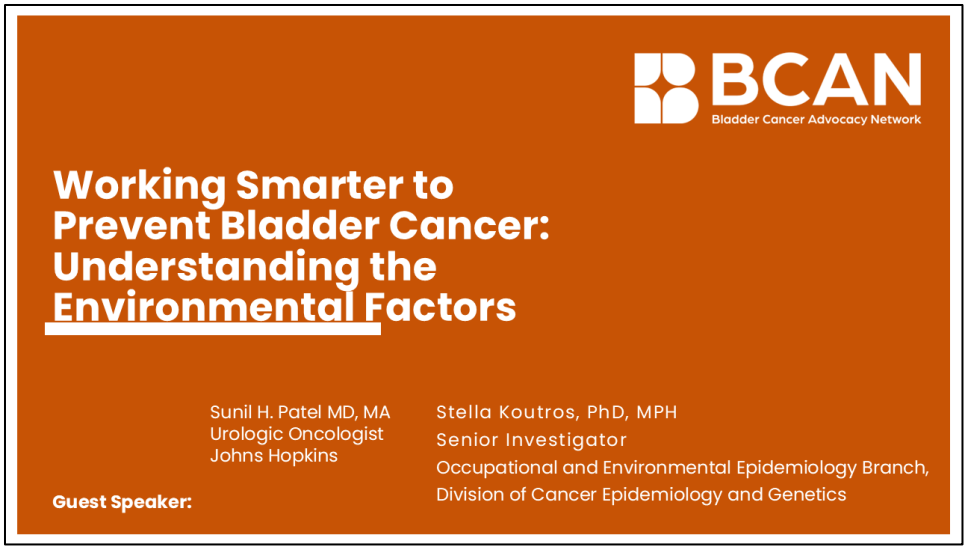


Patricia Rios:

Welcome, my name is Patricia Rios. I am the Director of Education Advocacy and your host for today's webinar on Working Smarter to Prevent Bladder Cancer: Understanding how jobs and environment affect risk.

Bladder cancer is a complex disease with many risk factors such as age, gender, and genetics. Exposure to harmful chemicals can also put people at risk. For example, people who smoke are two to three times as likely than non-smokers to be diagnosed with bladder cancer, yet many bladder cancer patients have never smoked.

Scientists are learning that other kinds of toxic chemicals in our environment, meaning chemicals that we come in contact with where we live, work and play, are important contributing factors that can increase a person's risk of developing bladder cancer. Based on growing body of evidence, more than a dozen chemicals and other industrial agents have been linked to bladder cancer alone. And to shed light on the connection between bladder cancer and toxins in the workplace and our environment, we are joined by two phenomenal speakers, Dr. Stella Koutros from the National Cancer Institute and Dr. Sunil Patel from John Hopkins Medicine.

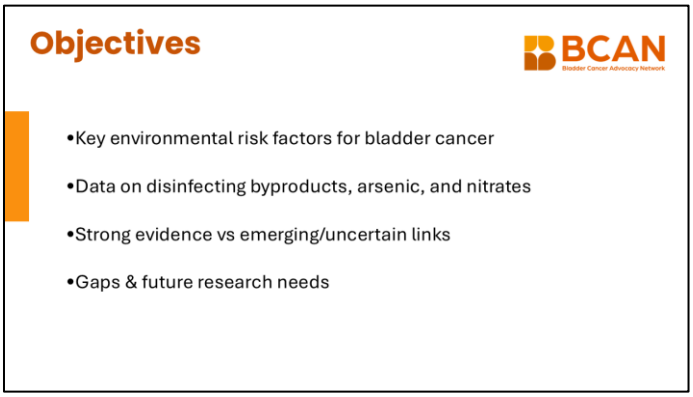
I'm going to introduce our speakers and then hand over the screen to them for the presentation. So Dr. Koutros is a cancer epidemiologist in the occupational and environmental epidemiology branch in the Division of Cancer Epidemiology and Genetics at NCI or the National Cancer Institute. She is an internationally recognized expert in the design and the conduct of epidemiological studies to evaluate workplace exposures as risk factors for cancer and to clarify the causes of bladder cancer.

