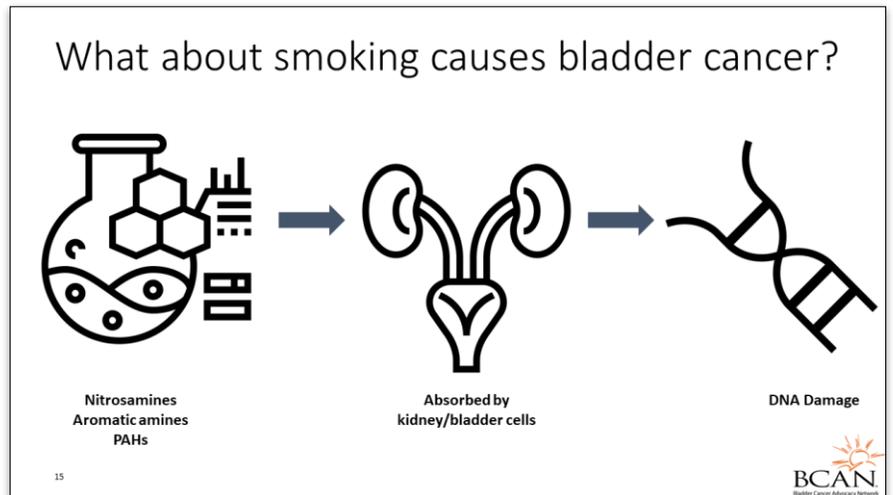


E-CIGARETTES, SMOKING, AND BLADDER CANCER
With Drs. Richard Matulewicz and Marc Bjurlin

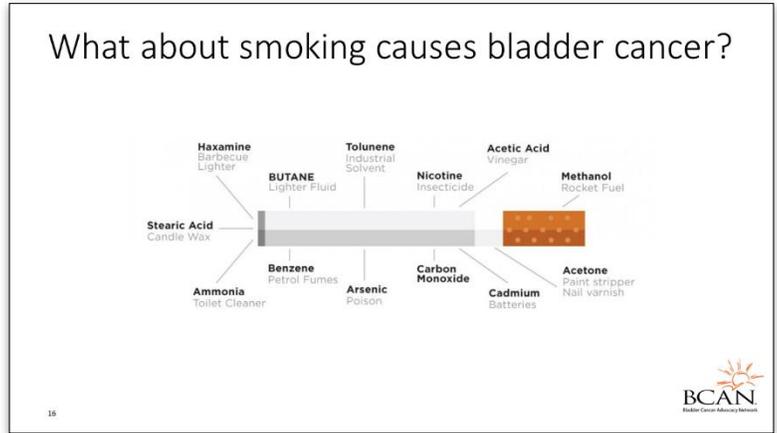
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Bladder Cancer Advocacy Network

Dr. Marc Bjurlin: So looking at this slide, you can see there are a number of compounds and chemicals that are produced by tobacco smoke that impact our health. You can see that many of these compounds in tobacco smoke are items that we normally do not consider consumable. You can see here that tobacco smoke has hexane and butane, which are found in barbecue, a lighter fluid and additional lighter fluid. Tallinn is an industrial solvent that's commonly used. Arsenic is a common poison, cadmium, a heavy metal battery. All that's found in the tobacco smoke which puts us at risk for developing a number of malignancy. Similar to combustible tobacco smoke, e-cigarette users also are exposed to a variety of these similar toxic and carcinogenic compounds during the vaping process, and specifically there have been found toxic in cancer causing compounds observed in the urine of e-cigarette users.



This has not been terribly well studied, but with that in mind, we studied it. And what we did is we reviewed the scientific literature on carcinogens in the urine of e-cigarette users. And we found that

there were about 1,400 different scientific papers on this topic. When we narrow them down, strictly to what we were looking at, that being the carcinogens in the urine e-cigarette users, we found 22 studies that met our topic inclusion criteria. When we reviewed those studies, we found that there appears to be 40 different parent compounds that are in the urine of e-cigarette users that are known to have a cancer cause in human, in addition to four metals that are cancer causing. Of these 40 different parent of compounds, our bodies metabolize them and as a result, we found that there are 63 unique toxicants in carcinogenic metabolites in the urine of e-cigarette users.



