LETTERS

Edited by **Jennifer Sills**

Cancer risk: Role of environment

THE REPORT "VARIATION in cancer risk among tissues can be explained by the number of stem cell divisions" (C. Tomasetti and B. Vogelstein, 2 January, p. 78) is dangerously misleading because it understates the role of prevention in cancer causation. It is widely acknowledged that many cancers can be explained by a two-step process: initiation by one or a series of mutations, followed by the promotion of the genetic "mistake" to a recognizable tumor or blood disease (*1*). The observation that replication of the mistake may proceed at different rates in different tissues is no doubt correct. However, some mutations are initiated by chemical or viral exposures, and others occur without a known cause.

Promotion of DNA damage to recognizable disease occurs in both cases. The conclusion that "stochastic effects of DNA replication can be…distinguished from external environmental factors" is an inaccurate statement that rests on a false dichotomy. An environmental influence can in fact create a DNA change which, if present when the DNA is copied, is subsequently "fixed" into the genome as a permanent change. The more replications, the less time there is for DNA repair to take place before the next copying/fixation event. Thus, the correlation between frequency of copying events and lifetime cancer risks among tissues does not imply that environmental influences play a lesser role in the causation of those same mutations. The fact that age-adjusted cancer rates for different tissues vary substantially among countries where statistics are kept, and between workplaces or communities that differ in environmental exposures, demonstrates that a large fraction of cancers are influenced by environmental factors (*2*).

What the authors' work suggests is that stochastic differences in effects of DNA replication on cancer occurrence in different tissues can be distinguished from effects of external environmental factors. This distinction is far from trivial. Furthermore, the conclusion that "[t]he concept underlying the current work is that many genomic changes occur simply by chance during DNA replication rather than as a result of carcinogenic factors" ignores the fact that an initiation event must have taken place for a mutation to be replicated. The paper obscures the distinction between differences in cancer incidence and differences in occurrence of initiating events leading to cancer.

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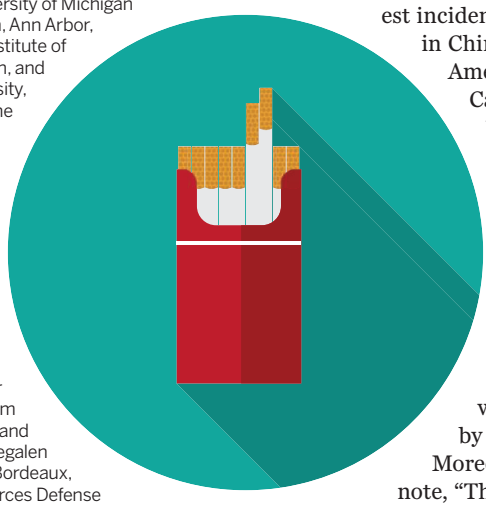

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Cancer risk: Tumors excluded

IN THEIR REPORT "Variation in cancer risk among tissues can be explained by the number of stem cell divisions" (2 January, p. 78), C. Tomasetti and B. Vogelstein discuss an interesting correlation (0.804) between estimated lifetime stem cell division number in 31 tissue types and corresponding cancer incidence rates in the United States. However, their assertion that only 35% of cancer risk variation is due to environmental or genetic factors is problematic.

The correlation analysis excluded many cancers (such as stomach, breast, prostate, cervix, kidney, endometrium, bladder, and lymphoma) that are common in the United States or worldwide, so no statement about overall cancer rate variation that is "explained" by stem cell divisions can be made. Furthermore, the correlation was anchored by five data points for osteosarcoma and included tumor subtypes having genetic (colorectal) and environmental influences (lung), but stem cell division rates were not estimated separately for organ subtypes. There are strong time trends in cancer incidence rates and large incidence-rate variations internationally for nearly all cancer types [for example, the rate of squamous esophagus cancer among men with the highest incidence (Jiashan County in China and African Americans in South Carolina) is more than 100 times the rate among men with the lowest incidence (Algeria) (*1*)]. If international rates were added to Figure 1, a much smaller fraction of incidence rate variation would be explained by stem cell divisions. Moreover, as the authors note, "The total number of stem cells in an organ and their proliferation rate may of course be influenced by genetic and environmental factors," so that stem cell division numbers could serve, substantially, as a mediator of genetic and environmental influences, rather than a distinct etiologic factor.

