

## **Bladder Cancer: Risks and Prevention**

### **Meet our Presenter**

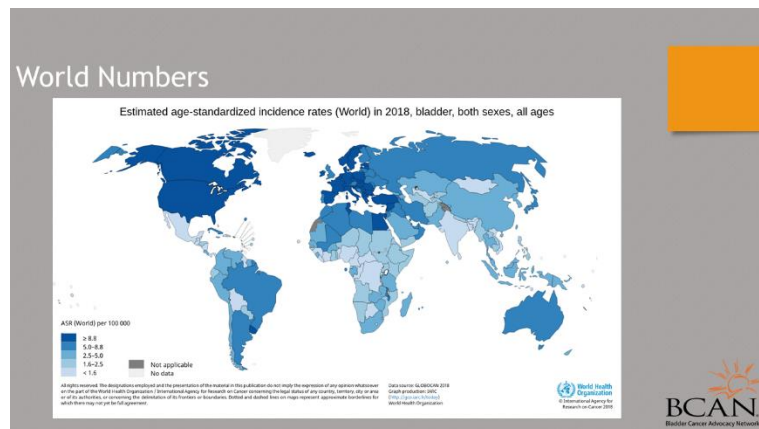


Dr. Wright is an Associate Professor of Urology at the University of Washington and the Medical Director of the University of Washington Medical Center Urologic Clinic. He's an associate member in Epidemiology at the Fred Hutchinson Cancer Research Center and holds the Paul Lange Endowed Professorship in Urologic Oncology. Dr. Wright is also a member of the National Comprehensive Cancer Network, Bladder Cancer Clinical Guidelines committee. As a specialist in Neurologic Oncology, he's involved in several clinical trials and biomarker studies aimed at improving outcomes in patients with bladder cancer, as well as conducting epidemiological studies of bladder cancer. Dr. Wright led the development of the Bladder Cancer Rapid Autopsy Program at the University of Washington, as well as establishing the UW Bladder Cancer Multidisciplinary Specialty Clinic.

## Background: Risk Factors for Bladder Cancer

**Dr. Wright:** So, I first just want to go over a little bit of the background numbers for bladder cancer. Many of you may be aware of some of these. Then identify some of the established risk factors that we have for bladder cancer and then try to go through and identify some of the studies, and some of the work that's been done thus far for looking at prevention of bladder cancer. I've also included a small bit about where we stand with screening for bladder cancer.

So, to start, this is a nice map that shows and reminds us that bladder cancer is a global disease. This map of the entire globe is color coded for how the incidence, so how common bladder cancer is in different parts of the world. Darker blue being those having the highest incidence of bladder cancer and as it gets more and more lighter blue, a lower incidence of bladder cancer. You can see that North America, in the dark blue, has one of the highest incidence. A lot of Western Europe does as well, but there certainly are some other areas across the globe that have little pockets where there's higher incidence of bladder cancer as well. You can see everywhere across the globe bladder cancer has an impact and of course it effects both men and women.



### Bladder Cancer Numbers in the USA

- 6<sup>th</sup> most common cancer diagnosed  
80,470 estimated new cases in 2019
- 10<sup>th</sup> most common cause of cancer death  
17,670 estimated deaths in 2019
- Average age at diagnosis: 73 years  
90% are over age 55 years

North American Association of Central Cancer Registries (NAACCR), 2018

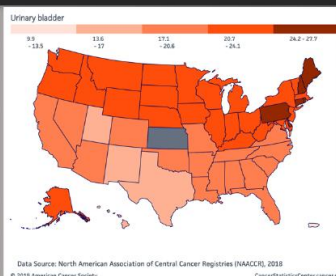


Now here in the United States, bladder cancer's the sixth most common cancer diagnosed overall. It's number four for men and about number 11 for women. Over 80,000 new cancers will be diagnosed in this year. It's the tenth most common cancer related death in the United States, and unfortunately it is estimated to have over 17,000 individuals die from bladder cancer this year. Now, bladder cancer is more common in those who are older. The average age for

diagnosis is 73 and 90% of patients are over the age of 55 at diagnosis, but there are still 10% that are younger than 55 and I certainly have many patients, both men and women, who are much younger than 55 with bladder cancer. So, although it is commonly thought of as a cancer that affects older patients, it does affect those of all ages as well.

This is a map just of the United States looking at the varying incidences, how common it is from state to state. Again, the dark colors have a higher incidence of

## Bladder Cancer Incidence Rates in US Per 100,000 individuals



bladder cancer and the lighter reds have a lower incidence of bladder cancer. There's one state that didn't have any data, hence the blue color. As a clinician and researcher and epidemiologist, this makes me think, well, what it is about the northern states? What is it about the exposures potentially that are leading to this? Since I first saw this slide, just a couple months ago, it's made me think and I try to identify ways that I could go

and study to understand because again, this could help us with targeted education, targeted screening and trying to understand what's the exposure, what's going on here as opposed to here. But again, every state has bladder cancer.

