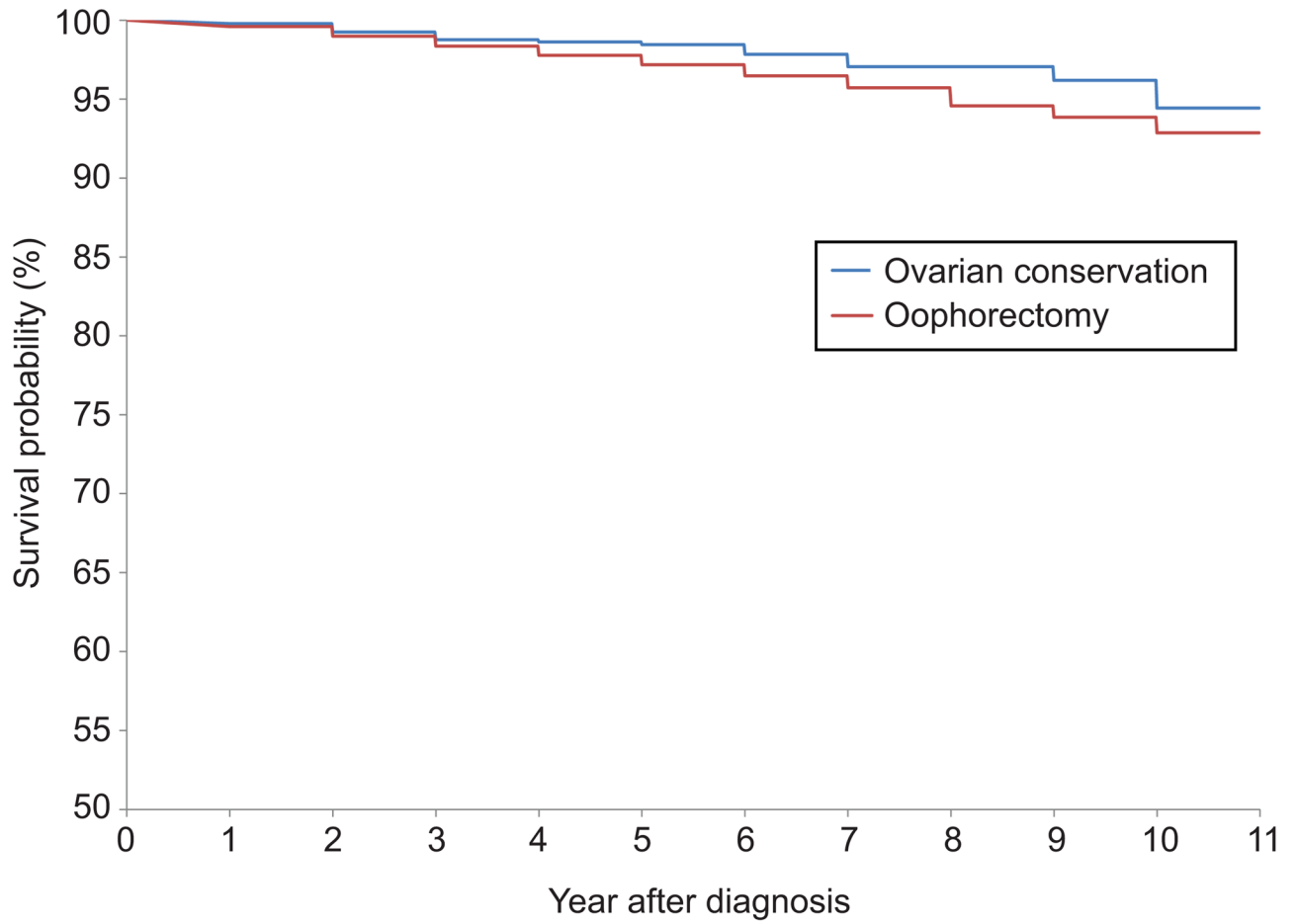
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**Figure 1.** Rate of ovarian conservation for stage I endometrial cancer ( $P=.93$ ).