Finally, high values of the authors' extra risk score (ERS) are described as arising when "there is high cancer risk relative to the number of stem cell divisions," but ERS is calculated not as the ratio, but as the product, of cancer incidence rates and stem cell division number. Hence the resulting classification into D and R tumors does not seem interpretable and, regardless, could aim only to identify tumors that have etiologic mechanisms other than stem cell division number.

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Cancer risk: Role of chance overstated

THE RECENT ASSERTION from C. Tomasetti and B. Vogelstein that most variation in cancer risk among tissues is due to "bad luck" demands close consideration, especially as they go on to argue for increased focus on early detection ("Variation in cancer risk among tissues can be explained by the number of stem cell divisions," Reports, 2 January, p. 78). Observations from cancer epidemiology and limitations in their analysis argue strongly against this conclusion. Most cancers show considerable differences in incidence rates between distinct populations. Rates change over time, and migrants soon exhibit incidence rates similar to their host country. Each of these is consistent with a major etiologic role for environment and lifestyle. Consequently, a majority of cancers are preventable, with primary prevention achieving notable successes and promising more (*1*).

In their analysis, the authors correlate total stem cell divisions in selected organs or sites, and lifetime risk of a particular cancer at those sites. There is much uncertainty in the estimates of total stem cell divisions for each cancer site, and the vast age-related fluctuations in cell division for some tissues are overlooked. Of greater concern is the lifetime risk of cancers. Their analysis excludes frequent cancers with major environmental causes (such as stomach, breast, and cervix) and oversamples cancers rare in all populations (such as osteosarcomas, small intestine, and medulloblastoma). Overall, the cancer sites included account for only 34% of the cancer cases in the United States (*2*). The choice of the U.S. population is also arbitrary. A different population with different cancer patterns would have provided different results.

We also take issue with the statistical analysis. Despite the reported correlation of 0.81, stem cell replication is a poor predictor of incidence rates at any given cancer site. The residual standard deviation of the log rates is 0.75, so the 95% confidence limits for the log rate of any cancer site are given by the linear predictor ±1.47 (i.e., 1.96 × 0.75). Converting from a log10 scale to an absolute scale gives an error factor of $10^{1.47}$=29.4; i.e., the incidence rate may be 30 times higher or 30 times lower than the value predicted by stem cell division rates alone. This residual variation is consistent with large effects of environmental and lifestyle factors.

The role of chance underlying the onset of any individual cancer has long been recognized (*3*). However, although important for the individual, chance has little to say about the incidence rate in a population, or differences between populations. These are far better explained by exposure to environmental and lifestyle factors, allowing important opportunities for, and supporting implementation of, primary prevention.

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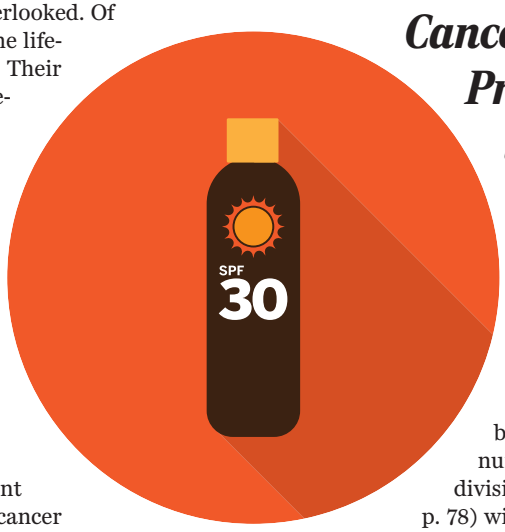

Cancer risk: Prevention is crucial

AS CANCER prevention scientists, we read C. Tomasetti and B. Vogelstein's Report "Variation in cancer risk among tissues can be explained by the number of stem cell divisions" (2 January, p. 78) with considerable interest. Many of the findings support previous research: Cancers vary in preventability, and the cancers that cause the most mortality in developed countries (lung and colon) are highly preventable (*1*). However, other findings in the Report do not reflect the current evidence.