And then the take home messages of all of these, there are six compounds in the urine of e-cigarette users that are directly linked to bladder cancer. So with that in mind, this has been the springboard from future investigations that we're doing at the [inaudible 00:03:30] level to look at the changes of bladder cells when it's exposed to carcinogens found in the e-cigarette vapor.

Dr. Richard Matulewicz: So we've discussed at this point, the real causal risk in developing bladder cancer. And I think it's important to understand that there is risk for continued use after the diagnosis of bladder cancer. and taking another step back here, hearkening back to some of that population level public policy discussion from earlier, we've seen very nicely that some of the progress made in preventing people from smoking and having people quit smoking has really translated into good outcomes as far as lung cancer goes and as far as some of the other very closely

Carcinogens in Urine of E-cigarette Users

- Systematic Review:
 - 1,385 Articles
 - 22 met inclusion
- 40 different parent compounds (International Agency for Research on Cancer Monographs on the Evaluation of Carcinogenic Risks to Humans)
- 4 metals
- 63 unique toxicant or carcinogenic metabolite biomarkers
- **6 carcinogens were strongly linked to bladder cancer** (Collaborative on Health and the Environment, Toxicant and Disease Database)

Bjorkin MA, Matulewicz RS, Roberts TR, Dearing BA, Schetz D, Sherman S, Gordon T, Shahawy OE. Carcinogen Biomarkers in the Urine of Electronic Cigarette Users and Implications for the Development of Bladder Cancer. A Systematic Review. Eur Urol Oncol. 2020 Mar 7;5(2588-9311(20)30029-8

related smoking related cancers. Now, one cancer's seen a decrease in the incidents, meaning how many new cases per year and it has also seen an improvement in the survival rate at one year. However, and unfortunately for bladder cancer, both the incidents rates, that's how many new cases per year, as well as the survival rates have remained largely stagnant despite all of this progress at the population level, in getting people to stop smoking.

So this is important because continued smoking after the diagnosis of bladder cancer has some well-described outcomes, and no matter what your treatment strategy or your treatment necessity is after your diagnosis of bladder cancer, smoking after that will actually relate to a worse outcome. Now that's whether you're having your bladder removed, having a bladder scraping procedure where just the

tumor's taken out of the bladder through the urethra, continued smoking will lead to higher risk of anesthetics, especially under general anesthesia when the ventilator's breathing for you because of some of the lung damage associated with it.

Dr. Richard Matulewicz:

There've been very nice papers recently published that have shown that continued smoking in patients getting chemotherapy actually makes chemotherapy less effective and it increases the risk of adverse effects in patients getting chemotherapy. Similar findings have been shown in patients who are undergoing radiation, where the radiation has worse side effects in the bladder and elsewhere, and also a lower and attenuated treatment benefit where it is not as effective. And all of this actually leads to real changes in the hard outcomes. These are the recurrence rates, the survival rates, the risk of secondary malignancies. And we know that continued smoking will increase the risk of patients having a recurrence in their bladder, whether that bladder recurrence is treated with chemotherapy in the bladder or just scraping. And it also increases the risk of second cancers. So these are cancers that are not bladder cancers, but about 12% of survivors of bladder cancer will go on to develop a second tobacco related cancer.

Now that's whether that's lung cancer, head and neck cancer, gastric cancer. So this isn't a substantial risk in people who continue to smoke afterwards. And other epidemiologic studies have really shown that quitting smoking is actually one of the most effective ways of improving your own chance of having a long-term good outcome and being a long-term survivor of bladder cancer. So this is really one of the most important things that anyone can do after diagnosis of bladder cancer in addition to hopefully quitting before this diagnosis happens. Now, what we've shown in some work that we've done

