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Stem cell divisions per se do not cause cancer

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Cancer is “bad luck”. That is the take-home summary of a highly cited analysis in *Science* suggesting that cancer risk across tissues is explained by the number of stem cell divisions in the tissue¹. If true, the policy conclusion follows that attempts to prevent most kinds of cancers (as opposed to detecting and treating them) are a waste of effort. This analysis has been criticized for disregarding important factors like environment^{2,3} and overinterpretation of the data⁴, but is the correlation itself robust? Here we show that, taking age into account, the same analytical approach proves that stem cell divisions alone do not cause cancer.

In the original analysis, the standing number of stem cells and their yearly division rate were retrieved from the literature for various tissues.¹ Lifetime cancer risks for these tissues were obtained from the SEER database.⁵ Assuming a lifespan of 80 years, the lifetime number of stem cell divisions was calculated.¹

In addition we retrieved, from the SEER database,⁵ the age distributions of the incidence of the cancers involved. We then calculated stem cell divisions and cancer risk up to ages 20 and 45 (Figure; see eAppendix; <http://links.lww.com/EDE/B153> for details). The reported correlation between stem cell divisions and cancer risk at age 80¹ is not present at age 20 and only suggested at age 45: the correlation materializes over age. What is more, a high number of stem cell divisions at young age poses a cancer risk that is orders of magnitude lower than the cancer risk posed by a low number of stem cell divisions at old age. Hardly anyone gets cancer by age 20, whereas various tissues have had a great many stem cell divisions by that age. Meanwhile, there are tissues with a relatively moderate number of stem cells divisions by age 80 that suffer from relatively high cancer risk. For instance, at age 20 the pancreas has experienced 100 billion stem cell divisions, whereas even by age 80 the esophagus has had 100-fold fewer such divisions. And yet the risk of cancer of the pancreas before age 20 is only one in 100,000, whereas the lifetime risk for the esophagus is a 100-fold more (Figure).

Suppose the hypothesis is correct that stem cell divisions introduce mutations.¹ Further suppose that the multiple-hit model of cancer is correct: several mutations, perhaps 3 to 8, are needed to cause cancer.⁶⁻⁸

Then for any fixed number of stem cell divisions, the number of mutations per stem cell rises much faster if a small standing number of stem cells divide frequently than when a large standing number of stem cells divide infrequently (eFigure; <http://links.lww.com/EDE/B153>). If a set of mutations produces cancer, then the set will be completed at much younger age in the former case than in the latter.⁹ The younger the age at which a cancer emerges, the higher the lifetime risk from that kind of cancer, because it then is more likely that the cancer occurs before death strikes from other causes. Hence, if the hypothesis is that stem cell divisions per se explain cancer risk, then for any number of stem cell divisions tissues with a high division rate should have a higher cancer risk than cancers with a high standing number of stem cells. There is, however, no clear signal in this direction. Among those cancers with a high lifetime cancer risk, some have a high number of stem cell divisions due to a high division rate (colorectal cancer, oropharynlaryngeal cancer and leukemia), whereas others have a high standing number of stem cells (hepatic cancer, pancreatic cancer and melanoma).¹ Indeed, if stem cell divisions alone were responsible for oncogenesis, then nearly all cancer would be in the gastrointestinal system, because these stem cells have the highest division rates. Other cancers would be unknown diseases that are hidden from observation because they potentially emerge only much later.

In conclusion, stem cell divisions alone do not cause cancer, the correlation between stem cell divisions and cancer risk is a product of age(ing), and the lifetime number of stem cell divisions is an inappropriate product of division rate and standing number of stem cells to predict risk. We propose that the best interpretation of these findings may be that stem cell divisions in some tissues and in old subjects pose different risks than stem cell divisions in other tissues and in young subjects. The mutation rate per stem cell division could be higher in some tissues and at older ages, or immune surveillance might be more effective in some tissues and might be compromised at older ages. Aging and cancer may have shared mechanisms¹⁰, and stem cell aging may make its mark.¹¹ In etiologic studies it is crucial to involve the age at which cancer occurs. Studies of changes that happen over age, such as reduced immune surveillance and stem cell aging, could yield interventions that help prevent cancer.

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Figure legend. The total number of stem cell divisions plotted against cancer risk up to ages 20 and 45, and for stem cell divisions up to age 80 versus against lifetime cancer risk. Spearman's correlation statistic r and its p -value are included in the graphs. The bottom panel is a reproduction of the original analysis for all cancers included in the present analysis.

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Figure 1.