**Figure 2.** Kaplan-Meier analysis of survival stratified by performance of oophorectomy ( $P=.15$ ).

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**Table 1**  
Clinical and demographic characteristics of the cohort stratified by performance of oophorectomy

	Ovarian Conservation			Oophorectomy			P-value	Multivariable Risk Ratio (95% CI)
	N	(%)	N (%)	N (%)	(%)			
<i>Year of diagnosis</i>	1121	(7.2)	14,527	(92.8)			0.91	
1998	31	(6.9)	417	(93.1)			Referent	
1999	36	(7.5)	443	(92.5)			1.08 (0.67–1.75)	
2000	49	(7.8)	581	(92.2)			1.12 (0.71–1.76)	
2001	54	(6.2)	818	(93.8)			0.94 (0.60–1.46)	
2002	76	(8.5)	823	(91.6)			1.21 (0.80–1.85)	
2003	68	(6.6)	967	(93.4)			0.98 (0.64–1.50)	
2004	71	(6.6)	1,003	(93.4)			0.98 (0.64–1.50)	
2005	88	(7.6)	1,065	(92.4)			1.14 (0.76–1.73)	
2006	90	(7.2)	1,167	(92.8)			1.08 (0.72–1.64)	
2007	94	(7.5)	1,163	(92.5)			1.13 (0.75–1.70)	
2008	87	(6.7)	1,219	(93.3)			1.01 (0.67–1.53)	
2009	98	(7.3)	1,245	(92.7)			1.11 (0.74–1.67)	
2010	100	(7.5)	1,238	(92.5)			1.14 (0.76–1.71)	
2011	90	(6.9)	1,215	(93.1)			1.05 (0.69–1.59)	
2012	89	(7.1)	1,163	(92.9)			1.07 (0.71–1.62)	
<i>Age (years)</i>							<0.0001	
45–49	357	(4.7)	7,191	(95.3)			Referent	
40–44	314	(7.4)	3,941	(92.6)			1.52 (1.30–1.77)**	
35–39	241	(10.4)	2,070	(89.6)			2.19 (1.85–2.58)**	
30–34	134	(12.1)	972	(87.9)			2.54 (2.07–3.10)**	
<30	75	(17.5)	353	(82.5)			3.64 (2.82–4.69)**	
<i>Race</i>							0.001	
White	914	(6.9)	12,312	(93.1)			Referent	
Black	112	(10.0)	1,013	(90.0)			1.36 (1.11–1.67)*	

	Ovarian Conservation			Oophorectomy			P-value	Multivariable Risk Ratio (95% CI)
	N	(%)	(%)	N	(%)	(%)		
Other/unknown	95	(7.3)		1,202	(92.7)		0.85	1.01 (0.81–1.26)
<i>Insurance status</i>								
Commercial	870	(7.2)		11,302	(92.9)			Referent
Medicare	53	(6.8)		727	(93.2)			0.95 (0.72–1.26)
Medicaid	89	(7.2)		1,150	(92.8)			0.89 (0.71–1.12)
Uninsured	69	(7.0)		920	(93.0)			0.87 (0.68–1.13)
Other	12	(7.5)		148	(92.5)			0.98 (0.55–1.76)
Unknown	28	(9.1)		280	(90.9)			1.23 (0.83–1.81)
<i>Comorbidity</i>							0.001	
0	729	(7.6)		8,892	(92.4)			--
1	129	(5.6)		2,179	(94.4)			--
2	17	(4.4)		374	(95.7)			--
Unknown	246	(7.4)		3,082	(92.6)			--
<i>Region</i>							0.0003	
New England	90	(9.1)		895	(90.9)			Referent
Middle Atlantic	133	(5.8)		2,170	(94.2)			0.65 (0.48–0.88)*
South Atlantic	234	(7.8)		2,763	(92.2)			0.77 (0.59–1.02)
East North Central	205	(6.3)		3,040	(93.7)			0.66 (0.50–0.87)*
East South Central	67	(6.7)		931	(93.3)			0.71 (0.50–1.02)
West North Central	68	(5.9)		1,090	(94.1)			0.64 (0.45–0.91)
West South Central	102	(8.0)		1,181	(92.1)			0.80 (0.58–1.10)
Mountain	70	(9.4)		679	(90.7)			1.02 (0.72–1.45)
Pacific	152	(7.9)		1,778	(92.1)			0.79 (0.59–1.06)
<i>Metropolitan location</i>							0.14	
Metropolitan	914	(7.3)		11,556	(92.7)			Referent
Urban	148	(6.4)		2,184	(93.7)			0.89 (0.74–1.06)
Rural	12	(4.8)		238	(95.2)			0.68 (0.38–1.22)
Unknown	47	(7.9)		549	(92.1)			0.97 (0.72–1.32)
<i>Hospital type</i>							<0.0001	

