Cancer & Environment Network of Southwestern Pennsylvania

A Year in Review: Reflections on 2021 Peer-Reviewed Research on Cancer

In its monthly Digest, the Cancer and Environment Network of Southwestern Pennsylvania (CENSWPA) provides links to peer-reviewed research articles published on the topic of environmental risk factors associated with cancer. This list is generated using searches of PubMed, as well as reviews of the table of contents of academic journals that routinely publish on the topic (e.g., Environmental Health Perspectives, Journal of Environmental and Occupational Medicine, Environmental Research, etc.). CENSWPA's monthly posting is not intended to be an exhaustive review. However, it captures seminal articles so that Network participants are kept up to date with relevant research on risks from chemical and radiological toxicants in our environment and workplaces.

Looking back across the 2021 Digests, the list of research articles is impressive. The literature continues to both substantiate known risks and provide insights into new environmental exposures of concern. The Science Support Workgroup of the CENSWPA reflected on the 2021 collection of articles and identified the following noteworthy themes:

- A range of additional types of cancers, not just lung cancer, show associations with exposure to air pollution.
- Research on causes of childhood cancers continue to substantiate risks associated with exposure to pesticides and air pollution. However, there is a paucity of research on topics of notable interest to CENSWPA, including risks to children from fracking and specific pesticides of concern, such as glyphosate.
- Exposure to emerging contaminants in the environment, such as per- and polyfluoroalkyl substances (PFAS), are demonstrating cancer risks.
- 2021 did little to fill a gap in the research literature: the effectiveness of a range of interventions to reduce environmental exposures associated with cancers.

Each of these themes are reviewed below.

A range of additional types of cancers, not just lung cancer, show associations with exposure to air pollution.

The evidence is clear: air pollution is a known cause of cancer. In addition to air pollution being classified as a "human carcinogen" by the World Health Organization's International Agency for Research on Cancer (IARC), there are dozens of chemicals in the air pollution mixture and/or exposure circumstances that are known to cause or suspected of causing lung cancer. But what about other types of cancer? For some, such as bladder cancer, the evidence is also compelling for pollutants such as diesel exhaust. In 2021, research studies explored connections with air pollutant exposure and a broader range of additional cancer types.

Breast cancer

- Amadou and colleagues found that exposure benzo[a]pyrene – a type of polyaromatic hydrocarbon (PAH) that is widely found as a byproduct of incomplete combustion of organic matter – increased the risk of breast cancer. Risk varied by menopausal status and breast tumor type.
- Gho and colleagues' meta-analysis found that exposure to fine particulate matter was associated with a 9% increased risk of breast cancer mortality and a 2% non-statistically significant increased risk of breast cancer incidence.
- Wei and colleagues' meta-analysis found increased risk of breast cancer associated with exposure to nitrogen dioxide, a marker of exposure to traffic, but no increased risk for particulate matter.
- Gabet and colleagues' meta-analyses found similar results to Wei and colleagues (above) – an increased risk of breast cancer associated with exposure to nitrogen dioxide.

- Although the increased risk levels across the above studies seems small, they translate into significant public health impacts as further explained in White's critique of the Gabet et al. study. White's critique also recognizes that Gabet's study was conducted in a primarily White population, whereas Black women tend to live in areas of higher exposure to industrial as well as traffic-related air pollution. White also argues the need for future studies to examine risk associated with air pollution exposures during susceptible periods of life as opposed to examining long-term exposure as did Gabet and colleagues. Previous studies (such as Shmuel and colleagues, and Bonner and colleagues) have revealed that breast tissue is most vulnerable to carcinogenesis during windows of susceptibility, such as early life, puberty and pregnancy.

Additional cancer types

- Chu and colleagues are among the first to study and report elevations in *colorectal cancer risk* associated with exposure to fine particulate air pollution. These researchers also suggest that specific genetic variants may modify the cancer risk.
- Viillanueva and colleagues' research is among a growing collection investigating how air pollution exposure impacts survival of people who have had cancer. Their research focused on *ovarian cancer* and found that exposure to fine particulate matter and nitrogen dioxide adversely impacted survival.
- Park and colleagues found early evidence for a possible role of exposure to nitrogen dioxide air pollution in increased risk of *thyroid cancer.*
- Bogumil and colleagues found a 61% increased risk for *pancreatic cancer* associated with fine particulate matter pollution. This association was strongest among Latinx populations and people who smoked.

Research on causes of childhood cancers continue to substantiate risks associated with exposure to pesticides and air pollution. However, there is a paucity of research on topics of notable interest to CENSWPA, including risks to children from exposure to fracking and specific pesticides of concern, such as glyphosate.

