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# Fertility-sparing surgery and survival among reproductive-aged women with epithelial ovarian cancer in two cancer registries

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## Abstract

**Objective:** We examined predictors of fertility-sparing surgery (FSS) among reproductive-aged women diagnosed with epithelial ovarian cancer (EOC). In addition, we assessed relationships between FSS and survival in models stratified by tumor characteristics.

**Methods:** We queried the Surveillance, Epidemiology, and End Results (SEER) Program and the National Cancer Database (NCDB) for women ≤ 44 years old with a primary EOC. FSS included unilateral salpingo-oophorectomy and uterine preservation while surgeries including a bilateral salpingo-oophorectomy or hysterectomy were categorized as non-FSS. We used logistic regression to estimate multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for associations between clinical characteristics (age at diagnosis, race, etc.) and FSS odds. Multivariable Cox regression was used to estimate hazard ratios (HRs) and 95% CIs of FSS and overall survival in subgroups defined by stage/grade or stage/histology. Analyses were stratified by database (SEER vs. NCDB).

**Results:** This analysis included 9,017 women (SEER, N=3,932; NCDB, N=5,085) with EOC diagnosed between the ages of 15 and 44 years. In both cohorts, factors associated with significantly higher FSS odds included younger age, more recent ovarian cancer diagnosis, and no adjuvant chemotherapy. FSS was significantly associated with lower overall survival among women with stages 2–4, serous EOC (SEER HR=1.61, 95% CI=1.22–2.12). Significant associations between FSS and survival were not observed in other subgroups defined by stage/grade or stage/histology.

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Author contributions

**Sarah Crafton:** Study concept, writing of the manuscript, interpretation of the data, and final review of the manuscript. **David E. Cohn:** Interpretation of the data, critical review, and final review of the manuscript. **Elyse Llamocca:** Data analysis, critical review, and final review of the manuscript. **Elaine Louden:** Data analysis, critical review, and final review of the manuscript. **Jennifer Rhoades:** Data analysis, critical review, and final review of the manuscript. **Ashley S. Felix:** Study design, data procurement, data analysis, writing of the manuscript, and final review of the manuscript.

**Conflict of interest**: The authors have no relevant conflicts of interest.

**Conclusion:** FSS appears safe in certain women with EOC but was related to poor survival among women with advanced stage serous EOC. Confirmatory studies with information on fertility intentions are needed.

## Precis:

Fertility-sparing surgery for ovarian cancer is associated with poor survival among women with advanced stage, serous epithelial ovarian cancer. No significantly increased risk of death associated with FSS was observed for women with other tumor characteristics.

### Keywords

survival; fertility preservation; ovarian cancer; reproductive function

## Introduction

In 2019, 14,000 deaths secondary to ovarian cancer are expected in the United States [1]. While ovarian cancer is most commonly diagnosed among women of post-menopausal age, an estimated 12% of ovarian cancer patients are diagnosed during their reproductive years [2]. Treatment for ovarian cancer includes surgery and chemotherapy, which have implications for younger patients, including loss of reproductive potential and menopause. These consequences may result in decreased quality of life, distress, and negatively impact survivorship 3,4. In 2006, the American Society of Clinical Oncology (ASCO) published clinical practice guidelines for cancer patients of reproductive age, which were updated in 2013 [5]. These guidelines recommend discussion of a patient's reproductive goals and implementation of fertility preservation among cancer patients of reproductive age. Potential methods of preservation include conservative surgery for gynecologic malignancies [5].

In the management of ovarian cancer, fertility-sparing surgery (FSS) is an option for fertility preservation in women without evidence of extra-pelvic disease and entails conservation of the uterus and at least a portion of one ovary. The staging component includes the removal of the affected ovary, omentectomy, peritoneal biopsies, pelvic washings with or without lymph node assessment 6,7. In addition to conserving reproductive ability, FSS has non-reproductive benefits of avoiding the negative sequelae of surgical menopause. In a recent survey of gynecologic oncologists, factors that influence selection of women with ovarian cancer for FSS include tumor histology, stage, grade, age, and reproductive plans and desires [8]. According to National Comprehensive Cancer Network (NCCN) guidelines, among women with select unilateral stage I tumors (stage 1A and 1C, but not stage 1B) and/or low-risk ovarian tumors (i.e. early-stage, grade 1 tumors; borderline tumors), FSS can be considered if fertility preservation is desired and if conservation is technically feasible from a surgical perspective [9]. These recommendations are based on a limited body of observational evidence demonstrating no difference in survival between FSS and standard treatment among women with these tumor characteristics 10–15. On the other hand, recommendations against FSS for women with other tumor characteristics (*e.g.* high-grade or advanced stage) are based on the aggressive nature and comparatively worse prognosis of these tumors; however, data for these recommendations are lacking.

