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A Case-Control Study of Male Colorectal Cancer in Aichi Prefecture, Japan: with Special Reference to Occupational Activity Level, Drinking Habits and Family History

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The relationships of occupational activity level, drinking habits and family history of cancer to the risk of male colorectal cancer by subsites were investigated in a case-control study involving 1,716 cases with colon cancer, 1,611 cases with rectal cancer and 16,600 controls with other sites of cancer identified from the Aichi Cancer Registry, Japan 1979–1987. An occupation with a low activity level was associated with an increased risk of colorectal cancer; the age-adjusted relative risk (RR) compared to the high activity level group was 1.92 (95% confidence interval (CI): 1.38–2.67) for proximal colon cancer, 1.52 (95% CI: 1.19–1.94) for distal colon cancer and 1.38 (95% CI: 1.17–1.62) for rectal cancer. Beer drinkers showed an increased risk of colorectal cancer; the age-adjusted RR was 1.49 (95% CI: 1.13–1.95) for proximal colon cancer, 1.65 (95% CI: 1.34–2.04) for distal colon cancer and 1.88 (95% CI: 1.62–2.18) for rectal cancer. The RR for family history of colorectal cancer was 3.40 (95% CI: 2.19–5.29) for proximal colon cancer, 2.54 (95% CI: 1.73–3.75) for distal colon cancer and 1.78 (95% CI: 1.28–2.49) for rectal cancer. Multivariate analysis controlled for age, residence, marital status and smoking in addition to occupational activity level, beer drinking and family history of colorectal cancer did not materially change the RRs. When these three variables were combined, the RR was 15.72 (95% CI: 5.40–45.78) for proximal colon cancer, 10.55 (95% CI: 4.24–26.27) for distal colon cancer and 6.69 (95% CI: 3.12–14.36) for rectal cancer.

Key words: Occupational activity level — Beer — Family history — Colorectal cancer

Colorectal cancer is generally prevalent in developed countries. The incidence and mortality of this cancer are highest in the US and Canada and lowest in Asian and South American countries.[1,2] In Japan, the mortality from colorectal cancer, especially colon cancer, has been increasing during the past few decades with the progression of industrialization and is higher in metropolitan areas compared to rural areas.[3] These marked geographical variations in the incidence and mortality have been suspected to be largely attributable to dietary habits, especially a high fat and/or low fiber diet.[3–9] The results of analytical epidemiological studies, however, have been inconsistent.[10] This has been considered to be due to homogeneity of dietary habits within populations.

Recently a non-dietary etiological hypothesis that low physical activity including both occupational and leisure time activities may increase the risk of colorectal cancer has been discussed.[11–16] This hypothesis could explain a part of the geographical variations of this cancer and needs further confirmation in various populations. Furthermore, evidence is accumulating that alcohol consumption, especially beer drinking, may increase the risk of colorectal cancer,[7,16–28] although the findings have been controversial. Therefore, we evaluated the relationships of occupational activity level and drinking habits to the risk of colorectal cancer in a Japanese local population based on data from a population-based cancer registry taking into consideration subsites of the colorectum and family history of cancer.

MATERIALS AND METHODS

Cases and controls were selected from male cancer cases aged 20 and over of the Aichi Cancer Registry who were diagnosed in 1979–87 and for whom data on occupation, drinking habits or family history of cancer were available. The cases consisted of 1,716 cases with colon cancer (445 cases with proximal colon cancer, 765 cases with distal colon cancer and 506 cases with colon cancer not otherwise specified) and 1,611 cases with rectal cancer. These corresponded to 89% of the total male reported cases with colorectal cancer aged 20 and over during the same period (3,721 cases). The proximal colon included cecum, ascending colon, transverse colon and the distal colon included descending colon, sigmoid colon and rectosigmoid junction. The diagnosis had been confirmed by biopsy for 89.6% of the cases studied and that for an additional 0.5% had been confirmed by autopsy. The controls consisted of 16,600 cases with other sites of cancer excluding known alcohol-related

