MEETING SUMMARY
PRESIDENT'S CANCER PANEL
MODIFIABLE RISK FACTORS FOR CANCER: OPPORTUNITIES FOR PREVENTION

June 8–9, 2026
Rockville, Maryland

The President's Cancer Panel (the Panel) hosted a two-day meeting in Rockville, Maryland, to explore lifestyle and environmental risk factors for cancers, including early-onset cancers, and identify potential approaches to reduce cancer risk. The meeting was open to the public, and members of the public were invited to submit written comments and questions during and after the event. Participants and observers were encouraged to post about the event on social media using the hashtags #PresCancerPanel and #CancerPrevention.

This meeting summary was prepared to satisfy requirements established by the Federal Advisory Committee Act. The summary provides an overview of presentations and discussions occurring as part of the workshop and does not necessarily reflect the views of Panel members.

President's Cancer Panel

Harvey Risch, MD, PhD, Panel Chair

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Carol A. Brown, MD, FACOG, FACS

National Cancer Institute, National Institutes of Health

Samantha L. Finstad, PhD, Executive Secretary, President's Cancer Panel

Participants

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Kyle Walsh, PhD, Director, National Institute of Environmental Health Sciences and U.S. National Toxicology Program

OPENING REMARKS

Dr. Harvey Risch welcomed attendees and invited Panel members and speakers to introduce themselves. Dr. Risch then reviewed the history of the President's Cancer Panel, which was established by the National Cancer Act of 1971 and charged with monitoring the activities of the National Cancer Program and reporting to the President of the United States on barriers to progress in reducing the burden of cancer.

Dr. Risch explained the purpose of the current meeting: to explore modifiable factors that contribute to the occurrence of cancer, especially early-onset cancers, and strategies for intervention. He also shared the definition of "modifiable risk factors" that the Panel would be using for this meeting. Modifiable risk factors are lifestyle and environmental factors that can be addressed to lower the risk of cancer. An estimated 40% of cancer occurrences in the United States have been linked to lifestyle factors including tobacco use, excess body weight, diet, heavy alcohol consumption, physical inactivity, and various carcinogenic infections. Additionally, evidence suggests a recent increase in the incidence of early-onset cancers, a topic of particular concern to the Panel. Dr. Risch noted that while cancer screening plays a role in early cancer diagnosis, it is outside the scope of the current meeting, as the Panel published a report focused on screening in 2022. Finally, Dr. Risch introduced meeting facilitator Mr. Scott Wheeler, who reviewed guidelines for the day's discussion.

SESSION 1: OVERVIEW OF CANCER TRENDS AND RISK FACTORS

TRENDS IN CANCER INCIDENCE AND MORTALITY IN THE U.S.

***Meredith Shiels, PhD, MHS**, Senior Investigator, Infections and Immunoepidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute*

The American Cancer Society estimates that in 2026, 5,800 Americans will be diagnosed with cancer each day, adding up to 1.1 million incidences of cancer among men and 1.02 million incidences of cancer among women. Additionally, the American Cancer Society estimates that 1,700 Americans will die of cancer each day in 2026, a total of about 330,000 men and 300,000 women.

From 2017 to 2021, the overall cancer rate among men remained stable. Rates of prostate, kidney, oral cavity, pharynx, and pancreatic cancer—the leading causes of cancer among men—increased significantly. Melanoma and leukemia remained stable, while lung, colorectal, bladder, and non-Hodgkin lymphoma declined significantly.

By contrast, over the same time period, the overall cancer rate among women declined slightly. Rates of breast, uterine, and pancreatic cancer and melanoma increased significantly; kidney cancer and leukemia were stable; lung, colorectal, non-Hodgkin lymphoma, and thyroid cancers declined significantly.

Since 2010, rates of certain cancers have increased in early-onset age groups. Dr. Shiels and her research team analyzed data from U.S. Cancer Statistics, focusing on incidence rates from 2010 to 2019 in three early-onset age groups (15- to 29-, 30- to 39-, and 40- to 49-year-olds). Of the more than 30 cancer sites reviewed, 14 sites had increased incidence in at least one of the early-onset age groups. While cancer registries do not collect detailed information about exposures or individual-level risk factors, surveillance data do include key details such as age, sex, race, ethnicity, geography, and timing of rate increases. These details can provide clues about potential drivers of incidence rates.

The U.S. Cancer Statistics data revealed that rates of breast, kidney, uterine, and pancreatic cancer increased across many age groups. Stomach cancer rates only increased among 40- to 49-year-olds, primarily among women; stomach cancer decreased significantly among older age groups. Colorectal cancer rates increased from ages 30 to 59, and rates at older ages decreased significantly. Colon cancer screening is driving the decreasing rates of colon cancer in older age groups. Rates of colorectal, kidney, and pancreatic cancer increased among every major racial and ethnic group for early-onset cancers. Breast, uterine, and stomach cancer saw increases across most racial and ethnic groups. However, the trajectories of these increases differed by racial and ethnic groups.

Dr. Shiels and team used Surveillance, Epidemiology, and End Results (SEER) 8 data, a set of registries dating back to 1975, to determine when cancer rates among people ages 20 to 49 began increasing. Exposures that caused the cancers must have preceded increases. This analysis showed that rates of early-onset kidney, colorectal, uterine, pancreatic, and stomach cancers have been increasing for decades. Early-onset breast cancer began increasing in 2013. For early-onset breast and stomach cancers, rates were significantly lower in non-metropolitan and small metropolitan counties than in large metropolitan counties. By contrast, for colorectal and kidney cancers, rates were significantly higher in small metropolitan and non-metropolitan counties than in large metropolitan counties. There was no difference across urbanicity for uterine and pancreatic cancer.

County-level obesity data from the 2017 Behavioral Risk Factor Surveillance System indicate that overall, people living in counties with the highest rates of obesity had a higher incidence of cancer. For example, kidney cancer rates were 72% higher in counties in the highest quintile for obesity compared to the counties in the lowest quintile for obesity. This trend also applied to uterine, pancreatic, and colorectal

cancer. However, breast cancer rates in the early-onset range were lower in the highest quintile of obesity counties. This is consistent with existing knowledge of premenopausal breast cancer, which is inversely associated with excess body weight.

Trends in cancer incidence may be partly driven by outside factors, including:

- **Screening guidelines.** When screening guidelines change and more people receive cancer screening, cancer rates may appear to rise. For example, the early-onset colorectal cancer rate accelerated in 2021, after the U.S. Preventive Services Task Force (USPSTF) changed its guidelines to recommend that people start colorectal cancer screening at age 45. The rise was much more pronounced among people ages 45 to 49 than people ages 20 to 44, indicating that the new screening guidelines played a role in the observed increase since 2021.
- **Incidental detection.** Imaging tests conducted to address other health concerns can incidentally detect cancer, which can contribute to rising cancer rates.
- **Coding artifacts.** International and national coding standards change over time. For example, appendix carcinoid tumors became classified as malignant around 2015 in the United States, leading to an uptick in appendix cancer rates. Because SEER classifies appendix cancer as colorectal cancer, appendix cancer has had a huge impact on the trend in colorectal cancer, especially in people under age 40. Appendix cancers were excluded from analysis in this presentation. Additionally, gastrointestinal stromal tumors were classified as malignant in 2021, leading to a large increase in stomach cancer rates in the early-onset age range.

Most early-onset cancer mortality rates are on the decline. While the incidence of breast, kidney, stomach, and pancreatic cancer increased, the mortality rates for these cancers declined significantly from 2010 to 2024. However, mortality rates for early-onset colorectal cancer and uterine cancer have increased significantly.

From 2010 to 2019, early-onset breast cancers had the largest absolute increases over time, with nearly 5,000 additional cases in the early-onset age range, followed by early-onset colorectal, kidney, uterine, and pancreatic cancers.

Presenter Responses to Panel Member Questions

- To calculate absolute increases, Dr. Sheils and team took the number of cases diagnosed in a single year (e.g., 2019) and subtracted the number of cases that would have been diagnosed in an alternate scenario where cancer rates had not increased. To generate the alternate scenario, age-specific cancer rates from 2010 were applied to the 2019 population. This approach has not yet been applied to more recent data.
- Dr. Shiels and team have not performed the same calculation to determine excess deaths, but for colorectal and uterine cancer, the calculation would result in a positive number.
- The updated USPSTF screening guidelines for colorectal cancer apply to all people ages 45 and older and are not tied to an individual's familial or genetic risk for colorectal cancer.

CANCER TRENDS IN ONTARIO, CANADA—IMPACT OF COVID

Christine Brezden-Masley, MD, PhD, MSc, FRCPC, *Medical Director, Cancer Program and Medical Oncologist, Mount Sinai Hospital; Director, Marvelle Koffler Breast Center, Sinai Health; Associate Scientist, Lunenfeld-Tanenbaum Research Institute*

Ontario Health Insurance Plan (OHIP) claims data were used to study cancer trends in Ontario, Canada. OHIP is a government-run, publicly funded provincial health insurance program that serves 16 million residents. The program's claims data provide near real-time insight into health care utilization trends and health-seeking behavior.

During the COVID-19 pandemic, Mount Sinai Hospital continued to provide systemic therapy for cancer patients. However, nonemergency care, including cancer screening, diagnostics, and certain surgeries, was suspended from March to May 2020. Additionally, many people missed health care appointments due to shelter-at-home orders and concern about COVID-19 exposure. In March 2021, Canada approved the COVID-19 vaccines via emergency use authorization and deployed vaccines to the public following months of safety testing. By December 2021, 80% of Ontario residents were fully vaccinated.

An interrupted time series analysis of billing data from 2015 to 2022 was performed to assess the real-world impact of the COVID-19 pandemic on cancer. Billing prevalence rates for breast, cervical, endometrial, and ovarian cancer dropped in 2020 following the onset of the pandemic. However, rates increased in 2021 and 2022, which could indicate a pattern of patients catching up on missed screenings as regular health care appointments resumed. The billing prevalence rates map onto Ontario Cancer Statistics data, which also showed a drop in 2020 followed by a rise across all four cancer types in 2021 and 2022. From 2019 to 2020, the data indicate a slight stage migration from stage 1 to stages 2, 3, and 4 for breast and cervical cancers. All-cause mortality increased among cancer patients by 4.5% in 2020 relative to 2019. Additionally, relative survival rates dropped from 2019 to 2020: the one-year relative survival rate dropped by 1.9%, and the two-year relative survival rate by 2.5%.

The same methodology was used to analyze a broader range of cancer types for a longer period of time (2015–2024), including breast, cervical, uterine and endometrial, ovarian, small intestine, colon, rectal, liver, and anal cancers. All followed the same general pattern: a drop in billing prevalence in April 2020 followed by an increase moving into 2021 and 2022. Billing prevalence remained high through the end of 2024 for breast, cervical, uterine, and colon cancer. Higher than predicted rates through 2024 were more pronounced in younger patients (under age 50) for all cancers analyzed. The billing prevalence and Ontario Cancer Statistics data align with key trends observed in SEER data from the United States.

Strategies to address modifiable risk factors include:

- **Preserving continuity of care.** Multidisciplinary policies should be developed to ensure that cancer screening, programs, and surgical schedules can continue during public health emergencies like the COVID-19 pandemic.
- **Disease surveillance and pharmacovigilance.** Further research is needed to understand whether COVID-19, mRNA vaccines, or both may increase an individual's cancer risk. Dr. Brezden-Masley and team are running a study called True North to examine the impact of immunity across Canada, continuity of care in British Columbia, and cancer rates among Indigenous populations and other populations at risk in Alberta.

Presenter Responses to Panel Member Questions

- The OHIP claims data reflect the number of clinical encounters for each cancer diagnosis (e.g., for uterine cancer). However, the data do not show specific services that were billed. Therefore,

it's not possible to identify why there were more clinical encounters related to a specific cancer type based on the OHIP data alone.

- In many of the billing prevalence rate graphs shown, the prediction intervals were considerably wider in recent years. The reason for this is unclear. Dr. Brezden-Masley confirmed that the data are not averaged across years.

ENVIRONMENTAL AND OCCUPATIONAL RISK FACTORS FOR CANCER

Rena Jones, PhD, MS, *Senior Investigator, Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute*

A number of environmental and occupational exposures are known or suspected carcinogens. Environmental epidemiologists use the term "exposome" to describe the exposure ecosystem of an individual or population. The exposome encompasses exposures from the air, climate, and social environment as well as external lifestyle-related exposures like medications, food, and cigarette smoke. The internal exposome is the body's biological response to these exposures.

Researchers face key challenges in understanding environmental or occupational exposures:

- **Mixture of exposures.** Often, exposures do not occur independently. Rather, a person may experience a mixture of exposures at the same time.
- **Chronic exposure.** People are chronically exposed to some substances at low concentrations, meaning it's important to consider the impact of lifetime exposure or exposures during specific periods of vulnerability.
- **Misclassification of exposure.** Researchers often use proxies or indirect measures, like surveys and models, to characterize exposures. This can lead to misclassification of exposure over long periods of time, which can prevent researchers from detecting associations.

Occupational studies have been instrumental in identifying human carcinogens. More than 50 classified carcinogens are specific to occupational settings, and up to 8% of cancers worldwide are estimated to be driven by occupational exposures. Some workplaces carry higher exposure risk than others. Occupational exposures are sometimes easier to detect because researchers can consult workplace recordkeeping. Many occupational exposures are also present in the general ambient environment, so occupational studies often serve as a guide for broader environmental research.

There are also a number of established environmental carcinogens. While it's harder to estimate the proportion of cancers attributable to the environment, outdoor air pollution is thought to contribute to 12% to 15% of lung cancer deaths. Environmental patterns of exposure are not equitable and vary substantially across the United States. For example, exposure to outdoor air pollution like fine particles is widespread, but concentrations vary by region, with higher levels in urban areas and industrial corridors. Agricultural regions may have higher levels of pesticides. Certain areas in the United States have greater radon exposure potential, higher levels of arsenic in drinking water, and higher industrial point source emissions. For example, there is an 85-mile spread from Baton Rouge to New Orleans with more than 200 point source industrial emissions. The area is colloquially known as "Cancer Alley" because it has seen elevated rates of breast and lung cancer for decades. Additionally, sources of industrial emissions are frequently located in communities of lower socioeconomic status. For example, people living closest to point source emissions of ethylene oxide are highly likely to be of low educational attainment and in poverty.

As smoking prevalence has declined, the histology of lung cancer has shifted. The proportion of adenocarcinomas rose as the proportion of smoking-associated lung tumors declined. Over the past decade, research has demonstrated a clear signal in association of lung adenocarcinoma with PM2.5, an aerosol pollutant defined as "fine," with comprising particles less than 2.5 μm in diameter. Spatial analysis identified an Appalachian region with elevated lung cancer mortality but relatively low smoking prevalence. Based on this analysis, Dr. Jones and her team have hypothesized that agricultural burning contributes to lung cancer in this area.

Uncovering the relationships between exposures and disease can take decades, and estimating exposures can be challenging. For instance, ultrafine particulate matter, defined as particles less than 0.1 μm in diameter, is predominantly a traffic emission. Dr. Jones and team collected measurements of ultrafine particulate matter at more than 200 monitoring sites along the freeways of Southern California, an area with high levels of traffic emissions. They used geospatial models to ascertain characteristics of the environment around each site. The study found a small association with lung cancer overall, but an increased risk of adenocarcinoma of the lung, particularly among men.

Dr. Jones and her team use population attributable risk (PAR) to ascribe population burden to specific exposures. The PAR formula incorporates the strength of the association, the relative risk observed across studies, and the exposure prevalence. PAR shows that even small environmental risks may translate to quite a large burden if many people are exposed. For example, although PM2.5 exposure only causes a modest individual increase in cancer risk, it contributes to a large number of cancers because a large segment of the population is exposed to high levels of PM2.5.

Not all environmental exposures have evidence for cancer as strong as air pollution. Per- and polyfluoroalkyl substances (PFAS), colloquially known as "forever chemicals," and microplastics are exposures of interest in the current environmental cancer epidemiology literature. Many of these exposures occur at low levels as mixtures, and patterns of use change over time, making the exposures hard to characterize. Although the two most common PFAS chemicals have been phased out for more than a decade, these chemicals are still present and detectable in the environment. Further research is needed to understand the impact of these exposures.

Presenter Responses to Panel Member Questions

- Dr. Jones and team make assumptions about the latent period between certain exposures, such as PM2.5, and lung cancer, based on observations about smoking exposures. Conducting research on large cohorts enables researchers to do temporal subanalyses. Implementing sensitivity analyses—by looking at diagnoses in the first 10 years of follow-up, for example—helps researchers better understand the impact of exposures over time.
- The effect of PM2.5 exposure is strongest in people who have never smoked. This finding supports the idea that air pollution is a significant driver of lung cancer risk.
- Dr. Jones and team are typically not directly involved in communicating their research findings to the public. However, their findings are often disseminated in the form of press releases and local newspaper articles.
- Ultrafine particles primarily come from the diesel emissions of trucks and other large vehicles. Dr. Jones and team are exploring additional opportunities to study the effects of ultrafine particles on younger populations.

