INTRODUCTION

Cigarette smoking is considered a major environmental risk factor for bladder cancer.1-5 Black men reportedly have a higher prevalence of smoking than White men.2 However, the incidence of cancer of the urinary bladder, ureter, and renal pelvis is higher in White men.6 Therefore, it is counter-intuitive that Black men, who are known to have higher rates of smoking, also have lower rates of urinary bladder cancer than White men.

The major histological types of bladder cancer are transitional cell carcinoma (TCC), squamous cell carcinoma (SCC), and adenocarcinoma (AC), comprising 90%, 5% and 2% respectively, of all carcinomas.7,8 The bladder is lined by transitional epithelium, which leads to a high percentage of TCC. Until recently, the prevalence rates of smoking have been higher among Blacks than among Whites.2,9,10 In 1985, the rate of smoking among Blacks was greater than the rate among Whites (35.4% versus 29.4% respectively), but the rates in 2008 are nearly equal between the two (21.3% and 22% respectively).2,9,10 In view of this trend, the incidence of TCC of the bladder should be higher among Blacks when compared with their White counterparts, especially since Blacks have higher rates of other tobacco-related cancers, including lung. We have explored this apparent dichotomy from a population-based perspective for urothelial cancers in both Black and White men. Our approach is based on the hypothesis that population-based age-incidence rate patterns of Black and White urothelial cancers could yield additional insights into cancer etiology and pathogenetic relationships in both groups. The current study was designed as a descriptive analysis of the urothelial cancers reported in the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute.11 Because the SEER Program is now very large, sufficient cases are available to include the ureter and renal pelvis in the analysis for comparative purposes.

METHODS

Data Source

Data were obtained from NCI’s SEER Program. SEER was
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instituted in 1973 with nine registries. In 1992, SEER expanded to include 13 registries in the states of Connecticut, Hawaii, Iowa, New Mexico and Utah and the greater San Francisco/Oakland, San Jose/Monterey, Los Angeles (California), Detroit (Michigan), Seattle (Washington) metropolitan areas as well as Atlanta and rural Georgia and the Alaska Native Registry. Ultimately, SEER collects and publishes data from population-based cancer registries representative of nearly 26% of the U.S. population. The estimated ascertainment rate of the SEER Program is approximately 95%.12

Rates for TCC of the bladder, ureter, and renal pelvis for Black and White men between 1973 and 2007 were calculated using the initial nine SEER registries, which included Katrina and Rita population adjustments. All other racial/ethnic groups were excluded. Overall, there were 231,298 cases of TCC of the urinary bladder in the U.S. Only 10,632 and 6,422 cases of TCCs of the renal pelvis and ureter, respectively, were available through SEER.11 For listing individual cases, the SEER 17 registry database was used, which includes all registries from SEER 13 as well as Greater California, Kentucky, Louisiana and New Jersey. This database makes cases diagnosed from 2000 available and is also adjusted for Hurricane Katrina.11 Incidence rates, expressed per 100,000 persons, were age-adjusted to the 2000 U.S. Standard Population.

Histopathologic Codes

Patients diagnosed with urothelial carcinomas were identified using SEER codes generated from the International Classification of Diseases for Oncology (3rd edition, ICDO-3) published by the World Health Organization (1992). ICD-O code numbers 8120, 8130, and 8131 were used for TCC; 8070, 8075, 8083, 8084, 8071, 8072, and 8052 for SCC; and 8140 for AC. In situ carcinomas were excluded. Information on anatomic site was using ICD-O-3 topography codes. Cases based only on death certificates or results of an autopsy were excluded.

County Data

Individual county rates for Black and White men were acquired through SEER for cancers of the urinary bladder, renal pelvis, and ureter. There were 210 counties available for analysis among White men and only 69 counties that contained sufficient cases for analysis among Black men. The county rates which deviated two standard deviation points from the mean were discarded. For renal pelvis cancers, there were 189 counties with sufficient cases of White men and only 29 counties with sufficient cases of Black men. Lastly, 174 counties were available among White men with cancers of the ureter, but only 25 counties were available for Black men.

