

Mortality difference by Gender and Race in Squamous Cell Cancer of the Bladder

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**Abstract**

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**Introduction.** Squamous cell carcinoma (SCC) of the bladder is a rare form of bladder cancer with unique clinical features. Prior studies have shown that gender and race influence survival following the diagnosis of bladder cancer, but no study has assessed the importance of these factors in SCC alone. We used a large, population-based cancer registry to assess the effect of gender and race on survival following the diagnosis of SCC of the bladder and identify factors that may modify this effect.

**Materials and Methods.** Cases of SCC of the bladder were identified from all registries available through the Surveillance, Epidemiology, and End Result (SEER) cancer registry from 1988 to 2008. In addition to cancer location and histology, data were collected on race and gender, as well as covariates such as age, treatment received, stage, and grade. Survival differences were assessed using Kaplan-Meier curves, log-rank testing, and cox-proportional hazards modeling.

**Results.** We identified 1,969 cases of SCC for analysis. The cohort was 49.5% female and 85.5% white. Stage and grade were found to modify the effect of gender on survival and the results for gender were stratified by these variables. Women with low-grade, low-stage disease had a 2.87 higher risk of death than their male counterparts (95% CI HR 1.27-6.47,  $p=0.011$ ) while a significant difference was not found for other stages or

grades. Women with localized disease and node-positive disease were also at higher risk of death (HR 1.20, CI 1.04-1.39, p=0.011 and HR 1.40, 95% CI 1.01-1.95, p=0.041, respectively). Finally, black men had a significantly increased risk of death over white men (HR 1.35, 95% CI 1.04-1.76, p=0.026) while black women had a non-significantly increased risk of death over white women (HR 1.16, 95% CI 0.92-1.47).

**Conclusions.** These results show gender and race are significant predictors of survival following the diagnosis of SCC of the bladder. These differences exist after stratifying by disease stage, grade, and primary treatment. Unmeasured factors related to either disease pathology or treatment may account for this survival difference.

## **Introduction**

Squamous Cell Carcinoma (SCC) of the bladder accounts for <3% of bladder cancer diagnoses in the United States, with unique clinical features compared to the more common Urothelial Carcinoma (UC).<sup>1</sup> While the most common risk factor for both SCC and UC in the United States is smoking, SCC has several other risk factors which are unique. Worldwide, SCC of the bladder is commonly associated with schistosomiasis infection, although this infection is not seen in the United States.<sup>2</sup> In the United States, SCC of the bladder is associated with conditions that cause chronic inflammation including long-term urinary catheterization, bladder calculi, recurrent urinary tract infection, and bladder stones. Many of these risk factors, such as recurrent urinary tract infection, are more common in females. As result, while SCC is more common in men than women, this disparity is not nearly as pronounced as it is for UC and appears to be

decreasing.<sup>3,4</sup> It is also notable that, in contrast to UC of the bladder, SCC of the bladder is twice as common among blacks as whites.<sup>4</sup> In addition to differences in risk factors, SCC also differs from UC in the pattern of recurrence and spread, with the vast majority of failures and deaths from SCC due to locoregional recurrence.<sup>5,6</sup>

Prior studies have documented survival differences among patients with UC of the bladder based on demographic factors, like gender and race. Unadjusted for stage or type of cancer, 5-year survival from bladder cancer is significantly better in men than in women and is significantly better among whites.<sup>7,8</sup> While this may be due, in part, to the tendency for women to present with more advanced stage tumors and a higher percentage of poor histology tumors, a recent study found that women have an increased mortality rate in the first three years after diagnosis even after adjusting for stage and histology.<sup>8</sup>

To our knowledge, no prior study as specifically assessed the survival difference by gender and race among those diagnosed with SCC of the bladder. Given that relative to UC a higher percentage of SCC cases involve women and blacks in the United States, a difference in mortality from SCC based on these factors would be significant. However because of the differences in etiology, biology, and pattern of recurrence between SCC and UC, it is possible the survival differences by gender and race seen with UC are different in SCC. To address this question, we used a prospective population-based cohort to assess the effect of gender and race on stage-specific survival following diagnosis of SCC of the bladder. We also assessed factors that could modify the potential survival difference including primary treatment, tumor stage and grade.

