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Review Article

Prevention of colorectal cancer: How many tools do we have in our basket?

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ABSTRACT

Prevention is the main strategy in order to reduce colorectal cancer incidence and mortality. It can be accomplished through primary prevention, using measures affecting factors known to confer higher risk of colorectal cancer, or through secondary prevention, aimed at early diagnosis of cancer or preneoplastic lesions in groups of subjects at increased risk of cancer. Although primary prevention should be the goal for future years, because it acts on the probable causes of colorectal cancer, at present it seems that secondary prevention is more effective on colorectal cancer survival, and the approaches which have yielded the most satisfying results, in terms of reduced mortality for cancer, are those aimed at detecting preneoplastic lesions, or cancer at an early stage in selected groups of subjects at average or increased risk of colorectal cancer. These groups are subjects aged 50 years or older, affected individuals (gene carriers) or family members of hereditary colorectal cancer syndromes (i.e., Lynch syndrome and familial adenomatous polyposis), and patients with inflammatory bowel diseases. The most effective procedures used, though with some drawbacks, are fecal occult blood tests and colonoscopy. Future research should be addressed to find new approaches that will render preventive strategies more acceptable for the population, and more cost-effective.

Introduction

Colorectal cancer (CRC) is a major cause of incidence and mortality in many countries, especially in more developed ones, though in very recent years its incidence is increasing also in developing areas of the world [1].

There is a wide epidemiological and observational evidence that the risk of colorectal cancer is strictly related to lifestyle, especially to diet and physical activity [2]. In analytical case–control and cohort studies, risk is directly associated with the consumption of red and processed meat, and with abdominal fatness, and inversely related to physical activity. Somewhat at a lesser extent, dietary fiber seems to reduce the risk.

For many years researchers have taken advantage of the fact that colorectal carcinogenesis is a stepwise process, lasting several years, since its beginning as a single mutational event in a cell, until detectable malignancy. Meanwhile, it is supposed that several actions might be taken or planned, or almost thought to be tested in several models, in order to change the course of the process, either stopping or slowing it.

At present, two main preventive strategies for colorectal cancer are being in action: primary prevention affecting risk factors, and secondary prevention aimed at the early detection of preneoplastic or neoplastic lesions in the large bowel, in populations at average or increased risk, mainly because of age, hereditary colorectal cancer syndromes, or inflammatory bowel diseases. Only some of them have reached strong and sound results in terms of decreasing incidence and mortality for CRC. We will discuss the effectiveness of these strategies, taking into account only solid evidence coming from randomized clinical trials or guidelines of scientific societies.

Articles have been selected using the following keywords: prevention of colorectal cancer, chemoprevention of colorectal cancer, colorectal cancer screening, Lynch syndrome, familial adenomatous polyposis, inflammatory bowel diseases, and the time period of the search was October–December 2014.

1. Primary prevention through measures affecting risk factors: Lessons from chemopreventive studies

The available evidence indicates that primary prevention of colorectal cancer is feasible. At least 70% of colon cancers may be – at least in theory – preventable by changes in diet and lifestyle [3]. The target of primary prevention is the general population at large. The perspective of reducing colorectal cancer incidence and mortality through multiple dietary modifications or adding substances to the diet is very attractive. However, we need studies on high colorectal cancer risk patients to gather information useful for the general population. The main problem of this approach is that actions are based only on hypotheses or epidemiological evidence linking lifestyle and colorectal cancer [4–6]. Another issue is the long time a randomized clinical trial would last in order to see any effect of an intervention, having cancer mortality as an end point [7]. To overcome that problem researchers have adopted "surrogate" end points for colorectal cancer mortality so far, either very early in carcinogenesis ("tumor markers") or later, i.e., aberrant

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crypt foci or microadenomas [8], adenomas, and colorectal cancer incidence. Earlier markers have the drawback to be linked too loosely with cancer. Indeed, despite interesting observations in animal studies [9,10], and in human short-term biochemical risk marker trials [11], major human intervention studies of dietary manipulations on patients at increased risk of colorectal cancer have largely failed to demonstrate any robust effect, or results were not consistent [12–14]. Similarly, chemoprevention with dietary supplementation with fiber, antioxidant vitamins, and minerals (mainly calcium) provided negative or inconsistent results on adenoma recurrence [15–20]. On the other hand, when considering chemoprevention with drugs, those more frequently investigated are non-steroid anti-inflammatory drugs (NSAIDs), and, among them, 5-aminosalicylic acid, sulindac, and cyclooxygenase 2 inhibitors (celecoxib and rofecoxib). Supplementations with these drugs were consistently effective in preventing adenoma onset or recurrence [21–23], but their gastrointestinal and/or cardiovascular toxicity render them not suitable for prevention. Taken together, results of prospective human randomized chemopreventive trials were not in line with those of observational studies, for different reasons [24]. In addition, primary prevention does not eliminate the need of follow-up or surveillance for the disease. Thus, at present, any dietary, lifestyle or chemopreventive recommendations aimed at reducing colorectal cancer mortality, is premature for the general population. The real problem is that we do not have completely unraveled the complex network of the causes of CRC. This fact reinforces the need for studies on risk factors, and it does not mean that active research on prevention based on lifestyle modifications should be stopped.

