Lycopene, β-carotene, and colorectal adenomas[1–3]

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ABSTRACT

Background: Epidemiologic studies found that high tomato intakes reduce the risk of colorectal cancers. This beneficial effect is assumed to be caused by high intakes of lycopene, a carotenoid with strong antioxidant activity that is present predominantly in tomatoes.

Objective: We assessed the relation between plasma lycopene concentrations and colorectal adenomas, the precursors for most colorectal cancers. In addition, the concentrations of 2 other antioxidants, β-carotene and α-tocopherol, were measured.

Design: White subjects undergoing a complete colonoscopy were included in the study (73 with adenomas, 63 without any polyps, and 29 with hyperplastic polyps). A detailed dietary history and information on alcohol consumption and smoking habits were collected from all subjects. Plasma lycopene, β-carotene, and α-tocopherol concentrations were measured by using HPLC.

Results: Patients with adenomas and control subjects without polyps did not differ significantly in body mass index; intakes of energy, fat, protein, carbohydrates, fiber, β-carotene, and alcohol; or prevalence of smoking, but patients with adenomas were slightly older. The median plasma lycopene concentration was significantly lower in the adenoma group than in the control group (−35%; $P = 0.016$). The median plasma β-carotene concentration also tended to be lower in the adenoma group (−25.5%), but the difference was not significant. In the multiple logistic regression, only smoking (odds ratio: 3.02; 95% CI: 1.46, 6.25; $P = 0.003$) and a plasma lycopene concentration < 70 μg/L (odds ratio: 2.31; 1.12, 4.77; $P = 0.023$) were risk factors for adenomatous polyps. Patients with hyperplastic polyps did not differ significantly from control subjects in any variable.

Conclusion: Our findings support the hypothesis that lycopene contributes to the protective effect of high tomato intakes against the risk of colorectal adenomas. *Am J Clin Nutr* 2003;78:1219–24.

KEY WORDS Carotenoids, β-carotene, colorectal adenoma, hyperplastic polyp, lycopene, α-tocopherol

INTRODUCTION

The risks of colorectal cancer and of adenomatous polyps, which are considered the precursors of most large-bowel cancers (1), are believed to be influenced by diet. Observational studies around the world found that the risk of colorectal cancer is lower in populations with a high intake of fruit and vegetables than in populations with a low intake and that a population's risk can be altered by changes in diet. However, the reasons for these findings are still not understood (2, 3). Burkitt's (4) idea that the intake of a high-fiber diet protects against colorectal cancer (2, 5, 6) and is associated with a decreased risk of developing colorectal adenomas (7, 8) has long been accepted. However, the results of several more recent studies do not support this claim. In an extensive cohort study in women over a period of 16 y, no protective action of fiber on the development of colorectal cancer or polyps was found (9). The results of 2 large intervention trials were also negative. Three to four years of either taking a daily wheat-bran supplement or eating a diet that was low in fat and high in fruit and vegetables had no effect on the incidence of new colorectal adenomas (10, 11). Similarly, the consumption of fruit and vegetables was reported not to be significantly associated with colorectal cancers (3, 12).

With regard to the negative results of the aforementioned studies, it has been pointed out that the benefits of a high-fiber diet may depend on the type of dietary fiber and that the benefits of diets high in fiber or fruit and vegetables may not be due to the fiber itself but may instead be due to the other contents of those diets (13). Among the compounds that appear to protect against the development of cancer in laboratory animals, cell cultures, and case-control or cohort studies are some carotenoids that inactivate reactive oxygen species and provide protection from oxidative damage (14, 15). In most studies concerning the relation between carotenoids and colorectal cancer, the dietary intake of β-carotene was measured. Although high intakes of β-carotene were associated with a reduced risk of colorectal cancer in some studies (16–19), other studies found no relation (20–22). In contrast to β-carotene, lycopene has received little attention in studies on colorectal neoplasias. Lycopene, the predominant carotenoid in tomatoes, has the highest antioxidant activity among all dietary carotenoids and contributes to a reduction in the risk of several experimental cancers (15, 23, 24). The possibility of a preventive effect of lycopene on the development of colorectal cancer is supported by the results of a case-control study in Italy, in

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which a high tomato intake was consistently associated with a reduced risk of cancer of the gastrointestinal tract, including the colon and the rectum (25).