Dr. Sunil Patel is an assistant professor of urology and oncology at the School of Medicine at John Hopkins. He serves as director of the urologic oncology fellowship. His clinical and research focus is obviously urologic oncology with areas of focus in bladder cancer, testes cancer and kidney cancer.

Dr. Patel joined the John Hopkins Medicine in June 2020 with interest in environmental factors contributing to oncogenesis or development of tumors in urological cancers, particularly bladder cancer.

That was a short description of their very extensive background, and so we are honored to have them both here today so we can learn a little bit more about the connection. And so with that, I am going to go off camera and hand the screen to our first presenter, which is Dr. Patel. After Dr. Patel's presentation, you will hear from Dr. Koutros. So without further ado, Dr. Patel, the screen is all yours.

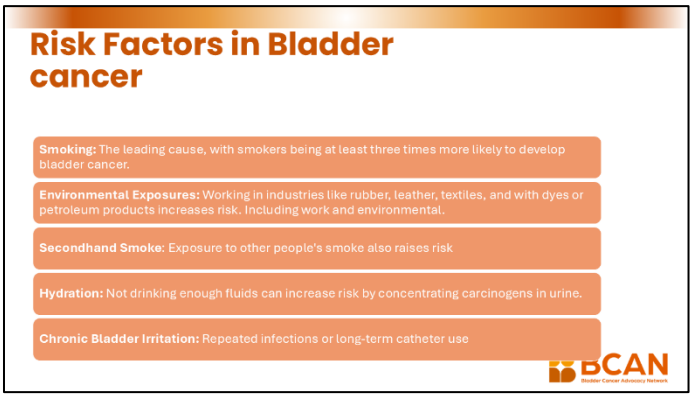
Dr. Sunil Patel:



The goal of this session is really for Dr. Koutros and myself to highlight some of the occupational and environmental factors that we've been targeting and discussing at our think tank over the last several years and going into some of the key studies and the study designs, as well as a little bit the data and the results on some key factors.

So we're going to highlight some environmental risk factors for bladder cancer. We're going to look a little bit on the data on disinfecting byproducts, arsenic and nitrates, and look at some of the evidence that is pretty strong that we have for carcinogenesis for these environmental risk factors and some emerging and kinda uncertain links. And then really talk about the gaps in future research needs. Next slide, please.

Dr. Sunil Patel:



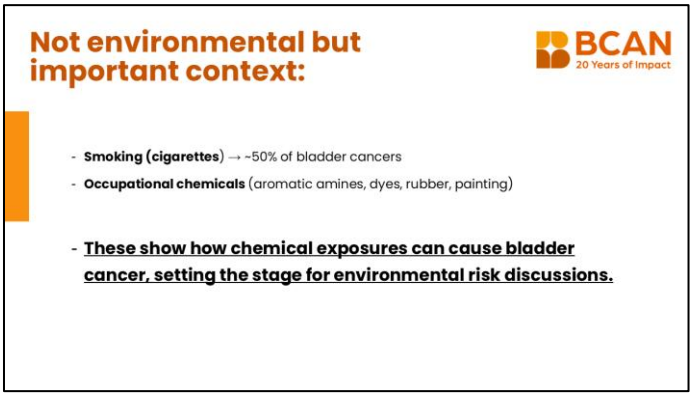
So as Patricia highlighted, again, and this is just a very general slide, but smoking again is the leading cause with smokers being two to three times more likely to develop bladder cancer. Environmental exposures, so we do know that working in certain industries like in the rubber, textile, leather, and/or with dyes, whether that's hair dyes or

aniline dyes or in clothing does increase risk.

And again, that includes both work and environmental. Secondhand smoke often gets misrepresented, but that is still another risk factor as we know for a lot of malignancies, bladder cancer included. Hydration is a very interesting one, and Dr. Koutros has done a lot of work in this as well, and we're going to highlight a study that challenges this not drinking enough water and the fluid intake, but historically it's been thought that poor PO intake or fluid intake increases bladder cancer risk by concentrating carcinogens in the urine, which potentially can be, but there's some more data that may contradict that.

