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Colorectal cancer and aspirin: significantly diverse results influenced by the cancer's *BRAF*-mutation status

A large study published by the *Journal of the American Medical Association* has explored how the effect of aspirin on reducing the risk of colorectal cancer is influenced by the cancer's *BRAF*-mutation status. Recently, randomized controlled trials have shown that taking regular aspirin can reduce the risk of developing colorectal cancer; however, the amount that the risk is reduced by has not been identified for specific types of colorectal cancer. In the study conducted by researchers at the Dana-Farber Cancer Institute (MA, USA), the amount that regular aspirin reduced the risk of developing colorectal cancer was examined and compared in *BRAF*-wild-type (wt) and *BRAF*-mutation colorectal cancer. It was discovered that the *BRAF*-mutant colorectal cancer was less sensitive to the antitumor effects of regular aspirin use.

The study involved 127,865 individuals completing a questionnaire every 2 years. Individuals were taken from either the Nurses' Health Study or the Health Professionals Follow-up Study, beginning in 1980 and 1986, respectively. After the questionnaires ended in July 2006 for cancer incidence and January 2012 for cancer mortality, data on 1226 individuals with rectal or colon cancers became available.

The researchers discovered several important differences for individuals that developed *BRAF*-wt and *BRAF*-mutant colorectal cancer. First, the administration of regular aspirin caused a 27% reduction in risk of developing *BRAF*-wt colorectal cancer, however, it was not associated with a significantly lower risk of developing *BRAF*-mutant cancer. Second, the specific frequency and amount of aspirin taken was shown to significantly affect people with *BRAF*-wt but not *BRAF*-mutation colorectal cancer. Finally, the time period that aspirin was taken for significantly affected people with *BRAF*-wt but not *BRAF*-mutant colorectal cancer, with a longer duration of aspirin administration leading to a reduced risk in *BRAF*-wt.

Commenting on these results, Nishihara *et al.* explained: "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*-wt cancer was observed among individuals who used 6–14 tablets of aspirin per week and among those who used more than 14 tablets of aspirin per week."

A particularly interesting discovery in this study is that the differing affect of aspirin on *BRAF*-wt and *BRAF*-mutant colorectal cancer is further influenced by the stage of the cancer, with the earlier stages being more susceptible to its beneficial effects: "There was no statistically significant interaction between postdiagnosis 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 stated.

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News

Journal Watch

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"Our data provide additional support for a causal association between aspirin use and risk reduction for a specific subtype of colorectal cancers," explained the authors.

The authors concluded by discussing the importance that the believe their large study has on understanding not only the mechanism that aspirin works to reduce the risk of colorectal cancer, but also to create a greater range of subtypes, which may lead to more tailored therapy in the future.

– Written by Natasha Galukande

Sources: Nishihara R, Lochhead P, Kuchiba A *et al.* Aspirin use and risk of colorectal cancer according to *BRAF* mutation status. *JAMA* 309(24), 2563–2571 (2013); American Medical Association news release: http://media.jamanetwork.com/news-item/gene-mutation-may-have-effect-on-benefit-of-aspirin-use-for-colorectal-cancer

Researchers discover that men should receive 'virtual colonoscopy' nearly a decade earlier then women

Researchers from Nuovo Regina Margherita Hospital (Rome, Italy) have studied the impact of several factors on developing advanced colorectal cancer to determine when certain people should be screened. The study found that woman can be screened approximately 5–10 years later then men and the screening can be conducted with computed tomographic colonography (CTC), otherwise known as 'virtual colonoscopy', which has several benefits over the more traditional colonoscopy, such as its less invasive nature. Although CTC has a similar accuracy to more traditional colonoscopy, there have been very few studies conducted on the factors that should be considered before it is performed.

The study involved analyzing information from 7620 patients who received first time CTC between 2004 and 2011. Of these patients, 276 (3.6%) were diagnosed with advanced colorectal cancer. Diagnosis of this was more common with increased age and if the patient was male, however, BMI and family history were not linked to increased diagnosis.

"We showed that the possibility for average-risk individuals to have clinically meaningful polyps detected by CTC is strictly associated with two main variables, namely age and sex," commented Cesare Hassan (Nuovo Regina Margherita Hospital), a member of the study group.

The authors hope that the findings, published online in *Cancer,* will help to establish guidelines for future CTC use: "If you are a man, the best age to have a virtual colonoscopy is between 55 and 60 years, but if you are a woman, you can at least wait until 60 years of age," Hassan concluded.

– Written by Natasha Galukande

Sources: Hassan C, Pooler DB, Kim DH, Rinaldi A, Repici A, Pickhardt PJ. Computed tomographic colonography for colorectal cancer screening. *Cancer* doi:10.1002/cncr.28007 (2013) (Epub ahead of print); Wiley via AlphaGalileo press release: www.alphagalileo.org/ViewItem.aspx?ItemId=131822&CultureCode=en

Transcriptome-based classification system shows promise in predicting colorectal cancer recurrence

A novel transcriptome-based classification system for predicting recurrence in colorectal cancer patients has been developed by researchers from INSERM (Paris, France). Published in *PLoS Medicine*, the researchers retrospectively analyzed a large number of well-characterized colon samples from seven different centers in France. The classification system is the first promising gene expression signature that can be used in the clinical setting for prognosis stratification.

The pathological stage of colorectal cancer normally dictates the prognosis and treatment options for colorectal cancer patients, with factors such as clinicopathological variables and DNA markers influencing the decisions made. However, pathological staging does not accurately predict recurrence in the patients, which is a matter that the researchers aimed to address.