Given a lack of empirical data on FSS-associated survival, particularly for subgroups of ovarian cancer patients defined by tumor characteristics, we evaluated these associations in two datasets: the population-based Surveillance, Epidemiology, and End Results (SEER) program and the hospital-based clinical cancer registry, the National Cancer Database (NCDB). In addition, we examined determinants of receipt of FSS among epithelial ovarian cancer (EOC) patients of reproductive age.

## Materials and Methods

### Data source and study population

We conducted a retrospective cohort study of women aged 15–44 years diagnosed with EOC ascertained using two data sources: 1.) the 18 SEER registries (includes Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, Rural Georgia, Alaska Native, Greater California, Greater Georgia, Kentucky, Louisiana, and New Jersey) and 2.) the NCDB. The SEER program covers approximately 28% of the U.S. population while the NCDB collects data from more than 1,500 hospitals in the United States, capturing more than 70% of all newly diagnosed cancers16,17. There is likely overlap in cancer cases between these two databases, as hospitals may contribute data to both registries. However, as both datasets are de-identified, we cannot directly determine the extent of overlap between these two data sources. Women with a diagnosis of ovarian cancer (C56.9) between 1992–2014 (SEER) and 2004–2015 (NCDB) were included. We selected 1992 as the entry year in the SEER population based on the FDA approval of paclitaxel for treatment of ovarian cancer, which has been subsequently implemented as a standard chemotherapeutic agent for EOC.

We developed databases for each cancer registry that included the following variables: age at diagnosis, race, diagnosis year, International Classification of Diseases for Oncology Third Edition (ICD-O-3) morphology, stage [American Joint Commission on Cancer (Third Edition for cases diagnosed 1992–2003 and Sixth Edition for cancers diagnosed after 2004], grade, site-specific surgery codes, chemotherapy, and survival time. We used ICD-O-3 morphology codes to restrict the study population to the following EOC: serous (8441, 8460, 8461), endometrioid/adenocarcinoma (8380, 8381, 8560, 8570), clear cell (8310, 8313), and mucinous (8470, 8471, 8480, 8481). Using the site-specific surgery codes, we classified women with unilateral salpingo-oophorectomy and uterine preservation as FSS and women with bilateral salpingo-oophorectomy or hysterectomy as non-FSS.

The SEER study sample was drawn from the 9,644 women aged 15–44 with an EOC diagnosis between 1992 and 2014. Of those, we excluded women who could not be categorized as FSS vs. no FSS [unknown hysterectomy status, unknown surgical status, surgery not otherwise specified (NOS), or salpingo-oophorectomy, NOS (n=2,732)], histological subtypes other than serous, endometrioid, clear cell, or mucinous (n=1,438), missing stage or stage I NOS (n=263), missing grade (n=1,230), and no follow-up time due to incomplete dates (n=49), leaving 3,932 patients in the SEER population. The NCDB study sample was drawn from the 16,302 women aged 15–44 with an EOC diagnosis between 2004 and 2015. Of those, we excluded women who could not be categorized as FSS vs. no FSS [unknown hysterectomy status, unknown surgical status, surgery not otherwise

specified (NOS), or salpingo-oophorectomy, NOS (n=4,650)], histological subtypes other than serous, endometrioid, clear cell, or mucinous (n=2,756), missing stage or stage I NOS (n=1,870), missing grade (n=1,438), no follow-up time (n=2), and missing vital status (n=501), leaving 5,085 patients in the NCDB population.

### Statistical Analysis

We created two tumor subgroup variables based on the cross classification of stage and grade and the cross-classification of stage and histology. Data were too sparse to categorize women according to all three tumor characteristics. The stage and grade variable was categorized as follows: 1.) stage 1A/1B, low-grade (grades 1 or 2); 2.) stage 1A/1B, high-grade (grade 3); 3.) stage 1C, low-grade; 4.) stage 1C, high-grade; 5.) stages 2–4, low-grade; 6.) stages 2–4, high-grade. The stage and histology variable was categorized as follows: 1.) stage 1C, serous; 2.) stage 1C, endometrioid; 3.) stage 1C, mucinous; 4.) stage 1C, clear cell; 5.) stages 2–4, serous; 6.) stages 2–4, endometrioid; 7.) stages 2–4, mucinous; 8.) stages 2–4, clear cell. These tumor characteristic variables were specifically created due to limited, observational data resulting in controversial clinical recommendation regarding FSS in these specific subgroups.

We examined frequency distributions of demographic and clinical variables according to FSS and used logistic regression to estimate multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for associations between clinical characteristics and odds of FSS receipt. The multivariable model included all clinical characteristics given univariable associations at $p<0.15$ (data not tabled).

