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Diet, alcohol, and smoking and the occurrence of hyperplastic polyps of the colon and rectum (United States)

John Kearney, Edward Giovannucci, Eric B. Rimm, Meir J. Stampfer, Graham A. Colditz, Alberto Ascherio, Ronald Bleday, and Walter C. Willett

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Hyperplastic polyps of the colon reveal a geographic distribution similar to that of colorectal cancer and adenomatous polyps. However, unlike adenomas—known precursors of colorectal cancer—little is known about the etiology or clinical significance of the hyperplastic polyp. In this prospective study, we set out to determine the main dietary and other lifestyle factors in the United States that might be associated with this lesion. Hyperplastic polyps of the distal colon and rectum were diagnosed in 219 of 12,922 men of the Health Professionals Follow-up Study having had an endoscopic procedure between 1986 and 1992, and 175 of 15,339 women of the Nurses' Health Study who had undergone an endoscopy for a variety of reasons between 1980 and 1990. After adjusting for age, family history of colon cancer, history of previous endoscopy, and total energy intake using multiple logistic regression, those consuming 30 g or more of alcohol per day were at increased risk relative to nondrinkers among men (relative risk [RR] = 1.69; 95 percent confidence interval [CI] = 1.01-2.80) and women (RR = 1.79, CI = 1.02-3.15). Current smoking also was found to be associated strongly positively with hyperplastic polyps in men (RR = 2.45, CI = 1.59-3.75) and women (RR = 1.96, CI = 1.16-2.86). High intake of folate was associated inversely with risk in both men (RR = 0.74, CI = 0.49-1.11, between high and low intakes of folate) and women (RR = 0.45, CI = 0.28-0.74, between high and low intakes of folate). Among macronutrients, a suggestive increase in risk existed with intake of animal fat, although this was attenuated in the full multivariate model (RR[men] = 1.48, CI = 0.94-2.41, and RR [women] = 1.22, CI = 0.77-1.94) between high and low quantities of animal fat intake. These prospective data provide evidence of associations between low folate intake, alcohol consumption, and current cigarette smoking, and risk of hyperplastic polyps of the distal colon and rectum. These same factors also have been found to be related to adenoma and cancer of the colon. The hyperplastic polyp is an indicator of populations at high risk for colorectal carcinoma, and it also may serve as a marker for factors that influence neoplastic evolution. *Cancer Causes and Control* 1995, 6, 45-56

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Drs Giovannucci, Stampfer, Colditz, and Willett are with the Channing Laboratory, Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, MA, USA. Authors also are affiliated with: the Department of Nutrition, Harvard School of Public Health, Boston, MA (Drs Kearney, Rimm, Stampfer, Ascherio, and Willett); the Department of Epidemiology, Harvard School of Public Health (Drs Rimm, Stampfer, Colditz, Ascherio, and Willett); and the Department of Surgery, New England Deaconess Hospital, Boston, MA (Dr Bleday). Address correspondence to Dr Giovannucci, Channing Laboratory, 180 Longwood Avenue, Boston, MA 02115, USA. *This project was supported by research grants number CA 55075 and HL 35464 from the National Institutes of Health and Special Institution Grant No. 18 from the American Cancer Society. Dr Colditz was supported by a Faculty Research Award (FRA-398) from the American Cancer Society.*

Introduction

The two most common polyps to be found in the colon and rectum are the adenomatous and hyperplastic polyps.[1] The unrestricted cell division and abnormal cell differentiation found in the adenoma distinguishes adenomatous from hyperplastic polyps, thereby defining it as a true neoplasm.[2] The adenoma is well-established as a precursor lesion for colorectal cancer and removing this lesion significantly decreases the risk of invasive carcinoma.[3] However, a biologic role for the hyperplastic polyp has remained elusive and the clinical significance of this lesion is unclear. To one school of thought,[4,5] the hyperplastic polyp is merely an innocuous non-neoplastic lesion of no clinical importance, while to the other,[6,7] it represents a significant marker of neoplasia. Others[8] suggest its true clinical significance may lie somewhere between these views. While hyperplastic polyps are usually small and located in the distal colon and rectum, little is known about their etiology, natural history, and growth rate. In addition, the hyperplastic polyp has never been incriminated seriously in the natural history of carcinoma development.[9] Despite this, hyperplastic polyps share a number of features with colorectal cancer:

(i) hyperplastic polyps are more likely than adenomas to be found in the rectum and sigmoid colon, the principal site for the development of colorectal cancer;[10]
(ii) the incidence of hyperplastic polyps is highest in populations at high risk of developing colorectal cancer;[11]
(iii) the incidence of hyperplastic polyp rises in populations who migrate from a low-risk to a high-risk area,[10] as is seen for colorectal cancer.[12]

Also, a number of immunohistochemical characteristics of hyperplastic polyps differ considerably from those of normal mucosa. Mucus, secreted by hyperplastic polyps, is more Pas-positive than from normal goblet-cell mucus.[13] Hyperplastic epithelium shows increased expression of carcinoembryonic antigen[13] and reduced secretory component and immunoglobulin (Ig)A.[14] Cells of hyperplastic polyps migrate from the crypt to the zone of exfoliation at much slower rates than normal, probably as a result of delayed exfoliation at the end of the cell cycle.[15] Some of these changes also are observed in neoplastic lesions. A number of enzymatic histochemical changes occur in hyperplastic polyps that are similar to adenocarcinoma. The hydrolytic enzymes esterase, acid phosphatase, and adenosine triphosphate (ATPase), and the respiratory enzyme, succinic dehydrogenase, all show reduced activity,[16] indicating a switch from aerobic to anaerobic metabolism. Such findings are not in accord with the hypothesis that the hyperplastic polyp is a simple hyperplasia of the mucosal epithelium and suggest a disorder in cellular differentiation. In view of these overlaps between hyperplastic polyps, adenomas, and colorectal carcinoma, and in their population distributions and histochemical changes, we hypothesized that the predictors of hyperplastic polyps and those of adenomatous polyps and colorectal cancer also might be similar.

Materials and methods

Study population

Our study population was chosen from two cohorts, the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS). The Nurses' Health Study commenced in 1976 in the United States when 121,700 female registered nurses, 30 to 55 years of age, were enrolled. At that time, participants completed a mailed questionnaire on risk factors for cancer and coronary heart disease.[17] In 1980, the mailing included a food frequency questionnaire that assessed diet over the past year.

