Cancer & Environment Network of Southwestern Pennsylvania

2022 Year in Review – A Research Brief

Reflections on Peer-Reviewed Research on Cancer and Environment

2022 was yet another year with an impressive array of peer-reviewed research articles examining cancer risks associated with environmental exposures. Every month, the Cancer and Environment Network of Southwestern Pennsylvania (CENSWPA) provides links to this literature in its monthly Digest using searches of research articles abstracted through PubMed, primarily epidemiologic studies. These monthly literature searches are intended to keep Network participants and other allied and interested organizations abreast of research on cancer risks from chemical and radiological toxicants in our environment and workplaces.

The Science Support Workgroup of the CENSWPA reflected on the 2022 collection of articles and identified the following as noteworthy:

1. Two significant studies conducted in Pennsylvania add to the growing literature about impacts on cancer survival associated with air pollution exposure and increased cancer risks associated with the fracking industry.
2. As CENSWPA observed in the 2021 literature, a range of cancers beyond lung cancer show increased risk associated with exposure to air pollution
3. With our nation now having a sharp focus on environmental injustices, new research sees clear links with increased risks of cancer.
4. Research continues to demonstrate increased risk of childhood cancers associated with exposure to pesticides and air pollution.

This 2022 Year in Review research brief reviews the literature related to the four highlights above. It is written in a format to simplify the science for a general audience. For terms such as "association," "risk," "meta-analyses" and "statistical significance," CENSWPA refers readers to its glossary of scientific terms.

1. Two significant studies in Pennsylvania add to the growing literature about impacts related to cancer survival from exposure to air pollution and increased cancer risks associated with fracking activities.

CENSWPA is particularly interested in research on cancer and the environment that is conducted in our state. Two significant studies elevate connections related to: (1) air pollution exposure and risks associated with poorer cancer survival outcomes and (2) increased risks of childhood cancers related to fracking activity.

McKeon and colleagues examined how exposure to air pollution impacts individuals diagnosed with lung cancer. They examined 4 types of air pollutants: NO_2, O_3, $PM_{2.5}$, and PM_{10}, each of which has strong prior evidence of their ability to influence carcinogenesis and contribute to chemotherapeutic drug resistance. Among people whose cancers had not metastasized, each of the pollutants studied was associated with reduced survival time. Increased risk was seen across all exposure quartiles (i.e., low to high levels of exposure). Risks related to survival did vary by the stage of the disease and by cell type. The authors suggest that interventions to reduce poor outdoor air quality exposure for those with early-stage lung cancer may improve survival.

Unconventional oil and gas development (UOGD), commonly referred to as hydraulic fracturing or "fracking," is a complex process with the potential for releases of known carcinogenic chemical and radiological contaminants into both water and air. The fracking industry includes extracting, processing and transporting of natural gas, using well pads, compressor stations, condensate tanks, process plants and many other pieces of infrastructure. This industry is highly prevalent in the western part of Pennsylvania (see maps through Fractracker). Because children are especially susceptible to hazardous chemicals in their environments – beginning at the fetal stage and continuing through adolescence given that bodies are in a dynamic state of growth, with cells multiplying and organ systems developing at a rapid rate – the potential impact on children living near fracking activities is a major public health concern. Clark and colleagues examined whether children living near fracking activities in Pennsylvania were at increased risk of acute lymphoblastic leukemia (ALL) – the most common childhood cancer. Compared to children not living within 2 km of a gas well, those with at least one gas well within 2 km of their birth residence were nearly two times more likely to develop ALL, and those whose mothers lived within 2 km of a well during the pregnancy were nearly 3 times more likely to develop ALL. The study suggests that contaminants in both air and water are of concern. The study demonstrates that Pennsylvania's current setback distance (the minimum distance between a private residence or other sensitive location and a gas well) of 152m (500 ft) is not providing adequate protection from harm.