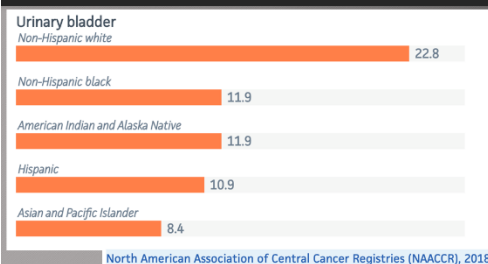
It certainly is more common in men than women, but as I said it affects both genders. It's about four to one. This is how many individuals per 100,000 individuals, so about four to one. More common in males to females, but again it affects both.

When we look at ethnicity, we also see that there are differences. With nearly double the incidence in non-Hispanic whites compared to non-Hispanic Blacks, American Indians, Alaskan natives and Hispanics as well. The lowest incidence of bladder cancer by ethnicity is seen in the Asian and Pacific Islanders. When we think about health disparity, we look at these data to try and understand what is the exposure and making sure that people have access to care even if their incidence is lower as well.

### More Common in Men



### Ethnicity and Bladder Cancer



## #1 Risk Factor is Smoking

- ~ 50% of bladder cancer deaths are due to tobacco use
- 200-400% increased risk of bladder cancer for smokers
- 2<sup>nd</sup> hand smoke also increases the risk
- Increased risk persists > 30 years out

Original article  
Persistence of urothelial carcinoma of the bladder risk among former smokers: Results from a contemporary, prospective cohort study  
Christopher J. Welty, M.D.<sup>a,\*</sup>, Jonathan L. Wright, M.D., M.S.<sup>a,b</sup>, James M. Hotaling, M.D., M.S.<sup>a</sup>, Parveen Bhatti, Ph.D.<sup>c</sup>, Michael P. Porter, M.D., M.S.<sup>c,d</sup>, Emily White, Ph.D.<sup>c,d</sup>



So, when we look specifically at risk factors, the number one risk factor is smoking.

Approximately half of all bladder cancer deaths are thought to be attributed tobacco use and certainly about half of all bladder cancer incidence are thought to be due to tobacco use. Those current smokers have a 200% to 400% increased risk of bladder cancer compared to non-smokers. Secondhand smoke, although not as strong,

certainly increases the risk to people and even for those that stop, and certainly stopping is absolutely advocated for and encouraged, there still is an increased risk of bladder cancer even up to 30 years out. Whereas for lung cancer, after 20 plus years, the risk approaches someone that was a lifelong non-smoker. For some reason, this increased risk in bladder cancer persists even up to 30 years after stopping smoking.

Emily White was the lead PhD on this study examining the risk of bladder cancer after quitting smoking and we saw the same thing. That yes, as you went from less than 10 years, 15 years, 20 years from when you quit smoking, there still was a significantly increased risk. Again, the highest risk was in those that are active smokers.

The second most common group of risks for bladder cancer is occupation or other exposures. This is thought to account for up to 20% of bladder cancers. Chemicals that we associated with it are benzene, aniline dyes, polycyclic hydrocarbons. Now, most people don't know they've been exposed to those specific items when we see them and ask about their exposures, but these are things that are exposed in the paint industry, rubber, leather, textile worker and the cement industry. Electrical workers and metal workers, miners additionally are of thought to have an increased risk of bladder cancer from their occupational exposures.

## Occupational exposures and risk of bladder cancer

Accounts for 10-20% of bladder cancer

- Chemicals
  - Benzene, aniline dyes, polycyclic hydrocarbons
- Paint, rubber, leather, textile, cement industry
- Metal and electrical workers
- Miners
- Hair dye workers
- Diesel exhaust
- Fire fighters?



Those that do a lot of work dyeing hair because of having the hands in the chemicals, have an increased risk as well. Now, an individual who dyes their hair is not going to be at increased risk. This is someone who is exposed day in day out, year in, year out, long term exposure in the workplace, to hair dyes. Diesel exhaust, another aspect of risk and firefighters. I put a question mark as there

have been some mixed studies about this, but given all that they're exposed to with the carcinogens when there's a fire are felt to be at higher risk as well. There have been some targeted screening studies looking at firefighters, but to date have not yet been shown to be beneficial.

Again, a lot of us, up to one in five bladder cancers that we are seeing could be traced to some sort of occupational or chemical exposure. As the rate of smoking is declining in our country, we're still seeing a pretty stable incidence of bladder cancer and so there may be more of these other etiologies or risk factors that are bringing out the bladder cancer that we're seeing.




