



Women & Bladder Cancer

A Woman-to-Woman Talk with Dr. Armine Smith

Wednesday, March 8, 2017

Part I: Diagnosis

Presented by



Dr. Armine Smith is an Assistant Professor of Urology at Johns Hopkins University and she's the Director of the Johns Hopkins Urologic Oncology at Sibley Hospital. She holds a position of Assistant Professor at George Washington University, and Clinical Associate at the National Cancer Institute. She earned her medical degree from the University of California in San Francisco and completed her Urologic Residency at the Cleveland Clinic and Urologic Oncology Fellowship at the NCI, the National Cancer Institute, where she focused on the development of targeted therapies for bladder cancer. Dr. Smith's area of expertise spans a wide range of urologic malignancies, with particular interest in bladder cancer. She specializes in complex urinary diversions, including continent orthotopic neobladder and continent catheterizable pouch techniques. Her research focus is on elucidating risk factors for the development of bladder cancer and overcoming resistance to conventional therapy regimens, including the development of personalized combinations targeted therapies.

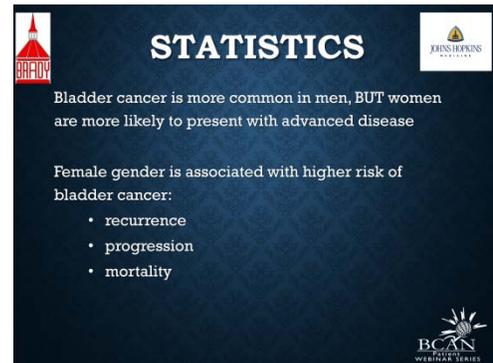
Stephanie Chisolm: Hello, and welcome to Women and Bladder Cancer, A Woman-to-Woman Talk with Dr. Armine Smith.



Dr. Smith: thank you everybody who was able to join today. My talk is titled, Gender Disparities in Bladder Cancer. Today is International Women's Day, we didn't really plan for this, it's just so it happens that this talk ended up being on March 8th. Welcome everybody. I will be talking about the diagnosis, treatment, and survivorship of bladder cancer. I try to group the slides to follow this guide. The purpose of my talk today is to provide general overview of bladder cancer, as much as we can

squeeze in this short hour, and to highlight gender-related differences. The differences are many and it's very important to be aware of that.

Starting with the statistics, the bladder cancer is more common in men. About three times more men develop bladder cancer than women, but women are more likely to present with advanced disease at the time of diagnosis. Additionally, female gender associated with the higher risk of bladder cancer and has been demonstrated in both recurrence, and the progression and the mortality from cancer and the overall mortality from that as well.



STATISTICS

Bladder cancer is more common in men, BUT women are more likely to present with advanced disease

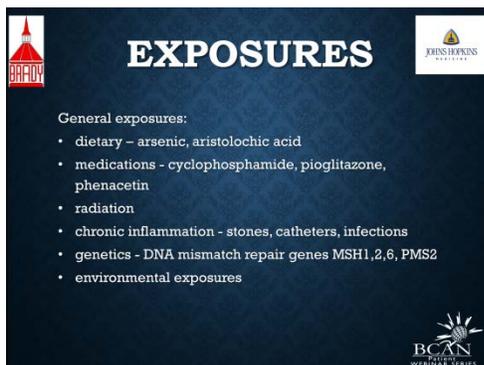
Female gender is associated with higher risk of bladder cancer:

- recurrence
- progression
- mortality

Logos for Johns Hopkins and BCAN (Bladder Cancer Action Network) are visible.

Interestingly enough, women usually do much better than men in all the cancers. However, bladder cancer is the aberration because this is the only malignancy with worse outcomes for women. It's mostly ... As this trend has been observed worldwide, and we have no answer for why this is happening. There are lots of theories, and there are a lot of ... We're starting to more and more pay attention to these trends and collecting more data. For now, there are a few trends that came out that may give us an idea of why this is the type of phenomena we're observing. The exposures, the biology and the delay in diagnosis have all been implicated into this disease's different state.