2. As CENSWPA observed in the 2021 literature, a range of cancers beyond lung cancer show increased risk associated with exposure to air pollution.

In 2013, the International Agency for Research on Cancer's Working Group on the Evaluation of Carcinogenic Risks to Humans, classified exposure to air pollution as carcinogenic to humans. At the time of the evaluation, the classification was based on *sufficient evidence* of increased risk in humans for lung cancer. As CENSWPA observed with the 2021 research literature, there is increasing evidence that exposure to air pollution is also associated with additional types of cancer.

Breast Cancer

Beyond lung cancer, the most studied type of cancer related to air pollution seen in the literature in 2022 was breast cancer. Hvidtfeldt and colleagues pooled data from six European cohorts to study the impacts of exposure to low levels of air pollutants for an extended number of years (i.e., long-term exposure). A statistically significant 6% elevation in breast cancer risk was seen for exposure to $PM_{2.5,}$ with higher estimates of effect seen among women ages 50-54 and among never smokers. Poulsen and colleagues also observed a 21% statistically significant elevated breast cancer risk associated with $PM_{2.5}$ exposure in a cancer registry case control study. In this study, higher risks were also seen in exposed women under the age of 55 years. This study also observed a 3% statistically significant elevation in risk in association with exposure to NO_2. Increased risk associated with long-term exposure to NO_2 was also seen in a study conducted by Amadou and colleagues; a 7% statistically significant increase in risk. Terre-Torras and colleagues similarly observed increased breast cancer risk associated with exposure to both PM2.5 and NO2 (3% and 5% respectively), while living in an area with green space was shown to be protective.

Using the Sister Study cohort, White and colleagues examined the impact of exposure to radioactive particles in the environment, which can come from a variety of sources as modeled by the US Environmental Protection Agency's Radiation Network, including surface level uranium, soil characteristics, transport characteristics of radium and radon, etc. The study found that exposure was not associated with breast cancer overall, but was associated with one type of breast cancer: estrogen-negative breast cancer. Since prior studies of atomic bomb survivors reveal that radiation exposure during childhood and adolescence are strong influencers of breast cancer risk, future studies would benefit by examining age of exposure.

Several studies published in 2022 focused on whether exposure to polyaromatic hydrocarbons (PAHs) in air pollution increase breast cancer risk. A meta-analysis of 17 case-control studies by Gamboa-Loira and colleagues report a 21% statistically significant elevation in breast cancer risk associated with exposure to PAHs. The sources of PAHs in these studies varied, from wood smoke, vehicular emissions, occupational exposures (such as work with coal tar pitch or work with automotive combustion sources), as well as dietary sources, such as eating grilled meat. Several studies included in the meta-analysis examined how effects on risk were modified based on genetic factors, primarily a group of genes involved in the metabolism of PAHs, predominantly in the CYP450 family. Multiple studies reviewed by Gamboa-Loira observed higher risks with specific polymorphisms (genetic variants), findings also substantiated in a study conducted by Lee and colleagues. Studies reviewed in this meta-analysis also found that the exposure to tobacco smoke and PAHs amplify breast cancer risk. Kehm and colleagues found that exposure to PAHs and tobacco smoke during pregnancy synergistically interact to impact the breast tissue of both mothers and daughters, which impacts subsequent cancer risk.

Gastrointestinal cancers

Gastrointestinal cancers include multiple types, including cancers of the colon, esophagus, liver, pancreas, stomach, and rectum among others. A recent meta-analysis conducted by Pritchett and colleagues examined exposure to outdoor particulate matter and risk for this group of cancers. Exposure to $PM_{2.5}$ was shown to impart a statistically significant 12% increase in the risk of gastrointestinal cancers overall, with the most robust associations observed for colon and liver cancers (35% increase in risk and 31% increase in risk, respectively). The authors note though that the evidence is based on a small number of studies as links between air pollution and risks of gastrointestinal cancers are under-researched. A separate meta-analysis by Wu and colleagues confirms similar findings of an increased risk for liver cancer as seen by Pricheet and colleagues.