MODIFIABLE CANCER RISK FACTORS: CURRENT EVIDENCE, NATIONAL PREVALENCE, AND OPPORTUNITIES FOR INTERVENTION

Priti Bandi, PhD, *Scientific Director of Risk Factors and Screening Research, American Cancer Society*

In 2019, 40% of all cancer cases and 44% of cancer deaths were attributed to modifiable risk factors. Cigarette smoking is the leading preventable cause of cancer, followed by excess body weight, alcohol consumption, dietary factors, physical inactivity, ultraviolet (UV) radiation, and infections.

According to the U.S. Surgeon General, cigarette smoking is linked to at least 12 cancers, but quitting reduces an individual's risk for all of these cancers. Other combusted forms of tobacco, like cigars and water pipes, and some smokeless products can also cause cancer. Interventions to reduce tobacco use include:

- **Regulating added menthol flavor in tobacco products.** While cigarette smoking among U.S. adults has declined dramatically, much of this decline is attributable to nonmenthol cigarettes, while menthol cigarette smoking has remained relatively stable. Menthol flavoring in cigarettes increases smoking uptake among youth, reduces cessation success, and directly causes disease. Menthol regulation presents an opportunity to further decrease smoking prevalence.
- **Addressing disparities and barriers to cessation.** Smoking prevalence is highest among American Indian and Alaska Native individuals and Black men. Adults with no high school education are more likely than more educated adults to smoke and have lower rates of cessation success. People with limited resources are less likely to access tools like evidence-based pharmacotherapies and counseling. Addressing these disparities could help increase tobacco cessation rates.
- **Funding tobacco control programs and strengthening policies at the state level.** Smoking is concentrated in states in the South and Midwest, which have weaker tobacco control policies. Decades of research have linked strong tobacco control policies to decreased cancer risk and prevalence. Funding tobacco control programs and strengthening tobacco control policies can help to address disparities at the state level.
- **Regulating added flavors in e-cigarette products**. While the United States has seen a significant decline in youth cigarette and cigar smoking, e-cigarette prevalence has increased rapidly, reaching about 28% of high school students in 2019. Added flavors such as candy, fruit, menthol, and mint make tobacco products more addictive, making teenagers more likely to continue using tobacco into adulthood. Among youth who use tobacco products, 88% of e-cigarette users and 86% of nicotine pouch users use flavored products, so regulating flavors is crucial to decreasing tobacco use.

Decrease the prevalence of excess weight. Excess weight is linked to risk of at least 13 cancers. In 2019, about 11% of cancer cases in women and 5% of cancer cases in men were linked to excess body weight. Among women, excess body weight was linked to about 53% of endometrial cancer cases and at least 30,000 breast cancer cases. Today, about 40% of U.S. adults and 15% to 23% of U.S. youth have obesity. DeCleene, et al., project that by 2035, 47% of U.S. adults will have obesity, and the largest increase of obesity rates will occur in women under 35. Southern and Midwestern states have the highest rates of obesity. Obesity is most prevalent among Black and Hispanic women and least prevalent among Black and White men.

Decrease alcohol consumption. Alcohol consumption is linked to an increased risk of seven cancers, according to a recent International Agency for Research on Cancer (IARC) perspective review. About 5%

of newly diagnosed cancer cases in 2019 were linked to alcohol consumption. Over the past three decades, alcohol consumption has declined among adolescents and young adults; however, it has increased among middle-aged adults. Heavy alcohol use (for men, more than two drinks per day over the last week, and for women, more than one drink per day over the last week) presents a unique risk for cancer. Prevalence of heavy alcohol use is higher among more educated women, White individuals, and American Indian and Alaska Native men.

Improve diet quality. Approximately 4% of all cancer cases in 2019 were attributable to dietary factors. Overall healthy eating patterns can reduce an individual's cancer risk by 7% to 18%. According to the American Heart Association, since 1999, poor diet quality has declined while intermediate diet quality has improved. These improvements were driven by increased consumption of whole grains, nuts, seeds, and legumes and decreased consumption of sugar-sweetened beverages. However, fruit and vegetable consumption has remained stable. Processed meat consumption, which presents unique cancer risks, has also remained stable. Increasingly, research has linked ultraprocessed food consumption to adverse outcomes including cancer risk. Over time, as ultraprocessed foods have become ubiquitous in the U.S. food system, mean caloric intake from ultraprocessed foods has increased, while intake from minimally processed foods has declined.

Increase physical activity. Physical activity lowers the risk of at least seven cancers. In 2019, 3% of all cancer cases were linked to physical inactivity. Sedentary behavior is independently associated with an increased risk of colon, endometrial, and lung cancer and even cancer-related death. Increasing step count is a simple intervention associated with reduced cancer risk. While self-reported rates of physical activity have increased among U.S. adults, they have declined among youth, with only 25% of children and teens reporting at least 60 minutes of activity within the past week.

Implement policies to enforce sun protective behaviors. In 2019, 5% of all cancer cases were attributable to ultraviolet radiation exposure, including solar exposure and exposure from indoor tanning. Over 90% of melanoma cases are attributable to ultraviolet radiation; 37% of adults and 55% of youth reported sunburn in the past year. Sunburn risk is highest among White individuals; it's also high among American Indian and Alaska Native individuals and youth of all race and ethnic groups. Adherence to sun protective behaviors is inconsistent, with a large proportion of U.S. adults reporting that they sometimes or rarely use sun protection. Implementing policies to enforce sun protective behaviors could help to reduce cancer risk.

Increase human papillomavirus (HPV) vaccine uptake. Several infectious agents are known to cause cancer and classified as group 1 carcinogens by IARC. In 2019, about 3% of all cancer cases were attributable to infections. HPV is linked to 100% of cervical cancer cases in the United States. The HPV vaccine is an effective tool to prevent cervical cancers. A recent publication by Dr. Bandi and colleagues showed a dramatic decline of cervical cancer in adults born between 1990 and 1999—the first cohort that had access to the HPV vaccine in the United States after its approval in 2006. States with the highest vaccine coverage in 2010 had the lowest cervical cancer incidence in the 1990–1999-born cohort. Today, 63% of eligible youth are up to date with HPV vaccine coverage, and 78% have initiated the vaccine series. However, uptake of the vaccine has stalled since 2021, coinciding with the COVID-19 pandemic, and varies widely by state. Increasing HPV vaccine uptake across the United States is key to reducing the prevalence of HPV-related cancers.

Presenter Responses to Panel Member Questions

- Substantial evidence shows the population-level effectiveness of the HPV vaccine for many HPV-related cancers, not only cervical cancer.

- The Nova classification scheme categorizes foods in four groups ranging from least to most processed. Under Nova, ultraprocessed foods—the fourth and final group—are those that include additives like emulsifiers and flavor enhancers, which transform food to such a degree that it is completely unrecognizable from its original form.
- Cancer risk can be an interaction of genetic and modifiable risk factors. Behavioral interventions that target modifiable risk factors often do not take genetic risk into account because behavioral interventions are more scalable when they address an average risk population. Clinical interventions, such as screening, can more easily be tailored based on genetic risk.

SESSION 1 DISCUSSION

Current Gaps and Opportunities for Intervention

- The research presented during Session 1 clearly shows that obesity is a major risk factor for many cancers. Factors outside of individual control, including a food supply engineered for the benefit of manufacturers, have contributed to the rise of obesity in the United States. Despite growing knowledge of the relationship between obesity and cancer, there is a lack of practical solutions to reduce or prevent obesity.
- There is a gap between the existing evidence for modifiable cancer risk factors and behavior change. Individuals—especially younger people, in the context of early-onset cancer—need to be educated on cancer risk factors so that they can change their behavior to reduce their risk.
- Targeted messaging to children could be effective for older age groups as well, because children often influence their parents' and grandparents' behavior. For example, campaigns promoting seatbelt use were largely directed at children, and some tobacco campaigns have taken a similar approach. The social acceptability of behaviors also plays a role in behavior change—for example, smoking in public places became unacceptable as norms evolved over time, and this has contributed to reductions in smoking.
- People who don't have access to primary care physicians often miss screening opportunities and other interventions such as HPV vaccinations. Improving access to primary care physicians could support increased screening and cancer prevention efforts.
- While changing individual behavior is difficult, tobacco control and HPV vaccination efforts have demonstrated tremendous success. Implementing successful strategies from tobacco control policy can enable individuals to change their behavior.

Rising Incidence of Colorectal and Uterine Cancer

- Increased detection is one factor that can contribute to the rising cancer incidence rates. Mortality for colorectal and uterine cancers is also on the rise, which indicates a true increase in disease burden for these cancers rather than just increased detection.
- It is challenging to suggest policy approaches to address the rise of early-onset cancers because researchers do not yet know what is driving the increases. Additionally, it is unlikely that there is a single cause; different cancers are likely driven by different factors. Major efforts are underway to identify potential causes, particularly for early-onset colorectal cancer.

Environmental Risk Factors and Policy

- The Air Quality Index (AQI) is a tool that individuals at increased risk, such as pregnant women and people with asthma, can use to reduce exposure. An individual can check the AQI and choose

to stay inside on days when the ambient air quality is poor. However, it's not practical for all individuals to manage their exposure on a daily basis. A population-scale intervention would require raising ambient air quality standards.

- States have different policies around acceptable levels of chemical exposures (e.g., acceptable levels of PFAS in drinking water). Multitier policy interventions and approaches that start small and lead to broader impact may be most effective.
- Improvements in ambient air quality from the Clean Air Act and its amendments over the past several decades have dramatically improved ambient air quality. Additionally, the National Ambient Air Quality Standard has been reduced from 12 to 9 $\mu g/m^3$, which should result in lower concentrations in exposure.
- Europe is ahead of the United States in terms of regulating ultrafine particles. Policy changes, including switching fuel for last-mile delivery and short-haul trucking, creating emission-free zones, and switching from diesel-powered vehicles to electric or hydrogen-powered vehicles, have resulted in significant reductions in fine and ultrafine particulates. This presents an opportunity for policy improvement.
- While levels of PM2.5 have declined, the composition of air pollution has changed over time with changes in diesel technology and other innovations, illustrating the complexity of environmental cancer risk factors.

SESSION 2: ENVIRONMENTAL RISK FACTORS FOR CANCER—PART 1

WHAT THE EPIDEMIOLOGY OF EARLY-ONSET CANCERS CAN TEACH US ABOUT ENVIRONMENTAL EXPOSURES, SUSCEPTIBILITY, AND PREVENTION

Mary Beth Terry, PhD, *Professor of Epidemiology and Environmental Sciences, Columbia University; Associate Director for Population Sciences, Herbert Irving Comprehensive Cancer Center; Executive Director, Silent Spring Institute*

In the United States and globally, two-thirds of cancers diagnosed in individuals under age 50 are diagnosed in women. The top 10 cancers diagnosed in young adults are all associated with environmental exposures, including UV radiation, pollution, heavy metal exposures, solvents, endocrine-disrupting chemicals (EDCs), and PFAS. Polycyclic aromatic hydrocarbons and EDCs have been associated with 8 out of the top 10 cancers that are rising in young adults.

Detecting epigenetic signatures can help researchers understand how environmental exposures may contribute to changes in cancer prevalence. The Silent Spring Institute has published a paper on how dichlorodiphenyltrichloroethane (DDT) leads to epigenetic changes in young girls. Some chemicals are direct carcinogens, some lead to epigenetic changes, and some disrupt hormonal signaling. Chemicals can alter our immune system and response, and they also can permanently mutate the genome through somatic mutations. Some of these impacts are intergenerational, meaning that the shared family history of early-onset cancer can be partially explained by germline or inherited mutations in addition to factors in the shared environment.

Based on datasets from IARC and the Environmental Protection Agency (EPA), a Silent Spring Institute study concluded that over 900 chemicals are linked to breast cancer via direct carcinogenic effect, hormonal signaling, or both. Additionally, an analysis of cancer registry data by Dr. Terry and colleagues

found that for breast, colorectal, and thyroid cancers, the time from initiation to malignancy is shorter for men and women born in the 1980s compared to cohorts born in the 1950s.

Most cancer cohorts study people in their 70s, 80s, and 90s—the age at which cancer is most likely to occur. However, Alice Whitmore and others have noted that it is hard to disentangle the signal when the bulk of cancers occur after age 70. It is easier to identify a consistent signal in younger adults, who do not have the background rate of endogenous aging. Studying individuals with early-onset cancer can help researchers reveal environmental exposures that also impact older adults.

The rise in early-onset cancers cannot be fully explained by increased screening or germline mutations. Data from 185 countries indicate that rates of early-onset breast cancer (diagnosed under age 40) started increasing in the 1930s, meaning the increased prevalence cannot be attributed solely to decreases in fertility that started in the 1970s. Additionally, the increased prevalence cannot be explained by childhood obesity because most early-onset breast cancer is inversely related to body size. That leaves one clear possibility: somatic mutations driven by changes in the environment. Increases in hormonal agents, alcohol consumption, and EDCs may contribute to the increasing prevalence of early-onset breast cancer. EDCs accelerate aging, alter the immune environment, and lead to earlier breast budding.

Relatively few breast cancer studies look at exposures during windows of susceptibility when the breast is changing in form and function. Among these studies, however, biomarker data consistently indicate associations between breast cancer and air pollution, suspended particulates, DDT, heavy metals, polycyclic aromatic hydrocarbons, and polychlorinated biphenyls. Additionally, Dr. Terry's research, including exposomic analysis, has demonstrated that breast density is a strong risk factor for breast cancer.

Opportunities for prevention include:

- **Chemical regulation.** Many chemicals, including those found in consumer products, are not regulated for their effects on the mammary gland.
- **Evidence-based interventions.** Interventions must be grounded in evidence. Household-level interventions can help to reduce individuals' and families' exposures to indoor air pollution and reduce environmental chemical exposures. Short-term interventions can also help individuals reduce their body burden of chemicals. For example, Silent Spring Institute has published a weeklong intervention to help individuals reduce their body burden of chemicals found in food packaging. A large study in Australia recently replicated findings of this trial.
- **Pan-cancer studies.** Identifying differences across cancers can help researchers learn more about early-onset breast cancer risk.

Presenter Responses to Panel Member Questions

- Windows of susceptibility are periods of time when people have increased susceptibility. In the context of breast cancer, windows of susceptibility are times when the breasts are changing, including puberty, pregnancy, and perimenopause.
- The age range for early-onset breast cancer is defined differently from study to study. Some studies use age 50 as the upper limit of the age range, while others use age 40. Using age 40 as the upper limit enables researchers to say that increases in breast cancer cannot be attributed solely to mammography, which increases at age 40.
- In the studies Dr. Terry referenced, fertility is defined based on the number of births per population level.

- Risk factors for recurrence are much less studied than risk factors for original occurrence in breast cancer, meaning researchers have limited insight into how environmental exposures, including chemicals, affect outcomes after first diagnosis. Because today most initial breast cancer is treated into remission, risk factors for recurrence are now of crucial importance to understand.
- The age of puberty has changed dramatically over recent age cohorts. The time between breast budding and the onset of menstruation (which remains around age 12 on average) has expanded, creating a much wider window of susceptibility for breast cells.

ENVIRONMENTAL DRIVERS OF EARLY-ONSET CANCER: RETHINKING EXPOSURE, SUSCEPTIBILITY, AND RISK

Charlotte Kuperwasser, PhD, *Professor of Developmental, Molecular, and Chemical Biology, Tufts University School of Medicine; Director, Tufts Convergence Laboratory of Biomedical, Physical, and Engineering Sciences; Co-founder, Naveris*

The incidence of early-onset breast cancer (defined as breast cancer in women ages 20 to 49) has been on the rise for decades. Within the past decade, this acceleration has become more pronounced. Increases in estrogen receptor (ER)-positive breast cancers, which are hormonally sensitive, are driving the uptick of early-onset cancers. This implies that there may be an underlying hormonal environmental driver.

Historically, early-onset breast cancers were generally associated with inherited predispositions linked to *BRCA1* and *BRCA2*; these tumors tend to be ER-negative and are not as hormonally sensitive. In families with *BRCA1*- or *BRCA2*-associated predisposition to cancer, in each subsequent generation, women are diagnosed with breast cancer earlier in life. This is a birth cohort effect rather than a genetic phenomenon, indicating that changes in the environment are contributing to the acceleration in cancer onset. Additionally, recent studies have identified a geospatial clustering of early-onset breast cancers in the United States. Dr. Kuperwasser and her team have identified associations between early-onset breast cancer clusters and EPA Superfund sites.