The relation between plasma lycopene concentrations and the prevalence of colorectal adenomas has, until now, been investigated in only one study, which led to a negative result (26). Because only the distal colon and rectum were explored in that study, the aim of the present study was to gain more information on this topic in subjects undergoing a complete colonoscopy. Blood samples from a subgroup of participants in a recent case-control study of dietary and lifestyle factors on the risk of colorectal adenomas (27) were used for the measurement of plasma concentrations of lycopene, β-carotene, and α-tocopherol, another vitamin with antioxidative capacity.

SUBJECTS AND METHODS

A total of 502 white subjects undergoing a complete colonoscopy were included in a recent case-control study on the effect of dietary factors, alcohol intake, and cigarette smoking on the risk of colorectal adenomas and hyperplastic polyps. The study was approved by the ethics committee of the Robert-Bosch-Hospital (Stuttgart, Germany), and all subjects gave written informed consent to participate in the study. One hundred sixty-five subjects (73 with colorectal adenomas, 29 with hyperplastic polyps, and 63 controls with no polyps) agreed to have blood samples collected for the measurement of certain vitamin concentrations. Details of the study design were published recently (27). Briefly, adult patients who reported to the Robert-Bosch-Hospital for a colonoscopy because of occult blood in the stool were eligible for the study. Exclusion criteria were any of the following: previous colon resection because of other diseases, previous polypectomy of a colon adenoma, age >80 y or <30 y, familial polyposis or history of familial nonpolyposis colorectal carcinoma, incomplete examination (ie, cecum not reached or unsatisfactory colon preparation), colitis of any type, and any other type of disease that might influence lifestyle, dietary habits, smoking, or alcohol consumption, such as diabetes, chronic heart failure, ischemic heart disease, liver disease (chronic hepatitis or cirrhosis), renal insufficiency, malabsorption, or a recent weight loss of >3 kg.

Colonoscopies were performed jointly by a staff gastroenterologist and an experienced endoscopy nurse, neither of whom were aware of the subjects' alcohol consumption and dietary habits. The completeness of the colonoscopies was judged either by inspection of the ileocecal valve or by fluoroscopy. Fluoroscopy was also used to determine the location of the polyps whenever doubt existed regarding the exact position of the tip of the colonoscope. Large polyps (diameter >5 mm) were removed by using a snare. Small polyps or raised lesions were resected by using biopsy forceps. After each procedure, the endoscopist completed a study report form that indicated the size, shape, and location of any polyp or suspected malignancy found. Polyps were classified as adenomatous or hyperplastic. Routine histologic assessment was performed by 2 staff pathologists from the Department of Pathology, Robert-Bosch-Hospital.

For the assessment of risk factors, all patients were interviewed either before the colonoscopy or, if this was impossible, the day after the procedure by a trained nutritionist using a computerized method for obtaining a diet history. The method has been validated against data obtained from 7-d diet records (28). The patients were asked in detail about their frequency of alcohol consumption and serving size in terms of medium glasses or bottles of wine, 0.3l-L cans or bottles of beer, or shots of hard liquor. For the calculation of mean alcohol consumption, the following alcohol concentrations (by vol) were assumed: beer, 4%; wine, 11%; hard liquor, 40%. All subjects were asked if they had ever regularly smoked >2 cigarettes/d for >1 y. Those who did were classified as "smokers," and those who did not were classified as "nonsmokers." All subjects completed the interview; however, for one subject in the control group and one subject in the group with hyperplastic polyps, data on some items were lacking (specified in Results).

