

# Why Does Rhode Island Have the Greatest Incidence of Bladder Cancer In the United States?

Katherine E. Faricy-Anderson, MD, MPH, John P. Fulton, PhD, Anthony E. Mega, MD

For years, Rhode Island (RI) has had the greatest incidence of bladder cancer in the United States for both men and women. In fact, compared with the United States (US) overall, all of the New England states and New Jersey have disproportionately elevated bladder cancer rates. (Figure 1) From 2002-2006, the age-adjusted incidence of bladder cancer for men was 53.1/100,000 in Rhode Island versus 37.4/100,000 in the US; for women, it was 13/100,000 versus 9.4/100,000, respectively.<sup>1</sup> (Table 1) In the US, urothelial (transitional cell) carcinoma accounts for about 90% of all bladder cancers. Less commonly, bladder neoplasms may be squamous cell (5%), adenocarcinoma (2%), and rarely small cell, lymphoma, or sarcoma. Because urothelial carcinoma is the predominant form of bladder cancer in the US and in RI, this review will focus on the epidemiology and risk factors of urothelial bladder carcinoma and some potential causes for the regional disparities.

## NATIONAL AND STATE EPIDEMIOLOGY

About 71,000 people (53,000 men and 18,000 women) were diagnosed with urothelial bladder cancer in the US in 2009. The median age at diagnosis was 69 years in men, 71 years in women. There were an estimated 14,000 deaths.<sup>2</sup> Nationally, bladder cancer is more common in men, with a 3:1 ratio of males to females. Among men, it is more common in Caucasians, with a 2:1 ratio of Caucasians to African Americans. Whether this racial disparity is due to differences in genetics, exposure patterns or other health-related behaviors remains under investigation. Although bladder cancer is more common in men and Caucasians, women and African Americans are more likely to present at later stages and have a worse prognosis.<sup>3</sup>

In RI, about 370 people were newly diagnosed with bladder cancer in 2008. Among Rhode Island men, bladder cancer is the fourth most common new can-

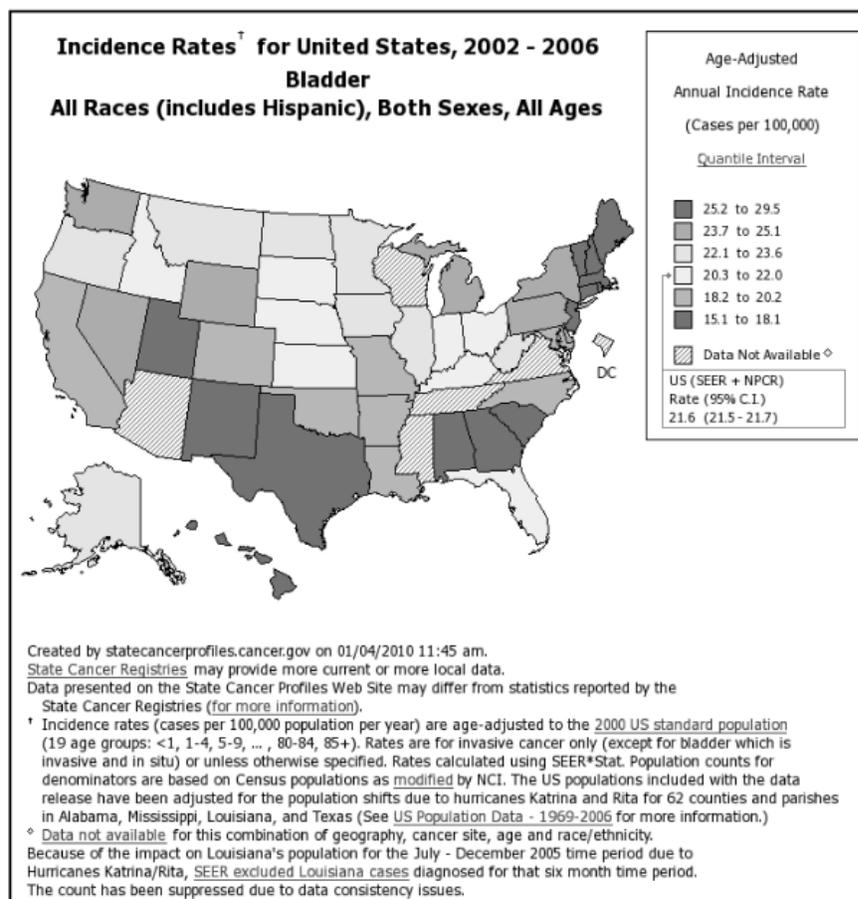
cer diagnosis, after prostate, lung, and colorectal cancer. Of the 6674 Rhode Islanders diagnosed with bladder cancer from 1987-2007, 73% were male and 27% female.<sup>1</sup> (Table 2) Most (58%) were 70 years or older, but 18% were younger than 60 years at diagnosis. The vast majority (98%) were Caucasian, which likely reflects Rhode Island's overall racial and ethnic distribution.