Ninety-five percent of Americans have detectable levels of complex, overlapping, chronic chemical mixtures in their urine and plasma, including EDCs, PFAS, bisphenols, phthalates, parabens, pesticides, heavy metals, and other industrial chemicals. Urine and plasma samples indicate that infants are born with these chemicals inside their bodies. Exposures from consumer products and industrial sources are found in the same individuals, implying multiple exposure routes. The specific chemicals identified in samples have changed over time as some chemicals are phased out and others are phased in; some of the chemicals that are phased in may be regrettable substitutions. Recently, exposure to parabens (a type of EDC) has increased among women of reproductive age.

Silicone wristbands can be used as a passive collection tool to assess an individual's environmental chemical exposures. In recent studies using these wristbands, nearly every sample contained evidence of exposure to EDCs. Women experienced greater exposure than men, and many of the chemicals identified through wristband samples exhibited estrogenic and anti-androgenic activities.

EDCs can bioaccumulate in adipose tissue and stay there for decades. Some EDCs, including bisphenol, are rapidly metabolized and excreted, but these chemicals are constantly reintroduced into the body through chronic exposure, producing the same effects as bioaccumulated exposure. There are two key windows of susceptibility for EDC exposure:

- **In utero.** In utero breast tissue is very sensitive to environmental exposures because it sets the cellular, epigenetic, and genetic basis for the tissue. In utero development also determines how the breast tissue is going to respond postnatally to environmental exposures and functionality.
- **From adolescence until first full-term pregnancy.** During this long window, breast tissue ages faster and is very susceptible to DNA damage, plasticity, and environmental stimuli and signals. Young girls and women who were exposed to DNA-damaging agents like radiation during this window have developed early-onset breast cancer much more rapidly and significantly than women who were exposed at later stages of development.

EDCs interfere with hormone receptor signaling and with other mechanisms that affect the immune system, metabolism, and other processes. This means EDCs operate more like network disruptors than like a specific toxicant. Because of their multitude and the many ways they can affect tissue responses and signaling, EDCs should be regulated differently from other chemicals.

Dr. Kuperwasser and her team have used healthy breast cells from women undergoing elective reduction mammoplasty surgeries to study how chemical exposure affects breast development. They found that EDC exposures can disrupt breast tissue development in many profound ways. These chemicals can prevent tissue from developing or create unusual tissue structures, suggesting that exposure to EDCs can have significant effects on the architecture of breast tissue even before signs of cancer are detectable. Mixing bisphenols together produced a much more pronounced disruption of development than a single bisphenol alone. Dr. Kuperwasser and team have identified molecular fingerprints of exposure that can be mapped to cancer tissues and specific subtypes of breast cancer. The molecular signature associated with bisphenol mixtures mapped to a specific type of ER-positive breast cancer called invasive lobular carcinoma—a very estrogen-sensitive tumor type.

Opportunities for intervention include:

- Using the molecular signatures and biomarkers identified through new technologies to develop an exposure risk score. This score could be used to categorize women who are at increased risk of developing breast cancer linked to environmental exposures. Health care professionals could then monitor these women for signs of breast cancer, just as they currently monitor women with a family history of breast cancer.
- Regulating EDCs in food, water, and consumer products, especially products put on the skin.
- Implementing category-based product labeling (e.g., bisphenol-free, phthalate-free, fragrance-free).
- Creating EDC-safe environments for children and for pregnant women.
- Educating pregnant women about chemical exposures in food, water, and consumer products.

Presenter Responses to Panel Member Questions

- There is no one-size-fits-all approach to testing individuals for chemical exposure. Future research is needed to determine whether passive sampling to identify exposures using silicone wristbands is as reliable as blood or urine tests. While urine testing is not as effective as blood testing, it is a promising monitoring mechanism that could be used more broadly to identify chemical exposures.

- In families with a history of breast cancer, the cancer may be manifesting at a younger age in each successive generation because environmental exposure is acting on the baseline risk of germline mutation.
- "Endocrine-disruptor chemical" is a term used by EPA to indicate that a chemical interacts with the hormone receptors in their assays.

SESSION 2 DISCUSSION

Assessing and Reducing Chemical Exposure

- Results from urine and silicone wristband samples do not correlate perfectly. While a urine test reflects exposure at a specific point in time, silicone wristbands are worn over a two-week period. Wristbands may absorb additional substances in the air; they cannot capture exposures via food and water. Other sample types are needed to capture additional routes of exposure.
- Driven by consumer demand, the beauty industry has taken steps to reduce EDCs in beauty products. There are opportunities for other industries to reduce chemical exposure by following a similar approach. However, focusing exclusively on substituting chemicals rather than eliminating them may lead to regrettable substitutions.
- Dr. Terry and her team at the Silent Spring Institute have conducted a series of studies analyzing the impact of Proposition 65 in California and implications for the rest of the United States. Biomarker data indicate that chemical exposure has decreased in California since the passage of Proposition 65; it has also decreased to a much smaller degree in other states. Companies are changing the chemical makeup of products sold throughout the United States to comply with California law, resulting in lower exposure across the country.
- While policy changes are critical, chemicals remain in the environment for decades after they are banned, so household-level intervention is also needed. At the household level, free online tools like Silent Spring Institute's Detox Me app enable consumers to reduce their chemical exposures indoors. Reducing individual exposure during susceptible windows, including childhood, is especially important.
- Prepublication research by Dr. Scarlet Gomez indicates that among California residents, first-generation U.S. immigrants are at highest risk for early-onset cancer. Occupational exposures may play a large role in cancer risk within the immigrant population.

SESSION 3: ENVIRONMENTAL RISK FACTORS FOR CANCER—PART 2

NIEHS AND NTP: IDENTIFYING ENVIRONMENTAL CARCINOGENS TO INFORM ACTION

Kyle Walsh, PhD, *Director, National Institute of Environmental Health Sciences and U.S. National Toxicology Program*

In fiscal year 2024, the National Institute of Environmental Health Sciences (NIEHS) invested $93.2 million in cancer research, which was 9.4% of the NIEHS budget. NIEHS' work has contributed to knowledge of exposures to carcinogens such as arsenic, PFAS, flame retardants, pesticides, and PM2.5. NIEHS continues to fund several efforts to identify and characterize potentially carcinogenic environmental and occupational exposures in the United States. The institute aims to produce data that can be easily applied by regulatory agencies such as the Food and Drug Administration (FDA), EPA,

Centers for Disease Control and Prevention (CDC), and National Institute for Occupational Safety and Health (NIOSH).

The following studies are funded through the NIEHS Superfund Research Program (SRP). All SRP projects must include a focus on environmental remediation.

- University of California, Berkeley, researchers have defined 10 key characteristics of cancer-causing agents (e.g., induces chronic inflammation, is immunosuppressive). This list of characteristics provides a practical framework for reviewing mechanistic data. The impact of agents on the immune system—through chronic inflammation and immunosuppression—are of particular interest to NIEHS. Research is looking at how lower immune competence reduces immunosurveillance, which can allow premalignant cells to progress to cancer.
- Massachusetts Institute of Technology researchers are developing assays and sensors to detect N-nitrosodimethylamine (NDMA) exposure and distinct NDMA-related DNA damage. Identification of a unique somatic mutation signature linked to chemical exposures could help determine which cancers are attributable to those exposures. Their work suggests that DNA repair capacity and age may influence susceptibility to NDMA-related cancer risk.
- University of Kentucky researchers are studying how nutrition-based interventions (e.g., high fiber) may mediate the harmful effects of PFAS, including intestinal damage and increased colorectal cancer risk.
- University of California San Diego researchers are investigating how a high-fat diet and sedentary lifestyle interact with triclosan exposure to increase liver disease and liver cancer risk in mice. Based on this group's work, triclosan has been banned in over-the-counter soaps.

The NIEHS Sister Study, which has been running for about 25 years, follows more than 50,000 women with a sister diagnosed with breast cancer to identify modifiable risk factors and better understand gene-environment interactions. The study has yielded findings related to exposures from personal care products air pollution, smoke and indoor combustion, and workplace chemicals. Findings suggest that modifiable risk factors may have outsized effects in women who carry known pathogenic variants (e.g., *BRCA1, BRCA2*). NIEHS is considering extending the study to include the children and grandchildren of the original participants to gain insights into transgenerational factors.

NIEHS is advancing exposomics to move beyond single exposures and gain insights into cumulative, mixture-based exposures across the life course. Exposomic studies include the external exposome (e.g., air pollution) as well as the personal exposome (e.g., diet, sleep) and biological responses to both types of exposures.

The NIEHS Worker Training Program conducts workshops to train workers in industries in which workers are at high risk for chronic health conditions (e.g., construction, transportation, health care, emergency response). The aim is to make prophylaxis a habit rather than just a requirement. Trainings have been done in partnership with the United Steelworkers, the International Association of Fire Fighters, and the Western Region University Consortium on topics like hazard identification, safe chemical handling, and correct personal protective equipment utilization.

The National Toxicology Program (NTP) Report on Carcinogens (RoC) supports efforts to prevent cancer by prioritizing substance regulation and exposure reduction strategies. The current 15th edition of the RoC lists 256 known or reasonably suspected carcinogens, including chemicals and infectious agents. Health hazard conclusions are reached using transparent systematic review methods, evidence integration, and established listing criteria. Findings can be viewed on a web-based interactive dashboard. Over its 40-year

history, the RoC has been the basis for numerous federal and state actions that have improved public health and led to savings of about $8 billion per year.

MUTATIONAL SIGNATURES FOR IDENTIFYING THE MUTAGENIC CAUSES OF CANCER

Ludmil Alexandrov, PhD, *Professor of Bioengineering and Cellular and Molecular Medicine, University of California San Diego; Deputy Director, Sanford Stem Cell Fitness and Space Medicine Center*

Mutational Signatures

Somatic mutations occur daily in every cell of the body. These mutations originate from lifestyle choices, defective cellular machinery, and, in some cases, normal cellular processes. As somatic mutations accumulate, the risk of developing "driver mutations"—genetic alterations that initiate cancer—increases significantly.

Scientists have developed machine learning approaches to identify the causes of DNA mutations in an unbiased way. These analyses reveal mutational signatures, which are consistent, specific patterns of DNA mutations; these signatures may be caused by endogenous processes, exposure to treatments (e.g., chemotherapy), or environmental exposures. For example, UV exposure and tobacco use are each associated with distinct mutational signatures. To date, over 150 mutational signatures have been identified; however, most cancer driver mutations are generated by mutational signatures with an unknown cause. The CAUSE (Connecting DNA Adducts, Unexplained Mutational Signatures, and Cancer Etiologies) project funded through the Cancer Grand Challenges initiative is investigating unexplained mutational signatures known to generate the majority of driver mutations in human cancers. The CAUSE team hopes that uncovering the mechanisms of these mutations will lead to opportunities for cancer prevention.

Using Mutational Signatures to Investigate Early-Onset Colorectal Cancer

Early-onset colorectal cancer incidence is increasing in the United States and many other countries, even as rates of colorectal cancer in older adults are falling. A global study identified 47 mutational signatures in about 1,000 sporadic colorectal cancer tumors. A closer look at early-onset tumors revealed enrichment of three mutational signatures. Two of these mutational signatures—SBS88 and ID18—are known to be caused by exposure to colibactin, a genotoxic metabolite produced by certain strains of *Escherichia coli* or other bacteria. Mathematical modeling suggested that the colibactin signatures were generated very early in cancer development.

To determine the timing of the colibactin exposure, the team sequenced DNA from laser-capture micro-dissected normal colon crypts from colorectal cancer patients. The phylogenetic trees generated using these data revealed that colibactin exposure likely occurred in the first five years of life. To validate this hypothesis, the research team sequenced healthy colorectal tissue from children. About 40% of these children already carried a colibactin mutational signature. In an extreme case, a 2-year-old child had a mutational burden that would be expected in a 50-year-old adult.

The team hypothesizes that colibactin exposure in early life generates many mutations, including driver mutations that yield a higher risk of developing colorectal cancer at a young age. To examine this hypothesis, follow-up studies are needed to determine whether colibactin exposure has increased over time. Case-control studies of early-onset colorectal cancer also are needed. Consideration is being given to how exposure could be modulated to reduce risk of mutations and cancer.

Presenter Responses to Panel Member Questions

- Microbiome researchers posit that the human microbiome has changed substantially even within the past 10 years or so. There are microbiome data from the early 2000s but not from earlier times, so it is not possible to determine the extent of changes over a longer time period.
- The reasons for microbiome changes are unknown, but antibiotic use is one hypothesis.
- Children with the colibactin signature often have mothers with the colibactin signature. However, it is unclear why the mothers were exposed to colibactin or how the exposure was transferred to their children.
- Individuals with family history of colorectal cancer or with known genetic risk factors (e.g., Lynch syndrome) were excluded from the studies presented, so it is unclear whether there is a relationship between the colibactin signature and hereditary colorectal cancer.
- The colibactin signature persists despite intestinal cell turnover. This suggests that the mutations occurred in intestinal stem cells.
- The team hypothesizes that large numbers of colibactin-associated mutations increase the likelihood of a driver mutation, such as in *APC*.
- The team is participating in a collaborative project led by the European Commission that is looking at differences in exposures and diet among people from about 26 countries. It is hoped that this will lead to insight into why the increases in colorectal cancer have occurred at different times in different countries.

OPERATIONALIZING THE EXPOSOME FOR CANCER PREVENTION AND CONTROL

Douglas Walker, PhD, *Associate Professor, Gangarosa Department of Environmental Health, Emory University*

Only 5% to 15% of diseases are attributable to heritability alone. The remaining 85% to 95% stem from environmental factors, lifestyle choices, and the interaction between genes and the environment. Humans are exposed to many chemicals. Over 350,000 chemicals have been registered for production and use worldwide. Many of these have not been tested for toxicity or persistence in the environment.

The exposome is defined as the integrated compilation of all physical, chemical, biological, and psychosocial influences that impact biology. Exposomics is the field that studies the comprehensive and cumulative effects of physical, chemical, biological, and psychosocial influences that impact biological systems by integrating data from a variety of interdisciplinary methodologies and data streams. The goal of exposomics is to enable discovery-based analysis of environmental influences on health.

Large-scale measurement of environmental exposures has lagged behind omics approaches developed to study biological processes (e.g., genomics, transcriptomics). The Walker lab focuses on developing technologies and workflows that will allow incorporation of the exposome into studies of human health, including cancer. To this end, open-source, high-throughput workflows of high-resolution mass spectrometry platforms have been developed to study biological samples (e.g., blood, urine, tissue). Automated sample preparation has increased throughput by 15-fold. The multiplex multimodal instrument setup runs four assays on 350 samples in about 10 minutes, which translates into analysis of about 30,000 samples per instrument per year.

The workflows generate “untargeted” data (i.e., measure what is present versus selecting specific chemicals for analysis); however, sub-workflows allow quantitative analysis of specific exposures of

interest. For example, the pipeline can provide data for up to 66 PFAS in each sample. PFAS measurements have been validated using third-party proficiency testing and comparisons with CDC laboratory assays. PFAS measurements have been generated for approximately 20,000 samples representing different time points, outcomes, populations, and geographical sites.

The team also has developed a fully automated, open-source analysis pipeline that separates signals from background noise, provides annotation, and generates easy-to-use reports that align with findable, accessible, interoperable, reusable (known as FAIR) data principles. Users are able to select the types of data included in their reports, ranging from well characterized chemicals to computational predictions and untargeted compounds. To assist with analysis of untargeted data, the lab has compiled a large database of reference standards (e.g., EPA's ToxCast Phase III library; agrochemical library of pesticides, herbicides) that allows high-confidence identification of over 25,000 unique chemicals, including environmental and endogenous metabolites.

The ultimate goal of this work is to move beyond individual studies and create cancer exposome atlases that integrate data across cancers, populations, and geographic regions to link exposures and disease. The Walker team is compiling data from several prospective cohort studies of lung, breast, liver, colon, and blood cancers. To date, data from 25,000 people from across the United States, Europe, Asia, and Africa have been analyzed using harmonized methods. This integrated framework will help identify shared and unique exposures linked to cancer types and outcomes.

Future directions include (1) continuing to increase the throughput and decrease the cost of exposomics assays, and (2) developing and refining analytical frameworks for emerging exposures of concern, such as microplastics. An ongoing project funded by the Advanced Research Projects Agency for Health (ARPA-H) is establishing high-throughput pharmacoexposomics for drug efficacy monitoring and population-scale exposome profiling. Efforts are ongoing to improve and reduce the cost of these methods.

Presenter Responses to Panel Member Questions

- Most of the samples analyzed are plasma or serum from blood, although other types of samples have been run.
- The goal of the ARPA-H–funded project is to develop approaches to determine how environmental factors interact with and influence the efficacy of different therapeutic agents. For example, an environmental exposure may change expression of an enzyme, which could in turn increase the rate of drug metabolism. These data could be used to inform treatment decisions.
- It is important that exposomic studies are large enough to allow for multiple testing corrections given the large number of exposures being measured.
- Correlations between exposures generally are class dependent (e.g., PFAS exposures tend to correlate).
- Efforts are under way to develop methods that consider the joint effects of mixtures of chemicals. Correlation structures in the data are used to group chemicals. Another approach assigns weights to individual exposures that represent their contributions to the outcome being measured.
- Most of the work of the lab looks at correlations of exposures to pre-defined endpoints. The top associations are analyzed further using other models to determine possible mechanisms.
- Exposomic data could be integrated with genome-wide association study or other omic data.

