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Review Article

Evidence in Favour of Lifestyle Intervention for Cancer Prevention with Special Reference to Colorectal Cancer

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Abstract

Randomized controlled trials are recognized as having the strongest type of study design for generating evidence on prevention of disease. They are, however, the most labor- and time-intensive and costly to conduct. Intervention studies on the recurrence of colorectal adenomas might serve as a model with relevance to the etiology of not only large bowel cancer but also other sites of neoplastic development. The results of intervention studies assessing the effect of calcium, antioxidants and fiber on the recurrence of colorectal adenomas have been conflicting, showing a beneficial effect in some cases but not others. There are methodological issues in intervention trials for colorectal cancer, regarding study subjects, end point, dose, interaction, duration and timing, and compliance, for example. Although relatively few trials have been conducted to investigate the effects of an explicit dietary change on the recurrence of adenoma, results obtained so far have demonstrated that modifying the lifestyle may reduce the risk of chronic diseases including cancer. Furthermore, recent progress in molecular epidemiology has allowed clarification of many of the molecular mechanisms underlying susceptibility. Eventually, it may be possible to target intervention programs to genetically susceptible individuals, including molecular targeting, for the prevention of cancer.

Key words: intervention, cancer prevention

Introduction

Randomized controlled trials are generally recognized as being most efficacious but are very labor- and time-consuming, as well as costly. Several practical reasons exist to explain why cancer primary prevention trials are rarely conducted. Cancer incidence cannot be used as the primary end point, given the length of follow-up that would be needed and the loss to follow-up that would likely occur. Intermediate end points that are biological markers of disease are more feasible; however, for most cancer sites, reliable and valid intermediate end points have yet to be established. It is relatively clear that the adenoma carcinoma sequence of colon cancer is a multi-step process, and cancer might be expected to be prevented if adenoma development were suppressed. There is also clear evidence that the diet has a major role in colon carcinogenesis. Thus, epidemiological and experimental studies have suggested that consumption of dietary fiber, vegetables, fruits, whole-grain cereals, and calcium may have a protective effect against the development of colorectal adenomas and cancers. The associations shown suggest that intervention studies using polyps as the end point might serve as models with relevance to the etiology of not only large bowel cancer but also other sites of cancer.

Overview of the evidence in intervention trials for colorectal cancer

Most trials tested the effects of pharmacologic intervention using dietary supplements, such as betacarotene, vitamin C, and wheat bran fiber. Other important challenges are non-pharmacologic interventions which emphasize modifying the lifestyle, especially dietary change. Behavioral research on dietary change can advance the application of knowledge about nutrition and health, and trials of non-pharmacologic intervention that can be implemented in primary health care are vital for the future. The authors here summarize two types of intervention trials for colorectal cancer as models.

Pharmacologic intervention

Pharmacological intervention trials are summarized in Table 1.

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Table 1 Summary of Pharmacologic Intervention Trial for Colorectal Cancer

