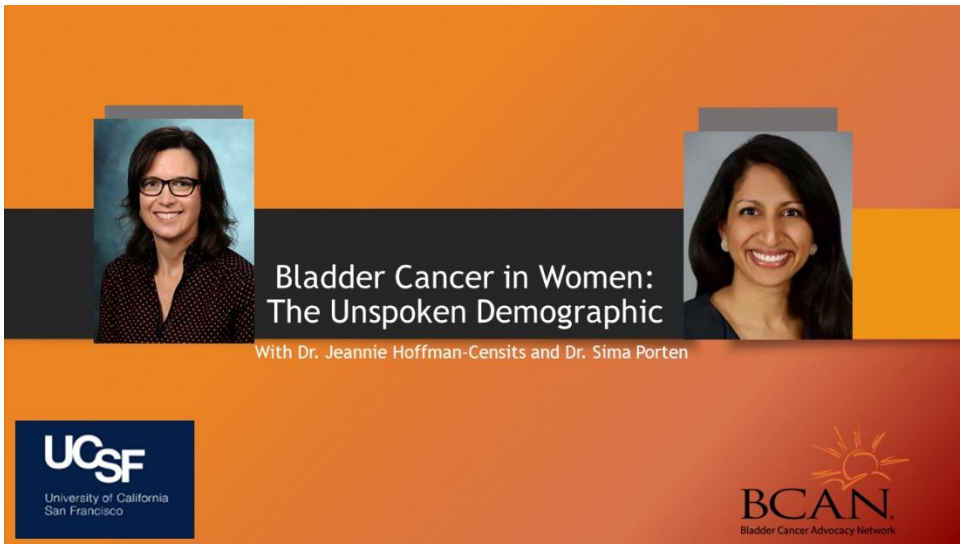
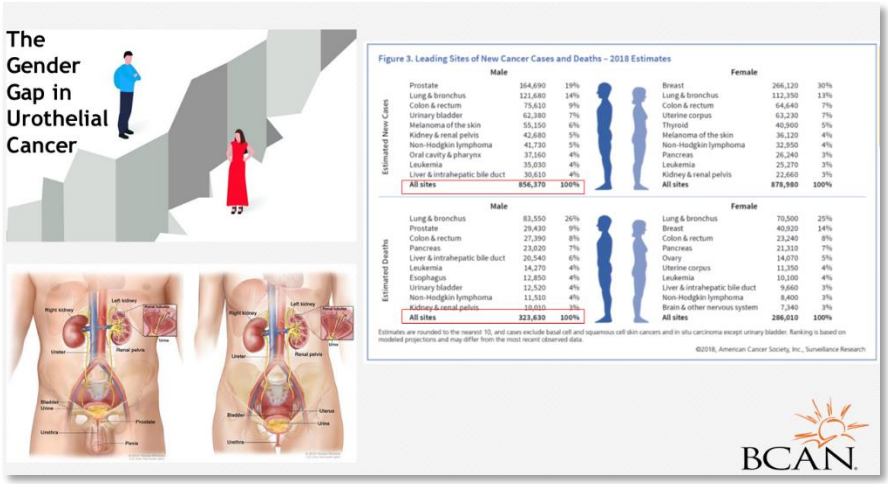


Gender Disparities for Women with Bladder Cancer



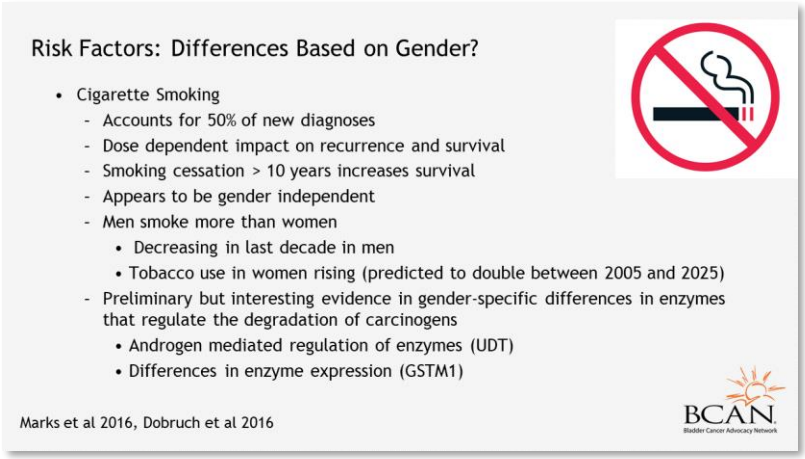
So let's talk a little bit about gender differences in bladder cancer and some of the risks. So we know that there is this gender gap when it comes to urothelial cancer. We look at some of the statistics and as well as the anatomy. It can be a just a brief overview. On the left hand panel is male anatomy and on the right hand panel is female anatomy. So the urine is made in the kidney and those kidneys that generate the urine then transmit that urine into the renal pelvis, which is at the top part of the kidney that's a reservoir, where urine is kept for a brief period of time. The urine is then transmitted through a really small straw that connects the renal pelvis down into the bladder. That's called the ureter. And then urine is housed in the bladder until it's time for your brain to tell you that it's time to go to the bathroom. And patients urinate through the urethra.