The rate of new diagnoses of childhood cancer has increased steadily since the mid-1970's. According to the National Cancer Institute, in the US, leukemia is the most common type of cancer in children in the U.S. and one of the best studied for environmental risk factors, followed by brain and other central nervous system (CNS) tumors and lymphomas. A recent report by the Childhood Cancer Prevention Initiative concludes that consistency in research findings shows that environmental agents are important risk factors for childhood cancer, including exposure to pesticides, near roadway/traffic air pollution, and paints and solvents. In 2021, research studies continue to substantiate these risk factors, especially pesticides and an extension of research on air pollution beyond near-roadway/traffic exposures.

Pesticides

- Iqbal and colleagues' review of meta-analyses found that the risk of developing childhood leukemia for children with maternal exposure to pesticides was 23% to 57% greater than for children whose mothers had not been exposed to pesticides.
- Another systematic review and meta-analysis by Karalexi and colleagues found similar excess risk among children whose mothers were exposed to pesticides and observed that these exposures have a much stronger association with childhood leukemia than exposures in early childhood.
- Feulefack and colleagues observed that that parental exposure to pesticides (particularly residential use of pesticides) before and after birth is associated with childhood brain tumors. Risk is slightly higher for prenatal exposure (32% increased risk) versus exposures after birth (22% increased risk).
- Studies are beginning to examine risk associated with specific pesticides, and more research is needed in this area. One study by Madrigal and colleagues examining the risk from exposure to specific classes of insecticides (carbamate, organophosphate and pyrethroid insecticides) found in house dust did not find any association with childhood leukemia. The researchers state that these results should be interpreted with caution because of limitations in the design of the study, such as

use of a single post-diagnosis household dust sample to quantify exposure of study participants rather than also assessing dust samples prior to diagnosis.

- Nguyen and colleagues found that residential proximity to plant nurseries resulted in a 240% increased risk of childhood leukemia while Lombardi and colleagues found that residential proximity to other agricultural locations using pesticides also increased the risk of central nervous system tumors. This study is notable as it found increased risk for CNS tumors associated specific types of pesticides, such as bromacil, chlorothalonil, propiconazole, among others; the majority of studies to date have examined general rather than specific pesticide use.

Air Pollution

The clearest evidence regarding air pollution and risk of childhood cancer relates to exposure to near roadway/traffic air pollution. Near traffic air pollution is a complex mixture of multiple contaminants, including fine particulate matter, diesel exhaust, benzene, formaldehyde among others. In 2021, the research literature affirmed associations between exposure to components of the near-traffic air pollution mixture and increased risk of childhood cancers.

- Lee and colleagues conducted a large retrospective study and found that long-term exposure to fine particulate matter ($PM_{2.5}$) increased the risk of childhood cancer.
- Mazzei and colleagues found suggestive risks for increased risk of childhood cancers (all types combined) based on residential proximity to a petrol/gas station.
- Wei and colleagues examined childhood leukemia risk associated with specific components of the air pollution mixture and found a 20% increased risk based on exposure to benzene and a 4% increased risk associated with nitrogen dioxide.

Substantial gaps still exist

There remain substantial gaps in our knowledge of the contribution of environmental exposures to childhood cancers. This is an important area of research given that increasing trends in childhood cancer incidence cannot be explained by risk factors commonly attributed to adult cancers, such as diet and smoking. Of concern to CENSWPA is the lack of research on potential associations between childhood cancers associated and unconventional natural gas development (UNGD) as well as specific pesticides of concern, in particular glyphosate (Roundup).

- UNGD activities include the processes of extracting, processing and transporting of natural gas, using well pads, compressor stations, condensate tanks, process plants and many other pieces of infrastructure. Among the 200+ air pollutants that have been measured in association with UNGD activities, nearly two dozen are considered known or suspected carcinogens; in a small pilot study, many of these were found in the bodies of residents as reported by a scientific investigation by Environmental Health News in 2021. Although some research has focused on the question of childhood cancers (such as McKenzie and colleagues in 2017), no new studies have examined this research question. Given CENSWPA's analysis showing elevated childhood cancer incidence in fracking-intensive counties in Southwestern Pennsylvania, this gap is particularly important for the region.
- Glyphosate is a widely used herbicide known as Roundup. It is considered a "probable" carcinogen by the International Agency for Research on Cancer (IARC) based on studies demonstrating increased risk in adults for non-Hodgkin's lymphoma (NHL). But what about children? NHL is one of the more common types of childhood cancers, and Round Up remains one of the most used "weed killers" for home and garden use, as well as for landscape and agricultural uses. Lack of direct evidence about childhood NHL related to glyphosate exposure does not mean evidence of safety, especially given that evidence (such as Vinson and colleagues) points to increased risk of childhood cancers (including lymphomas) associated with residential and professional use of pesticides. The carcinogenicity evidence for glyphosate warrants deeper investigations into links with childhood cancers.

