Body weight and colon cancer\textsuperscript{1,2}

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ABSTRACT In 1994, there were \~160 000 new cases of colon cancer in the United States with 58 000 fatalities, making this form of cancer the second most common cause of cancer deaths. Up to 50\% of colon cancers may have a strong inherited factor, but in the remaining cases, diet and lifestyle factors are thought to play essential roles in the carcinogenic process. Various epidemiologic studies have examined the relation between obesity and colon cancer. The largest prospective study of 750 000 men showed that mortality from colorectal cancer was significantly elevated in men who were \~40\% overweight. No such increase was found in women. Subsequent studies reported conflicting results. Overweight is likely a surrogate. Other risk factors include a high-fat, energy-dense diet; inadequate consumption of fruit and vegetables; and lack of physical activity, which have been associated with a high incidence of colon cancer. \textit{Am J Clin Nutr} 1996;63(suppl):442S–4S.

KEY WORDS Colon cancer, obesity, risk factors

INTRODUCTION Colon cancer claims \~58 000 lives annually in the United States. It is second only to lung cancer as a cause of cancer death and is equally prevalent in men and women (1). Inheritance and numerous environmental and lifestyle factors such as diet, exercise, and overweight have been implicated in carcinogenesis of the colon.

About 5\% of colon cancers are caused by well-defined inherited syndromes that include familial polyposis, Gardner syndrome, hereditary nonpolyposis colon cancer, and a few other rare syndromes (2). Inflammatory bowel diseases (ie, ulcerative colitis and Crohn disease) also predispose to colon cancer. In these diseases, long-standing inflammation leads to hyperproliferation in the colonic mucosa and this appears to predispose to neoplastic changes. Neither the inherited cancer syndromes nor inflammatory bowel diseases are known to be associated with obesity.

Between 10\% and 20\% of patients who develop colon cancer have a family history of first-degree relatives with the disease, which enhances the risk by two- to threefold (2). It is not known to what extent, if any, diet and lifestyle factors influence the carcinogenic process in this group. Clarification of the complex relation between overweight and colon cancer may contribute to the discussion of healthy weight.

RISK FACTORS It is estimated that in up to 50\% of patients with colon cancer the disease is sporadic, without any apparent inherited predisposition (2). In this group, environmental and lifestyle factors appear to be the primary driving forces behind the carcinogenic process. There is strong evidence from epidemiologic studies and experimental studies in animals that a diet high in fat and energy and low in fruit, vegetables, and dietary fiber strongly predisposes to the development of colon cancer (3). Obesity and lack of adequate physical activity have also been associated with increased risk (4, 5).

There is a complex relation between increased energy intake, metabolic rate, and physical activity. Thus, a significant statistical correlation between overweight and colon cancer incidence may reflect the adverse effects of increased intake of energy or fat, rather than the risk of obesity per se. Most of the epidemiologic studies on the correlations between body weight and colon cancer have not taken diet or physical activity into consideration and have not made adjustments for the effects of inheritance.

The hypothesis that excess body weight is a factor in carcinogenesis was presented >50 y ago (6) and has since been supported by experimental evidence from animal studies indicating that a diet severely restricted in energy as well as low body weight were associated with a low cancer rate (7). In Western societies, there is a high prevalence of overweight as well as cancer in various organs (8, 9).

BODY MASS AND COLON CANCER Increased body mass has been associated with excess cancer mortality including that from colon cancer, in some but not all epidemiologic studies (10–14). Studies on the relation between overweight and colon cancer include case-control studies and cohort studies. Case-control studies with mostly hospitalized patients as control subjects did not find obesity to be associated with increased risk for colon cancer (15–19).

An American Cancer Society study, begun in 1959, followed a cohort of 419 080 men and 336 442 women to elucidate the relation between body weight and various illnesses (20). Participants were mostly from the middle class and were in good health at the time of enrollment. The results of the study showed that in males, increased body weight was associated

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with proportionally increased mortality risk from colon cancer. A 40% increase in body weight conferred a relative risk of 1.73. In females, no such association was found.