## **Materials and Methods**

*Case Identification.* Cases were identified from the Surveillance, Epidemiology, and End Result (SEER) cancer registry from 1988 to 2008. From 1988 onward, data from the following 9 registries were available: Atlanta, Ga; Detroit, Mich; San Francisco-Oakland, California; Seattle-Puget Sound, Wash; Connecticut; Hawaii; Iowa; New Mexico; and Utah. Beginning in 1993, data from 4 additional registries were available: Alaska; San Jose-Monterey, California; Los Angeles, California; and Rural Georgia. Finally, in 2000 four additional registries were added: Greater California; Kentucky; Louisiana; and New Jersey. Cases of pure squamous cell carcinoma of the bladder were identified using the International Classification of Disease-Oncology (ICD-O-3) codes 8070-6 and 8078 representing SCC in situ, SCC, keratinizing SCC, large cell non-keratinizing SCC, small cell non-keratinizing SCC, spindle cell SCC, adenoid SCC, carcinoma in situ with questionable stromal invasion SCC, microinvasive SCC, and SCC with horn formation. Gender was available for all cases. Those without information available on cause specific death were excluded from analysis. Because cause specific death is only available through SEER for a patient's first tumor, those who had a first tumor other than SCC of the bladder were excluded from analysis.

*Outcome.* The primary outcome was death due to SCC as determined through hospital or death certificate data by the SEER registry. Survival data was available through 2010.

*Covariates.* Additional covariates were age (in years), year of diagnosis, race (white, black, or other), tumor stage, histologic grade, lymph node status, presence of metastases, and primary treatment. Tumor stage was classified according to the American Joint Committee on Cancer (AJCC) guidelines as follows: Ta – superficial papillary, Tis – superficial in situ, T1 – invasive to lamina propria, T2 – invasive to muscularis propria, T3 – Extends into perivesical fat, T4 – direct extension to adjacent organs. Tumors were graded on a scale according to the ICD-O-3 grading system as follows: 1 – well differentiated, 2 – moderately differentiated, 3 – poorly differentiated, 4 - anaplastic. For the purposes of reporting, grade was further classified as low (grade 1 or 2) or high (3 or 4). Lymph nodes were defined as negative, regional (pelvis only), or distant (common iliac or above). Metastases were defined as not present (M0), present (M1), or not assessed (Mx). Primary treatment was classified as none, transurethral only, surgery, radiation, or combination.

*Statistical Analysis.* Differences in disease specific survival and overall survival between men and women were first assessed using Kaplan-Meier curves. Adjusted survival analysis was then performed using Cox proportional hazards regression modeling. Condensed variables for stage and grade were created because of the small number of cases for the individual strata of these variables. Groups were based on clinically meaningful cut-points. For stage, the presence of muscle invasion is often an important clinical factor that guides treatment. Therefore, stage was condensed as follows – non muscle-invasive or low stage (Ta,Tis,T1), muscle invasive or high stage (T2-T4). For grade, tumors classified as grade 1 or 2 are thought of more differentiated, and therefore

low stage, while the reverse is true for grade 3 or 4 tumors. The initial hazards model included the condensed variables and the covariates described above.

The validity of the proportional hazards assumption was assessed using Schoenfeld residuals analysis. This showed that the proportional hazards assumption was not valid for the all-inclusive model and, therefore, results of this model are not reported. There was also a clear interaction between tumor stage and grade and the survival difference between men and women. To address this issue, further analyses were stratified based on tumor grade and stage. These models were again assessed using Schoenfeld residuals analysis and visual inspection. The proportional hazards assumption was not violated for these models. Therefore, results of the adjusted analysis are reported as stratified by the covariates of interest.