Statistics

The age frequency distribution was obtained by dividing the number of cases in each age group by the total number of cases listed for Black and White men. Linear regression was performed between lung cancer and bladder cancer, using rates from individual counties. The purpose was to determine whether variations in lung cancer, and by extension, smoking, affected the rates of bladder cancer in both racial groups. This was essentially a dose-response relationship within a population as opposed to a stratification of individuals with respect to exposure history and disease occurrence. Data points that were more than two standard deviations from the mean were considered outliers and were removed. The Pearson correlation coefficient and the R-squared value were also obtained. Additionally, the linear models were extrapolated to the Y-axis to estimate the incidence of bladder cancer in the hypothetical absence of lung cancer, that is, when there is no smoking in the population and the rate of lung cancer is “0.0”. Rate data were imported into the computer program Mathematica® for regression analysis. Since the study was limited to men, lung cancer rates were calculated only for men in the SEER counties.

RESULTS

Table 1


<table>
<thead>
<tr>
<th></th>
<th>Overall Rate</th>
<th>Blacks</th>
<th>Whites</th>
<th>Men</th>
<th>Women</th>
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<tbody>
<tr>
<td>Bladder</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCC</td>
<td>20.9</td>
<td>22.5</td>
<td>22.5</td>
<td>28.8</td>
<td>9.8</td>
</tr>
<tr>
<td>SCC</td>
<td>0.3</td>
<td>0.6</td>
<td>0.3</td>
<td>0.5</td>
<td>0.3</td>
</tr>
<tr>
<td>AC</td>
<td>0.2</td>
<td>0.2</td>
<td>0.1</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>Renal Pelvis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCC</td>
<td>0.9</td>
<td>0.5</td>
<td>0.9</td>
<td>1.8</td>
<td>0.6</td>
</tr>
<tr>
<td>SCC</td>
<td>0.61</td>
<td>0.03</td>
<td>0.62</td>
<td>0.61</td>
<td>0.02</td>
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<tr>
<td>AC</td>
<td>0.004</td>
<td>0.003</td>
<td>0.004</td>
<td>0.004</td>
<td>0.003</td>
</tr>
<tr>
<td>Ureter</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCC</td>
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<td>0.7</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>SCC</td>
<td>0.003</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>AC</td>
<td>0.003</td>
<td>0.002</td>
<td>0.003</td>
<td>0.003</td>
<td>0.002</td>
</tr>
</tbody>
</table>

This study included 182,858 men with urinary bladder cancer; of these, 170,502 (93.4%) had TCC, 1,880 (1.1%) had SCC, and only 1,019 (0.57%) had an AC. For the total number of bladder cancer cases evaluated, the majority was White (167,776 men) with 7,405 Black cases. There were 4,370 men with cancer of the ureter; of these, 4,082 had
TCC, 56 had SCC, and only 14 had an AC. For the total number of ureter cancer cases, 6,080 were White and only 294 were Black. There were 6,762 men with renal pelvis cancer; of these, 6,288 had TCC, 100 had SCC, and only 29 had an AC. For the total number of renal pelvis cancers evaluated, there were a total of 3,961 White cases along with only 125 Black cases. Generally these trends held true for each histological type of bladder cancer. Table 1 provides the rates for each group and anatomic site. For cases of malignant tumors of the urinary bladder, the mean age was 65 for Black men and 67 for White men.

Trends
From 1973 through 2007, rates for TCC of the urinary bladder in White men were significantly higher than for Black men (Figure 1). Overall, the average age-adjusted TCC incidence for Whites was 20 cases per 100,000 men. The average incidence rate for Blacks in the same period was 10.7 cases per 100,000 men. The difference in rates between Blacks and Whites was more pronounced among men than among women (Data not shown).

Figure 1
Age-Adjusted Incidence Rates for TCC of the Urinary Bladder by Year of Diagnosis Among Men (SEER, 1973-2007)

Comparatively, the trend for incidence rates of TCC of the renal pelvis was evaluated to determine if any congruency existed. Figure 2 shows that White men consistently had higher rates in comparison to Black men similar to the trend in the urinary bladder. However, due to the limited number of cases, there is considerable variation seen in the trend. Rates for TCC of the ureter (Figure 3) show a similar pattern.

