

Working Smarter to Prevent Bladder Cancer: Understanding the Environmental Factors

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Dr. Stella Koutros:

So today, as the others said, I'm going to be talking about occupational exposures in bladder cancer. Like Dr. Patel, I should say, and I think we always say that the number one risk factor and the number one way you can prevent bladder cancer is to quit smoking. Smoking is really the most important risk factor for bladder cancer, but we've also recognized that occupational exposures are really important as well and can account for up to a quarter of bladder cancer cases. So I'll be focusing in on those in my next few slides.

Bladder Cancer Risk Factors

- Smoking
- Occupational exposures
 - 5%–25% in males
 - 8%–11% in females
- Environmental exposures
- Age
- Male Sex
- Genetics

RISK FACTOR

Occupational exposures are the second leading cause of bladder cancer.

Red= Modifiable
Black= Non-modifiable

Dr. Stella Koutros:

I'll talk a little bit quickly and briefly about some of the terms we use when we think about occupational studies and the different types of studies. And then I'll dive into what key things we know already about occupational risk factors in bladder cancer, and then just a few words at the end about prevention.

Occupational Exposures

- Exposure Assessment
- Types of Occupational Studies
- What do we know about occupational bladder cancer?
- Occupational cancer prevention

Dr. Stella Koutros:

So, one of the primary considerations when reading an occupational study or a study about an exposure is the assessment of that exposure. So we call that exposure assessment, and that is really just a fancy word for how you obtain accurate and precise estimates in the most efficient and cost-effective way. So if a study's trying to look at a relationship between an exposure in bladder cancer, we really want to understand what they're doing to kind of characterize that for a person and how they characterize it over that person's life.

Exposure Assessment

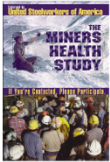
- **To obtain accurate, precise, and biologically relevant exposure estimates in the most efficient and cost-effective way**

Dr. Stella Koutros:

This has really important implications for the quality of the study. So today I'll talk about some of the exposures that have some of the most evidence for bladder cancer, but also if there's one thing I can leave you with is thinking about if you end up reading a study on your own, what you might consider about the exposure assessment will really help you understand what is really key about understanding the quality of that study.

Exposure Assessment and Occupational Studies

- Type of Exposure Assessment/Study
 - Occupation or industry only
 - Occupation/Industry and duration employed
 - Ever/never for specific exposures
 - Qualitative estimates
 - Quantitative estimates



JOB STARTER	JOB STOPPER	JOB TITLE	TASKS, CHEMICALS
1943	1964	LIVESTOCK WORKER	Collect turkeys, eggs
1954	1956	MOTOR VEHICLE OPERATOR	Fuels, oils
1966	1987	DRYWALL INSTALLER	Drywall, painting
1987	1998	MECHANIC, MAINTENANCE	All kinds of repair work

So sometimes in occupational studies, we study sort of occupational groups like truck drivers, and that's what we sort of call occupation or industry only. We sort of look at just a group of people who are working in a certain type of job. It's even better if we have some more information, like how long a person did that, like how many years they did that, but it's even better when we have really more detailed information about specific exposures.

Like if you're a truck driver, were you exposed to engine exhaust, and if you were exposed to engine exhaust, even better if we can sort of quantify that in a more quantitative way. So the more we can do that, the sort of better the quality of the study tends to be and sort of the better the inferences we can make about the risks for bladder cancer.

Dr. Stella Koutros:

So, one source of compiled information about cancer comes from the International Agency for Research on Cancer. This table's a lot, but it's a little bit of a summary about many of the occupations and workplace exposures that have been classified as bladder carcinogens because there's been decades of research in showing certain positive links and the things that are in the light blue are those with which they have considered have sufficient evidence in humans. And the little PDF link at the bottom is a link to a table where you can look at sort of what's known about bladder cancer. I've just put some of the occupational things here, but they include other things as well.

