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A Comparative Case-Control Study of Colorectal Cancer and Adenoma

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We conducted a comparative case-control study of colorectal cancer and adenoma involving 221 cases with colorectal cancer, 525 cases with colorectal adenoma and 578 neighborhood controls. Daily vegetables intake was associated with lower risks of distal colon adenoma (relative risk (RR)=0.59, 95% confidence interval (CI): 0.39–0.89) and rectal cancer (RR=0.46, 95% CI: 0.25–0.84). Daily beans intake was associated with lower risk of colon adenoma (RR=0.58, 95% CI: 0.37–0.91 for the proximal colon and RR=0.63, 95% CI: 0.45–0.88 for the distal colon) and daily intake of seaweeds was associated with lower risk of rectal cancer (RR=0.42, 95% CI: 0.22–0.82). Daily intake of fish and shellfish also showed an inverse association with the risk of colon adenoma (RR=0.67, 95% CI: 0.45–0.99 for the proximal colon and RR=0.70, 95% CI: 0.52–0.94 for the distal colon). Generally, intakes of animal or vegetable fat-rich foods, especially meats, were associated with decreases in risks of both adenoma and cancer, though the association of cancer was not statistically significant. Other than dietary factors, daily alcohol drinking was associated with an increased risk of adenoma in the proximal colon (RR=1.95, 95% CI: 1.15–3.29) and ex-drinkers showed higher risks for colon adenoma and colorectal cancer. Sports or occupational activities and coffee drinking were inversely associated and family history of colorectal cancer was positively associated with the risks of both colorectal adenoma and cancer.

Key words: Colorectal cancer — Adenoma — Dietary habits

It has been generally accepted that adenomas in the large intestine are precancerous lesions for colorectal cancer,[1–5] though some evidence against the adenoma-carcinoma sequence has been reported recently.[6–9] The concept of the adenoma-carcinoma sequence is indirectly supported by similarities in the epidemiological features of the two diseases. There are striking correlations in geographical distribution[10–14] and site distribution[1, 12, 13] between the prevalence of adenomas and the incidence of colorectal cancer and the increase of the prevalence of adenoma in migrants from low-to-high incidence areas of colorectal cancer.[12, 15] The size, multiplicity and degree of atypia of adenomas have also been geographically paralleled with the incidence of colorectal cancer.[10–12] Although the previous studies have suggested that dietary habits, especially a high fat[16, 17] and/or a low fiber diet,[18, 19] and some other factors such as drinking[20, 21] habits and physical activity[20, 21] may play an important etiological role in colorectal cancer, little work has been done on the etiology of colorectal adenoma. If risk factors are generally common in the two diseases, this will further support the adenoma-carcinoma sequence. Identification of specific risk factors for each disease may also provide useful information on possible means to interrupt each step of the sequence to colorectal cancer. Therefore, we conducted a comparative case-control study on colorectal cancer and adenoma taking subsites into consideration, as it has been hypothesized that the influences of environmental and endogenous factors may be different between the proximal and distal colon.[22]

MATERIALS AND METHODS

We conducted a questionnaire survey of patients who had received a colonoscopic examination at Aichi Cancer Center Hospital from June 1986 to March, 1990. A total of 2,052 questionnaires were distributed and 1,776 were collected (86.5%). Of the respondents, 525 cases with colorectal adenoma and 221 cases with colorectal cancer were histologically diagnosed. Population controls were randomly selected through the telephone directories and were categorically matched to cases by sex, five-year age group and municipality. Questionnaires were distributed and collected by mail. A total of 586 controls responded (91.3%) to the mail survey and after excluding 8 subjects with a history of colorectal polyp, 578 subjects were used as a control group. The same questionnaire was applied to both cases and controls. It was self-recorded and included items on frequency of intakes of 25 foods, preference of several tastes, smoking habits, alcohol and beverage drinking habits, medical and family histories, sport and occupational activities, occupation, reproductive factors (only for females) and changes in dietary habits.