SESSION 4: ENVIRONMENTAL RISK FACTORS FOR CANCER—PART 3

ENVIRONMENTAL RISK FACTORS FOR CANCER: AGRICULTURAL AND OCCUPATIONAL EXPOSURES

Peter Thorne, PhD, MS, *University of Iowa Distinguished Chair; Professor, Department of Occupational and Environmental Health; Director and Co-Founder, Human Toxicology Program, University of Iowa*

Occupational exposures account for approximately 5% of cancers worldwide, including mesothelioma; leukemia; and cancers of the trachea, bronchus, lung, larynx, nasopharynx, ovary, and kidney. The highest burden of occupational cancers is concentrated in industrialized regions like North America, Western Europe, and Australasia. However, countries such as Honduras, Vietnam, and Indonesia, with emerging manufacturing and mineral extraction sectors, are experiencing the fastest increases in occupational cancer rates.

Occupational exposure to 13 chemicals caused 350,000 cancer deaths in 2021. Asbestos exposure has decreased globally, but because of its long latency period, asbestos remains the leading cause of occupational cancer deaths. On the other hand, trichloroethylene currently is linked to far fewer cancers, but incidence rates for these cancers have increased by over 30% in recent decades.

In the United States, approximately 177 million individuals are in the civilian paid workforce, with 21.6 million working in categories with a high potential for toxicant exposure. Of the 40,000 chemicals in regular commercial use in the United States, roughly 4,000 are classified as known or probable human carcinogens. These include chemicals used for industry and agriculture.

Industrial occupational exposures come from feedstock chemicals used to make plastics, rubber, pharmaceuticals, and consumer products, as well as fuels for energy and transportation. Overall hazard exposures in the United States are declining, largely due to EPA restrictions, industry controls, and automation. However, workers in several sectors remain at elevated risk, including those in construction; manufacturing; mining, oil, and gas extraction; the chemical industry; and agriculture, landscaping, and groundskeeping. It is often difficult to draw a direct relationship between a specific carcinogen and a particular occupational cancer. Disentangling occupational exposure from environmental confounders (like fine particulate matter) and behavioral risks (like smoking or lack of screening) is also challenging.

Agriculture differs from standard industrial occupations due to its family-centric nature and the blurring of boundaries between the workplace and the home. Over 2 million documented workers are in agriculture, though this undercounts the self-employed, unpaid laborers, and many children who participate in farm labor. Agricultural exposures begin early in life and often extend to the end of life. Households often are adjacent to the workplace; chemicals infiltrate the home via airborne drift, tracked-in soil, and work clothes laundered with family laundry. Workers and families are exposed to a complex mix of chemicals. There also is limited oversight of farms, with smaller farms exempt from Occupational Safety and Health Administration enforcement and inspections and right-to-farm laws in some states limiting regulations. The private wells used by over 70% of farming households are generally exempt from the stringent testing required for public water systems. Agricultural exposures include pesticides, sunlight, diesel engine exhaust, welding fumes, solvents and degreasers, crystalline silica, nitrates from manure and fertilizer, and well contaminants.

The Agricultural Health Study (AHS) is a longitudinal study of nearly 90,000 licensed pesticide applicators and spouses. AHS analyses revealed that while this population is generally healthier than the wider public (lower body mass index [BMI], lower smoking and drinking rates), they face elevated risks for cancers of the lip and prostate, as well as B-cell lymphomas and acute myeloid leukemia. These

cancers have been linked to compounds like alachlor, benzene, lindane, and phenoxy herbicides. Strategies to control pesticide exposure include regulations, substitution with less toxic products, engineering controls (e.g., secure ventilated storage, safe transportation and handling); administrative controls (e.g., wash clothes and boots in barn or shed), and use of personal protective equipment.

AHS and other studies have highlighted concerns about nitrates in drinking water in agricultural settings. Nitrates enter private wells through seepage and spills of nitrogen-based fertilizers and land-applied animal manure. When consumed, nitrate is biologically converted into carcinogenic nitrites and N-nitrosamines. An analysis of AHS data showed that agricultural workers consuming private well water with higher levels of nitrate have elevated risks of prostate, colorectal, and ovarian cancers. A study out of Denmark (which accounted for lifetime residential history and dietary nitrate intake) demonstrated that those with high levels of nitrate in their drinking water had nearly double the risk of gastric adenocarcinoma.

Presenter Responses to Panel Member Questions

- Vegetables are generally associated with lower risk of cancer, even though they contain nitrates—and some, such as beets and radishes, are high in nitrites. A study in Denmark found that the risk of gastric cancer from nitrate-containing drinking water is reduced by co-consumption of vitamin C and other dietary antioxidants.
- Glyphosate research remains somewhat controversial because real-world agricultural use is confounded by simultaneous exposure to other pesticides, such as 2,4-D and malathion, for which there is stronger evidence of cancer causation. The NTP and IARC reached differing conclusions on glyphosate's carcinogenicity. Glyphosate is a high-volume pesticide in the United States, so it would be good to clarify its link to cancer.
- Military personnel are typically excluded from general occupational cancer datasets because the Bureau of Labor Statistics tracks and categorizes the civilian workforce separately from active-duty military personnel. Military personnel are monitored via separate databases.
- The term “feedstock chemicals” in an industrial manufacturing context refers to chemical raw materials used to synthesize other products (such as plastics, rubber, and pharmaceuticals).
- AHS enrolled about 90,000 participants in the early 1990s. Data collection for Phase 5 was completed between 2019 and 2021. There have been efforts to reach out to the children of the original AHS participants. AHS—funded by the National Cancer Institute (NCI), NIEHS, EPA, and NIOSH—stands as a foundational dataset that has shaped understanding of pesticide toxicology, including long-term cancer outcomes.

MEASUREMENTS FOR UNDERSTANDING AIR TOXICS EXPOSURE AND CANCER RISK AROUND INDUSTRIAL FACILITIES

Peter DeCarlo, PhD, Professor and Vice Chair, Department of Environmental Health and Engineering, Johns Hopkins University

The United States regulates different air pollutants in different ways. Criteria air pollutants form the basis of the AQI and include well-known pollutants such as particulate matter (PM2.5 and PM10), ozone, nitrogen dioxide, and carbon monoxide. Criteria air pollutants are measured regularly in every city across

the United States. The United States also regulates hazardous air pollutants known to impact health, including cancer. These 188 air toxics are not measured to the same extent as the criteria air pollutants.

Cancer risks from exposure to industrial air toxics are related to the emission strength, proximity to the source, toxicity of the chemicals emitted, and length of the exposure. EPA uses multiple tools to assess chemical exposure and risk. The Risk-Screening Environmental Indicators (RSEI) tool calculates a cancer risk score by taking into account the volume of emissions from facilities, the specific toxicity of those chemicals, how they disperse in the air, and the population exposure dose. According to the RSEI tool, the highest cancer risk scores are concentrated along the Gulf Coast (specifically Louisiana and Texas) and the Rust Belt. RSEI breaks down risk by industry and chemical. The chemical manufacturing sector, combined with primary and fabricated metals, accounts for roughly two-thirds of the total RSEI cancer risk score. For chemicals, ethylene oxide represents about a third of the risk, and chromium and related compounds represent another third. A significant limitation of screening models like RSEI and the EPA's Air Toxics Screening Assessment (AirToxScreen) is that they rely on self-reported emissions data from the industrial facilities. These self-reported figures are often underestimates of actual emissions, so models cannot accurately characterize risk without direct, physical air measurements.

To evaluate the actual exposures at the neighborhood level, Dr. DeCarlo's team initiated the Hazardous Air Pollutant Monitoring Assessment Project (HAP-MAP). The project utilizes a mobile chemistry laboratory equipped with research-grade instruments capable of measuring numerous hazardous air pollutants. Data on 65 compounds, including 17 carcinogens, were collected every day for a month in an industrial corridor between Baton Rouge and New Orleans, which again, is known as “Cancer Alley.” The resulting data maps reveal tracts with high levels of specific carcinogens. For example, measurements taken near ethylene oxide facilities revealed levels of the chemical that are known to be associated with elevated risk of cancer. In all tracts near Cancer Alley, the measured values of most chemicals were significantly higher than the modeled levels reported in AirToxScreen, in some cases more than 10 times higher.

Because of the known cancer risk associated with ethylene oxide, EPA has issued rules regarding continuous monitoring of this chemical around industrial facilities; however, these rules are not enforced. Monitoring can make a difference. Control technologies capable of reducing air toxic emissions are available. EPA monitoring around the Denka facility in Cancer Alley led to a decrease in ambient chloroprene at the facility fenceline, thus reducing exposures for people living in the surrounding neighborhoods.

Presenter Responses to Panel Member Questions

- The current regulatory system relies on annual, self-reported emissions inventories from industrial facilities. The technology for continuous, direct measurement is available but not used.
- The proximity of a hospital and elementary school to the chloroprene-emitting Denka facility are highly concerning. Given the impact of early exposures, the location of the elementary school right next to the facility is of particular concern.
- The public-facing AQI is based only on criteria pollutants (like PM2.5 and ozone) and does not reflect cancer risk from specific hazardous air pollutants like ethylene oxide or chloroprene, which are not included in the index.
- The majority of ethylene oxide produced is used as a feedstock for making plastics and ethylene glycol. A smaller fraction is used for medical and food sterilization. Ambient ethylene oxide levels can be high in the areas around both production facilities and facilities where the chemical

is used. Medical sterilizing facilities have engineering controls to reduce ethylene oxide emissions, but there are still emissions that result in detectable levels. Sterilization occurring in hospitals and medical facilities is generally on a smaller scale than what is being done at dedicated sterilization facilities, although detectable emissions can occur.

- Enforcement of the EPA rule on fenceline monitoring of ethylene oxide facilities was supposed to begin in July 2026, but enforcement of the rule has been paused. The rule did not include consequences, but monitoring and reporting can lead to change. In some cases, state governments have shut down facilities or denied permits due to high emissions.
- It would be interesting to see whether rates of cancer change around chemical facilities following enforcement of rules designed to reduce emissions.
- The technology to mitigate hazardous emissions at the source is well-established. Methods include capturing the chemicals for disposal or, more commonly, using thermal destruction to break down the harmful compounds before they are released into the atmosphere.

MID-MEETING GROUP DISCUSSION

Establishing Causation

- The field of epidemiology has spent decades identifying risk factors for cancer (e.g., childbearing age, height, *BRCA1/2* mutation status for breast cancer). The Bradford Hill aspects of causal reasoning (e.g., magnitude of association, consistency of observation) are helpful for assessing whether statistical associations are likely causal, but this approach is subjective and not completely foolproof.
- Epidemiology studies provide information about population-level risk. It can be difficult to extrapolate individual risk or determine the cause of any single individual's cancer, although estimates of "more likely than not" can sometimes be derived.
- Several types of studies have helped establish ethylene oxide as a cause of disease. Experiments in animal models and cells have established a mutagenic mode of action. Occupational health studies on workers who are exposed only to ethylene oxide at work have provided insight into potential links to disease. Air measurements have been taken in areas near facilities that are releasing ethylene oxide, with urine analyses done to confirm exposures. Gradient analyses were done to see if disease risk correlates with level of exposure. Establishing causality using occupational studies is more challenging when workers are exposed to mixtures of chemicals over their lifetimes, as is the case with people who apply pesticides.
- Establishing gradients of exposure is very important. Comparing disease risk between people with high versus low exposure can provide valuable insight. Even if the measurements are imprecise, a consistent association is evidence of causality.
- The literature provides convincing evidence that bisphenol A (BPA) can cause cancer. It is possible to identify people with high exposure to BPA using short-term monitoring (e.g., 2 weeks) and recommend ways to mitigate their risk.
- Descriptive analyses can be hypothesis generating. Correlations between smoking-related diseases and cervical cancer led to studies that confirmed the direct link between smoking and cervical cancer.

- The technology exists to measure the impact of various exposures on the body (e.g., DNA mutations, epigenetics, tissue changes), but these approaches are not applied in clinical settings. Primary care providers measure markers for cardiovascular disease risk but not cancer.
- Geographic mapping can help researchers annotate past environmental exposures of participants in large cohort studies, including exposures that occurred during windows of susceptibility. A study of early-onset cancer suggests that geographic risk explains more variation in cancer risk than polygenic risk scores.
- For early-onset breast cancer, early radiation exposure could be used in combination with family history and other factors to help determine whether a woman should be screened for breast cancer before the recommended age for the general population.
- Dietary exposures have typically been measured using recall, which is challenging. However, signals from large population-based diet studies can be followed up with more precise studies in the lab in which a controlled diet can be linked to metabolic processes and carcinogenic intermediates.
- Identifying mutational signatures that map to specific exposures would help characterize individual risk and potential identify opportunities for mitigation. For example, the gut microbiome can be modified by changing the diet; this may reduce the mutational burden enough to prevent early-onset colorectal cancer.

Cancer Risk Mitigation Strategies

- A model of cancer risk was proposed: genetic risk (nonmodifiable), risk from personal behaviors (e.g., diet, smoking), and risk from environmental exposures. Risks from behaviors and exposures are modifiable but not necessarily addressable through personal choice. Some people may not have access to healthy foods. Many people are not aware of their environmental exposures and most have limited power to change what they are exposed to.
- Interactions between genetic, behavioral, and environmental factors are important with respect to cancer risk. The reductionist approach of focusing on a single factor is not advisable.
- Multilevel approaches that target both individual behavior and system-level issues must be pursued to effectively reduce cancer risk. Limiting marketing of ultraprocessed foods to children is an example of a policy to address a system-level issue.
- Consideration must be given to how to reconcile and integrate different levels of influence on cancer risk, such as time, geography, and demographics.
- Rather than looking at risk factors that affect large populations, consideration should be given to opportunities to address the high risks faced by segments of the population that bear the burden of high exposures, such as to industrial chemicals. For example, implementing best available control technologies for chemicals such as ethylene oxide or chloroprene could be very effective.
- More attention should be paid to the geographic distribution of cancer risk and the elevated cancer risk experienced in some communities. One option would be to increase access to screening in high-risk communities. Continuing medical education about differences in cancer risk by geographic area could help ensure that young people at high risk have access to the care they need, including early access to screening tests. In some cases, young people's symptoms are dismissed or overlooked because providers think they are too young to have cancer.

- Communication is important. The general public is not aware of many of the things that increase risk of cancer (e.g., environmental exposures, ultraprocessed foods). People should be informed of these risks and ways to mitigate them.
- Quantifying the number of people affected by various exposures or cancer risk factors would be powerful and would help inform prioritization of risk mitigation efforts. From a cost-benefit perspective, it would be best to focus on the factors with the highest impact. About 40% of cancer deaths could be avoided by addressing tobacco use, excess body weight, alcohol consumption, and other modifiable risk factors.

Tobacco

- There are 27 million smokers in the United States. Approximately 20% of U.S. cancer cases and 30% of U.S. cancer deaths are attributable to smoking. More than 350,000 deaths per year from cancer and other diseases could be avoided by eliminating smoking.
- Less than 10% of the U.S. population uses tobacco, which is a significant drop over the past several decades. This decline is due to regulation and smoking cessation. The effectiveness of smoking cessation has been well documented. Lessons learned from tobacco could be applied to obesity. In particular, policy and low-cost interventions (e.g., pharmacotherapy, behavioral interventions) could be helpful.

Diet, Physical Activity, and Obesity

- Regulation of ultraprocessed food production, marketing, and consumption could reduce cancer risk by improving diets. However, regulations should be carefully crafted to make sure that all people have access to affordable nutritious foods. Healthy eating is not really a choice if there are not affordable options.
- NCI encourages dietary studies to collect information on food insecurity. Food security and access must be addressed in order for people to reduce their cancer risk through dietary change.
- GLP-1 medications may provide opportunity to reduce obesity on a population level. Subsidizing the cost of these drugs could increase access for people who would benefit from them. People taking GLP-1 medications should be counseled about the need for good nutrition and exercise, especially given the loss of muscle mass observed in some people taking these drugs. The goal should be to transition people into a sustainable way to maintain a healthy lifestyle.
- The United States could learn from other countries and cultures. Europeans tend to be more active and eat smaller portion sizes than people in the United States.

Environmental Exposures

- Environmental exposures can be modified through regulation. Different regulations in Europe and the United States result in different exposures. In some cases, the same product made by the same manufacturer includes different ingredients in Europe versus the United States. Food packaging is also different—Europe tends to use more metal and cardboard instead of plastic.
- The approach to regulation in the United States likely will need to be different than it is in Europe where centralized health planning is the norm. In the U.S., it may be more effective to use a legal or moral framing and point out how exposures violate rights, including of vulnerable populations like children or those with genetic predisposition to disease.