Plasma carotenoid and α-tocopherol analysis

Blood samples were drawn while the subjects were in the fasting state (between 0800 and 0900) and before they had started the cleaning procedure for the colonoscopy. Plasma was stored at -80 °C until analyzed. On the basis of earlier observations (29), storage at -80 °C for up to 6 mo was assumed not to influence the results. Plasma concentrations of lycopene, β-carotene, and α-tocopherol were measured by using HPLC (30, 31). Repeated (10 times) measurements of lycopene, β-carotene, and α-tocopherol showed CVs of 5.1%, 3.5%, and 4.5%, respectively. The CVs for the analysis from day to day were between 3.9% and 7.3%.

Statistical analysis

Nonnormally distributed continuous variables are expressed as medians and 10th−90th percentile ranges, and the values for the cases were compared with those for the controls by using the Mann-Whitney *U* test or two-factor analysis of variance–like tests that were based on ranks for lycopene, β-carotene, and α-tocopherol and that included sex as both a covariate and an interaction term. Discrete variables are expressed as numbers and percentages, and the values were compared by using Fisher's exact test. Data are presented with nominal two-tailed *P* values (unadjusted for multiple comparisons). In the further analysis, the same risk variables were included as were included in our recent publication (27): age, sex, body mass index (BMI; in kg/m^2), smoking, and alcohol intake. The Mantel-Haenszel method was used to estimate odds ratios and corresponding 95% CIs for the risk factors in univariate analyses. In multiple analyses, a stepwise, forward, unconditional regression analysis was used to estimate odds ratios and corresponding 95% CIs. All analyses were carried out with SAS for WINDOWS, version 6.12 (SAS Institute Inc, Cary, NC).

RESULTS

The demographic characteristics of the study groups are shown in **Table 1**. The patients with adenomas did not differ significantly from the controls in BMI; intakes of energy, fat, protein, carbohydrates, and alcohol; and prevalence of smoking, but the patients with adenomas were slightly older. The patients with hyperplastic polyps did not differ significantly from the controls in any of the variables (Table 1). When the data were analyzed for both sexes separately, the only significant differences between the controls and the patients with adenomas were older age and higher BMI in the female pa-

TABLE 1
Descriptive characteristics of the study population

	Controls (n = 25 M, 38 F)	Patients with adenomas (n = 41 M, 32 F)	Patients with hyperplastic polyps (n = 14 M, 15 F)
Age (y)	54 (39–69)[1]	59 (47–70)[2]	56 (40–70)
BMI (kg/m^2)	25.4 (21.1–28.4)	25.1 (22.6–29.4)	25.9 (20.6–30)
Smoker (%)	15.9	16.4	17.2
Intake			
Energy (kJ/d)	9870 (6640–12 550)	10 030 (7160–13 410)	9180 (7160–14 250)
Fat (g/d)	95.8 (58.7–129)	100.8 (66–143.2)	88.7 (57.3–141.1)
Protein (g/d)	88 (55.3–111.6)	90.6 (65.8–118.8)	82.6 (62.7–135.7)
Carbohydrates (g/d)	230 (163–323)	241 (157–347)	233 (168–333)
Alcohol (g/d)	8.8 (0.1–37.5)	9.3 (0–47.5)	18.2 (0.1–55.2)
Fruit (g/d)	256.0 (43–670)	258 (83–601)	199.0 (26–765)
Vegetables (g/d)	166.0 (77–344)	166.0 (70–267)	150.0 (68–327)
Fiber (g/d)	25.0 (15.0–34.1)	23.3 (15.4–36.7)	23.1 (13.8–43.4)
β-Carotene (mg/d)	3.3 (1.6–5.0)	3.0 (1.7–5.1)	3.3 (1.4–7.2)
Vitamin C (mg/d)	112.8 (65.6–219.1)	112.2 (63.6–205.3)	93.4 (42.1–195.8)
Iron (mg/d)	15.1 (10.8–18.9)	14.6 (11.1–21.5)	13.8 (11.0–20.2)

[1] Median; 10th–90th percentile range in parentheses.
[2] Significantly different from the controls, $P = 0.026$ (Mann-Whitney U test).

tients with adenomas and higher fat intake in the male patients with adenomas (**Table 2**). Compared with the women, the men had significantly higher intakes of energy, protein, and alcohol and a significantly higher percentage of smokers in both the control group and the adenoma group ($P < 0.05$; Table 2). Intakes of fruit, vegetables, fiber, β-carotene, vitamin C, and iron did not differ significantly between the controls and the patients with adenomas for either sex (Table 2).

