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Dietary and Non-Dietary Aspects in Colon and Rectal Cancer

Edward Giovannucci
Channing Laboratory, Department of Medicine
Harvard Medical School & Brigham and Women's Hospital, Boston, MA
and Departments of Nutrition and Epidemiology, Harvard School of Public Health, Boston, MA

Introduction

Colorectal cancer (CRC) is one of the most common malignancies in Western countries. This cancer occurs with high frequency in both sexes. In North America, the lifetime risk of invasive CRC is approximately 1 in 17 in both men and women[1]. After cancers of the breast and lung, CRC is the third most commonly occurring nonskin cancer site and cancer cause of death in women. In women 75 years and older, the number of CRC deaths exceeds those from breast cancer[1]. In men, CRC incidence is exceeded only by lung and prostate cancer.

The majority of CRCs are adenocarcinomas, which arise from an existing benign adenomatous polyp, also called an adenoma. The majority of adenomas do not progress to malignancy; even when they do, 10 or more years may elapse before malignant transformation[2]. Removal of the premalignant adenomas, typically by colonoscopy, would prevent cancer. Treatment for colon cancer is generally removal of half or more of the large bowel. Following surgery, chemotherapy may be used to treat micro-metastases. Overall 5-year survival rates are about 50-60%, but survival rates are much lower with advanced stage disease. Endoscopic procedures are important both in identifying and removing precursor adenomas and in detecting cancers at earlier and more treatable stages.

Individuals with a first-degree relative with CRC have about a two-fold increased risk for the disease[3]. While an inherited component is important, a strong genetic predisposition accounts for only a small proportion of cases[3]. Thus, the risk of CRC is largely related to external or non-genetic causes. About two decades ago, the eminent epidemiologists Doll and Peto used international comparisons of exposure prevalences and disease rates to estimate that up to 90% of colon cancers may have a non-genetic, primarily dietary, contribution[4]. For example, high fiber, fruit and vegetable, folate, calcium, and vitamin D intakes have been proposed to be protective, while high animal fat, red meat, and alcohol consumption may increase risk. In recent years, it has become evident that non-dietary factors, particularly smoking, obesity and sedentary lifestyle, are also quite important. The evidence supporting a role for these external factors on CRC risk is briefly reviewed in the following report.

Obesity

In numerous epidemiologic studies[5,6], higher body mass index (weight divided by the square of height), a measure of obesity, is related to an elevated risk of CRC. This relation is stronger in men than in women, but is present in both. Lowering energy intake has long been known to reduce tumor incidence in rodents. The mechanism may be related to the reduction in circulating insulin, a tumor growth promoter[7]. Also supporting a role of insulin is that central obesity, as determined by a high waist-to-hip ratio for example, accompanies hyperinsulinemia and is also an independent risk factor for CRC[5]. Recent studies have also linked type 2 diabetes mellitus, and high levels of insulin and insulin-like growth factor to increased risk of CRC.

Physical Activity

More than 50 studies have examined the relation of occupational and recreational activities with CRC risk[8]. These have consistently shown that the most active individuals have about a 50% reduction in risk relative to inactive people[8]. The gradient of the benefit occurs across activity levels spanning from low to high[7]. In the Nurses' Health Study, women whose leisure-time physical activity exceeded the equivalent of running 2 hours/week had about half the risk of total colon cancer as those with very low activity levels[6]. Even brisk walking was beneficial. Physical activity may affect CRC risk by helping in maintenance of body weight, which influences hyperinsulinemia[7], by directly reducing insulin levels by heightening response of muscle to insulin, and by stimulating bowel motility[9].

Smoking

Smoking tobacco is now established as a clear risk factor for CRC[10]. This fact may be surprising to some because many earlier studies had not shown a relation between cigarette smoking and CRC[3]. However, most of these studies had not considered a sufficiently long induction or latency period between time of smoking exposure and risk for CRC. Numerous studies now show that smoking does increase risk of CRC, but only after a time lag of approximately 35 to 40 years[10]. These findings indicate that tobacco smoke constituents are likely initiators in the carcinogenesis pathway. This conclusion is also supported by many studies that show that smokers have a higher risk of the precursor adenoma[11]. An increased risk of CRC may only become apparent decades after one begins smoking.

Alcohol

Although not all studies are consistent, most epidemiologic studies support a positive association between alcohol consumption and CRC risk[3]. For example, in a large prospective study, men who had more than 2 drinks/day of alcoholic beverages had about double the risk of CRC relative to abstainers or infrequent drinkers[12]. Recent evidence suggests that alcohol intake may be deleterious primarily when intake of one or more micronutrients is low. The best micronutrient candidate is folate or folic acid because alcohol is a strong antagonist of folate metabolism and low levels of folate appear to increase risk of CRC. It appears that the excess risk of CRC associated with high alcohol consumption is most apparent when folate intake is low, but that risk of CRC in drinkers is not appreciably elevated when folate intake is relatively high[12]. The role of folate is discussed in more detail below.