Table I. Age Distribution of Cases and Controls

Age	Controls		Proximal colon[a]		Distal colon[b]		Total colon[c]		Rectum	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
–29	254	(1.5)	10	(2.3)	6	(0.8)	18	(0.7)	10	(0.6)
30–34	307	(1.8)	5	(1.1)	12	(1.6)	25	(1.5)	24	(1.5)
35–39	538	(3.2)	8	(1.8)	10	(1.3)	30	(1.7)	44	(2.7)
40–44	695	(4.2)	29	(6.5)	25	(3.3)	85	(5.0)	78	(4.8)
45–49	1,178	(7.1)	38	(8.5)	57	(7.5)	134	(7.8)	142	(8.8)
50–54	1,746	(10.5)	60	(13.5)	86	(11.2)	215	(12.5)	235	(14.6)
55–59	2,006	(12.1)	58	(13.0)	117	(15.3)	258	(15.0)	265	(16.4)
60–64	2,094	(12.6)	46	(10.3)	92	(12.0)	204	(11.9)	213	(13.2)
65–69	2,451	(14.8)	60	(13.5)	107	(14.0)	229	(13.3)	194	(12.0)
70–74	2,499	(15.1)	59	(13.3)	121	(15.8)	249	(14.5)	198	(12.3)
75–79	1,749	(10.5)	37	(8.3)	85	(11.1)	161	(9.4)	138	(8.6)
80–	1,083	(6.5)	35	(7.9)	47	(6.3)	108	(6.3)	70	(4.3)
Total	16,600	(100.0)	445	(100.0)	765	(100.0)	1,716	(100.0)	1,611	(100.0)

a) From the cecum to the transverse colon.
b) From the splenic flexure to the rectosigmoid junction.
c) Including 506 cases with colon cancer not otherwise specified.

Table II. Distribution of Cancer Site in Controls

Site of cancer	No.	%
Stomach	7,633	46.0
Biliary tract	525	3.2
Pancreas	682	4.1
Nose, sinus	114	0.7
Larynx	392	2.4
Lung	3,212	19.3
Bone, soft tissue	141	0.8
Skin	163	1.0
Prostate	605	3.6
Testis	140	0.8
Urinary bladder	917	5.5
Kidney, urinary organs	400	2.4
Brain, nervous system	154	0.9
Thyroid gland	106	0.6
Malignant lymphoma	657	4.0
Leukemia	386	2.3
Others	373	2.2

cancers[29]; cancers of mouth, pharynx, esophagus and liver and cancers of unknown primary sites. The age distribution was not much different between cases and controls (Table I). In the controls, stomach cancer was most common (46.0%), followed by cancers of the lung (19.3%) and urinary bladder (5.5%), as shown in Table II. In addition to clinical data, the registry has routinely collected data on occupation, marital status, family history of cancer (parents, siblings and grandparents) and the questions about smoking and drinking have been included in the report format since 1980. The cases diagnosed in 1979 were included in the analysis because more than a half of them were reported in 1980 and after.

Occupation has been coded according to the modified census index. Retired cases were included in the analysis of occupation, when information on the main job in life was available. Each occupation coded was divided into one of three groups according to the classification of Garabrant *et al.* (1984), which was based on the proportion of physically active time on the job.[11] The present analysis was limited to male cases because we felt that nonoccupational activity constitutes a proportionally greater part in women's physical activity and because the proportion of drinkers was much smaller in females than in males in Japan. The age-adjusted relative risk (RR) for each single variable and RRs adjusted for other variables in addition to age were calculated by using the unconditional logistic regression analysis.[30]

RESULTS

Occupations of 72.2% of the total subjects (14,388 cases and controls) were classified into three levels of occupational activity; 42.0% was low activity, 31.3% was moderate activity and the rest of 26.7% was high activity. The occupations which account for a large number of cases and controls in each activity level are presented in Table III.

Table IV shows the age-adjusted RR for each single variable. The risk for proximal colon cancer increased

Table III. Classification of Occupation in the Study Subjects by Activity Level

Activity level	Occupation	No.	(%)
Low	Clerks	4,786	(73.9)
	Administrative workers	931	(14.4)
	Professional workers		
	Priests	84	(1.3)
	Accountants	55	(0.8)
	Technologists	62	(1.0)
	Artists	29	(0.4)
	Others	98	(1.5)
	Transportation & communication		
	Bus and car drivers	283	(4.4)
	Communications	13	(1.7)
	Production process		
	Cutting & sewing	108	(1.7)
	Others	27	(0.4)
Total		6,476	
Moderate	Teachers	377	(8.4)
	Physicians & dentists	127	(2.8)
	Other medical & health workers	102	(2.3)
	Shopkeepers, retailers	1,671	(37.1)
	Other sales workers	324	(7.2)
	Service workers	352	(7.8)
	Production process		
	Filature & spinning	220	(4.9)
	Ceramics	106	(2.4)
	Food & drink	129	(2.9)
	Wooden products	147	(3.3)
	Others	634	(14.1)
	Others	319	(7.1)
Total		4,508	
High	Farmers	1,360	(40.0)
	Fishermen	79	(2.3)
	Production process		
	Ironworks	254	(7.5)
	Metal processors	209	(6.1)
	Vehicle mechanics	126	(3.7)
	Carpenters	214	(6.3)
	Construction contractors	199	(5.8)
	Plasterers	66	(1.9)
	Other constructors	294	(8.6)
	Others	197	(5.8)
	Laborers	97	(2.8)
	Policemen, firemen	63	(1.9)
	Others	246	(7.2)
Total		3,404	