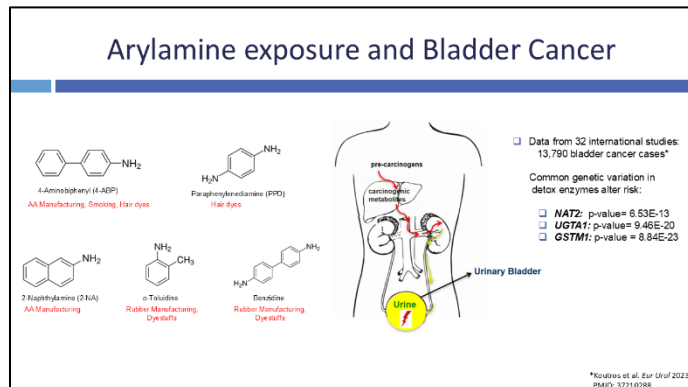
Occupational Group	Established/Suspected Carcinogen
<i>Aromatic Amine Manufacturing</i>	<i>4-Aminobiphenyl, β-Naphthylamine</i>
<i>Dyestuffs worker</i>	<i>o-Toluidine, Benzidine, Auramine</i>
<i>Aluminum production</i>	<i>Polycyclic aromatic hydrocarbons (PAHs)</i>
<i>Rubber manufacturing</i>	<i>o-Toluidine, Benzidine</i>
<i>Painters</i>	<i>Benzidine-based dyes, Solvents</i>
Leather workers	<i>Aromatic amine dyes, leather dust, fibers</i>
Truck Drivers	<i>Diesel engine exhaust, gasoline</i>
Hairdressers	<i>Hair dyes (4-Aminobiphenyl, Paraphenylenediamine)</i>
Metal workers	<i>Metal-working fluids, PAHs</i>
Dry cleaning	<i>Chlorinated Solvents (Tetrachloroethylene)</i>
Textile manufacturing	<i>Fibers, dyes</i>
Printing	<i>Printing dyes</i>
<i>Firefighters</i>	<i>Heterogeneous exposures</i>

Carcinogenic agents with sufficient evidence in humans

https://monographs.iarc.who.int/wp-content/uploads/2019/07/Classifications_by_cancer_site.pdf

Dr. Stella Koutros:

One kind of key or commonality between a lot of the chemicals that were in that table are these group of chemicals that have a similar chemical structure. They're called aromatic amines. And we know that these particular chemicals are specifically damaging to the bladder and have largely been identified in studies of workers who ended up developing very high rates of bladder cancer in sort of different occupational settings.



My group also has conducted some really large scale genetic studies where we've also shown that important sort of inherited genetic variation and certain key genes that are responsible for sort of metabolizing these chemicals and getting rid of them from the body are important modifiers of risk. And many of the people affected by these exposures are typically in industrial and manufacturing settings, which have become a little bit less common over the last several decades. So next, I'll just talk about a few other exposures that are more commonly reported among contemporary occupations.

Dr. Stella Koutros:

So metal-working occupations have been associated with increased bladder cancer in over 20 studies. So some specific jobs that have these exposures are precision metal workers or metal-working or plastic-working machine operators. And people who do these jobs are using what are called metal-working fluids. So they're used in metal machining to lubricate cool and remove debris from metal parts that are being drilled, ground or milled or some kind of type of machining work. So these metal-working fluids contain some certain chemicals that are suspected, some known and some suspected to be carcinogenic.


**Metal-working fluids (MWFs)
and bladder cancer risk**

BMJ Colt JS, et al. *Occup Environ Med* 2014;71:663-674. doi:10.1136/oemed-2013-102056

ORIGINAL ARTICLE

A case-control study of occupational exposure to metalworking fluids and bladder cancer risk among men

Joanne S Colt,¹ Melissa C Friesen,¹ Patricia A Stewart,^{1,2} Park Donguk,³ Alison Johnson,⁴ Molly Schwenn,⁵ Margaret R Karagas,⁶ Karla Armenti,⁷ Richard Waddell,⁶ Castine Verrill,⁸ Mary H Ward,¹ Laura E Beane Freeman,¹ Lee E Moore,¹ Stella Koutros,¹ Dalsu Baris,¹ Debra T Silverman¹



Bladder cancer risk was elevated among men who reported using straight MWFs
OR=1.7 (95%CI 1.1–2.8)

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Dr. Stella Koutros:

Another sort of exposure that's been linked to bladder cancer is exposure to diesel exhaust because of several studies of specific occupational groups who have high levels of exposure that have had increased bladder cancer risk, in particular truck drivers and bus drivers, but not a lot of studies really could go beyond that and get to those more quantitative estimates of exposure.

Diesel exhaust and bladder cancer

- Studies of occupation:
 - Truck drivers, bus drivers, heavy equipment operators, railroad workers, shipyard workers, mechanics
- Meta-analyses
 - RR among truck drivers: 1.17 (1.06–1.29)
 - RR among bus drivers: 1.33 (1.22–1.45)
 - Lack of quantitative estimates, limited mechanistic studies
- IARC- Group 1, sufficient evidence for lung cancer, BUT "limited evidence for bladder carcinogenicity"

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And initially, when IARC reviewed some of the literature, they said, "Well, we're not really sure there's not really enough good data about this for bladder cancer yet."

