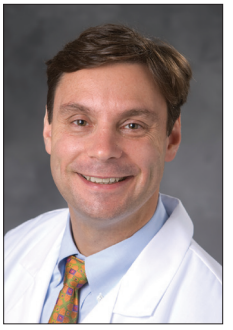
The Cancer in Your County



Cancer in individuals is largely a random occurrence. Sure, some people have a strong family history of cancer or harbor a germline mutation in DNA repair or a critical tumor suppressor gene, but people are usually surprised when they receive a cancer diagnosis. Adding to the randomness is the equal opportunity nature of cancer, which occurs in people of all races and ethnicities and across the spectrum of wealth, education, age, and gender. And yet, cancer death rates differ widely depending on where people live in the United States.

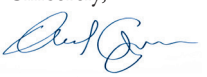
One of the more fascinating research articles I have read in recent years is a 2017 epidemiologic report by Mokdad and colleagues in *JAMA* describing the trends and patterns of disparities in cancer mortality in the United States, by county. It was a herculean effort, in which the authors used 35 years of de-identified death records from the National Center for Health Statistics and population counts from the Census Bureau to estimate county level mortality rates for 29 cancers. What emerge from this work are distinct patterns of cancer mortality, with the highest rates through much of Appalachia, down the Mississippi River to the Mississippi Delta, and across much of the southeastern United States. Maybe this pattern is not so surprising, given that these areas include some of the most economically impoverished counties in the country, with reduced access to healthcare, education, and nutritional resources and high levels of environmental pollutants. But a deeper dive into specific cancer types and cancer mortality reveals a very different picture.

Examination of the patterns of age-adjusted prostate cancer mortality, for instance, reveals peaks across the southeastern United States that extend to the Mississippi River and Mississippi Delta. However, unlike on our overall cancer mortality map, the rates of death from prostate cancer in West Virginia, southern Ohio, and Kentucky are low. Differences in racial representations in these populations may partially explain the discrepancy between prostate cancer mortality and overall cancer mortality. The differences in patterns are even more stark when we look at kidney cancer; the highest mortality rates are seen in certain counties in North and South Dakota, Texas, Oklahoma, Louisiana, West Virginia, Ohio, Indiana, and Alaska, whereas relatively few pockets of high kidney cancer mortality rates are seen in the southeastern United States. It is possible that more fossil fuels are being mined or pumped from the ground in these high-risk counties, and the data certainly raise a concern for environmental risk factors for kidney cancer beyond smoking. But what about other smoking-related cancers? Interestingly, when we look at the mortality patterns for bladder and lung cancer, two other smoking-related cancers, the patterns are quite different.

The highest rates of lung cancer mortality are clustered in Appalachia, whereas the mortality rates for bladder cancer peak across historically industrial states—from Michigan, Ohio, northern Pennsylvania, and New York to New England. How can the same inhaled carcinogens result in very different patterns of mortality rates for two smoking-related cancers? To shed light on this dilemma, we can look to a recent study by Hill and colleagues from Charles Swanton's group, published in *Nature* in 2023.

For decades, the prevailing dogma of carcinogenesis has been that cancer is a multistep process that begins when normal cells acquire genetic alterations and is promoted by subsequent mutations, ultimately culminating in cancer. Over a lifetime, we are exposed to multiple carcinogens in our environment, including the air we breathe, the water we drink, the foods we ingest, and the sun under which we live, all of which can damage DNA and lead to cancer. However, additional mutations do not develop in all patients with these exposures, so what else could these carcinogens be doing if not directly causing mutations? Through a combination of epidemiologic data and mouse models, Hill and colleagues demonstrated that environmental particulate matter can cause macrophage infiltration into the lung and the release of interleukin-1β, promoting carcinogenesis in *EGFR*- and *KRAS*-mutant cells independently of additional mutational alterations. Perhaps some tissues (eg, lung tissue) are more prone to cancer formation in the presence of inflammatory stimuli, whereas others (eg, bladder tissue) require secondary mutations. Perhaps the type of carcinogen matters (tobacco vs industrial pollutants). More questions remain, but one thing is clear: cancer risks are local.

Sincerely,



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