- Enforcement of existing regulations could help reduce cancer risk for communities around industrial facilities. There also should be a shift from a reactive to a proactive approach when it comes to environmental carcinogens.
- Exposure to plastics is ubiquitous. Many foods have plastic packaging. Safer food packaging would be a way to reduce exposures of children and pregnant women to potentially toxic chemicals. Reducing demand for and use of plastics also will reduce production, which will reduce exposures to the chemicals used in production. Plastics will continue to be used for some applications, but it would be possible to reduce exposures to plastics in people's daily lives.
- A potentially high impact policy would be to ban all bisphenols from all food-related products, including packaging (e.g., lining of cans, plastic containers). BPA has been banned, but some of the substitutes being used may be just as dangerous. There are ways to make plastics without bisphenols. Some countries have banned bisphenols from food products.

Early-Onset Cancers

- Many young women diagnosed with breast cancer have more aggressive disease than would have been expected in the past. One reason that mortality rates for breast cancer are not increasing may be because they are excellent treatments for breast cancer (unlike for some other cancers). Consideration should be given not only to how to prevent early-onset breast cancers but also how to reduce the risk of recurrence.

AI in Research and Monitoring

- Artificial intelligence (AI) is being used to help with research and analysis. Dr. Alexandrov predicted that his lab would have fewer software developers in the future due to increased use and efficiency of AI. AI is prone to errors, but it is possible to put strict guardrails on AI agents and control how and when they respond.
- Satellite systems are collecting information about wildfire smoke exposure, and AI and machine learning approaches are being used to develop exposure algorithms for different regions of the country, including regions where there are no other tools to assess exposure.
- In the future, it may be possible for AI to provide people with information about their exposures and potential interactions between exposures based on a list of household products used.

Research

- The U.S. should continue to invest in research on the causes of cancer and opportunities to reduce risk of cancer.
- Research should be done on protective factors as well as risk factors. For example, obesity is a known risk factor for endometrial cancer but not all people with obesity get endometrial cancer. Research could be done to determine if there are genetic, dietary, or other factors that impart protection.
- Deciduous teeth can provide information about a child's cumulative exposure to many substances between gestation and the age that they lost the tooth. Exposomics could be done on these deciduous teeth. Many National Institutes of Health (NIH) programs are collecting deciduous teeth. The Environment and Children's Health Outcomes (ECHO) program has deciduous teeth from about 20,000 children.

SESSION 5: LIFESTYLE RISK FACTORS FOR CANCER

EARLY-ONSET COLORECTAL CANCER: ADVANCING RISK FACTORS TO PREVENTIVE INTERVENTIONS

***Andrew Chan**, **MD, MPH,** Chief, Clinical and Translational Epidemiology Unit, Massachusetts General Hospital; Daniel K. Podolsky Professor of Medicine, Harvard Medical School; Professor of Immunology and Infectious Diseases, Harvard T.H. Chan School of Public Health*

Epidemiological studies have identified risk factors for early-onset colon cancer, including:

- Obesity and metabolic comorbid conditions, including diabetes and fatty liver disease
- Sedentary behavior
- Poor diet quality, sugar-sweetened beverages, low vitamin D, and alcohol consumption, particularly consuming alcohol without food
- Microbiome components such as the sulfur microbial diet

A metabolic axis seems to underlie many of these risk factors. Drs. Chan and Cao established Team PROSPECT, a multidisciplinary Cancer Grand Challenges team that brings together investigators across the globe to understand the pathways, risk factors, and molecular drivers of early-onset colorectal cancer—and translate those insights into prevention. Because metabolic dysfunction occurs across the life course, early-onset colorectal cancer interventions must consider windows of susceptibility that occur at different stages of life. Data from the Nurses' Health Study (NHS I and II) and Health Professionals Follow-Up Study reveal an uptick in colorectal cancer incidence and mortality in individuals born after the 1950s. Women who were in the highest BMI category in their 40s and 50s (based on self-reported weights) had nearly double the incidence of early-onset colorectal cancer compared to women in the lowest BMI category. Women who had been in the highest BMI category around age 18 also had a 60% higher incidence of early-onset colorectal cancer.

In the early 2000s, Dr. Chan and team administered a questionnaire to the mothers of cohort study participants to assess in utero and childhood exposures, diet, and physical activity. Children of women with the greatest amount of gestational weight gain had nearly double the incidence of colorectal cancer later in life. These findings suggest that exposures in utero could be mediated through epigenetic regulation, creating lasting physiologic scars that lead to cancer susceptibility in adulthood.

National Health and Nutrition Examination Survey data show that children's intake of ultraprocessed foods has increased over the last several decades, coinciding with the rise of early-onset colorectal cancer. Ultraprocessed foods are also linked with changes in BMI and adiposity in children. The Growing Up Today Study (known as GUTS) tracked the children of NHS II participants to assess the children's dietary habits and weight gain. A 10% increase in ultraprocessed food intake over a four- to five-year period in childhood was linked to a 0.08 increase in BMI. NHS II data also indicate an association between maternal intake of ultraprocessed foods during pregnancy and greater incidence of childhood overweight or obesity. Children of mothers who ate the highest quintile of ultraprocessed food in pregnancy had a 40% increased risk of overweight compared with children of mothers who ate the lowest quintile of ultraprocessed food. Ultraprocessed food is also associated with abdominal obesity, overweight, and type 2 diabetes in adulthood. Based on NHS II data, women in the highest quintile of ultraprocessed food intake had a 50% higher risk of developing an early-onset adenoma or precancerous polyps compared with women in the lowest quintile.

Insulin resistance is a key pathway of interest in early-onset colon cancer research. A study led by Dr. Chan and Dr. Mengxi Du indicates that individuals with the highest likelihood of hyperinsulinemia had a nearly 30% higher incidence of early-onset adenoma. This seems to particularly affect women born after 1955.

Team PROSPECT is exploring links between gut microbial dysbiosis and colorectal cancer. The team identified microbial species that were associated with colorectal cancer as well as species that were anticorrelated with colorectal cancer. There was also a correlation of approximately 20% between microbes linked with colorectal cancer and microbes linked with cardiometabolic disease.

Potential touchpoints for intervention include:

- **Glucagon-like peptide-1 (GLP-1) receptor agonists.** Dr. Chan and team are currently leading a single-arm clinical trial called PROSPECT, in which participants between the ages of 18 and 49 with prior adenoma resection are treated with tirzepatide over a six-month period. Through detailed biospecimen collection, the investigators aim to explore potential mechanistic associations between GLP-1 receptor agonists and cancer risk.
- **Anti-inflammatory drugs like aspirin.** Inflammation may induce cancer risk in multiple ways. Anti-inflammatory drugs like aspirin have been shown to reduce cancer risk, particularly in high-risk populations such as individuals with Lynch syndrome.
- **Whole foods-focused diet interventions.** Implementing diet interventions early in life could help to reduce obesity, type 2 diabetes, and other risk factors in line with a life-course approach to early-onset colon cancer prevention.

Presenter Responses to Panel Member Questions

- In the PROSPECT trial, each participant received a dosage of tirzepatide determined by weight center physicians.
- For the purposes of Dr. Chan's work, microbial dysbiosis describes an aggregate combination of microbes that could be linked to higher risk of colorectal cancer. This information could be used to develop a microbiome risk score. Certain microbes are consistently linked with colorectal cancer risk across studies. These include *Fusobacterium nucleatum* and certain species of *E. coli*. There is no working definition of a "normal" gut microbiome, but certain microbiome characteristics are consistent with nondisease states like lower cardiometabolic risk.
- Mothers of participants in NHS I and II and the Health Professionals Follow-Up Study were asked to recall how much weight they gained while pregnant with the participant. Excess weight gain during pregnancy was defined as more than 14 kilograms.
- Dr. Chan and team are currently conducting a prospective study using stool microbiome data to identify a clear microbiome signature that could be implemented as a screening tool, alongside other risk factors, to stratify people for preventive interventions.
- While it would be difficult to implement a pharmacological intervention on pregnant women or children, dietary guidelines could be implemented to influence windows of colorectal cancer susceptibility (i.e., during pregnancy and early childhood) and reduce risk of downstream metabolic diseases.
- Dr. Risch contemplated what changes might be linked to the increase in colorectal cancer risk starting with the 1950 birth cohort (e.g., increase in availability of household refrigeration,

changes in consumption of smoked and processed meats, changes in consumption of vitamin D, frequency of *Helicobacter pylori* infection). To date, data on *H. pylori* and colorectal cancer have been inconsistent, but there is some plausible mechanistic information that could suggest a link. Additionally, there is clear association between increased use of food preservatives like nitrites and processed meat and rising rates of colorectal cancer.

METABOLIC DRIVERS OF GYNECOLOGIC CANCER: OPPORTUNITIES FOR PREVENTION

Victoria Bae-Jump, MD, PhD, *Professor and Associate Division Director of Gynecologic Oncology, University of North Carolina at Chapel Hill; Leader, UNC Lineberger Endometrial Center of Excellence; Leader, UNC Lineberger Gynecologic Oncology Trials Pod; Medical Director of Clinical Operations, UNC Lineberger Clinical Trials Office*

Obesity is one of the most important and potentially modifiable drivers of cancer risk in the United States. More than 40% of U.S. adults are living with obesity, and excess adiposity has been linked to 13 major cancer types to varying degrees. Endometrial cancer is by far the most obesity-driven cancer, with greater than 60% of cases linked to obesity. It is the fourth most common cancer among women in the United States and one of the few cancer types that is increasing in both frequency and mortality. In 2026, more than 68,000 U.S. women will be diagnosed with endometrial cancer, and more than 14,000 women will die of the disease.

More than 65% of endometrial cancer patients are obese. In addition to obesity, diabetes and insulin resistance are well-known risk factors associated with a higher risk of developing and dying from endometrial cancer. Rates of endometrial cancer are rising in younger women, with a 3% to 4% annual increase in women ages 20 to 39. This presents unique challenges for many young female patients as hysterectomy is a key treatment for endometrial cancer. Progestin is the only fertility-sparing treatment option; it's only effective about 60% of the time, and recurrences are common. Endometrial cancer harbors one of the worst disparities for Black women among all cancers. Black women are three times more likely than White women to develop endometrial cancer and twice as likely to die of the disease.

Obesity is thought to lead to endometrial cancer through several mechanisms:

- Hyperglycemia and hyperinsulinemia resulting from overnutrition provide abundant nutrients and growth factors to tumor cells, creating an enhanced environment for tumor growth.
- Chronic inflammation, immunosuppression, and increased cytokine production are hallmarks of obesity that are conducive to cancer development.
- Bioavailable estrogen levels, which are higher in obese women due to enhanced conversion of androgens to estrogens in peripheral adipose tissue, lend increased growth factor stimulation to tumor cells.
- Increasing evidence shows that obesity leads to microbiome changes, potentially in the uterus as well as in the gut, that may be advantageous to cancer development.
- Obesity-related pathways are linked to molecular alterations in endometrial cancer. Obesity leads to increased signaling via the insulin/IGF-1 pathway, culminating in activation of the mTOR pathway, stimulation of cell proliferation, and ultimately, the development of genetically aberrant cells and cancer.
- Increased circulating glucose leads to inhibition of AMPK and further stimulation of the mTOR pathway, culminating in increased cell proliferation and the development of endometrial cancers.

In 1983, gynecologic oncologist Dr. Jan Bokhman categorized endometrial cancer into two subtypes:

- **Type 1 cancers** comprise 80% of endometrial cancers. These cancers are endometrioid, are typically diagnosed at stage 1, and have a better prognosis than Type II cancers (although outcomes are worsening for endometrial cancers in general).
- **Type II cancers,** the remaining 20% of endometrial cancers, are non-endometrioid cancers including serous, clear cell, and carcinosarcomas. These are more aggressive cancers that often present in advanced stage and have a much poorer survival rate compared to Type I cancers. Type II cancers disproportionately affect Black women.

The Cancer Genome Atlas Project divided endometrial cancer into four molecular subtypes: *POLE* mutated (POLEmut; ultramutated), mismatch repair deficiency (MMRd)/microsatellite instability (MSI)-high (hypermutated), copy-umber low (CNL; no specific molecular profile), and copy-number high (CNH; p53 abnormal). POLEmut, MMRd/MSI-high, and CNL are comprised mostly of endometrioid histology tumors. CNH comprises most nonendometroid and more aggressive tumors, along with about 25% of endometroid tumors. Obesity and insulin resistance are associated with both Type I and Type II subtypes, but the link is much stronger for Type I. The strongest obesity link among the molecular subtypes is with MMRd/MSI-high and CNL.

The gut microbiome is known to affect biological pathways for both obesity and cancer, as well as the efficacy and toxicity of chemotherapy and immunotherapy. A landmark 2009 study by Walsh, et al., assessed women undergoing hysterectomy for either endometrial cancer or benign uterine condition and collected microbiome samples from the lower and upper reproductive tract. The study found that postmenopausal status, obesity, and the presence of endometrial cancer increased microbial diversity—a sign of poor reproductive health. Seventeen taxa were associated with endometrial cancer. In the years since, several small studies have found gut microbiota differences that distinguish endometrial cancer patients from healthy controls. These gut microbiota differences have also been linked to increased fatty acids and lipids in the tumors of endometrial cancer patients, suggesting a potential interrelationship between obesity, endometrial cancer, and the microbiome.

Dr. Bae-Jump and her research team have compared the uterine microbiomes of women with benign uterine disease and those with stage 1 endometrioid endometrial cancers. They found increased microbial diversity in the malignant versus benign uterus, as well as genus-level differences in many bacteria. Obese women had higher microbial diversity than non-obese women, and there were phylum and genus-level differences between the cancers of obese women and non-obese women. Metabolomic profiling showed that excess free fatty acids (oxidative stress), inflammation, and lipid toxicity were in the endometrial cancers of women with obesity. Obesity promotes dysbiosis of the gut and leads to many systemic changes, including estrogen metabolism as well as chronic inflammation, metabolic pathways, and immune pathways that then reach the endometrial microenvironment and potentially impact the microbiome of the uterus.

Dr. Bae-Jump and team are currently conducting a prospective endometrial cancer microbiome study. The goal is to correlate microbiome profiles with obesity, molecular subtypes, and outcomes. Dr. Bae-Jump also leads the Carolina Endometrial Cancer Study, a population-based study in the North Carolina that aims to better understand worsening disparities and outcomes in endometrial cancer through molecular profiling, methylation studies, and microbiota profiling of tumors.

Diet is a modifiable factor that could help to disrupt the obesity microbiome and endometrial cancer risk. Studies on diet and endometrial cancer are limited, but an Italian case-control study found that strict adherence to a Mediterranean diet was associated with a 50% lower endometrial cancer risk. Another study showed that higher diet-induced gut microbiota scores, indicative of better gut microbial health, was

associated with 27% reduced risk of gynecologic cancers, including endometrial, cervical, and ovarian cancer.

There are interventions that have been shown to break the obesity-cancer link. A Women's Health Initiative study found that intentionally losing 10 pounds reduced cancer incidence. Bariatric surgery and GLP-1 drugs can help patients achieve weight loss. GLP-1 therapies offer a unique opportunity to potentially alter cancer risk at a population level. These drugs work by complementary mechanisms to reduce energy intake, improve metabolic efficiency, and increase energy expenditure to improve weight loss. GLP-1 medications have evolved over the years, with more recent versions resulting in higher mean weight loss. Tirzepetide, the first dual agonist with FDA approval, targets GLP-1 as well as glucose-dependent insulinotropic polypeptide (GIP). Retatrutide is the first triple agonist, targeting GLP-1, GIP, and the glucagon receptor.

Early preclinical studies have shown that GLP-1 receptor agonists have anti-tumorigenic effects in endometrial cancer. For example:

- Dr. Bae-Jump's research in mice found that tirzepatide and retatrutide increase weight loss, decrease tumor proliferation, impact mTOR signaling, impact lipogenesis, and lead to activation of T cells.
- A study of type 2 diabetes patients found a lower overall cancer risk and endometrial cancer risk in GLP-1 drug users compared with insulin users. Another study of people with overweight and obesity found an overall reduced cancer risk, endometrial cancer risk, and ovarian cancer risk in GLP-1 medication users compared to nonusers.
- A study of women with benign uterine disease or endometrial hyperplasia found that participants taking GLP-1 medications and progestins had better outcomes than those taking progestins alone and those taking a combination of metformin and progestin. Ongoing clinical trials and a window-of-opportunity study continue to explore GLP-1–based therapies in endometrial hyperplasia and cancer.
- A recent study of cancer patients showed that GLP-1 drug users have lower overall mortality compared to nonusers. Ongoing studies are exploring the possibility of using tirzepatide or semaglutide during chemotherapy.