Continued smoking after diagnosis

Worse RC/TURBT outcomes
Higher anesthetic risk

Greater risk of chemo adverse effects
Less benefit of NAC in smokers

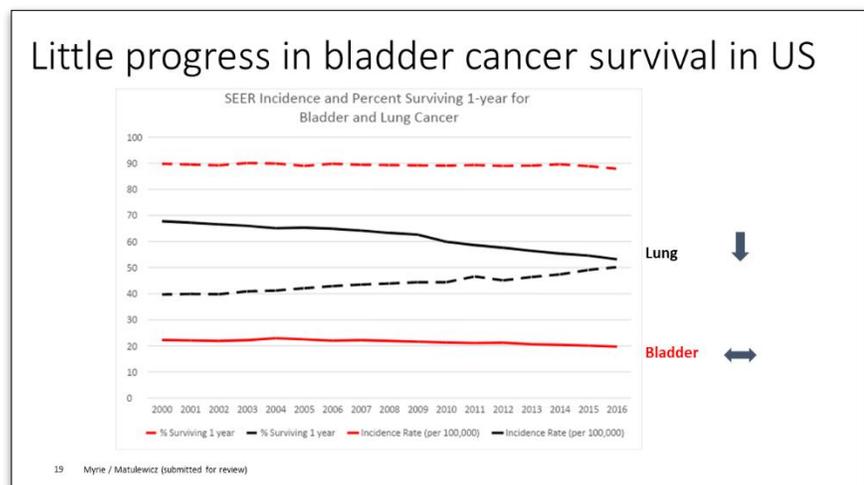
Greater risk of radiation adverse effects
Attenuated therapeutic benefit

20

Continued smoking after diagnosis

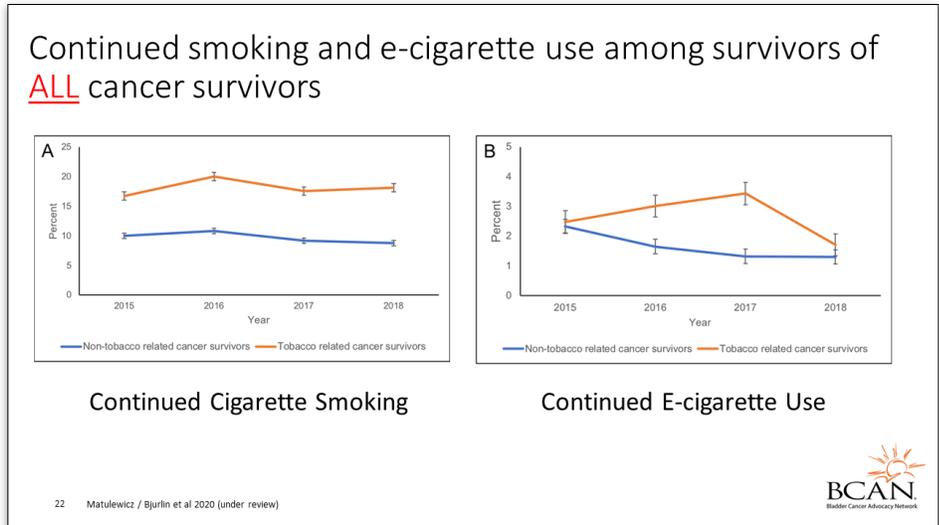
- Possible increased risk of recurrence in NMIBC
- Increased risk of second cancers (~12% of survivors develop 2nd tobacco-related cancer)
- **Quitting smoking can be considered one of the most effective means of improving bladder cancer survival**

21 Liss et al (Clin Genitourin Cancer 2017); Bassett et al (JCO 2012)

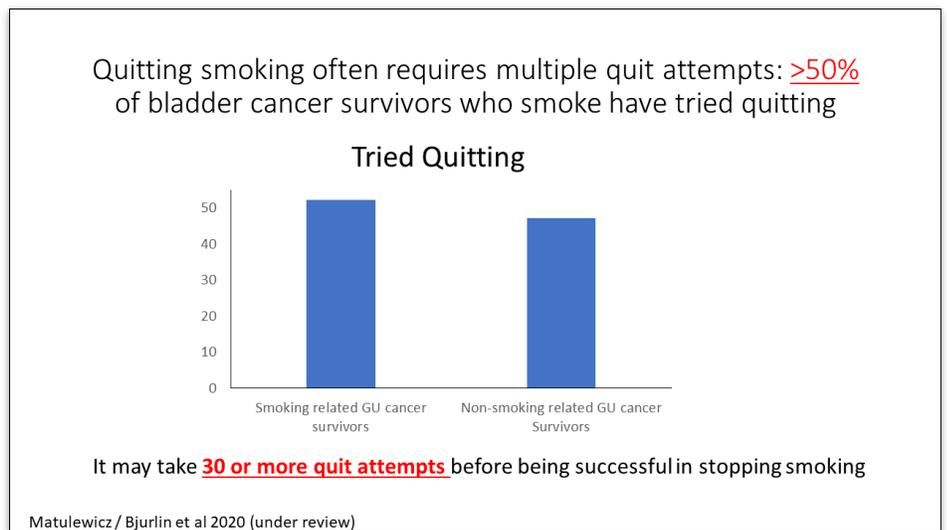


recently actually, is that despite the fact that most patients' bladder cancer diagnosis is related to smoking, there is still a troublingly high percentage of patients who do continue to smoke. And we looked at both kidney and bladder cancer, which are tobacco related cancers, and that's in the orange there, and then the blue is prostate cancer.