Authors (reference no., year)	Patient characteristics	Trial design	Location of study population	Treatment	Dose	End point	Length of follow-up
Alder et al. (12, 1993)	Age range, 40–60 years 68 male volunteers	Randomized, placebo-controlled	Ontario, Canada	calcium carbonate	3 g/day	change of fecal bile acid level	1 week
Greenberg et al. (21, 1994)	Age, <80 years patients with resected colonic polyp (n=864)	Randomized double-blind placebo-controlled	multi-center in US	4 treatment groups 1) beta carotene 2) vitamin C 3) vitamin E 4) 1+2+3	25 mg/day 1 g/day 400 mg/day	recurrence of colorectal adenomas	4 years
Bostic et al. (14, 1995)	Age range, 30–74 years sporadic adenoma patients (n=193)	Randomized double-blind placebo-controlled	Minneapolis, US	calcium	1 g/day or 2 g/day	change in cell proliferation rate	6 months
Alberts et al. (13, 1996)	Age range, 50–75 years patients with resected colonic polyp (n=52)	Randomized double-blind placebo-controlled	Arizona, US	wheat bran fiber calcium	2 or 13.5 g/day 250 or 1500 mg/day	change of fecal bile acid level	9 months
Hofstad et al. (16, 1998)	Age range, 50–76 years polyp-bearing patients (n=116)	Randomized double-blind placebo-controlled	Oslo, Norway	daily mixture beta-carotene vitamin C vitamin E selenium calcium	15 mg 150 mg 75 mg 101 μg 1.6 g	growth and recurrence of colorectal polyps	3 years
Baron et al. (17, 1999)	Age, <80 years patients with resected colonic polyp (n=930)	Randomized double-blind placebo-controlled	multi-center in US	calcium	1200 mg/day	recurrence of colorectal adenomas	4 years
Bonithon-Kopp et al. (18, 2000)	Age range, 35–75 years patients with a history of colorectal adenomas (n=665)	Randomized double-blind placebo-controlled in parallel design	multi-center in Europe	2 treatment groups 1) calcium 2) fiber	2 g/day 3.5 g ispaghula husk	recurrence of colorectal adenomas	3 years
Alberts et al. (27, 2000)	Age range, 40–80 years patients with resected colonic polyp (n=1429)	Randomized double-blind	Arizona, US	wheat-bran fiber	2 or 13.5 g/day	recurrence of colorectal adenomas	3 years

Calcium: In the early 1930s, Cook et al. reported that methylcholanthrene, a highly active carcinogen, could be produced chemically from cholic acid (1) and thereafter much evidence has accumulated that supports the important role of bile acids as colon cancer promoters. Newmark et al. proposed that calcium binds to bile acids in the bowel lumen, inhibiting their proliferative and carcinogenic effects (2). Dietary calcium supplementation has in fact consistently been found to reduce colon cancer occurrence in experimental studies (3–9) and an epidemiological investigation provided evidence that high calcium consumption might reduce colon cancer incidence (10). However, a meta-analysis of 24 case-control and cohort studies did not support any protective effect of calcium against colorectal cancer (11). In most early trials, a change in the fecal bile acid level with calcium supplementation was investigated as an intermediate end point. A randomized trial conducted in Ontario, Canada, failed to detect reduction in fecal bile acid levels with calcium supplementation, but the period of the intervention was very short (7 days) (12). In another randomized, double-blinded, phase II study conducted in Arizona, a reduction in the fecal concentration of total bile acids was observed with high-dose calcium supplementation (13). Use of colorectal epithelial cell proliferation as a biomarker to measure effects of calcium interventions on the colon has been reported in five small uncontrolled clinical trials, nine small randomized placebo-controlled trials, and three full-scale randomized placebo-controlled trials. The reports indicated that it is unlikely that calcium supplementation can substantially lower the cell proliferation rate, but it may normalize the distribution of proliferating cells within colon crypts (14, 15). The results of intervention studies on the recurrence of colorectal adenomas have been conflicting, showing a beneficial effect of calcium in some but not in others. In one trial, a mixture of calcium and antioxidants (selenium, betacarotene, vitamin C and E) showed a protective effect on adenoma recurrence, but not on adenoma growth (16). In the Calcium Polyp Prevention Study conducted at six clinical centers in the US (17), the subjects assigned to the calcium supplementation group were found to have a lower risk of recurrent adenomas with an adjusted risk ratio of 0.81 (95 percent confidence interval, 0.67 to 0.99; P=0.04). Furthermore, the adjusted ratio for the average number of adenomas in the calcium group to that in the placebo group was 0.76 (95 percent

confidence interval, 0.60 to 0.96; P=0.02). The authors concluded that calcium supplementation is associated with a significant, though moderate, reduction in the risk of recurrent colorectal adenomas. In the European Cancer Prevention Organization Intervention Study, a placebo-controlled trial aimed at assessing the efficacy of calcium and fiber, the adjusted odds ratio for recurrence was 0.66 (95 percent confidence interval, 0.38 to 1.17; P=0.16) for calcium treatment (18).