The median plasma lycopene concentration for the total group (ie, both sexes) of patients with adenomas was significantly lower than that for the total group of controls ($P = 0.016$; **Table 3**). There was also a trend for lower plasma β-carotene concentrations in the adenoma group than in the control group ($P = 0.094$; Table 3). When the data were analyzed according to sex, there were no significant sex × group interactions. Plasma α-tocopherol concentrations did not differ significantly between the patients with adenomas and the controls (Table 3).

The median plasma concentrations of lycopene and β-carotene in the patients with hyperplastic polyps did not differ significantly from those in the controls (Table 3). β-carotene concentrations in the patients with hyperplastic polyps tended to be lower than those in the controls, but the difference was not significant.

In the stepwise multiple logistic regression adjusted for age, sex, BMI, alcohol intake, smoking, low carotenoid concentration, and low α-tocopherol concentration, only smoking (odds ratio: 3.02; 95% CI: 1.46, 6.25; $P = 0.003$) and a low plasma lycopene concentration (< 70 μg/L; odds ratio: 2.31; 95% CI: 1.12, 4.77; $P = 0.023$) were risk factors for adenomatous

TABLE 2
Intakes of nutrients and alcohol and smoking habits in controls and patients with adenomas according to sex

	Men		Women	
	Controls (n = 25)	Patients with adenomas (n = 41)	Controls (n = 38)	Patients with adenomas (n = 32)
Age (y)	54 (36–69)[1]	59 (45–66)	54 (40–70)	58.5 (50–70)[2]
BMI (kg/m^2)	25.9 (21.7–28.4)	25.5 (22.2–29.3)	23.4 (20.1–30.1)	24.9 (22.9–30.5)[2]
Smoker (%)	24	22	10.5	9.4
Intake				
Energy (kJ/d)	10 680 (8230–13 660)	11 120 (8500–13 770)	8980 (5440–12 150)	8750 (6730–11 390)
Fat (g/d)	97.2 (69.3–127.1)	116.3 (76–156.9)[2]	95.2 (54.9–129.5)	91.3 (62.6–120.3)
Protein (g/d)	97.6 (67.4–123)	99.4 (74.7–120.7)	75.1 (51.9–105.6)	82.4 (56.8–104.9)
Carbohydrates (g/d)	259 (184–376)	244 (160.1–372.7)	216 (142–303)	229 (153–319)
Alcohol (g/d)	19.7 (2.4–41.6)	19.8 (2.5–56.9)	3.7 (0–21.9)	4.3 (0–32.1)
Fruit (g/d)	300 (48.2–706.6)	227 (62.8–473.4)	261 (51.7–578.1)	320.5 (86.3–762.6)
Vegetables (g/d)	135 (58.8–272.4)	140 (71–238.6)	159 (96.7–372.2)	159 (65.2–270.2)
Fiber (g/d)	25 (16.6–39.2)	24.5 (14.3–38.5)	25.2 (14.7–31.2)	22.5 (15.9–33.7)
β-Carotene (mg/d)	2.8 (1.45–4.6)	2.8 (1.7–5.0)	3.45 (1.7–5.7)	3.4 (2.1–5.3)
Vitamin C (mg/d)	119 (56–188)	111.6 (64.1–156.4)	110.1 (65.6–219.5)	115.7 (63.6–234.3)
Iron (mg/d)	16.2 (12.3–19.3)	15.6 (12.6–22.7)	13.5 (9.5–18.9)	13.0 (10.5–18.9)

[1] Median; 10th–90th percentile range in parentheses.
[2] Significantly different from the controls of the same sex, $P = 0.03$.