Medications: Aspirin and Post-Menopausal Estrogen Use

Two widely used medications, aspirin and post-menopausal estrogen replacement, have shown promise as anti-CRC agents. Although the data are not definitive, an inverse association for each of these agents has been seen consistently in a very large number of studies[13-16]. For post-menopausal estrogens, recent use is more protective than past use, whereas for aspirin, the reduction is greatest for long-term consistent use[17]. Although the epidemiologic evidence is quite compelling for each of these, especially aspirin, each has potential downsides as well as other benefits. Thus, the question of whether these should be used is not confined to risk of CRC but to overall health.

Diet

As discussed above, diet is important for CRC to the extent that it contributes to energy balance and possibly hyperinsulinemia. However, there may be some specific components of the diet that may increase or decrease risk of CRC. For example, red meat increases risk while some potentially beneficial agents including fruits, vegetables, fiber, and some specific vitamins and minerals, particularly folate and calcium.

Animal Fat and Red Meat

Across countries, age-adjusted incidence and mortality of CRC is correlated with national *per capita* consumption of animal fat and meat[18]. However, *per capita* fat and meat intake may be a marker of Western lifestyle, such as physical inactivity and obesity. Epidemiologic studies have not generally confirmed total fat or animal fat as an independent predictor of colorectal cancer risk, at least apart from any contribution of these on obesity. However, in aggregate, prospective studies tend to show a positive association between red meat intake, particularly

processed meats, and CRC risk[19]. Why red or processed meat is associated with increased risk is unknown. Recent hypotheses emphasize the presence of mutagenic heterocyclic amines that are formed when meat is cooked at high temperatures (e.g. barbecuing, grilling, frying), or nitrates used in processing[19], although the evidence is not conclusive[20].

Fruits, Vegetables, and Fiber

Over three decades ago, Burkitt observed low colon cancer rates in regions of Africa where fiber intake is high, prompting him to propose the hypothesis that fiber reduces risk of CRC[21]. Dietary fiber consists of plant cell wall polysaccharides (pectin, cellulose, hemicellulose) and lignin, which are not hydrolyzable by human digestive enzymes. Fiber may increase fecal bulk, possibly diluting carcinogens[21]. Despite the intuitive appeal of the fiber-CRC hypothesis, prospective dietary epidemiologic studies and randomized clinical trials using recurrent colorectal adenomas have generally not supported the fiber hypothesis[22,23]. Also, many earlier studies had suggested a protective effect of vegetable and possibly fruit consumption[3], but recent studies have also cast some doubt on the importance of vegetables and fruits[24]. In many early studies, high vegetable and fruit intake may have indicated a generally healthy lifestyle. In more recent studies, when investigators controlled statistically for recently identified CRC risk factors, including physical activity, smoking, and obesity, the effect of fiber and vegetables was substantially weaker[25]. Nonetheless, as discussed below, there is increasing evidence that some micronutrients for which vegetables and fruits are good sources may have a beneficial role.

Folate

The folate class of compounds provides methyl groups for a variety of biochemical pathways, including thymine synthesis from uracil and the conversion of homocysteine to methionine, the major methyl donor for DNA methylation[26]. The adverse effects of reduced methyl status (*i.e.*, enhanced DNA misincorporation of uridylate for thymidylate and subsequent damage from attempted repair, and DNA hypomethylation and hypermethylation leading to perturbed gene expression), suggest that folate plays a role in the carcinogenic pathway. Most relevant studies have shown a reduction in CRC and adenoma risk with increasing intake of folate[27]. Long-term (10+ years) use of folate from supplements was associated with about half the risk of CRC in several studies[27]. These data suggest that long-term use of multivitamins lowers risk of colorectal cancer. This benefit appears to be at least partly related to folate, although additional benefits from other micronutrients are possible.

Calcium and Vitamin D

I*n vitro* and *in vivo* studies suggest a beneficial effect of calcium on colonic cell proliferation and differentiation and tumor incidence[28]. Many epidemiologic studies have evaluated the calcium-CRC relation, and in general a modest protective effect is observed. A randomized clinical trial indicated a benefit of calcium on risk of recurrent colorectal adenomas[29]. Also, recent epidemiologic data indicate a protective role of dietary calcium, with the benefit leveling off at about 700 mg/day of calcium[30]. Vitamin D may also have a role, but data are too limited at this time to make definitive statements.

Summary and Conclusions

Increasing evidence indicates that CRC is quite preventable. Maintaining a health body weight, frequent exercising, and avoiding tobacco are clearly important. There may be beneficial roles for aspirin and replacement estrogens for post-menopausal women, although use of these should not be recommended solely based on CRC risk. Dietary factors are clearly important. Red and processed meats appear to be deleterious, so consumption should be minimized. Heavy alcohol consumption (>2 drinks/day) probably increases risk, especially when dietary folate is inadequate. Moderate alcohol consumption in individuals with a micronutrient-rich diet may not appreciably elevate risk. Adequate folate (at least 400 micrograms/day) and calcium (approximately 700-1,000 mg/day) from either dietary or supplementary sources is likely to lower risk of CRC by optimizing lifestyle and diet, at least 3 out of 4 CRCs may be preventable[31]. Moreover, these same factors would provide additional benefits for many conditions.

The Whitehall-Robins Report is a Whitehall-Robins publication that focuses on current issues on the role of vitamins and minerals in health promotion and disease prevention. Complimentary copies are distributed to Canadian health care professionals active or with a special interest in nutrition. Each issue is written and/or reviewed by independent health care professionals with expertise in the chosen topic.

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