Subsequently, detailed dietary-intake data have been collected in 1984, 1986, and 1990, using an expanded semi-quantitative food-frequency questionnaire.[18] The Health Professionals Follow-up Study comprises 51,529 male dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians in the US, who were 40 to 75 years of age at the onset of the study in 1986. They responded to a mailed questionnaire which also included a validated semi-quantitative food-frequency questionnaire.[19] Participants in both cohorts also provided information on age, weight, height, physical activity, and tobacco use. Family history of colon or rectal cancer, professionally diagnosed medical conditions, information on screening and medications, are updated every two years, as is present weight. Both of these studies have been described more comprehensively in previous publications.[20,21]

Diet assessment

In 1980, the semi-quantitative food-frequency questionnaire used in the NHS included 61 items; this was updated in 1984 and the number of items expanded to 121. In 1986, the questionnaire used in the HPFS included 131 food items which collectively comprised over 90 percent of the intake of most nutrients.[21,22] In each of the questionnaires, participants were asked how often, on average, over the previous year, they had eaten the specified portion (commonly used unit or portion size) of each food. There were nine possible responses ranging from never to six or more times per day. All

questionnaires also sought information about the brand and frequency of multivitamin use and individual vitamin-supplement use and the types of fat commonly used at the table and for cooking.

Nutrient intakes were computed by multiplying the frequency of intake of each unit of food by the nutrient composition of the specific portion size, using composition values from US Department of Agriculture sources[23] supplemented by other sources. The intake frequencies with and without vitamin and mineral supplements were computed. Analyses were conducted with energy-adjusted nutrient intakes based on residuals from the regression of nutrient intake on total caloric intake.[24] The reliability and validity of the 1980 (NHS) and 1986 (HPFS) questionnaires were assessed in subsamples of 173 women (1980) and 127 men (1986) from the Boston (Massachusetts) areas.[18,22] This involved participants completing detailed dietary records and providing a fasting blood sample. Mean daily intakes of nutrients, including alcohol, as assessed by the questionnaire and by the dietary records were generally similar. Spearman correlations between the diet record and questionnaire estimate of alcohol was 0.90 in women and 0.86 in men.[25]

Identification of cases of colorectal hyperplastic polyps

The response rate was almost 96 percent to follow-up questionnaires up to 1990 in the NHS, and 94 percent in the HPFS to 31 January 1992. A total of 1,471 women reported having the diagnosis of a polyp of the colon or rectum between 1980 and 1990, with 1,452 men reporting the same diagnosis between 1986 and 1992. Of these 2,923 men and women, 2,708 (91 percent) replied to a follow-up letter, of whom 2,404 granted permission to review their medical records; 220 denied having had a polyp; 81 confirmed they had a polyp but denied permission to review their records; and three had died. We had based the diagnosis of hyperplastic polyp solely on the review of the pathology report from the medical records. Upon review of the pathology reports, a diagnosis of an adenomatous or hyperplastic polyp was confirmed in 1,880 participants (902 women and 978 men). During the study period, 15,539 women and 12,922 men had had an endoscopy. After excluding adenomas and any hyperplastic polyps proximal to the descending colon, as well as any individual having both a hyperplastic and an adenomatous polyp, there were 175 women (prevalence, 1.14 percent) and 219 men (prevalence, 1.70 percent) with hyperplastic polyps of the distal colon or rectum.

Data analysis

Our analysis was confined to participants who had undergone a sigmoidoscopy or colonoscopy within the follow-up period (15,984 women between 1980 and 1990, and 12,922 men between 1986 and 1992). This was to minimize the potential for detection bias, as most hyperplastic polyps are diagnosed when individuals have an endoscopic procedure for routine screening or for gastrointestinal conditions unrelated to the hyperplastic polyp. We also excluded as cases subjects who simultaneously had an adenomatous polyp, because the presence of a large adenoma may have led differentially to a more thorough examination and tissue retrieval by the endoscopist. If so, risk factors for adenomas could appear spuriously as risk factors for hyperplastic polyps. Since a sigmoidoscopy is limited to the rectum and sigmoid and descending colon, only cases with polyps in these locations were included in the analysis. Cases where individuals with a hyperplastic polyp who had not reported previous cancer (except nonmelanoma skin cancer), colon polyps, ulcerative colitis, or a familial polyposis syndrome. Also excluded were those individuals with implausibly high or low total caloric-intakes (<800 or $>4{,}200$ kcal for men and <600 or $>3{,}500$ kcal for women) and those who left whole sections of the baseline questionnaire blank.

Participants were categorized by levels of intake of total alcohol and specific beverage types (beer, wine, and liquor), by cigarette smoking (current and past), and the numbers of cigarettes smoked per day (three categories), and by quintile of intake for folate and all other nutrients according to the distribution in the studied population. Relative risks (RR) of hyperplastic polyp for each category of intake were determined relative to nonsmokers, nondrinkers, or to those in the low quintile of folate intake or other nutrient of interest. Folate intake was considered with and without the intake of supplements. For all RRs, we also calculated 95 percent confidence intervals (CI); all *P*-values are two-sided. We used multiple logistic regression models to control for several potentially confounding variables such as age (in seven categories), total energy intake, history of colon cancer in either parent, and previous endoscopies before the study period, and the simultaneous influence of two or more nutrients. We tested for trend by modeling the quintile of nutrient intake as a continuous variable in a logistic model. We analyzed the data from the two cohorts separately.

Results

From among the cohort, men and women who had undergone an endoscopic procedure tended to smoke less, be slightly thinner, drink slightly less alcohol, eat less animal fat and cholesterol, and more fiber, folate, vitamin D, calcium, and carotene (Table 1). Other than smoking, these differences tended to be slight, especially

Table 1. Age standardized characteristics of unscreened participants of the HPFS[a] (men) and NHS[b] (women) and participants who have had a colonoscopy or sigmoidoscopy (the study population for this analysis)

	Men		Women	
	No endoscopy	Endoscopy	No endoscopy	Endoscopy
Current smokers (%)	9.5	6.5	30.3	23.4
Body mass index (kg/m^2)	25.6	25.3	24.5	24.3
Alcohol (g/day)	12.6	12.4	7.0	6.9
Animal fat (g/day)	39.8	38.5	52.4	51.9
Vegetable fat (g/day)	32.4	32.7	17.5	17.4
Cholesterol (mg/day)	333	324	337	338
Dietary fiber (g/day)	22.6	23.4	16.7	17.2
Folate (μg/day)	461	477	364	376
Vitamin D (IU/day)	398	416	290	299
Calcium (mg/day)	946	959	729	737
Carotene (μg/day)	10,342	10,615	8,034	8,319

[a]HPFS = Health Professionals Follow-up Study.
[b]NHS = Nurses' Health Study.

among the women. The proportion of indications for endoscopy were as follows: screening, asymptomatic, including positive family history (men 70.2 percent, women 45.5 percent); abdominal pain (men 6.0 percent, women 11.8 percent); change in bowel habits (men 5.2 percent, women 16.3 percent); positive, occult fecal-blood test (men 3.3 percent, women 4.3 percent); overt fecal blood (men 15.3 percent, women 22.1 percent).