Dr. Stella Koutros:

One thing that I have been involved in is a combination of two case control studies that were conducted around the same time period, and they were similar in size.

One was in Spain, and another one is here in New England, which is the study that Dr. Patel had mentioned. Both of these studies had identical questionnaires. We collected really detailed information about a person's lifetime occupational history, as well as these job modules to get really detailed information on different exposures.

And we pulled the data from these two studies.

	Spanish Bladder Cancer Study	New England Bladder Cancer Study
Time:	1998-2001	2001-2004
Size:	1219 cases 1271 controls	1213 cases 1418 controls
Place:	18 hospitals in 5 areas of Spain	Maine, New Hampshire, Vermont
Interview:	Lifetime occupational histories Exposure-oriented job modules	Lifetime occupational histories Exposure-oriented job modules

Dr. Stella Koutros:

And in 2020, we published results that found that workers had elevated levels of diesel exhaust exposure had a higher risk for bladder cancer compared to people who were not exposed.

And so this was, I think, a study where we were able to provide some of that quantitative exposure data, which was sort of an element that had been missing on this topic before.

Diesel exhaust and bladder cancer risk

Environment International 135 (2020) 105296
Content lists available at ScienceDirect
Environment International
journal homepage: www.elsevier.com/locate/envint

Diesel exhaust and bladder cancer risk by pathologic stage and grade subtypes

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- Quantitative estimates of lifetime respirable elemental carbon (REC) ($\mu\text{g}/\text{m}^3\text{-yrs}$)
- Workers with cumulative REC >396 $\mu\text{g}/\text{m}^3\text{-yrs}$ had an OR of **1.61 (95%CI 1.08–2.40)**


Dr. Stella Koutros:

Another set of exposures of interest that we've been sort of studying lately are organic solvents. So many of the occupational groups that have been noted to have higher bladder cancer rates happen to also have exposure to solvents, including people in dry cleaning and rubber textile manufacturing, painting.

And there's sort of a diverse sort of set of tasks and chemicals that would sort of include the use of solvents, including degreasing

Organic Solvents: Background

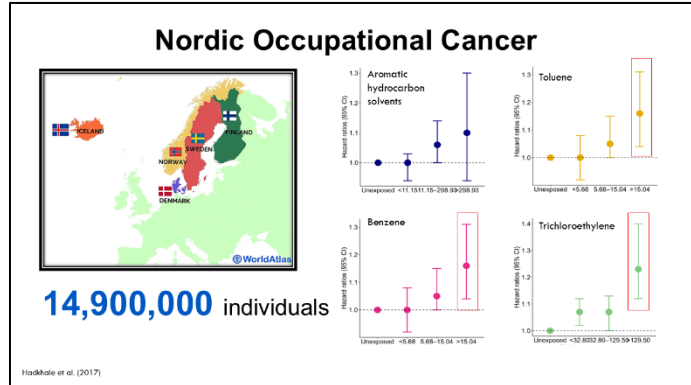
- Several high-risk occupations **with likely solvent exposure** linked to bladder cancer
 - Dry-cleaning
 - Rubber, Textile Manufacturing
 - Painting
- Uses include:
 - Production of industrial chemicals
 - Degreasing and cleaning
 - Present in gasoline
 - Glues/adhesives, paints, lacquers, etc.
- Perchloroethylene (dry-cleaning) probable evidence for bladder carcinogenicity
- Cancer risk is unclear for other commonly used solvents



and cleaning. It's also present in gasoline and a lot of paints and glues. So there are a lot of different sort of sources for potential exposure to solvents.

Dr. Stella Koutros:

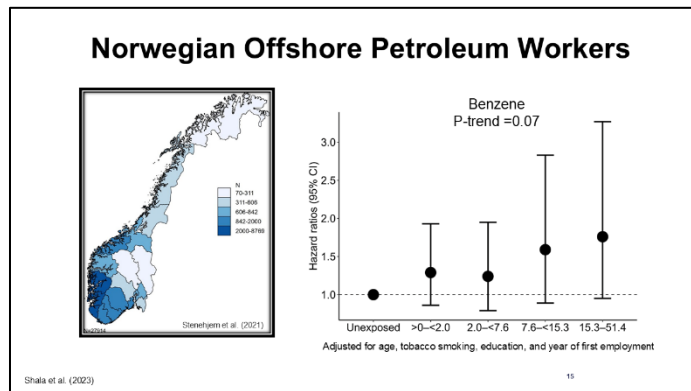
So a few years ago, there was this really large study from the Nordic countries that showed that there was some suggestion of an association between certain organic solvents and bladder cancer risk. And two of the solvents in this group seemed to be associated with a risk at the highest levels of exposure.