Table I. Age Distributions of Cases and Controls

Age	Control	Adenoma				Cancer		
		Total	Proximal[a]	Distal[b]	Rectum	Total	Colon	Rectum
–39	3.8%	2.9%	2.5%	2.0%	3.4%	5.4%	4.5%	6.6%
40–44	6.4	5.7	4.3	6.6	3.4	5.0	4.5	5.5
45–49	11.9	12.0	14.1	10.5	10.2	6.8	5.3	8.8
50–54	15.2	15.8	14.7	16.8	17.8	13.1	14.4	11.0
55–59	16.1	21.3	15.3	23.1	19.5	14.9	15.9	13.2
60–64	19.2	20.6	23.3	21.4	16.1	18.6	18.9	17.6
65–69	13.3	13.0	14.7	12.3	17.8	17.6	15.9	22.0
70–74	7.4	5.9	8.6	4.8	8.5	9.5	9.8	8.8
75–	6.6	2.9	2.5	2.6	3.4	9.0	10.6	6.6
Total	578	525	163	351	118	221	132	91
M	377	339	124	219	80	138	79	60
F	201	186	39	132	38	83	53	31
M/F	1.88	1.82	3.18	1.66	2.11	1.66	1.49	1.94

a) From the cecum to the transverse colon.
b) Descending and sigmoid colon. M, males; F, females.

The cases with colorectal cancer comprised 132 cases with colon cancer and 91 cases with rectal cancer (2 cases had both cancers). The cases with colorectal adenoma comprised 163 cases with adenoma in the proximal colon (from the cecum to the transverse colon), 351 cases with adenoma in the distal colon (descending and sigmoid colon) and 118 cases with rectal adenoma and included 181 cases with multiple adenomas. Since the extent of endoscopic examination was determined based on the findings from barium enema, it is less likely that those who had an examination up to the proximal colon were much biased against those who did not. The age distributions, the numbers of the cases and controls by sex and sex ratios are shown in Table I. The proportion of middle age groups (50–64) was higher in the cases with adenoma and that of older age groups (over 64) was higher in the cases with cancer compared with the controls.

Relative risks (RRs) and their confidence intervals (CIs) were calculated by using the unconditional logistic regression model[23] adjusted for sex, age and residence (metropolis, other cities and counties within Aichi Prefecture and outside of Aichi Prefecture). The RRs were first calculated for dichotomized exposure categories except smoking and drinking habits and then calculated for each exposure level of some of the selected variables to look for a dose-response relationship.

RESULTS

Sex-age-residence-adjusted RRs are presented in Tables II and III.

Daily intake of total vegetables was inversely associated with adenoma, especially adenoma in the distal colon (RR=0.59, 95% CI: 0.39–0.89), and rectal cancer (RR=0.46, 95% CI: 0.25–0.84). When types of vegetables were considered, an intake of green-yellow vegetables was inversely associated with the risk of adenoma in the distal colon (RR=0.69, 95% CI: 0.52–0.91) and that of raw vegetables was inversely associated with the risk of rectal cancer (RR=0.51, 95% CI: 0.29–0.90). Daily intake of pickled vegetables was also statistically significantly inversely associated with the risk of adenoma in every site of the colorectum, but not with the risk of colorectal cancer. Daily intake of seaweeds was inversely associated with the risk of rectal cancer (RR=0.42, 95% CI: 0.22–0.82) and that of beans was inversely associated with the risks of adenomas in both the proximal (RR=0.58, 95% CI: 0.37–0.91) and distal colon (RR=0.63, 95% CI: 0.45–0.88). Daily intake of fruits showed rather increased RRs for colon cancer (1.51, 95% CI; 1.00–2.28) and adenoma in the proximal colon (1.42, 95% CI: 0.98–2.07). Daily intake of fish & shellfish was associated with decreases in risks of adenomas in both the proximal (RR=0.67, 95% CI: 0.45–0.99) and distal colon (RR=0.70, 95% CI: 0.52–0.94). Inverse associations with daily intake of meats was significant for adenomas in both the proximal (RR=0.51, 95% CI: 0.31–0.85) and distal colon (RR=0.52, 95% CI: 0.36–0.76) and nearly significant for colon cancer. Daily intake of egg was associated with a decreased risk of rectal adenoma (RR=0.63, 95% CI: 0.41–0.95) and daily use of dressing was associated with a decreased risk of adenoma in the proximal colon (RR=0.48, 95% CI: 0.27–0.88). Rice and