The prevalence of hyperplastic polyp of the distal colon or rectum increased linearly with age. Individuals having a family history of colon cancer were at an elevated risk of having a hyperplastic polyp among men (age-adjusted RR = 1.95, CI = 1.39-2.74) and among women (age-adjusted RR = 2.03, CI = 1.39-2.95). In addition, an inverse association between having a previous negative endoscopy and risk of hyperplastic polyps was found in men (age-adjusted RR = 0.66, CI = 0.48-0.88) but not in women (age-adjusted RR = 1.05, CI = 0.75-1.48). Consequently, all further analyses were controlled for age, family history of colon cancer, and previous endoscopic procedure.

High alcohol consumption was associated directly with the occurrence of hyperplastic polyps in both men and women (Table 2). Compared with nondrinkers among men, individuals consuming over 10 g per day were at a significantly elevated risk (RR = 1.72, CI = 1.05-2.79, P for trend = 0.003). The association remained unchanged in the fully adjusted model (RR = 1.73, CI = 1.06-2.83, P for trend = 0.006). For women, the positive association for risk of hyperplastic polyp became significant only when they consumed over 30 g per day (RR = 2.46, CI = 1.82-3.63, P for trend = 0.0004). In the fully adjusted model, this association was attenuated although it remained statistically significant (RR = 1.79, CI = 1.02-3.15 P for trend = 0.02). When we examined the alcohol from beer, spirits, and wine, independently as continuous variables, a positive association was found only for beer among men (P for trend = 0.008). There was no association between spirits and wine and the occurrence of hyperplastic polyps.

A total of 6.6 percent of men and 36.2 percent of women currently smoked cigarettes. Current smoking was related strongly to hyperplastic polyp risk in both men (RR = 2.45, CI = 1.59-3.75, $P < 0.0005$) and women (RR = 1.96, CI = 1.16-2.86, $P < 0.0002$). Past smoking was not related to the occurrence of hyperplastic polyps in either men (RR = 1.21, CI = 0.91-1.62, $P < 0.19$) or women (RR = 1.14, CI = 0.88-1.52, $P < 0.21$). Among men, no clear dose-response relation was seen with number of cigarettes smoked per day, but CIs were wide due to the small number of smokers (Table 3). In women, the highest risk was seen among those smoking over 15 cigarettes per day (RR = 2.30, CI – 1.65-3.21, P for trend <0.00005). The association was attenuated only slightly when further adjusted for alcohol and folate intake (RR = 1.96, CI = 1.39-2.77, P for trend = 0.0002).

On examining the relationship of micronutrient intakes and risk of hyperplastic polyps, the strongest association was found for folate intake which was related strongly to reduced risk for hyperplastic polyp (Table 4). The inverse association between total folate and risk for hyperplastic polyp was present among men and women, although the relationship was stronger for women than men, with the RR between the highest and

Table 2. Relative risk of hyperplastic polyp of the distal colon and rectum by intakes of alcohol among men (HPFS)[a] and women (NHS)[b]

	Alcohol consumption (grams/day)						
	0 (ref.)	0.1-5.0	5.1-10.0	10.1-15.0	15.1-30	>30	*P*-value for trend[c]
Men							
Cases/total	33/2,644	49/3,295	31/1,893	33/1,554	42/1,884	31/1,433	
RR[d]	1.0	1.21	1.33	1.72	1.84	1.79	0.003
(CI)	—	(0.77-1.89)	(0.81-2.19)	(1.05-2.79)	(1.16-2.93)	(1.09-2.96)	
RR[e]	1.0	1.19	1.30	1.73	1.77	1.69	0.006
(CI)	—	(0.76-1.87)	(0.79-2.14)	(1.06-2.83)	(1.11-2.83)	(1.01-2.80)	
Women							
Cases/total	48/4,779	58/5,045	14/1,679	12/1,435	24/1,474	19/751	
RR[d]	1.0	1.18	0.84	0.84	1.58	2.46	0.0004
(CI)	—	(0.79-1.75)	(0.46-1.58)	(0.44-1.60)	(0.96-2.59)	(1.82-3.53)	
RR[e]	1.0	1.18	0.86	0.85	1.47	1.79	0.02
(CI)	—	(0.80-1.74)	(0.47-1.57)	(0.44-1.61)	(0.89-2.43)	(1.02-3.15)	

[a]HPFS = Health Professionals Follow-up Study.
[b]NHS = Nurses' Health Study.
[c]Test for trend determined by modeling intake of alcohol as a continuous variable.
[d]Relative risk and 95% confidence interval (CI) adjusted for age, energy intake, previous endoscopy, and family history of colorectal cancer by multiple logistic regression.
[e]Relative risk and 95% confidence interval (CI) adjusted for age, energy intake, family history of colorectal cancer, previous endoscopy, cigarette smoking, and intakes of folate by multiple logistic regression.

Table 3. Relative risk of hyperplastic polyp of the distal colon and rectum by cigarette smoking among men (HPFS)[a] and women (NHS)[b]

	Never smokers (ref.)	Past smokers only	Cigarettes/day		
			1-14	15+	*P*-value for trend[c]
Men					
Cases/total	89/6,322	101/5,752	10/286	19/562	
RR[d]	1.0	1.23	2.44	2.41	0.002
(CI)	—	(0.92-1.64)	(1.25-4.75)	(1.46-3.99)	
RR[e]	1.0	1.14	2.25	2.14	0.03
(CI)	—	(0.85-1.53)	(1.15-4.42)	(1.28-3.59)	
Women					
Cases/total	55/7,048	51/4,773	19/1,081	50/2,386	
RR[d]	1.0	1.36	2.30	2.85	<0.0001
(CI)	—	(0.92-1.99)	(1.36-3.90)	(1.94-4.21)	
RR[e]	1.0	1.34	2.16	2.44	<0.0001
(CI)	—	(0.90-1.98)	(1.26-3.68)	(1.63-3.65)	

[a]HPFS = Health Professionals Follow-up Study.
[b]NHS = Nurses' Health Study.
[c]Test for trend determined by modeling cigarettes per day (current smoking) as a continuous variable (excluding past smokers).
[d]Relative risk and 95% confidence interval (CI) adjusted for age, energy intake, previous endoscopy and family history of colorectal cancer by multiple logistic regression.
[e]Relative risk and 95% confidence interval (CI) adjusted for age, energy intake, family history of colorectal cancer, previous endoscopy

Table 4. Relative risk of hyperplastic polyp of the distal colon and rectum according to quintile of folate, and folates excluding the use of supplements among men (HPFS)[a] and women (NHS)[b]

