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Diploma Thesis

The role of Aspirin in the prevention of Colorectal Cancer

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Written Declaration

I declare that I completed the submitted work individually and only used the mentioned sources and literature. Concurrently, I give my permission for this diploma/bachelor thesis to be used for study purposes.

Prague, April 28th 2009-04-28

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Contents:

Introduction

Physicians and medical staff alike are confronted with a wide distribution of Colorectal Cancer worldwide today. Its spread and epidemiology have resulted in new aspects of treatment of this widely malignant disease.

Yet, in most cases, an alternative treatmant other than surgery and Chenotherapy is not known and today the focus is centred to prevent Colorectal Cancer by educating patients at risk and promoting a healthy lifestyle.

Fortunately, with the introduction of several laboratory tests and especially with the diagnostic tool of Colonoscopy, patients with an early onset of the disease can be detected and forwarded to appropriate treatment.

This work focuses on the preventional aspect of Colorectal Cancer in terms of the use of Non-steroidal Antiinflammatory Drugs and Cyclooxygenase II Inhibitors.

Furtheron, one aspect of this thesis will focus on the geographical spread of Colorectal Cancer.

I truly hope that this work will be helpful in some ways to understand the above mentioned aspects of the disease and will contribute to a better focus on its prevention, as far as this is possible.

1. Chapter

1.1 Pathology and Pathophysiology

A great majority of all cancers in the large intestine are adenocarcinomas. They represent one of the prime challenges to the medical profession, because they almost always arise in adenomatous polyps that are generally curable by resection.

The Adenoma-Carcinoma Sequence:

The development of carcinoma from adenomatous lesions is referred to as the adenoma-carcinoma sequence and is documented by these observations:

1. Populations that have a high prevalence of adenomas have a high prevalence of colorectal cancer, and vice versa.
2. The distribution of adenomas within the colorectum is more or less comparable to that of colorectal cancer.
3. The peak incidence of adenomatous polyps antedates by some years the peak of colorectal cancer.
4. When invasive carcinoma is identified at an early stage, surrounding adenomatous tissue is often present.

5. The risk of cancer is directly related to the number of adenomas, and hence the virtual certainty of cancer in patients with familial polyposis syndromes.
6. Programs that assidiously follow patients for the development of adenomas, and remove all that are identified, reduce the incidence of colorectal cancer.

Colorectal Carcinogenesis:

It is now believed that there are two pathogenetically distinct pathways for the developmant of colon cancer, both of which involve the stepwise accumulation of multiple mutations. However, the genes involved and the mechanisms by which the mutations accumulate are different.

The first pathway, also called the APC/ß-catenin pathway, is characterized by chromosomal instability that results in stepwise accumulation of mutations in a series of oncogenes and tumor suppresor genes.

The molecular evolution of colon cancer along this pathway occurs through a series of morphologically identifiable stages. Initially, there is localized colon epithelial proliferation. This is followed by the formation of small adenomas that progressively enlarge, become more dysplastic, and ultimately develop into invasive cancers.

This is referred to as the adenoma-carcinoma sequence. The genetic correlates of this pathway are loss of the APC tumor suppressor gene, which is the earliest

event in the formation of adenomas. Furtheron, there is a mutation of K-RAS. The K-RAS gene encodes a signal transduction molecule that oscillates between an activated guanosin triphosphate-bound state and an inactive guanosin diphosphate-bound state.

The second pathway is characterized by genetic lesions in DNA mismatch repair genes. It is involved in 10% to 15% of sporadic cases. Defective DNA repair caused by inactivation of DNA mismatch repair genes is fundamental and the most likely initiating event in colorectal cancer that develops in this pathway.

Morphology:

About 25% of colorectal carcinomas are in the caecum or ascending colon, with a similar proportion in the rectum and distal sigmoid. An additional 25% are in the descending colon and proximal sigmoid, the remainder are scattered elsewhwere.

Tumors in the proximal colon tend to grow as polypoid, exophytic masses that extend one wall of the capacious cecum and ascending colon. When carcinomas in the distal colon are discovered, they tend to be annular, encircling lesions that produce so-called napkin-ring constrictions of the bowel and narrowing of the lumen.

1.1.1 Epidemiology

Colorectal cancer is an important public health problem: there are nearly one million new cases of colorectal cancer diagnosed world-wide each year and half a million deaths. Recent reports show that, in the US, it was the most frequent form of cancer among persons aged 75 years and older. Given that the majority of cancers occur in elder people and with the ageing of the population in mind, this observation gives further impetus to investigating prevention and treatment strategies among this subgroup of the population. Screening research, recommendations and implementation is an obvious priority.

While there are many questions to be resolved, it is apparent that many facets of colorectal cancer are becoming increasingly understood and prospects for prevention are becoming apparent. Achieving colorectal cancer control is the immediate challenge.

Colorectal cancer has a worldwide distribution, with the highest incidence rates in the United States, Canada, Australia, Denmark, Sweden, and other developed countries. Its incidence is substantially lower, up to 30-fold less, in India, South America, and Africa. The incidence in Japan, which formerly was very low, has now risen to the intermediate levels observed in the United Kingdom.
Environmental factors, particularly dietary practices, are implicated in these striking geographical contrasts.

The dietary factors receiving the most attention are a low content of unabsorbable vegetable fiber, a corresponding high content of refined carbohydrates, a high fat content (as from meat), and decreased intake of protective micronutrients such as vitamins A, C, and E.