Follow-up time began on the date of surgery and ended on the date of death from any cause or end of follow-up. Kaplan–Meier curves and log-rank tests were used to compare survival distributions according to receipt of FSS and Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% CIs for multivariable-adjusted associations with overall survival. The Cox regression model was stratified by both tumor subgroup variables (i.e. stage/grade and stage/histology) and adjustment factors included age at diagnosis, race, SEER registry or facility location, diagnosis year, histology, and chemotherapy treatment. We tested the proportional hazards assumption by visually examining plots of the Schoenfeld residuals vs. the log of follow-up time for each of the predictors.

All analyses were completed using SEER Stat and SAS/STAT software (version 9.4 of the SAS System for Windows, SAS Institute, Cary, NC, USA). This study was considered exempt by the Institutional Review Board of the Ohio State University as all data are de-identified and intended for public use.

## Results

### Determinants of FSS

This analysis included 9,017 women (SEER: N=3,932; NCDB: N=5,085) with an EOC diagnosed between the ages of 15 and 44 years. The proportion of women with FSS was slightly higher in SEER than in NCDB (26.1% vs. 24.8%). Table 1 shows distributions of patient characteristics according to FSS and multivariable-adjusted ORs stratified by dataset.

In SEER and NCDB, younger age was associated with higher FSS odds (15–19 vs. 40–44 years, SEER OR=30.23, 95% CI=13.83–66.09; NCDB OR=25.13, 95% CI=12.78–49.43). In both databases, there was a statistically significant increase in the proportion of women receiving FSS over time. In SEER, 23% of women diagnosed between 1992 and 1995 had an FSS compared to 34% of women diagnosed in 2012–2014 (OR=2.12, 95% CI=1.52–2.95). In NCDB, the proportion of women with an FSS increased from 21% in the time period 2004–2007 to 29% in 2012–2015 (OR=1.26, 95% CI=1.05–1.51. Tumor characteristics were associated with FSS receipt in both datasets. Compared to women with mucinous tumors, women with endometrioid (SEER OR=0.69, 95% CI=0.56–0.85), serous (SEER OR=0.66, 95% CI=0.52–0.85; NCDB OR=0.67, 95% CI=0.54–0.83) or clear cell tumors (SEER OR=0.62, 95% CI=0.42–0.91; NCDB OR=0.68, 95% CI=0.49–0.95) had lower odds of FSS receipt. As expected, women with stages 2–4, low-grade (SEER OR=0.59, 95% CI=0.45–0.77; NCDB OR=0.69, 95% CI=0.54–0.88) and stages 2–4, high-grade disease (NCDB OR=0.59, 95% CI=0.45–0.78) had lower odds of FSS compared to women with stage 1A/1B low-grade disease. As expected, women who underwent FSS had lower odds of receiving adjuvant chemotherapy (SEER OR=0.67, 95% CI=0.55–0.81; NCDB OR=0.75, 95% CI=0.63–0.89).

### FSS and overall survival stratified by tumor subgroup

Over a median of 6.5 years and 4.6 years of follow-up in SEER and NCDB, respectively, 987 (25.1%) and 1,014 (19.9%) women died. Supplemental figures 1 and 2 show Kaplan-Meir plots of FSS and overall survival stratified by stage/grade in SEER and NCDB. In the SEER population, FSS was not associated with overall survival among most tumor subgroups (Supplemental figure 1a–1e); however, among women with stages 2–4, high-grade disease (Supplemental figure 1f), FSS was associated with lower overall survival compared to no FSS. In the NCDB population, we observed no significant relationships between FSS and overall survival for any tumor subgroup (Supplemental figure 2a–2e). Supplemental figures 3 and 4 show Kaplan-Meir plots of FSS and overall survival stratified by stage/histology in SEER and NCDB.

In the SEER population, FSS was not associated with lower overall survival among most tumor histology subgroups (Supplemental figure 3); however, among women with stage 1C serous (Supplemental figure 3a) or 1C clear cell (Supplemental figure 3f) FSS was associated with lower overall survival compared to no FSS. In the NCDB (Supplemental figure 4a–4e) population there was no significant relationship between FSS and overall survival for any of the histology/stage subgroups.

Findings from the stage/grade and stage/histology-stratified multivariable Cox regression models are shown in Tables 2 and 3. The HRs in these tables compare overall survival for women with FSS compared to no FSS (reference category) for each tumor subgroup. We observed no significant association between FSS and overall survival for any stage/grade subgroup in the SEER or NCDB populations (Table 2). In analyses of subgroups defined by stage/histology (Table 3), we observed significantly lower survival associated with FSS among women with stages 2–4, serous EOC in the SEER population (HR=1.61, 95% CI=1.22–2.12). We also observed a lower survival associated with FSS among women with

stage IC, serous (SEER HR: 2.87, 95% CI=0.60–13.65; NCDB HR: 2.45, 95% CI=0.66–9.14) and among women with stage 1C, endometrioid EOC (SEER HR: 1.98, 95% CI=0.68–5.77); however these results were not statistically significant.

