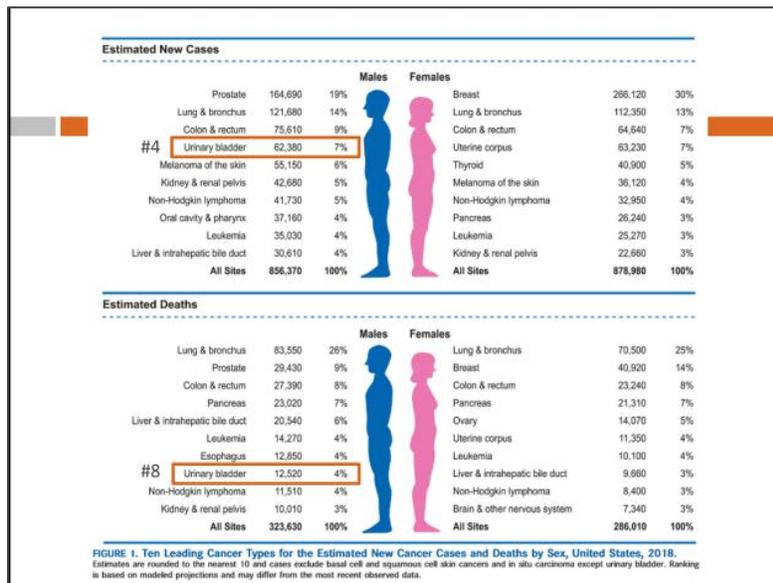


Presented by:



Dr. Lambros Stamatakis is the Director of Urologic Oncology at MedStar Washington Hospital Center and an Assistant Professor in Urology at the Georgetown University School of Medicine. He completed his medical training at the University of Maryland, and then completed his urology training at Baylor College of Medicine in Houston Texas. He returned to the mid-Atlantic in 2012 to complete a fellowship in urologic oncology at the National Cancer Institute in Bethesda, Maryland. After that, he started his academic practice in Washington, DC. His research interests include novel therapies for BCG, unresponsive non-muscle invasive bladder cancer, and he serves as a local primary investigator on two clinical trials available at MedStar for non-muscle invasive bladder cancer.

Dr. Stamatakis: This is a brief overview of what I hope to cover today. I will talk a bit about the epidemiology of bladder cancer, and then focus our discussion on symptoms and other warning signs that are associated with bladder cancer, and also review the risk factors for developing bladder cancer, with a particular emphasis on smoking.



This figure depicts the estimated incidence of new cases of cancer in the United States in 2018, and it's broken down into the organ or origin and between males and females. As you can see at the top of the screen here, there will be approximately 62,000 new cases of bladder cancer in men diagnosed this year. That makes it the fourth most common malignancy in males in the United States. The bottom section of this figure shows the estimated number of deaths due to cancer in 2018, and, as shown,

about 12,500 patients will die of bladder cancer this year, making it the eighth most common cause of cancer death in males in the United States.

As shown in the previous figure, bladder cancer is more common in men than in women. While the reason behind this discrepancy in incidence is unclear, what we do know is that women with bladder cancer do tend to present with more advanced stages of the disease than their male counterparts, and this is something that we're going to dive into with a little bit more detail later on in the presentation, but suffice it to say that this is a disease that is more common in men than in women.

Geographically there's a wide variation in the incidence of bladder cancer, with western Europe and North America having the highest incidence, while countries in eastern Europe and Asian having the lowest incidence. Even within the United States there are significant regional differences in bladder cancer incidents, with the highest being in the northeast and the lowest incidence in states like Utah and Hawaii. These differences do seem to hold when controlled for other factors like smoking rates amongst different parts of the country, which may suggest that there is some sort of environmental factor that is unaccounted for in these high-risk areas.

How about race? In the United States, white males have the highest risk, with roughly twice the incidence seen in African American and Hispanic males, but despite the increased incidence in Caucasians, African-American patients do have worse survival rates, as shown in the next graph we'll see in a second that will depict five-year survival rates based on bladder cancer stage, so let's get to that graph, which is next.

As seen here, the green bars depict survival rates of Caucasians, and the blue bars depict survival rates amongst African Americans. As you can see there, for all stages of bladder cancer, African Americans fare worse in terms of bladder cancer survival compared to Caucasians. The difference is maybe due to different biologic or genetic factors. It could be due to occupational differences, or perhaps variations in access to cancer care. It is something that is a major area of research interest that's ongoing.