About 75% of urothelial cancers are diagnosed at a superficial stage and 25% are muscle invasive or metastatic at diagnosis. According to data from 2004-2007, about 77% of Rhode Island cases were diagnosed at a superficial stage, compared with 74% of US cases in that period.<sup>1</sup> (Table 3) This is a critical distinction because superficial cancers are gen-

erally managed with localized therapies and careful urologic surveillance. In contrast, muscle invasive or metastatic cancers may also require systemic therapy and have a worse prognosis. Unfortunately, about 80% of those with superficial disease eventually have a recurrence or progression.

Because most bladder cancers are diagnosed at an early stage, the prevalence of people living with bladder cancer is quite high. It is estimated that over 500,000 people are living with bladder cancer in the United States, with about 390,000 men and 140,000 women. In fact, among middle-aged and elderly men in the United States, bladder cancer is the 2<sup>nd</sup> most prevalent malignancy, after prostate cancer. In addition, the United

Figure 1.



**Table 1. Age-adjusted bladder cancer incidence rates in states with greatest incidence, 2002-2006**

	Men	Women
Rhode Island	53.1	13.0
Maine	49.4	13.4
New Hampshire	48.0	13.4
Massachusetts	46.7	12.9
New Jersey	46.2	12.2
Connecticut	45.4	12.6
United States (2004)	37.4	9.4

\*Per 100,000, age-adjusted to the 2000 US standard population.

Sources: SEER (Connecticut only) and National Program of Cancer Registries

States spends about \$3.7 billion per year on surveillance and treatment for patients with bladder cancer, making this one of the most expensive malignancies to monitor and treat.<sup>4</sup>

#### **PATHOGENESIS**

As the surface epithelium lining the urinary tract mucosa, the urothelium is exposed to carcinogens excreted in the urine or activated from precursors by

hydrolyzing enzymes in the urine. The latency period from carcinogen exposure to urothelial cancer development lasts from years to decades. Aberrations in either carcinogen activation or detoxification may lead to neoplastic development. Several metabolic pathways are involved in carcinogen activation, including the cytochrome P450 enzymes. Some research has shown that smokers with a genotype for extensive metabolic activa-

**Table 2. Characteristics of Rhode Islanders diagnosed with bladder cancer, 1987-2007**

Variable	Count	Percent
Sex		
Male	4,846	73 %
Female	1,828	27 %
Age at Diagnosis (median)		
< 50	478	6 %
50-59	826	12 %
60-69	1,585	24 %
70-79	2,265	34 %
80 +	1,620	24 %
Unknown	6	0 %
Race		
White	6,550	98 %
African American	71	1 %
All Other	53	1 %

Source: Rhode Island Cancer Registry

tion have an increased incidence of urothelial carcinoma.<sup>5</sup> Conversely, aberrations in carcinogen detoxification have also been implicated. For example, aromatic amines are detoxified by acetylation. "Slow" acetylators may have increased risk of cancer development, especially when faced with additional toxic exposures.<sup>6</sup> In addition, several oncogenes and tumor suppressor genes have been implicated in the development of urothelial carcinoma, including p53, retinoblastoma, and p16.<sup>7</sup>

#### **RISK FACTORS AND REGIONAL SIGNIFICANCE**

In examining the etiology of Rhode Island's persistently elevated bladder cancer incidence, it is important to consider risk factors for bladder cancer and specifically those factors that may be more prevalent in Rhode Island. Cigarette smoking and occupational exposures are the leading identified risk factors for bladder cancer in the United States and in Rhode Island. Other possible risk factors have been described (Table 4).