## Discussion

Loss of reproductive capability and surgical menopause can negatively impact survivorship and quality of life among young women with ovarian cancer. ASCO has published guidelines to address the importance of implementing fertility preservation counseling as standard of care for all cancer patients of reproductive age. However, the safety of such procedures should be thoroughly assessed in ongoing analyses. Our results agree with the current body of literature that supports the safety and feasibility of FSS among most young women with EOC. Null relationships between FSS and overall survival were consistently observed in both datasets that we explored, providing greater confidence in our findings. However, we noted an increased risk of death associated with FSS among women with advanced stage, serous EOC in the SEER population. Significant determinants of higher FSS receipt included younger age, more recent diagnosis, and diagnosis with mucinous histology, while diagnosis with stages 2–4, high-grade disease were related to lower odds of FSS receipt. In addition, FSS was associated with lower odds of adjuvant chemotherapy receipt.

In general, our findings regarding survival support the current NCCN recommendations that FSS can be considered as an alternative for traditional, comprehensive staging for those patients who desire fertility, in which ovarian retention is technically feasible, and with early stage disease. Our observation of an increased risk of death associated with FSS among women with advanced stage, serous EOC in the SEER population supports clinical recommendations that the decision to pursue FSS should be individualized based on patient/provider counseling and disease characteristics.

In both the SEER and NCDB cohorts, FSS was unrelated to survival in subgroups defined by stage and grade, findings in line with other single institution retrospective studies 10,18. Previously published data report high grade tumors should not be considered for FSS due to increased risk of recurrence; however, the inclusion of stage and grade concurrently in the analyses are inconsistent 7,13,19,20.

In the stage and histology-stratified models, increased risk of death was noted for women with stages 2–4, serous EOC. Further, we noted elevated, but not statistically significant, risk of death among women with stage 1C disease of either serous or endometrioid histology. Others have noted increased risks associated with FSS in these subgroups7,20–22, which supports recommendations that FSS in these clinical scenarios should be considered on a case-by-case basis with thorough patient counseling. It should be noted that the sample sizes within tumor categories were relatively low; therefore, whether our results indicate safety of FSS or underpowered analyses is unclear, warranting additional studies.

In our analysis of determinants of FSS we observed that women of younger age and more recent diagnosis more commonly had FSS. Women with more aggressive disease characteristics, including histology other than mucinous, higher stage, and higher grade were

less likely to receive FSS. In 2009, Wright and colleagues [13] published an analysis of ovarian and uterine preservation among reproductive age ovarian cancer patients. The authors report similar findings that younger age and later year of diagnosis were associated with ovarian and/or uterine preservation at the time of surgery. Similarly, an NCDB study of 1,726 stage I EOC reported increased provision of FSS in younger vs. older patients with no difference in mortality [23]. In line with the findings from Wright et al. [13] we observed that FSS odds increased with later years of diagnosis, possibly reflecting changes in provider behaviors following publication of ASCO guidelines.

There are several limitations of our study including potential misclassification of surgery (FSS vs. non FSS) and lack of central pathology review. One of the primary components of offering FSS is the assessment of a patient's desire to retain fertility. The decision to pursue FSS for the treatment of ovarian cancer is an individualized one, and the presence or absence of this discussion cannot be definitively ascertained from the data available. Further, this dataset does not reflect which patients have already undergone prior oophorectomy and/or hysterectomy. Moreover, we lacked information on prior permanent sterilization procedures, completion of childbearing, and information on alternative means of fertility preservation (oocyte/embryo cryopreservation). The major strengths of our study were the evaluations of FSS in two large cohorts of ovarian cancer patients and stratification by tumor characteristics.

In summary, we observed that FSS was not associated with overall survival among reproductive-aged women with EOC; however, certain subgroups of women, particularly those with aggressive tumor characteristics, may experience an increased risk of death associated with FSS. To build on our findings, future studies should prospectively document patient intent to maintain fertility to best interpret FSS data and inform clinical guidelines. While a randomized, prospective clinical trial is not feasible, efforts to maintain comprehensive tumor registries or pool multiple institutional datasets with long-term follow-up data on ovarian cancer patients with FSS should be undertaken.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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## REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA: a cancer journal for clinicians. 2019;69(1):7–34.2.
2. National Cancer Institute. Cancer Stat Facts: Ovarian Cancer. Accessed February 20, 2019 https://seer.cancer.gov/statf acts/html/ovary.html.
3. Carter J, Chi DS, Brown CL, et al. Cancer-related infertility in survivorship. Int J Gynecol Cancer. 2010;20(1):2–8. [PubMed: 20130497]
4. Carter J, Rowland K, Chi D, et al. Gynecologic cancer treatment and the impact of cancer-related infertility. Gynecol Oncol. 2005;97(1):90–95. [PubMed: 15790443]