Antioxidants: Epidemiological studies have linked the intake of vegetables and fruits rich in antioxidant vitamins with a lower risk of cancer. Although several trials have tested the ability of antioxidant vitamins, particularly vitamin C (ascorbic acid), vitamin E (tocopherols) and betacarotene, to prevent colorectal adenomas, the results have been inconsistent. A Canadian study of patients with sporadic adenomas found no effect of supplemental vitamin C and E on the rate of recurrence of adenomas over a two-year period among 143 patients randomly assigned to vitamins or placebo (19). However, an Italian trial revealed a statistically significant reduction in the incidence of adenomas after supplementation with vitamins A, C and E (20). In the Polyp Prevention Study involving six clinical centers in the US, treatment for four years with either betacarotene or vitamins C and E did not affect the rate of occurrence of new adenomas in patients who had had an adenoma removed before entering the study (21). The lack of benefit of antioxidants in these studies appears to conflict with the results of epidemiological and experimental studies. Interpretation of the discrepancies found in intervention trials is not very easy although the influence of other dietary factors should be considered as a confounder.

Fiber: An inverse correlation has been observed between mortality rates from colon cancer and per capita cereal consumption (22). Burkitt proposed that a high fiber diet protects against colon cancer on the basis of a low incidence rate for colorectal cancer in Africa (23). Fiber increases stool weight, reduces transit time, dilutes colonic contents, and stimulates bacterial anaerobic fermentation. A review of the findings from 37 observational studies showed that only half of them were strongly or moderately supportive of a protective effect of fiber against colon cancer (24). A meta-analysis of 13 case-control studies of colon cancer provided evidence of the beneficial effects of dietary fiber (25), although the results from large prospective studies have been conflicting (26). The European Cancer Prevention Organization Intervention Study found that calcium supplementation for 3 years had a slight but not significant beneficial effect on adenoma recurrence, whereas fiber supplementation with a mucilaginous substance resulted in a significant increase in the recurrence rate (18). In the Wheat Bran Fiber trial, 1429 subjects with resected colorectal adenomas were recruited (27). Participants who successfully completed a six-week run-in period by consuming at least 75 percent of the amount of a low-fiber supplement supplied (2 g per day) were randomly assigned to receive a high-fiber supplement (13.5 g per day) or a low-fiber supplement (2 g per day) of wheatbran cereal. The multivariate adjusted odds ratio for recurrent adenoma in the high-fiber group, as compared with the low-fiber group, was 0.88 (95 percent confidence interval, 0.70 to 1.11; P=0.28), and the relative risk of recurrence according to the number of adenomas in the high-fiber group was 0.99 (95 confidence interval, 0.71 to 1.36; P=0.93). The conclusion was that the dietary supplement of wheatbran fiber used did not protect against recurrent colorectal adenomas.

Nonpharmacologic intervention

Overseas trials: Relatively few trials have been conducted to investigate the effects of an explicit dietary change on the recurrence of adenoma. Table 2 summarizes the results of nonpharmacologic intervention. Participants (a total of 201 subjects) in the Toronto Polyp Prevention Trial were randomized to receive counseling on a diet low in fat (the lesser of 50 g/day or 20% of energy) and high in fiber (50 g/day), or to follow a normal Western diet (28). The study group demonstrated no significant difference in recurrence of colorectal adenoma after an average of two years of follow-up. The Australian Polyp Prevention Project, a randomized, partially double-blinded, placebo-controlled factorial investigation to examine the effects on the incidence of adenomas of reducing dietary fat to 25% of total calories and supplementing the diet with 25 g of wheat bran daily and a capsule of betacarotene (20 mg daily) (29), found no statistically significant prevention of total new adenomas with any of the intervention arms, although a statistically non-significant reduced risk of large adenoma (=10 mm) was apparent with the low-fat intervention. These two pioneering studies did not demonstrate that low-fat diets (coupled with fiber supplementation) reduce the recurrence of adenomas, but their small size limited the statistical power. Schatzkin et al. reported the results of the Polyp Prevention Trial, conducted as a large, multi-center, randomized-controlled trial of the effect of a comprehensive dietary intervention on the recurrence of colorectal adenoma (30). Participants in the study were assigned to a diet low in fat and high in fiber, fruits, and vegetables. The study failed to detect any significant difference in the rate of recurrence of colorectal adenomas between the intervention and control groups.

