Original Article

Lifestyle and Colorectal Cancer : A Case-control Study

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Abstract

A case-control study has been conducted to investigate the relationship between lifestyle and risk of colorectal cancer. Cases are one hundred patients diagnosed with colon and rectal cancer in Tokai University Hospital between 1986 and 1994. Three controls per case were individually matched by age, sex, local areas and date of health checkups at the Automated Multi-phasic Health Testing and Services (AMHTS) Center of the hospital. The results were analyzed by multi-factorial logistic regression models. Positive history of maternal cancer, large consumption of alcohol, frequent consumption of potato products and white-collar job were predominant risk factors while frequent intake of seaweed was a protective factor. Frequent intakes of dairy foods and lack of exercise showed no significant tendency to increase risk of colorectal cancer. Smoking habits, intakes of meat and egg were shown not to be related to this disease. These findings suggest that family history of cancer and dietary factors play a key role in causation and prevention of colorectal cancer.

Key word: colorectal cancer, lifestyle, epidemiologic study, risk factors, health education

Introduction

The incidence of colorectal cancer is increasing in Japan after World War II. The tendency of such increase is more and more conspicuous in the recent years. In 1993, among all kinds of cancer, colorectal cancer was the third most common cause of death in Japan (12 percent of all death from cancer), accounting for 27,287 deaths in 1993, and had increased almost eightfold in the past forty years[1]. The rise in incidence rate [2,3], the difficulty in treatment and the high mortality rate[4,5] all indicate that emphasis should also be placed on preventive measures.

It is clear from works already reported that the development of colorectal cancer is thought to be a multistage process involving both genetic and environmental factors[6-9]. For the past several decades, many epidemiologic and experimental researches have demonstrated fairly consistent relationship between lifestyle and colorectal cancer. The results from most of these studies suggested that the epidemiologic risk factors of this malignancy included reduction of all fiber intake[10-15], increase of meat intake[16-20], low physical activity and increase of alcohol intake[21-25], although contradictory results were also reported[26-29].

However, in the majority of the previous epidemiologic studies on the relationship between lifestyle and colorectal cancer, the case subjects were limited to the in- or out-patients with colorectal cancer and exposure information was collected after the diagnosis. Therefore, errors of recall may influence the results. The significant point of our study is that the questionnaire was executed before the patients (cases) were diagnosed with colorectal cancer. This can avoid bias that can occur by knowing the result of the diagnosis. The notification will affect the answers to the questionnaire when cases recall their lifestyle. This bias-free result of the questionnaire can contribute to the accuracy of a study.

Materials and Methods

1) Colorectal cancer patients

The present study included one hundred cases of colon and rectum cancer patients (ICD 9, 153.0 to 154.1) from the surgical departments of Tokai University Hospital who had undergone health checkups at the Automated Multi-phasic Health Testing and Services (AMHTS) Center[30] of the hospital within one year preceding the diagnosis. Their identification code, primary diagnoses and the results of histological examinations were checked.

2) Control subjects

Controls were also examinees from the AMHTS who had no evidence of malignant tumors. For each case with colorectal

cancer, three controls were matched by age (within two years), sex, date of health checking (within three months) and their residential areas. If there were more than three possible controls for a case, three were selected at random. The thirty-five controls were excluded from this study because of lack of data in their questionnaires. Final number of controls was two hundred and sixty-five.

3) Data collection

This study was a case-control one conducted during the period between 1 April 1986 and 31 March 1994. Information of the subjects was collected from the medical records of the AMHTS Center and the Tokai University Hospital.