5. Loren AW, Mangu PB, Beck LN, et al. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2013;31(19):2500–2510. [PubMed: 23715580]
6. Gershenson DM. Fertility-sparing surgery for malignancies in women. Journal of the National Cancer Institute Monographs. 2005(34):43–47. [PubMed: 15784822]
7. Bentivegna E, Gouy S, Maulard A, et al. Fertility-sparing surgery in epithelial ovarian cancer: a systematic review of oncological issues. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2016;27(11):1994–2004.
8. Shah JS, Guerra R, Bodurka DC, Sun CC, Chisholm GB, Woodard TL. Factors influencing fertility-sparing treatment for gynecologic malignancies: A survey of Society of Gynecologic Oncology members. Gynecol Oncol. 2017;147(3):497–502. [PubMed: 28941656]
9. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer, Including Fallopian Tube Cancer and Primary Peritoneal Cancer (version 2.2018). https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf Accessed January 25, 2019.
10. Schlaerth AC, Chi DS, Poynor EA, Barakat RR, Brown CL. Long-term survival after fertility-sparing surgery for epithelial ovarian cancer. Int J Gynecol Cancer. 2009;19(7):1199–1204. [PubMed: 19823055]
11. Schilder JM, Thompson AM, DePriest PD, et al. Outcome of reproductive age women with stage IA or IC invasive epithelial ovarian cancer treated with fertility-sparing therapy. Gynecol Oncol. 2002;87(1):1–7. [PubMed: 12468335]
12. Fader AN, Rose PG. Role of surgery in ovarian carcinoma. J Clin Oncol. 2007;25(20):2873–2883. [PubMed: 17617518]
13. Wright JD, Shah M, Mathew L, et al. Fertility preservation in young women with epithelial ovarian cancer. Cancer. 2009;115(18):4118–4126. [PubMed: 19670446]
14. Satoh T, Hatae M, Watanabe Y, et al. Outcomes of fertility-sparing surgery for stage I epithelial ovarian cancer: a proposal for patient selection. J Clin Oncol. 2010;28(10):1727–1732. [PubMed: 20194858]
15. Gershenson DM. Treatment of ovarian cancer in young women. Clin Obstet Gynecol. 2012;55(1):65–74. [PubMed: 22343230]
16. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2016 Sub (1973–2014 varying) - Linked To County Attributes - Total U.S., 1969–2015 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2017, based on the November 2016 submission. Accessed September, 2015.
17. Merkow RP, Rademaker AW, Bilimoria KY. Practical Guide to Surgical Data Sets: National Cancer Database (NCDB). JAMA surgery. 2018;153(9):850–851. [PubMed: 29617542]
18. Park JY, Suh DS, Kim JH, Kim YM, Kim YT, Nam JH. Outcomes of fertility-sparing surgery among young women with FIGO stage I clear cell carcinoma of the ovary. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2016;134(1):49–52.
19. Ditto A, Martinelli F, Bogani G, et al. Long-term safety of fertility sparing surgery in early stage ovarian cancer: comparison to standard radical surgical procedures. Gynecol Oncol. 2015;138(1):78–82. [PubMed: 25969349]
20. Satoh T, Yoshikawa H. Fertility-sparing surgery for early stage epithelial ovarian cancer. Japanese journal of clinical oncology. 2016;46(8):703–710. [PubMed: 27284094]
21. du Bois A, Heitz F, Harter P. Fertility-sparing surgery in ovarian cancer: a systematic review. Onkologie. 2013;36(7–8):436–443. [PubMed: 23921764]
22. Morice P, Leblanc E, Rey A, et al. Conservative treatment in epithelial ovarian cancer: results of a multicentre study of the GCCLCC (Groupe des Chirurgiens de Centre de Lutte Contre le Cancer) and SFOG (Societe Francaise d'Oncologie Gynecologique). Human reproduction. 2005;20(5):1379–1385. [PubMed: 15817592]
23. Melamed A, Rizzo AE, Nitecki R, et al. All-Cause Mortality After Fertility-Sparing Surgery for Stage I Epithelial Ovarian Cancer. Obstet Gynecol. 2017;130(1):71–79. [PubMed: 28594773]