#### **Tobacco Use**

The association between tobacco use and bladder cancer has been described extensively. Cigarette smoke contains numerous chemicals identified as urothelial carcinogens, including aromatic amines and polycyclic aromatic hydrocarbons. In the US, smoking is implicated in 50-60% of bladder cancer cases in men and 30% in women.<sup>8</sup> The rate of bladder cancer in smokers is two to three times that in nonsmokers, with long-term heavy smokers having a five-fold or more increased risk. The latency period from exposure to cancer development is thought to be 20 years or more. Smoking cessation has been found to reduce bladder cancer risk, but not to return it to baseline; a meta-analysis of eleven case-control studies found that after one to four years of smoking cessation, bladder cancer risk decreased by 35%. After 25 years, it decreased by 60%, but remained greater than that in never smokers.<sup>8</sup>

In 1978, the National Cancer Institute initiated the landmark **National Bladder Cancer Study (NBCS)**, the largest and most detailed bladder cancer investigation of its time. The NBCS was the

**Table 3. Stage at diagnosis by AJCC\* stage groupings, Rhode Island vs. United States (SEER, 17 Registries), newly diagnosed cases of bladder cancer, 2004-2007**

Stage at Diagnosis	Rhode Island		United States	
	N	%	N	%
Superficial	1,120	77.1	45,920	74.2
Muscle Invasive	291	20.0	13,962	22.6
Metastatic	42	2.9	2,009	3.3
Total	1,453	100%	61,891	100%

\* American Joint Committee on Cancer

Sources: US: SEER System, via SEERStat; RI: Rhode Island Cancer Registry

first study to use data from the entire Surveillance, Epidemiology, and End Results (SEER) network of 10 centers, and included nearly 3000 cases diagnosed over one year and 5800 controls. Interview data examined occupational, medical, environmental, and lifestyle influences on risk. This was the first study to report excess bladder cancer risk associated not just with cigarette use but also with pipe or cigar smoking. It also found that smoking cessation was associated with a reduction in risk.<sup>9</sup>

According to the Centers for Disease Control and Prevention, over 50% of men and 34% of women smoked cigarettes in the US in the 1960s.<sup>10</sup> Although Rhode Island did not officially monitor cigarette smoking prevalence until the 1970s, local health officials have estimated that smoking rates in men in the 1950s exceeded this already high national average and remained elevated for many years. Over the last 50 years, however, Rhode Islanders have made significant progress in smoking cessation, and it is estimated that they have had below average smoking rates for several decades. Currently, Rhode Island has the 12<sup>th</sup> lowest rate of tobacco use in the country, with about 19% of men and 20% of women continuing to smoke cigarettes.<sup>11</sup> Given the long latency period and the persistently elevated risk of bladder cancer in former smokers, the state's historical tobacco use patterns may play a role in the elevated rates seen in more recent decades. However, this effect should attenuate with time, and it is unlikely that smoking alone is causing Rhode Island's persistently elevated bladder cancer rates.

### Occupational Exposures

Numerous studies have identified an association between certain occupational exposures and bladder cancer. Occupational exposures are thought to account for 10-20% of bladder cancers. The most compelling and consistent evidence implicates textile workers including dye users and weavers, dyestuff manufacturers, aromatic amine manufacturing workers, rubber workers, leather workers, painters, aluminum workers, and truck drivers. It is thought that occupation-related exposures to aromatic amines, including 2-naphthylamine and benzidine, are responsible for these elevated bladder cancer rates, particularly in dyestuff and rubber workers.<sup>12</sup> Exposure to diesel exhaust and decreased micturition have been suggested as potential risk factors in truck drivers. As with exposure to carcinogens in cigarette smoke, the latency period for these exposures is likely 20 years or more. New England has had a long history in the textile industry, and it is likely but not proven that these and other occupational exposures have contributed to our increased incidence of bladder cancer.