Table II. Relative Risk Estimates of Daily Intakes[a] of Selected Food Items

Factors	Adenoma			Cancer	
	Proximal[b]	Distal[c]	Rectum	Colon	Rectum
All vegetables	0.74 (0.43–1.26)[d]	0.59 (0.39–0.89)	0.67 (0.37–1.21)	1.15 (0.56–2.34)	0.46 (0.25–0.84)
Green-yellow vegetables	0.74 (0.52–1.06)	0.69 (0.52–0.91)	0.93 (0.62–1.40)	1.03 (0.69–1.53)	0.74 (0.46–1.18)
Raw vegetables	0.70 (0.47–1.05)	0.84 (0.62–1.13)	0.82 (0.52–1.28)	0.89 (0.58–1.37)	0.51 (0.29–0.90)
Pickled vegetables	0.65 (0.45–0.93)	0.59 (0.44–0.78)	0.56 (0.37–0.85)	1.01 (0.68–1.50)	0.80 (0.50–1.29)
Seaweeds	0.80 (0.52–1.22)	0.82 (0.59–1.13)	0.95 (0.59–1.52)	1.02 (0.65–1.59)	0.42 (0.22–0.82)
Beans	0.58 (0.37–0.91)	0.63 (0.45–0.88)	0.78 (0.48–1.26)	0.99 (0.64–1.54)	0.74 (0.43–1.29)
Fruits	1.42 (0.98–2.07)	1.01 (0.76–1.35)	1.11 (0.72–1.71)	1.51 (1.00–2.28)	0.98 (0.60–1.60)
Fish & shellfish	0.67 (0.45–0.99)	0.70 (0.52–0.94)	0.94 (0.62–1.44)	0.95 (0.63–1.43)	0.88 (0.55–1.43)
Meats	0.51 (0.31–0.85)	0.52 (0.36–0.76)	0.86 (0.52–1.42)	0.59 (0.34–1.02)	0.58 (0.30–1.13)
Egg	1.07 (0.75–1.52)	0.90 (0.68–1.18)	0.63 (0.41–0.95)	1.38 (0.92–2.06)	0.85 (0.54–1.35)
Dressing	0.48 (0.27–0.88)	0.80 (0.54–1.16)	0.65 (0.35–1.21)	0.72 (0.41–1.29)	0.75 (0.39–1.45)
Oil-frizzled foods	0.78 (0.42–1.44)	0.60 (0.36–1.00)	1.29 (0.70–2.39)	0.77 (0.38–1.56)	0.41 (0.15–1.17)

a) Relative risks of daily intake compared with less than daily intake.
b) From the cecum to the transverse colon. *c*) Descending and sigmoid colon.
d) Figures in the parentheses indicate 95% confidence intervals.

bread intakes did not show any associations with adenoma and cancer.

As to drinking habits, ex-drinkers showed statistically significantly increased RRs for both adenoma and cancer except rectal adenoma. The RR of daily drinkers was statistically significantly increased for adenoma in the proximal colon (1.95, 95% CI: 1.15–3.29) and whiskey showed the strongest association (RR=1.77, 95% CI: 1.12–2.82). Beer drinking was not associated with risks of adenoma and cancer in any site of the colorectum. Daily coffee drinking was inversely associated with the risks of both adenoma and cancer except rectal adenoma, while daily black tea drinking was associated with an increased risk of colon cancer (RR=2.50, 95% CI: 1.19–5.26). Daily intake of hot green tea was inversely associated with the risks of distal colon and rectal adenomas and colon cancer. Participating in sports activities once or more a week showed decreased risks of both cancers and adenomas except adenoma in the proximal colon and a high occupational activity level judged by respondents themselves was inversely associated with the risks of adenomas in the proximal (RR=0.32, 95% CI: 0.19–0.53) and distal colon (RR=0.59, 95% CI: 0.43–0.82). Professional or administrative workers showed statistically significantly increased RRs for colon adenoma and cancer. Family history of colorectal cancer was significantly positively associated with adenoma and cancer in any site of the colorectum (RR=2.31–3.69). Ages at menarche and first birth and number of births were not associated with female adenoma and cancer.