**Table 1.**

Frequency distributions, multivariable-adjusted odds ratios and 95% confidence intervals for associations between patient characteristics and fertility preserving surgery among women aged 15–44 in SEER (1992–2014) and NCDB (2004–2015)

| | SEER | | | | NCDB | | | |
|---|---|---|---|---|---|---|---|---|
| | Fertility preserving surgery, N (%)[a] | | | | Fertility preserving surgery, N (%)[a] | | | |
| | No | Yes | | p | No | Yes | | p |
| | N=2,905 | N=1,027 | OR (95% CI)[b] | | N=3,823 | N=1,262 | OR (95% CI)[c] | |
| **Age at diagnosis** | | | | <0.001 | | | | <0.001 |
| 15–19 | 8 (14.5) | 47 (85.5) | 30.23 (13.83–66.09) | | 11 (17.2) | 53 (82.8) | 25.13 (12.78–49.43) | |
| 20–24 | 25 (18.4) | 111 (81.6) | 27.35 (16.96–44.10) | | 49 (24.3) | 153 (75.7) | 19.08 (13.34–27.29) | |
| 25–29 | 115 (41.1) | 165 (58.9) | 9.07 (6.78–12.15) | | 158 (44.9) | 194 (55.1) | 7.39 (5.72–9.55) | |
| 30–34 | 336 (58.9) | 234 (41.1) | 4.66 (3.71–5.84) | | 432 (60.5) | 282 (39.5) | 4.13 (3.38–5.06) | |
| 35–39 | 787 (76.3) | 245 (23.7) | 2.21 (1.79–2.71) | | 1000 (78.1) | 280 (21.9) | 1.83 (1.51–2.20) | |
| 40–44 | 1634 (87.9) | 225 (12.1) | 1.00 | | 2173 (87.9) | 300 (12.1) | 1.00 | |
| **Race** | | | | 0.44 | | | | 0.09 |
| White | 2319 (74.5) | 792 (25.5) | 1.00 | | 3236 (75.7) | 1038 (24.3) | 1.00 | |
| Black | 181 (71.5) | 72 (28.5) | 1.24 (0.89–1.73) | | 250 (71.8) | 98 (28.2) | 1.28 (0.97–1.68) | |
| Other | 405 (71.3) | 163 (28.7) | 1.04 (0.81–1.32) | | 337 (72.8) | 126 (27.2) | 1.20 (0.94–1.53) | |
| **Diagnosis year** | | | | <0.001 | | | | 0.03 |
| 1992–1995 | 395 (77.3) | 116 (22.7) | 1.00 | | --- | --- | --- | |
| 1996–1999 | 336 (75.7) | 108 (24.3) | 1.26 (0.89–1.76) | | --- | --- | --- | |
| 2000–2003 | 680 (77.5) | 197 (22.5) | 1.15 (0.85–1.58) | | --- | --- | --- | |
| 2004–2007 | 590 (73.7) | 211 (26.3) | 1.55 (1.14–2.12) | | 1557 (78.6) | 424 (21.4) | 1.00 | |
| 2008–2011 | 562 (72.1) | 218 (27.9) | 1.58 (1.16–2.16) | | 1331 (74.3) | 461 (25.7) | 1.18 (0.99–1.39) | |
| 2012–2014[d] | 342 (65.9) | 177 (34.1) | 2.12 (1.52–2.95) | | 935 (71.3) | 377 (28.7) | 1.26 (1.05–1.51) | |
| **Histology** | | | | 0.001 | | | | 0.004 |
| Mucinous | 537 (55.9) | 423 (44.1) | 1.00 | | 682 (59.7) | 461 (40.3) | 1.00 | |
| Endometrioid | 1060 (77.0) | 316 (23.0) | 0.69 (0.56–0.85) | | 1308 (75.8) | 418 (24.2) | 0.85 (0.71–1.02) | |
| Serous | 1058 (81.9) | 233 (18.1) | 0.66 (0.52–0.85) | | 1465 (82.6) | 309 (17.4) | 0.67 (0.54–0.83) | |

