[CANCER RESEARCH 49, 1049–1051, February 15, 1989]

Coffee Consumption and Digestive Tract Cancers[1]

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ABSTRACT

The relationship between coffee drinking and the risk of digestive tract neoplasms was analyzed in a case-control study of 50 cases of cancer of the mouth or pharynx, 209 of the esophagus, 397 of the stomach, 455 of the colon, 295 of the rectum, 151 of the liver, 214 of the pancreas, and 1944 control subjects admitted for acute, non-digestive tract disorders. There was no significant or consistent association between coffee and cancers of the mouth or pharynx, esophagus, stomach, liver, or pancreas. In particular, for pancreatic cancer, the multivariate relative risks for the intermediate and upper tertiles were 1.05 and 1.01, respectively. There were significant inverse trends in risk with measures of coffee consumption for colon and rectal cancers, the multivariate relative risks according to tertiles of coffee consumption being 0.86 and 0.64 for colon and 0.97 and 0.66 for rectum. This apparent protection is in agreement with some (but not all) previous epidemiological evidence and finds a possible biological interpretation in terms of interference on bile secretion, causing reduced bile acid and neutral sterol concentrations in the bowel. In conclusion, the results of this study, the major interest of which lies in the opportunity of drawing up an overall pattern of risk for various digestive neoplasms, offer further reassurance as regards the effects of coffee on digestive tract carcinogenesis.

INTRODUCTION

Coffee is widely drunk and induces a series of metabolic and pharmacological effects, including, specifically on the digestive tract, increased gastric acid, reduced bile acid, and neutral sterol secretions (1, 2). Further, coffee may contain mutagens, such as chlorogenic acid and naphthylglyoxal, and at high doses caffeine impedes DNA repair (3–5). It is thus possible that coffee interferes with the risk of cancers of the digestive tract. Since direct epidemiological evidence on this issue is largely inconsistent, we investigated the relation between coffee consumption and the risk of various digestive tract neoplasms on the basis of a network of case-control studies conducted in Northern Italy. The large data set and the possibility of simultaneous comparison of the patterns of risk for various sites give particular interest to this analysis.

SUBJECTS AND METHODS

The present data were derived from an ongoing case-control study of several neoplasms of the digestive tract, based on a network of teaching and general hospitals from the Greater Milan area. Recruitment of cases of various cancers started between 1983 and 1985, and the present report is based on data collected up to March 1988.

The general design of this investigation has already been described (6). Briefly, trained interviewers identified and questioned patients admitted to university and general hospitals in the area under surveillance for various cancers of the digestive tract and for a wide spectrum of other conditions. On the average, less than 2% of eligible subjects (cases and controls) refused to be interviewed.

Cases. The cases studied were subjects below the age of 75 with histologically confirmed cancer of the mouth or pharynx (n = 50), esophagus (n = 209), stomach (n = 397), colon (n = 455), rectum (n = 295), liver (n = 151), and pancreas (n = 214) diagnosed within the year before interview, who had been admitted to the National Cancer Institute, to several university clinics (chiefly of surgery), and to the Ospedale Maggiore, which includes the four largest teaching and general hospitals in Milan.

Controls. Patients admitted for a wide spectrum of acute conditions to several specialized university clinics and to the Ospedale Maggiore of Milan were eligible as controls. None of these patients had malignant tumors, digestive tract disorders, or any condition related to coffee, alcohol, or tobacco consumption or which might have resulted in long-term modification of diet. A total of 1944 controls (1334 males, 610 females) were interviewed. Of these, 38% were admitted for traumatic conditions (mostly fractures and sprains), 15% had nontraumatic orthopedic disorders (mostly lower back pain and disc disorders), 34% were admitted for acute surgical conditions (including plastic surgery), and 13% had other illness, such as ear, nose, and throat, skin, or dental disorders. The median age of the comparison group was 56 years, and the distribution of cases and controls according to age and sex is given in Table 1. The catchment areas of cases and controls were well comparable. Overall, 86% of the cases and 83% of the controls resided in the same region, Lombardy; 6% of the cases and 4% of the controls came from other Northern Italian regions; 8% of the cases and 13% of the controls were from Central or Southern Italy.

A standard questionnaire was used to obtain information on socio-demographic factors and general characteristics and habits, including smoking, alcohol, coffee, and other methylxanthine-containing beverage consumption; a brief diet history based on 33 indicator foods; related personal and family medical anamnesis; and history of use of selected drugs.

Data Analysis and Control of Confounding. Relative risks of various digestive tract neoplasms in relation to measures of coffee consumption, together with their 95% approximate confidence intervals, were first derived from data stratified for sex and age in decades (7). Secondly, to account simultaneously for the potential confounding effect of several factors, unconditional multiple logistic regression equations were fitted (8), including terms for social class, education, marital status, smoking, and alcohol consumption, besides age and sex.

