



# Risk of Ovarian Malignancy in Patients Undergoing Radical Cystectomy for Bladder Cancer

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<b>OBJECTIVE</b>	To determine whether there is an increased risk of ovarian cancer in women undergoing radical cystectomy (RC) for bladder cancer using a large population-based data source. Current American Urologic Association guidelines suggest removal of ovaries during RC in women with bladder cancer, presumably to mitigate the risk ovarian cancer. However, recent data have demonstrated an increased risk of all-cause mortality, cardiovascular disease, osteoporosis, cognitive impairment, and diminished sexual function in some populations of women after oophorectomy.
<b>METHODS</b>	We queried the surveillance, epidemiology and end results (SEER) database for all women with a diagnosis of primary bladder cancer who underwent RC between 1998 and 2010. Patients with concurrent or subsequent primary ovarian cancer were then identified using the SEER multiple primaries dataset. Multiple primary standardized incidence ratio was calculated as an estimate of the relative risk of a concurrent or subsequent ovarian malignancy using SEER*Stat software.
<b>RESULTS</b>	A total of 1851 women met inclusion criteria for analysis. Of this population, 221 (11.9%) women developed a subsequent nonbladder malignancy, of which 2 (0.11%) women developed subsequent ovarian cancer during the observation period. Multiple primary standardized incidence ratio for development of an ovarian malignancy was 2/4 (0.50).
<b>CONCLUSION</b>	The risk of concurrent or subsequent ovarian malignancy in women undergoing RC for bladder cancer is very low. Therefore, oophorectomy at the time of RC may be obviated in order to mitigate the undue risk of cardiovascular disease, osteoporosis, cognitive impairment, and diminished sexual function. UROLOGY 123: 181–185, 2019. © 2018 Elsevier Inc.

There will be an estimated 18,810 new cases of bladder cancer in women in 2018 with a median age of 73 at diagnosis.<sup>1,2</sup> Approximately 30% of these cases will be muscle-invasive at the time of presentation.<sup>3</sup> Many of these women will undergo radical cystectomy (RC) as it is the gold standard for treatment of muscle-invasive bladder cancer (MIBC) and non-MIBC refractory to Bacillus Calmette-Guérin (BCG) intravesical therapy.<sup>4</sup>

The 2017 American Urological Association (AUA) guideline on treatment of nonmetastatic MIBC states that a standard RC in women should include removal of the uterus, fallopian tubes, ovaries, and anterior vaginal wall.<sup>5</sup> This guideline is based on the clinical principle that these

organs may have a high risk of harboring tumors that extend beyond the bladder through direct extension and metastatic spread. With regard to the ovaries, some advocate oophorectomy in the event there is occult ovarian cancer at the time of RC.<sup>6,7</sup> Presently, there are no high-quality studies to substantiate this clinical principle.

Several studies on oophorectomy have demonstrated an increased risk of all-cause mortality, cardiovascular disease, and osteoporosis in both premenopausal and postmenopausal women.<sup>8-14</sup> Additionally, premenopausal women may bear an increased risk of cognitive impairment and diminished sexual function.<sup>15,16</sup> Furthermore, it is now understood that most ovarian malignancies originate in the fallopian tubes, suggesting that salpingectomy at time of RC is warranted as a prophylactic measure.<sup>17,18</sup> Despite the potential benefits of ovary-sparing surgery in postmenopausal women, a standard RC in women continues to include oophorectomy.<sup>5</sup>

We sought to determine whether there is an increased risk of concurrent or subsequent primary ovarian cancer in women undergoing RC for bladder cancer using a large population-based data source in order to evaluate the necessity of performing oophorectomy at the times of RC.

This study received approval from the University of Oklahoma Institutional Review Board.