The RRs were further calculated by exposure level of the selected factors (Table IV), unless the percentage of the lowest exposure level was less than 5% (all vegetables, green-yellow vegetables and fish and shellfish). Dose-

Table III. Relative Risk Estimates for Drinking and Smoking Habits and Others

Factors	Adenoma			Cancer	
	Proximal[a]	Distal[b]	Rectum	Colon	Rectum
Ex-drinkers[d]	3.35 (1.51–7.43)[c]	2.41 (1.24–4.68)	1.62 (0.68–3.87)	2.81 (1.33–5.97)	4.30 (1.76–10.52)
Daily drinkers[d]	1.95 (1.15–3.29)	1.43 (0.96–2.13)	0.80 (0.46–1.41)	0.77 (0.44–1.33)	1.64 (0.84–3.18)
Whiskey drinkers[e]	1.77 (1.12–2.82)	1.36 (0.92–2.01)	1.21 (0.67–2.20)	0.93 (0.50–1.75)	1.16 (0.59–2.31)
Ex-smokers[f]	1.03 (0.57–1.85)	0.93 (0.59–1.49)	0.95 (0.46–1.94)	1.12 (0.60–2.10)	1.54 (0.70–3.42)
Current smokers[f]	0.75 (0.43–1.29)	0.83 (0.55–1.27)	1.06 (0.56–2.02)	0.59 (0.32–1.11)	1.44 (0.69–2.99)
Coffee (daily)[g]	0.53 (0.36–0.77)	0.63 (0.47–0.83)	0.74 (0.49–1.14)	0.47 (0.31–0.72)	0.57 (0.35–0.93)
Black tea (daily)[g]	1.20 (0.52–2.74)	1.03 (0.53–2.01)	0.69 (0.20–2.37)	2.50 (1.19–5.26)	0.27 (0.04–2.03)
Hot green tea (daily)[g]	0.82 (0.56–1.19)	0.62 (0.46–0.82)	0.61 (0.40–0.92)	0.61 (0.41–0.91)	1.32 (0.78–2.23)
Sports activity $\geq$1–2/week[h]	0.67 (0.44–1.03)	0.57 (0.41–0.79)	0.48 (0.28–0.82)	0.60 (0.37–0.96)	0.57 (0.32–1.00)
High occupational activity[i]	0.32 (0.19–0.53)	0.59 (0.43–0.82)	0.79 (0.50–1.26)	0.69 (0.43–1.12)	0.61 (0.35–1.07)
Professional or administrative occupations	2.44 (1.52–3.92)	2.04 (1.36–3.07)	1.60 (0.88–2.92)	2.09 (1.19–3.65)	1.47 (0.75–2.87)
Family history of colorectal cancer	3.18 (1.66–6.11)	3.42 (2.00–5.86)	3.27 (1.56–6.90)	2.31 (1.07–5.01)	3.69 (1.69–8.07)

a) From the cecum to the transverse colon. *b*) Descending and sigmoid colon.
c) Figures in the parentheses indicate 95% confidence intervals.
d) Compared with non-drinkers. *e*) Compared with non-whiskey-drinkers.
f) Compared with non-smokers (never smoked). *g*) Compared with less than daily drinkers.
h) Compared with less than once a week. *i*) Compared with moderate or low activity.

response relationships were observed between colon adenoma and intakes of pickled vegetables, beans, meat, coffee and occupational activity and between colorectal cancer and coffee drinking and sport activity. Other factors which showed significant associations in Tables II and III also showed similar trends, but the associations between proximal colon and dressing intake and between rectal cancer and raw vegetables intake were only observed at the highest exposure level.

