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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.

**Nicholas A. Ashford,<sup>1\*</sup>  
Patricia Bauman,<sup>2</sup> Halina S.  
Brown,<sup>3</sup> Richard W. Clapp,<sup>4,5</sup>  
Adam M. Finkel,<sup>6,7</sup> David Gee,<sup>8</sup>  
Dale B. Hattis,<sup>9</sup> Marco  
Martuzzi,<sup>10</sup> Annie J Sasco,<sup>11</sup>  
Jennifer B. Sass<sup>12,13</sup>**

<sup>1</sup>Sociotechnical Systems Research Center, Massachusetts Institute of Technology, Cambridge, MA 02139, USA. <sup>2</sup>Bauman Foundation, Washington, DC 20009. <sup>3</sup>Department of International Development, Community, and Environment, Clark University, Worcester, MA 01610.

<sup>4</sup>Boston University School of Public Health, Boston, MA 02118.

<sup>5</sup>University of Massachusetts, Lowell, MA 01854. <sup>6</sup>Penn Program on Regulation, University of Pennsylvania Law School, Philadelphia, PA 19104. <sup>7</sup>Department of Environmental Health Sciences, University of Michigan School of Public Health, Ann Arbor, MI 48109.

<sup>8</sup>Institute of Environment, Health, and Societies, Brunel University, London, United Kingdom SW11 6HT.

<sup>9</sup>The George Perkins Marsh Institute, Clark University, Worcester, MA 01610. <sup>10</sup>World Health Organization - Regional Office for Europe, European Centre for Environment and Health, Bonn, Germany 53113. <sup>11</sup>Epidemiology for Cancer Prevention, Team on HIV, Cancer and Global Health, Inserm U 897 - Epidemiology and Biostatistics, Bordeaux Segalen University, Bordeaux, FR 33076.

<sup>12</sup>Natural Resources Defense Council, Washington, DC 20005. <sup>13</sup>George Washington University, Washington, DC 20037.

\*Corresponding author. E-mail: nashford@mit.edu

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