Risk Factors | Race

- Caucasians have the highest risk
 - 2x incidence compared to African-Americans and Hispanics
 - Unclear as to why...
 - Occupational differences leading to different carcinogen exposures?
 - Genetic differences resulting in variation in biologic mechanisms to counteract carcinogen exposure (i.e. variations in acetylator phenotypes)?
- Despite lower incidence, African-Americans tend to have more advanced stage tumors at presentation (limited access to care?)



Risk Factors | Environmental Factors

- Chemicals
 - Cigarette Smoke
 - Occupational chemical exposures
 - Arsenic in drinking water
 - Chlorinated water (?)
 - Aristolochic acid (Chinese herbs)

Some of the risk factors that are associated with the development of bladder cancer, with a focus on chemical exposures, particularly smoking. We're also going to talk about occupational chemical exposures, chemicals that potentially could be found in our drinking water, and other miscellaneous chemicals. The idea is that these chemicals enter our body and ultimately get dumped into our urine and interact with the urothelium, which, again, is the lining of the

bladder, as well as the urethra and the upper urinary tract. This interaction between these chemicals presumably leads to genetic changes that can lead to the development of malignant tumors.

Let's start with smoking. Cigarette smoking is the most important factor contributing to the overall incidence of bladder cancer in western countries, with an estimate that over 50 percent of bladder cancer cases are due to smoking. While the specific carcinogen or carcinogens in cigarette smoke that lead to the development of bladder cancer aren't completely known, there are over 60 to 70 unique

Risk Factors | Smoking

Cigarette smoking is the most important factor contributing to the overall incidence of bladder cancer in western countries

- It is estimated that over 50% of cases of bladder cancer are attributed to smoking
- Over 60 known carcinogens in cigarette smoke
- Despite this, the specific carcinogen(s) that is responsible for bladder cancer development is still unknown
- Emerging evidence that Vaping may also increase cancer risks

carcinogens that have been characterized in cigarette smoke. There is some emerging data that suggests that even vaping could be associated with cancer development. Just before this presentation I just looked up any sort of new studies that have been associating vaping with bladder cancer, and I didn't find any substantive data that would suggest that there is a direct association between vaping and bladder cancer, but certainly there is a lot of variability about what people could potentially be inhaling with these electronic cigarettes, etc., so there's a lot to still be discovered about this.

Risk Factors | Smoking

- NIH-AARP Diet and Health Study Cohort
 - 465,000 individuals followed from 1995-2006
 - Risk of developing bladder cancer...
 - Current smokers – approx 4x higher than never smokers
 - Former smokers – approx 2.5x higher than never smokers
 - Pipes and cigars... not as bad as cigarettes, but still increased risk
 - Heavy smokers (>30 pack/years) were more likely to have high grade tumors and to have muscle invasive disease at presentation



Interestingly, just to play devil's advocate, there are a lot of publications about the potential benefits of using electronic cigarettes in smoking cessation programs, so really the jury is still out on this issue, but I do think it's something that we as a bladder cancer community need to be very aware of as we counsel patients about this.

The relationship between smoking and the risk of bladder cancer is very well illustrated by a prospective study that was published in the Journal of the American Medical Association in 2011.

This is known as the National Institutes of Health and the AARP Diet and Health Study Cohort. This study followed approximately 465,000 individuals from 1995 to 2006, and the goal of this study was really to improve the understanding of the relationship between diet, as well as other lifestyle factors like smoking and ultimate health outcomes.

What the study found was that current smokers have an approximately four times higher risk of developing bladder cancer than individuals who have never smoked. While the risk decreases in patients who are former smokers, their relative risk never normalizes to the level seen in people who have never smoked, and will remain elevated throughout their lifetime. Also from this study they looked at people who had smoked things other than cigarettes, like pipes and cigars, and while it looks like those individuals had a slightly lower risk of developing bladder cancer compared to cigarette smokers, their risk overall was still higher than people that have never smoked before.

The extent of smoking also appears to be related to the aggressiveness of bladder cancer. In another study of approximately 740 patients, heavy smokers, which is defined as those who smoked an average of a pack per day for 30 years or more, were much more likely to have a high-grade tumor or muscle invasive disease at original presentation compared with nonsmokers.

