

Prevention of Bladder Cancer

Impaired detoxification of carcinogens

- NAT1, NAT2 genes
 - Detoxify aromatic amines that cause bladder cancer
 - Some people have mutations in these genes leading to "slower" detoxification
 - increased risk of bladder cancer
- GSTM1 gene
 - Detoxifies carcinogens in urine
 - - 1/2 of Caucasians in USA don't have this gene
 - Increased risk of bladder cancer



There are two interesting scenarios that they've identified through some great research looking at how our body detoxifies the carcinogens, so detoxifies these occupational exposures or smoking that we're exposed to. The NAT1 and NAT2 genes both detoxify these aromatic amines that cause bladder cancer. What they found is that

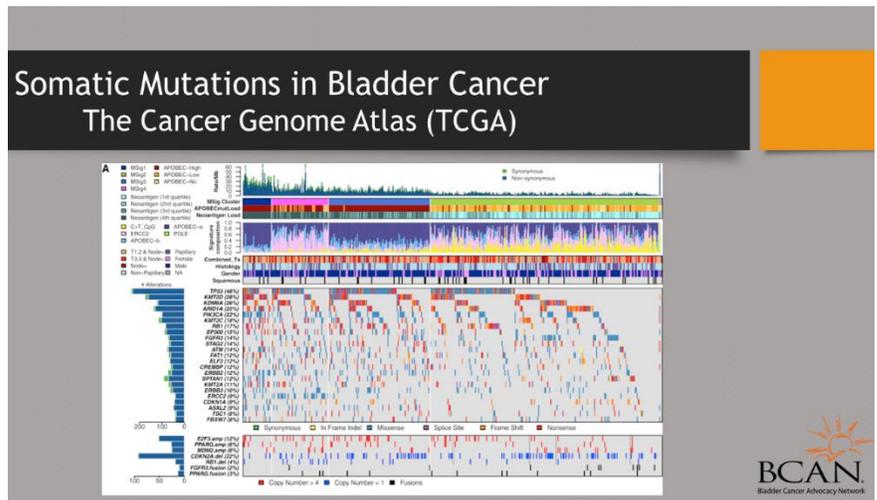
some people, not very many, but some have a mutation in these genes that leads them to detoxify slower. So, the toxins in their system, rather than breaking it down at a normal rate, the mutation causes them to break it down slower so there's more exposure to that individual carcinogen. Especially in those that are smokers, there's an increased risk of bladder cancer that has been observed.

Then, there's another gene, which actually is fairly common in Caucasians in the United States, a mutation in GSTM1 gene, which also works to detoxify carcinogens in the urine. Although it's relatively common, it doesn't commonly lead to bladder cancer, but there does appear to be an increased risk to bladder cancers in those that have this gene.

Now, neither of these are common enough that we're going around looking specifically for these mutations, but it is interesting especially where you can see

the genes that we have and the environment that we're exposed to, can lead to cancer. Again, not very common.

This slide shows what we more commonly encounter in bladder cancer. This is from the Cancer Genome Atlas, there's a tremendous amount of data on this screen. This is what our people's publications look like that we read about bladder cancer and these are a bunch of somatic mutations. Mutations that occur in the tumor themselves, that then led to the bladder cancer. So, T53, Arid 1A, these are the genes that we see, not that they're inherited or that they're born with, but that develop in the bladder tissue and lead to tumor. Most of these bladder cancers occur that way.



So, what about prevention? We all want to do things that we can help to prevent from getting cancers and there's been quite a bit of research looking at this area too. I want to define two different types of prevention. There's first primary prevention and that's where we take people who don't have the disease, who don't have bladder cancer, and try to do something to prevent it from occurring. The other is secondary prevention. So, that's in the scenario where someone has had the disease, someone has had bladder cancer treated and we're trying to do something to help prevent the disease from recurring. That's called secondary prevention.

We'll take a look at primary prevention first, there's no clear evidence that there is a specific item we can do to help prevent bladder cancer from occurring in those that don't have it. There have been very large studies looking at Vitamin A, it's called the ATBC study. 29,000 male smokers, looking at Vitamin E and beta keratins to see if they could reduce the incidence of cancers. If not, see a reduction in the incidence of bladder cancer. Selenium in a large study, the SELECT study, also looked at Vitamin E too. Very large studies, tens of thousands of patients where we have not seen a reduction in the development of bladder cancer. Certainly multivitamins, many of you are aware of