The majority of bladder cancers, about 90%, happen in the bladder, but we do see rare tumors that happen in what's called the upper tract and that's the ureter and the renal pelvis. These tumors tend to be lumped together either with bladder cancer or with kidney cancer that we tend to treat them much more like bladder cancer. And then also can rarely happen in the urethra. We tend to call all of these cancers urothelial cancer, or coming from the tissue that lines the entire urinary system, but some of them can be different subtypes than that. That's also rare.

So if you look at the statistics that are on this slide and this is data from the American Cancer Society in 2018. We know that for men, the estimated new cases of all cancers are listed here and bladder cancer is about the fourth most common cancer in men and it's about the eighth most common cause of cancer related death in men. In women urothelial cancer isn't even on the list and sometimes we believe that

may be why because it's so much less common in women than in men. This might not be the first thing that comes to mind when women present to their doctors or other practitioners with a complaint of urinary symptoms or gross hematuria. What this slide doesn't capture is that the risk of potentially dying when women are diagnosed with bladder cancer is higher than that of men. Next slide.

Sima: So we put this section out mainly to talk about why is there a less chance of women getting bladder cancer and could some of these differences be based on gender and then when women get bladder cancer, why do we see worse outcomes and then we'll get into that part of it next. So in terms of risk factors, are there any differences based on gender? Cigarette smoking is the number one risk factor for bladder cancer. It accounts for half of all new diagnoses.

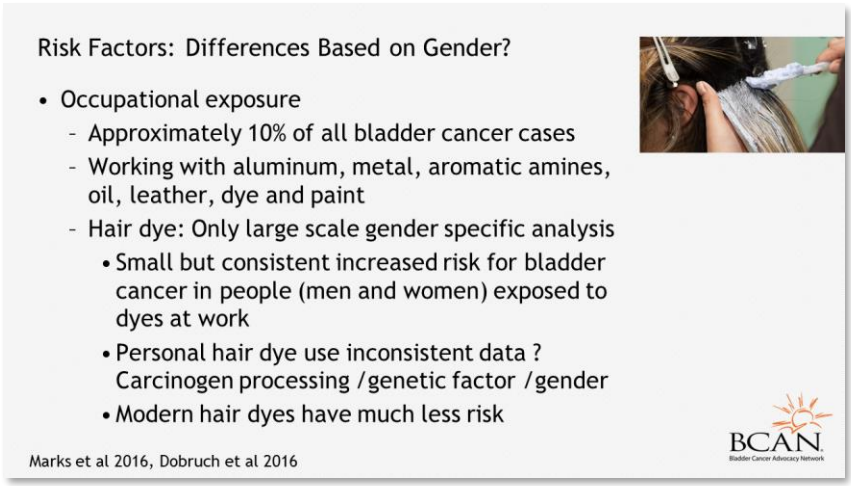


It is dose dependent and its impact on recurrence and survival. The more tobacco exposure you have, the worse chance that you have of survival and that increased chance you have of recurrences. So it definitely has a huge impact in terms of something that we think is modifiable or changeable even though it may be a very difficult and hard change to make. Smoking cessation, if you quit smoking for more than 10 years, it dramatically increases survival and it also decreases recurrence. This observation that's seen across many different studies and case control studies and large data sets appears to be gender independent.

However, what we do know is that men do smoke more than women, but this has been decreasing in the last decade in men and there's been a little bit of an alarming trend in that tobacco use in women is rising. There's a prediction out there that it's supposed to double back in 2005 and looking ahead to 2025. And so we may see a reversal in some of these incidents estimates that Jeannie showed on the slide before. The other thing that's been really interesting in looking at risk factors in terms of cigarette smoking and gender is that there might be a difference in the enzymes that our bodies use to process these carcinogens.