When the RRs for multiple adenomas were compared to those for single adenomas (Table V), the decreased risks of daily intake of total vegetables, beans, meats and dressing were more clearly observed for multiple adenomas. Drinking habits were only associated with the risk of multiple adenomas and the increased RR of family history of colorectal cancer was much larger in multiple adenomas (RR=4.63, 95% CI: 2.56–8.39) than in single adenomas (RR=2.52, 95% CI: 1.43–4.43).

We further calculated the RRs of dietary factors adjusting for non-dietary factors, i.e., alcohol and beverage drinking, sports and occupational activities, occupation and family history of colorectal cancer, but the adjusted RRs for adenomas and rectal cancer did not materially change. The increased RRs of ex-drinkers, daily drinkers, professional or administrative workers and family history of colorectal cancer, the decreased RRs of sports activity except that for rectal cancer, the decreased RRs of a high occupational activity level and the decreased RRs of coffee drinking except that for multiple adenomas observed in the univariate analyses also virtually did not change by adjusting for other dietary and non-dietary factors.

Table IV. Relative Risk Estimates of the Selected Items by Exposure Category

Factors		Adenoma			Cancer	
		Proximal[a]	Distal[b]	Rectum	Colon	Rectum
Pickled vegetables[d]	2–3 times/w	0.86 (0.52–1.44)[c]	0.73 (0.50–1.09)	1.10 (0.61–1.99)	0.37 (0.20–0.66)	0.70 (0.36–1.39)
	Daily	0.58 (0.35–0.97)	0.47 (0.32–0.70)	0.60 (0.33–1.10)	0.55 (0.33–0.91)	0.63 (0.33–1.21)
Beans[d]	2–3 times/w	0.93 (0.53–1.62)	0.71 (0.46–1.07)	1.17 (0.58–2.36)	0.71 (0.38–1.31)	0.65 (0.33–1.27)
	Daily	0.54 (0.28–1.05)	0.47 (0.29–0.77)	0.89 (0.41–1.94)	0.74 (0.38–1.46)	0.51 (0.23–1.13)
Meats[d]	2–3 times/w	1.00 (0.53–1.88)	0.80 (0.51–1.27)	0.89 (0.45–1.78)	1.96 (0.85–4.52)	0.91 (0.42–2.00)
	Daily	0.51 (0.24–1.09)	0.43 (0.25–0.74)	0.78 (0.36–1.70)	1.08 (0.42–2.79)	0.54 (0.21–1.39)
Coffee[e]	Occasional	0.92 (0.55–1.53)	0.94 (0.63–1.40)	0.91 (0.50–1.66)	0.86 (0.52–1.44)	0.90 (0.48–1.69)
	Daily	0.50 (0.30–0.84)	0.60 (0.40–0.89)	0.72 (0.40–1.30)	0.43 (0.25–0.73)	0.53 (0.27–1.03)
Sport activity[f]	$<$Once/w	1.15 (0.75–1.76)	1.39 (1.00–1.92)	1.22 (0.76–1.95)	0.72 (0.44–1.19)	0.86 (0.50–1.50)
	$\geq$1–2 times/w	0.71 (0.45–1.11)	0.64 (0.45–0.91)	0.51 (0.29–0.90)	0.55 (0.33–0.89)	0.54 (0.30–0.97)
Occupational activity[g]	Moderate	0.91 (0.61–1.35)	0.91 (0.66–1.24)	0.54 (0.36–0.87)	0.58 (0.37–0.90)	1.24 (0.72–2.15)
	High	0.30 (0.17–0.53)	0.56 (0.38–0.81)	0.56 (0.33–0.95)	0.51 (0.30–0.87)	0.70 (0.36–1.38)

a) From the cecum to the transverse colon. *b*) Descending and sigmoid colon.
c) Figures in the parentheses indicate 95% confidence intervals.
d) Compared with once or twice a month or less. *e*) Compared with non-drinkers.
f) Compared with almost no activity. *g*) Compared with sedentary job.