**Financial Disclosures:** The authors declare that they have no relevant financial interests.

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Submitted: August 27, 2018, accepted (with revisions): October 3, 2018

## MATERIALS AND METHODS

The National Cancer Institute's (NCI) surveillance, epidemiology, and end results (SEER) database captures 28% of all cancer cases diagnosed in the United States.<sup>19</sup> Thirteen core registries of the SEER database were queried to identify eligible women who underwent RC for bladder cancer. The search included all women above the age of 18, who were diagnosed between 1998 and 2010 with the following bladder cancer subtypes as their first reported malignancy: transitional cell carcinoma, adenocarcinoma, squamous cell carcinoma, papillary transitional cell carcinoma, and papillary carcinoma (ICD-03: 8120, 8140, 8070, 8130, 8131, and 8050). We further narrowed our cohort by including only women who then underwent RC (surgery codes 50–80: 50 = simple/total/complete cystectomy; 6× = complete cystectomy with reconstruction; 7× = pelvic exenteration; 80 = cystectomy, not otherwise specified). It is important to note that there is no code to specify ovary-sparing surgery.

The SEER Multiple Primary and Histology Coding Rules are a set of rules used to standardize cancer registries, thereby facilitating the process of forming a dataset of patients with multiple primaries.<sup>20</sup> This process allowed for the identification of women in the RC cohort with concurrent or subsequent ovarian malignancy diagnoses. SEER\*Stat software was then used to estimate relative risk of ovarian cancer incidence by calculating a multiple primary standardized incidence ratio (MP-SIR). The SEER MP-SIR, as previously described,<sup>21</sup> is the number of women observed to have a malignancy of interest in the study population divided by the number of age/gender/time-matched patients in the general population expected to have that malignancy during the observation period.

## RESULTS

A total of 1851 eligible women with primary bladder cancer diagnosed between 1998 and 2010 were treated with RC and met our inclusion criteria. **Table 1** presents the demographic and clinical characteristics of this cohort. A majority of patients had regionally advanced disease (n = 1489, 80.4%), while fewer had localized (n = 167, 9.0%) or distant disease (n = 182, 9.8%). Pelvic exenterations (surgery codes 70–74) were the most common surgeries recorded (n = 1550, 83.7%).

A second malignancy was reported in 221 (11.9%) women, only 2 (0.11%) of which were ovarian. **Table 2** describes the ovarian cases. One case involves a non-Hispanic, Caucasian female who was diagnosed with grade IV clinical stage T2 localized muscle-invasive bladder cancer at age 75-79 in 2006 and left local ovarian serous cystadenocarcinoma 24 months later. She then died 103 months after her bladder cancer diagnosis due to a noncancer cause. The second case involves an Asian/Pacific Islander female who was diagnosed with grade III clinical stage T1 non-muscle-invasive bladder cancer at age 55-59 in 1999 and

**Table 1.** Demographic and Clinical Characteristics of the Study Cohort

	Total Population N = 1851 n (%)
Race	
White	1539 (83.1)
Black	184 (9.9)
Asian/Pacific Islander	118 (6.4)
American-Indian	5 (0.3)
Age at diagnosis	
21-30 y	2 (0.1)
31-40 y	25 (1.4)
41-50 y	133 (7.2)
51-60 y	331 (17.9)
61-70 y	521 (28.1)
71-80 y	587 (31.7)
≥81 y	251 (13.6)
Unknown	1 (0.1)
Mean, Median, (Range)	67.7, 69, [24-99]
Year of diagnosis	
1998-2001	570 (30.8)
2002-2005	571 (30.8)
2006-2010	710 (38.4)
Stage at diagnosis	
Local	167 (9.0)
Regional	1489 (80.4)
Distant	182 (9.8)
Grade	
I	13 (0.7)
II	121 (6.5)
III	782 (42.2)
IV	860 (46.5)
Unknown	75 (4.1)

left local ovarian small cell carcinoma 5 months later. She is still living as of the last SEER update in 2014. MP-SIR for development of an ovarian malignancy in our study cohort compared to the general population of age/gender/time-matched controls is 2/4 (0.50).

