Cyclo-oxygenase 2 and breast cancer prevention

Non-steroidal anti-inflammatory agents are worth testing in breast cancer

A new interest in chemoprevention in oncology has been stimulated by good evidence that aspirin and to a lesser degree other non-steroidal anti-inflammatory drugs may have an important role in reducing the risk of colorectal cancer.[1] One of the targets for the activity of non-steroidal anti-inflammatory drugs is cyclo-oxygenase, the enzyme responsible for forming prostaglandins from arachidonic acid.[2] At key stages of colorectal carcinogenesis non-steroidal anti-inflammatory drugs inhibit prostaglandin synthesis, induce apoptosis, and block immunosuppression induced by prostaglandins, all of which help prevent cancer. With the discovery that there are two isoforms of cyclo-oxygenase the ultimate goal of preventive-therapeutic efficacy combined with good tolerability is within reach,[3] and researchers are now considering the place of cyclo-oxygenase inhibition, and therefore of non-steroidal anti-inflammatory drugs, in breast cancer.

Cyclo-oxygenase-1, the constitutive isoform, produces prostaglandins such as PGE2 and PGI2, which are important in many physiological processes, notably in the kidney and stomach. Cyclo-oxygenase-2 can undergo rapid induction in response to various stimuli, including cytokines, growth factors, and hormones. Cyclo-oxygenase-2 inhibition by non-steroidal anti-inflammatory drugs appears to be an important mechanism of cancer chemoprevention. This hypothesis is mechanistically plausible since inflammation of gastrointestinal organs is often associated with an increased risk of cancer, and cyclo-oxygenase-2 is an integral part of the inflammatory process. Evidence also exists that regular consumption of aspirin may reduce the risk of gastric and oesophageal cancers.[4 5]

The potential of non-steroidal anti-inflammatory drugs in the chemoprevention of breast cancer has been less clear. Egan et al found no association between regular aspirin use and the incidence of breast cancer in a cohort study of 89 528 registered nurses in the United States in 1990.[6] The analyses were based on 2414 cases identified over 12 years' follow up (relative risk 1.0). By contrast, in their case-control study of 511 women with newly diagnosed breast cancer and 1534 women who had undergone screening mammography Harris et al found a reduced risk of breast cancer associated with use of any non-steroidal anti-inflammatory drug three or more times weekly for at least a year (relative risk 0.66).[7] The protection was similar for users of aspirin alone, ibuprofen alone, and all non-steroidal anti-inflammatory drugs combined. The most heavily exposed women had the lowest risk, although the study was limited by incomplete descriptions of the study population, the participation rates, and exposure categories.

It was thus of great interest when Parrett et al showed for the first time that cyclo-oxygenase-2 was overexpressed in primary breast cancers.[8] They detected the cyclo-oxygenase-2 isoform only in breast tumours and not in normal breast tissue. Their results suggest that cyclo-oxygenase-2 may serve as a target for inhibition of breast cancer growth and progression. The cyclo-oxygenase-2 overexpression may also account, at least partly, for the high levels of prostaglandins found in breast cancers without oestrogen receptors, which show high metastatic potential.[9] Prostaglandins are thought to play an important part in promoting cancer growth and metastases and subverting host immune responses.

The cyclo-oxygenase-2 hypothesis in breast cancer has far reaching implications, given that the future development of non-steroidal anti-inflammatory drugs will be towards specific cyclo-oxygenase-2 inhibition. Cyclo-oxygenase-2 inhibitors could provide a novel means for chemoprevention of breast cancers and possibly an alternative to prophylactic mastectomy and a complement to tamoxifen in women at high risk. The parallel example in the chemoprevention of colon cancer is the efficacy of the non-steroidal anti-inflammatory drug sulindac in regressing polyps in patients with familial adenomatous polyps. Selective cyclo-oxygenase-2 inhibitors might also help to prevent relapse in patients in remission from a primary breast cancer. In both primary and secondary chemoprevention in vitro data indicate that selective cyclo-oxygenase-2 inhibitors may be particularly useful in patients with receptor negative breast tumours.[10]

Thus, as in colorectal cancer, cyclo-oxygenase-2 may serve as a target for chemoprevention of breast cancers. Although the mechanisms underlying the cancer preventive properties of non-steroidal anti-inflammatory drugs are not fully understood, recent studies have identified several possibilities. The clinical applicability of these findings is testable in a chemoprevention trial in women at high risk of breast cancer.

Harri Vainio *Chief*

Gareth Morgan *Technical officer*

Unit of Chemoprevention, International Agency for Research on Cancer, 69372 Lyons Cedex 08, France (Vainio@iarc.fr)

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