The theory is that reduced fiber content leads to decreased stool bulk, increased fecal retention in the bowel, and an altered bacterial flora of the intestine. Potentiallly toxic byproducts of carbohydrate degradation by bacteria are therefore present in higher concentrations in the small stools and are held in contact with the colonic mucosa for longer periods of time. Moreover, high fat intake enhances the synthesis of cholesterol and bile acids by the liver, which in turn may be converted into potential carcinogens by intestinal bacteria. Refined diets also contain less of vitamins A, C, and E, which may act as oxygen radical scavengers.

2. Chapter

2.1 Pharmacological Prevention of Colorectal Cancer:

Several recent epidemiologic studies suggest that use of aspirin and other NSAID's exerts a protective effect against colon cancer. In the Nurses' Health Study, which was initiated in 1976,women who used four to six tablets of aspirin per day for ten years or more had a decreased incidence of colon cancer. Possible mechanisms of this form of chemo prevention include induction of apoptosis in tumor cells and inhibition of angiogenesis. The latter effect seems to be mediated by inhibition of cyclooxygenase-2. This enzyme in the prostaglandin synthesis pathway seems to favor angiogenesis by enhancing production of vascular endothelial growth factor. Some Drug Administrations have approved the use of cyclooxygenase-2 inhibitors as chemopreventive agents in patients with familial adenomatous polyposis syndrome.

Observational studies and randomized intervention trials have found that regular use of aspirin reduces the risk of colorectal neoplasms. The mechanism by which aspirin influences the risk of colorectal cancer is not well understood. Aspirin inhibits cyclooxygenase, which catalyzes the rate-limiting step in the metabolic conversion of arachidonic acid to prostaglandins and related eicosanoids. One form of cyclooxygenase, termed cyclooxygenase-2 (COX-2), promotes inflammation and cell proliferation, and colorectal cancers often overexpress this enzyme. Randomized trials have demonstrated that selective inhibitors of COX-

2 reduce the risk of recurrent adenoma in participants at high risk. However, aspirin and nonsteroidal antiinflammatory drugs (NSAIDs) decrease proliferation and increase apoptosis of colorectal cancer cell lines that have no detectable cyclooxygenase activity. Aspirin has other effects that are unrelated to cyclooxygenase, including inhibition of nuclear factor-B, induction of apoptosis by activation of p38 kinase, and catabolism of polyamines. If aspirin exerts its effect on the formation of adenomas and cancers by inhibiting COX-2 or its downstream effectors, then the use of aspirin should preferentially reduce the risk of tumors for which growth depends on COX-2 function.

COX-2 is upregulated at an early stage in colorectal carcinogenesis and generates prostaglandins, which promote cancer cell proliferation, impair apoptosis and enhance angiogenesis, promoting tumour growth and metastasis. There are ample data from animal models and human studies to demonstrate enhanced tumour progression associated with COX-2 activity in cancer cells. Conversely, NSAIDs including aspirin inhibit COX-2 and, therefore, have anti-neoplastic properties. There has been sustained interest in COX-2 as a chemopreventive target in colorectal cancer (CRC) and although both aspirin and COX-2 selective NSAIDs have demonstrated efficacy, adverse effects have limited their widespread adoption. In particular, evidence of the cardiovascular effects of COX-2 selective inhibitors has led to questioning of the suitability of COX-2 as a target for chemoprevention.

Recent preclinical as well as clinical trials have provided data on the potential benefit of a number of drugs and nutritional elements in the field of CRC prevention. Currently, only celecoxib is FDA approved for chemoprevention of CRC and only for high-risk patients with Familial Adenomatous Polyposis (FAP). This is mainly due to cardiovascular toxicity reported in individuals with a personal history of sporadic adenomas. Aspirin and sulindac have also repeatedly demonstrated efficacy in this setting. However, due to increased risk of associated GI toxicity their benefit will have to be weighed against their risk. Combination therapy, using lower doses of each medication, is drawing a great deal of attention and many studies utilizing a variety of chemopreventive agents are presently under study. Promising results have recently been published using sulindac.

Conclusion: Many agents have shown positive results in the field of chemoprevention however, the ideal chemopreventive agent remains to be discovered with great emphasis on need not to harm. Combining different agents may maximize effectiveness while limiting drug toxicity.

Conclusion

Despite a wide spread of colorectal cancer worldwide, researches and scientific studies show that there is a chance of prevention in patients who are believed to be more susceptible than others because of a family history or signs of familial adenomatous polyposis. The extent of prevention and the amount of chemotherapeutic agents used remains a question of controversion.

In countries with higher incidents of colorectal cancer, programs of education concerning right nutrition and diet regimens adjusted to the prevention of the disease should be supported.

As dietary factors such as high fat and increased consumption play a significant role in the formation of the disease, care should be taken to educate patients to avoid these potentially harmful factors of nutrition. Furtheron, as shown before, decreased consumption of Vitamins A, C, and E contributes to the development of colorectal cancer, as they act as oxygen radical scavenger cells.

Patients should be supplied with these vitamins in order to prevent hypovitaminosis.

Summary

Non-steroidal Antiinflammatory Drugs have been shown to play an important role in the chemotherapeutic prevention of Colorectal Cancer. Their mechanism in doing so has been proven as far as scientific works today allow results and an understanding of this mechanism. Without a doubt, many aspects of this drug in terms of chemotherapy tailored to the treatment of Colorectal Cancer remain to be illuminated and are subject to further investigations.

Whether a cyclooxygenase inhibitor can be used as a chemopreventive agent needs to be assessed in each case individually and the whole view of a patient must be taken into account considering his overall status of health and the exclusion of the potential harm of side effects.

Given the fact that these drugs provide protection of Colorectal Cancer to a certain extent, their use will most probably increase in countries where they are easily accessable.

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