The New Hampshire Bladder Cancer Study (NHBCS) further investigated occupational and other exposure risks.<sup>13</sup> A population based case-control study begun in 1994 and expanded to include Maine and Vermont as the New England Bladder Cancer Study (NEBCS) in 2002, this study collected not just interview data but also water samples, toenail clippings, blood, and urine samples for analysis. The NHBCS confirmed the results of previous studies showing excess

risk in male truck drivers, and male metal/plastics workers, after adjusting for age and smoking status. Among truck drivers, they found a positive trend of increasing risk with duration of employment. In addition, they identified excess risk in female sales clerks and female health service workers, mainly nursing aides. The etiology of these associations was unclear, but the authors postulated that decreased micturition in the former and possibly exposure to chemotherapeutic agents in the latter group could play a role. Unfortunately, this study was limited in its ability to identify workers in the specific fields of textile, rubber, leather, and aromatic amine manufacturing industries.<sup>13</sup>

### Water Contaminants

In addition, drinking water contaminants have been associated with bladder cancer. By-products of water chlorination, such as halogenated hydrocarbon compounds,<sup>14</sup> and elevated arsenic levels<sup>15</sup> have been associated with increased risk. A well-described bladder carcinogen, arsenic has been associated with cancers of the bladder, skin, and lung. Specifically, arsenic concentrations greater than 150 ug/L have been associated with bladder cancer, and researchers have described a dose-response relationship between arsenic levels and cancer development.<sup>16</sup>

Under the Safe Drinking Water Act, the US Environmental Protection Agency (EPA) regulates the arsenic concentration of drinking water in the United States. In response to risk assessments suggesting a link to cancers at even lower arsenic concentrations than previously thought, the EPA reduced the maximum accepted contaminant level from 50ug/L to 10ug/L.<sup>15</sup> While the EPA regulates arsenic concentrations in public water supplies, it has no regulatory capacity over private well use. In parts of New England, particularly New Hampshire and Maine, as many as 40% of residents use private wells. Researchers have reported elevated arsenic levels in bedrock aquifers in some regions in these states.<sup>16</sup> Noting these elevated arsenic levels and the fairly common use of unregulated private well water in this area, researchers hypothesized that this might be contributing to the elevated

**Table 4. Potential risk factors for bladder cancer\***

Risk Factor	Comments	Association
Cigarette smoking	Exposure to aromatic amines and other carcinogens (tobacco hydrocarbons, tar)	Real
Occupations Aromatic amine manufacture Dyestuff manufacture Rubber industry Painting Leather industry Aluminum industry Truck drivers	Exposure to aromatic amines and other chemical carcinogens  Diesel exhaust or reduced bladder voiding (drivers)	Real for aromatic amine exposure, possible for others
Drugs Phenacetin Cyclophosphamide		Real Real
Urinary tract infections, particularly with <i>Schistosoma haematobium</i>  Carcinogens in drinking water (arsenic, chlorination by-products)	Chronic inflammation/altered metabolism associated with squamous cell not urothelial bladder cancer  Direct carcinogenic action	Real for <i>Schistosoma haematobium</i>  Likely
Decreased fluid intake  Genetic polymorphisms of genes involved in aromatic amine detoxification (NAT1/NAT2, GSTM1)	Less dilution of carcinogens, decreased voiding frequency  Inefficient aromatic amine detoxification may lead to increased production of carcinogenic metabolites	Possible  Possible

\* Modified from Negri E, La Vecchia C. Epidemiology and prevention of bladder cancer. *Eur J Cancer Prevention* 2001;10:7-14.

rates of bladder cancer in New England. In fact, this was a key question posed by the NHBCS.

Unfortunately, the effects of arsenic exposure on bladder cancer risk have proven complicated to define clearly in these populations. In analyses completed to date, the NHBCS has found no association between arsenic exposure and bladder cancer risk among never smokers. However, among smokers, those smokers in the uppermost arsenic exposure category did demonstrate a non-statistically significant excess risk (OR 2.17, 95% CI 0.92 – 5.11).<sup>17</sup> Research is ongoing to better define this potential interaction. Other researchers have also suggested that tobacco use may enhance the carcinogenic effect of arsenic exposure. In addition, researchers are investi-

gating the potential role of DNA methylation and other epigenetic events which may be associated with increased bladder cancer risk.

While arsenic from well water remains a possible contributor to elevated bladder cancer rates in Rhode Island, it seems unlikely that it contributes significantly if at all. While 30-40% of New Hampshire residents rely on private well water, only about 10% of Rhode Islanders do. In addition, Rhode Island does not appear to have the elevated levels of arsenic in bedrock aquifers found in parts of northern New England. Other potential sources of arsenic exposure include soil contamination and pressure-treated lumber. In most areas with elevated arsenic levels, this has been associated with prior land use, including arsenic-containing pesticides at

former orchard sites. Currently, the public water sources are in compliance with the state's regulations on safe arsenic levels, and there is no evidence to suggest that the 10% of residents who obtain water from private wells have elevated arsenic levels in their water, although this data is not currently monitored.