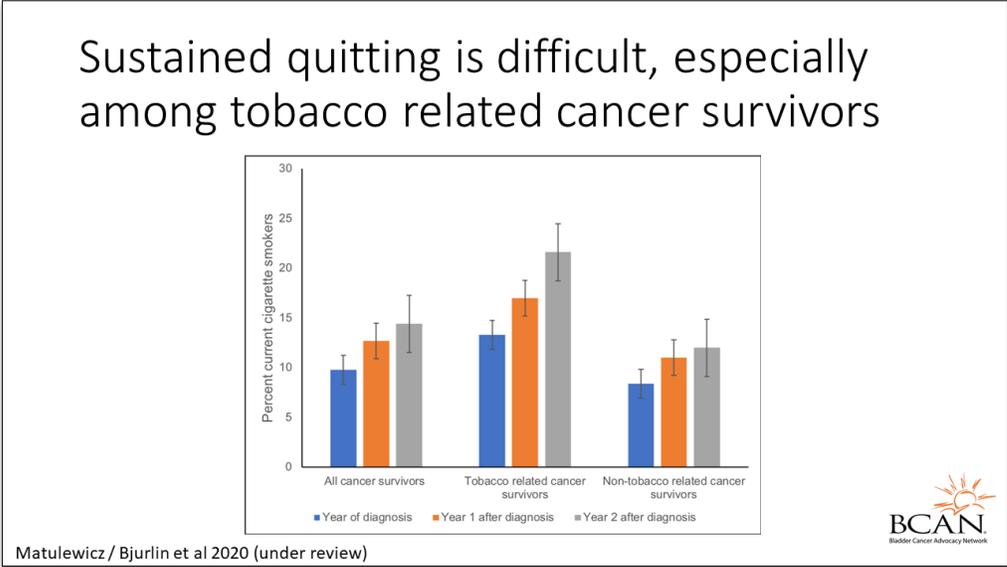
Dr. Richard Matulewicz: And although some of the rates of smoking before diagnosis were certainly higher in those tobacco related cancers, persistent smoking afterwards was upwards of almost 20% of people diagnosed. And you can see here on the right in panel B, the use of e-cigarettes, although not as high as traditional cigarettes is still persistent, and this is potentially an issue because of what Dr. Bjurlin mentioned that we're not certain that e-cigarettes are actually any safer than tobacco cigarettes. And there may be some persistent risk because of the carcinogens in the urine. So when we look at bladder cancer and kidney cancer patients in isolation here a little bit, roughly 15 to 20% continue to smoke. And this is more so than prostate cancer survivors who do not have a direct tobacco related cancer.



Now we know quitting is hard, there is most certainly no judgment or blame being placed on anyone who continues to smoke after diagnosis. That is most certainly not the goal of any of the work we do. This is a truly a partnership and something that we want to help patients do. And I think it's important to understand just how difficult quitting is and how this does require help from your support system, from your family and from your physicians, certainly. Most of the patients who have been diagnosed with bladder cancer have tried quitting, and this is more than 50%. And this just shows basically how often people are trying to quit and how important it is to continue to try to quit. And it has been shown that roughly 30 or more quit attempts are at times necessary for someone to actually be successful in quitting. And a lot of this may relate to a less effective quit strategies, but that's really where us as the urologists hope to come in and really help intervene at that point.



Dr. Richard Matulewicz: The other thing that's important is not only helping someone quit right off the bat, but it's also maintaining that quit and maintaining the abstinence from cigarettes. And what we showed in this study here was that as time went on after the diagnosis, the percentage of patients with a cancer history actually increased in each year after diagnosis. So people were seemingly very motivated to quit after diagnosis and then as time went on, people did not have the same level of abstinence and the use of cigarettes was increasing as time went on. And that's why it's really important, not only to quit at the onset, but also have support from your doctor and from your family and your support system to remain abstinent from cigarettes after the diagnosis.



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