Japanese trials: In Japan, a dietary intervention for patients polypectomized for tumors of the colorectum (DIPP study) has been started to elucidate potential beneficial effects of n-3 polyunsaturated fatty acids (PUFAs) (31). Not only epidemiological and ecological (32, 33), but also experimental studies (34, 35) have provided evidence that n-3 PUFAs, including α-linolenic acid, eicosapentanoic acid (EPA) and docosahexanoic acid (DHA), may have a tumor-suppressive role. Although n-6 PUFAs (mainly linoleic acid) enhance the growth and promotion of tumors, n-3 PUFAs suppress them. The n-6/n-3 PUFA ratio is, therefore, an important additional factor for tumorigenesis. An international ecologic study revealed that Japanese consume 6.21% of total energy as fish, major contributors of n-3 PUFA intake, while the figure for US Caucasians is 0.74% (36). Intervention trials to allow the assessment of modification effects of n-3 PUFAs intake on the risk of tumors of the colorectum can most easily be carried out in countries, including Japan, where fish and marine foods are routinely eaten. This randomized controlled trial is now in the process of securing sufficient patients to assess the tumor-suppressive effects of n-3 PUFAs, with sizes and incidence rates of colorectal tumors as end points.

Table 2 Summary of Nonpharmacologic Intervention Trials for Colorectal Cancer

Study (reference no., year)	Patient characteristics	Trial design	Location of study population	Treatment	End point	Length of follow-up
Toronto Polyp Prevention Trial McKeown-Eyssen et al. (28, 1993)	Age, <80 years patients with resected colorectal adenoma (n=201)	Randomized	Toronto, Canada	counselling on 1) a diet low in fat (<50 g/day or 20% of energy) 2) a diet high in fiber (50 g/day)	recurrence of colorectal adenomas	2 years
Australian Polyp Prevention Project Mac Lennan et al. (29, 1995)	Age range, 30–74 years patients with resected colorectal adenoma (n=424)	Randomized partially double-blind placebo-controlled factorial trial	Sydney, Australia	7 intervention group 1) reduction of dietary fat 2) 25 g wheat bran daily 3) 20 mg betacarotene daily	recurrence of colorectal adenomas	4 years
Polyp Prevention Trial Schatzkin et al. (30, 2000)	Age, >35 years patients with resected colonic polyp (n=2079)	Randomized	New York, USA	counselling on 1) a diet low in fat (<20% of E) 2) a diet high in fiber (18 g dietary fiber per 1000 kcal) and fruits and vegetables (3.5 servings per 1000 kcal)	recurrence of colorectal adenomas	4 years
DIPP study Tokudome et al. (31, 2002)	patients polypectomized for tumors of the colorectum	Randomized	Nagoya, Japan	1) reduction of intake of fats as a whole 2) decreased consumption of n-6 PUFAs 3) increased intake of n-3 PUFAs a) from fish/marine foods b) from perilla oil c) from eight capsules of fish oil/day	recurrence of colorectal adenomas	2 years

Methodological issues in intervention trials for colorectal cancer

Study subjects

Intervention studies focusing on cancers themselves are difficult owing to the large number of patients required. Because adenomatous polyps are considered precursors of most large-bowel cancers, many studies have set the recurrence of adenomas as the primary end point. Most have been performed in patients after resection of colorectal adenomas, examining the recurrence rate after polypectomy. Hofstad and colleagues recruited 116 polyp-bearing patients and conducted a prospective intervention study (16). While most previous intervention studies had focused on effects on the reappearance rate of colorectal polyps, they planned to examine the effect on growth as well and reported the results of effects of calcium and antioxidants on this parameter and formation of polyps.