So whenever we're exposed to a toxin, our body has a system to get rid of it. And that might be different in men and women. And that might also be the reason maybe why men might get cancers more because there is some androgen or the male hormone mediated regulation of one of these enzymes. And it may also be a reason why when we see with women who smoke, why they might have worse bladder cancer outcomes because there's a different enzyme expression in women that might lead to more aggressive disease. All of this evidence is preliminary, but it's definitely interesting and it's really amazing that people are paying attention and looking at it to get to the place where we're not treating every patient the same and we're really trying to personalize our medicine.

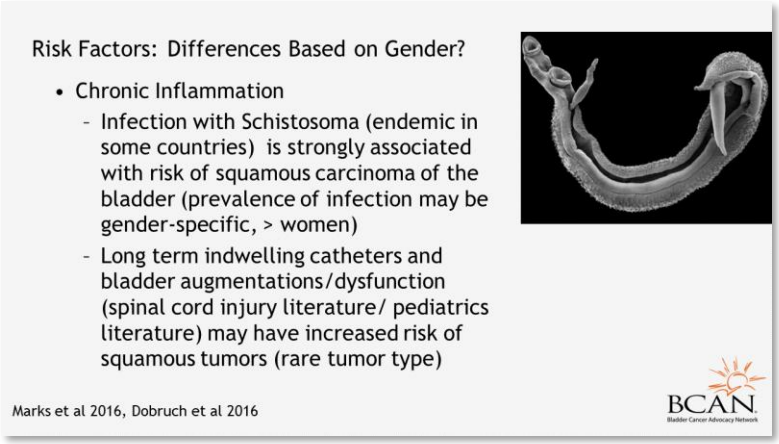
So what about occupational exposure? Approximately 10% of all bladder cancer cases might have to do with something that you're exposed to in your daily job. We do know that working with aluminum, metal, aromatica means, oil, leather, dye, and paint all put you at an increased risk of developing bladder cancer and in the past and when these studies have been done in early 70's, early 80's this has mainly been occupations that were done by men and that's changing as today's world is changing.



There was a lot of press and interest in looking at hair dye across many different cancers. It's the only large scale gender specific analysis done in terms of looking at occupational exposure in women. How I summarize all of the studies is that there is a small but consistent increased risk for bladder cancer in people, both men and women, who are exposed to dyes at work.

So mainly hairdressers and barbers. Personal hair dye use has a lot of inconsistent data. We think that that might be as a result of both how we process carcinogens, which might be related to gender or some intrinsic genetic factors. And so although there might be an increased risk, many studies have actually not born out to show that. The other thing that we do know is that the modern hair dyes have a much less risk.

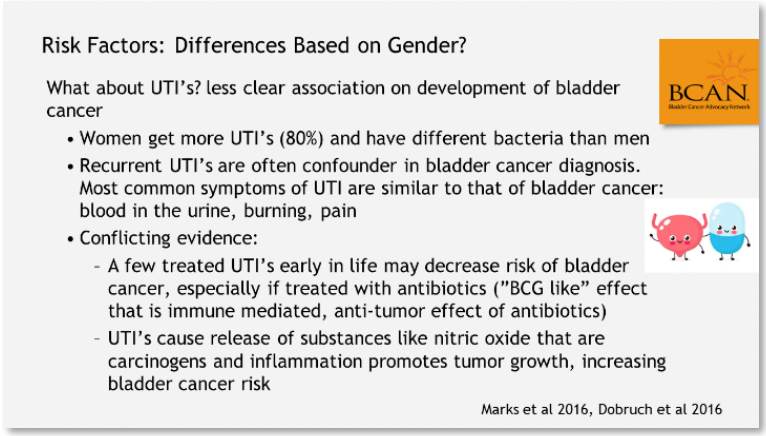
So when you look at older studies, when tar was used to die hair dark or black, there was a lot higher risk in sort of exposure for a carcinogen that could cause bladder cancer. Whereas, now there's many different more plant-based modern hair dyes that don't use things like tar. And so that's definitely factor nowadays.



A lot of people ask about chronic inflammation. And then that will lead us into our next slide, which is on your urinary tract infections. So we do have evidence that inflammation in the bladder can result in developing a bladder cancer. But this is a specific kind of bladder cancer called squamous carcinoma. And we have this evidence mainly from areas which have endemic infection Schistosoma which is a worm that can travel into someone's body from water sources.

