New research shows how aspirin may act on blood platelets to improve survival in colon cancer patients

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Researchers believe they have discovered how aspirin improves survival in patients diagnosed with colon cancer, the 2013 European Cancer Congress (ECC2013) [1] heard today (Monday).

Although previous research has shown that taking low dose aspirin after being diagnosed with colon cancer improves patient outcome, the reasons why this happens remain unknown. The new research has shown that aspirin improves outcome in patients whose tumour cells express a specific protein on their surface; the protein is known as Human Leukocyte Antigen class I (HLA class I), a cell-surface protein produced by a collection of genes involved in the functioning of the immune system.

The results mean that HLA class I could be used in the future to predict whether or not a patient would benefit from aspirin. The findings also suggest that aspirin's role in improved patient survival could be explained by the interaction of the body's immune system with the effect of aspirin on platelets (cell fragments in the blood that are involved in clotting).

Dr Marlies Reimers, MD, a PhD student, in the Department of Surgery, Leiden University Medical Center, The Netherlands, said: "We think that platelets are involved in cancer spreading to other parts of the body by shielding tumour cells in the bloodstream so that they cannot be recognised by the immune system and can finally colonise distant organs.

Aspirin could help to 'unmask' those tumour cells by attacking platelet formation, so that the immune cells can detect and eliminate them."

Dr Reimers and her colleagues used tissue microarray technology [2] to investigate the pattern of protein expression in colon cancer patients whose aspirin use after cancer diagnosis was known and who were registered with the Eindhoven Cancer Registry between 1998 and 2007. They studied 999 colon cancers to look at HLA class I expression, and expression of the COX-2 enzyme. They also extracted DNA from 663 tumours to look for mutations in the PIK3CA gene. Both COX-2 expression and PIK3CA mutations are known to be involved in the onset of cancer.

They found that low dose (80mg a day) aspirin use after diagnosis improved survival only in patients with tumours expressing HLA class I; if these patients used aspirin they were half as likely to die during the average four years of follow-up as patients with tumours expressing HLA class I that did not use aspirin. This effect of aspirin was not seen in patients without HLA class I expression. "Therefore, HLA class I might serve as a predictive biomarker to help identify patients who would benefit from aspirin therapy after diagnosis," said Dr Reimers.

"Our results showed that there was no difference in the effect of aspirin in relation to COX-2 expression and PIK3CA mutation."

Until now it was assumed that COX-2 expression or PIK3CA gene mutation played a role in the effectiveness of aspirin use. Dr Reimers explained: "When we stratified our analyses for COX-2 expression and PIK3CA mutation status, we did not see differences in survival benefit. For example, patients with aspirin use after diagnosis with strong COX-2 expressing tumours had the same survival benefit as tumours with weak COX-2 expression."

Dr Reimers and her colleagues believe their results suggest that aspirin may be acting on two different pathways in colon cancer: one in the preventive setting and the other through the control of metastasis – the spread of cancer to other parts of the body from its primary site.

She said: "The first pathway is through PIK3CA mutations and COX-2 expression in the tumours, which seem to show more effect in the preventive setting. Studies of hereditary colorectal cancers have shown that aspirin can help to prevent the onset of cancer by limiting the formation of polyps in the bowel, which are often the forerunners of cancer, and that this is linked to PIK3CA mutations and COX-2 expression.

"The second pathway, revealed by our results today, is more involved in metastasis, by influencing the platelets in the bloodstream. Although speculative, it may be that the interaction of platelets with HLA positive tumour cells circulating in the blood promotes the metastatic potential of these cells. Aspirin interferes with this interaction, thereby decreasing the risk of metastatic disease and colon cancer-related death."

The researchers say that more evidence from larger studies and clinical trials is required to support their findings. Some randomised clinical trials have started in the UK and one in Asia – a multi-centre prospective randomised controlled phase III trial of aspirin use in colorectal cancer patients, called the ASCOLT study.

Professor Peter Naredi, who is a member of the Board of Directors of the European CanCer Organisation (ECCO), commented: "The results presented by Dr Reimers and colleagues are very interesting. The idea that aspirin can enhance the effect of our immune system and that we might be able to identify those cancer patients who best benefit from it, is worth further studies. Ongoing placebo-controlled randomised trials evaluating the effect of aspirin in colorectal cancer can hopefully

strengthen the evidence that aspirin is useful in patients with HLA class 1 expression." [3]

More information: [1] The 2013 European Cancer Congress is the 17th congress of the European CanCerOrganisation (ECCO), the 38th congress of the European Society for Medical Oncology (ESMO) and the 32nd congress of European Society for Therapeutic Radiology and Oncology (ESTRO).

[2] Tissue microarray technology involves using a punching instrument to precisely place up to 1000 tissue samples in a paraffin block for analysis of multiple components.

[3] Professor Naredi is professor of surgery and chair of the department of surgery, Sahlgrenska University Hospital, Gothenburg, Sweden.

[4] This study received no external funding.

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