Although antioxidant supplements have failed to reduce the incidence of tumors in some studies, lower mortality due to cancer and other causes was found after supplementation with betacarotene, alpha-tocopherol, and selenium in a trial in China (37). The results suggest that the beneficial effects of antioxidants occur very early and improve the general health condition rather than avert cancers in marginally nourished individuals.

End points

Since an adenoma-carcinoma sequence with a long latency period appears to be involved in the development of most sporadic colorectal cancers, colorectal cancer incidence cannot be used as the primary end point, and biological markers need to be employed instead as intermediate end points. In the early 1930s, attention was first drawn to a relationship between bile acids and colon cancer, because of the body of evidence supporting an important promotion role. Consequently, fecal bile acid concentration was examined in some studies. In most previous clinical trials, intermediate biomarkers such as the concentration of fecal bile acid or the cell proliferation rate have been targeted parameters. Most intervention studies have focused on the recurrence rate of colorectal adenoma after polypectomy, and therefore have not been able to directly address whether intervention affects the risk of a first adenoma or of progression to invasive cancer. Unfortunately, for most sites of cancer, biologically meaningful intermediate end points have yet to be established.

Dose

Important aspects of dose determination are the presence or absence of a threshold dose and harmful effects, as well as the dose-dependence of individual vitamins. In studies with betacarotene, doses larger than 15 mg have been applied (21, 38) with a recorded increased risk of lung cancer and overall cancer mortality, which does not point to any benefit for a general increase in doses of antioxidants. In fact, it is conceivable that the dose used in these studies was too high. The dietary intake of betacarotene derived from eating fruits and vegetables is at a low level, and this is presumably only one of the ingredients that reduce the risk of cancer. Another possibility is that betacarotene may not be the active cancer-inhibiting

component of the fruits and vegetables identified as protective in observational studies. The betacarotene level may simply be an index for the intake of fruits and vegetables or a nonspecific marker of lifestyle.

Interactions

There have been several studies conducted to test mixtures of antioxidants. The European Cancer Prevention Organization Intervention Study was a placebo-controlled trial aimed at assessing the efficacy of ispaghula husk and calcium supplementation for over 3 years, with the aim of prevention of adenoma recurrence (18). The results in fact suggested adverse effects. The study group showed that the adverse effect of fiber supplementation was significantly stronger in patients with a high dietary calcium intake than in those with a low calcium intake. One possibility is that ispaghula husk fiber binds more strongly to calcium than to fecal bile acids, so that secondary bile acids are free to exert toxic effects on the colonic mucosa. This result typifies the complexity of dietary interventions. The effects of dietary fiber intake are likely to be confounded by factors such as intake of calories, dietary fat, and use of vitamins, and mineral and antioxidant supplements.

Duration and timing of interventions

When the intervention study is aimed at assessing effects on the incidence of cancer, the study subjects at baseline are generally middle-aged or elderly populations. If dietary factors influence critical events in colorectal cancer at the molecular level early in life, supplementation and modification in later life may not be effective. It is also possible that a relatively short period of dietary intervention might fail to exert detectable effects so that differences between intervention and control groups are not significant. A longer period of intervention as well as follow-up might allow the development of enough adenomas to reveal protective effects of interventions.