**Iatrogenic Factors**

Cyclophosphamide, a chemotherapeutic agent often used to treat non-Hodgkin's lymphoma, is an established bladder carcinogen with a dose-dependent relationship. One case-control study reported a four-fold increased risk of bladder cancer and an absolute risk of between three and seven excess cancers, depending on cumulative doses, per 100 non-Hodgkin's lymphoma patients after fifteen years of follow up.<sup>18</sup> Pelvic irradiation for prostate, ovarian, and cervical cancer has been associated with a 1.5 to four times increased risk of bladder cancer and a latency period of only five to ten years.<sup>19</sup> Historically, heavy use of phenacetin-containing analgesics has been associated with increased risk of cancer of the bladder, renal pelvis, and ureter, prompting its classification as a carcinogen in 1987 and its removal from most of the European countries and the United States.

**ADDITIONAL FACTORS**

Decreased fluid intake has been associated with increased bladder cancer incidence. In the Health Professionals Follow Up study with 48,000 participants, those who drank <1.3 liters of fluid daily had twice the risk of bladder cancer as those who drank over 2.5 liters daily.<sup>20</sup> Chronic bladder irritation has been implicated in the development of squamous cell bladder cancer, rather than urothelial carcinoma. Classically, infection with *Schistosoma haematobium* has been associated with squamous cell bladder cancer, likely due to chronic bladder inflammation. In regions with endemic schistosomiasis, such as the Middle East, Asia, and Africa, most bladder cancers are squamous cell carcinomas, rather than urothelial carcinomas. Similarly, some data have shown that spinal cord injury patients with neurogenic bladder may be at increased risk of squamous cell bladder cancers.<sup>21</sup>

In that Rhode Island welcomes many new residents each year, it is important to consider not only local factors but also exposures in recent immigrant populations. Currently two of the largest immigrant populations are Hispanics and Africans.<sup>1</sup> New residents may bring both old and new exposures with them, and environmental factors elsewhere may affect cancer incidence in our state. On the basis of current immigration patterns, there is no reason to expect a great impact on our current trends in bladder cancer incidence, but this remains another factor to monitor.

## CONCLUSIONS

In summary, Rhode Island has the greatest incidence of bladder cancer in the nation. The cause of this disparity remains unproven, although compelling explanations have emerged. The two historical exposures that appear to have had the greatest impact are high rates of tobacco use and specific occupational exposures. Given the very long latency period of bladder cancer development, it is likely that we are continuing to see the delayed effects of these exposures. The impact of arsenic and other water contaminants on our state's bladder cancer incidence appears to be small, if any, and any effects they may have are likely to be constant over time. Research is ongoing in this area.

As Rhode Island's rates of tobacco use and specific occupational exposures have significantly declined in the last several decades, the magnitude of their combined effects should attenuate with time. If these truly are the main factors influencing our currently elevated bladder cancer incidence rates, then we predict that these rates will level off and start to decline over the next several years to decades. We will continue to monitor these trends vigilantly. Realizing that a heightened awareness of bladder cancer risk could translate into increased surveillance and increased detection of superficial cancers, we will also continue to monitor trends in the stage at which these cancers are diagnosed. Bladder cancer continues to have a significant impact on the health of Rhode Islanders, and we will continue to investigate ways to better understand and reduce this burden for our residents.

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*Katherine E. Faricy-Anderson, MD, MPH, is a Fellow, Division of Hematology and Oncology, The Warren Alpert Medical School of Brown University.*

*John P. Fulton, PhD, is Administrator, the Rhode Island Cancer Registry, Rhode Island Department of Health, and Clinical Associate Professor of Community Health, The Warren Alpert Medical School of Brown University.*

*Anthony E. Mega, MD, is Associate Professor of Medicine, Division of Hematology and Oncology, The Warren Alpert Medical School of Brown University.*

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## CORRESPONDENCE

Katherine E. Faricy-Anderson, MD  
The Miriam Hospital  
164 Summit Ave  
Providence, RI 02906  
Phone: 401-7934645  
E-mail: kfaricyanderson@lifespan.org