And another one of these chemicals, one at the bottom there, trichloroethylene is something that's used very similar to a chemical that's used in, it's a dry cleaning solvent, which has been also linked to bladder cancer before. So there was some initial sort of signal here there might be something going on for bladder cancer.

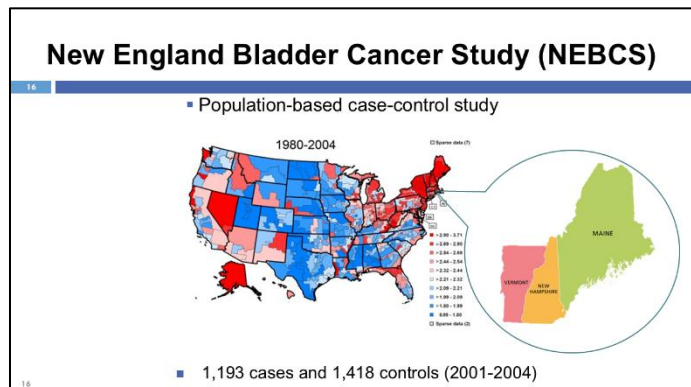
Dr. Stella Koutros:

And a little after this study, there was a large prospective case cohort study of Norwegian offshore petroleum workers, which showed an increasing exposure to benzene after adjusting for smoking and other factors and an increased risk of bladder cancer, sort of building on this literature for linking solvents in bladder cancer.



Dr. Stella Koutros:

So to follow up on these findings, my colleagues and I at the NCI looked at the relationship between solvents and in the general population of people who developed bladder cancer in the New England region where our study was conducted.



Dr. Stella Koutros:

And we were able to use these lifetime job histories and specific details again about the tasks and chemicals that people used on the job and found that there was also, we did find these increasing risks with exposure to sort of benzene, toluene and xylene. And then the three is a group, which is called BTX because they kind of often co-occur. And an important additional element of this is that we've also been able to really carefully adjust for smoking and also other types of occupational exposures because there are many that have been linked to bladder cancer as well.

Solvents	
Ever exposure	Odds Ratio, 95% CI
Mononuclear aromatic hydrocarbons	1.84 (1.16, 2.91)
Benzene	1.63 (1.14, 2.32)
Toluene	1.60 (1.06, 2.43)
Xylene	1.67 (1.13, 2.48)
Styrene	0.94 (0.57, 1.55)
BTX	1.63 (1.20, 2.21)

*Adjusted for age, race, smoking status, state, race, ethnicity (Hispanic) and non-solvent exposed high-risk occupations for bladder cancer.
(Xie, Friessen, ... Silverman, Koutros; 2024)

Dr. Stella Koutros:

This chart just shows some of the jobs that were reported to have the highest levels of exposure to BTX. And you can sort of see here, they're color coded. Several types of machine operators in different industries can be exposed in shoes and textiles, but also auto mechanics and workers involved in autobody repair.

Top five jobs with the highest exposure to benzene, toluene and xylene		
Benzene	Toluene	Xylene
Shoe machine operators and tenders	Shoe machine operators and tenders	Automotive body and related repairers
Miscellaneous textile machine operators and tenders	Miscellaneous textile machine operators and tenders	Shoe machine operators and tenders
Automobile mechanics	Carpet and soft tile installers	Miscellaneous textile machine operators and tenders
Assemblers	Automotive body and related repairers	Assemblers
Cementing and gluing machine operators and tenders	Cementing and gluing machine operators and tenders	Miscellaneous machine operators and tenders, NEC

This group was particularly interesting because they ended up reporting a lot of gasoline use as a solvent. It turns out it's fairly common for people to use gasoline as sort of a cheap solvent for degreasing and cleaning parts.

Dr. Stella Koutros:

And shortly after our study, IARC summarized sort of the overall cancer literature on gasoline and found that there was enough sufficient evidence in the literature in human studies that exposure to gasoline was shown to increased the risk for bladder cancer. And this is the summary of those findings which are online.