The examinees at the AMHTS completed a self-administered questionnaire before undergoing a whole-body examination included detail general assessment, chest radiography, and abdominal-ultrasonic, examinations of blood and urine. The questionnaire contains personal data (state of health, recent weight loss, mental stress, state of bowel movement), diet, smoking, alcohol intakes, occupation, physical activity, family history of cancer. On diet, details were asked regarding the usual consumption patterns of rice, bread, grain, meat, fish, egg, products of soybean, dairy products, vegetables, fruits, potato products, seaweed, condiments and cakes. Simple subjective scores (Freguemt, moderate or a little) were used as measures of usual intakes for these fourteen food groups; On smoking, details were asked regarding the average number of cigarettes smoked per day (0-10 cigarettes/day, 11-20, 21-40, 41 and over); Concerning alcohol drinking, details were asked regarding the usual amounts consumed per day as well as by individual scores for beer, wine, whiskey, sake and liquor. For ex-smokers or ex-drinkers, details were asked regarding the number of cigarettes smoked or the amount of alcohol consumed per day and the corresponding frequency when they were smokers or drinkers. On occupation, details were asked regarding their fields of jobs (e.g. white- or blue-collar job); Concerning physical activity, details were asked regarding their activity levels during leisure and at work.

4) Statistical analysis

Statistical differences between the patients with colorectal cancer and the controls on the thirty-seven lifestyle factors were tested by Mann-Whitney U test using the SPSS for Windows rev. 8 statistical computer software package. The factors with p values greater than 50 percent were rejected. Multi-factorial-logistic-regression analysis was then carried out with colorectal cancer as a dependent variable. Each colorectal cancer patient has a value of one and each matched control subject has a value of zero. Each variable was used as a dichotomous one for the statistical method. Conditional logistic regression was performed for m:n matching with PHREG procedure of SAS package by forming a stratum for each matched set. Variable reduction method (backward elimination) was used and significant lifestyle factors were observed.

We applied an artificial neural network to the data as another discriminant function. Such algorithm was derived from 'the vanilla backpropagation algorithm'[31] and this algorithm has some processing units in a hidden layer.

To evaluate the effect of the number of processing units in the hidden layer, we employed three artificial neural networks having two, three or four processing units in the hidden layer.

The number of the input variables was five or sixteen which consisted of the same variables in the multi-factorial-logistic-regression analysis.

Random value were used to all the inter-layer connections and were repeated several times to ensure minimum error. The number of repeats (1,444-4,206) was determined empirically.

The data were divided randomly into two groups (A and B). We applied the data in Group A ('training data') to the new artificial neural network. A neural network pattern obtained from the training data was then applied to the data in group B ('applying data'). We evaluated the trained artificial neural networks using the C index (area under the ROC curve) with the data in each group [32, 33]. We also assigned the data in group B as training data and the data in group A as applying data to check exchangeability of the data in the groups.

Results

Mean age of the patients with colorectal cancer was 54.4 (standard deviation [SD] 8.1, range 40 84) years, and that of the controls was 54.6 (SD 8.1, range 40 83) years. Fifty-seven percent of patients were diagnosed before fifty-five years of age. The proportional ratio of the sex was coincident with that of all the examinees. The profiles of the 100 cases are shown in Table 1. Seventy-seven percent had adenocarcinoma, 12 percent had tubular adenoma with adenocarcinoma and 4 percent had tubulovillous adenoma with adenocarcinoma, the remaining 7 percent had other histological types. The sites were distributed as follows: cecum, 1 percent; ascending colon, 12 percent; transverse colon, 10 percent; descending colon, 10 percent; sigmoid colon, 40 percent; rectosigmoid, 10 percent; rectum 17 percent.

Table 1　Age, sex, site and histological type of colorectal cancer in 100 cases

Age(years)	40 - 45	12%
	46 - 50	14%
	51 - 55	30%
	55 <	44%
Sex	Male	77%
	Female	23%
Site	Cecum	1%
	Ascending colon	12%
	Transverse colon	10%
	Descending colon	10%
	Sigmoid colon	40%
	Rectosigmoid colon	10%
	Rectum	17%
Histological type	Adenocarcinoma	77%
	Tubular adenoma with adenocarcinoma	12%
	Tubulovillous adenoma with adenocarcinoma	4%
	Others	7%

The frequencies of thirty-seven lifestyle factors in the patients and controls are shown in Table 2. Thirty-seven lifestyle factors were tested by Mann-Whitney U test and the following sixteen factors were survived because these p values were less than 50 percent: in poor shape, weight loss ($\geq$ 5kg) within one year, diet built around intake of rice, frequent intakes of bread, foods made of soybean, dairy products, vegetables, fruits, potato products and seaweed, a large comsumption of alcohol for former drinkers, a large consumption of alcohol for current drinkers, white-collar job, lack of exercise, father and mother's history of cancer (Table 2).

