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Gene mutation may have effect on benefit of aspirin use for colorectal cancer

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In two large studies, the association between aspirin use and risk of colorectal cancer was affected by mutation of the gene BRAF, with regular aspirin use associated with a lower risk of BRAF-wild-type colorectal cancer but not with risk of BRAF-mutated cancer, findings that suggest that BRAF-mutant colon tumor cells may be less sensitive to the effect of aspirin, according to a study in the June 26 issue of *JAMA*.

Colorectal cancer is a leading cause of cancer-related death worldwide. Randomized controlled trials have demonstrated that aspirin use reduces the risk of colorectal cancer, according to background information in the article. Experimental evidence has suggested that BRAF-mutant colonic cells might be less sensitive to the antitumor effects of aspirin than BRAF-wild-type (the typical form of a gene as it occurs in nature) neoplastic cells.

Reiko Nishihara, Ph.D., of the Dana-Farber Cancer Institute, Boston, and colleagues examined the association of aspirin use with the risk of colorectal cancer according to BRAF mutation status. The researchers collected biennial questionnaire data on aspirin use and followed up participants in the Nurses' Health Study (from 1980) and the Health Professionals Follow-up Study (from 1986) until July 2006 for cancer incidence and until January 2012 for cancer mortality.

Among 127,865 individuals, 1,226 incident rectal and colon cancers were identified with available molecular data. The researchers found that regular aspirin use was associated with a significantly lower risk (27

percent) of BRAF-wild-type cancer. Regular aspirin use was not associated with a lower risk of BRAF-mutated cancer. "The association of aspirin use with colorectal cancer risk differed significantly according to BRAF mutation status."

The authors also observed a lower risk of BRAF-wild-type cancer with increasing aspirin tablets per week; however, there was not a significant trend in risk reduction for BRAF-mutated cancer. "The association of aspirin tablets per week with cancer risk differed significantly by BRAF mutation status. Compared with individuals who reported no aspirin use, a significantly lower risk of BRAF-wild-type cancer was observed among individuals who used 6 to 14 tablets of aspirin per week and among those who used more than 14 tablets of aspirin per week."

In addition, longer duration of aspirin use was associated with significant risk reduction for BRAF-wild-type cancer, whereas duration of aspirin use was not significantly associated with BRAF-mutated cancer risk.

"There was no statistically significant interaction between post-diagnosis aspirin use and BRAF mutation status in colorectal cancer-specific or overall survival analysis. This suggests that the potential protective effect of aspirin may differ by BRAF status in the early phase of tumor evolution before clinical detection but not during later phases of tumor progression," the authors write.

"The identification of specific cancer-subtypes that are prevented by aspirin is important for several reasons. First, it enhances our understanding of the molecular pathogenesis of colorectal neoplasia and the mechanisms through which aspirin may exert its antineoplastic effects. Second, development of clinical, genetic, or molecular predictors of specific subtypes of colorectal cancer might lead to the development of more tailored screening or chemo-preventive strategies. Nevertheless, given the modest absolute risk difference, further

investigations are necessary to evaluate clinical implications of our findings. Lastly, our data provide additional support for a causal association between aspirin use and risk reduction for a specific subtype of colorectal cancers. Accumulating evidence supports preventive effect of aspirin against colorectal cancer."

In an accompanying editorial, Boris Pasche, M.D., Ph.D., of the University of Alabama at Birmingham, (and *JAMA* contributing editor), comments on the findings of this study.

"Nishihara el al derived their report from the Nurses' Health Study and the Health Professionals Follow-up Study, which include a large number of female and male health professionals. This population is predominantly white: 98 percent of the participants in the Nurses' Health Study and 95 percent of participants in the Health Professionals Follow-up Study are of a non-Hispanic white ethnic background. However, black individuals have the highest incidence of colorectal cancer in the United States and represent the ethnic group for whom colorectal cancer prevention may have the greatest benefit. Therefore, it will be important to determine whether the findings reported by Nishihara et al are confirmed in black individuals."

"In summary, these results identify biomarkers of response to aspirin administered either preventively or therapeutically and are likely to help tailor the use of aspirin in the prevention and treatment of colorectal cancer."

More information: JAMA. 2013;309(24):2563-2571
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