	Quintile					
	1 (ref.)	2	3	4	5 (high)	*P*-value for trend[c]
Men						
Total folate (μg/day)	< 280	280-346	347-437	438-671	≥ 672	
Cases/total	55/2,525	43/2,525	41/2,574	37/2,537	43/2,542	
RR[d]	1.0	0.78	0.72	0.66	0.75	0.11
RR[e]	1.0	0.77	0.70	0.67	0.74	0.12
(CI)	—	(0.51-1.16)	(0.47-1.07)	(0.44-1.03)	(0.49-1.11)	
Folate excluding supplements (μg/day)	< 261	261-309	310-358	359-427	≥ 428	
Cases/total	58/2,536	40/2,556	40/2,523	37/2,559	44/2,529	
RR[d,f]	1.0	0.66	0.65	0.58	0.68	0.07
RR[e,f]	1.0	0.67	0.66	0.58	0.72	0.11
(CI)	—	(0.44-1.00)	(0.43-0.99)	(0.37-0.91)	(0.46-1.12)	
Women						
Total folate (g/day)	< 198	198-255	256-333	334-568	≥ 569	
Cases/total	55/3,050	37/3,025	39/3,018	20/3,063	24/3,058	
RR[d]	1.0	0.64	0.65	0.32	0.40	<0.00005
RR[c]	1.0	0.68	0.73	0.37	0.45	0.0001
(CI)	—	(0.44-1.03)	(0.48-1.11)	(0.22-0.62)	(0.28-0.74)	
Folate excluding supplements (g/day)	< 185	185-228	229-272	273-333	≥ 334	
Cases/total	50/3,010	36/3,025	34/3,061	35/3,002	20/3,066	
RR[d,f]	1.0	0.69	0.64	0.64	0.35	0.0002
RR[e,f]	1.0	0.74	0.69	0.73	0.41	0.003
(CI)	—	(0.48-1.14)	(0.45-1.09)	(0.47-1.14)	(0.24-0.70)	

[a]HPFS = Health Professionals Follow-up Study.
[b]NHS = Nurses' Health Study.
[c]Test for trend determined by modeling intake of folate as a continuous variable.
[d]Relative risk and 95% confidence interval (CI) adjusted for age, energy intake, previous endoscopy, and family history of colorectal cancer by multiple logistic regression.
[e]Relative risk and 95% confidence interval (CI) adjusted for age, energy intake, family history of colorectal cancer, previous endoscopy, cigarette smoking, and intakes of alcohol by multiple logistic regression.
[f]Adjusted also for folate supplements.

lowest quintile of total folate intake being 0.75 (CI = 0.50-1.13, *P* for trend = 0.11) among men and 0.40 (CI = 0.25-0.65, *P* for trend < 0.00005) among women. These associations did not change after adjustment for smoking and alcohol consumption. In addition to examining total folate intake (that is, folate from diet and supplements), we also examined folate intake excluding supplements (Table 4). As for total folate intake, similar inverse associations were found between folate intake without supplements and risk of hyperplastic polyp among men and women. When folate from supplements was included in the model with dietary folate, supplemental folate was related inversely, though not significantly, to hyperplastic polyp.

Because of collinearity, many nutrients common in plant foods and vitamin supplements were related inversely to hyperplastic polyps. However, when added in a multivariate model with folate, only the inverse association with folate persisted (Table 5). For vitamins A, D, and carotene, the inverse association clearly was related to folate. Vitamins E and C did have nonsignificant though suggestive inverse associations in the multivariate model; nonetheless, the significant inverse association with folate persisted.

Because of potential biologic interaction between folate and alcohol, a folate antagonist, we examined the joint effect of these two (Table 6). The highest RR was associated with a 'high-alcohol low-folate' intake (RR = 3.80, CI = 1.83-7.89). High alcohol countered with high folate intakes was not associated appreciably with risk, but the CIs were wide.

We also examined the relationship between macronutrient intake and the risk for developing hyperplastic polyps (Tables 7 and 8). Weak and

Table 5. Relative risks (RR) and 95 percent confidence intervals (CI) of hyperplastic polyp of the distal colon and rectum between the highest quintile of folate and the specified nutrient intake relative to the lowest quintile of each using a multiple logistic model which includes folate and the specified nutrient as well as age, gender, energy intake, family history of colon cancer and history of endoscopy prior to the study period

	RR	(CI)
Vitamin A	0.85	(0.55-1.33)
Folate	0.58	(0.40-0.88)[b]
Vitamin D	0.99	(0.65-1.51)
Folate	0.60	(0.42-0.89)[b]
Vitamin E	0.72	(0.48-1.10)
Folate	0.67	(0.47-0.93)[a]
Vitamin C	0.71	(0.47-1.07)
Folate	0.58	(0.41-0.89)[b]
Carotene	0.95	(0.58-1.49)
Folate	0.55	(0.37-0.82)[b]

[a] $0.01 < P \leq 0.05$.
[b] $0.001 < P \leq 0.01$.

nonsignificant positive associations were found between total fat intake and hyperplastic polyp risk among men (P for trend = 0.79) and women (P for trend = 0.12). For animal fat, we observed a stronger positive trend, with risk in the highest compared with the lowest quintile being 1.61 (CI = 1.04-2.49, P for trend = 0.02) among men and 1.52 (CI = 0.97-2.38, P for trend = 0.12) among women. Vegetable fat was related inversely to hyperplastic polyp risk in both men and women, although this association was not as strong as that for animal fat and was not statistically significant (Tables 7 and 8). When either animal or vegetable fat was included in a model with smoking, alcohol, and folate intakes, these associations were not significant (Table 7 and 8). Increased energy-adjusted intakes of both carbohydrates and dietary fiber were related strongly to reduced risk for hyperplastic polyp (P for trend = 0.01 for carbohydrates and 0.03 for dietary fiber among men, and 0.003 for carbohydrates and 0.001 for dietary fiber among women). But when they were entered in a model adjusted for folate intake, smoking, and alcohol consumption, the association weakened considerably for carbohydrate intake among men and women, and did not persist for dietary fiber among men. Protein intake was related positively to risk for hyperplastic polyps after adjustment for smoking, alcohol, and folate intake; the RR in the highest compared with the lowest quintile was 1.74 (CI = 1.08-2.73, P for trend = 0.23) among men. This relationship, while not significant, was in the same direction among women, adjusted RR = 1.48 (CI = 0.88-2.48, P for trend = 0.09).

Table 6. Joint influence (relative risk [RR] and 95% confidence interval [CI] of alcohol and folate intake among men (HPFS)[a] and women (NHS)[b] combined

Folate tertile	Alcohol (g/day)		
	0-5	5.1-19.9	≥20
High			
RR	1.0	2.06	1.45
(CI)	—	(1.06-4.02)	(0.49-4.31)
Medium			
RR	1.91	1.11	3.69
(CI)	(1.08-3.38)	(0.49-2.47)	(1.68-8.11)
Low			
RR	2.85	2.04	3.80
(CI)	(1.67-4.89)	(1.03-4.03)	(1.83-7.89)

[a] HPFS = Health Professionals Follow-up Study.
[b] NHS = Nurses' Health Study.