statistically significantly in subjects with moderate and low occupational activity levels compared to high occupational activity level. The risk of proximal colon cancer decreased in sake drinkers and increased in beer drinkers. The risk also decreased in smokers and increased in singles and residents in the metropolis. Family history of colorectal cancer was positively associated.

The risk of distal colon cancer increased in subjects with both moderate and low occupational activity levels compared to high occupational activity level. The RRs for drinking habits increased for both occasional drinkers and daily drinkers and beer drinkers. The risk of distal colon cancer decreased in smokers and increased in residents in the metropolis. A positive association with family history of colorectal cancer was also observed.

When all colon cancers were combined, the RR was 1.79 for moderate occupational activity level, 1.87 for low occupational activity level, 1.54 for beer drinking, 0.62 for smoking, 1.27 for living in the metropolis and 2.78 for family history of colorectal cancer.

The risk for rectal cancer increased in moderate and low occupational activity levels compared to high occupational activity level. The positive association with beer drinking was strongest among subsites of the colorectum. The risk of rectal cancer was inversely associated with smoking and positively associated with living in the metropolis. As to the family history of cancer, the risk of rectal cancer was high in cases with family history of colorectal cancer, whereas the risk was low in cases with family history of stomach cancer.

The RRs for smoking was recalculated based on the controls without smoking-related cancers[31]; cancers of the larynx, lung, pancreas and urinary bladder. The age distribution of this control group was closer to that of the cases. The age-adjusted RR of smokers was still statistically significantly decreased for colon cancer, but was almost unity for rectal cancer.

The RRs were further examined based on the controls excluding cases with stomach cancer, which constituted nearly a half of the controls after including cases with smoking-related cancers. The age distribution of this control group showed a slight shift to the older age group. For all colon cancers combined, the RR was 1.82 (95% confidence interval (CI): 1.51–2.19) for moderate occupational activity level, 1.86 (95% CI: 1.56–2.22) for low occupational activity level and 1.51 (95% CI: 1.29–1.77) for beer drinkers. For rectal cancer, the corresponding RRs were 1.32 (95% CI: 1.11–1.58), 1.37 (95% CI: 1.16–1.62) and 1.85 (95% CI: 1.58–2.16), respectively. The RRs for family history of colorectal cancer and the results by subsites of the colon also did not differ materially from the results based on the total control group.

Multivariate analysis including variables of age, occupational activity level, beer drinking, smoking, residence, family history of colorectal cancer and marital status (only for proximal colon cancer) were conducted based on 9,040 cases and controls for whom data on all these

Table IV. Age-adjusted Relative Risks (RRs) for Male Colorectal Cancer by Subsite in Single Variate Analyses

Factors	% in controls	Proximal colon[a]		Distal colon[b]		All colon[c]		Rectum	
		RR[d]	95% CI[e]	RR	95% CI	RR	95% CI	RR	95% CI
Occupational activity level[f]									
Moderate	31.0	1.76**	1.24–2.48	1.70**	1.33–2.19	1.79**	1.50–2.15	1.30**	1.10–1.55
Low	44.0	1.92**	1.38–2.67	1.52**	1.19–1.94	1.87**	1.58–2.23	1.38**	1.17–1.62
Drinking[g]									
Occasional	15.3	1.09	0.83–1.45	1.40**	1.12–1.74	1.23*	1.05–1.44	1.39**	1.19–1.63
Daily	31.7	0.80	0.63–1.02	1.33**	1.11–1.58	1.10	0.97–1.25	1.06	0.93–1.22
Sake	28.3	0.75*	0.59–0.96	1.15	0.97–1.37	1.00	0.88–1.13	1.10	0.97–1.25
Beer	14.0	1.49**	1.13–1.95	1.65**	1.34–2.04	1.54**	1.32–1.79	1.88**	1.62–2.18
Whiskey	2.6	1.09	0.59–2.02	1.33	0.85–2.08	1.18	0.85–1.66	1.35	0.98–1.85
Smoking[h]	69.4	0.57**	0.46–0.69	0.66**	0.56–0.77	0.62**	0.56–0.70	0.74**	0.66–0.84
(Smoking)[i]	64.9	0.70**	0.57–0.87	0.83*	0.71–0.98	0.78**	0.70–0.88	0.93	0.82–1.05
Family history									
All sites	25.5	0.99	0.78–1.25	1.09	0.91–1.31	1.04	0.91–1.18	0.87	0.75–1.00
Stomach	12.8	0.84	0.60–1.17	0.83	0.64–1.07	0.84	0.70–1.00	0.77*	0.63–0.93
Colorectum	1.9	3.40**	2.19–5.29	2.54**	1.73–3.75	2.78**	2.12–3.65	1.78**	1.28–2.49
Marital status									
Single	2.7	1.88*	1.10–3.21	1.18	0.70–1.99	1.15	0.81–1.63	1.08	0.76–1.53
Residence									
Metropolis	40.7	1.30*	1.08–1.57	1.44**	1.25–1.67	1.27**	1.15–1.40	1.12*	1.01–1.25