And as we know, chronic bladder irritation can cause bladder cancer. Again, a little bit different type of bladder cancer. We usually see that in squamous cell carcinoma, so a little bit different than neurothelial carcinoma of the bladder. However, that is still in the umbrella of bladder cancer. Next slide, please.

Dr. Sunil Patel:

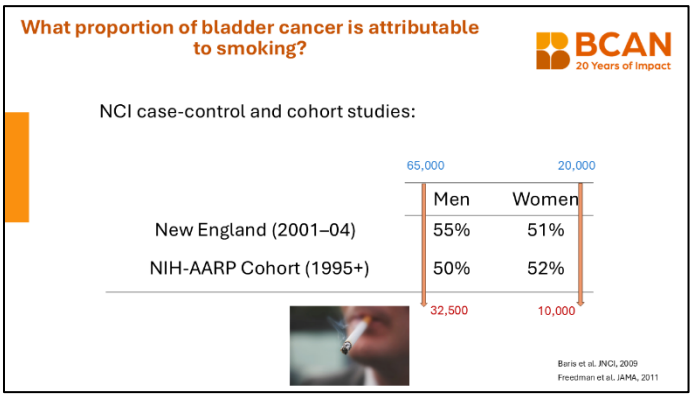


So again, so smoking roughly attributes to around 50% of the bladder cancers. I know we highlighted this at the last year's think tank, but it's really what about the other 50%? As Patricia highlighted eloquently, that there are a lot of our patients in modern era that really aren't smoking cigarettes and they're developing bladder cancer. If we look at the historical trends, I believe around the 1940s and '50s, there's around 50%, at least the US population that smoked cigarettes or said that they did. If you look at the recent data probably in the late 2000 teens and 2020 or so, that number dropped down significantly down to anywhere from the 10 to 15% range.

So there has been a significant drop in smoking, but we haven't seen that in the bladder cancer incidence rates. And so that begs the question again, what are the other factors? And so we do know from occupational studies, and again, Dr. Koutros is going to highlight this that, there are other risk factors, and this is really how we utilize our knowledge and how we learned about carcinogenesis in these other two areas and how that can lay the platform and set the field for how to really study these environmental risk factors. Next slide, please.

Dr. Sunil Patel:

And so this was just a really nice study that really looked at a case control, looking at men and women and looked at just smoking and its attribution to bladder cancer. And if you look at two different cohorts, it's pretty consistent that smoking attributes to roughly around 50% of bladder cancer, both men and women. And so that has been really well studied.

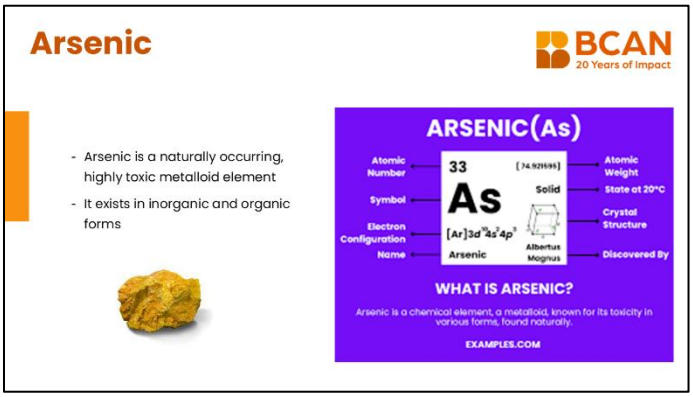


And these large case control studies, again, done by our expert epidemiologist, namely at the NCI and a lot of colleagues of Dr. Koutros, as well as a lot of studies she's done, has really led to our knowledge of population-wide studies on how these case controls can show what are the risk factors. Next slide, please.

That just tells you how many thousand patients were in each kind of cohort. So a very large case control study. Next slide.

Dr. Sunil Patel:

So let's shift over to arsenic. So arsenic is naturally occurring metalloid, however, it's also highly toxic. It exists in inorganic as well as in an organic form.