Secondhand smoke is also a risk factor for developing bladder cancer. In a study from Los Angeles County which included 148 patients with bladder cancer, as well as 292 patients without bladder cancer that served as controls, all of whom were nonsmokers, showed a couple of interesting findings. One is that women who lived with two or more smokers during childhood had an approximately threefold

increased risk of developing bladder cancer compared with those without any childhood exposure to secondhand smoke. In addition, women with a domestic partner who smoked for 10 or more years had a twofold increased incidence compared with those without such an exposure. This was interesting because this study did not identify similar associations in males who had never smoked, and it may be due to some limitations of the study or perhaps some biologic differences between men and women, but the bottom line is that secondhand smoke exposure does also seem to increase your risk of developing subsequent bladder cancer.

Risk Factors | Smoking

- Secondhand smoke
 - ▣ Also a risk factor for developing bladder cancer
 - ▣ One study from LA County demonstrated...
 - Women who lived with 2 or more smokers during childhood had a 3x risk of developing bladder cancer
 - Women who lived with a domestic partner who smoked for > 10 years had a 2x risk of developing bladder cancer
 - These associations were not seen in male never-smokers

Risk Factors | Smoking

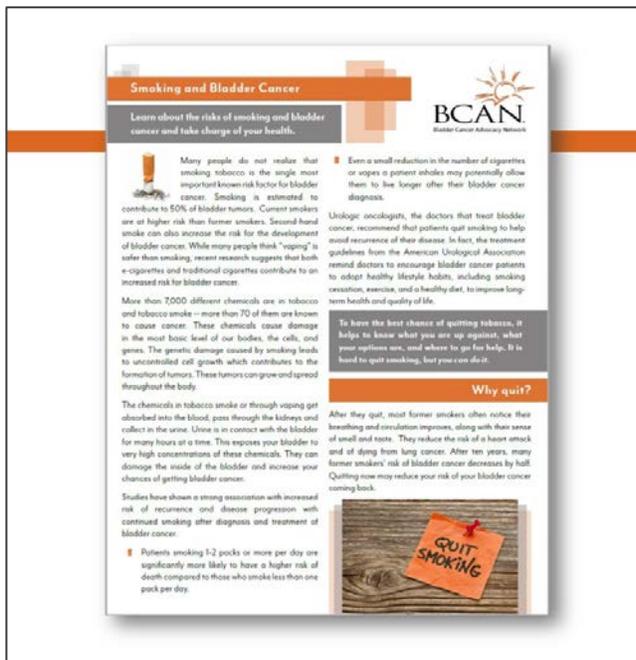
- Smoking cessation
 - ▣ While quitting does not eliminate the increased risk of developing bladder cancer, it does decrease it!
 - ▣ Smoking cessation also decreases recurrence rates for patients already diagnosed with non-muscle invasive bladder cancer

Smoking cessation is probably the only modifiable factor that can reduce one's risk of bladder cancer



While smoking cessation does not completely eliminate the heightened risk of developing bladder cancer, it certainly helps. In patients who already have bladder cancer, quitting smoking does appear to decrease the rate of tumor recurrence in patients with non-muscle invasive bladder cancer, and may also have some beneficial cancer specific effects in those with more advanced bladder cancer. The bottom line and major take-home point from this presentation is that smoking

cessation is likely the only easy modifiable factor that can reduce ones risk of bladder cancer. It's something that we really as providers as well as patient advocates should be focusing on.



To put all of this together, BCAN has created this really fantastic handout that includes a lot of the information that I spoke about in the previous slides, as well as some other resources. There are also some additional great resources that our patient advocates at BCAN can provide interested parties with from groups like the National Cancer Institute that can help you or your loved ones quit. For example, a website that I should have put on this presentation is www.smokefree.gov, and that's through the National Cancer Institute, and it has a plethora of information on how to get started with smoking cessation. It's also something that you should talk to your primary care providers about, as well as your cancer providers, because all of us should really be

equipped at being able to help a patient stop smoking and hopefully get those improved outcomes that we discussed previously.

This is one of those handouts for everybody to know is in the webinar room. When you go in there, there's a whole bunch of handouts for you. You will be able to get access to this later on.

