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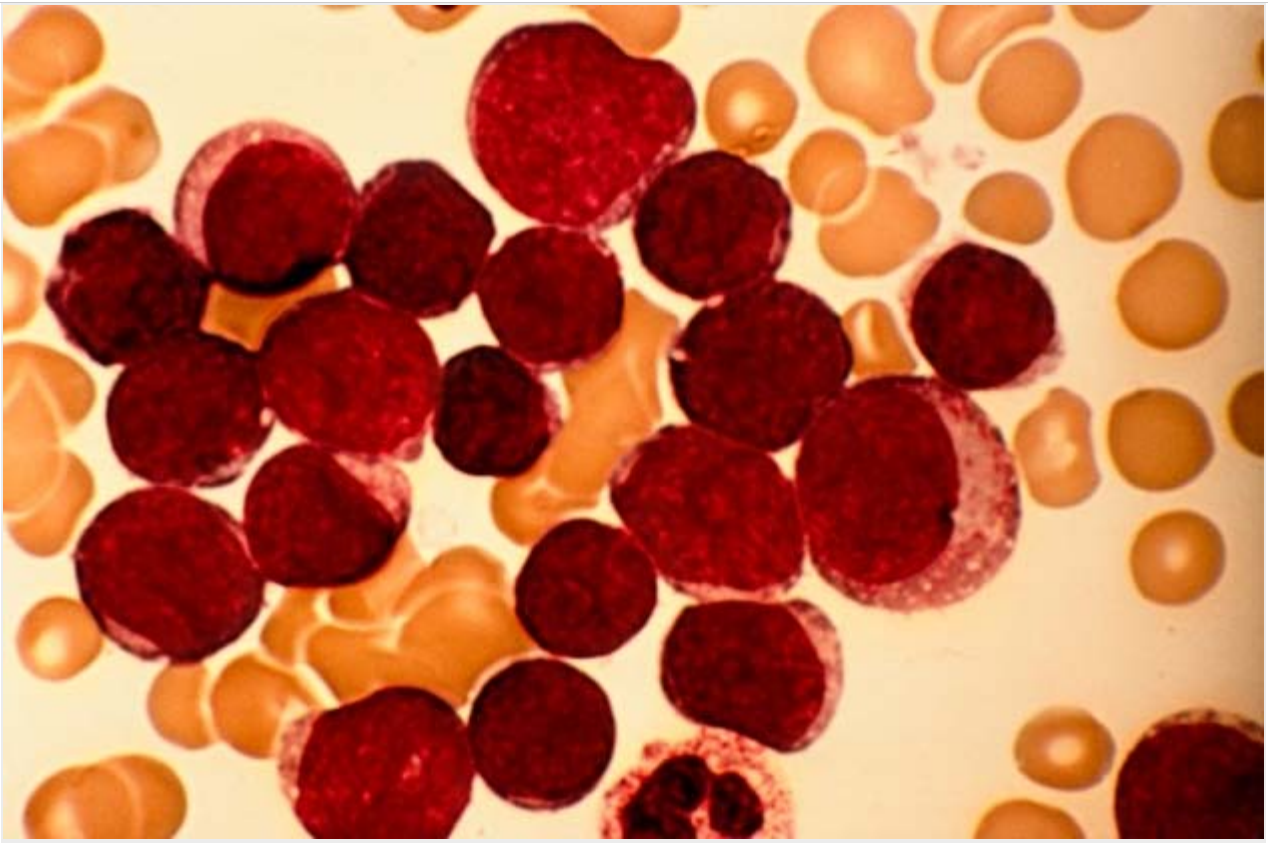
Cancer studies clash over mechanisms of malignancy

Debate surrounds relative importance of environmental and intrinsic factors.

Heidi Ledford

16 December 2015



J. Bernard/CNRI/SPL

The proliferation of blood cells in leukaemia is just one example of unchecked tissue growth associated with cancer — but the extent to which external and internal factors drive this process is open to debate.

Most cases of cancer result from avoidable factors such as toxic chemicals and radiation, contends a study published online in *Nature* on 16 December (S. Wu *et al. Nature* http://dx.doi.org/10.1038/nature16166; 2015). The paper attempts to rebut an argument that arose early this year, when a report in *Science* concluded that differences in inherent cellular processes are the chief reason that some tissues become cancerous more frequently than others (C. Tomasetti and B. Vogelstein *Science* 347, 78–81; 2015).

The work led to assertions that certain forms of cancer are mainly the result of “bad luck”, and suggested that these types would be relatively resistant to prevention efforts. “There’s no question what’s at stake here,” says John Potter of the Fred Hutchinson Cancer Research Center in Seattle, Washington, who studies causes of cancer. “This informs whether or not we expend energy on prevention.”