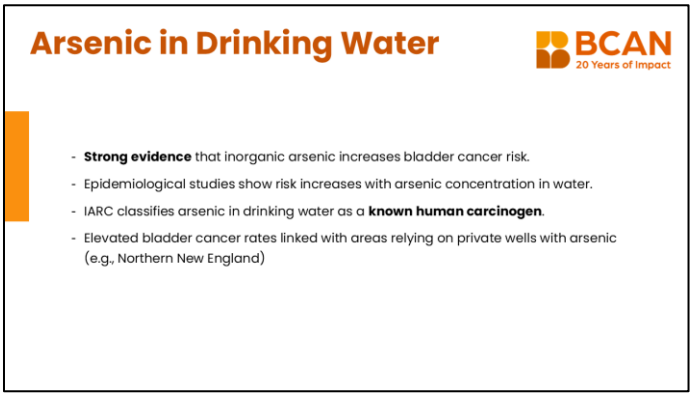
And arsenic has been one of those ones that have been studied for some time, and there is a strong association with bladder cancer. And over the next few minutes, we're going to highlight a little bit about the studies in arsenic and what we know about arsenic and potential mechanisms. Next slide.

Dr. Sunil Patel:

And so arsenic exposure is a little bit variable. So right now, what we really think about exposure, we're really attributing it to private wells. And so in the US, unregulated private wells are a major concern. For instance, in the Northern New England, bladder cancer rates are much higher. We're going to highlight a key study, again, done by the NCI that showed this, but it's much higher than the national average, and it's largely attributed to arsenic in well water.

Historical pesticides, which were really done about probably 60, 70 years ago, were probably the biggest culprit. However, they're not really used in modern era, but they still have a lot of leaching into the ground, hence into our wells as well. And then dietary exposures. So certain foods, particularly rice, can absorb arsenic from the soil, especially the water as well. And a lot of that has been done, and we see that in a lot of our Asian cohorts, and that's been well studied, at least in Southeast Asia, as well as other areas of Asia. Next slide.

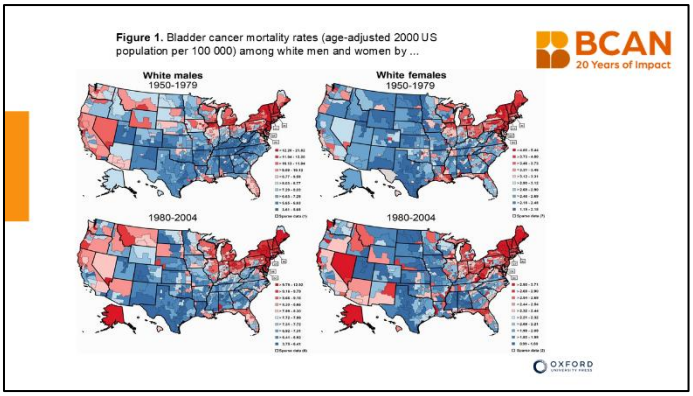
Dr. Sunil Patel:



Again, so arsenic has a pretty strong evidence that... Well, there is a strong evidence that inorganic arsenic increases bladder risk. Studies show that there is an increased risk with arsenic concentration in water as well. And we're going to highlight a little bit about time and dose-dependent variables. And the IARC classifies arsenic in drinking water as a known carcinogen.

And again, a lot of this work was done and a lot of these statements have really come out from the key study done in 2016 by the NIH NCI linking bladder cancer rates and elevated bladder cancer incidents to the arsenic found in these private wells. Again, the New England study as we all, kind of New England water study, as we all call it. Next slide.