TABLE 3
Plasma concentrations of lycopene, β-carotene, and α-tocopherol in controls and patients with adenomas or hyperplastic polyps[1]

	Lycopene	β-Carotene	α-Tocopherol
	μg/L	*mg/L*	*mg/L*
Controls ($n = 63$)	80 (25–70)	0.51 (0.16–1.31)	14.03 (8.94–22.23)
Patients with adenomas ($n = 73$)[2]	52 (21–130)[3]	0.38 (0.11–0.97)	13.17 (7.95–21.16)
Patients with hyperplastic polyps ($n = 29$)	80 (30–160)	0.35 (0.13–1.04)	14.0 (8.9–19.0)

[1] Median; 10th–90th percentile range in parentheses. There were no significant sex × group interactions.
[2] $n = 72$ for α-tocopherol.
[3] Significantly different from the controls, $P = 0.016$ (two-factor ANOVA based on ranks).

polyps. No other interactions between the explanatory variables in the final model were found.

The size of the adenoma, or of the largest adenoma if more than one polyp was present, was ≤ 5 mm in 20 cases, 6–10 mm in 19 cases, and > 10 mm in 34 cases. There was no association between the size of the adenomas and any of the variables mentioned in Tables 1-3.

DISCUSSION

Interest in lycopene, a carotenoid consumed mainly from tomatoes, has increased recently because of its potential anticancer properties (15, 23, 24). Lycopene is a 40–carbon atom, open-chain hydrocarbon that, unlike β-carotene, lacks a β-ionone ring structure and, therefore, has no provitamin A activity (15). For most populations in Europe and North America, tomatoes and tomato-based products are by far the most important dietary sources of this carotenoid (15, 32). Other rich sources of lycopene are watermelon, pink grapefruit, pink guava, and papaya (15, 32). In vitro studies indicated that, of all the major dietary carotenoids, lycopene is the most potent scavenger of reactive oxygen species (33, 34). Strong evidence exists from numerous experimental and epidemiologic studies that high intakes of tomatoes and tomato-based products, as well as high serum or plasma lycopene concentrations, are associated with decreased risks of cancers of the lung, stomach, and prostate gland (23, 24). Further suggestive evidence has been published for other cancers of the gastrointestinal tract, including cancers of the colorectum (23–25).

β-carotene acts as provitamin A and an antioxidant. On the basis of numerous epidemiologic studies, an inverse association between β-carotene intake or blood β-carotene concentration and the risk of cancer has been postulated (14, 35). The results of case-control studies of dietary β-carotene intake and colorectal cancer have been equivocal (16–22).

The main aim of the present study was to investigate the hypothesis that plasma concentrations of lycopene and β-carotene are inversely associated with the risk of colorectal adenomatous polyps. In fact, the mean plasma concentrations of both carotenoids were lower in the group of patients with colorectal adenomas than in the control group; however, the difference was significant only for lycopene (Table 3). After the data were controlled for various potentially confounding factors, only smoking and plasma lycopene concentration remained inversely associated with adenoma prevalence. In the stepwise multiple logistic regression, neither plasma β-carotene concentrations nor plasma α-tocopherol concentrations were related to adenoma prevalence.

The relation between tomato intake and colorectal cancer risk was investigated in 5 case-control studies. Three of those studies reported that a high intake of tomatoes was associated with a reduced risk (25, 36, 37), whereas 2 found no relation (38, 39). The association between plasma lycopene and adenomas of the distal colon was explored in one case-control study (26). Although lower plasma concentrations of 5 other carotenoids, including β-carotene, were found in the subjects with adenomas than in the controls without adenomas, lycopene concentrations did not differ significantly between the 2 groups. The negative results of the latter study may be due, at least partially, to the facts that the patients underwent sigmoidoscopy only and only polyps on the left side of the colon could be detected (26). Because only ≈65% of adenomatous polyps are localized distally of the splenic flexure (40, 41), it is likely that ≈30–35% of the controls without detectable polyps in the rectosigmoid region had polyps in more proximal parts of the colon. On the assumption that adenomas located proximally and distally of the splenic flexure share a common etiology, the inclusion of these "false-negative" controls may have produced a bias toward the null. An additional factor that may have contributed to the negative results of the earlier study is ethnicity: almost one-half of the subjects were nonwhite (26).