In their *Science* paper, mathematician Cristian Tomasetti and cancer researcher Bert Vogelstein at Johns Hopkins University in Baltimore, Maryland, calculated the relationship between the number of stem-cell divisions and the risk of developing cancer in various tissues. Every instance of cell division comes with a risk that DNA will be incorrectly copied, leading to mutations — some of which could contribute to cancer. The duo’s analysis found a correlation: the more stem-cell divisions that occur in a given tissue over a lifetime, the more likely it is to become cancerous.

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Tomasetti and Vogelstein then sorted types of cancer according to how much of the variability in risk is due to stem-cell divisions versus to some 'extrinsic' factor, such as environmental exposure to carcinogens. The authors argued that although some cancers clearly had strong environmental links — such as liver cancers caused by hepatitis C infection or lung cancer resulting from smoking — there were others for which the variation was explained mainly by defects in stem-cell division. In those cases, they argued, early detection and treatment would be more effective than prevention.

Something about that did not sit right with Yusuf Hannun, a cancer researcher at Stony Brook University in New York. "What they did was interesting, but I was startled by the conclusion," he says.

The original work, Hannun and his colleagues argue, assumed that the two variables — intrinsic stem-cell division rates and extrinsic factors — were entirely independent. But what if environmental exposures affect stem-cell division rates, as radiation is known to do?

A different take

Hannun and his team also used other lines of evidence to try to pinpoint the contribution of environmental factors to cancer risk. They looked at epidemiological data showing that, for example, people who migrate from regions of lower cancer risk to those with higher risk soon develop disease at rates consistent with their new homes. The authors also examined patterns in the mutations associated with certain cancers; ultraviolet light, for example, tends to create a tell-tale signature of mutations in DNA. And they used other mathematical models, expanding the data set used in the earlier work to include prostate and breast cancer — two of the most common cancers.

> "There's no question what's at stake. This informs whether or not we expend energy on prevention."

The models suggested that mutations during cell division rarely build up to the point of producing cancer, even in tissues with relatively high rates of cell division. In almost all cases, the team found that some exposure to carcinogens or other environmental factors would be needed to trigger disease.

Tomasetti counters that he never intended to explain why cancers develop. His analysis, he says, was based on normal stem-cell division in healthy tissue and was meant to explain only why some cancers are more prevalent than others. He also argues that the models created by Hannun and his colleagues make too many assumptions and fail to incorporate some features of tumour growth.

Some specialists in cancer prevention welcome the *Nature* paper because of fears that the public — and possibly also funders of scientific research — might conclude that prevention efforts are not worthwhile, says Edward Giovannucci, who studies cancer prevention at the Harvard T. H. Chan School of Public Health in Boston, Massachusetts. "By not smoking, your lifetime risk of lung adenocarcinoma drops dramatically," he says. "The fact that your risk of pelvic sarcoma is even lower because there's less stem-cell division — so what?"

Nature 528, 317 (17 December 2015) | doi:10.1038/528317a

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Heidi writes about biology and medicine, and has a PhD from the University of California, Berkeley. Heidi has written for *The Oregonian*, edited for the *Berkeley Science Review*, and freelanced for a few other publications.

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Sydney Singer • 2015-12-18 05:18 PM

I am a medical anthropologist breast cancer researcher, and co-author of Dressed to Kill: The Link Between Breast Cancer and Bras. This vital information showing a lifestyle cause of breast cancer has been denied by the cancer industry for the past 20 years, despite numerous studies now supporting the bra-cancer link. I have personally witnessed corruption within the medical establishment to suppress and censor this information, including corruption in cancer charities, including the ACS and Komen Foundation, and government agencies like the National Cancer Institute. There is a vast media network also involved in the cover-up. With billions of dollars annually at stake in both bra sales and breast cancer detection and treatment, the truth will unfortunately be suppressed if it can harm profits. Part of the problem is that cancer treatment is so profitable,

and medical care is, above all else, a business. Meanwhile, we have numerous cultural causes of disease embedded in our way of life, with industries and jobs depending on those harmful industries. The medical system profits from the diseases caused by our lifestyle and culture, and people wrongly turn to these disease detection and treatment professionals for disease prevention information. Preventing disease, including cancer, is not in the best interests of the medical industry. People, you are on your own.

Viktor Müller • 2015-12-18 08:48 AM

The results of Tomasetti and Vogelstein apply to the variation of cancer risk between different tissues, not to variation between individuals. In terms of human health and prevention, only the latter is relevant, and confusing the two has done great harm.