Arsenic contaminates our water supplies and it is known to increase the risk of bladder cancer. There have been a couple of what they call ecologic studies in a couple of areas, one in Taiwan and one down in Chile where the water supply got contaminated with arsenic and they saw a significant increase in bladder cancer and also lung cancer. Then, when it got cleaned up the rates dropped down. The map that I'm

showing here is looking at the levels of arsenic across the country in private domestic wells, so well water. With the darker colors having a higher level of arsenic in them. Certainly the recommendations are to have to be less than 50 micrograms per liter. So, there are certainly areas here where high levels of arsenic in the water could be leading to bladder cancer.

Now, thinking back to that other map that just looked at the overall incidence, north versus south, you can see arsenic is not explaining all of those differences, but there certainly are a lot of darker colors up here and where I live here, there are some very dark areas as well. So, again it's pretty fascinating some of these things that are available and how can we use them to help us reduce our cancers.

### Other Risk Factors for Bladder Cancer

- Recurrent UTIs
- Chronic catheterization
- Bladder augmentation (stomach or bowel)
- Pelvic radiation (for prostate, rectal or cervical cancer)
- Medications
  - Cyclophosphamide (chemotherapy)
  - Phenacetin (analgesic)
  - Actos (diabetes)



There are certainly other risk factors. Those that have recurrent UTI's or Urinary Tract Infections. The thought being it turns on an inflammatory aspect of cancer development. Similarly those that have chronic catheterization, spinal chord injuries or neurogenic bladders. Again, likely through an infectious inflammatory pathway and in some cases these more commonly have a different histology with more squamous cell



carcinomas as opposed to urothelial cell carcinomas. Areas where there's a lot of talk about should there be targeted screening and surveillance of individuals. Again, there's debate on that issue.

Bladder augmentation, this is a unique scenario when someone has a small, contracted bladder that doesn't work very well and more common in children with myelomeningocele where the bladder isn't as effective and a piece of intestine is patched onto the top of the bladder to try to increase the capacity and to lower the pressures in the bladder and improve incontinence and protect the kidneys. There was quite a bit of interest in doing gastrocystoplasties or stomach augments to the bladder and we've been seeing more and more of these coming back with cancer. In these augmented bladders, again it's often a different histology being an adenocarcinoma commonly as opposed a urothelial carcinoma. So, certainly another group where the exposure is the contact of the intestine versus one of the other etiologies.

Then, pelvic radiation. We have lots of people that get radiation for prostate cancer. Rectal cancer is treated commonly with a combination of chemotherapy and radiation. Cervical cancer gets radiation as well. Although the risk of radiation induced cancer is very low, a lot of people getting treated and then we see these 20, 30 years after the radiation. In my practice where we're seeing people living longer and longer, which is outstanding, but I'm seeing these patients come in in their late 80's with radiation induced bladder cancer. So, certainly that is a risk, but again, the risk of radiation induced cancers is quite low, but it is not zero.

Then, there are a couple of medications that can lead to bladder cancer as well. Cyclophosphamide is a specific type of chemotherapy that is used that can lead to bladder cancer, again decades later. Phenacetin is a pain medication, it's no longer on the market in the United States, but it had been associated with bladder cancer, and I have a few patients that had significant exposures to that in their past. Then, Actos is a diabetes medication which has had some reports of leading to an increased risk of bladder cancer as well. So, even just some of the medications that we are taking can put us at risk for bladder cancer.

## Genetics

- Bladder cancer is heritable, but most are thought to be mutations in the bladder tissue
  - Small increase in risk, especially in families with bladder cancer in younger patients (<60 years)
- Examples
  - Lynch Syndrome (HNPCC)
  - Cowden's Disease (*PTEN* mutation)
  - Retinoblastoma *RB1* mutations
  - Costello Syndrome (*HRAS*)



Then, genetics. Certainly we're learning more and more about genetics of not just cancers, but lots of other diseases and there is a heritable aspect to bladder cancer, but it's not as strong as some of the other cancers that we deal with. Breast cancer, prostate cancer, et cetera. Most bladder cancers are thought to be due to mutations in the bladder tissue itself. A mistake happens in the bladder tissue that becomes tumor. As opposed to an inherited mutation that

we're born with, but there does appear to be a small increase in risk especially in families where bladder cancer is seen in other members of the family at a younger age, less than 50, less than 60 for example.

There are a couple of syndromes, I think the most common one is Lynch Syndrome, also known as hereditary non-polyposis colon cancer. This is a DNA repair gene mutation and patients with Lynch Syndrome are at risk for a number of different malignancies, the most common being colon cancer, but they're also at risk for bladder cancer and what we call upper tract cancer in the lining of the renal pelvis and the ureters. There's quite a bit of focus on doing some screening and surveillance for these individuals.

Then, there are some other rarer, inherited mutations that can be passed through a family, but these are quite rare disease. Cowden's Disease, people that have Retinoblastoma and other mutations. Again, quite rare, but they are there.

