Study identifies low-dose aspirin's mechanisms of action in reducing cancer mortality

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Low-dose aspirin may lower the risk for cancer metastasis and mortality by inhibiting both COX-1 and COX-2 pathways, according to data presented at the 13th Annual AACR International Conference on Frontiers in Cancer Prevention Research, held Sept. 28–Oct. 1.

The involvement of the COX-2 pathway is new, as prior studies suggested that low-dose aspirin lowers cancer risk only by inhibiting the COX-1 pathway.

"Studies have shown that aspirin administration for five or more years reduces the incidence of all cancers by 38 percent. This benefit is seen even at the low doses of aspirin [e.g., 81 mg daily] required to inhibit platelet aggregation via inhibiting the COX-1 pathway, a finding consistent with the known participation of platelets in the metastatic process," said Pierre Massion, MD, professor of medicine and cancer biology in the Division of Allergy, Pulmonary and Critical Care Medicine at Vanderbilt University School of Medicine in Nashville, Tennessee.

In this study, Massion and his colleagues Oates and Boutaud, sought to determine whether low-dose aspirin, in addition to blocking platelet function by inhibiting the COX-1 pathway, also reduced levels of the pro-metastatic molecule prostaglandin E2 (PGE2) through inhibition of the COX-2 pathway.

"We found that the potency of low-dose aspirin in inhibiting COX-2 in the tumor cells is as great or greater than its potency as an inhibitor of COX-1 in the platelet," Massion said. "This indicates that at a cellular level, aspirin is not selective for the platelet, but could also block COX-2 in cancers.

"The conventional wisdom held that at low doses, aspirin is selective for the platelet and that it does not block extra-platelet COXs. Thus, the finding that it blocked PGE2 production is likely surprising to most investigators in the field," said Massion. "Our findings may explain how even a very low dose of aspirin taken daily can produce such a substantial reduction in cancer deaths and metastasis."

Using three lung adenocarcinoma cell lines, the researchers first found that the doses of aspirin required to inhibit COX-2-dependent PGE2 production were equal to or less than the doses required for the inhibition of COX-1-dependent platelet aggregation.

Next, using urine samples of 54 subjects who took the low-dose 81 mg aspirin tablets for two weeks, the researchers demonstrated that aspirin inhibited PGE2 production by 45 percent and reduced the levels of a metabolite of PGE2, prostacyclin, by 37 percent.

The researchers also found that by blocking platelet COX-1, aspirin inhibits the adherence of platelets to the cancer cells to prevent metastasis, suggesting that the two mechanisms described act in concert to reduce the risk for cancer mortality.

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