For example, many of the "R-tumor" type cancers that the authors hypothesize to be unlikely to be preventable have well-known modifiable risk factors, such as tobacco and alcohol use for esophageal and head and neck cancers, radon exposure for lung cancer in nonsmokers, and ultraviolet light exposure for melanoma (*1*). There is also well-documented variation in cancer incidence rates for these and other cancers, globally and due to migration, as well as over time (*1*). These kinds of changes do not seem to be compatible with the theory that these cancers originate primarily from random stem cell mutations.

Tomasetti and Vogelstein found an interesting statistical relationship between rates of stem cell division and cancer rates in selected tissues, but they overinterpret the results by implying a causal relation. Emerging evidence suggests that stem cell division rates, and errors in division, are not simply a product of time and chance; they vary due to many external influences, including obesity, environmental pollution, infections, and inflammation (*2*, *3*).

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Cancer risk: Many factors contribute

IN THEIR REPORT "Variation in cancer risk among tissues can be explained by the number of stem cell divisions" (2 January, p. 78), C. Tomasetti and B. Vogelstein found a high correlation between the number of lifetime stem cell divisions of a given tissue and the lifetime risk of cancer in that tissue. Based on the finding that 65% of the variation in cancer risk among different tissues can be explained by the number of stem cell divisions in those tissues, the authors concluded that "these results suggest that only a third of the variation in cancer risk among tissues is attributable to environmental factors or inherited predispositions." This conclusion presumes that the total contribution of different components to variation in cancer risk among tissues adds up to 100%. However,

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most cancers are caused by multiple overlapping factors, and the attributable fractions for individual factors can add up to more than 100%. Furthermore, Tomasetti and Vogelstein suggest using the extra risk score (ERS) to direct allocation of primary versus secondary prevention for different cancers. However, although the ERS indicates how important the stochastic effects of DNA replication are for the variation in cancer rates across organs, it does not inform about the preventability of a certain cancer in the population. As shown in Figure 1 in the Report, a wide variation in cancer rates exists even within highly proliferative tissues, indicating a substantial role of non-stochastic factors in carcinogenesis (such as sun exposure for melanoma, tobacco for lung cancer, viruses and obesity for hepatocellular carcinoma, and obesity and tobacco for pancreatic ductal adenocarcinoma) and an enormous potential for primary prevention. The proportion of cancer cases that can be potentially prevented by environmental (mainly lifestyle) modification should be estimated on the basis of the comparison of cancer rates across populations with different risk factor profiles (*1*, *2*), rather than the comparison of cancer rates across tissues within individuals.

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Cancer risk: Accuracy of literature

WE READ WITH INTEREST the recent cancer etiology Report "Variation in cancer risk among tissues can be explained by the number of stem cell divisions" (2 January, p. 78), in which C. Tomasetti and B. Vogelstein claim that most cancer risk can be explained by chance mutations. However, the selection criteria used for cancer types included in the study are not robust. First, the authors report using an "extensive literature search" to identify eligible tissue types. There is no evidence that a systematic literature review was conducted. Second, the assessment of literature quality and subsequent inclusion criteria is not clear. According to the authors, "Other cancer types could not be assessed, largely because details about the normal stem cells maintaining the tissue in homeostasis have not yet been agreed upon or accurately quantified." There have been volumes written about the necessity of systematic literature reviews and subsequent appraisal as a critical component of obtaining accurate and unbiased research results (*1*).

The method used by Tomasetti and Vogelstein leads to the exclusion of breast and prostate cancer, together accounting for ~25% of all newly diagnosed cancers (*2*). No doubt other cancer types are excluded as well. Breast and prostate cancer have been closely studied, in many cases to a much greater extent than those cancers that the authors select. Lack of agreement regarding accurate quantification of these cell types should be addressed by sensitivity analysis rather than exclusion. Large bodies of literature will invariably contain disagreement between authors. This is hardly justification for exclusion.

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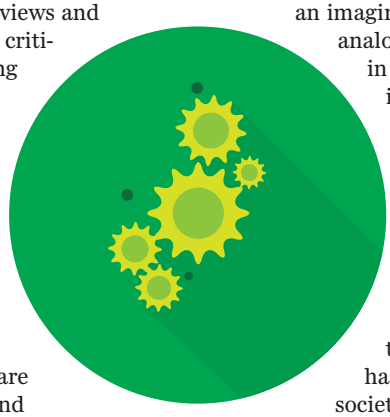
Response

THESE LETTERS CONTINUE the healthy and intelligent debate among scientists and the public about the root causes of cancer and the best way to reduce cancer deaths. The debate hinges on the following question: What causes the mutations that are responsible for cancer? Two causes—environmental and hereditary factors—have long been recognized. A third cause—mutations that arise during normal stem cell divisions in the absence of exogenous factors—was also known, but there had been no way to measure the relative importance of these mutations in cancers and compare them to the other causes. Our analysis enabled such a measurement, and we found evidence for a surprisingly large role of these mutations, henceforth called replicative mutations.