**Table 2.** Characteristics of Women with Subsequent Ovarian Malignancy

	Woman #1	Woman #2
Age	75-79	55-59
Race	White, non-Hispanic	Asian/ Pacific Islander
Marital status at BC diagnosis	Widow	Widow
Year of BC diagnosis	2006	1999
Clinical BC stage at diagnosis	T2b	T1
BC grade	IV	III
Year of ovarian cancer diagnosis	2008	2000
Ovarian cancer stage	Local	Local
Laterality	Left ovary	Left ovary
Cause of death	Noncancer cause	Living as of 2014

## DISCUSSION

Our results demonstrate that women undergoing RC for bladder cancer have a negligible risk (0.11%) of concurrent or subsequent primary ovarian malignancy compared with the general population. These results are consistent with a 2012 retrospective pathological analysis of 360 female RC cases in which all ovaries removed were normal regardless of bladder cancer stage, and all preserved ovaries showed no signs of disease upon follow-up.<sup>22</sup>

Based on the recent work of Liedberg et al<sup>6</sup> and a survey completed by 159 members of the Society of Urologic Oncology,<sup>7</sup> there are 4 cited rationales for oophorectomy at time of RC: (1) the risk of bladder cancer metastasis to the ovaries, (2) the risk of reoperation for future ovarian disease, (3) the belief that there is little impact on quality-of-life and all-cause mortality, and (4) the efficiency of en bloc hysterectomy with bilateral salpingo-oophorectomy (BSO) during lymph node dissection. Despite the recommendation of the AUA guideline on treatment of nonmetastatic MIBC to remove ovaries, there is a lack of high quality evidence to support it.

A 2006 NCI monograph written to provide incidence data on multiple primary cancers found that among 24,029 women with any stage of bladder cancer diagnosis, 81 (0.34%) developed a subsequent primary ovarian malignancy. This produced an MP-SIR (O/E) of 0.99.<sup>21</sup> The discrepancy between the NCI and our MP-SIR (0.99 and 0.50 respectively) may be explained by the fact that all women with bladder cancer regardless of the method of treatment were included in the monograph's calculations. This means that the effects of oophorectomy at the time of RC are minimized when calculating MP-SIR as it is unclear how many women underwent RC, and whether the RC's were standard or ovary-sparing. More data on the outcomes of women who underwent specified ovary-sparing RC are needed.

The postmenopausal ovary continues to operate as a site of androgen production, which provides precursors for estrogen. Oophorectomy causes a significant decrease in free and total testosterone levels that is not seen in natural menopause because ovarian stromal testosterone continues to function after all follicles are lost.<sup>8,9</sup> Loss of androgen production from the ovaries may be a major factor in the development of issues associated with oophorectomy including increases in all-cause mortality, cardiovascular disease, osteoporosis, and psychosocial distress.

Multiple large cohort studies have noted an association between all-cause mortality and oophorectomy, including the Mayo Clinic Cohort Study of Oophorectomy and Aging,<sup>23</sup> the Nurses' Health Study,<sup>14</sup> the Breast Cancer Detection Demonstration Project,<sup>24</sup> and the English Healthcare Registries.<sup>25</sup> Only 1 such study—the Women's Health Initiative<sup>26</sup>—did not find a similar association. The Nurses' Health Study, a prospective observational study of 30,117 women over 28 years, found a significantly increased risk of death from any cause in women who underwent hysterectomy with BSO compared with simple

hysterectomy, with a number needed to harm of only 8.<sup>14</sup> Additionally, a Dutch breast cancer screening cohort (n = 12,134) found that each year of delayed menopause decreased total mortality by 2% per year.<sup>27</sup> Taken together, the preponderance of data suggests an increased risk of all-cause mortality was seen particularly for women age <50, with no survival benefit noted in any age group.<sup>8</sup>