The exposures, starting with the general exposures to development of bladder cancer. There are known general exposures such as dietary-arsenic, and aristolochic acids have been implicated. There are medications that are known to cause bladder cancer or associated with the development of bladder cancer. Cyclophosphamide, which is a chemotherapy agent, Pioglitazone, which is a diabetes agent, and Phenacetin, which was a pain relief medication which was actually taken off the market some time ago. The ionizing radiation, for a variety of reasons, to the pelvic area, has been implicated. There are states of chronic inflammation, which are stones, kidney stones or bladder stones, the catheters, chronic use, and colon catheters, and recurrent infections can also be a cause of the inflammation.



EXPOSURES

General exposures:

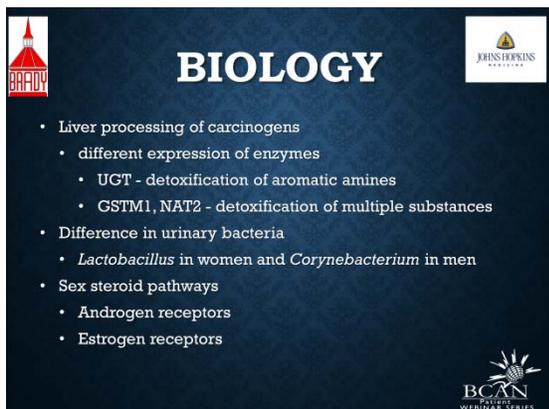
- dietary - arsenic, aristolochic acid
- medications - cyclophosphamide, pioglitazone, phenacetin
- radiation
- chronic inflammation - stones, catheters, infections
- genetics - DNA mismatch repair genes MSH1,2,6, PMS2
- environmental exposures

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We are starting to learn more about the genetics of bladder cancer and the most well-known set of genes that has been implicated is the DNA mismatch repair genes and those are the MSH1, 2 and 6, and the PMS2. I know the names may not say a lot, but they are usually implicated in stuff that's called a Lynch Syndrome, which characterizes by development of urothelial kidney and bladder cancers. I'm sure there will be more developments in the genetics in the next few years.

Finally, the one that is probably the hardest to quantify and prove but has, in my mind, has played a huge role in this is environmental exposures. These exposures are fairly equivalent for both men and women. On the next slide, these are the exposures that have been different in different sexes. The known differences are smoking. To look at these numbers, these are the 2012 numbers in adults age more than five years old. Men smoke much more than women do,

about 30% of men and 6% of women. Men smokers are diagnosed more than women, so four times as more, so that's one difference in exposure. There's been a lot of talk on the hair dye use, of permanent dye. There's been evidence one way or another, proving and disproving the use of hair dyes with the development of bladder cancer. The jury's still out, but this is another thing that can be contributing to women's exposure. Then there are the occupational exposures, which are dyes, petroleum, tar and exhaust fumes. These, depending on the differential exposure by sexes, can also play a role.



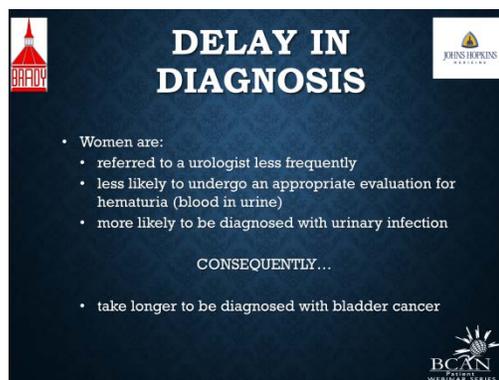
The other aspect that we're also starting to learn more and more about nowadays, is the biology of the processing of carcinogens and other environments in our body that protect us from developing cancer. Some of the things that are known now is the liver processing of carcinogens is different among different individuals. The expression of enzymes, that have been implicated are the UGT enzyme, which is detoxifying the aromatic amines, and the GSTM and NAT2, those are also liver enzymes that detoxify multiple substances that are foreign to our body. Like I said, different individuals

express different isoforms of these enzymes with different activity, so that can be a contributing factor. There have been some data, which is not solidified yet, but there's been observation that in urine of different sexes there are prevalence of different bacteria. *Lactobacillus* in women and *Corynebacterium* in men, and *Lactobacillus*, there has been some evidence that is may be protective of the development of bladder cancer, so more research to be done on this front.

