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Chemoprevention of colorectal cancer

KEYWORDS: Colorectal Neoplasms; Chemoprevention; Food Habits

ABSTRACT

Colorectal cancer is one of the most common forms of cancer, with 400 000 death per year worldwide. CRC is potentially preventable disease. Methods to be considered for prevention should include intervention in the general population, adenoma and cancer prevention in high-risk individuals, and trials for patients treated for cancer using "adjuvant chemoprevention" to slow tumor progression, local recurrence, and metastases. Dietary measures such as increased dietary fibers, vegetables and fruits, decreased alcohol intake, and complete restriction of nicotine are recommended by the World Health Organization. Candidates for chemoprevention include: vitamins A, C, D, and E, calcium, folate, H2 blockers and acetylsalicylic acid (ASA) and nonsteroid anti-inflammatory drugs (NSAIDs). Cyclooxygenase-2 inhibitors have also recently become available. The authors have been concluded that cancer may be prevented by avoiding exposure to agents and lifestyle factors known of the increase cancer risk (primary prevention), as well as by detection of the early stages on the pathway to cancer (secondary prevention).

EPIDEMIOLOGY AND PREVENTION

Colorectal cancer (CRC) is one of the most common forms of cancer, with 678 000 new cases and 400 000 deaths per year worldwide. The disease is most frequent in Europe, North America, Australia and New Zealand, while the lowest rates are found in sub-Saharan Africa: Incidence rates in the world for colonic and rectal carcinoma for males were higher (28.7%) than those for females (22.4%). Incidence increases with age: carcinomas are rare before the age of 40 years except in individuals with genetic predisposition or predisposing conditions such as chronic inflammatory bowel disease. Early detection of CRC using screening tests for fecal occult blood or endoscopy is directed at preventing progression of the adenoma-carcinoma sequence, or at detection of cancer before invasion and metastases have occurred (1-3). Molecular screening methods are presently not available of the frequent, spo-

radic form of CRC. CRC is potentially preventable disease. The marked geographic variation in incidence, and the fact that migrants rapidly acquire the incidence rates of their new country, suggests an important environmental component for the risk of developing CRC (4). Methods to be considered for prevention should include intervention in the general population, adenoma and cancer prevention in high-risk individuals, and trials for patients treated for cancer using "adjuvant chemoprevention" to slow tumor progression, local recurrence, and metastases (3,5,6). Chemoprevention agents chosen for study should be capable of long-term administration and should be largely or totally free of adverse side effects.

DIETARY MEASURES

Dietary measures such as increased dietary fibers, vegetables and fruits, decreased alcohol intake, and complete restriction of nicotine, are logical, and are recommended by the World Health Organization guidelines (4). Regular physical exercise and maintenance of normal body weight are also protective measures.

CHEMOPREVENTION

Chemoprevention of CRC seems to be promising, but an ideal, save chemopreventive agent has not yet been identified. Candidates for chemoprevention include: vitamins A, C, D, and E, calcium, folate, H2 blockers, ASA and NSAIDs in particular (7,8); cyclooxygenase-2 inhibitors have also recently become available (9,10). Case control and cohort studies have provided some evidence that NSAIDs prevent the development of adenomatous polyps and their progression (1). Cancer probably arises as a result of several cellular and molecular changes that convert a normal epithelial cell into a colorectal cancer cell. The mechanisms for this are not quite clear. ASA irreversibly acetylates prostaglandin H synthase, thereby inactivating cyclooxygenase activity, whereas most of other NSAIDs inhibit this enzyme in a reversible, concentration-dependent fashion. ASA is therefore a more potent inhibitor of prostaglandin synthesis than the other NSAIDs (3,8,10)

Cyclooxygenase-2 (COX-2) is overexpressed in 50% of adenomas and 85% of adenocarcinoma of the colon. Increased levels of COX-2, prostaglandin, or both are demonstrated in patients with familial adenomatous polyps (FAP). It has been hypothesized that COX-2 overexpression is secondary to mutations of the APC gene or other genes. It is possible that both tumor and stromally derived COX-2 influence tumor angiogenesis and/or immune function, thus contributing tumor growth (8-10). NSAIDs inhibit adenoma and CRC formation in rodents, inhibit adenoma development in human subjects with FAP, and interfere with early stages of the adenoma-carcinoma sequence (8). However, NSAIDs have serious adverse effects on the kidney, liver, lung and skin, and most importantly may lead to peptic ulcer formation bleeding.

Colorectal cancer patients with levels of COX-2 in their tumor cells have reduced five-year survival rate of 40.5%, compared with patients whose tumors are negative for COX-2 who have a five-year survival rate of 91.6% (10). The new class of COX-2 inhibitors inhibits the overexpression of the COX-2 gene early in carcinogenesis, and thereby inhibit the formation of aberrant crypts (11). The authors believe that COX-2 will serve as an important molecular target for chemoprevention of cancer-not only in the colon, but in other organs as well. CRC with a strong genetic component is found in only 5%-10% of cases (5,6,12). There is now enough evidence to say that 90% of CRC cases are induced by environmental factors, mainly in the diet. If CRC is a lifestyle tumor, a change of habits and alteration of environmental factors should influence the occurrence of this tumor.

CONCLUSION

Prevention and early detection of CRC are the ultimate aim of all researchers (1). Cancer may be prevented by avoiding exposure to agents and lifestyle

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factors known to increase cancer risk (primary prevention). However, even after exposure to a carcinogen, the multi-step process of cancer development may be slowed, halted or even reversed by a variety of strategies, thus preventing progression to clinical disease. (2) Detection of early stages on the pathway to cancer is therefore important (secondary prevention). (3) Chemoprevention has the potential to reduce the incidence of CRC in the twenty-first century.

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