Other cancers

Additional research articles published in 2022 focusing on risks associated with air pollution examined associations with ovarian, prostate and testicular cancers. Dehghani and colleagues found support in their systematic review for increased risk of *ovarian cancer* associated with ambient air pollution. Youogo and colleagues found that both exposure to PM2.5 and NOx demonstrate increased risk for *prostate cancer*. Increased risk of papillary thyroid cancer associated with exposure to PM2.5 was observed by Karazi and colleagues. Lastly, Taj and colleagues found an increased risk of testicular cancer associated with early life exposure to ozone.

3. With our nation now having a sharp focus on environmental injustices, new research sees clear links with increased risk of cancer.

Significant attention to racial inequities in the U.S., including significant racial disparities in people's experience with Covid-19, has prompted an increase in health studies examining impacts associated with environmental injustices. These studies focus in part on exposures in environmental justice communities – communities where higher percentages of residents are people of color or living below the poverty line. Studies published in 2022 document increased risk of cancer among people living in environmental justice communities, such as the study by Rubio and colleagues. Studies also elevate specific exposures of concern in such communities, including agricultural chemicals as reported by Temkin and colleagues, elevated uranium levels in community water systems serving primarily Hispanic communities across the country as reported by Ravalli and colleagues, and PAHs as described by Sansom and colleagues in relation to a recently confirmed cancer cluster in an environmental justice community in Houston Texas.

Studies also examined the impact of historical federal redlining – a policy which systematically denied home mortgages to minorities in more than 200 US cities, and which shaped racial housing segregation still seen today. Shkembi and colleagues found that redlined neighborhoods in Detroit, Michigan have significantly higher environmental hazards than non-redlined neighborhoods, including hazards associated with exposure to diesel particulate matter, high traffic volumes and living near hazardous waste sites. These sources contribute to a lifetime cancer risk that is 4.4 times higher in redlined communities versus non-redlined communities. Lane and colleagues found similar results nationally – significant air pollution disparities, particularly for exposure to NO_2 and $PM_{2.5}$ are associated with redlining.

A review by Donley and colleagues on the implementation of pesticide policies found that environmental injustices are perpetuated by inadequate worker standards, failure to implement environmental justice executive orders, failure to account for the unintended use of pesticides, inadequate training and support, failure to effectively monitor and follow-up with vulnerable communities where approved pesticides are being applied and failure to implement essential protections for children. Authors conclude that this unjust system impacting pesticide use in the U.S. is not just a pesticide issue, but a broader public health and civil rights issue.

4. Research continues to demonstrate increased risk of childhood cancers associated with pesticides and air pollution.

CENSWPA's 2021 Year in Review documented that research studies continued to substantiate findings of a report from the Childhood Cancer Prevention Initiative which described consistency in research findings that environmental agents are important risk factors for childhood cancer, particularly childhood leukemia associated with exposure to pesticides, near roadway/traffic related air pollution, and paints and solvents. For pesticides, the 2022 literature continues to confirm these findings, yet also expands links with other types of cancers, such as Wilms' tumor, retinoblastoma and neuroblastoma. In addition, across various exposures and cancer types, findings emphasize the exposures prior to birth as driving cancer risks in early childhood. Regarding links between childhood cancer and air pollution, the 2022 literature examined other types of air pollution, including emissions from gas stations and $PM_{2.5}$.