Contributors to increased mortality after BSO include cardiovascular disease, increased osteoporotic fracture risk and cognitive decline, with risk most pronounced among women who undergo oophorectomy at younger ages. A secondary analysis of the Women's Isoflavone Soy Health trial demonstrated that the rate of bone mineral density loss and vascular thickening was double in women who had undergone oophorectomy compared to those with retained ovaries, an effect that grew more pronounced further from menopause.<sup>11</sup> Among large cohort studies that have reported on the question of cardiovascular disease after oophorectomy, several<sup>14,28,29</sup> but not all<sup>26</sup> have largely noted a deleterious effect. Because there is clear evidence that estrogen deficiency is a contributor to bone loss,<sup>30</sup> women who undergo BSO prior to natural menopause can be expected to have greater risk of bone loss following surgery, but there is some evidence that even postmenopausal women can experience adverse fracture outcomes following oophorectomy. A retrospective study of 340 postmenopausal women who underwent oophorectomy an average of 14 years postmenopause investigated the risk of bone fractures. This group experienced a 32% increase in overall fracture risk and a 54% increase in fractures traditionally associated with osteoporosis (hip, spine, or distal forearm fractures) compared to expected population rates.<sup>12</sup>

In addition, poor psychosocial outcomes after surgical menopause have been documented, particularly in premenopausal women. A 2016 secondary analysis combining data from 3 randomized controlled trials found that surgical menopause after age 45 decreased performance in verbal learning and visual memory, and before age 45 decreased performance in semantic memory compared with natural menopause.<sup>16</sup> A 2015 cross-sectional study showed that subjectively, both pre- and postmenopausal women experience similar rates of sexual dysfunction (including lack of desire, dyspareunia, and difficulty achieving orgasm) after BSO, with greater sexual distress and dissatisfaction, poorer emotional wellbeing, and greater psychological distress related to their surgery among premenopausal women.<sup>15</sup>

The American College of Obstetricians and Gynecologists now recommends bilateral salpingectomy (with ovarian preservation) when performing hysterectomy or sterilization procedures as prophylaxis to reduce the risk of ovarian cancer.<sup>18</sup> This recommendation is based on research that suggests most ovarian cancers originate in the distal fallopian tube.<sup>17</sup> According to a 2017 survey completed by 159 Society of Urologic Oncology members, only 14.2% were aware that salpingectomy alone decreases the risk of ovarian cancer.<sup>7</sup>

The 2017 AUA guideline on treatment of nonmetastatic MIBC states that a standard RC in women should include removal of the uterus, fallopian tubes, ovaries, and anterior vaginal wall. Based on our findings demonstrating a negligible risk of ovarian malignancy, and the risks associated with oophorectomy, consideration should be given to exclude the removal of ovaries, and emphasize that salpingectomy alone reduces future risk of ovarian cancer. The guideline should encourage an individualized approach in which surgeons lead an open and informed discussion of the risks and benefits of ovarian conservation with each patient. For example, in a patient with known risk factors for developing ovarian cancer such as a BRCA mutation and nulliparity, oophorectomy at the time of RC may be warranted. Whereas, in a multiparous, sexually active postmenopausal patient with osteoporosis and no strong familial history of breast or ovarian cancer, the risks of oophorectomy may outweigh the benefits. In concordance with our findings, the current European Urological Association guideline for the extent of a standard RC in women omits removal of ovaries.<sup>31</sup>

We acknowledge a number of limitations in our study. Primarily, there is no way to track the presence of ovaries in these women using the SEER database. Therefore, our study makes the following 2 assumptions: (1) most women had ovaries at the time of bladder cancer diagnosis, and (2) most women had their ovaries removed at the time of RC. Our incidence ratio is affected by these assumptions, which may explain the very low value. Further studies specifically designed to follow women who underwent ovary-sparing RC are needed to more conclusively determine the risk of subsequent ovarian malignancy.

Additionally, subsequent malignancies are underreported for women who migrate out of the areas covered by the SEER registries or who die of other causes while harboring subclinical malignancies. Despite the limitations, this study provides evidence that ovary-sparing RC should be offered to patients when discussing treatment options.

## CONCLUSION

There is a negligible risk of primary ovarian malignancy at the time of RC. Given the potential health benefits of ovarian preservation, even in postmenopausal women, ovarian sparing cystectomy should be more strongly considered. Thus, guidelines describing a standard RC should exclude the removal of ovaries with an individualized approach in which there is an open and informed discussion of the risks and benefits prior to RC. However, more rigorously designed studies are needed to precisely gauge the risks of ovarian conservation in the population of women undergoing RC for bladder cancer.

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