**Results** During the years 1988-2008, we identified 2516 people with SCC of the bladder. Of these cases, 547 were excluded due to lack of data on cause specific death, leaving 1,969 cases for analysis, 974 women and 995 men. There were 1,559 deaths, 1,216 due to SCC of the bladder, 638 among women and 578 among men. Among those who died, the median time to death was 5 months (interquartile range (IQR) 2-11 months) while among those who did not die the median follow-up time was 29 months (IQR 5-84 months). Women tended to be older at diagnosis than men (Women: 71.9 standard deviation (SD) 13.3; Men: 69.5 SD 13.1 years;). Women were more likely to have endoscopic only or no treatment while men were more likely to have surgery. A similar percentage of women and men had radiation treatment (14.4% v. 13.7%, respectively). A higher percentage of men were white (85.9% v. 83.6%, respectively) while a higher percentage of women

were black (12.8% v. 10.1%). The distribution of stage, grade, lymph node involvement, and metastases were similar between the genders (Table 1).

Unadjusted analysis showed that survival differed by gender and race. For all stages and grades, women had poorer survival than men (log-rank p-value = 0.0007). When grouped by stage and grade, women with low grade-low stage disease had worse survival than men (log-rank p-value = 0.0012). However, survival was not significantly different between men and women in the other stage and grade categories (Figure 1). Blacks also had poorer unadjusted survival than whites (log-rank p-value = 0.0006). When stratified by race, black males had significantly worse survival than white males (log-rank p-value = 0.0022) while black females had an insignificant trend toward worse survival (log-rank p-value = 0.0901). There were no differences in survival between men and women among those with metastatic disease or among any of the treatment strata.

Multivariate adjusted analysis using cox-proportional hazards modeling, stratified as described above, revealed similar results to the unadjusted analysis. Women with low-grade, low stage disease had an increased risk of death due to SCC of the bladder (HR 2.87 CI 1.27-6.47, p=0.011) as did women with localized (HR 1.20, CI 1.04-1.39, p=0.011) and node positive cancer (HR 1.40, 95% CI 1.01-1.95, p=0.041). There was no difference in survival by gender among those with metastatic disease or within any treatment category. (Table 2) When stratified by gender, black men had a significantly increased risk of death over white men (HR 1.35, 95% CI 1.04-1.76, p = 0.026) while the

difference between black women and white women was not significant (HR 1.16, 95% CI 0.92-1.47). (Table 3)

## **Discussion**

In this study, we found that both gender and race were predictors of survival following the diagnosis of squamous cell carcinoma of the bladder. Women with low-grade, low-stage disease had the most pronounced decrease in survival compared to men, although poorer survival was also seen among women with localized and lymph node positive disease. Survival was similar among men and women with higher stage and metastatic disease. In terms of race, both black men and women had higher estimated risks of death from SCC than whites, though the differences was not statistically significant among women.

To our knowledge, this is the first study to report the impact of both gender and race on survival from SCC of the bladder. This study extends the findings of a study by Ploeg and colleagues using a Netherlands-based cohort with 730 patients with muscle-invasive SCC and 26,594 patients with UC. Relative survival was 6.7% worse among women with SCC than men.<sup>9</sup> A previous study by Scosyrev and colleagues using the SEER cohort from 1988-2003 found that those with advanced stage SCC of the bladder had worse survival than those with advanced stage UC, but the impact of race and gender were not reported.<sup>3</sup> While several studies have reported differences in the incidence of SCC by gender and race, these studies did not assess mortality.<sup>1,4</sup> Outcomes from a recent case

series of SCC of the bladder including 27 patients reported that treatment with radical cystectomy was associated with improved survival but did not assess for a difference by gender.<sup>10</sup>