Let's talk about some other risk factors, and we'll focus on this slide on occupational exposures. The relationship between workplace exposure to various chemicals and an increased risk of bladder cancer was first noted over a century ago, and such exposures are thought to account for about 10 to 20 percent of bladder cancers. Occupations that have been linked to an increased risk of bladder cancer are listed here, and include painters, hairdressers because of increased exposure to hair dyes that can contain carcinogens that are known to potentially lead to the development of bladder cancer, metal workers, rubber industry workers, leather workers, textile and electrical workers, miners, cement workers, firefighters, and those who help in the manufacturing of carpets, paints, plastics, and other industrial chemicals. These are something we should think about when we're taking a history, at least from a provider's perspective, and certainly as a patient or patient advocate we should be perhaps eliciting that information from folks who are potentially affected with bladder cancer.

Risk Factors | Occupational Exposure

- Occupations include...
 - ▣ Painters
 - ▣ Hairdressers (due to high exposure to hair dyes)
 - ▣ Metal workers
 - ▣ Rubber industry workers
 - ▣ Leather workers
 - ▣ Textile and electrical workers
 - ▣ Miners
 - ▣ Cement workers
 - ▣ Firefighters
 - ▣ Manufacturers of carpets, paints, plastics, and other industrial chemicals



Risk Factors | Chemicals in Drinking H₂O

- Arsenic
 - ▣ Had been linked to development of bladder cancer in certain countries with high levels in drinking water (Chile and Taiwan)
 - ▣ Subsequent removal of arsenic from water sources has led to decline in bladder cancer incidence
- Chlorination (used to decontaminate drinking water)
- Fluid intake may have a protective effect!
 - ▣ Dilutes concentration of carcinogens in the urinary tract

How about the water we drink? There's some interesting studies out there about this. First off is arsenic. There are several studies that establish a link between high concentrations of arsenic and drinking water and the development of bladder cancer. This relationship has been particularly defined in areas of Chile and Taiwan, where subsequent removal of arsenic from water sources led to a significant decline

in the incidence of bladder cancer. Moreover, in high arsenic areas, there is data to suggest that patients from these parts of the world develop bladder cancer that tends to be more aggressive at the time of presentation, so something to think about. Chlorination is another potential link to bladder cancer. Chlorination is one of the most common processes by which drinking water is decontaminated for use by the general population, and some of the byproducts of this process can be harmful if ingested at high concentrations, and the government has actually set limits on the maximal permissible levels of these chlorinated byproducts in drinking water. There have been several studies that have been published that have investigated a possible relationship between chlorinated drinking water and bladder cancer, and there, indeed, may be an association with long-term consumption of such water.

While this information may convince you to stop drinking altogether, there are other reports that show increasing ones total fluid intake actually reduce ones risk of developing bladder cancer, and this sort of makes sense, because, again, by doing that, by consuming more fluids, you're actually diluting the concentration of carcinogens in the urinary tract and perhaps that would lead to less interaction with the urothelium and possible mutations that would lead to tumor development. Personally, in my opinion, I think that the beneficial effects of water and fluid consumption likely outweigh any potential adverse effects from the decontamination process, so my suggestion is to continue to drink your water and perhaps use a water filter when you can.

Aristolochic acid is a compound that's found in some Chinese herbs derived from a plant known as the birthwort plant, and it's been used in eastern medicine for various medical indications, including to induce labor during childbirth to prevent infections after childbirth to treat infectious ulcers and wounds, and even to treat asthma and bronchitis. Consumption of these Chinese herbs that contain aristolochic acid or prescription of this compound has been associated with an increased incidence of urothelial malignancies

Risk Factors | Other Chemicals

- Aristolochic acid
 - ▣ Found in some Chinese herbs (birthwort plants)
 - ▣ Has been associated with increased risk of bladder cancer, upper urinary tract cancer, liver cancer, and renal failure



of the bladder, of the ureter, of the renal pelvis, otherwise known as the upper urinary tract, as well as been associated with liver cancer and even kidney failure. It is something when you're considering taking herbal supplements, you've got to be careful that there isn't anything in there that perhaps could be related to this particular compound.

Risk Factors | Miscellaneous

- Chronic cystitis
 - ▣ Due to recurrent UTIs, prolonged indwelling catheters, bladder stones, etc.
- Previous history of upper urinary tract cancer
- Previous history of bladder augmentation surgery
- Radiation therapy

Chronic inflammation of the bladder, which is also known as cystitis, can also be a risk factor for the development of bladder cancer. Causes of cystitis that are known to be risk factors include inflammation that we often see in patients with recurrent urinary tract infections; some patients who have prolonged urinary catheters, for example patients who have spinal cord injuries that aren't able to empty their

bladder in a normal fashion otherwise; patients who have bladder stones that can cause inflammation; etc. That is something that certainly puts these folks at risk and, again, as providers we have to have a heightened suspicion for considering an occult malignancy in folks who may have chronic cystitis.