| | SEER | | | | NCDB | | | |
|---|---|---|---|---|---|---|---|---|
| | Fertility preserving surgery, N (%)[a] | | | | Fertility preserving surgery, N (%)[a] | | | |
| | No | Yes | | p | No | Yes | | p |
| | N=2,905 | N=1,027 | OR (95% CI)[b] | | N=3,823 | N=1,262 | OR (95% CI)[c] | |
| Clear cell | 250 (82.0) | 55 (18.0) | 0.62 (0.42–0.91) | | 368 (83.3) | 74 (16.7) | 0.68 (0.49–0.95) | |
| **Tumor subgroup** | | | | 0.006 | | | | <0.001 |
| Stage 1A/1B, low-grade | 844 (64.2) | 471 (35.8) | 1.00 | | 994 (66.5) | 500 (33.5) | 1.00 | |
| Stage 1A/1B, high-grade | 207 (75.5) | 67 (24.5) | 0.83 (0.58–1.19) | | 248 (73.4) | 90 (26.6) | 1.02 (0.74–1.41) | |
| Stage 1C, low-grade | 381 (70.2) | 162 (29.8) | 0.91 (0.70–1.17) | | 565 (69.3) | 250 (30.7) | 0.98 (0.79, 1.22) | |
| Stage 1C, high-grade | 148 (74.8) | 50 (25.2) | 1.00 (0.67–1.52) | | 227 (76.2) | 71 (23.8) | 1.11 (0.79–1.57) | |
| Stages 2–4, low-grade | 602 (80.6) | 145 (19.4) | 0.59 (0.45–0.77) | | 780 (79.1) | 206 (20.9) | 0.69 (0.54–0.88) | |
| Stages 2–4, high-grade | 723 (84.6) | 132 (15.4) | 0.76 (0.57–1.02) | | 1009 (87.4) | 145 (12.6) | 0.59 (0.45–0.78) | |
| **Chemotherapy treatment** | | | | <0.001 | | | | <0.001 |
| No/unknown | 1073 (65.5) | 566 (34.5) | 1.00 | | 1254 (67.2) | 611 (32.8) | 1.00 | |
| Yes | 1832 (79.9) | 461 (20.1) | 0.67 (0.55–0.81) | | 2569 (79.8) | 651 (20.2) | 0.75 (0.63–0.89) | |

[a] Row percentage

[b] SEER logistic regression model adjusted for age at diagnosis (15–19, 20–24, 25–29, 30–34, 35–39, 40–44), race (White, Black, Other), histology (serous, endometrioid, mucinous, clear cell), chemotherapy (no/unknown, yes), tumor subgroup (stage 1A/1B, low-grade; stage 1A/1B, high-grade; stage 1C, low-grade; stage 1C, high-grade; stages 2–4, low-grade; stages 2–4, high-grade), diagnosis year (1992–1995, 1996–1999, 2000–2003, 2004–2007, 2008–2011, 2012–2014), and SEER registry

[c] NCDB logistic regression model adjusted for (15–19, 20–24, 25–29, 30–34, 35–39, 40–44), race (White, Black, Other), histology (serous, endometrioid, mucinous, clear cell), chemotherapy (no/unknown, yes), tumor subgroup (stage 1A/1B, low-grade; stage 1A/1B, high-grade; stage 1C, low-grade; stage 1C, high-grade; stages 2–4, low-grade; stages 2–4, high-grade), diagnosis year (2004–2007, 2008–2011, 2012–2015), and region

[d] NCDB years of diagnosis include 2015

**Table 2.**

Multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between FSS and overall survival according to stage and grade in SEER (1992–2014) and NCDB (2004–2015)

| | SEER | | | NCDB | | |
|---|---|---|---|---|---|---|
| | deaths, n (%)[a] | HR (95% CI)[b] | p[c] | deaths, n (%)[a] | HR (95% CI)[d] | p[c] |
| | **Stage 1A/1B, Low-grade** | | | | | |
| **FSS** | | | 0.66 | | | 0.84 |
| No | 80 (9.5) | 1.00 | | 59 (5.9) | 1.00 | |
| Yes | 42 (8.9) | 1.10 (0.71–1.70) | | 26 (5.2) | 1.05 (0.62–1.78) | |
| | **Stage 1A/1B, High-grade** | | | | | |
| **FSS** | | | 0.97 | | | 0.43 |
| No | 29 (14.0) | 1.00 | | 28 (11.3) | 1.00 | |
| Yes | 9 (13.4) | 0.98 (0.37–2.64) | | 12 (13.3) | 1.38 (0.62–3.07) | |
| | **Stage 1C, Low-grade** | | | | | |
| **FSS** | | | 0.33 | | | 0.30 |
| No | 35 (9.2) | 1.00 | | 43 (7.6) | 1.00 | |
| Yes | 14 (8.6) | 1.45 (0.69–3.07) | | 17 (6.8) | 0.70 (0.36–1.38) | |
| | **Stage 1C, High-grade** | | | | | |
| **FSS** | | | 0.25 | | | 0.22 |
| No | 32 (21.6) | 1.00 | | 32 (14.1) | 1.00 | |
| Yes | 11 (22.0) | 1.74 (0.67–4.52) | | 13 (18.3) | 1.56 (0.76–3.21) | |
| | **Stages 2–4, Low-grade** | | | | | |
| **FSS** | | | 0.34 | | | 0.40 |
| No | 204 (33.9) | 1.00 | | 206 (26.4) | 1.00 | |
| Yes | 50 (34.5) | 1.19 (0.83–1.70) | | 46 (22.3) | 0.86 (0.61–1.21) | |
| | **Stages 2–4, High-grade** | | | | | |
| **FSS** | | | 0.13 | | | 0.47 |
| No | 398 (55.1) | 1.00 | | 463 (45.9) | 1.00 | |
| Yes | 83 (62.9) | 1.23 (0.94–1.61) | | 69 (47.6) | 1.10 (0.85–1.43) | |