DISCUSSION

In spite of the importance of adenomas as putative precancerous lesions for colorectal cancer, little has been clarified about the etiology of this disease. The numerous previous epidemiological and experimental studies on colorectal cancer have suggested several possible etiological factors such as diets with high fat,[16, 17] especially animal fat or animal fat-rich foods, and high calories,[17] diets with low fiber or vegetables[18, 19] and low calcium,[17] drinking,[20, 21] especially beer, low physical activity[20, 21] and a family history of colorectal cancer.[21] Some of these factors may also contribute to the development of adenoma and the others may only be associated with the development of colorectal cancer. The limited number of previous studies on colorectal adenoma have not shown consistent results. Lower intakes of oil,[24] potatoes,[24] carbohydrate,[24] cruciferous vegetables,[25] higher intakes of sugar,[24] alcohol[26] and beer[27] and cigarette smoking[27] were associated with a higher risk of adenoma in those studies. Compared with the previous studies, the number of cases with adenoma in the present study was much larger so that analyses were made by subsite of the large intestine. In the present study, inverse associations of adenoma with intakes of vegetables and other fiber-rich foods, fish & shellfish, meats and other animal fat- or vegetable fat-rich foods were generally more clearly observed for colon adenoma, while the inverse associations with vegetables and seaweeds were observed only for rectal cancer. Almost no dietary factors were associated with the risk of colon cancer. Because of the absence of an inverse association with rice intake, which is responsible for a large part of fiber intake in Japanese, the observed inverse associations with intakes of vegetables, seaweeds, and beans may not necessarily indicate

Table V. Relative Risk Estimates[a] for Single and Multiple Adenomas

Factor	Single		Multiple	
	RR	(95% CI)	RR	(95% CI)
Daily intakes of				
All vegetables	0.80	(0.52–1.24)	0.60	(0.37–0.98)
Green-yellow vegetables	0.72	(0.54–0.95)	0.80	(0.57–1.13)
Pickled vegetables	0.57	(0.43–0.75)	0.66	(0.47–0.94)
Beans	0.79	(0.57–1.08)	0.56	(0.36–0.87)
Fish & shellfish	0.71	(0.53–0.95)	0.83	(0.57–1.19)
Meats	0.59	(0.41–0.85)	0.49	(0.29–0.80)
Dressing	0.87	(0.60–1.27)	0.55	(0.31–0.95)
Coffee	0.61	(0.46–0.81)	0.68	(0.47–0.96)
Black tea	0.64	(0.30–1.37)	1.42	(0.66–3.07)
Hot green tea	0.59	(0.44–0.79)	0.70	(0.49–1.01)
Ex-drinkers	1.91	(1.00–3.65)	2.96	(1.34–6.56)
Daily drinkers	0.90	(0.61–1.34)	2.17	(1.31–3.62)
Whiskey drinkers	1.14	(0.76–1.71)	1.68	(1.07–2.65)
Ex-smokers	0.89	(0.56–1.40)	1.14	(0.63–2.08)
Current smokers	0.67	(0.44–1.01)	1.13	(0.65–1.95)
Sports activity ≧1–2/week	0.56	(0.40–0.78)	0.61	(0.40–0.92)
High occupational activity	0.58	(0.41–0.80)	0.49	(0.32–0.76)
Professional or administrative occupations	1.92	(1.27–2.90)	2.19	(1.36–3.50)
Family history of colorectal cancer	2.52	(1.43–4.43)	4.63	(2.56–8.39)

a) Reference categories in calculating relative risks are the same as those in Tables II and III (see the footnotes).