Figure 2
Age-Adjusted Incidence Rates for TCC of the Renal Pelvis by Year of Diagnosis Among Men (SEER, 1973-2007)

Figure 3
Age-Adjusted Incidence Rates for TCC of the Ureter by Year of Diagnosis Among Men (SEER, 1973-2007)

Age Frequency Patterns
Age frequency plots are seen in Figure 4 for TCC of the bladder for Black and White men. Age frequency plots for TCC of the bladder, ureter, and renal pelvis are shown in Figure 5. Data from both groups were combined because of the limited number of cases of TCC of the ureter and renal pelvis in Blacks. The results reveal congruence in the age frequency distribution of tumor development even though TCC of the bladder is significantly more common in White men.
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Figure 4
Age Frequency Distribution for TCC of the Bladder in Men (SEER, 1973-2007)

Figure 5
Age Frequency Distribution for Cancers of the Urinary Bladder, Renal Pelvis and Ureter in Men (SEER, 1973-2007)

Log-Log Transformation
Figure 6B shows a log-log transformation plot of the age-specific incidence rates for bladder cancer for Black and White men as seen in Figure 6A. While the incidence of bladder cancer is significantly higher in White men, the log-log plot shows parallel rate patterns, which indicate that bladder cancer develops at the same rate in both Black and White men.

Regression and Correlation
To determine the effect of smoking on the rate of bladder cancer, we used lung cancer as a proxy for smoking because in the U.S., an estimated 90% of lung cancer deaths in men are directly associated with cigarette smoking. Regression for Black men (Figure 7) was essentially a
horizontal line and did not significantly differ from 0.0. The R-squared value of 0.0038 for this regression’s best-fit line indicates that the incidence of lung cancer in the population and by extension, smoking, has no significant impact on the incidence of bladder cancer in Black men. However, for White men (Figure 8), the regression did significantly differ from 0.0. The R-squared value of 0.1135 for this best-fit line indicates that lung cancer rates explain over 11% of the variance in bladder cancer rates. The regression equation had a Y-intercept of 25.63 bladder cancer cases per 100,000 men, and a slope of 0.46, indicating that per increase of one case of lung cancer per 100,000 White men, the bladder cancer rate increases by 0.46 cases per 100,000 White men.

Figure 7
Regression of lung cancer and bladder cancer rates for black men

Figure 8
Regression of lung cancer and bladder cancer rates for white men

Since the regression for Black men was based on 56 counties, it seemed prudent to test whether this number was sufficient for analysis. Accordingly, regression was used to test 56 counties randomly selected from the 206 available for White men. The results were similar to the 206 counties, with the regression line differing significantly from 0.0. Thus, we concluded that the regression analysis for Black men was accurate despite only having 56 counties worth of data.

DISCUSSION

Due to the anatomy of the urinary tract, it comes as no surprise that the White rates of TCC in the bladder as well as in the ureter and renal pelvis are higher than in Blacks, which reflects the observation that these sites constitute a field effect.14,15 Thus, the differences in the incidence of urothelial cancers in Black and White men exist along this entire field. The variation in incidence along the bladder, ureter, and renal pelvis most likely reflects the variation in the epithelial surface area of these three sites.

Trends
Since the initiation of SEER in 1973, which was the starting time of our study, White men have clearly had higher rates of carcinomas than Black men along the entire urinary tract; this finding is not surprising since the urinary tract constitutes a carcinogenic field, and therefore may be susceptible to similar carcinogenic agents.

Regression Analysis
While multiple studies have associated cigarette smoking with urinary bladder cancer,2 we have also demonstrated the association in men by using the incidence of lung cancer in counties covered by SEER as a proxy for the incidence of smoking. This approach takes advantage of the large SEER database and substantiates the results of more definitive case-control studies.2,12 The results for White men revealed a decreasing rate of bladder cancer as the rate of lung cancer decreased among the counties.12 Thus, we conclude that there exists an association between the rate of smoking and bladder cancer in White men. However, under the assumption that a linear relationship exists between the incidence of lung and bladder cancers, the extrapolation of the regression to the hypothetical limit of “0.0” cases of lung cancer, i.e. no smoking in the population because of no lung cancer, revealed a base rate of bladder cancer of 25.63 per 100,000 White men and a Pearson’s correlation of 0.3365. This decrease in rate suggests that smoking, as reflected by the rate of lung cancer, does have a role in bladder cancer for White men, but there are other risk factors that are associated with the development of bladder cancer as well.16 Such an extrapolation assumes a linear relationship between the incidence of lung and bladder cancer.