	Ovarian Conservation			Oophorectomy			P-value	Multivariable Risk Ratio (95% CI)
	N	(%)	N	(%)	N	(%)		
Academic	442	(6.3)	6,556	(93.7)			Referent	
Comprehensive community cancer program	563	(7.4)	7,025	(92.6)			1.74 (1.40–2.17)**	
Community cancer program	114	(11.2)	908	(88.9)			1.19 (1.03–1.37)*	
Other <sup>†</sup>	-	-	-	-				
<i>Grade</i>							<0.0001	
1	790	(8.4)	8,627	(91.6)			Referent	
2	205	(4.9)	3,955	(95.1)			0.61 (0.52–0.71)**	
3	52	(5.2)	940	(94.8)			0.70 (0.53–0.93)*	
Unknown	74	(6.9)	1,005	(93.1)			0.85 (0.67–1.08)	
<i>Stage</i>							0.001	
IA	997	(7.2)	12,945	(92.8)			Referent	
IB	67	(5.7)	1,105	(94.3)			0.76 (0.58–0.99)*	
INOS	57	(10.7)	477	(89.3)			0.65 (0.45–0.93)*	

<sup>†</sup> Due to co-linearity, we were not able to fit comorbidity and year of diagnosis in the same model.

<sup>†</sup> Data suppressed due to small sample size within the categories.

\* P<0.05

\*\* P<0.0001

**Table 2**

Rate of ovarian conservation stratified by stage and grade (%).

<i>Stage IA</i>	Grade 1		Grade 2		Grade 3	
	N*	(95% CI)	N*	(95% CI)	N*	(95% CI)
All patients	8615	8.3% (7.7–8.9%)	3627	5.0% (4.3–5.7%)	761	4.7% (3.4–6.5%)
<30 years	236	20.3% (15.7–25.9%)	96	12.5% (7.3–20.6%)	14	7.1% (1.3–31.5)
30–34 years	630	14.3% (11.8–17.2%)	25	8.8% (5.9–12.9%)	40	7.5% (2.6–19.9%)
35–39 years	1296	12.2% (10.5–14.1%)	556	7.2% (5.3–9.6%)	84	8.3% (4.1–16.2%)
40–44 years	2400	8.6% (7.6–9.8%)	940	4.4% (3.2–5.9%)	1784	4.2% (2.2–8.1%)
45–49 years	4053	5.3% (4.6–6.0%)	1784	3.7% (2.9–4.7%)	434	3.9% (2.5–6.2%)

\* Total patients (ovarian conservation and oophorectomy).

**Table 3**

Multivariable models of predictors of mortality.