Discussion

These prospective data suggest associations between low folate intakes, alcohol, and current smoking, and the occurrence of hyperplastic polyps of the distal colon and rectum. The prospective design minimizes bias due to the influence of disease on dietary patterns or on recall of past diet.

The prevalence rate of hyperplastic polyps in this population (about two percent) was somewhat lower than that of adenomas (about three percent).[20] The ratio of hyperplastic polyps to adenomatous polyps shows considerable variability among different populations and different countries. In autopsy studies from Hawaii (US), England (UK), and New Jersey (US), a threefold excess of hyperplastic over adenomatous polyps was seen,[11] whereas a ratio closer to unity was seen for Finland and Aberdeen (Scotland, UK),[26] while adenomas outnumbered hyperplastic polyps in autopsy surveys from Colombia, Hong Kong, Norway, Mexico, and among the Maoris and Polynesians in New Zealand.[27] It would seem that a low ratio of hyperplastic polyps to adenoma characterizes populations at low risk for colorectal cancer, indicating that the hyperplastic polyp is a better marker for high risk populations than adenoma. While there is no clear explanation for this variability, autopsy studies are likely to yield very different results compared with those using flexible endoscopy.[9]

The low prevalence rate of hyperplastic polyps may reflect the atypically 'healthy' diets and lifestyles of these cohorts, in which the prevalence of adenomatous polyps and the incidence of colon cancer are also considerably lower than that of the general US

Table 7. Relative risk of hyperplastic polyp of the distal colon and rectum according to quintile of total energy intake, macronutrients, and dietary fiber among men of the Health Professionals Follow-Up Study

	Quintile					
	1 (ref.)	2	3	4	5 (high)	*P*-value for trend[a]
Total energy (kcal/day)	<1,406	1,406-1,703	1,704-2,000	2,001-2,394	≥ 2,395	
Cases/total	43/2,542	52/2,532	46/2,538	38/2,547	40/2,544	
RR[b]	1.0	1.22	1.08	0.88	0.93	0.20
RR[c]	1.0	1.18	0.98	0.82	0.84	0.08
(CI)	—	(0.78-1.78)	(0.65-1.50)	(0.53-1.28)	(0.54-1.32)	
Total fat (g/day)	<60	60-68	69-75	76-82	≥83	
Cases/total	41/2,533	47/2,558	42/2,520	47/2,556	42/2,536	
RR[b]	1.0	1.16	1.05	1.17	1.04	0.79
RR[c]	1.0	1.11	0.99	1.08	0.96	0.86
(CI)	—	(0.72-1.69)	(0.63-1.53)	(0.70-1.68)	(0.66-1.52)	
Animal fat (g/day)	<28	28-34	35-40	41-47	≥48	
Cases/total	33/2,558	39/2,321	40/2,689	54/2,498	54/2,637	
RR[b]	1.0	1.31	1.17	1.65	1.61	0.02
RR[c]	1.0	1.25	1.09	1.52	1.48	0.05
(CI)	—	(0.78-2.00)	(0.68-1.75)	(0.07-2.37)	(0.94-2.41)	
Vegetable fat (g/day)	<24	24-29	30-34	35-40	≥41	
Cases/total	54/2,539	47/2,540	36/2,534	41/2,540	41/2,550	
RR[b]	1.0	0.89	0.68	0.79	0.77	0.13
RR[c]	1.0	0.89	0.68	0.79	0.79	0.21
(CI)	—	(0.60-1.33)	(0.44-1.18)	(0.51-1.20)	(0.50-1.21)	
Protein (g/day)	<77.3	77.3-85.6	85.7-92.9	93.0-101.9	≥102.0	
Cases/total	32/2,553	49/2,534	62/2,519	28/2,554	48/2,543	
RR[b]	1.0	1.53	1.95	0.86	1.47	0.69
RR[c]	1.0	1.62	2.07	0.98	1.74	0.23
(CI)	—	(1.03-2.54)	(1.33-3.21)	(0.58-1.64)	(1.08-2.73)	
Carbohydrate (g/day)	<206	206-230	231-250	251-274	≥275	
Cases/total	55/2,531	40/2,539	51/2,539	47/2,531	26/2,563	
RR[b]	1.0	0.73	0.94	0.85	0.46	0.01
RR[c]	1.0	0.83	1.13	1.11	0.64	0.48
(CI)	—	(0.54-1.27)	(0.75-1.72)	(0.72-1.72)	(0.38-1.08)	
Dietary fiber (g/day)	<17.1	17.1-20.7	20.8-24.3	24.4-29.2	≥29.3	
Cases/total	53/2,508	42/2,543	49/2,564	43/2,532	32/2,556	
RR[b]	1.0	0.79	0.91	0.79	0.57	0.03
RR[c]	1.0	0.86	0.95	0.96	0.96	0.13
(CI)	—	(0.57-1.31)	(0.69-1.43)	(0.61-1.49)	(0.46-1.25)	

[a]Test for trend determined by modeling intake of nutrient as a continuous variable.
[b]Relative risk and 95% confidence interval (CI) adjusted for age, energy intake (except for total energy), previous endoscopy, and family history of colorectal cancer by multiple logistic regression.
[c]Relative risk and 95% confidence interval (CI) adjusted for age, energy intake (except for total energy), family history of colorectal cancer, previous endoscopy, cigarette smoking, and intakes of alcohol and folate by multiple logistic regression.

population. The particularly low number of participants currently smoking cigarettes and the relatively high folate intakes may be contributing to the low prevalence rate. To study this question of low prevalence in our study population, endoscopy reports were requested from 200 participants from the HPFS cohort. These were selected randomly from all individuals who indicated on their questionnaire having had a negative endoscopy. A total of 140 out of the 200 responded and, of these, only one was found to have a diminutive polyp (~ 1 mm and unidentified). This result suggests that the participants are reporting the outcome of their endoscopy procedure correctly and that the low prevalence of hyperplastic polyps found in this population is true. It is also possible that more hyperplastic polyps, owing to their relatively small size (very often being <5 mm), have an increased likelihood of being missed. As many as 25 percent of

Table 8. Relative risk of hyperplastic polyp of the distal colon and rectum according to quintile of total energy intake, macronutrients, and dietary fiber among women of the Nurses Health Study