Effects of GLP-1 receptor agonists include reducing adiposity, improving insulin sensitivity, improving glucose metabolism, reducing chronic inflammation, and decreasing proliferation, as well as important changes in the immune system. Because the GLP-1 receptor is expressed in the uterus and in endometrial cancer tumors, it is unclear whether these effects simply come from weight loss or if GLP-1 receptor agonists have a more direct effect on gynecological tissues.

Risks of GLP-1 medication use include increased thyroid cancer risk, bone loss, and loss of fat-free mass, including skeletal muscle, which can lead to sarcopenia risk and impair cardiovascular fitness. Mitigation strategies include resistance training, adequate protein intake, and monitoring body composition. Additionally, many people discontinue GLP-1 medications within the first year of treatment due to side effects or cost. However, new oral forms are better tolerated than subcutaneous injections. Strategies like tapering, induction, maintenance dosing, and intermittent dosing can also increase tolerability.

More research is needed to explore key questions about GLP-1 agonists and endometrial cancer that remain, including:

- Will GLP-1 receptor agonists prevent all or some of the histological molecular subtypes of cancer?
- Which receptor combinations are optimal?
- How do these agents affect the microbiome?
- How should therapy be individualized for cancer prevention?
- How should GLP-1 receptor agonists be combined with diet and physical activity?
- How does discontinuation affect prevention and endometrial cancer risk?

Additionally, rigorous clinical trials are needed to define the right doses, ages, schedules, and target populations for GLP-1–based therapies. Success depends on strategic partnerships among researchers and clinicians, including obesity specialists, primary care doctors, and oncologists, as well as industry, government, and patient advocates.

Presenter Responses to Panel Member Questions

- Obesity interferes with estrogen metabolism, changing the microbiome of the uterus.
- Research to date has not identified similarities in bacteria between an endometrial cancer microbiome and colon cancer microbiome.
- Obesity is defined as a BMI of 30 or higher; 65% of endometrial cancer patients are classified as obese, and most of the remaining patients are classified as overweight.

DIET, METABOLISM, AND CANCER RISK: FROM EVIDENCE TO PREVENTION IN U.S. POPULATIONS

Fred Tabung, PhD, MSPH, *Associate Professor, The Ohio State University College of Medicine and Comprehensive Cancer Center*

Diet and metabolic health represent one of the largest remaining opportunities for cancer prevention in the United States. Colorectal, kidney, uterine, and female breast cancers account for more than 80% of additional early-onset cancer cases. These are the cancers most strongly linked to diet, metabolic dysfunction, and obesity. In the United States, 40% of all cancers are attributable to modifiable risk factors, and more than one in five cancer cases are linked to diet, excess body weight, and physical inactivity combined.

Dietary patterns that are high in refined grains, ultraprocessed foods, added sugars, and red processed meats drive two key metabolic states: hyperinsulinemia (chronically elevated insulin) and chronic low-grade systemic inflammation. These two metabolic states promote uncontrolled cell growth, DNA damage, and evasion of apoptosis, all of which are features of cancer. Gut microbial alterations and epigenetic modifications close the loop.

For decades, nutritional epidemiology focused on single nutrients or single foods, but the results were inconsistent because these do not take combined exposures into account. The field then moved to looking at dietary patterns. Conventional dietary patterns like the Mediterranean dietary pattern, the Dietary Approaches to Stop Hypertension (known as DASH) Eating Plan, and the Healthy Eating Index (HEI) have shown real but modest effects. The World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) have moved in the direction of looking at biologically defined dietary patterns that look at the totality of diet as an exposure and incorporate biomarkers linked to major chronic disease. Dr. Tabung and his research team used the following approach to develop the reversed empirical

dietary index for hyperinsulinemia (rEDIH) and the reversed empirical dietary index for dietary inflammatory pattern (rEDIP):

- Specify the cancer-relevant biological pathway.
- Select the biomarkers that represent this pathway. For rEDIH, use fasting C-peptide. For rEDIP, use three markers: C-reactive protein, interleukin-6, and tumor necrosis factor alpha receptor 2.
- Use machine learning approaches to answer the question: What combination of foods and beverages maximally predicts circulating concentrations of these markers?
- Use regression coefficients to weight the foods that are retained in the final models and summarize the data into a single metric to quantify the inflammatory or insulinemic potential of an individual's diet.

In line with Dr. Tabung's research, the Global Cancer Update Programme (CUP Global) made the following recommendations in its 2025 report:

- Healthy body weight reduces the risk of at least 12 major cancer types.
- Anti-inflammatory and lower insulinemic dietary patterns are associated with lower risk of colorectal cancer and breast cancer.
- Adherence to the WCRF recommendations reduces colorectal and breast cancer risk.

The evidence underpinning the anti-inflammatory and lower insulinemic dietary patterns (rEDIP and rEDIH) was explicitly reviewed and incorporated into these recommendations.

Dr. Tabung and team compared rEDIH and rEDIP to multiple guideline-based dietary patterns using NHS I and II and Health Professionals Follow-Up Study data. rEDIH and rEDIP outperformed the guideline-based dietary patterns in terms of the composite endpoint or the individual component endpoints, especially type 2 diabetes and obesity-related cancers. Higher adherence to all the guideline-based dietary patterns was associated with significantly reduced risk of cancer and major chronic disease. This finding indicates that there is high potential in dietary interventions for major chronic disease prevention, and focusing more on the metabolic properties of the dietary pattern could maximize the benefits of diet-focused interventions.

The Consortium of Metabolomics Studies (COMETS) includes more than 1 million people across six prospective cohort studies followed for a median of nearly 15 years and more than 16,000 incident colorectal cancer cases. Dr. Tabung's analysis of COMETS data revealed that adhering to a low insulinemic dietary pattern and anti-inflammatory dietary pattern (according to the rEDIH and rEDIP indices) was associated with a 16% lower risk of colorectal cancer. This translates to about 12 colorectal cancer cases prevented per 100,000 person years. The associations were stronger among African Americans and Hispanics than European Americans. Findings were consistent across geographies, food supplies, and genetic backgrounds.

HEI tracks adherence to the Dietary Guidelines for Americans. The average HEI score in the United States is 56 out of 100 points. Among Americans, 9 in 10 have at least one metabolic abnormality. People who are food secure have higher dietary quality, and people with lower incomes have poorer diets. This pattern holds across income, education, insurance status, and race and ethnicity. The benefits of nutritional progress are not reaching the populations that stand to gain the most. While the U.S. food system has supported modest improvements in dietary quality, it has not delivered equitable progress across populations. Without targeted policies that prioritize nutrition security, such as strengthening

nutrition assistance, improving food affordability, and integrating Food Is Medicine interventions, diet-related health disparities will only get worse.

Dr. Tabung and team have created a three-step framework to translate the low insulinemic and anti-inflammatory dietary patterns into clinical practice:

- **Identify.** Use a blood-based rEDIP polymetabolite biomarker to identify patients with the highest diet-driven inflammatory cancer risk.
- **Intervene.** A registered dietitian delivers medical nutrition therapy based on the rEDIP dietary pattern, personalized to the patient's culture, food access, and readiness for change.
- **Monitor.** Repeat the biomarker measurement to determine whether levels have improved with dietary behavior changes. This monitoring approach closes the feedback loop and provides a validated surrogate endpoint for clinical trials.

This framework has been tested in a 12-week Phase I feasibility trial of 32 postmenopausal women at elevated breast cancer risk, resulting in a 139% improvement in the rEDIH dietary pattern score over 12 weeks. All participants completed the study, and 97% said they could follow this dietary pattern long-term. To scale the evidence, Dr. Tabung and team are planning a 12-week randomized controlled trial of 126 adults with high-risk colon adenomas (the precursor to colorectal cancer) and a 12-month study of an anti-inflammatory dietary intervention in 600 Medicare beneficiaries with metabolic syndrome.

Recommended interventions to reduce cancer risk include:

- **Clinical integration.** Integrate dietary risk assessments and metabolic syndrome screening into routine cancer prevention encounters. Expand Medicare and Medicaid coverage for medical nutrition therapy and cancer prevention and control. Fund training of registered dietitians in oncology, nutrition, and precision nutrition training.
- **Research.** Prioritize NCI funding for dietary intervention trials with cancer incidence endpoints. Mandate dietary biomarkers in NCI-funded cancer prevention trials. Accelerate the development and validation of objective dietary biomarkers for cancer prevention and research and clinical implementation, ensuring racial diversity in precision nutrition trials.
- **Policy.** Incentivize Supplemental Nutrition Access Program (SNAP) and Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) benefits for fruit, vegetables, and whole grains. Support reformulation of food to limit ultraprocessed foods and added sugars. Align school nutrition standards with cancer prevention dietary patterns. Address food and environmental inequities that drive adverse dietary patterns.

Presenter Responses to Panel Member Questions

- Dr. Risch asked what differentiates whole grains from refined grains. Dr. Tabung noted that refining grains removes fiber, which reduces the grains' nutritional value.

ZIP CODE TO GENOMIC CODE: NEIGHBORHOOD DISADVANTAGE AND CANCER BIOLOGY

Neha Goel, MD, MPH, *Associate Attending Surgeon; Chief of Disparities of the Department of Surgery; Jeanne A. Petrek Junior Faculty Chair, Memorial Sloan Kettering Cancer Center*

Dr. Goel's research has identified breast cancer survival disparities associated with neighborhood disadvantage. Neighborhood disadvantage is a social determinant of health shaped by policies and societal structures that create and maintain under-resourced neighborhoods.

Using the neighborhood deprivation index, a multidimensional measure of block-level variables, Dr. Goel and her research team reviewed data for 5,000 breast cancer patients treated in Miami-Dade County between 2005 and 2017. Living in the most disadvantaged neighborhoods was associated with shorter breast cancer survival, even after controlling for individual-level factors like alcohol use, obesity, tumor characteristics, and receipt of National Comprehensive Cancer Network guideline-concordant treatment.

Redlining is the practice of denying home loans to communities of color and economically disadvantaged populations based on perceived financial risk. Dr. Goel and team assessed the impact of redlining and subsequent racial and ethnic segregation on breast cancer survival using the index of concentration at the extremes. Non-Hispanic White people and non-Hispanic Black people living in economically marginalized neighborhoods had increased breast cancer-specific mortality. The same was true for White women living in disadvantaged, predominantly Black or Hispanic neighborhoods, who may have experienced additional stress due to isolation. Although living in a disadvantaged neighborhood was associated with shorter survival, living in an ethnic enclave moderated that association and reduced breast cancer-specific mortality. Enclaves may offer a protective effect due to social support and cohesion that could buffer the effect of social adversity-associated stress.

Social genomic determinants of health are physiological gene regulatory pathways, such as the sympathetic nervous system, through which contextual factors like neighborhood adversity and an individual's perceptions of that adversity can affect cancer biology. Perceptions are critical because they serve as modifiable end points that can potentially influence biology. When the sympathetic nervous system is activated, it leads to beta adrenergic receptor-mediated signaling that induces a gene expression profile in circulating immune cells consistent with upregulation of proinflammatory pathways, downregulation of immune response genes, and upregulation of CREB, a mediator of sympathetic nervous system signaling. Monocytes and other myeloid cells enter the tumor microenvironment and foster a prometastatic state via macrophage recruitment, angiogenesis, cell proliferation, and tumor invasion.

Since 2019, Dr. Goel has led the Miami Breast Cancer Study, a prospective cohort study that collects in-depth survey information on various types of stressors, including neighborhood, cancer, and everyday life-related stressors, and integrates these data with biospecimens. Increasing neighborhood disadvantage was independently associated with upregulation of proinflammatory pathways; downregulation of the immune response genes; and upregulation of CREB, a marker of sympathetic nervous system activity. Increasing subjective neighborhood disadvantage was associated with an increase in threat to safety subscores, which were also independently associated with increased NFκ B; downregulation of immune response genes, and upregulation of CREB.

In summary, the study has found associations between living in a disadvantaged area, a more aggressive tumor transcriptomic profile consistent with sympathetic nervous system activation, upregulation of

social genomic transcription factors, and ultimately shorter survival. To validate these findings, Dr. Goel has launched another prospective cohort study at Memorial Sloan Kettering in New York City.

Dr. Goel's team has also studied tumor registry data of about 5,000 women treated at Memorial Sloan Kettering for stage 1 through 3 breast cancer from 2013 to 2024. Neighborhood disadvantage was associated with higher odds of poorly differentiated disease and increased odds of mortality.

Policy change is needed to address the root causes of neighborhood disadvantage. Blocking the sympathetic nervous system response is an intervention that can be implemented at the individual level. There are two ways to block the sympathetic nervous system response: through medication or stress management. In Phase II clinical trials, patients given a nonselective beta blocker demonstrated reversal of social genomic transcription factors. Psychologist Dr. Mike Anthoni has developed a stress management program associated with improved recurrence-free survival in breast cancer.

Presenter Responses to Panel Member Questions

- All patients in the New York studies were treated at Memorial Sloan Kettering, and findings remained after controlling for receipt of guideline-concordant treatment.
- Stress management programs have been shown to improve outcomes in patients with depression and anxiety regardless of where they live.

SESSION 5 DISCUSSION

Reducing Colon Cancer Risk

- The gut is one of the few organs that directly interacts with the environment. It is possible that direct contact of food contents, nutrients, metabolites, or microbial associations contribute to colon cancer risk separately from the systemic effects discussed in Dr. Chan's presentation (e.g., hyperinsulinemia, IGF pathways).
- Dietary intervention cannot reduce cancer risk in every individual because there will always be some individuals who cannot or will not adjust their diet. A multipronged strategy may be the most effective approach.
- Advising people to take fiber supplements to reduce colon cancer risk might be more palatable than advising people to change their dietary pattern, but there is not much evidence to suggest fiber supplements would be effective. Past fiber supplement trials have not shown a direct effect on neoplasia risk.
- Taking aspirin to reduce colon cancer risk makes sense for people who are genetically predisposed or at high risk, including people with unhealthy lifestyles. However, taking aspirin regularly may not be appropriate for children due to the risk of Reye's syndrome or for people over age 65 due to bleeding complications. A randomized controlled trial could help researchers assess the efficacy of aspirin-based interventions.
- While popular media messaging suggests that probiotics can lower colon cancer risk, there have not been rigorous randomized controlled trials to show probiotics meaningfully affect cancer risk or other major health outcomes. The effects of probiotics may be insufficient to durably change the microbiome in the same way that dietary changes like increasing whole food consumption can. Because there is so much variation in the types of probiotics manufactured, recommended, and used in the general population, it is difficult to assess the efficacy of probiotics. Additionally,

there are some data to suggest that probiotics may do more harm than good for people who are receiving chemotherapy or other cancer treatments.

Disparities in Early-Onset Endometrial Cancer

- Black patients are most impacted by the increased incidence and mortality of early-onset endometrial cancer in people age 40 and under.

Stress Reduction-Based Interventions

- Current cognitive behavioral stress therapies are ineffective in reversing cancer risk markers in patients living in disadvantaged neighborhoods. Potential effects of meditation on cancer risk markers have not been studied.

SESSION 6: ADDRESSING MODIFIABLE RISK FACTORS

USING STATE-LEVEL INFRASTRUCTURE TO ADVANCE CHRONIC DISEASE PREVENTION

Ciara Ruske, DrPH, MPH, *Branch Head, Cancer Prevention and Control Branch, North Carolina Department of Health and Human Services, Division of Public Health*

North Carolina's unified public health infrastructure creates a strong foundation for cancer prevention work. The North Carolina Department of Health and Human Services Division of Public Health (DPH) translates federal funding, evidence-based guidance, and national priorities into impactful local-level programing. DPH acts as connective tissue within the state's cancer prevention system by providing a shared direction for prevention work and maintaining centralized infrastructure for technical assistance, administrative support, data collection, and coordination. Community feedback flows back through the system as local-level organizations identify successful strategies and opportunities for improvement and share their input with DPH. This ongoing exchange enables DPH to improve its approach to cancer prevention over time. DPH's approach focuses on risk reduction, addresses upstream factors that drive cancer risk, and extends prevention into places where people learn, work, worship, and age.

Cancer remains one of the leading causes of death in North Carolina, and disparities in diagnosis and access to care persist. North Carolina is home to the second largest rural population in the nation, with uneven access to specialists, screening, and follow-up care. Tobacco agriculture has had economic and environmental impacts in North Carolina and remains relevant to the state's cancer burden. At the same time, North Carolina has strong assets for cancer prevention, including major academic and cancer research institutions and a strong data infrastructure. DPH leverages surveillance data to shape the North Carolina Cancer Plan, chronic disease priorities, funding strategies, and measurable objectives; engage local health departments, health systems, federally qualified health centers, community-based organizations, coalitions, and trusted messengers; and identify gaps in local capacity, technical assistance needs, navigation support, provider training, and public health workforce development.

DPH also relies on a network of coalitions, including the North Carolina Advisory Committee on Cancer Coordination and Control (ACCCC), a legislatively mandated cancer coalition with more than 100 partners. ACCCC works closely with the state Comprehensive Cancer Control Program, which provides the CDC-funded infrastructure for statewide planning, coalition support, partner alignment, implementation tracking, and progress on state cancer plan implementation.