[a] row percentage

[b] SEER Cox regression model adjusted for age at diagnosis (15–19, 20–24, 25–29, 30–34, 35–39, 40–44), race (White, Black , Other), histology (serous, endometrioid, mucinous, clear cell), chemotherapy (no/unknown, yes), SEER registry, and diagnosis year (1992–1995, 1996–1999, 2000–2003, 2004–2007, 2008–2011, 2012–2014)

[c] p-value from multivariable-adjusted Cox model

[d] NCDB Cox regression model adjusted for age at diagnosis (15–19, 20–24, 25–29, 30–34, 35–39, 40–44), race (White, Black , Other), histology (serous, endometrioid, mucinous, clear cell), chemotherapy (no/unknown, yes), diagnosis year (2004–2007, 2008–2011, 2012–2015), and region

**Table 3.**

Multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between FSS and overall survival according to stage and histology in SEER (1992–2014) and NCDB (2004–2015)

| | SEER | | | NCDB | | |
|---|---|---|---|---|---|---|
| | deaths, n (%)[a] | HR (95% CI)[b] | p[c] | deaths, n (%)[a] | HR (95% CI)[d] | p[c] |
| | **Stage 1C, Serous** | | | | | |
| **FSS** | | | 0.18 | | | 0.18 |
| No | 16 (15.4) | 1.00 | | 13 (9.1) | 1.00 | |
| Yes | 8 (26.7) | 2.87 (0.60–13.65) | | 5 (12.2) | 2.45 (0.66–9.14) | |
| | **Stage 1C, Endometrioid** | | | | | |
| **FSS** | | | 0.21 | | | 0.37 |
| No | 22 (8.5) | 1.00 | | 29 (7.5) | 1.00 | |
| Yes | 6 (7.0) | 1.98 (0.68–5.77) | | 6 (4.4) | 0.65 (0.25–1.67) | |
| | **Stage 1C, Mucinous** | | | | | |
| **FSS** | | | 0.14 | | | 0.85 |
| No | 14 (14.6) | 1.00 | | 19 (12.8) | 1.00 | |
| Yes | 6 (7.3) | 0.36 (0.09–1.38) | | 16 (13.6) | 0.93 (0.41–2.08) | |
| | **Stage 1C, Clear Cell** | | | | | |
| **FSS** | | | 0.51 | | | 0.75 |
| No | 15 (21.4) | 1.00 | | 14 (12.5) | 1.00 | |
| Yes | 5 (35.7) | 1.83 (0.30–10.99) | | 3 (11.1) | 1.25 (0.32–4.96) | |
| | **Stages 2–4, Serous** | | | | | |
| **FSS** | | | 0.0008 | | | 0.76 |
| No | 371 (45.9) | 1.00 | | 452 (38.7) | 1.00 | |
| Yes | 70 (47.9) | 1.61 (1.22–2.12) | | 66 (33.2) | 1.04 (0.80–1.36) | |
| | **Stages 2–4, Endometrioid** | | | | | |
| **FSS** | | | 0.94 | | | 0.46 |
| No | 126 (36.3) | 1.00 | | 87 (22.9) | 1.00 | |
| Yes | 22 (36.1) | 1.02 (0.61–1.70) | | 19 (24.7) | 1.23 (0.71–2.14) | |
| | **Stages 2–4, Mucinous** | | | | | |
| **FSS** | | | 0.09 | | | 0.50 |
| No | 56 (65.9) | 1.00 | | 55 (51.4) | 1.00 | |
| Yes | 30 (57.7) | 0.59 (0.33–1.08) | | 23 (41.8) | 0.82 (0.45–1.48) | |
| | **Stages 2–4, Clear Cell** | | | | | |
| **FSS** | | | 0.47 | | | 0.44 |
| No | 49 (57.6) | 1.00 | | 75 (55.6) | 1.00 | |
| Yes | 11 (61.1) | 0.71 (0.28–1.80) | | 7 (35.0) | 0.72 (0.31–1.65) | |

[a] row percentage

[b] SEER Cox regression model adjusted for age at diagnosis (15–19, 20–24, 25–29, 30–34, 35–39, 40–44), race (White, Black , Other), grade (1, 2, 3), chemotherapy (no/unknown, yes), SEER registry, and diagnosis year (1992–1995, 1996–1999, 2000–2003, 2004–2007, 2008–2011, 2012–2014)

[c] p-value from multivariable-adjusted Cox model

[d] NCDB Cox regression model adjusted for age at diagnosis (15–19, 20–24, 25–29, 30–34, 35–39, 40–44), race (White, Black , Other), grade (1, 2, 3), chemotherapy (no/unknown, yes), diagnosis year (2004–2007, 2008–2011, 2012–2015), and region