	Quintile					
	1 (ref.)	2	3	4	5 (high)	*P*-value for trend[a]
Total energy (kcal/day)	<1,130	1,130-1,389	1,390-1,639	1,640-1,959	≥1,960	
Cases/total	43/2,938	25/3,022	33/3,211	28/3,010	46/2,890	
RR[b]	1.0	0.57	0.70	0.63	1.11	0.60
RR[c]	1.0	0.60	0.74	0.66	1.14	0.52
(CI)	—	(0.38-1.01)	(0.48-1.14)	(1.42-1.04)	(0.75-1.72)	
Total fat (g/day)	<58	58-66	67-73	74-80	≥81	
Cases/total	34/3.042	25/3,049	38/3,039	38/3,010	40/3,024	
RR[b]	1.0	0.76	1.19	1.22	1.29	0.12
RR[c]	1.0	0.71	1.12	1.06	1.02	0.49
(CI)	—	(0.42-1.21)	(0.69-1.80)	(0.65-1.73)	(0.62-1.68)	
Animal fat (g/day)	<39	39-47	48-55	56-64	≥65	
Cases/total	35/3,153	26/2,951	31/3,208	38/2,939	45/2,913	
RR[b]	1.0	0.84	0.93	1.29	1.52	0.03
RR[c]	1.0	0.79	0.84	1.11	1.22	0.17
(CI)	—	(0.47-1.32)	(0.51-1.37)	(0.70-1.79)	(0.77-1.94)	
Vegetable fat (g/day)	<9	9-14	15-18	19-23	≥24	
Cases/total	38/2,849	48/3,575	23/2,834	37/2,762	29/3,144	
RR[b]	1.0	1.05	0.64	1.05	0.71	0.21
RR[c]	1.0	1.10	0.67	1.12	0.74	0.29
(CI)	—	(0.71-1.69)	(0.40-1.14)	(0.70-1.79)	(0.45-1.23)	
Protein (g/day)	<64	64-72	73-79	80-88	≥89	
Cases/total	31'/2,895	36/3,264	38/3,080	36/2,964	34/2,961	
RR[b]	1.0	1.05	1.151	1.17	1.03	0.84
RR[c]	1.0	1.21	1.42	1.44	1.48	0.09
(CI)	—	(0.74-1.98)	(0.87-2.32)	(0.87-2.36)	(0.88-2.48)	
Carbohydrate (g/day)	<125	125-146	147-164	165-184	≥185	
Cases/total	55/3,043	30/3,036	34/3,017	27/2,968	29/3,100	
RR[b]	1.0	0.55	0.62	0.50	0.51	0.003
RR[c]	1.0	0.67	0.81	0.71	0.74	0.27
(CI)	—	(0.42-1.09)	(0.52-1.28)	(0.44-1.17)	(0.45-1.20)	
Dietary fiber (g/day)	<12.1	121.1-14.9	15.0-17.8	17.9-21.9	≥22.0	
Cases/total	50/3,051	36/2,955	38/3,016	27/3,085	24/3,057	
RR[b]	1.0	0.73	0.73	0.50	0.42	0.0001
RR[c]	1.0	0.93	1.02	0.77	0.79	0.33
(CI)	—	(0.59-1.46)	(0.72-1.64)	(0.45-1.32)	(0.48-1.35)	

[a]Test for trend determined by modeling of nutrient as a continuous variable.
[b]Relative risk and 95% confidence interval (CI) adjusted for age, energy intake (except for total energy), previous endoscopy, and family history of colorectal cancer by multiple logistic regression.
[c]Relative risk and 95% confidence interval (CI) adjusted for age, energy intake (except for total energy), family history of colorectal cancer, previous endoscopy, cigarette smoking, and intakes of alcohol and folate by multiple logistic regression.

polyps less than 5 mm in size of the sigmoid colon and rectum were missed on endoscopic examination in a prospective study examining the frequency and size distribution of polyps missed by colonoscopy.[28]

Some detection bias might result due to family history—whereby the colonoscopists may examine patients with a family history for colon cancer more thoroughly than those without a family history. This could contribute to the strong positive association between family history of colon cancer and risk for hyperplastic polyp. Consequently, analyses were adjusted for family history of colon cancer. However, there is little reason to suspect that detection bias by the colonoscopists would account in full for the associations observed in this study with regard to smoking, alcohol, and folate intake, as it is unlikely that colonoscopists would have been aware of prior hypotheses relating these factors to the risk of

colorectal cancer. In restricting our study population to those individuals who had undergone an endoscopy, we reduced the likelihood that the associations observed were merely the result of detection bias. Further, only left-sided hyperplastic polyps were considered, as many individuals may have undergone only flexible sigmoidoscopy. Despite our efforts to minimize the potential for bias, we cannot be entirely certain that some of our analyses are not influenced by bias; thus, it is important to replicate these analyses in other settings.

Both total folate intake and folate without supplements were associated inversely with risk of hyperplastic polyps in men and women, although the associations were stronger in women. An inverse association with increasing folate intake also has been noted in colorectal cancer[29] and adenomatous polyps of the distal colon and rectum.[30] This association occurred even though very few individuals had folate intakes below 200 μg per day, the current Recommended Dietary Intake.[31] Thus, intakes higher than those thought to be necessary to prevent megaloblastic anemia may reduce the occurrence of hyperplastic polyps. Since these two cohorts are generally health-conscious, the protective effect of folate may have been underestimated and could be considerably greater in populations with more persons having lower folate intakes. In a number of developing countries, where folate intakes are low enough to cause folate deficiencies, a low incidence of colon cancer is observed.[32] Thus, additional factors must be required, either at the initiation stage or later during promotion, to result in the development of neoplastic lesions of the colon. The observed association between folate intake and the occurrence of hyperplastic polyps might be due merely to chance or possibly to other unconsidered factors in vegetables. However, the consistency with earlier findings for colon adenomas and the dose-response relationships suggests that the associations may be causal.

A direct association between alcohol intake and occurrence of hyperplastic polyps in the distal colon and rectum was found in both cohorts. Among men, alcohol from beer was associated directly with hyperplastic polyp risk. A direct relationship between alcohol consumption and colorectal adenoma has been demonstrated consistently in studies of colorectal adenomas.[30,33-37] The association between colorectal cancer and alcohol intake is somewhat less consistent, with some case-control studies showing a positive association with colon cancer[38,39] and others failing to show any direct relationship.[40,41] Cohort studies[42-45] have been more consistent, almost always showing a positive association between alcohol consumption and colorectal cancer, though there have been exceptions.[46] There is no particular explanation for these conflicting findings, but acquisition of data on alcohol consumption may have contributed to the discrepant results. In many of these studies, alcohol was not a major focus, and in only a few studies[43,47] was a cumulative index of alcohol intake developed.