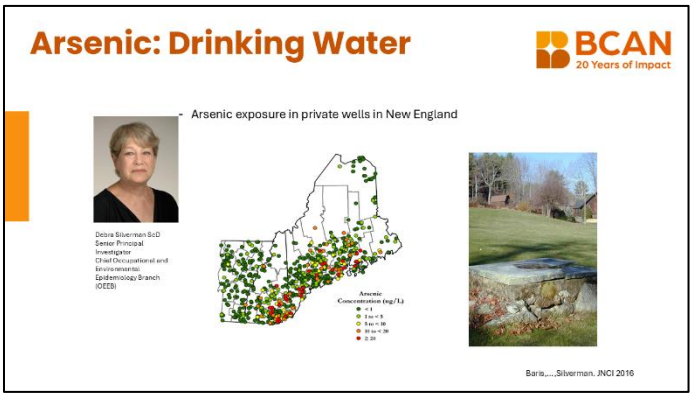
Dr. Sunil Patel:



And so this is a really nice figure that really highlights the incidence of bladder cancer and the mortality rates. And so when we're looking at this slide, this really looks at two key time points. We're looking at Caucasian men and women, and looks like, again, two time points, '50 to '79, 1950 to '79, as well as the relative modern era, so the '80s to 2000s. And again, the striking thing you can see is that bladder cancer mortality rates are clearly higher and concentrated, you see in the northeast, much higher than you see all over the rest of the US.

Also, Alaska's in there as well, but this really was a big launch pad for that big pivotal study. Next slide.

Dr. Sunil Patel:



And so this slide, or excuse me, this study was led by Deborah Silverman over one of Dr. Koutros's colleagues, and they looked at the very comprehensive study. And Dr. Koutros did talk about this study in detail at our think tank, but long story short is that this study was really well done and it really looked at two key things. One is that really showing that the arsenic exposure in private wells in New England varied. However, the higher amount there were higher incidents of bladder cancer.

They did talk, and they really looked at also different differences in the well types, in the shallow and deep. And we essentially found out that arsenic concentration was correlated to bladder cancer incidents. Additionally, again, when I earlier mentioned that the concentration or the volume of water potentially altered incidents, and this study did show that there was a little bit of a increased incidence.

So the higher volume or tap water that was drunk by these patient or volume of water, excuse me, not tap water, increased the incidence of bladder cancer, so challenges that dogma. Additionally, we found that there's roughly a latency period around 40 years-ish from the exposure and this chronic exposure to the development of bladder cancer.

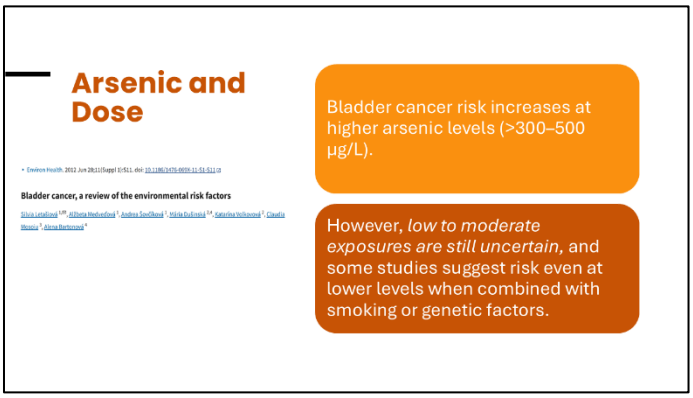
So unfortunately, it's not one of those ones that if you drink well water once in your life, you're probably going to get bladder cancer. This is usually repetitive over a period of numerous years in order to develop bladder cancer.

And interestingly, Dr. Koutros actually did a follow-up study similar to this, but you can see that the arsenic exposure in carcinogenesis was almost augmented in smokers. So arsenic has never been thought to be a mutagen by itself, but almost in synergy with smokers thought to be a kind of co-mutagen.

And Dr. Koutros in one of our studies found that that did increase the risk of bladder cancer. So arsenic exposure in combination with smoking did increase incidence. Next slide.

Dr. Sunil Patel:

And again, so talking about dosing. So when we talk about exposures and risk factors, we always think about, what is the time needed in order for you to be exposed under X chemical or toxicant, and also at what dose? And I think that comes into play. And so what we found in this study, that bladder cancer increases at higher levels of arsenic.



And this study found at a little bit higher levels than what the NCI found. However, that low to moderate still is uncertain, but there's still studies that do show that it does increase the risk when you combine it with smoking, which Dr. Koutros found, and other genetic factors. And again, the genetic factors, it's still an ever-changing kind of landscape right now, and that's what we're trying to learn a little bit more about. And again, sets the platform for how to really study these.