Pesticides

In an umbrella review of meta-analyses, Iqbal and colleagues summarized the state of the evidence regarding maternal pesticide exposure and risk of childhood cancer and found that exposure is associated with childhood leukemia, with studies finding increased risks ranging from 23% to 57%. Although Rossides and colleagues' examination of parental occupational exposure to pesticides in Denmark did not observe similar findings, their study demonstrated a non-significant association for maternal occupational exposures to pesticides and increased risk of childhood lymphoma and other solid tumor. In a meta-analysis of neuroblastoma and pesticide exposure, Kahn and colleagues found a statistically significant 60% increased risk associated with prenatal exposure. These investigators also elevate possible connections to specific pesticides and neuroblastoma based on IARC's evaluations, including diazinon, glyphosate, malathion, parathion, and tetrachlorvinphos. In a study conducted by Swartz and colleagues, prenatal exposure to two organophosphate pesticides, malathion and acephate, and a carbamate pesticide, carbaryl, were all associated with an increased risk of adolescent testicular germ cell tumors.

In 2022, Khan and colleagues conducted a meta-analysis that included 12 case-control studies examining risk of Wilms' tumor associated with pesticide exposure. The analysis revealed that parental exposure to pesticides prior to birth was associated with a 2-fold increase in risk in children. A separate analysis examining prenatal exposure related to the use of home and garden pesticides specifically demonstrated a 40% increased risk of Wilms' tumor.

Thompson and colleagues examined the risk of childhood retinoblastoma – a rare tumor of the retina – from prenatal exposure to pesticides based on residential proximity to agricultural pesticide application. The investigators found that several pesticides, both herbicides and insecticides, increased the risk of retinoblastoma. Exposure to acephate resulted in a statistically significant 70% increase in risk; exposure to bromacil resulted in a statistically significant 87% increase in risk, and exposure to pymetrozine and kresoxim-methyl resulted in non-significant increases in risk of 45% and 60%, respectively.

Using a multi-variable principal component model, Joseph and Kolok assessed childhood cancer incidence data in relation to water quality parameters and pesticide application rates across Iowa counties, a type of ecological study. Based on classifying counties as low, medium and high environmental burden, they found that childhood cancer was significantly associated with environmental burden and primarily driven by pesticide usage.

Air pollution

Mazzei and colleagues investigated whether exposure to ambient benzene from gas stations, based on measuring residential proximity, was associated with a greater incidence of childhood cancers. Given the small number of cases in the study, the most robust conclusion was that benzene at gas stations is associated with an increase in risk for childhood cancers overall. There were not statistically significant increases in the risk of individual types of cancer associated with benzene exposure, although overall cancer risk (all types combined) was elevated. When the investigators pooled their results in a meta-analysis of prior studies examining childhood cancer risk associated with proximity to gas stations, they observed a 2-fold statistically significant increase in childhood leukemia for children living relatively near to gas stations.

Lee and colleagues examined the association between long-term exposure to particulate matter and childhood cancer. They demonstrated that exposure to $PM_{2.5}$ conferred a 3-fold statistically significant increased risk of childhood cancer..

Other Exposures

The 2022 literature also included studies that documented a range of exposure related to childhood cancer risk beyond pesticides and air pollution. In their meta-analysis, Brabant and colleagues examined both case-control and cohort studies and separated out different types of exposure assessment, from direct measurement of electromagnetic fields, to use of specific appliances, to living near power lines. Their findings suggest that exposure to extremely low frequency magnetic fields higher than 0.4 μT can increase the risk of developing childhood leukemia.

Ahern and colleagues examined childhood cancer risk associated with exposure to medications formulated with phthalates. The study revealed that childhood phthalate exposure was associated with nearly a 3-fold statistically significant increased risk of osteosarcoma. Researchers observed a 2-fold statistically significant increased risk for lymphomas–primarily Hodgkin and non-Hodgkin lymphomas– among children exposed to phthalates. Through the Childhood Cancer and Leukemia International Consortium, Onyije and colleagues examined a range of parental occupational exposures around the time of conception. They found a strong association between parental occupational exposure to crystalline silica and two types of childhood leukemia, Exposure to hexavalent chromium and diesel exhaust also conferred elevated risk, though results did not achieve statistical significance.

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