Although the association between alcohol intake and hyperplastic polyps in our study was independent of smoking, weight, and dietary factors, it may be possible that some other, unidentified third variable, which is related closely to alcohol use and risk for hyperplastic polyps, may account for all or part of the observed association. The mechanism by which alcohol imposes an increased risk for colorectal cancer and adenomatous or hyperplastic polyps is not known. Alcohol is not a direct-acting carcinogen, but beer, wine, and spirits are known to contain 1,200 different compounds including phenols, higher alcohols, nitrosamines, and aldehydes.[48] One hypothesis for alcohol involves acetaldehyde, a known carcinogen and metabolic intermediate of alcohol in humans.[49] In rodents, levels of acetaldehyde were found to be significantly higher in the left colon and rectum than in the proximal colon in rats and increased in response to ethanol intake,[50] and ethanol increased the frequency of acetoxymethylnitrosamine-induced cancers of the distal but not proximal colon. Such site specificity could be the result of increased cell turnover in the mucosa,[51] or to a toxic effect of acetaldehyde.[50]

Folate metabolism is known to be affected adversely by alcohol,[52] which also may be related to acetaldehyde produced during alcohol catabolism. When acetaldehyde is oxidized by xanthine oxidase, superoxide radicals are produced that catabolize folates by cleaving them at the C^9-N^{10} bond.[53] Moreover, ethanol binds to and inactivates N^5-methyltetrahydrofolate.[54] Thus, the positive relationship seen between alcohol and hyperplastic polyps may be reflecting the influence which alcohol has on folate metabolism; however, there was no evidence of an interaction between folate intake and alcohol in our analyses.

The strong positive association between current cigarette smoking and risk for hyperplastic polyps of the distal colon and rectum in both men and women corroborates results from a previous prospective study.[55] However, in that study, hyperplastic and adenomatous polyps were not distinguished. In a case-control study[35] involving colonoscopy candidates, smoking was found to be an independent risk-factor for colonic adenomas. A recent prospective study in men[56] concurs with their findings where the level of current cigarette smoking was related to risk of colorectal adenomas. If smoking is an initiating factor, it may be

associated more closely with polyps than with colon cancer. Our findings of a strong positive association between smoking and risk of hyperplastic polyps indirectly may support such a theory. Hyperplastic polyps have a similar geographic distribution[57] and are found with increased frequency in high-risk areas and among patients with colon cancer.[58]

In summary, these data suggest that low folate, alcohol consumption, and cigarette smoking increase the occurrence of hyperplastic polyps of the distal colon and rectum. Because these predictors also are associated with risk for adenomas, these findings may help explain autopsy data that have demonstrated a relationship between the prevalence of both adenomatous and hyperplastic polyps and the incidence of colorectal cancer in different populations.[11,26] Whether hyperplastic polyps are involved in the pathogenesis of colon cancer or only a marker of increased risk remains to be determined.

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References

1. Fenoglio-Preiser CM. Polyps and the subsequent development of carcinoma of the colon and rectum: definitions and hints on tissue handling. In: Feneglio-Preiser CM, Rossini FP, eds. *Adenomas and Adenomas Containing Carcinoma of The Large Bowel: Advances in Diagnosis and Therapy.* New York, NY (USA): Raven Press, 1985: 15-29.
2. Fenoglio CM, Pascal RR. Colorectal adenomas and cancer. Pathologic relationships. *Cancer* 1982; **50:** 2600-8.
3. Gillbertsen VA. Proctosigmoidoscopy and polypectomy in reducing the incidence of rectal cancer. *Cancer* 1974; **34:** 936-43.
4. Arthur JF. Structure and significance of metaplastic nodules in the rectal mucosa. *J Clin Pathol* 1968; **21:** 735-43.
5. Fenoglio CM, Lane N. The anatomical precursor of colorectal carcinoma. *Cancer* 1974; **34:** 819-23.
6. Provenzale D, Martin ZZ, Holland KL, *et al.* Colon adenomas in patients with hyperplastic polyps. *J Clin Gastroenterol* 1988; **10:** 46-9.
7. Ansher AF, Lewis JH, Fleischer DE, *et al.* Hyperplastic colonic polyps as a marker for adenomatous colonic polyps. *Am J Gastroenterol* 1989; **84:** 113-7.
8. Jass JR. Nature and clinical significance of colorectal hyperplastic polyp. *Semin Colon Rectal Surg* 1991; **2:** 246-52.
9. Jass JR. Relation between metaplastic polyp and carcinoma of the colorectum. *Lancet* 1983; **i:** 28-30.
10. Stemmermann GN, Yatani R. Diverticulosis and polyps of the large intestine. A necropsy study of Hawaii Japanese. *Cancer* 1973; **31:** 1260-70.
11. Correa P. Epidemiology of polyps and cancer. In: Morson BC, ed. *The Pathogenesis of Colorectal Cancer. Major Problems in Pathology, Vol. 10* Philadelphia, London, Toronto: WB Saunders, 1978: 126-52.
12. Haenszel W, Kurihara M. Studies of Japanese migrants. I. Mortality from cancer and other diseases among Japanese in the United States. *JNCI* 1968; **40:** 43-68.
13. Jass JR, Filipe MI, Abbas S, *et al.* A morphologic and histochemical study of metaplastic polyps of the colorectum. *Cancer* 1984; **53:** 510-5.
14. Jass JR, Faludy KA. Immunohistochemical demonstration of IgA and secretory component in relation to epithelial cell differentiation in normal colorectal mucosa and metaplastic polyp: A semiquantitative study. *Histochem J* 1985; **17:** 373-80.
15. Hayashi T, Yatani R, Apostol J, Stemmermann GN. Pathogenesis of hyperplastic polyps of the colon: a hypothesis based on ultrastructure and *in vitro* cell kinetics. *Gastroenterology* 1974; **66:** 347-56.
16. Czernobilsky B, Tsou KC. Adenocarcinoma, adenomas and polyps of the colon. *Cancer* 1968; **21:** 165-77.
17. Stampfer MJ, Willett WC, Colditz GA, *et al.* A prospective study of postmenopausal estrogen therapy and coronary heart disease. *N Engl J Med* 1985; **313:** 1044-9.
18. Willett WC, Sampson L, Stampfer MJ, *et al.* Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol* 1985; **122:** 51-65.
19. Rimm EB, Stampfer MJ, Colditz GA, *et al.* Effectiveness of various mailing strategies among nonrespondents in a prospective cohort study. *Am J Epidemiol* 1990; **131:** 1068-71.
20. Giovannucci E, Stampfer MJ, Colditz GA, *et al.* Relation of diet to the risk of colorectal adenoma in men. *JNCI* 1992; **84:** 91-8.
21. Willett WC, Sampson L, Browne ML, *et al.* The use of a self-administered questionnaire to assess diet four years in the past. *Am J Epidemiol* 1988; **127:** 188-99.
22. Rimm EB, Giovannucci E, Stampfer MJ, *et al.* Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. *Am J Epidemiol* 1992; **135:** 1114-26.
23. United States Department of Agriculture. *Agriculture Handbook No. 8 Series. Composition of Foods: Raw, Processed and Prepared.* Washington, DC: US Government Printing Office, 1963-88.
24. Willett WC. The search for the causes of breast and colon cancer. *Nature* 1989; **339:** 389-94.
25. Giovannucci E, Colditz GA, Stampfer MJ, *et al.* The assessment of alcohol consumption by a simple self-administered questionnaire. *Am J Epidemiol* 1991; **133:** 810-7.
26. Clark JC, Collan Y, Eide TJ, *et al.* Prevalance of polyps in an autopsy series from areas with varying incidence of large bowel cancer. *Int J Cancer* 1985; **36:** 179-86.
27. Jass JR, Young PJ, Robinson EM. Predictors of presence, multiplicity, size and dysplasia of colorectal adenomas. A necropsy study in New Zealand. *Gut* 1992; **33:** 1508-13.
28. Hoff G, Vatn M. Epidemiology of polyps in the rectum and sigmoid colon: endoscopic evaluation of size and location of polyps. *Scand J Gastroenterol* 1985; **20:** 356-60.
29. Freudenheim JL, Graham S, Marshall JR, *et al.* Folate intake and carcinogenesis of the colon and rectum. *Int J Epidemiol* 1991; **20:** 368-74.