Table 2 Frequency distribution of 37 lifestyle factors in 100 patients with colorectal cancer and 265 controls and the statistical probabilities by Mann-Whitney U test

lifestyle factors	patients %	controls %	p
in poor shape	33.0	27.5	0.31
weight loss within one year($\geq$ 5kg)	6.0	10.2	0.21
great mental stress from job and others	31.0	31.7	0.90
constipation and/or diarrhea	16.0	14.7	0.76
irregular mealtime	21.0	18.1	0.53
polyphagia or eat lightly	25.0	27.5	0.62
diet built around rice	95.0	92.5	0.39
skipping meals or frequent intakes of instant food	29.0	29.4	0.93
frequent consumption of bread	34.0	39.2	0.36
frequent consumption of noodles	30.0	29.1	0.86
frequent consumption of meat	42.0	42.6	0.91
frequent consumption of fish	70.0	72.5	0.64
frequent consumption of egg	57.0	56.2	0.89
frequent consumption of foods made of soybeans	64.0	57.7	0.28
frequent consumption of dairy products	56.0	51.7	0.46
frequent consumption of vegetables	89.0	86.0	0.46
frequent consumption of fruits	53.0	60.0	0.23
frequent consumption of potato products	37.0	28.7	0.13
frequent consumption of seaweed	45.0	50.6	0.34
frequent consumption of condiments	34.0	35.1	0.85
frequent consumption of cakes	9.0	9.8	0.81
restrict intakes of salt, sugar and/or fat	48.0	51.3	0.57
cigarette smoking habit(ex-smoker)	52.0	51.7	0.96
cigarette smoking habit(current smoker)	41.0	38.5	0.66
alcohol drinking habit(ex-drinker)	70.0	68.7	0.81
alcohol drinking habit(current-drinker)	74.0	70.9	0.56
large consumption of alcohol(ex-drinker)	46.0	33.2	0.02
large consumption of alcohol(current-drinker)	39.0	28.7	0.06
white-collar job	55.0	43.0	0.04
hard daily work	38.0	37.4	0.91
lack of sleep($<$6 hours)	16.0	15.1	0.83
physical inactivity	57.0	53.6	0.56
lack of exercise	50.0	41.9	0.16
brothers' history of cancer	11.0	10.6	0.90
father's history of cancer	16.0	11.7	0.27
mother's history of cancer	21.0	11.3	0.02
grandparents' history of cancer	7.0	6.8	0.94

Table 3 Multi-factorial logistic regression analysis of lifestyle variables as risk factors for colorectal cancer among patients with colorectal cancer and the controls and the odds ratios

independent variables (dichotomous)	all variables(16) B	all variables(16) p	variables(5) after reduction B	variables(5) after reduction p	odds ratio and 95% limits OR	odds ratio and 95% limits lower	odds ratio and 95% limits upper
in poor shape	0.29	0.30			1.30	0.79	2.13
weight loss within one year($\geq$5kg)	-0.49	0.33			0.56	0.23	1.41
diet built around rice	-0.67	0.25			0.64	0.24	1.77
frequent consumption of bread	-0.18	0.53			0.80	0.49	1.29
frequent consumption of foods made of soybeans	0.32	0.29			1.30	0.81	2.09
frequent consumption of dairy products	0.31	0.28			1.19	0.75	1.89
frequent consumption of vegetables	0.45	0.27			1.31	0.64	2.69
frequent consumption of fruits	-0.51	0.09			0.75	0.47	1.19
frequent consumption of potato products	0.62	0.06	0.63	0.03	1.46	0.90	2.37
frequent consumption of seaweed	-0.67	0.02	-0.59	0.03	0.80	0.50	1.27
large consumption of alcohol(ex-drinker)	0.58	0.15	0.75	0.01	1.71	1.07	2.74
large consumption of alcohol(current-drinker)	0.30	0.47			1.58	0.98	2.57
white-collar job	0.75	0.01	0.62	0.02	1.62	1.02	2.57
lack of exercise	0.36	0.16			1.39	0.87	2.20
father's history of cancer	0.45	0.21			1.44	0.75	2.76
mother's history of cancer	0.76	0.02	0.69	0.04	2.08	1.13	3.84