Oliver Slay • 2015-12-17 04:05 PM

The authors of the paper talk about 'unavoidable intrinsic factors' it doesn't mean that ALL extrinsic factors are thus avoidable.... how do you avoid inflammation when you are injured?

Janet McMahan • 2015-12-17 02:49 PM

After my son Ben, my 2 dogs & I developed Cancer during the same time as 4 small Children who live 7 miles North of us, we found Arsenic & Lead in our deep well water. My husband is a Physician. We asked our Cancer Patients to test their water as well. They also found Arsenic &/or Lead in their water, including those who lived in the City. There needs to be much emphasis on Prevention.. especially Preventing Cancer Caused by Drinking Water. Every Home Needs a Water Filter at least for Cooking & Drinking. Every Home needs to flush Water Heaters (if they have them) monthly to remove Arsenic, Radon, Lead, etc that comes into shower through Steam. NIEHS told my husband that they have known since the 80s that there is enough Arsenic in Water here to cause Cancer Clusters but they are not allowed to warn anyone. Jane Perry at Ga Dept of Health wants to warn everyone, including Doctors, "below the gnat line" to Test Water for Arsenic, but so far she has not. Now 4 Children who live South of us in Waycross Community have been diagnosed with Sarcomas within 58 DAYS. Please Google Georgia Water Lady and Waycross Cancer Clusters for more info. http://www.georgiahealthnews.com/2014/09/water-lady-front-lines-campaign-arsenic-georgia-wells/

Silvio Pitlik • 2015-12-17 05:56 AM

We should not forget that the human microbiota stands in the interface between the environment and Homo sapiens. Consequently, it may regulate many if not all of the external carcinogenic factors.

Oliver Slay • 2015-12-17 04:04 PM

such as UV light and hepatitis B?

Nitin • 2015-12-17 05:51 AM

If a person has a fall in bathroom and dies -its called bad luck; if a person falls from three storey building and comes-out without even a scratch - is called good luck! Probably truth is in between.

William B. Grant • 2015-12-17 03:33 AM

Actually, cancer rates are not similar in different countries or states. See this paper for country comparisons for lung and stomach cancer incidence rates: Global Cancer Incidence and Mortality Rates and Trends—An Update Lindsey A. Torre,Rebecca L. Siegel,Elizabeth M. Ward, and Ahmedin Jemal Cancer Epidemiol Biomarkers Prev; Published Online First December 14, 2015; doi:10.1158/1055-9965.EPI-15-0578 http://cebp.aacrjournals.org/content/early/2015/12/10/1055-9965.EPI-15-0578.abstract This paper provides an analysis of risk-modifying factors for many types of cancer based on a multi-country analysis, finding dietary differences are very important. Armstrong B, Doll R. Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. Int J Cancer. 1975 Apr 15;15(4):617-31. And this paper does the same for U.S. states, finding that UVB doses (a source of vitamin D) and smoking are very important: Grant WB, Garland CF. The association of solar ultraviolet B (UVB) with reducing risk of cancer: multifactorial ecologic analysis of geographic variation in age-adjusted cancer mortality rates. Anticancer Res. 2006 Jul-Aug;26(4A):2687-99. http://ar.iiarjournals.org/cgi/pmidlookup?view=long&pmid=16886679 The cancer rates by state can be seen at http://ratecalc.cancer.gov/ratecalc/archivedatlas/ http://ratecalc.cancer.gov/ Thus, there is strong epidemiological evidence for the importance of environmental risk factors for cancer.

James Spivack • 2015-12-16 07:07 PM

My understanding, now admittedly some years old, is that overall cancer rates (excluding lung: clearly associated with smoking) are similar the world over. For example, in Japan and the US. While the Japanese tend toward stomach cancer the US tends toward cancer of the intestines, with overall cancer rates similar.If environmental factors are important how do we explain the same rates in different cultures? I have often wondered if the same people who get stomach cancer in Japan would have gotten intestinal (or some other) cancer in the US. Actually it would be possible to answer this question by looking at identical twins raised and living separately in two cultures. A positive result would imply that something particular to the individual predisposes toward getting some form of cancer: perhaps aspects of the immune system. This might help reveal mechanisms of cancer initiation. In the example of Japan vs US we might imagine that differing diets lead to different cancers (perhaps even in genetically identical people). Hence carcinogens might well be involved but the cancers could still be seen as also genetically caused.

Mason Lim • 2015-12-17 11:39 AM

You just slapped yourself in the face, good sir. Whatever you mentioned in fact SUPPORTS the findings of this article. Japan's increased incidence of stomach cancer and US's increased incidence of colon cancer are both supported by the fact that Japanese diet is known to be rich in raw food (sashimi) and the US diet is full of processed food. Diet is an EXTRINSIC factor.

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