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RESEARCHING THE ENVIRONMENT AND WOMEN'S HEALTH

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Cancer is More Than Bad Luck

Our perspective on the Tomasetti and Vogelstein article "Variation in cancer risk among tissues can be explained by the number of stem cell divisions," published in Science, January 2, 2015

This new study by researchers at Johns Hopkins University tries to explain the differences in cancer rates in different organs in the body. It shows that cancer rates in different organs are correlated with the rate of mutations that are expected based on the number of stem cell divisions in each organ. Breast and prostate cancers were not included because scientists don't have as much information about stem cells in those tissues.

Many scientists have been troubled by the interpretation that this study shows that two-thirds of cancers are due to "bad luck" – unavoidable, random mutations. This idea that two-thirds of cancers are due to bad luck, and therefore not preventable, is not supported by the study for various reasons.

We're glad the study authors posted a clarification about this point. They use an analogy to car accidents: The chance of an accident increases with more miles travelled, and, similarly, the risk of cancer increases with more stem cell divisions. There are many risks along the way, including some that we can control and some we can't. The authors write about the length of the trip (stem cell division and chance mutations), mechanical condition of the car (inherited genetics) and driving conditions (environmental exposures). We would add that drivers can influence their environment by advocating for many types of protections, such as road repairs, guardrails, and traffic signals to create better driving conditions for everyone. Dr. Ted Schettler offers a helpful summary of the study and its interpretation. We add our perspective here.

To begin with, we want to underline that the study is about the variation in cancer risk in different organs in the body – why is there more colon cancer than cancer of the small intestine? And the proportion of variation across organs that is associated with stem cell division is not the same as the proportion of overall cancer risk that is due to bad luck. Consider this example: If we had a population where everyone got cancer because they were all exposed to high radiation, we would still expect to see more cancers in some organs than in others, correlated with stem cell division rates. Yet this variation across organs wouldn't tell you what was causing all those cancers in the first place.

It's troubling to estimate bad luck from a worst case. The U.S. today has among the highest cancer rates in the world. (Is that very bad luck?) The study considers the risk of getting cancer per stem cell division for people in the U.S. now, but that ratio is not immutable and is different for different populations. The relationship between the number of cell divisions and the chance of getting cancer is influenced by environmental, lifestyle, and genetic factors. The authors show extra risk associated with certain rare genetic factors, infectious agents and smoking. Many other factors that weren't included also influence risk. Extra risks are also known to exist for people exposed to carcinogens – for example, asbestos, radon, and air pollution – and for factors such as alcohol consumption, obesity, and physical inactivity.

Also, the proportion of variation explained may not be as strong as the authors suggest. Dr. Lumley, a statistician writing on StatChat, thinks the statistical method gave too much weight to rare cancers. Using the same data, Dr. Lumley calculated "bad luck" estimates as low as 10%.

In addition to the role of stem cell division and mutation, it's also important to think about how the body repairs errors and eliminates rogue cells and what makes tumors grow and metastasize. We know that in addition to agents that cause direct DNA damage, chemical exposures can also influence tissue structure, tumor growth, and tissue susceptibility to cancer later in life. Various factors can influence the number and division of stem cells. All of these processes offer opportunities for prevention. Cancer is so common that preventing as many cases as we can will affect the lives of many families.

The authors of the study have been talking in the news media about the idea that people don't want to have to think about what caused their cancer. That's not what we hear from women diagnosed with breast cancer. Silent Spring Institute was founded by women who do want to know how to protect our daughters and women everywhere. In *The New York Times,* Dr. Vogelstein talks about wanting to reassure parents that their child's leukemia was bad luck. But common pollutants, including benzene, butadiene, and formaldehyde, *do* cause leukemia, and public policies can reduce exposure if people have the information to take action. We agree it's important to emphasize that cancer isn't something you can entirely control, but we think it's more helpful to provide information and support rather than false reassurance.

The idea that this study implies that early detection should be the focus for many types of cancer is troubling in light of the bad experiences with early detection for prostate and breast cancers. We are learning that some tumors don't grow enough to cause problems in a lifetime and some even regress, so early detection has resulted in over-treatment with large consequences for quality of life.

We hope this study doesn't diminish the investment in cancer prevention, which has enormous potential to save lives. The study authors conclude (from Figure 2) that prevention won't be very effective for many types of cancer, but some cancers they consider mostly due to "bad luck" (on the left side of the graph) are known to have environmental causes that we can change. The study's ability to identify cancers as preventable depended on having data for cancer rates in subpopulations with elevated risk (for example, smokers). There are many other subpopulations with preventable risks, too, and there's much more to learn.

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