In a study by Phillips and Snowdon (21), 25 000 Seventh-day Adventists completed questionnaires that included information on body weight. After a follow-up of 23 y, it was found that a 25% excess of body weight was associated with increased mortality from rectal cancer in both sexes and from colon cancer in males only.

In the Framingham study (22), an 18-y follow-up of 5200 males and females did not show an association between overweight in excess of 20% and a high incidence of colorectal cancer. Three studies from the United States, Iceland, and Hawaii, in which body mass index (BMI) was used as a measure of overweight, did not find an association between a high body mass and incidence of colon cancer, with the exception of an increased risk in Hawaiian males (23–25).

**BODY WEIGHT IN ADOLESCENCE AS A PREDICTOR OF COLON CANCER**

Because the development of cancer is a lengthy, multistep process, it is conceivable that if overweight is a risk factor, it has to be present at an early age. Must al et al (26) examined the long-term effects of overweight in adolescence on health in middle and old age. They used data from the Harvard Growth Study, which recorded heights and weights of 3000 children from 13 to 18 y of age. Fifty-five years later, it was found that a high BMI during adolescence was significantly associated with an increased risk from colorectal cancer in men but not in women. However, the statistical analysis was based on six deaths in the male group; as such, the results are not definitive.

Another study addressing this issue relied on questionnaires, completed by Harvard University alumni in 1962 and 1966, that gathered information on height, weight, sociodemographic characteristics and medical history (27). There were 17 595 participants who were followed for > 20 y. Information on weight and height was also obtained from college records. The 20% of the alumni who were heaviest on entering college and during the 1962–1966 questionnaire period had close to 2.5 times the risk for colon cancer compared with the leanest 20% of the group. However, when adjustments were made for physical activity, the increased risk for colon cancer in the overweight group was apparent only in those who were less physically active. It was concluded that obesity during adulthood and middle age was associated with increased risk for colon cancer, but in those overweight subjects who were physically active, no such increase in risk was found.

Le Marchand et al (28) investigated the role of obesity in early adulthood in 52 539 men born between 1913 and 1927 who resided in Hawaii. The cohort was linked to the Hawaii Tumor Registry and 737 cases of colon cancer were identified between 1972 and 1986. Each case was matched with an average of 3.8 control subjects. The case-control analysis by anatomic site of the colon showed that increased body weight during early and middle age was associated with an increased risk for development of sigmoid cancer in a dose-dependent manner. No increase in risk was found for other segments of the colon. This study did not adjust for physical activity.

The studies addressing overweight in adolescents and adults in middle age suggest that obesity early in life may predispose to colon cancer (26–28). However, when adjustments are made for physical activity, it is less clear that overweight is an independent risk factor. It may well be a surrogate for other factors such as decreased activity or excess energy consumption.

**OBESITY AND COLONIC ADENOMAS**

As noted, the development of colon cancer is a multistep process that proceeds from the normal mucosa to a state of hyperproliferation. This state gives rise to small adenomatous polyps, some of which grow and become dysplastic, eventually becoming cancerous. Any environmental or lifestyle factors that contribute to the rise of cancer in the colon may exert an effect on one or more stages of this process. A few studies analyzed the relation between obesity and colon adenomas, the precursor lesions of colon cancer. A case-control study of 301 patients with adenomas and 806 control subjects found that an increased BMI in women, but not in men, was a risk factor for an adenoma (29). A German study found no association between overweight and colonic adenomas in either men or women (30). However, there was an increased incidence of high-risk adenomas in obese men. High-risk adenomas are those with villous or tubulovillous components, dysplasia, a diameter ≥ 2 cm, and multiple adenomas. These features indicate an increased potential for the adenoma to turn into cancer.

**SUMMARY**

In conclusion, there is no sufficient evidence to clearly support the hypothesis that overweight per se is associated with increased risk for colon cancer incidence, morbidity, or mortality. Nevertheless, some epidemiologic studies support such an association. At the very least, obesity could be a surrogate marker for increased risk for colon cancer as well as a marker for increased consumption of energy from fat and a marker for decreased physical activity. Currently, good nutrition and exercise are the best ways to deal on a public level with this problem because proper diet and regular physical activity are directly related to weight.

**REFERENCES**