The available epidemiological evidence for colon and rectal cancers suggests that physical activity decreases the risk, whereas body (especially abdominal) fatness, and the consumption of red and processed meat, and of alcoholic beverages increase the risk. Thus, from a practical point of view, recommendations should be given to the general population, in order to encourage a healthy lifestyle. At present, the "milestones" recommendations for colorectal cancer are: be as lean as possible within the normal range of body weight, be physically active as part of everyday life, eat mostly foods of plant origin (especially foods containing dietary fiber), limit intake of red meat and avoid processed meat, and limit alcoholic drinks [2].

2. Secondary prevention

Secondary prevention of colorectal cancer is targeted at populations at average or increased risk of colorectal cancer. At present, they are: general population at increased risk because of age, subjects belonging to families with hereditary colorectal cancer syndromes, and patients with longstanding and widespread inflammatory bowel diseases.

2.1. General population

Screening programs are mostly targeted at adults older than 50–55 years, a population at increased risk of developing adenomas and cancer [25]. These programs have been implemented at regional and national levels all over the world, though they differ considerably across countries. At present screening is based on some methods with different advantages and drawbacks, and different economic impact. The most employed are fecal occult blood tests (FOBT) or, more recently, fecal immunological tests (FIT), flexible sigmoidoscopy (FS) and colonoscopy (C). FOBT and FIT are based on the assumption that a colorectal adenoma or cancer bleeds, but this is not always the case. FS and C may allow to remove adenomas and to detect a malignancy at an early stage. Adenoma removal reduces long term colorectal cancer mortality [26]. The effectiveness of screening policies in reducing cancer-related mortality has been evaluated with randomized clinical trials and systematic reviews of their results, or indirectly by observational studies based on incidence and mortality data from cancer registries at the population level. Indeed, colorectal cancer screening with FOBT, flexible sigmoidoscopy or colonoscopy has been shown to reduce incidence of colorectal cancer and cancer-related mortality [27–34], though for screening colonoscopy randomized clinical trials are still lacking. Cancer registries are particularly useful in order to evaluate the impact of prevention strategies [35]. However, caution should be used when interpreting mortality data from cancer registries, because of wide differences in stage distribution among countries [36]. It is necessary to develop new screening approaches, for example using new innovative technologies such as computed tomographic colonography and stool screening for molecular markers [37,38].

Where available, a screening program for colorectal cancer is probably the best way to prevent colorectal cancer. This would provide the most benefit for the population, though the participation rates for the various screening programs should be improved. A valid alternative for us could be performing a once-in a lifetime colonoscopy at the age of 50–55, in line with the age-specific incidence of colorectal cancer at the population level [25].

2.2. Hereditary colorectal cancer (HCRC)

The most frequent forms of HCRC are Lynch syndrome (LS) and familial adenomatous polyposis (FAP). The genetic bases of both diseases have been clarified in the early 1990s. Prevention of CRC in gene carriers (i.e., patient carriers of a deleterious mutation in a DNA mismatch-repair [MMR] gene, and in adenomatous polyposis coli [*APC*] or *MUTYH* genes, respectively) can be accomplished through follow-up colonoscopies with removal of adenomas (when feasible), or prophylactic colectomy (in selected cases) (Table 1).

2.2.1. Lynch syndrome

LS is the most frequent autosomal dominant hereditary colorectal cancer syndrome. It accounts for approximately 1%–2% of the whole colorectal cancer burden in the population, at least in western countries, considering only MMR gene carriers [39].

Our approach used to identify DNA MMR gene carriers is based on a careful evaluation of the nuclear family pedigree (limited to first-degree relatives of the proband affected by colorectal cancer), in order to find out the clinical feature of a Lynch syndrome, according to some criteria which, if present, prompt us to expand the pedigree to second and third-degree relatives [40]. Then, in this expanded pedigree, we evaluate whether the international validated criteria for the clinical diagnosis of Lynch syndrome (the so-called Amsterdam II criteria [41]) are satisfied. The molecular genetic test for the identification of the deleterious mutation in a DNA MMR gene is offered to the proband and then to all the family members at risk.

DNA MMR gene carriers have a high life-time risk of developing cancer in the large bowel [42], and in other organs. Surveillance colonoscopies have been shown to reduce CRC-related mortality [43]. At present, prevention of CRC through colonoscopies every 1–2 years in gene carriers, starting at ages 20 to 25 years, is the recommended schedule of colorectal follow-up [44].

Indeed, it is mandatory for the MMR gene mutation carriers to perform a full colonoscopy every 1–2 years for the whole life, because of the high penetrance of the diseases. It should be also offered to selected patients the option of a prophylactic colectomy, though there are still few data to recommend it in all gene mutation carriers. Furthermore, in some families an increased risk of endometrial and ovarian cancers has been observed, and they must undergo screening also for gynecological cancers through transvaginal ultrasound starting from 25–30 years, and then every 2–3 years, though this approach has not yet proven to be effective in reducing cancer mortality.

2.2.2. Familial adenomatous polyposis

FAP is the most frequent hereditary colorectal polyposis syndrome. Data from cancer registries show that classical FAP (at least 100 adenomas in the colorectum of affected patients) accounts for less than 1% of

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