RESULTS

Table 2 gives the distribution of cases of various digestive tract neoplasms and the comparison group according to daily consumption of caffeine-containing coffee. The corresponding age- and sex-adjusted and multivariate relative risk estimates according to approximate consumption tertiles (≤1; 2; ≥3 cups/day) are reported in Table 3. No appreciable association was evident with cancers of the mouth or pharynx, esophagus, stomach, liver, and pancreas. For the latter neoplasm the point estimates were 1.05 for 2 and 1.01 for 3 or more cups/day. There were significant inverse trends for coffee consumption in relation to cancers of the colon (multivariate relative risk, 0.64 for upper *versus* lower tertile) and rectum (relative risk, 0.66). Both estimates were statistically significant.

The association between coffee drinking and cancers of the

Received 7/1/88; revised 10/13/88; accepted 10/20/88.

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[1] This work was conducted within the framework of the CNR (Italian National Research Council) Applied Project "Oncology" (Contract 87.01544.44). The contributions of the Italian League Against Tumours, Milan, Italy, and of the Italian Association for Cancer Research are gratefully acknowledged.

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Table 1 *Distribution of cases of selected digestive tract cancers and controls according to sex and age: Milan, Italy, 1983–1988*

Type of cancer	Males by age group (yr)				Females by age group (yr)				
	<45	45–54	55–64	65–74	<45	45–54	55–64	65–74	Total
Mouth or pharynx	1	24	12	6	1	3	3		50
Esophagus	10	46	71	35	5	8	19	15	209
Stomach	21	51	85	86	14	31	52	57	397
Colon	22	36	77	86	19	45	75	95	455
Rectum	12	27	65	66	8	18	45	54	295
Liver	12	19	54	30	8	6	12	10	151
Pancreas	11	37	47	41	4	11	28	35	214
Controls	276	392	384	282	69	127	218	196	1944

Table 2 *Distribution of selected digestive tract cancers and controls according to sex and coffee consumption: Milan, Italy, 1983–1988*

Type of cancer	Males, cups/day					Females, cups/day				
	0	1	2	3	≥4	0	1	2	3	≥4
Mouth or pharynx	9	9	14	5	6	1		1	2	3
Esophagus	19	36	45	33	29	7	15	9	10	6
Stomach	41	48	65	47	42	33	42	36	26	17
Colon	51	54	63	27	26	48	70	64	33	19
Rectum	30	57	50	16	17	19	34	38	18	16
Liver	25	27	32	15	16	8	11	7	5	5
Pancreas	18	33	43	17	25	12	21	18	16	11
Controls[a]	194	287	373	233	247	106	139	160	114	90

[a] The sum of strata does not add up to the total because of some missing values.

Table 3 *Relative risks of selected digestive tract cancers according to coffee consumption: Milan, Italy, 1983–1988*

Type of cancer	Coffee consumption (cups/day)			χ_1^2 (trend)
	0–1	2	≥3	
Mouth or pharynx				
A[a]	1[b]	0.99	0.79	0.42
B	1[b]	0.86	0.81	0.79
Esophagus				
A	1[b]	0.93	1.13	0.46
B	1[b]	0.90	0.98	0.02
Stomach				
A	1[b]	0.89	1.01	0.00
B	1[b]	0.94	1.26	0.17
Colon				
A	1[b]	0.83	0.59	14.89[c]
B	1[b]	0.86	0.64	10.37[c]
Rectum				
A	1[b]	0.91	0.62	8.23[c]
B	1[b]	0.97	0.66	4.80[d]
Liver				
A	1[b]	0.74	0.64	4.89[d]
B	1[b]	0.79	0.78	2.87
Pancreas				
A	1[b]	1.04	1.03	0.03
B	1[b]	1.05	1.01	0.04

[a] A, estimates adjusted for sex and age only; B, estimates from multiple logistic regression including terms for sex, age, social class, education, marital status, smoking, coffee, and alcohol consumption.
[b] Reference category.
[c] $P < 0.01$.
[d] $P < 0.05$.

colon and rectum was further examined in Table 4 in separate strata of age, sex, and other major covariates. No noticeable interaction emerged with reference to colon cancer, the difference between various point estimates being compatible with random variation and an overall pattern of protection by greater coffee drinking.

The picture was less consistent in relation to rectal cancer. The protection was apparently restricted to males, the younger age groups, or the heavy alcohol drinking categories, although the interactions were not formally significant (except for sex). These subgroup analyses, moreover, are rather insidious and

Table 4 *Relative risks[a] of colon and rectal cancer according to coffee consumption in separate stratax, of age, sex, and other covariates: Milan, Italy, 1983–1988*