Suppose we had discovered a mutagenic, industrial agent that was present in human tissues at concentrations that were very highly correlated with cancer incidence. The implications of this discovery would be obvious. But such an imaginary discovery is highly analogous to the one reported in our paper. The difference is that the "agent" is not exogenous. Replicative mutations are unavoidable. They are in a sense a side-effect of evolution, which cannot proceed without them. That they play a larger role in cancer than previously believed has important scientific and societal implications.



At least three reactions to our paper have emerged. To some, the idea that we cannot completely control our cancer destinies by living a perfect lifestyle in a perfect environment, even when we have no hereditary predisposition to cancer, has proved unsettling. To others, our paper had a completely different message. That a child has cancer is bad enough; that a parent may feel guilty for failing to avoid a certain life-style or environment, and thereby "causing" that cancer, is agonizing. We chose to use the word "bad luck" particularly because we were aware of the unjustified guilt felt by many patients and their families about cancers that were beyond their control. The third reaction is fear that recognition of a major role for "bad luck" in cancer could lead individuals to conclude that all types of cancer are unpreventable and there is nothing they can do to avert any of them. We and many others, including those who have written Letters to *Science*, have vigorously campaigned against this mistaken belief (*1*, *2*).

Ashford *et al.* state that "some mutations are initiated by chemical or viral exposures, and others occur without a known cause," leaving open the possibility that other mutations are caused by chemical or viral exposures that have not yet been identified. The views of Ashford *et al.* stem from influential studies carried out in 1947 in which mice were treated topically with a single dose of a strong mutagen (i.e., initiator), followed by repeated topical doses of croton oil (i.e., promoter) (*3*). Ashford *et al.* thus state that our study "ignores that fact that an initiation event must have taken place for a mutation to be replicated." In contrast,

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our view is that no exposure to an exogenous agent is required for tumor initiation. Replicative mutations can be responsible for either initiating the process of tumorigenesis or for driving tumor progression.

Potter and Prentice and Wild *et al.* suggest that if we had been able to include other cancer types, particularly common cancer types such as those of the prostate and breast, we might have concluded that less than two-thirds of the variation in cancer risk across tissues is ascribable to replicative mutations. We stated in our Report that we could only include cancers in which normal stem cells had been well-characterized, and agree that this was a limitation of our study. However, Cancer Research UK estimates that no cases of prostate cancer and only 27% of breast cancers are preventable (*4*). Therefore, once adequate research on the stem cells in these organs is performed, we expect that the inclusion of these cancers will not significantly affect the correlation coefficient we observed [see (*5*) for more details].

We agree with Potter and Prentice and Wild *et al.* that the evaluation of data from other countries in the same way will be valuable. However, those data will not affect our conclusion that "stochastic effects associated with DNA replication contribute in a substantial way to human cancer incidence in the United States." Although replicative mutations are expected to vary little among populations, inherited mutations and environmentally based mutations are known to vary considerably. For example, in a country where everyone smokes and is obese, the correlation between stem cell divisions and cancer rates will be far lower than 0.80 because avoidable factors play a greater role.

Potter and Prentice criticize our multiplication of two logarithms to derive extra risk score (ERS). It may seem unintuitive to multiply rather than add logarithms, but both are valid mathematical operations to apply, with different interpretations. A detailed explanation of the mathematical basis of the ERS was provided in the Supplementary Materials and is expanded upon in our Technical Report (*5*).

Potter and Prentice and Gotay *et al.* state that genetic and environmental influences could influence the total number of stem cell divisions. We agree, which is why we defined replicative mutations to exclude such effects. Replicative errors occur at rates that can be measured in totally normal cells in vitro in the absence of any carcinogens. Carcinogens and hereditary factors add extra mutations to the baseline level established by the unavoidable replicative mutations.