Finally, the sex steroid pathways, which are the androgen and estrogen

pathways have become more and more recognized in their differences in the bladder cancer. There's a difference in the expression of these receptors. They are different in the more aggressive cancers and the recurrent cancers. There is more research that's being done on this front as well.

Another major factor that's been consistently recognized over the past years is the delay in diagnosis of bladder cancer in women. There are multiple sources of data that are proving that women are referred to urologists less frequently, are less likely to undergo an appropriate evaluation for the hematuria, which is the blood in urine. When they present with the blood in urine, they are more likely to be diagnosed with urinary infections and so forth and so on. Consequently, they take longer to be diagnosed with bladder cancer.



This is a paper that quantifies these numbers. If you look at this number in men versus women you can see the mean number of days from presentation with the blood in urine to the diagnosis was definitely

much shorter in men than women. There was a much higher delay in nine to 12 months for the diagnosis in women. Why does this matter? It's because in bladder cancers a delayed diagnosis is fairly deadly. There was another paper that looked at these large volume data, and the delay in diagnosis, nine to 12 months, increases the risk of both cancer-specific and all-cause mortality after the diagnosed bladder cancer. These are the things that are important.

SYMPTOMS OF BLADDER CANCER

- Blood in urine only visible under microscope
 - ≥ 3 RBC/hpf in absence of obvious benign case
- Visible blood - gross hematuria
- Irritative voiding symptoms
 - pain on urination
 - frequency
 - urgency

I THINK IT'S TIME TO SEE A DOCTOR

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Just to go over quickly the symptoms of bladder cancer. It can be either the blood in urine. The blood in urine can be visible with the naked eye, such as in the picture here. This is fairly obvious and needs to be evaluated. However, there are also instances where the blood in the urine can only be seen under the microscope. So there is strict criteria that we follow when we decide whether this needs to be worked up or not. For us, our professional society recommends more than three red blood cells per high-power field in the microscopic urine specimen, in the absence of

obvious benign causes such as infection or stones or anything of that nature, menses, those are the things that need to be investigated. Also, bladder cancer can present with an irritative voiding symptom. One type of bladder cancer, called CIS, is fairly notorious for having these irritative symptoms. Those can be pain on urination or dysuria, frequency and urgency of urination.

The appropriate evaluation is also fairly straightforward, lined out by our professional society. One is a look in the bladder, which is called cystoscopy. Then there are multiple ways to look at the upper tract, which is the kidneys and the ureters. The recommended way is the CT or computerized tomography of abdomen/pelvis, with delayed contrast phase to see the tubes, also kidneys. Meaning the renal pelvis and the ureters. If a person cannot undergo a CT for one reason or another they can obtain MRI of the abdomen/pelvis with delayed phase. If none of that is feasible, ultrasound can be obtained combined with something that's called retrograde pyelogram, which is pretty much instillation of the dye into the kidneys and ureters during the cystoscopy which achieves the same effect as the CT and abdomen and pelvis with contrast, or the MRI. If the person cannot get a contrast for one reason or another they can have a non-contrast CT or MRI combined with a retrograde pyelogram. Also it's recommended to obtain a cytology, which is a preparation of the urine to send it down and look for the malignant cells if there are irritative urinary symptoms, this is also an aid in the diagnosis of cancer. This sums of the diagnosis, so we will proceed to the treatment of bladder cancer.

Thank You

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