COX-2 inhibitors delay pancreatic cancer precursors in mice

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Nimesulide, a cyclooxygenase-2 (COX-2) inhibitor, delays the progression of precancerous pancreatic lesions in mice, according to researchers at David Geffen School of Medicine at UCLA. While inflammation has been shown to be a factor in many forms of cancer, the researchers say this is the first study to demonstrate the effect of an anti-inflammatory COX-2 inhibitor on the development of pancreatic cancer.

The study, published in the August 1 issue of *Cancer Research*, a journal of the American Association for Cancer Research, suggests a potential role for COX-2 inhibitors in pancreatic cancer prevention among high-risk patients. Pancreatic cancer is one of the leading causes of cancer death in America – over 33,000 Americans will likely die from the disease in 2007, according to projections from the American Cancer Society.

“By inhibiting COX-2 in human patients, we may have an option to delay the progression of lesions,” said lead author Guido Eibl, M.D., scientific director of the Hirshberg Laboratory of Pancreatic Cancer Research and adjunct assistant professor at UCLA .

Researchers believe pancreatic cancer arises from abnormal tissues, or lesions in the pancreas, known as pancreatic intraepithelial neoplasias (PanINs). By stalling the growth of PanINs, researchers hope to slow the development of or prevent pancreatic cancer.

COX-2, an enzyme which causes inflammation, is no stranger to cancer researchers. Studies of breast, colon, and pancreatic cancers have led researchers to believe COX-2 plays a key role in the development and growth of tumors.

To study the effects of COX-2 on PanIN progression, Dr. Eibl and colleagues focused on the KrasG12D mouse, an animal model that mimics the early stages of pancreatic cancer. In the KrasG12D mouse, low-grade PanINs (stage I or II) begin to appear in the pancreas of mice at one month. Starting at six months, high-grade PanINs (stage III) can be found in the mouse pancreas. According to Dr. Eibl, most researchers agree that stage III PanINs are a direct precursor to pancreatic cancer in humans as well as mice. Between 12 and 15 months, Dr. Eibl says the majority of KrasG12D mice will develop pancreatic tumors.

The UCLA researchers divided the mice into two groups – one set received a nimesulide-enriched diet for 10 months; the other was offered only regular mouse chow. Their analyses revealed that the nimesulide diet greatly reduced the number of late-stage PanINs in KrasG12D (10 percent of pancreatic ducts had PanIN-2 or -3 in KrasG12D mice on nimesulide diet versus 40 percent of pancreatic ducts had PanIN-2 or -3 in KrasG12D mice on normal diet).

Because the pancreases of mice were analyzed at 10 months, before the typical appearance of pancreatic tumors, additional studies will be needed for researchers to conclude whether or not nimesulide can delay the onset of or prevent pancreatic cancer.

“With these results, I certainly wouldn’t say everyone should be taking COX-2 inhibitors to protect against cancer,” said Eibl. “However, with additional studies, we may find COX-2 inhibitors could help prevent pancreatic cancer in high risk populations.”

“Pancreatic cancer is so deadly because it often goes undetected until it’s too late,” said Dr. Eibl. “If a patient is at a high-risk for developing pancreatic cancer, a COX-2 inhibitor may offer some protection.”

In the future, Dr. Eibl and others plan to study the long-term effects of nimesulide and additional COX-2 inhibitors on the onset and progression of pancreatic cancer.

Source: American Association for Cancer Research