The results for Black men were rather different. The rate of bladder cancer remained almost constant and the regression line was not significantly different from 0.0, which suggests that smoking has only a minimal effect on the incidence of bladder cancer in a population of Black men with a correlation of 0.0197. A potential limitation of this data is that only 56 counties had sufficient cases of bladder and lung cancer of Black men compared to the 206 counties with sufficient cases of White men, despite the results of a regression analysis of 56 randomly selected counties from
the 206 counties, which showed similarity of the 56 randomly selected counties to the 206 counties, allowing the conclusion that 56 counties was acceptable for the analysis of the Black population.

Log-log Plot
Graphical demonstration of the log-log transformation of age-specific rate patterns suggests that rate analyses can provide a useful approach for evaluating the differences in bladder cancer rates between Black and White men. In 1954, Armitage and Doll demonstrated that the age specific incidence rates of certain epithelial tumors have a linear slope when plotted against the age of diagnosis on logarithmic scales.17 The logarithmic transformation of population data confirmed a theoretical equation relating the development of carcinomas to a series of cellular events. In the multistage and derivative 2-step models of carcinogenesis17-19, the development of cancer reflects a series of stochastic cellular changes, which accumulate with age. The relation of the age-specific rate patterns is demonstrated in the log-log plot. A derivative assumption is that the log-log plots of cancers should reflect similarities in etiology or pathogenesis if the slopes are parallel.

While bladder cancer is more common in White men, the log-log plot shows that Black and White men have similar potentials to develop carcinomas with a transitional phenotype albeit at different incidence rates. We conclude, therefore, that despite differences in incidence, the pathogenetic mechanisms for TCC of the bladder are likely to be similar in Black and White men. This suggests that the reason for the lower rates of urothelial cancer in Blacks does not reside in the bladder, but perhaps in the metabolism of cigarette smoke or smoking habits. Many investigators have exploited logarithmically-scaled plots to investigate both the rates and origins of human cancer.20-22

Our results based on population analyses indicate that the causes of cancers all along the urinary tract are most likely similar. With age frequency plots showing similar patterns for the urinary bladder, renal pelvis, and ureter and similar rates of tumor development in log-log plots for the bladder, it seems reasonable to conclude that these cancers most likely share a similar pathogenesis. Specifically, the development of cancer by age frequency is the same in all three sites even though the incidence of cancer varies among the sites. These results also indicate that carcinogenic fields based on clinical observations can be substantiated through descriptive studies in populations.23

Explaining the Differences in Blacks and Whites

Due to the scope of our population study, it was not possible to determine the reason for the differences in urothelial cancers in Black and White men; however, other researchers continue to explore possible reasons for the differences at molecular and metabolic levels. Evidence from such work points to the rate of acetylation as a factor. Cigarette smoke contains a number of carcinogenic compounds including arylamines, which may be responsible for bladder cancer among smokers. As a population, Whites do not detoxify these arylamines as quickly as Blacks through the acetylation reaction. This reaction is catalyzed by N-acetyltransferase, which has two phenotypes, fast and slow reacting;24 this fact may account for the differences in the rate of bladder cancer, which keeps with our observation that the differences will not be found in the bladder mucosa.

Other studies exist including some that suggest that smoking may affect the progression of bladder cancer through the COX-2 signaling pathway.25

Limitations of the Study
Limitations include the relatively small number of cases available for analysis among the Black population. Additionally, SEER does not provide data regarding different risk factors that contribute to observed cancer rates and we were unable to control for them. Ultimately, using lung cancer rates as a proxy measure for smoking requires three assumptions, namely that lung cancer is associated with smoking, that all smokers are at an average risk, and that there is an average intensity and duration for the population due to the effects of smoking.12 The strength of a population-based study rests on the robust nature of the database and the ease of analysis.

CONCLUSIONS

Urothelial carcinomas are more common in White than in Black men and affect the entire field of urothelium. Although more common in White men, malignant tumors of the bladder mucosa develop at the same rate in both Black and White men. Therefore, the pathogenetic mechanisms in the transitional epithelium of the urinary bladder are similar in both racial groups. Consequently, the reason for the different incidence rates in the Black and White male populations is not likely to be found in the bladder mucosa. Overall in the population, smoking seems to be less than a risk factor for cancer of the urinary bladder in Black men in comparison to White men.
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References

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