The 2025–2030 North Carolina Cancer Plan focuses on six detectable or preventable cancers, including breast, colorectal, HPV-related, lung, prostate, and skin cancer. The plan is built on a modifiable risk factor framework, grounded in the belief that a substantial share of cancers is preventable when states

address shared modifiable risk factors systematically. The plan creates a shared road map for North Carolina, giving partners a common language, a coordination structure, data-driven goals, and a clear way to align factors so cancer prevention efforts are connected rather than fragmented across the state.

North Carolina's cancer prevention infrastructure consistently generates new, replicable models and approaches; reaches populations across the state; integrates care across the health care system; and sustains results over time. Strategies that make North Carolina's prevention approach successful include:

- Cross-sector partnerships
- Clinical–community linkages
- Coalitions and regional networks
- Data systems and surveillance
- Integrated service delivery models
- Cross-disease collaboration

Adult smoking in North Carolina declined from 22% in 2011 to 11.5% in 2024, a change that reflects more than a decade of coordinated work across state and local partners. QuitlineNC and provider referrals, regional technical assistance, youth vaping and nicotine-use prevention, policy and systems change, and ongoing data tracking contributed to this success, demonstrating that durable change is possible when prevention efforts are sustained.

North Carolina's Breast and Cervical Cancer Control Program (BCCCP) and Well-Integrated Screening and Evaluation for Women Across the Nation (WISEWOMAN) Program show how shared service delivery infrastructure can support integrated prevention and early detection. BCCCP provides breast and cervical cancer screening and diagnostic services for eligible uninsured and underinsured women. WISEWOMAN builds on the same local infrastructure by adding cardiovascular risk screening, lifestyle counseling, and referrals to prevention services. BCCCP and WISEWOMAN share common provider networks, aligned navigation and referral pathways, data expectations, and coordinated quality improvement processes. With this approach, a woman who enters the system through cancer screening can also be assessed for cardiovascular risk, connected to tobacco cessation or lifestyle-change support, and navigated through follow-up care without having to start over again in a separate system.

North Carolina's Community and Clinical Connections Branch shows how prevention works best when local partners are supported to change the conditions that shape overall health—not just by encouraging individual behavior change, but by making healthier choices easier to access and sustain. The Branch addresses upstream factors linked to cancer prevention, including healthy eating, tobacco-free living, active living, diabetes prevention, cardiovascular health, and stroke prevention. It funds local partners, convenes them around shared priorities, changes the settings where people live and receive care, and tracks performance so impactful strategies can be strengthened or scaled.

Opportunities to build on North Carolina's success in cancer prevention include:

- Strengthening local implementation and workforce
- Improving data-sharing across programs
- Garnering multisector investment in health
- Building on shared risk and protective factors

- Elevating and engaging trusted community champions
- Enhancing performance management and accountability systems

Presenter Responses to Panel Member Questions

- While North Carolina's tobacco branch was eliminated in 2025 due to cuts in federal funding, the strong partnerships and mechanisms built by the tobacco branch have enabled the state to sustain its cancer prevention work. Relationships with non-state partners have played a key role. DPH also learns from neighboring states that receive federal funding, adapting strategies that have proven successful in other states to North Carolina's context.

FROM WILLPOWER TO WILLINGNESS: TECHNOLOGY-BASED PSYCHOLOGICAL APPROACHES TO HEALTHY BEHAVIOR CHANGE

Jonathan Bricker, PhD, *Endowed Chair in Cancer Prevention and Professor of Public Health Sciences, Fred Hutch Cancer Center; Affiliate Professor of Psychiatry and Behavioral Sciences, University of Washington*

Dr. Bricker's Health and Behavioral Innovations in Technology (HABIT) Lab develops behavior change interventions to prevent cancer with a focus on tobacco use, excess calorie consumption, and physical inactivity. Risk education is not enough to achieve widespread behavior change because many people struggle to change habits that offer short-term relief from discomfort or stress. HABIT has developed free apps based on Acceptance and Commitment Therapy (ACT) to address the prevention translation gap—the challenge of translating risk knowledge into realistic and sustainable action.

ACT helps people notice and cope with difficult internal experiences and work toward behavior change guided by their values. HABIT uses an adaptive model of ACT called the willingness model. In contrast to willpower, which aims to suppress urges, the willingness model teaches people to notice urges, make room for discomfort, reconnect with their values, and take actions that support their health.

HABIT developed a tobacco cessation app called iCanQuit based on the willingness model. iCanQuit is a gamified program where participants set a quit date and earn rewards as they learn ACT skills. iCanQuit is the only app that is listed on NCI's Evidence-Based Cancer Control Programs database as an efficacious digital tool for smoking cessation.

iCanQuit was tested in a randomized clinical trial of 2,415 adults across all 50 states. The trial compared iCanQuit with NCI's QuitGuide, which follows the U.S. clinical practice model. Twelve months after the conclusion of the trial, 28% of iCanQuit participants had quit smoking, compared to 21% of QuitGuide participants. iCanQuit saw higher quit rates among groups with high burdens of tobacco use, including American Indian and Alaska Native participants (30%) and Hispanic participants (34%). Following the iCanQuit trial, HABIT worked with cultural advisory boards to create tailored versions of the app for American Indian and Alaska Native adults (IndigeQuit) and Hispanic adults (DecideACT). An ongoing clinical trial is assessing the efficacy of combining DecideACT with nicotine replacement therapy medication.

HABIT also developed Quit2Heal, the first known digital intervention for smoking cessation among cancer patients. Quit2Heal addresses barriers that may prevent cancer patients from seeking help to quit smoking, like shame, stigma, self-blame, anxiety, and depression. In a recent NCI-funded Phase III

clinical trial of 424 U.S. adults, 28% of Quit2Heal participants reported that they had quit smoking six months post-trial compared to 20% of QuitGuide participants.

Building on the success of these apps, HABIT developed QuitBot, an app featuring an AI chatbot. The bot, named "Ellen," offers ACT-based guidance to help users with common challenges like coping with urges, choosing medications, or getting back on track. HABIT also worked with a community advisory board to develop NAITIVE, a chatbot-based smoking cessation app for American Indian and Alaska Native adults.

In a clinical trial called the Weight Loss, Nutrition, and Exercise Study (WeLNES), HABIT tested a yearlong, phone-based weight loss coaching program modeled on ACT. The program has been compared to the National Diabetes Prevention Program. Twenty-eight percent of trial participants lost 10% or more of their body weight, while only 21% of participants who received standard behavior therapy achieved the same goal. WeLNES demonstrated strong results among men, who are less likely to enroll in weight loss programs, and Black adults, who have the highest burden of obesity among all racial and ethnic groups in the United States. While WeLNES does not incorporate weight loss medication, this behavior intervention model could help to address the challenge of GLP-1 discontinuation. Additionally, combining pharmacotherapy with behavioral intervention may lead to higher adherence and long-term improvements in weight loss.

HABIT's apps are available free of cost and are downloaded about 25,000 times per month, resulting in a cost to HABIT of $0.11 per download. To expand reach, the apps could be promoted on app stores, quitlines, and government websites like smokefree.gov. By contrast, interventions that require FDA approval or prescriptions create barriers to access, potentially exacerbating inequities.

Dr. Bricker's presentation concluded with 4 key recommendations:

- Move beyond risk communication toward scalable behavior change support.
- Invest in digital interventions for tobacco cessation and obesity-related behaviors, including diet and physical activity.
- Fund public health dissemination models for low-risk behavioral prevention tools.
- Evaluate dissemination success by looking at reach, engagement, effectiveness, cost, equity, and sustained outcomes.

Presenter Responses to Panel Member Questions

- iCanQuit's quit rates (i.e., the number of clinical trial participants who quit smoking using the app) are similar to or better than those achieved by telephone-based quitlines, group-based interventions, and individual-level interventions. Tailoring tools like iCanQuit to specific populations and expanding dissemination efforts can help to improve success rates.
- People typically make multiple attempts to quit smoking before they are successful. Aiming for a 100% quit rate is unrealistic, but the strategies discussed in this session can meaningfully improve quit rates over time.

OPPORTUNITIES TO IMPROVE THE U.S. DIET THROUGH POLICY AND REGULATION

Christina Roberto, PhD, *Mitchell J. Blutt and Margo Krody Blutt Presidential Professor of Health Policy, Perelman School of Medicine, University of Pennsylvania; Founding Director, Center for Food and Nutrition Policy, University of Pennsylvania*

Most Americans' eating patterns do not align with the current Dietary Guidelines for Americans. The U.S. food industry has engineered the U.S. food supply to be highly addictive, with toxic levels of added sugars, salt, and saturated fat. Ultraprocessed junk foods with a highly palatable taste and mouthfeel, attractive colors, and added flavors are cheap and widely available. Additionally, the food industry uses manipulative tactics to influence Americans' purchasing decisions, like placing candy in checkout lanes and crafting packaging copy to frame unhealthy foods as healthy choices. Poor diet quality has contributed to rising obesity rates; as of June 2026, approximately 70% of Americans are overweight or have obesity.

Policies and regulations are needed to restrict access to and promotion of unhealthy foods and support intake of healthy foods. Strategies that worked to reduce tobacco use provide a road map that can be adapted to make our food environment and supply safer. These strategies include:

- **Taxation:** Taxes on sodas and other sweetened drinks and on ultraprocessed junk foods could help reduce consumption of these products. The tax revenue could be leveraged to subsidize the cost of healthy foods. After Philadelphia passed a tax on sugar-sweetened and artificially sweetened drinks, sales declined by 50% percent, and the reduction in sales has been sustained over time. The city leveraged revenue from this tax to subsidize access to high-quality prekindergarten in under-resourced neighborhoods. Dr. Roberto and her team conducted one of the largest studies to date on soda taxes and their impact on consumption habits. The study found that soda taxes were associated with a reduction in soda consumption, amounting to approximately 0.81 soda servings per week in the general population and 1.2 servings per week among people with obesity. Other studies have found associations between soda taxes and a 1 to 2 percentage point decrease in obesity prevalence.
- **Warning labels:** Nutrition labels on food packaging could promote healthier purchasing decisions. Chile implemented stop sign-shaped food labels to identify foods that are high in sodium, saturated fat, and calories. These labels made it easier for Chile to implement other nutritional policies, including policies on school nutrition and marketing tactics on food packaging. These policy changes were linked to a 14% reduction in calorie consumption, along with reductions in sodium and sugar consumption. Dr. Roberto and her team conducted a study of 961 parents and caregivers of young children to investigate how nutrition labels shape parental purchasing decisions. An image-based label highlighting sugar content (the number of grams of sugar in a drink) was associated with fewer sugary drink decisions. The image-based label was more effective than a text-based label and equally as effective as a label featuring a graphic image of tooth decay.
- **SNAP Food Restriction Waivers:** Expanding the implementation of SNAP Food Restriction Waivers could help reduce soda consumption. As of June 2026, more than 20 states had applied to the U.S. Department of Agriculture (USDA) for the waivers, which stipulate that SNAP benefits cannot be used to purchase soda. Increasing SNAP funding and subsidizing minimally processed foods through SNAP could help improve diet quality. People who receive SNAP benefits are more likely to live longer and have lower rates of obesity and metabolic syndrome.

However, Dr. Roberto argued that the federal government effectively subsidizes the soda industry as many Americans use SNAP benefits to purchase soda.

- **Hospital and school food:** Improving the quality of food served in hospitals and schools in alignment with a Food Is Medicine approach could be a meaningful step toward better nutrition for U.S. children and adults. Enhancing school food quality provides an opportunity to improve the nutritional intake of most children living in the United States. The Dietary Guidelines for Americans recommend that schools serve minimally processed foods. However, schools need infrastructure investment to meaningfully implement this recommendation. An evaluation by Erica Kenney of the Healthy, Hunger-Free Kids Act indicates that limiting calories, sodium, and sugars in school food is associated with reduced obesity among low-income children.
- **Sodium limits:** Implementing mandatory sodium limits could lower the amount of sodium in the U.S. food supply. Twenty-one countries have set mandatory sodium limits, and the United Kingdom (UK) implemented voluntary sodium targets. A UK case study showed associations between sodium reduction and reductions in blood pressure and deaths from cardiovascular disease. However, when enforcement of the voluntary targets relaxed over time, blood pressure and cardiovascular disease deaths increased again. While the FDA is currently reviewing a proposal for voluntary sodium targets, mandatory sodium limits are more likely to produce meaningful changes in consumption. Consumers' taste buds adapt when they adopt a lower-sodium diet, making sodium reduction a manageable change for many consumers.
- **Countermarketing campaigns:** Countermarketing campaigns could be developed to highlight deceptive food industry tactics in the vein of The Truth campaign, which illustrates deceptive and manipulative tactics used in the tobacco industry. Dr. Roberto and her team conducted a study to explore whether countermarketing tactics influenced parents' drink purchasing choices. About 1,600 Hispanic parents viewed a variety of Facebook ads related to drink products, including ads with countermarketing messages. Parents who saw the countermarketing messages were less likely to buy sugary drinks for their kids.

The public has an appetite for change in nutrition policy. This creates a window of opportunity to advance cancer prevention by improving the dietary intake of U.S. children and adults.

Presenter Responses to Panel Member Questions

- Improving the nutritional quality of school lunches should be a top policy priority.
- In general, policies focused on ultraprocessed foods more broadly are preferable to those focused on individual nutrients. Sodium is an exception to this rule—there is a clear path to implementation because other countries have successfully implemented sodium limits, and reducing sodium throughout the food supply would help relieve the burden on individuals to make healthy food choices. There may also be opportunities to restrict the amount of added sugar in the food supply, although this is challenging from a food science perspective. There are no clear policy solutions to limit saturated fat in foods.
- Dr. Roberto and her colleagues recently published a paper in *Nature Medicine* on the topic of defining ultraprocessed food for policy. Their recommendation is not to define or list ultraprocessed foods because food companies would likely attempt to circumvent policies based on a definition or list. For example, if one type of food dye is included in a list of restricted ingredients, food companies could simply switch to a different type of dye that is not listed. To avoid this issue, Dr. Roberto and colleagues recommend identifying acceptable "real foods." For

example, a policy could name "real food" ingredients allowed for use in yogurt. If a food company were to add other ingredients, their product would not be classified as yogurt.

- Dr. Risch noted that food companies calibrated the sodium content of their products based on consumer preferences from 40 years ago, when more U.S. consumers smoked cigarettes. As tobacco use has declined, Dr. Risch theorized that lower-sodium foods may be just as palatable to today's consumers.
- Philadelphia's lawmakers included artificially sweetened drinks alongside sugar-sweetened drinks to ensure the tax would not be regressive, as wealthier people are more likely to purchase artificially sweetened drinks. The tax does not apply to 100% juice drinks. The link between obesity and 100% juice is not strong and consistent in existing research; as a result, 100% juice drinks have not been included in many tax policies.

REDUCING EDC EXPOSURES, ADVANCING HEALTH: POLICY AND MARKET-FACING APPROACHES

Jennifer McPartland, PhD, *Director, Safer Chemicals Project, The Pew Charitable Trusts*

The Pew Charitable Trust Safer Chemicals Project aims to protect public health by reducing Americans' exposures to EDCs. Decades of research have linked EDCs to obesity, reproductive and neurodevelopmental disorders, heart disease, and other adverse health outcomes. Several EDCs are associated with increased cancer risk, including hormone-related cancers like prostate, breast, and ovarian cancer.

EDC exposure during sensitive windows of development like pregnancy, early life, and puberty influences cancer risk later in life. Due to this latency, a mechanistic understanding of toxicity is key to identifying potentially harmful chemicals and early warning signs. IARC uses key characteristics of carcinogens to inform their cancer classifications, and other researchers have developed a framework of key characteristics of endocrine-disrupting substances. Overlapping mechanisms are at play in both frameworks, including the eighth key characteristic in the carcinogens framework, which focuses on receptor-mediated effects.

A recent study published by the Silent Spring Institute identified more than 600 substances as potentially relevant to breast cancer due to their ability to either alter the production of estrogens and progesterone or act similarly to these hormones on receptors.

Barriers to addressing EDC exposure include:

- **Nonlinear dose response curves:** Traditional regulatory frameworks for assessing chemical hazard and risk can miss concerns presented by EDCs because conventional assumptions of linearity in dose response do not apply to all EDCs. In 2014, the National Academies launched a committee to evaluate nonmonotonic dose response relationships between chemical exposures and health effects. The committee identified that certain EDCs have nonlinear dose response curves. For example, BPA presents a U-shaped curve. At low environmentally relevant doses, BPA exposure alters tissue and mammary gland development. However, this effect disappears at mid-range doses, and higher doses have different toxic effects.
- **Regrettable substitution:** Historical phthalate biomonitoring data from CDC's National Exposure Survey shows that regulation of one phthalate effectively led to decreased exposure in the American population over time. However, this decrease coincided with rising exposure to another phthalate that presents similar health concerns. Similarly, as BPA use has been reduced,

use of other bisphenols like bisphenol S and bisphenol F has increased. This phenomenon has led many experts to emphasize the importance of class-based approaches to chemicals management to avoid regrettable substitution.