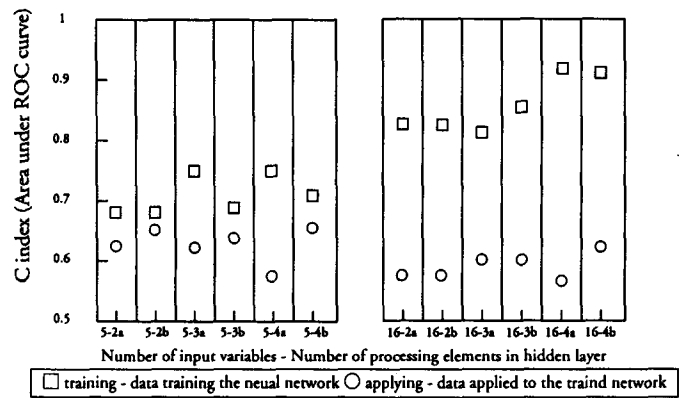B:coefficients; OR:odds ratio; negative B:factors of reduced risk for colorectal cancer.

Figure 1. Result of the Artificial Neural Network
the data (100:cancer / 265:nomal)were divided into two groups
a:training - group A,applying - group B
b:training - group B,applying - group A

We also examined the risk of colorectal cancer in relation to the sixteen lifestyle factors by multi-factorial logistic regression analysis (Table 3). The results from backward variable elimination have shown that five factors were significantly related to risk of colorectal cancer. Within these factors, frequent potato products consumption (B=0.63), large amount of alcohol consumed by former drinkers (B=0.75), white-collar job (B=0.62) and positive mother's history of cancer (B=0.69) were associated with increasing risk for colorectal cancer. Frequent intake of seaweed (B=-0.59) was associated with decreasing the risk.

The C indices of the data with the trained artificial neural networks are shown in Figure 1. It shows that (1) C indices of the applying data are always worse than those of the training data, (2) C indices of the training data with 16 inputs are better than those with 5 inputs but C indices of the applying data are not, (3) C indices of the training data are good as the processing units increase but those of the training data are not.

Discussion

Our study shows significant increased risk of colorectal cancer associated with frequent intakes of potato products, large amount of alcohol consumption, white-collar job and positive mother's history of cancer, whereas increased intake of diet rich in seaweed may offer some protection from colorectal cancer. Such associations were already described previously[6-25]. However in this study, all information was collected before the diagnosis of this disease. In addition, this investigation focused exclusively on the relationship between lifestyle factors and risks of colorectal cancer. This is because the pattern of lifestyle in each person is capable of improving and leading a favorable, non-cancer-inducing lifestyle by having knowledge and consciousness of the

diseases . Thus, investigation exclusively on the lifestyle can serve as a means in prevention of cancer.

It is clear that several genetic abnormalities undoubtedly are important in the development of colorectal cancer[4,34]. One of the most consistent findings from epidemiological case-control studies of family history of colorectal cancer was that people having first degree relatives with the disease are themselves at two to three times higher risk getting it. Among the hereditary factors, familial adenomatous polyposis (FAP) and hereditary no polyposis colorectal cancer (HNPCC) have been studied extensively[35-37]. Our results fit well with the knowledge of colorectal cancer among the first degree of kinship, although the types of tumors were not completely consistent. Therefore, someone whose family member, especially a mother and/or a father have a history of cancer should be categorized in "high risk population" and screening should be considered.

Our results suggested that mother's history of cancer was strongly positively associated with colorectal cancer. It can be explained that the incidence of children's cancer will be affected not only by the mothers' genetic factors but also by their lifestyles. In Japan, the lifestyle of a father is considerably different from those of the other family members. Therfore the positive father's history may not strongly affect the children's risk of cancer.