Gasoline: Sufficient evidence in humans

Who is exposed
Service station attendants, mechanics, and workers in production and transportation of gasoline. The general population via air pollution or gasoline vapours at service stations.

Automotive gasoline
Group 1
Carcinogenic to humans

Sufficient evidence in humans for bladder cancer and acute myeloid leukaemia.
Limited evidence in humans for non-Hodgkin lymphoma (excluding chronic lymphocytic leukaemia), multiple myeloma, myelodysplastic syndromes, cancers of the stomach and kidney, and childhood acute lymphoblastic leukaemia.

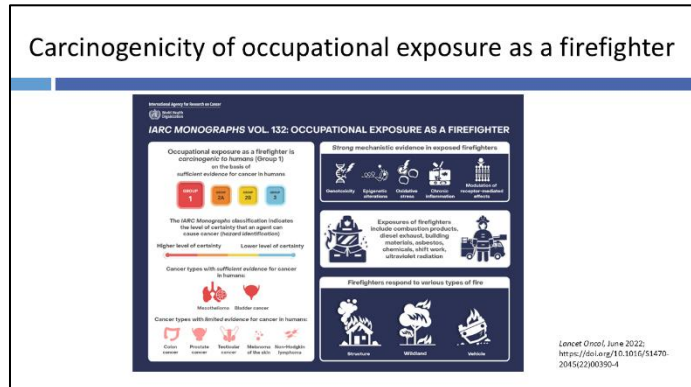
Strong mechanistic evidence in exposed workers.
Genotoxicity, Oxidative stress, DNA damage

And it includes several... This would impact and sort of cover several working populations, including service station attendance, mechanics and workers in sort of production and transportation of gasoline. So potentially a lot of occupational groups exposed.

Dr. Stella Koutros:

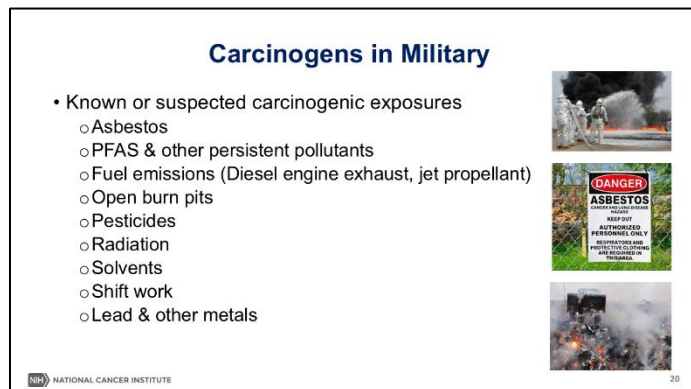
So as I mentioned earlier, there's evidence that some occupational groups have these higher rates of bladder cancer and recently evidence had also been synthesized about firefighters and the increased risk for bladder cancer observed in this population.

And sometimes we can observe these higher rates in working populations, but we sort of have to do more work to understand what are the underlying specific exposures causing these elevations and risk. And so firefighters are exposed to a really wide range of things, including combustion products, diesel exhaust, asbestos, other building materials, and several other really heterogeneous exposures.



Dr. Stella Koutros:

Another group of interest are those who serve in the military. Like firefighters, this group is exposed to a really wide range of suspected carcinogens depending on the timing and location of military service and occupation. So there's still a lot more work needing to sort of help us understand what the direct connections are between exposures and military service and potential risks for bladder cancer.



Dr. Stella Koutros:

Ultimately, the studies we sort of really quickly covered today are important for identifying sort of occupational carcinogens in the workplace so that we can take some action to minimize these exposures and decrease any exposures when we can. For example, over time, diesel technology has changed really significantly to drastically reduce emissions compared to engines decades ago.

Occupational Cancer Prevention	
<input type="checkbox"/>	Identification of occupational carcinogens necessary for action
<input type="checkbox"/>	Setting of permissible exposure limits (PELs)
<input type="checkbox"/>	May lead to changes in industrial processes that reduce exposure to other chemicals
<input type="checkbox"/>	Use of personal protective equipment
<input type="checkbox"/>	Improved ventilation
<input type="checkbox"/>	Screening exposed workers

And our education about the risks from workplace exposures and how we can protect ourselves is also really an important strategy for reducing the burden of these exposures. In the future, we may even be able to develop some strategies for screening high risk populations for early detection as those kind of methods improve in the clinic and to try to prevent the development of bladder cancer altogether.

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