The slide is titled "Primary Prevention of Bladder Cancer". It contains the following text: "No clear evidence". Below this, it lists "Randomized studies have looked at:" followed by a bulleted list: "Retinoids (Vitamin A)", "Alpha-tocopherol (Vitamin E)", and "Selenium". Underneath, it asks "Multivitamins?". A box contains the text: "Long-Term Use of Supplemental Vitamins and Minerals Does Not Reduce the Risk of Urothelial Cell Carcinoma of the Bladder in the VITamins And Lifestyle Study". At the bottom, it lists the authors: "James M. Hotaling*, Jonathan L. Wright, Gaia Pocobelli, Parveen Bhatti, Michael P. Porter and Emily White". A small footnote at the bottom reads: "From the Department of Urology, University of Washington School of Medicine L&M1, JLW, MPH; Department of Epidemiology, School of Public Health GSP, PSE, DSW, University of Washington, and Cancer Prevention Program L&M1, GSP, MPH, PDS and Program in Epidemiology PBI, Fred Hutchinson Cancer Research Center, Seattle, Washington". The BCAN logo is in the bottom right corner.

the large study looking at a multivitamin that overall reduced cancers and maybe in part just not enough events and enough bladder cancers themselves, have not seen a convincing reduction in multivitamins and bladder cancer.

Some of these studies are just limited by the fact that you're studying a large group of people, but you have to have enough events, enough people develop the tumor to be able to show statistically that there is a difference. I think that the other thing that these studies do show too is that at higher levels of some of these supplements, they can lead to other adverse events too. So, I think everything in moderation. I have had an interest in looking in this as well, again with Dr. White and some other researchers where we looked at a study looking at supplemental vitamin use and minerals. We did not see a reduction in the risk of bladder cancer in this large cohort study where they were looking specifically at vitamin use and lifestyle, and development of different cancers or other different diseases over time.

Primary Prevention of Bladder Cancer

- Non-steroidal anti-inflammatories (NSAIDS?)
 - Mixed results
 - Cohort studies showing reduction in risk among non-smokers (Daugherty, AJE 2011)

Original article
Long-term NSAID use and incident urothelial cell carcinoma in the VITamins and Lifestyle (VITAL) study²²

Cheryl Shih, M.D.^{a*}, James M. Hotaling, M.D., M.S.^a, Jonathan L. Wright, M.D., M.S.^{a,b}, Emily White, Ph.D.^{a,c}

- We saw a reduction in risk for those who had quit smoking > 10 years before



Non-steroidals have had a lot of interest in them, these are the anti-inflammatories. As I mentioned earlier, inflammation can be one of the hallmarks that can lead to development of cancer and could non-steroidal medications help reduce it. There's mixed results, there have been some studies showing a reduction among non-smokers. This is a study that we did, if I can get it to come back up, where

we looked at whether or not long-term NSAID use was associated with bladder cancer and we saw a reduction in a subset of patients, in those that had quit smoking. So, maybe similar to what the other studies had shown. Where this was non-smokers having a reduced risk and we were seeing it in those that had quit smoking 10 years before. We see a lot of this in these prevention studies. A hint of something, but not conclusive.

Secondary prevention, I am not talking about BCG or Mitomycin or Gemcitabine that a patient may receive from their physician as an active treatment to prevent bladder cancer. That is a secondary prevention, but I'm just going to focus on non-therapeutic interventions that the physician might give. There have been several randomized studies looking at these, these

Secondary Prevention of Bladder Cancer

- Randomized studies
 - Retinoids
 - Vitamin B6
 - Selenium
 - DFMO (polyamine synthesis blocker)
 - Celecoxib (NSAID)
 - Multivitamins



are some of the more common ones. Retinoids again, there was some pretty exciting pre-clinical data about retinoids in prevention. Unfortunately in the studies that they did with some synthetic retinoids, there actually were more adverse effects in those receiving them and thus not used. Vitamin B6, very small study showed an effect, larger study did not. Here's the NSAID's again. Interesting studies looking at mega-multivitamins associated with BCG. One small study showing an effect, a larger study, randomized study, showing no effect, so conflicting data about things.

Similarly we talk a lot about just increasing your fluid intake. Dilute out the toxins better or flush them out better by drinking more water. Certainly a fairly easy thing to do to try to help prevent cancer, bladder cancer, and there has been one large study, observational study, that did show an affect. Although a more recent longer term follow up of that study, did not show as much as an effect there. So, again unfortunately despite significant effort looking at different things, we do not have convincing evidence that different items are useful for secondary prevention of bladder cancer. Not to say they're bad for you, but we don't have enough data that to conclusively say something.