Recent Pew polling data show broad public support for action by both government and industry to address harmful chemicals. A survey of 1,300 Americans found that broad bipartisan majorities were concerned about exposures to harmful chemicals in food, drinking water, baby products, and through other pathways.

There are a variety of policy interventions in place across federal, state, and local governments to reduce exposure to EDCs. These interventions include:

- **Bans:** North Carolina and California have banned the use of di(2-ethylhexyl) phthalate (DEHP) in medical IV bags.
- **Reporting requirements:** Under the National Defense Authorization Act (2020), EPA requires manufacturers to electronically report information regarding PFAS exposure, production volumes, disposal, and available information regarding hazards.
- **Phase-out and labeling requirements**: New Mexico's PFAS Protection Act (2025) phases out the intentional addition of PFAS in a variety of consumer products and implements labeling requirements for products that contain PFAS.
- **Catalyst programs:** The New York State Green Procurement Program sets standards around the composition of products that can be used by state agencies, focusing on cleaning products.

In the private sector, retailers have implemented policies to reduce EDCs in their products. These policies typically establish hazardous substances targets and goals such as obtaining EPA's Safer Choice certification. They also set standards around transparency—the retailer needs to know what is in the products it is selling and disclose that information to the consumer. Additionally, lessons learned from investor-led climate change initiatives may guide investors in developing similar initiatives to reduce EDC exposure.

Opportunities for improvement span science, policy, and the private sector:

- **Science:** Continue to support and advance scientific research to better understand the health effects of EDCs. Ensure regulatory agencies are adequately resourced to conduct independent science and fulfill their statutory obligations to the public. Translate research into actionable guidance and interventions that can be meaningfully used to protect public health.
- **Policy:** Follow a class-based approach to implement restrictions and bans while minimizing regrettable substitution. Incorporate transparency and reporting requirements into policies related to EDCs.
- **Private sector:** Explicitly address endocrine disruption in product decision-making. Prioritize safer design during chemical research and product development and strengthen transparency across the supply chain, from the retailer to the consumer.

CLOSING DISCUSSION

General/Overarching

- Many of the ideas suggested are ambitious, but the President's Cancer Panel is in a good position to issue ambitious recommendations. Some of these ideas may take many years or decades to

accomplish, but it is important to start working in the right direction. Tobacco-related efforts that started more than 50 years ago led to public health interventions, but it took time.

GLP-1 Medications

- Subsidizing GLP-1 medications would be a practical way to address obesity in the United States. It would likely be more feasible to do this than to roll out AI tools for tobacco cessation or implement policies to reduce consumption of unhealthy foods. Pharmaceutical companies would be interested in this idea if it meant that many people would use their products.
- If GLP-1 subsidies are implemented, there should be conditions established to make sure that people are not on the drugs indefinitely. A system should be set up to help people transition to more sustainable solutions.
- GLP-1 medications should be tested in cancer prevention trials. NCI may need to fund these trials since pharmaceutical companies are unlikely to do so. The trials could look at intermediate outcomes (e.g., methylation markers).

Research Funding and Priorities

- More funding is needed for cancer prevention research. Only a small proportion of cancer research funding is focused on prevention. Large companies generally do not invest in prevention research, and there are fewer patient advocates in this area.
- NIEHS accounts for about 2% of the NIH budget and is almost exclusively focused on prevention.
- The private sector is investing in blood-based cancer screening and multicancer early detection tests.
- Pan-cancer research, particularly on early-onset cancers, could yield helpful insights. One similarity across many cancers is the potential role of EDCs. The absolute increase in cancer risk for women should be considered in light of recent changes in exogenous hormone use by young women and adolescent girls. Hormone formulations and prescription patterns have changed. Many young women are being treated for conditions such as fibroids or debilitating periods. Research is needed on how these treatments impact cancer risk. Hormonal contraception has been previously shown to reduce ovarian cancer risk.
- Research is needed on the impact of EDCs on second cancers, including among people who are receiving long-term endocrine therapies after treatment for their initial cancer.

Standards of Success for Prevention Studies

- Many in the research community are skeptical about prevention efforts, in part because designing prevention studies that meet the gold standard used for other types of interventions is very challenging. The research community should recalibrate expectations about the level of evidence needed to implement actionable interventions in the near term. Prevention interventions have potential to have a large population-level impact.
- In 2016, the USPSTF recommended aspirin for prevention of colorectal cancer and cardiovascular disease; however, this recommendation was reversed in 2023 based on evidence that aspirin was potentially harmful in older adults. This illustrates the high bar for prevention interventions—the recommendation was reversed for all age groups based on evidence in one age

group. Although there are no Phase 3 or 4 clinical trials on aspirin for cancer prevention, many people at low risk for harm by its use would likely benefit from using this low-cost drug.

- Prevention requires acting with some uncertainty. Interventions should be developed and implemented based on the best available science; impact at the public level should be measured, and the approach should be iteratively improved.

Tobacco

- The U.S. federal tax for a pack of cigarettes is only $1. Experience has shown that increasing taxes on tobacco increases quit attempts. Pairing a tax increase with proven cessation interventions could build on the progress made since 1964 and significantly reduce the smoking rate. Tobacco industry lobbyists would pressure politicians not to increase taxes, but the denormalization of tobacco use is likely to increase support among politicians for antitobacco measures. Many states have successfully increased tobacco taxes, which shows it is possible.
- Most tobacco control and weight loss interventions—including those developed with NCI funds—are reported in journal articles but never reach the public. Most prevention interventions are not self-sustaining. Current grant mechanisms primarily fund intervention development and efficacy testing. Dissemination studies are sometimes funded, but these grants are of limited duration. This system rewards knowledge generation rather than public impact. A long-term mechanism for government support could help sustain prevention interventions and benefit the public. At $24 per cancer averted, the digital tools developed by the HABIT Lab would be cost effective for the government and would cost significantly less than subsidizing GLP-1 medications.
- About 27 million people in the United States currently smoke. Helping these people quit using tobacco will be crucial to reducing cancer risk of the U.S. population in the coming decades.

Obesity and Diet

- Evidence is still emerging about the extent to which obesity increases cancer risk; however, even if the increase is modest, the absolute impact of obesity on the cancer burden will be high given that 126 million people in the United States are expected to be living with obesity by 2035. Regulation of food production, marketing, and consumption should be explored to address this. At the same time, the United States must ensure that people have access to healthy, affordable foods.
- Diet, food packaging, and food preparation methods can affect cancer risk. Addressing these issues in school-based programs could help reduce cancer risk among young people.
- School lunch program requirements should align with dietary recommendations to reduce cancer risk, including risk of early-onset colorectal cancer. The new Dietary Guidelines for Americans could serve as a blueprint. This is an opportunity to shift school food. The WCRF and AICR could help with these efforts. It will be important to ensure that schools have access to enough money to bring lunches into alignment with the Dietary Guidelines for Americans.
- Obesity may pose national security risks as well as public health risks. It would be interesting to look at trends in fitness levels and military readiness alongside U.S. trends in obesity.
- Regulations that prevent use of SNAP and WIC funds to purchase things like soda and sugary cereals should be implemented. This could help improve the diets of program recipients and

reduce the flow of money to companies that sell foods with high levels of added sugar. Regulation would be more effective than advising recipients on what they should eat.

- Many foods, even those that would not be considered ultraprocessed, contain oils with inflammatory properties (e.g., palm oil). Changing the oils used in foods could help reduce risks associated with inflammation.
- Regulation could encourage companies to offer less-processed foods. Defining whole foods could be an effective strategy. Whole foods can be appealing; for example, high-fat plain yogurt is tastier than lower fat varieties.
- There has been progress related to food policy. Guidance on voluntary sodium reduction targets is being developed by FDA. More than 100 countries have implemented taxes on food. Multiple U.S. states have banned food additives. California passed a law to get ultraprocessed foods out of schools. Texas passed a law that requires warning labels on foods that have certain chemical additives.
- The Panel could consider looking at vitamin D supplementation to reduce cancer mortality.

Environmental Exposures

- System-level solutions are needed, particularly for environmental exposures. Most of the challenges discussed cannot be fully addressed with individual choice. Solutions must be multipronged; these may include policy, market leadership, and scientific investment. The Panel should consider how the available tools could be used together to maximize impact.
- Pregnant women should receive education about the long-term health risks to them and their babies of exposure to toxins through food and topical products (e.g., lotions).
- Consideration should be given to engineering solutions to reduce exposure to environmental carcinogens. There is precedent for this: the PM2.5 standard was reduced from 12 $\mu g/m^3$ to 9 $\mu g/m^3$ based on strong epidemiological evidence that the former level was linked to asthma, chronic obstructive pulmonary disease, and other adverse health effects. A similar approach could be taken to nitrate levels in drinking water. Between 70 and 78 million Americans have drinking water with nitrate levels that exceed the current maximum contaminant level (MCL). The current nitrate MCL is based on risk of blue baby syndrome, not cancer. There is a growing body of epidemiologic evidence that, even when controlling for vegetable and meat consumption, levels of nitrate well below the current MCL are linked to colorectal cancer. The Safe Drinking Water Act could be modified to reduce the nitrate MCL from 10 mg/L to something closer to 3 mg/L to reduce cancer risk. This target is attainable for public drinking water systems, although some rural water districts may need financial assistance. Currently, many rural communities dilute their ground water to reach allowable nitrate levels rather than invest in technology to remove it. Lowering the MCL also would force adoption of farming best practices that would reduce levels of nitrogen from agricultural sources in groundwater (e.g., less nitrogen application, less animal waste in farm fields, less tiling of fields). Reducing nitrate levels would likely also result in lower levels of other contaminants (e.g., disinfectant byproducts).
- Research should be done to monitor changes in cancer risk following the reduction in the PM2.5 standard.
- The class of bisphenols should be banned from food packaging and bottles. It is possible to make plastic without bisphenols. BPA was banned from baby bottles in the United States in the 2000s

and has been phased out of many products since that time. European countries banned BPA before the United States. Data linking reduced BPA exposure to health outcomes are hard to come by because there was legacy use of the substance and it can take decades for the health impact to become apparent. Although there is not extensive epidemiologic evidence about other bisphenols, toxicology studies have shown that other bisphenols, such as bisphenol S and bisphenol F, have toxicity similar to BPA.

- A canonical example of the public health benefit of bans on chemicals is the removal of lead from gasoline; population-level increases in IQ were observed and an economic analysis demonstrated the overall benefit of the intervention.
- EPA recently announced the draft Sixth Contaminant Candidate List (CCL 6). This list will eventually determine what will be regulated under the Safe Drinking Water Act. CCL 6 includes 75 chemicals and 4 chemical groups, including PFAS, disinfection byproducts, and microplastics. The class-based approach to environmental policy should be encouraged.
- Rates of leukemias and lymphomas have been rising. These cancers often provide a quicker signal on exposures to environmental carcinogens given their shorter induction time.
- Dr. Thorn will share information on what was learned about environmental toxins in studies of the World Trade Center cohort. Dr. Terry will share related studies on multiple myeloma by Albert Einstein College of Medicine researchers.

Screening

- A risk-benefit analysis using up-to-date data should be done to determine whether the increased rate of colorectal cancer in younger age groups warrants lowering the recommended age for initiation of colorectal cancer screening from 45 to 40. The impact on the health care system and the importance of access to screening also should be considered. The American Cancer Society and USPSTF have recommendations for colorectal cancer screening, although USPSTF recommendations are generally used to determine insurance coverage. Both colorectal and cervical cancer screening can be viewed as prevention because such screening identifies precursor lesions.
- Screening is not a replacement for other preventive interventions. While it is appropriate to periodically reassess screening recommendations, investments also are needed in primary prevention.
- The lack of a screening test for endometrial cancer is a gap that should be addressed. There has been work on approaches (e.g., using tampons or brushes).

Early-Onset Cancers

- Early-onset cancers are a signal that something in the environment is affecting cancer risk. Data suggest that colorectal cancer rates are starting to rise in people between ages 50 and 55 as well. These cancers may be caused by one or a compendium of factors; either way, there is opportunity to think about near-term interventions to reduce risk.

Poverty

- Poverty is linked to obesity and diagnosis of aggressive cancers. For example, among Black women, those living in disadvantaged areas are more likely to be diagnosed with triple-negative breast cancer. Consideration could be given to updating breast cancer screening guidelines for populations with high rates of triple-negative breast cancer.

- Policy interventions to reduce the burden of poverty could include addressing food deserts. Putting restrictions on products that can be purchased with SNAP will not be effective unless SNAP beneficiaries have access to healthy foods. Farmers markets are one way to address food deserts. Studies in New York City have shown that farmers markets in disadvantaged areas are well utilized, often more so than those in more advantaged areas of the city. Many people in the United States are from cultures that shop for their food every day, so there is a demand for fresh food.

Implementation

- Targeted precision prevention approaches are more realistic than population-based approaches for pharmacologic interventions. It will be important to identify people who are at high risk for cancer and thus most likely to benefit from cancer prevention drugs. These targeted approaches would be complemented by population-wide strategies such as policy changes.
- Precision prevention approaches must be implementable in real-world settings. Primary care and general medicine doctors have only 5 to10 minutes with each patient, so there must be clear guidelines about how to identify high-risk patients and how to determine the best interventions for them.
- Consideration must be given to how recommendations will be operationalized, for example, through state health departments or in clinical settings. Who will be implementing these policies? How will enforcement be done? What can be done to ensure things are done equitably?
- There should be discussion about the level of evidence needed for prevention studies. It is frustrating that prevention studies often are expected to show reduction in mortality, while approval of drugs like GLP-1s often does not require demonstration of impact on mortality. Shifts in disease stage at diagnosis could be an alternative endpoint. Surrogate biomarkers for incident cancer also are needed. Perhaps polyps and breast density could be used as proxies for colorectal and breast cancer, respectively, in the same way that statin studies have used low-density lipoprotein as a proxy for cardiovascular disease.
- Many risk factors for cancer also affect risk of other chronic diseases. State departments of health should receive support—including federal support—for integrated chronic disease prevention programs.
- The cancer community should be intentional about organizing around shared risk and protective factors, particularly when developing state-level programs.

Biomarkers

- Development of biomarkers for risk will facilitate quantitative studies on cancer prevention. These could be blood, stool, or behavioral biomarkers. The Panel could recommend that NIH invest in research to develop biomarkers.
- The Gail Model quantifies breast cancer risk based on reproductive factors. Resource limitations have prevented development of similar models for EDC exposures. The wristbands that monitor chemical exposure cost about $1,000 each; work is needed to innovate that technology.
- Decades of work have led to identification of biomarkers for both exposure and effect. The exposomics work illustrates progress on biomarkers of exposure. In some cases, biomarkers are reactive intermediates. Biomarkers of effect include things like A1C or biomarkers of kidney disease, heart attack, or stroke. For cancer, it is possible to look at DNA adduct formation and

cytokine levels for inflammation. The challenge is that many biomarkers (e.g., inflammation) are shared among diseases. It would be helpful to have more specific biomarkers. Investments in high-throughput methods could help accomplish this.

- DNA repair capacity is a good biomarker for susceptibility to multiple cancer types.
- Many biomarkers are currently expensive to measure, but the costs will come down as they did for genomic analyses.
- There are several biomarkers, but the challenge is to determine how to use them and demonstrate their clinical utility.
- Biomarkers may be helpful for determining who would benefit most from earlier screening.
- It would be helpful to have a clinical marker for inflammation and the ability to link levels of the inflammation marker to cancer risk. Doctors could counsel their patients about how to lower their inflammation levels through diet, and the results could be measured within a few months. Patients may be more responsive to this type of goal setting than they are to general recommendations to lose weight.

PUBLIC COMMENTS

The Panel opened the floor to comments from members of the public.

- The food industry has engineered food to be addictive, with ingredients that trigger dopamine in the brain, contributing to increased early-onset colorectal and endometrial cancer. Policy could be implemented to limit the percentages of sugar, fat, and salt in food to help mitigate rising obesity.

CLOSING REMARKS

Dr. Risch thanked the presenters and all participants for their input and expertise. The Panel will continue to solicit input and engage with the cancer community on this subject. Additional written testimony and comments can be submitted at any time to the President's Cancer Panel via email (PresCancerPanel@mail.nih.gov) or the Panel website (https://prescancerpanel.cancer.gov).

CERTIFICATION OF MEETING SUMMARY

I certify that this summary of the President's Cancer Panel meeting, Modifiable Risk Factors for Cancer: Opportunities for Prevention, held on June 8–9, 2026, is accurate and complete.

Certified by: _____ Date: August 21, 2026

Harvey Risch, MD, PhD
Chair
President's Cancer Panel