In total, the records of 750 patients who had surgery for stage I–IV colorectal cancer between 1987 and 2007 were analyzed for associations between factors such as molecular subtype, common DNA alterations and prognosis.

The researchers were able to classify the samples into six molecular subtypes based on gene expression data that showed great diversity in clinical and pathological characteristics, molecular alterations, specific gene expression signatures and deregulated signaling pathways. These subjects also showed variation in the probability of colorectal cancer recurrence, with 50% greater chance of relapse-free survival occurring in subtypes C1–C3 and C5, compared with C4 and C6. These factors demonstrate the biological relevance of the subtypes, and the potential of using a transcriptome-based classification system in the future.

– Written by Natasha Galukande

Source: Marisa L, de Reynies A, Duval A *et al.* Gene expression classification of colon cancer into molecular subtypes: characterization, validation, and prognostic Value. *PLoS Med.* 10(5), e1001453 (2013).

Breakthrough study elucidates mechanism of Ras cancer cell nutrient ingestion

A study published online in *Nature* has been described as a 'breakthrough' in the understanding of how some cancerous cells ingest nutrients. The mutated protein, Ras, is involved in the growth and proliferation of cancer cells in numerous cancers including colon cancer. Ras cells are known to have special nutrient requirements in order to grow and survive but the mechanisms allowing them to meet these requirements have remained largely unknown.

In their recent study, researchers from NYU School of Medicine (NY, USA) found Ras-transformed pancreatic cancer cells to use macropinocytosis to ingest external protein sources. Imported albumin then undergoes proteolytic degradation to yield amino acids for exploitation by the cell. Importantly, the released amino acids include glutamine, which can subsequently enter the central carbon metabolism pathway. The group tested the dependence of Ras cancer cells on macropinocytosis by blocking this route of nutrient uptake with a pharmacological inhibitor. Such inhibition led to reduced tumor growth in Ras-transformed pancreatic tumor xenografts and in some mice regression of the pancreatic tumors was observed. Pancreatic cells from mice were also observed to contain greater numbers of macropinosomes (the transport vesicles necessary for macropinocytosis) than nontumor cells, further supporting the group's hypothesis.

The researchers are hopeful that their findings will allow for the development of novel therapies to target Ras-transformed cells and their dependence on free extracellular glutamine via suppression of macropinocytic protein uptake. As this mechanism is postulated to be specific to certain cancer cells, such therapies may have the potential to attack Ras-transformed cells without causing collateral damage to healthy cells. These findings may also allow exploitation of this import process to direct chemotherapeutic molecules directly into cancerous cells.

Lead investigator of the study Dafna Bar-Sagi (NYU School of Medicine) summarized her group's study stating "This work offers up a completely different way to target cancer metabolism. It's exciting to think that we can cause the demise of some cancer cells simply by blocking this nutrient delivery process."

– Written by Hannah Wilson

"The group tested the dependence of Ras cancer cells on macropinocytosis by blocking this route of nutrient uptake with a pharmacological inhibitor."

Sources: Commisso C, Davidson SM, Soydaner-Azeloglu RG *et al.* Macropinocytosis or protein in an amino acid supply route in Ras-transformed cells. *Nature* doi:10.1038/nature12138 (2013) (Epub ahead of print); New York University Langone Medical Center press release: http://communications.med.nyu.edu/media-relations/news/breakthrough-understanding-how-pancreatic-cancer-cells-ingest-nutrients-point-0

MET identified as potential marker of treatment-resistant colorectal cancer

Study results released at the American Society of Clinical Oncology Annual Meeting 2013 in Chicago (IL, USA) have shown that levels of MET protein are strongly correlated with a treatment-resistant phenotype of colorectal cancer, known as epithelial–mesenchymal transition phenotype (EMT), and may have potential for use as a surrogate biomarker.

The study, carried out by researchers from the University of Texas MD Anderson Cancer Center (TX, USA), involved exploratory analysis of 139 untreated primary colorectal cancer samples using data

obtained from the Cancer Genome Atlas. Reverse-phase protein array and RNA sequencing were employed to measure protein and gene expression, respectively. The data obtained were then subject to statistical analysis. Results of the analysis showed higher MET levels to be observed more frequently in colon tumors than rectal tumors. In addition, MET overexpression was found to be associated with: decreased overall survival; increased gene expression of 28 markers of EMT; and higher gene scores taken from three previously published EMT gene signatures. MET protein expression was also found to not correlate with MET gene expression.

"When the epithelial cells that line the colon become cancerous, some of them develop special features to allow migration, causing the cancer to be more aggressive," explained Kanwal Pratap Singh Raghav, a fellow in MD Anderson's Division of Cancer Medicine. "Although EMT is a dominant molecular subtype, a biomarker suitable for clinical use has not been found. This research gives us an important step toward learning more about treating this colorectal cancer subtype."

The group plan to apply their approach to other colorectal subtypes in the future in the hope of defining additional simple and readily available biomarkers. "The ultimate success in targeting colorectal cancer requires understanding molecular subsets of the disease," explained the study's senior author Scott Kopetz (MD Anderson Cancer Center). "If we can identify and group cancers with similar behaviors, we'll be closer to identifying vulnerabilities and optimal therapies for each subset."

– Written by Hannah Wilson

Source: MD Anderson Cancer Center press release: www.mdanderson.org/newsroom/news-releases/2013/met-protein-levels.html

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