My Recommendations for Prevention

- Smoking cessation
- Healthy well balanced diet
- Exercise
- Weight loss



What do I tell patients for prevention? Smoking cessation, that's number one. Stop smoking or if you're exposed to secondhand smoke, reduce that as well. A healthy well balanced diet, most of us don't get five servings a day of fruits and vegetables, we don't eat enough complex sugars, as opposed to the simple sugars, we need to eat, and then trying to reduce some of our fat intake. All these things that are

certainly helpful for not only for our heart, but helpful from the development of cancer. Exercise, there's certainly something about the immune system and having a better immune system with exercise and other different pathways as well and weight loss too. So, basic recommendations, but are heart healthy and good for you and bad for cancer and I like that combination. So, certainly things that we all can do.

Screening for Bladder Cancer

Not recommended by any major organization

- US Preventative Services Task Force
- National Cancer Institute
- American Cancer Society
- This is regarding screening in asymptomatic adults
 - Insufficient high quality evidence that screening improves outcomes in bladder cancer
 - Would result in unnecessary testing in individuals with associated risks and morbidity



Briefly, screening for bladder cancer. At this time, it is not recommended that we do routine screening for bladder cancer. The way we would be screening is primarily looking at a urinalysis for microscopic hematuria. Other things like routine cystoscopies are definitely not recommended. The US Preventative Services Task Force, The National Cancer

Institute, The American Cancer Society do not recommend screening. I will point out, this is regarding screening in asymptomatic adults, so that's someone who has no symptoms. If you come in with symptoms, different story. This was the language, "insufficient high quality evidence that screening improves outcomes in bladder cancer and results in unnecessary testing individuals with associated risks and morbidity". So, at present, we do not recommend routine screening for asymptomatic adults.

There are scenarios where although there aren't clear guidelines, we do think, or many of us believe that there is a role for screening in very high-risk individuals. Obviously someone with this Lynch Syndrome, inherited syndromes, where there's such a high risk of developing bladder cancer, to watch those patients. Urinalysis versus cystoscopies, there's debate about what the best way to do it is. Bladder cancer birth defects that have these augmentations, especially those with gastrocystoplasty, those stomach augments. Then, also the discussion of what to do if you have someone that's a very high smoker, who is catheter dependent, recurrent UTI's, is there a role there? Can't say there is, but I think we can take on a case by case basis and look at someone's exposure. If we knew they were exposed to a highly contaminated well with arsenic, that's someone I would certainly consider doing some screening on. Different than the asymptomatic person.

Screening for Bladder Cancer

Very high risk individuals may warrant screening

- Inherited syndromes (Lynch Syndrome)
- Bladder cancer birth defects
- Bladder augmented with bowel
 - Especially stomach (gastrocystoplasty)



This is the main thing that most of you listening here know, that when you have hematuria, you need to go get it checked. Gross hematuria or red urine, the blood you can actually see in the urine, about a quarter of these patients are going to be found to have urologic malignancy. It could also be kidney, urethral, ureteral. Another 20% have a benign urologic cause. So, gross hematuria needs a work up soon. Microscopic hematuria, there is a much lower prevalence of finding bladder cancer, but still when we see patients that have microscopic hematuria, the recommendation is for evaluation. Especially in someone who's older and has been a smoker, we can get up to a 5% risk or higher of those individuals having bladder cancer found on their workup for microscopic hematuria.

Hematuria - blood in the urine
Most Common Symptom

- **Gross hematuria**
 - 24% with urologic malignancy
 - 21% significant benign surgical disease
- **Microscopic hematuria**
 - Approximately 5% risk of malignancy if person is > 50 years
 - Higher if current/former smoker

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We do a lot trying to educate our primary care colleagues. If they happen to be getting a urinalysis on an individual as part of their care and if they see microscopic hematuria to not ignore it, but to then refer to a urologist for a discussion of evaluation.

CONCLUSIONS

- Bladder cancer is common
 - Age, gender and race differences
- Smoking and occupational exposures are the primary risk factors
 - We often don't know what caused it in an individual
- No established prevention at this time
 - Healthy lifestyle
- Asymptomatic screening not recommended

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So, in conclusion, bladder cancer's common. It's, like I said, the number six cancer overall, not just in the US, but worldwide as well. There are specific epidemiologic features. It's common in older, but affects all ages. Effects both genders, but is more common in males. There are race differences, but all races are affected. Smoking and occupational exposures are the primary risk factors that we have

identified. Unfortunately we don't often know what exactly caused the cancer in an individual, but certainly there are occupational exposures and we can work on smoking cessation.

There's no established prevention at this time, but again, I really advocate for a healthy lifestyle, which is certainly going to be good for you in many, many ways. At present, asymptomatic, so those without symptoms, screening is not recommended.

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