	Hazard ratio for mortality (95% CI)
<i>Oophorectomy</i>	
Oophorectomy	Referent
Ovarian conservation	0.94 (0.65–1.37)
<i>Year of diagnosis</i>	
1998	Referent
1999	1.05 (0.67–1.67)
2000	1.26 (0.81–1.95)
2001	1.27 (0.83–1.94)
2002	0.91 (0.57–1.43)
2003	0.76 (0.48–1.22)
2004	1.05 (0.67–1.65)
2005	1.04 (0.66–1.64)
2006	1.00 (0.62–1.59)
2007	0.99 (0.60–1.63)
2008	0.68 (0.39–1.20)
2009	0.86 (0.49–1.50)
2010	0.61 (0.31–1.21)
2011	0.78 (0.36–1.68)
2012	--
<i>Age (years)</i>	
45–49	Referent
40–44	0.76 (0.52–1.09)
35–39	0.56 (0.42–0.75) *
30–34	0.75 (0.61–0.93) *
<30	0.48 (0.23–0.97) *
<i>Race</i>	
White	Referent
Black	1.17 (0.86–1.59)
Other/unknown	0.94 (0.66–1.34)
<i>Insurance status</i>	
Commercial	Referent
Medicare	3.78 (2.88–4.97) **
Medicaid	2.85 (2.19–3.69) **
Uninsured	1.88 (1.34–2.65) *
Other	1.04 (0.38–2.83)
Unknown	2.28 (1.48–3.51) *
<i>Comorbidity</i>	
0	--

	Hazard ratio for mortality (95% CI)
1	--
2	--
<i>Region</i>	
New England	Referent
Middle Atlantic	0.90 (0.58–1.41)
South Atlantic	1.46 (0.97–2.18)
East North Central	1.06 (0.70–1.61)
East South Central	1.30 (0.79–2.15)
West North Central	0.95 (0.56–1.61)
West South Central	1.38 (0.85–2.22)
Mountain	1.18 (0.68–2.05)
Pacific	1.18 (0.77–1.82)
<i>Metropolitan location</i>	
Metropolitan	Referent
Urban	1.10 (0.86–1.40)
Rural	1.63 (0.93–2.86)
Unknown	1.90 (1.30–2.78) *
<i>Hospital type</i>	
Academic	Referent
Comprehensive community cancer program	0.86 (0.61–1.23)
Community cancer program	0.97 (0.80–1.18)
Other	1.10 (0.13–9.36)
<i>Grade</i>	
1	Referent
2	1.54 (1.26–1.89) **
3	2.76 (2.12–3.59) **
Unknown	2.05 (1.45–2.90) **
<i>Stage</i>	
IA	Referent
IB	2.09 (1.64–2.67) **
INOS	1.01 (0.58–1.76)

\* P&lt;0.05

\*\* P&lt;0.0001

**Table 4**

Follow-up time for women in the cohort based on Kaplan-Meier analysis.

	Follow-up Time																
	1-year	2-year	3-year	4-year	5-year	6-year	7-year	8-year	9-year	10-year	11-year	12-year	13-year	14-year	15-year	16-year	
<i>Ovarian conservation</i>																	
Women at risk	982	910	825	720	621	508	396	311	227	180	121	77	50	23	9	3	
Dead	2	5	3	1	1	3	3	0	2	3	0	1	2	2	0	0	
Censored	70	80	102	98	112	109	82	84	45	56	44	26	25	12	6	3	
Cumulative deaths	2	7	10	11	12	15	18	18	20	23	23	24	26	28	28	28	
<i>Oophorectomy</i>																	
Women at risk	12,906	11,999	10,784	9,327	8,010	6,593	5,198	4,069	3,156	2,352	1,691	1,117	669	347	138	33	
Dead	51	72	64	51	46	41	35	45	22	22	20	9	5	7	1	0	
Censored	856	1,143	1,393	1,266	1,371	1,354	1,094	868	782	639	554	439	317	202	104	33	
Cumulative deaths	51	123	187	238	284	325	360	405	427	449	469	478	483	490	491	491	