The explanation for the survival difference between women and men in this study being limited to localized or low stage disease is unclear. Many prior studies have suggested that women and African Americans have worse survival from bladder cancer because of differences in stage at presentation.<sup>11, 12</sup> However, more recent studies have shown survival is worse among these groups after controlling for stage.<sup>3, 13, 14</sup> The current study supports the hypothesis that for SCC, the survival difference by gender and race is not fully accounted for by differences in stage at diagnosis. Some of these same studies have shown that women and African Americans are more likely to present with higher risk tumor types, SCC being one of them.<sup>8</sup> This study addresses that by limiting our analysis to SCC only. It is possible that among patients with SCC, women and African Americans tend to have more biologically aggressive variants of the disease. This has been hypothesized, particularly to explain racial differences, in prostate and breast cancer.

A recent paper by Jacobs and colleagues addressing the poorer survival seen among women and African Americans with bladder cancer argues that the causes are likely multifactorial.<sup>15</sup> Differences in access to care, both at time of presentation and for ongoing disease monitoring and treatment, are likely to be important. Differences like this could only be assessed in a limited way in this study, mainly by controlling for primary treatment received. While women were less likely to receive cystectomy than

men, the difference in survival by gender did persist after controlling for this factor. The possibility that a difference in follow-up, disease monitoring, and other aspects of care accounts for this difference remains. Since lower stage bladder tumors are often treated with endoscopic resection followed by close follow-up, many times with repeat resection, to prevent disease progression, this may explain why the survival difference by gender was limited to low stage disease.

Several limitations must be acknowledged when interpreting this data. Death data obtained through the SEER database comes from death-certificate data, which may not accurately reflect true cause of death. Prior studies have suggested a high level of agreement between death certificate data and medical record abstracted cause of death in cancer patients, especially for those patients with a single primary cancer.<sup>16</sup> Also, there is neither central pathology review through the SEER database nor for this study in particular. We attempted to limit the potential impact by including only those pathology codes used for pure SCC of the bladder and excluding those with squamous differentiation of another histologic tumor type. With regard to race, it is certainly possible that survival differences for other races exist. However, in this study the analysis of race is limited to black and white because of the low number of cases of other races. Missing data could also affect risk estimates. While there was no missing data for gender and it was rare for race, percent data missing for stage and grade variables ranged from 14.5-19.7%. Importantly, the percent missing for any individual variable was similar between the two sexes, which would argue against missing data biasing the final risk estimates toward the positive. It is more likely that missing data would make a true

difference harder to detect. As discussed above, the possibility of unmeasured treatment, monitoring and demographic factors creating residual confounding exists. Data regarding treatment is limited to initial surgery or radiation and data regarding behavioral and lifestyle factors as well as follow-up are not available. It is possible that one of these unmeasured factors could explain the observed survival difference. The finding that the survival difference by gender is most pronounced among those with low-grade, low-stage disease is provocative; however, there were a limited number of observations in this group.

Despite these limitations, the current study used a larger number of SCC cases, a higher proportion of women, and a wider range of disease stages than previous studies to demonstrate that survival following the diagnosis of SCC of the bladder is influenced by gender and race. While the rarity of pure SCC of the bladder in the western world makes it difficult to study prospectively, there are several possibilities for further study. The most important of these would be validating the findings of the current study using a similarly large cohort. The National Cancer Database (NCDB) may provide a cohort of similar size with the necessary information. While this cohort would also come from the United States, it is different from SEER in that it include data from all 50 states. The NCDB does track the necessary data on disease stage and grade and captures approximately 40,000 cases of bladder cancer per year.<sup>17</sup> One of its limitations is that it is not truly population-based and relies on hospitals to capture diagnoses. However, adequate information should be available to perform a similar analysis. In addition, use of a cohort in which information is available regarding intensity of follow-up and additional

treatments may provide additional information on the disparities seen here. Identifying this cohort may be challenging given the resources required to track this data and the rarity of SCC of the bladder. A prospective, multi-center effort may be required to achieve this goal.

## Conclusions

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