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Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention

Cancers are caused by mutations that may be inherited or induced by environmental factors or that may result from DNA replication errors. The mutations due to random mistakes made during normal DNA replication may explain why cancers occur much more commonly in some tissues than others. Approximately three mutations occur every time a normal human stem cell divides. The authors of this study proposed that mutations resulting from DNA replication errors play a major role in cancer development. They studied the relationship between the number of normal stem cell divisions and the risk of 17 cancer types in 69 countries worldwide that represented a variety of environments. They had previously studied just the U.S. population, assuming that the environmental conditions to which study participants were exposed were more uniform. In the current study, the authors analyzed data from 423 cancer registries that were made available by the International Agency for Research on Cancer. For each country, they calculated the correlation between the number of stem cell divisions in 17 different tissues and the lifetime incidence of cancer in those tissues. The results showed a strong correlation between cancer incidence and normal stem cell division in subjects in all countries, regardless of environment. The conclusions were supported by an independent approach based on cancer genome sequencing and epidemiological data, which suggested that the mutations resulting from DNA replication errors were responsible for two-thirds of the mutations in human cancers. The authors concluded that this study accentuates the importance of early detection and intervention to reduce deaths from many cancers that arise from unavoidable DNA replication errors. They also noted that this study provides a well-defined molecular explanation for the large and unpreventable component of cancer risk that has long puzzled epidemiologists.

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Trends in use of the *BRCA* mutation test in the United States

BRCA mutation testing is used to screen women at high risk for ovarian and breast cancer and to select the best treatment for those with breast cancer. The testing has been recommended by the U.S. Preventive Services Task Force, since 2005, for women whose family history demonstrates an increased risk for *BRCA*-related cancers. Approximately five to 10 percent of breast cancers and 10 to 18 percent of ovarian cancers are due to germline *BRCA* mutations. However, the majority of at-risk women do not get referrals for genetic counseling or testing. BRCA testing is also often used for women in whom the testing may not be indicated by practice guidelines. The authors conducted a study to examine trends in the use of *BRCA* mutation testing in ovarian and breast cancer patients and unaffected women in the United States from 2004 to 2014. They performed a retrospective study on 53,254 women with insurance claims for *BRCA* mutation testing, from the Clinformatics Data Mart database. Data analysis showed that the proportion of BRCA tests performed in unaffected women in the study group increased significantly from 24.3 percent in 2004 to 61.5 percent in 2014. In particular, the proportion of study participants aged 20 to 40 years who received *BRCA* mutation testing was much higher in unaffected women than in women with previously diagnosed breast or ovarian cancer (41.7 percent versus 17.6 percent, respectively). The authors concluded that during the past decade, the role of *BRCA* testing has gradually shifted from being used primarily for cancer patients to being used for unaffected women in the United States. Most of the patients referred for genetic

testing and counseling do not meet the referral requirements based on family history. The authors suggest that since the cost of such genetic testing is low, at roughly $200 to $300, practical guidelines may further loosen the testing criteria, and more unaffected women and cancer patients will choose *BRCA* mutation testing, even when they have to pay out of pocket.

Guo F, Hirth JM, Lin Y, et al. Use of *BRCA* mutation test in the U.S., 2004–2014 [published online ahead of print March 18, 2017]. *Am J Prev Med.* doi:10.1016/jamepre.2017.01.027.

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