a, b, c) See footnotes in Table I.
d) Age-adjusted relative risks.
e) Confidence interval.
f) Reference category is high activity group.
g) Reference category is non-drinkers.
h) Reference category is never smoked.
i) RRs were calculated based on the controls excluding patients with smoking-related cancers.
* $P<0.05$. ** $P<0.01$.

Table V. Adjusted Relative Risks (RRs) for Male Colorectal Cancer by Subsite in Multiple Logistic Regression Analyses

Factors		Proximal colon[a] (n=223)		Distal colon[b] (n=374)		All colon[c] (n=756)		Rectum (n=753)	
		RR[d]	95% CI[e]	RR	95% CI	RR	95% CI	RR	95% CI
Occupational activity level[f]	(moderate)	1.89**	1.24–2.88	1.59**	1.17–2.16	1.66**	1.32–2.09	1.36**	1.10–1.68
	(low)	1.82**	1.21–2.74	1.50**	1.12–2.03	1.75**	1.41–2.18	1.25*	1.02–1.54
Beer drinking		1.51*	1.10–2.09	1.44**	1.11–1.87	1.45**	1.20–1.75	1.72**	1.44–2.06
Family history of colorectal cancer		3.66**	2.13–6.27	2.74**	1.70–4.39	2.90**	2.05–4.10	1.69*	1.10–2.58

a) From the cecum to the transverse colon.
b) From the splenic flexure to the rectosigmoid junction.
c) Including cases with colon cancer not otherwise specified.
d) Adjusted for occupational activity level, beer drinking, family history of colorectal cancer, smoking, residence and marital status (only for proximal colon), but excluding the factor to be adjusted.
e) Confidence interval.
f) Reference category is high activity group.
* $P<0.05$. ** $P<0.01$.

variables were available. All of the RRs were statistically significant and did not change materially from the results of univariate analyses (Table V).

In Table VI, we calculated the RRs in the combination of occupational activity level, beer drinking and family history of colorectal cancer adjusting for age, residence

Table VI. Adjusted Relative Risks (RRs) for Male Colorectal Cancer by Subsite for Combinations of Risk Factors

Site of cancer	No. of cases	Occupation[f] + beer		Occupation + family history[g]		Occupation + beer + family history	
		RR[d]	95% CI[e]	RR	95% CI	RR	95% CI
Proximal colon[a]	228	2.69**	1.60–4.50	6.13**	2.84–13.20	15.72**	5.40–45.78
Distal colon[b]	373	2.14**	1.46–3.14	2.95**	1.45–6.00	10.55**	4.24–26.27
All colon[c]	755	2.44**	1.84–3.23	4.64**	2.90–7.42	10.07**	4.77–21.29
Rectum	753	2.14**	1.65–2.78	1.68	0.91–3.09	6.69**	3.12–14.36

a) From the cecum to the transverse colon.
b) From the splenic flexure to the rectosigmoid junction.
c) Including cases with colon cancer not otherwise specified.
d) RRs were calculated based on the reference group without the three risk factors and adjusted for age, residence and smoking habits.
e) Confidence interval.
f) Low or moderate occupational activity level.
g) Colorectal cancer.
** $P<0.01$.

and smoking habits. Low and moderate activity groups were combined in this analysis. The combination of beer drinking and family history of colorectal cancer was omitted because of the small numbers of cases and controls. Compared to the group without these three variables, the RR for the combination of low or moderate occupational activity, beer drinking and family history of colorectal cancer was 15.72 for proximal colon cancer, 10.55 for distal colon cancer, 10.07 for all colon cancer combined and 6.69 for rectal cancer.