Until now the data on the association between β-carotene and colorectal cancers have been inconclusive (2). In 4 case-control studies, high intakes of β-carotene were associated with a reduced risk of colorectal cancer (16–19), whereas in 3 other case-control studies (20–22) and 1 prospective cohort study (42), no relation was found. In accordance with the latter data are the results of studies of the association between plasma concentrations of β-carotene and certain other carotenoids and colorectal adenomas. In 2 case-control studies, high concentrations of β-carotene and certain other carotenoids were associated with a decreased prevalence of adenomas in univariate analyses (26, 43), but after potentially confounding factors were controlled for, neither total carotenoid concentrations nor concentrations of individual carotenoids were inversely associated with polyp prevalence. Similar results concerning the relation between plasma β-carotene concentrations and adenomas were obtained in the present study.

Findings from case-control and cohort studies have not shown a clear or substantial association between dietary intakes of vitamin E and colorectal cancer, but in several prospective studies, serum α-tocopherol concentrations in subjects who subsequently developed colorectal cancer were lower than those in control subjects (reviewed in reference 2). The results of the present study give no support to the idea that plasma

α-tocopherol concentrations are related to the risk of developing adenomatous polyps.

The design of our study had certain advantages. Taking adenomatous polyps as the study's endpoint instead of colorectal cancer supported the attempt to separate possible risk factors from potential nutritional and metabolic consequences of cancer. Because it may take 1–2 decades for the progression from adenoma to carcinoma (41), this endpoint enabled us to study the neoplasia closer in time to the etiologic events of interest. Furthermore, subjects with any type of disease that might have influenced dietary habits or that might have led to changes in lifestyle were excluded to avoid biases (27).

There were also several potential sources of bias in the study. Blood samples were available from only about one-third of the total number of participants of the earlier study (27). Despite this fact, it is unlikely that a selection bias influenced the results. According to the study protocol as mentioned in Subjects and Methods, blood samples were drawn only from patients who expressly agreed to this procedure, and the decision to measure plasma concentrations of the 2 carotenoids and α-tocopherol was made after termination of the earlier study. When the descriptive characteristics of the study population in the earlier study (27) are compared with those of the population in the present study (Table 1), the data of the latter closely resemble those of the former. The significant interaction between male sex and the presence of adenomas that was observed in the larger group of patients in the earlier study (27) was not observed in the present study.

With regard to the hypothesis of a preventive effect of lycopene on the development of colorectal adenomas, the plasma concentration necessarily served as a marker for contents in the colorectal mucosa. Lycopene is known to accumulate in human tissues. However, information regarding the relation between plasma concentrations and tissue contents, especially lycopene concentrations in the intestinal mucosa, is lacking (15). Until now the only published data regarding this point stem from a recent small study. In this study, the contents of 7 antioxidants, including lycopene, in mucosal biopsy samples from 10 patients with adenomatous polyps were lower than those in mucosal biopsy samples from 15 controls without polyps, although serum antioxidant status did not differ significantly between the 2 groups (44). In general, tissue contents of carotenoids are assumed to reflect long-term carotenoid intake, whereas plasma concentrations may reflect more recent consumption (43). Using single measurements of plasma lycopene concentration as an approximate value for concentrations present during a period of many years of initiation and progression of colorectal neoplasias may also produce exposure misclassification (15, 23, 24).

In conclusion, the results of the present study suggest that plasma lycopene concentrations are inversely associated with adenoma risk. This finding provides further evidence in support of the hypothesis that lycopene is responsible for the protective effect of high tomato intake against the risk of colorectal cancer (25, 36, 37).

The relative contribution of the authors to the production of the article was as follows: study design, JGE = CB > JCB; data collection, JGE > CB > JCB; data analysis, CM > JGE > JCB; writing of the manuscript, JCB > CM > CB. None of the authors had any real or potential conflicts of financial or personal interest with the Mildred-Scheel-Foundation or any other institution or company.

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