I did want to mention that there is a condition known as interstitial cystitis which is associated with chronic bladder pain in the absence of an identifiable etiology. This term is a bit of a misnomer, because there's no clear evidence that bladder inflammation is involved in the etiology of this condition, nor is there any evidence that the condition is associated with any abnormalities of the bladder itself, and it's often thought that there may be some sort of systemic neurologic or inflammatory condition that leads to this diagnosis of interstitial cystitis. As such, there's really no known association between interstitial cystitis and the subsequent development of bladder cancer.

How about other miscellaneous risk factors? A previous history of having an upper urinary tract cancer, for example within the ureter or the renal pelvis, would put patients at risk for subsequently developing bladder cancer. Patients who have had a previous bladder augmentation surgery, so for example if a child is born with a congenitally small bladder due to another condition, there are surgeries that we do that we could use a piece of intestine to make the bladder bigger, but that does have a risk down the road of the potential of developing bladder cancer. Radiation therapy that is used for another pelvic malignancy, for example somebody who has had a previous history of cervical cancer and got radiation as part of their treatment, or they got prostate cancer and they got radiation for treatment. Those individuals have a slightly increased risk of developing bladder cancer down the road compared to people that have never seen radiation. Again, this is important for us as a community to think about and have a heightened suspicion when we see someone who has, for example, blood in the urine, and has had a history of some of these medical conditions.

Certain medications can also increase the risk of developing bladder cancer. Patients treated with cyclophosphamide, which is a chemotherapeutic agent that's often used for lymphoma, have up to a nine fold increase in the risk of developing bladder cancer, and the reason for that is because the cyclophosphamide gets metabolized to this compound known as acrolein, and that has a very inflammatory effect to the bladder. Often it will cause blood in the urine while patients are getting

Risk Factors | Drugs/medications

□ Drugs

- Cyclophosphamide (chemotherapy for lymphoma)
- Phenacetin (old pain killer)
- Thiazolidinediones (diabetic medication – link to bladder cancer is controversial)

treatment with this particular agent, but down the road they can develop potential bladder cancer. There is an uroprotectant medicine known as Mesna that inactivates this compound and can lower the subsequent risk of developing bleeding, as well as that risk of developing bladder cancer when used in conjunction with cyclophosphamide.

Medical oncologists who use this drug currently known to use Mesna along with it. It is standard of care.

Phenacetin is an older painkiller that's no longer in use, but is a recognized carcinogen, and it was related to bladder cancer. More recently, though, are these oral hypoglycemic medications used for patients with Type 2 diabetes known as thiazolidinedione. In 2011 there was a report that found a link between pioglitazone, which is manufactured under the brand name Actos, and the subsequent development of bladder cancer.

Back to Actos. When this association was initially described, it led to an announcement by the USFDA that pioglitazone used for more than a year may be associated with an increased risk of bladder cancer, and since then the label for this drug was updated with this warning about this risk. Interestingly, though, in 2017 a meta-analysis of different diabetes drugs, including pioglitazone, was performed and found no difference in the rates of bladder cancer that was initially attributed to this medication. So the data is certainly controversial, but I do think that in patients who are diabetic, you may want to have a discussion with your healthcare provider about this medication, especially if you otherwise have risk of having bladder cancer, if you're a cigarette smoker, etc., and ask if there's another diabetic medication that perhaps you can take that would give you the same benefits for your diabetes, but perhaps not give you that increased risk of developing bladder cancer.

A number of other factors have been postulated as risk factors for bladder cancer, but ultimately found not to be associated with an increased risk. These include air pollution and a webinar on environmental risk is currently being scheduled it looks like. Artificial sweeteners are something that we have talked about, and there have been studies done in rats that looked at super-physiologic concentrations of saccharin and the subsequent development of cancers, but, frankly, the concentrations that were given are much higher than anything that we would ever consume in our normal diet. Coffee and tea and personal use of hair dyes also have not been actually associated with increased risk. These are all things that, again, we should probably be safe with.

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