the effect of fiber intake. Some kinds of vitamins,[28] indoles,[29] and vegetable sterols[30] in vegetables and others which have been demonstrated to have inhibitory effects on carcinogenesis could be protective for adenoma in the large intestine. Fish oils also have been reported to have inhibitory effects on mammary carcinogenesis[31] and development of preneoplastic lesions in the pancreas[32] in animal experiments. Inverse associations between daily intakes of meats and other fat-rich foods and risks of adenoma and cancer were the unexpected results in the present study, though the results from the previous analytical epidemiological studies have not consistently shown a positive association. In a cohort study for Hawaiian Japanese, fat, especially saturated fat, intake was inversely associated with not only the risk of colorectal cancer[33] but also the number of adenomas in the autopsied cases,[26] though the latter association was not statistically significant. Moreover, a large-scale cohort study conducted in Japan showed a decreased risk of colon cancer in the subjects who had eaten meats daily.[34] Since the average amounts of intakes of animal fat and protein of Japanese are still much lower than those in western countries,[35] daily intake of meats may not necessarily mean an overintake of animal fat/protein and may possibly indicate well-balanced dietary habits.

We suspected that the increased risks of adenoma and cancer in ex-drinkers and the decreased risks in daily coffee drinkers may be attributable to the presence of gastrointestinal symptoms in the cases. Although the results did not materially change after adjustment for the presence of gastrointestinal symptoms, we could not rule out the possibility that the course of the disease may have influenced drinking habits because no information was available on the time of quitting. The increased risk of multiple adenomas in daily drinkers is compatible with the positive correlation between alcohol consumption and the number of adenomas observed in Hawaiian Japanese.[26] The decreased risk of colon cancer in coffee drinkers was also reported in some of the case-control studies[16, 18, 36, 37] and this association was supported by a pharmacological effect of caffeine, which reduces the excretion of bile acids.[38]

The present study also confirmed that a low physical activity level and family history of colorectal cancer were

associated with the risk of adenoma in the large intestine. The associations with family history of colorectal cancer and some other environmental factors were stronger in multiple adenomas than in single adenomas, which may enhance the coherence of the associations.

Because the present study was based on the data from self-administered questionnaires, we checked the reproducibility of the answers of the 132 study subjects in the course of the study by calculating kappa statistics.[39] The kappa statistics, which ranged from 0.973 ($z=15.43$) for smoking to 0.423 ($z=6.40$) for a meat intake, were highly statistically significant, so that the data were considered sufficiently reliable to analyze. One of the greatest disadvantages in using the self-administered questionnaire is the difficulty in obtaining quantitative information. We could not obtain any quantitative estimates for intakes of nutrients, such as fat, fiber, vitamins and calories. This made interpretation of the results difficult and their biological implications ambiguous.

In the preliminary analyses, the subjects who were diagnosed colonoscopically as having no colorectal lesions, i.e., potential controls, were clarified to have biased life style characteristics, especially a much lower percentage of smokers compared to the general population. Therefore, we used neighborhood controls. Since neighborhood controls did not receive a colonoscopic examination, some of the controls may have had asymptomatic colorectal adenoma. The prevalence of colorectal adenoma, which depends on age,[10, 11, 15] was around 30% in an autopsy study conducted in Japan.[11] Therefore, the results for adenoma in the present study are likely to be underestimated. Meanwhile, the neighborhood controls responding to a questionnaire survey may have some self-selection biases,[40, 41] i.e., healthier life style, such as a higher intake of vegetables and frequent participation in sports activities. This may have exaggerated some of the associations observed in the present study.

Despite the above-mentioned study limitations, the present study showed that several dietary and non-dietary factors were associated with the risks of adenoma and/or cancer in the large intestine and that some of the associations were similar between adenoma and cancer. However, the associations with dietary habits were in part inconsistent between adenoma and cancer, especially when we considered subsites of the large intestine. Therefore we could not definitely conclude that colorectal adenoma and cancer have common etiological factors and that specific factors were involved in the development from adenoma to cancer. Further studies are required to obtain consistency of observations and to investigate possible biological relations.

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