Covariate	Colon cancer			Rectal cancer		
	Coffee consumption (cups/day)		χ_1^2 (trend)	Coffee consumption (cups/day)		χ_1^2 (trend)
	2	≥3		2	≥3	
Sex						
Males	0.81	0.61	5.61[b]	0.82	0.50	8.04[c]
Females	0.88	0.63	5.37[b]	1.23	0.92	0.06
Age (yr)						
<50	0.13	0.75	5.78[b]	0.79	0.37	3.72
50–59	0.81	0.61	4.44[b]	1.09	0.82	0.28
60–74	0.96	0.74	2.13	0.96	0.28	1.70
Marital status						
Never married	1.13	0.61	2.22	0.90	0.50	1.69
Ever married	0.87	0.65	8.10[c]	0.99	0.69	3.31
Education (yr)						
<7	0.92	0.65	4.87[b]	0.86	0.67	3.19
≥7	0.82	0.60	6.07[b]	1.25	0.71	1.09
Social class[d]						
I–III highest	0.81	0.68	6.30[b]	0.78	0.52	3.98[b]
IV–V	1.00	0.55	2.92	1.03	0.66	2.75
Smoking						
Never smokers	0.98	0.66	3.86[b]	1.01	0.69	1.89
Ex-smokers	0.89	0.71	2.11	1.02	1.08	0.09
Current smokers	0.63	0.48	5.45[b]	0.88	0.22	8.11[c]
Alcohol consumption						
Nondrinkers	0.91	0.42	9.08[c]	0.98	0.57	2.38
<4 drinks/day	0.97	0.82	0.63	1.21	1.02	0.09
≥4 drinks/day	0.68	0.55	5.67[b]	0.81	0.37	8.50[c]

[a] Estimates from multiple logistic regression including the above variables. Reference category: 0–1 cups/day.
[b] $P < 0.05$.
[c] $P < 0.01$.
[d] Based on the head of the household's occupation.

the overall picture may well be reconciled within the general smaller inverse association of coffee with rectal than with colon cancer.

DISCUSSION

The findings of this network of case-control studies are largely reassuring in relation to the effects of coffee consumption on the risk of digestive neoplasms. There was no association with neoplasms of mouth or pharynx, esophagus, stomach, liver, and pancreas, and the risk of colorectal cancers was reduced by greater levels of coffee consumption. For the latter neoplasms, the protection was apparently stronger for colon than for rectal cancer; in consideration of the difficulties in the exact attribution of neoplasms arising at the colorectal junction at one rather than the other site, it is indeed possible that the reduced risk is largely or totally restricted to colon cancer. This protection is consistent with some (9–12) but not all (13, 14) previous epidemiological evidence of coffee and colonic cancers and finds a plausible biological interpretation in terms of the possible interference of coffee on bile secretion, reducing bile acid and neutral sterol concentration in the bowel (15).

Other possible explanations include the inhibition of chemical carcinogenesis by caffeine (16–18) or other compounds in coffee beans [*i.e.*, kahweol palmitate, or cafesol palmitate (19)] and an interaction with body weight (20). The first explanation, however, is at present difficult to evaluate, since both inhibitory and promotive (21, 22) effects of caffeine have been reported, as well as to interpret in terms of site-specific carcinogenesis.

In relation to the second explanation, in this study there was no relation between measures of body weight and colorectal cancer.

Considering the still largely unsettled epidemiological state of knowledge, however, the present findings should chiefly be viewed as offering further evidence on a debate of major relevance from the etiopathological and public health viewpoints.

With reference to another issue of substantial relevance in the recent epidemiological debate, *i.e.*, the possible positive association between coffee and pancreatic cancer (23), the present analyses [which update a previous paper dealing with the issue in detail (24)] are reassuring, since the point estimates for various levels of consumption were close to unity.

The present study is open to a series of criticisms. Although, in fact, cases and controls came from well comparable catchment areas, they were interviewed in a similar setting, and allowance was possible for major potential confounding factors (such as social class, alcohol, or smoking) in multivariate analyses, the use of hospital controls for the analysis of life-style risks, such as coffee, is still open to debate. It has been shown, for instance, that patients admitted for chronic diseases tend to report lower coffee consumption than those in hospital for acute conditions (25). We excluded, therefore, all chronic and digestive tract diseases from our comparison group and checked the consistency of coffee drinking with the four major diagnostic categories of controls (trauma, other acute orthopedics, acute surgical, and other miscellaneous).

A major strength of this study, in our opinion, lies in the fact that it provides an opportunity to obtain an overall pattern of risk for various digestive tract neoplasms. In this regard, it is reassuring that the relative risks were not elevated for any of the neoplasms considered (and, indeed, various point estimates tended to be below unity), which is clearly inconsistent with the hypothesis of a substantial reduced coffee consumption in the comparison group.

The effects of coffee in relation to various neoplastic diseases were previously considered within the framework of three prospective studies, based on cohorts of Seventh-Day Adventists (13, 26), Japanese men in Hawaii (14), and Norwegian men (12). In the first study (13, 26), there was a significant positive trend for colon, while in the second (14) some moderate (and nonsignificant) protection was evident for rectal cancer. The Norwegian prospective study (12) gave some hints of a lower incidence of colon cancer with increased levels of coffee consumption, but no noticeable trend with any other digestive tract neoplasms was observed. The absolute numbers of cases for each single digestive tract neoplasm, however, were substantially lower in those cohort studies than in the present work.

In conclusion, therefore, the findings of this study, as well as the overall previous evidence, are largely reassuring in relation to the effect of coffee on digestive tract carcinogenesis. For no site was there any consistent increase in risk, and there was even a possibility of some protection by elevated coffee consumption on large intestine carcinogenesis.

ACKNOWLEDGMENTS

We wish to thank Judy Baggott, Gigliola Brambilla Pisoni, and the G. A. Pfeiffer Memorial Library Staff for editorial assistance.

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