And the prevalence of infection in countries which have Schistosoma tend to be that women get this more than men and it's a squamous tumor, which again is rare when you look at all of the bladder cancers across multiple different countries. We also do know in patients who have long term indwelling catheters and have had bladder augmentations or surgeries done when they were kids because of a spinal problem or what we call a nerve problem with how the bladder stores and empties our urine.

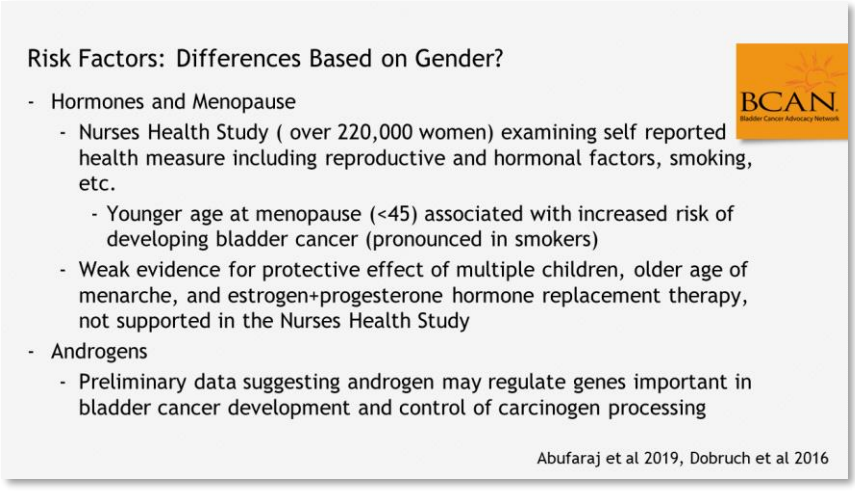
We do know in those patients there is an increased risk of these same squamous tumors again, which are rare and which are related to inflammation. And so then that brings us to the question that most people have. What about urinary tract infections? It is interesting because there's a less clear association in the development of bladder cancer and how that plays into urinary tract infections.



We do know that women get more UTI's. About 80% of UTI's are in women. We do know the bacteria looks different in women than in men. It's a different type of flora or pathogens that cause urinary infections. Urinary infections especially those are recurrent are often a confounder in bladder cancer diagnosis. The most common symptoms of urinary tract infection are very similar to that of bladder cancer, blood in the urine, burning, pain.

Those can be a sign of an infection or those can be a sign of bladder cancer. And so a lot of studies have a hard time teasing out what was the chicken, what was the egg. And what's actually the truth for a large group of patients when you look at these big data sets. And there's a lot of conflicting evidence. Some researchers have showed that if you have a couple treated urinary tract infections early in life that decreases your risk of bladder cancer. And they hypothesize, or guess, that maybe this is sort of a BCG like immune mediated effect, meaning that the bacteria generates inflammation, which then primes your immune system to actually fight off cancer.

They also mentioned an antitumor effect of antibiotics. Again, this is all just theories. There's other researchers who say that urinary infections actually are toxic. They cause a release of substances that may promote tumor growth, which may increase bladder cancer risk. So again, it's great that people are looking at this, but I don't think we have as clear of an association of urinary infections and bladder cancer and how those two may interplay and might be a good thing or a bad thing in patients.



Another common topic is, well how do female hormones and menopause play into getting bladder cancer or having a risk for bladder cancer? So we do have one very large data set, which is from the Nurses' Health Study. It's over 200,000 women who looked at their own self-reported health measures,

looking at reproductive and hormonal factors, medications they were taking, and also other things that might play a role in bladder cancer such as smoking. And the only thing this very large study found is that having a younger age of menopause is associated with an increased risk of developing bladder cancer.

And that this was augmented or more pronounced in patients who are smokers. In the past many researchers have said that there's a protective effect of multiple children. There's a protective effect of having an older age when you start your period. There's a productive effect of taking hormone replacement therapy, but you have to take both estrogen and progesterone.

None of these were supported in this very large Nurses' Health Study and the only real finding had to do with what age of menopause you were at being associated with any kind of increased risk in developing bladder cancer. I also put in there the male hormone or androgens. A lot of people have started putting effort in looking at mainly animal models suggesting that androgens, which also women have this hormone too, may regulate genes that are important in bladder cancer development and how again we process the chemicals in our body.

And it remains to be seen how important this is in bladder cancer and women as it might be or is this something that plays a role more in men and potentially maybe a pathway to have different therapies for people that might be more based on tumor biology and at a host biology. And Jeannie, we'll talk about that a little later in the talk.