DISCUSSION

Recent studies have shown that non-dietary factors may have some role in the development of colorectal cancer. Low physical activity occupationally and during leisure time has been associated with an increase in risk of colorectal cancer in both retrospective[11–14] and prospective studies.[15, 16] The odds ratio or relative risk for the low activity group was distributed from 1.2 to 3.5 in those studies, but the relation to subsites of the large intestine was inconsistent. A physiological mechanism, i.e., that physical activity stimulates peristalsis of the colon and affects the transit time, has been postulated.[11] In the present study, the RR of colorectal cancer for the low and moderate occupational activity groups increased statistically significantly compared to the high occupational activity group and the association was strongest in the proximal colon and weakest in the rectum. These results are similar to those of Gerhardsson *et al.*[15] and Vena *et al.*[12] Because of the limitations of cancer registry data, we analyzed only occupational activity at the time of diagnosis and could not assess cumulative occupational activity and leisure time activity. Therefore, the relative risks for low physical activity obtained in the present study (RR=1.3–1.9) may have been underestimated to some extent, as observed in the studies of Garabrant *et al.*[11] and Gerhardsson *et al.*,[15] where only occupational activity was analyzed. However, because Japanese men generally work longer and change jobs less frequently compared to men in western countries, the classification of physical activity used in the present study may be close to that of total physical activity. The second problem in cancer registry data is the classification of occupations. According to the coding system, employees with no specified occupation in companies were classified as clerical workers. Some of those cases would have been classified into other occupations such as sales workers, production workers and service workers if more detailed information had been obtained. Thus, the effects of misclassification may have diminished the dose-response trend between moderate and low activity levels. For 27.8% of the study subjects, occupations could not be classified into any activity group. The major reason for this was no information on the cancer reports, especially for older patients. However, it was likely that the effect of missing data was similar between cases and controls within the same age groups.

Another problem related to the classification of occupations is a close association between occupational activity level and socioeconomic status. The high occupational activity group contained a greater proportion of workers of low socioeconomic status. Since a positive association between colon cancer and high socioeconomic status has been reported,[11, 21, 32] the effects of socioeconomic status, especially dietary habits, may possibly have confounded the results.

Alcohol consumption, especially beer drinking, has been implicated in the etiology of colorectal cancer. Positive associations between beer consumption and

rectal cancer and between total alcohol consumption and rectal or colorectal cancer have been reported in case-control[21-26] and cohort studies[16, 27, 28] in addition to strong correlations between beer consumption and mortality from rectal cancer.[7, 17-20] The present study also showed a positive association with beer drinking which was strongest for rectal cancer and weakest for proximal colon cancer. Nitrosamines may be possible carcinogens present in some alcoholic beverages including beer,[33] but we can not rule out some confounding effect other life style factors.

Generally, smoking has not been related to the risk of colorectal cancer in the previous studies, but an inverse association between smoking and colon cancer has been reported in some case-control[32, 34-36] and cohort studies[37, 38] where it was hypothesized that nicotine in the cigarette smoke might stimulate colonic peristalsis.[35] The present findings on smoking supported this hypothesis and the association was strongest for proximal colon cancer, like the association with occupational activity level.

Bisides environmental factors, an involvement of genetic factors in the development of colorectal cancer has been suggested. A 2- to 5-fold greater risk of colorectal cancer has been observed for subjects with a family history of colorectal cancer[39-42] and it has been reported that familial patients manifested a clear excess of right-sided colon cancer.[43] Our findings on family history of colorectal cancer by subsites were consistent with this and the combination with environmental factors greatly increased the risk of colorectal cancer. We should consider the constitution of family members in analyzing family history. If the patients with colorectal cancer had a larger number of family members or more family members of older age, the RRs for all sites of cancer increased. Therefore, it was considered that the effect of constitution of family members was not large in this analysis.

Because the present study was based on data from a population-based cancer registry, there were several methodological limitations. First, we could not use non-cancer controls. Therefore, we should consider potential biases associated with cancer controls, in spite of there being some advantages in using cancer controls, such as little recall or interviewer bias.[44] In the present analyses, we used several sets of controls, eliminating smoking-related cancers and stomach cancer, but the results for factors other than smoking did not materially change. Thus, it is considered that the findings of the present study can not be explained only by biases of the control group. Second, we could not consider other important risk factors such as dietary and nutritional factors.

In spite of several limitations, the results of the present study suggested that the risk of colorectal cancer was inversely associated with occupational activity level and positively associated with beer drinking and a family history of colorectal cancer, and that the strength of the associations showed a gradient along the subsites of the colorectum.

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