Wild *et al.* state that "a majority of cancers are preventable." The Centers for Disease Control (CDC) estimates that 21% of cancer deaths are potentially preventable in the United States (*6*). The most recent estimate from Cancer Research UK is that 42% of cancers in the UK are preventable (*4*). These two organizations, as well as the World Health Organization Wild *et al.* represent, are committed to cancer prevention efforts and to identifying and implementing strategies to reduce cancer risk. Nothing in our study contradicts their estimates of potentially preventable cancers. To the contrary, our data provide a mechanism to help understand the molecular basis for the CDC's estimate (as noted above, our cancer incidence data were derived from a U.S. population).

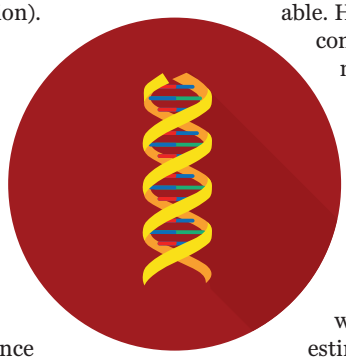
Wild *et al.* also state that "although important for the individual, chance has little to say about the incidence rate in a population" and comment about prediction of "incidence rates at any given cancer site." Our results specifically demonstrate that chance plays an important role in the incidence rate in a population. Our approach explains variation in cancer incidence across tissues, rather than providing prediction at any particular cancer type.

Wild *et al.* support their claim that "the role of chance…has long been recognized" with a reference to the classic studies of Armitage and Doll (*7*). This claim illustrates that the role of replicative mutations in cancer is not adequately appreciated, even today. Armitage and Doll's work was directed to understanding "carcinogenesis" considering "the ages at which the subjects are exposed" to various carcinogens. There are no such exposures required for replicative mutations.

Song and Giovannucci state that the "attributable fractions for individual factors could add up to more than 100%." The potential causes of mutations, and therefore cancer, can be partitioned in two subsets: factors related to the number of stem cell divisions and factors unrelated to those divisions. Thus, by assumption, these two causes add up to explain exactly 100% of the variation in risk.

We agree with Song and Giovannucci that the preventability of specific cancer types is more precisely estimated by epidemiologic evaluations than by ERS. The ERS provides a rough idea of the potential preventability of individual cancer types, but only in relation to other cancer types rather than in absolute terms (*5*). At the same time, our work provides a way to calculate the evidence for such extra risks that is free from all assumptions used previously. The idea that two-thirds of the relative variation in cancer risk can be explained (correlation coefficient of 0.80), and the relative environmental or hereditary influences roughly estimated, from a single biological feature (number of stem cell divisions) is unprecedented.

With respect to comments of O'Callaghan, our study was not intended to be a meta-analysis such as that used to evaluate clinical interventions. We used PubMed to find all the references we could and used our judgment to select 146 that we considered among the most reliable. However, we did not have complete trust in our judgment, nor complete trust in the estimates made in the original references. We therefore performed rigorous tests for robustness of the conclusions based on these estimates. For example, statistical significance persisted even when we allowed the reported estimates of stem cell divisions to vary by ~100-fold in either direction [see our Report, Supplementary Materials]. Few meta-analyses would survive robustness tests like these.



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TECHNICAL COMMENT ABSTRACTS

Comment on "Using ecological thresholds to evaluate the costs and benefits of set-asides in a biodiversity hotspot"

Christopher Finney

Banks-Leite *et al.* (Reports, 29 August 2014, p. 1041) conclude that a large-scale program to restore the Brazilian Atlantic Forest using payments for environmental services (PES) is economically feasible. They do not analyze transaction costs, which are quantified infrequently and incompletely in the literature. Transaction costs can exceed 20% of total project costs and should be included in future research.

Full text at http://dx.doi.org/10.1126/science.aaa0916

Response to Comment on "Using ecological thresholds to evaluate the costs and benefits of set-asides in a biodiversity hotspot"

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Finney claims that we did not include transaction costs while assessing the economic costs of a set-aside program in Brazil and that accounting for them could potentially render large payments for environmental services (PES) projects unfeasible. We agree with the need for a better understanding of transaction costs but provide evidence that they do not alter the feasibility of the set-aside scheme we proposed.

Full text at http://dx.doi.org/10.1126/science.aaa1602