30. Giovannucci E, Stampfer MJ, Colditz GA, *et al.* Folate, methionine, and alcohol intake and risk of colorectal adenoma. *JNCI* 1993; **85:** 875-84.
31. National Academy Press. *Recommended Dietary Allowances, 10th Edition.* Washington DC: NAP, 1989.
32. Colman N. Addition of folic acid to staple foods as a selective nutrition intervention strategy. *Nutr Rev* 1982; **40:** 225-33.
33. Diamond M. Adenomas of the rectum and sigmoid in alcoholics: a sigmoidoscopic study. *Am J Dig Dis* 1972; **19:** 47-50.
34. Stemmermann GN, Heilbrun LK, Nomura AMY. Association of diet and other factors with adenomatous polyps of the large bowel: a prospective autopsy study. *Am J Clin Nutr* 1988; **47:** 312-7.
35. Kikendall JW, Bowen PE, Burgess MB, *et al.* Cigarettes and alcohol as independent risk factors for colonic adenomas. *Gastroenterol* 1989; **97:** 660-4.
36. Kono S, Ikedu N, Yanai F, *et al.* Alcoholic beverages and adenomatous polyps of the sigmoid colon: a study of male self-defence officials in Japan. *Int J Epidemiol* 1990; **19:** 848-52.
37. Honjo S, Kono S, Shinchi K, *et al.* Cigarette smoking, alcohol use and adenomatous polyps of the sigmoid colon. *Jpn J Cancer Res* 1992; **83:** 806-11.
38. Tuyns AJ, Pequinot G, Gignoux M, *et al.* Cancers of the digestive tract, alcohol and tobacco. *Int J Cancer* 1982; **30:** 9-11.
39. Miller AB, Howe GR, Jain M, *et al.* Food items and food groups as risk factors in a case-control study of diet and colorectal cancer. *Int J Cancer* 1983; **32:** 155-61.
40. Martinez I, Torres R, Frias Z, Colon JR, Fernandez N. Factors associated with adenocarcinoma of the large bowel in Puerto Rico. In: Birch JM, ed. *Advances in Medical Oncology, Research and Education. Vol. 3.* New York, NY (USA): Pergamon Press, 1979: 45-52.
41. Manousos O, Day NE, Trichopoulos D, *et al.* Diet and colorectal cancer: a case-control study in Greece. *Int J Cancer* 1983; **32:** 1-5.
42. Klatsky AL, Armstrong MA, Friedman GD, *et al.* The relations of alcoholic beverage use to colon and rectal cancer. *Am J Epidemiol* 1988; **128:** 1007-15.
43. Wu AH, Paganini-Hill A, Ross PK, *et al.* Alcohol, physical activity and other risk factors for colorectal cancer: A prospective study. *Br J Cancer* 1987; **55:** 687-94.
44. Hirayama T. Association between alcohol consumption and cancer of the sigmoid colon: observations from a Japanese cohort study. *Lancet* 1989; **ii:** 725-7.
45. Stemmermann GN, Nomura AMY, Chyou PH, *et al.* Prospective study of alcohol intake and large bowel cancer. *Dig Dis Sci* 1990; **35:** 1414-20.
46. Garland C, Shekelle RB, Barrett-Connor E, *et al.* Dietary vitamin D and calcium and risk of colorectal cancer: a 19-year prospective study in men. *Lancet* 1985; **i:** 307.
47. Williams RR, Horm JW. Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: interview study from the third National Cancer Survey. *JNCI* 1977; **58:** 525-47.
48. Bingham S. Diet and large bowel cancer. *J Royal Soc Med* 1990; **83:** 420-2.
49. International Agency for Research on Cancer. *Allyl and Allylic Compounds, Aldehydes, Epoxides and Peroxides.* Lyon, France: IARC, 1985; *IARC Monogr Eval Carcinog Risk Humans*, Vol. 36.
50. Seitz HK, Simanowski UA, Garzon FT, *et al.* Possible role of acetaldehyde in ethanol-related rectal carcinogenesis in the rat. *Gastroenterol* 1990; **98:** 406-13.
51. Simanowski UA, Seitz HK, Baier B, *et al.* Chronic alcohol consumption selectively stimulates rectal cell proliferation in the rat. *Gut* 1986; **27:** 278-82.
52. Herbert VD, Colman N. Folic acid and vitamin B12. In: Shils ME, Young VR. *Modern Nutrition in Health and Disease. 7th Ed.* Philiadelphia, PA (USA): Lea and Febiger, 1988: 388-416.
53. Shaw S, Jayatillek E, Herbert V, Colman N. Cleavage of folates during ethanol metabolism. *Biochem J* 1989; **257:** 277-80.
54. Barak AJ, Beckenhaur HC, Tuma DJ, Halsted CH. Effects of prolonged ethanol feeding on methionine metabolism in rat liver. *Biochem Cell Biol* 1987; **65:** 230.
55. Hoff G, Vatn MH, Larsen S. Relationship between tobacco smoking and colorectal polyps. *Scand J Gastroenterol* 1987; **22:** 13-6.
56. Giovannucci E, Rimm EB, Stampfer MJ, *et al.* A prospective study of cigarette smoking and risk of colorectal adenoma and cancer in men. *JNCI* 1994; **86:** 183-91.
57. Vatn MH, Stalsberg H. The prevalence of polyps of the large intestine in Oslo: An autopsy study. *Cancer* 1982; **49:** 819-25.
58. Eide TJ, Stalsberg H. Polyps of the large intestine in Northern Norway. *Cancer* 1978; **42:** 2839-48.