Exposure to emerging contaminants in the environment, such as per- and polyfluoroalkyl substances (PFAS), are demonstrating cancer risks.

Per- and polyfluoroalkyl substances (PFAS) are a class of 9,000+ chemicals. PFAS are used in a wide array of consumer products to resist stains (e.g., stainproof carpets and upholstery), water (e.g., waterproof/durable water-resistant shoes and apparel), and oil (e.g., non-stick pans, pizza boxes, compostable food ware) as well as industrial products, such as fire retardant foams. These compounds are highly persistent in the environment and in our bodies. The most studied chemicals in the class are perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS); both have been associated with developmental toxicity, immunotoxicity, and cancer. The vast majority of other PFAS have little to no data demonstrating their safety and available studies indicate similar health concerns. Although PFOA and PFOS are no longer produced in the US, because of their persistence in the environment, they are still ubiquitous throughout the U.S., particularly in drinking water.

The 2021 research literature focused on additional investigations of the links between PFOS and PFOA and cancer, using epidemiologic, exposure assessment as well as toxicological studies. Studies also explored other types of PFAS, including fluorotelomer alcohols, which are commonly used as replacements to PFOS and PFOA.

- Li and colleagues studied a cohort of individuals in Sweden exposed to PFAS contaminated drinking water associated with firefighting foams. The study found suggestive evidence for an increased risk of kidney cancer, which is consistent with the current state of the evidence.
- Telomeres are complexes of repetitive DNA sequences and proteins that cap the ends of chromosomes to protect against degradation and fusion during cell division. Telomere length have been linked to an array of diseases, including cancer. Clarity and colleagues found that PFAS exposure among a cohort of women fire fighters was associated with telomere length, suggesting a possible mechanism by which these chemicals may affect carcinogenesis.
- Imir and colleagues used an animal model to investigate the impact of PFAS on prostate cancer. They found that PFAS exposure in combination with a high-fat diet advanced the progression of prostate tumors.
- Itoh and colleagues researched serum levels of 20 different types of PFAS and did not find links with breast cancer risk. Prior research in animal models suggest that PFOA and PFOS affect mammary gland development, which increase susceptibility to mammary tumors.
- The primary routes of exposure to PFAS are assumed to be ingestion, including contaminated drinking water and food. However, a study by Morales-McDevitt and colleagues reveals that indoor air exposures (e.g., fluorotelomer alcohols used in carpeting) are ubiquitous, highlighting an important exposure pathway and opportunity for reduction.

In addition to the above research, Fenton and colleagues and Ng and colleagues provide extremely useful review articles that update the state of the evidence on PFAS related to health impacts and outline critical research questions that need to be addressed.

2021 did little to fill an important gap in the research literature: the effectiveness of a range of interventions to reduce environmental exposures associated with cancers.

It is common sense that reducing exposures to environmental carcinogens will prevent some cancers in a population. Yet when resources are constrained, or when exposure reduction approaches such as new policies or redesign of products may confer unforeseen risks, it is important to understand the effectiveness of interventions. Interventions can range from policy changes to education for individual behavior change to technological innovations and more. However, intervention studies related to environmental toxicants and health, including cancer are not commonplace. Over the years, studies have examined the effectiveness of air pollution interventions, interventions to reduce exposure flame retardants in upholstered furniture, and interventions to reduce exposure to toxicants in personal care products. Yet intervention studies are challenging, and we found a lack of such studies in 2021. Cancer is a multi-factorial disease, so interventions are most likely to be effective if they too are multi-factorial, and yet there are inherent methodological hurdles

to studying multi-factorial interventions. The long latency period between exposure and the development of many cancers need not be an impediment, however; the outcome variables for intervention studies can be reduced exposure levels. In the long history of tobacco reduction research, studies showing biological changes resulting from exposure relevant to the development of cancers were also important in building the case for reducing exposures.

The California Breast Cancer Research Program (CBCRP) continues to lead in providing funding for primary prevention intervention research. In 2021, the CBCRP announced a Request for Proposals to study community-level intervention strategies aligned with interventions identified in the statewide primary prevention of breast cancer plan. More such funding in other regions is needed.