Compliance

Since an increase in the efficacy of treatment over time may be counterbalanced by decreasing compliance, the latter should be properly tested. At follow-up visits, participants should be encouraged to continue in the study. In a prospective intervention study conducted in Oslo, compliance was tested with serum betacarotene and serum alpha-tocopherol measurements, and only 13% of the patients were lost to follow-up (16). A significantly higher fecal concentration of calcium in the active medication group was observed and there was a 150% increase after 1.6 g of daily calcium carbonate. The study group demonstrated an excellent follow-up and compliance was properly tested.

A model program of obesity control for cancer prevention

A case-referent study using Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC) data has provided clear evidence that the risk of postmenopausal breast cancer and endometrial cancer in Japanese women is markedly increased by obesity (39, 40). From a practical viewpoint for primary breast and endometrial cancer prevention, obesity is thus one of the most important intermediate targets. Therefore, the authors planned an intervention trial for obese women in Aichi Cancer Center Hospital (41). After obtaining informed consent, we recruited patients over 30 years old with a BMI of 24 or more. Forty patients were randomly assigned into study groups A and B. Group A started the prevention program at entry and Group B started 3 months later, according to the protocol. This trial was designed to evaluate the effectiveness of the intervention trial during the first 3 months by comparison with the second group. At the baseline, and after 3 and 6 months, participants were checked for body size, dietary intake and serum chemistry. It was stressed that they should record a diary not only of their food intake but also their physical activity over 3 months. Every weekend they returned their diaries by mail and we gave them appropriate comments by telephone and/or mail after review. After the period of 3 months, we observed significant improvement in BMI, and waist and hip size in Group A. There was a 4.2% decrease of initial body weight on average after intervention but a 0.3% increase in the group without intervention, the difference being statistically significant. With regard to changes in key biomarkers, serum triglycerides related to the reduction of BMI over 3 months were decreased, but not total cholesterol. This intervention trial for obese women at Aichi Cancer Center Hospital thus demonstrated benefits including efficacy, convenience, low cost and the relatively minimal time needed for professional intervention. The strategy not only promotes versatility but also supports the continuation of healthy eating patterns.

Current epidemiological evidence suggests that the recent increment in type 2 diabetes and colorectal cancer in Japan might be associated with the Westernization of the dietary habits of the Japanese since 1950 (42). Recently, Tuomilehto and colleagues reported the results of the Finnish Diabetes Prevention Study, which examined the effect of changes in lifestyle on the development of type 2 diabetes in high-risk subjects (43). Although the average weight loss in response to the intervention was small (4.2±5.1 kg), the incidence of diabetes was reduced by 58 percent by modification of lifestyle. This study revealed the possibility of achieving appreciable primary prevention of type 2 diabetes by a nonpharmacologic intervention implemented in a primary health care setting.

Concluding remarks

The recent increase in types of cancers prevalent in the West, e.g., colorectal cancer, prostate cancer, breast cancer and endometrial cancer, among the Japanese might be highly associated with the drastic Westernization of Japanese dietary habits after World War II, especially from 1955–1975. The results obtained from overall epidemiological studies demonstrate that modifying the lifestyle may reduce the risk of lifestyle-related diseases, including cancer. However, further studies are needed for confirmation in different populations, and physicians and policymakers must be encouraged to consider that intervention programs should be routinely covered under primary care. In worldwide cancer statistics, the incidence rates of colorectal cancer among Japanese immigrants in the US have been higher

than those among Americans in the US. Furthermore, the incidence rates of colorectal cancer and type II diabetes among Japanese immigrants may be higher than for the Japanese population in Japan. This evidence suggests that the Japanese in general might be susceptible to cancers associated with Westernized dietary habits. Recent progress in molecular epidemiological studies of human disease should allow the clarification of many of the molecular mechanisms underlying susceptibility to disease. Eventually, it may be possible to target intervention programs to genetically susceptible individuals, and molecular interventions for the prevention of cancer may have promise. We cannot avoid the difficulties which accompany inducing and sustaining changes in lifestyle, however, we should modify our current lifestyles to prevent the lifestyle-associated diseases which are showing a current increment.

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