Studies of groups that have moved from areas where the risk of colorectal cancer is low to areas of high risk have established the importance of environmental factors in causing this disease[38]. Among environmental factors, epidemiologic studies have shown that diet and behavior were two of the most important components influencing the risk of colorectal cancer[6-29]. Dietary factors, for example, high consumption of vegetables and fruits, decrease of fat (or meat) intakes are linked to a reduced incidence of this disease. It is well known in Japan that westernization of the lifestyle, especially its dietary habit was rapidly introduced after World War II and has been influential. It is clear from works previously reported that western style diets, namely high fat (or meat) intakes, low vegetable and fruit intakes were associated with the incidence of colorectal cancer. The results of this study suggested that high intake of seaweed appeared to have significant protective effect of colorectal cancer, but failed to confirm the previously reported findings that all kinds of fat were related to increase risk of colon cancer. This difference observed from our finding may be due to the less amount of meat consumed by Japanese than by Europeans and Americans. Such mechanism is possibly through the metabolism of secondary bile acids. The role of secondary bile acids in promoting colonic carcinogenesis is probably mediated by their cytotoxic effect on colonic mucosa, leading to compensatory increases in proliferation[19,39,40]. Another possible mechanism by which vegetable and fruit intake might alter risk of colorectal cancer is that a large number of potentially anticarcinogenic agents are found in these food sources, including carotenoids, vitamins C and E, selenium, dietary fiber, dithiolthiones, glucosinolates and indoles, isothiocyanates, flavonoids, phenols, protease inhibitors, plant sterols, allium compounds, and limonene. These agents have both complementary and overlapping mechanisms of action, including the induction of detoxification enzymes, inhibition of nitrosamine formation, provision of substrate for formation of antineoplastic agents, dilution and binding of carcinogens in the digestive tract, alteration of hormone metabolism, antioxidant effects, and others[41].

Although previous analytic epidemiologic studies have revealed that physical inactivity or lack of exercise is associated with colorectal cancer[21,24,42-46], only a weak positive association was found in our study. However, a strong positive association with white-collar job and colorectal cancer was observed. Usually, this class of workers generally requires low level of physical activity or is mentally strained at workplaces. It can thus be speculated that lack of physical activity and presence of mental stress may influence the incidence of colorectal cancer. In addition, the deleterious effect of a sedentary lifestyle among these people may at least partly account for the higher rates of this disease. Several biological mechanisms may contribute to the beneficial influences of physical activity on risk of colorectal cancer, including constipation which is often improved by physical activity. Walking[47], running[42] and strength training[43] have generally been found to reduce gastrointestinal transit time. Contact between the colon mucosa and potential carcinogens in the fecal stream may be decreased by exercise because of the shortened transit time. A decrease in the ratio of secondary to primary bile acids has been observed in obese patients after treatment with subcaloric diet and graded physical activity[44]. This effect of physical activity may be of importance since a high excretion of bile acids may increase the risk of colorectal cancer. Physical activity may also increase colonic blood flow so that fecal mutagens are transported away from the mucous membrane[45].

Alcohol has also been suggested as risk factors for colorectal cancer in many cohorts or case-control studies[22-25, 46,48-50]. The mechanism whereby the alcohol influences the incidence of a large bowel tumor is probably as follows: a direct carcinogenic effect (cytotoxic) of one metabolite of alcohol, acetaldehyde (CH_3CHO)[46]; a direct action of ethanol on the fecal microflora[48] and others[49,50]. However, until now, few of these studies have focused on recent abstainers. It is interesting to note that a statistically significant positive association was shown between large amount of alcohol consumption among drinkers who recently stopped drinking and the risk of colorectal cancer in this study. This supports a potential role for alcohol in carcinogenesis and suggests that the total amount rather than duration of alcohol in the lifetime had a stronger effect on risk. There were clear rises in the risk when amount increased no matter they are former or current drinkers. The result of the stronger association in recent abstainers is probably because these subjects stopped drinking after the development of symptoms. On the other hand, a relationship between the type of alcohol beverages and the risk of this disease was not shown in this study.

The statistically significant positive association for potato products consumption observed in the present study is in accord with some previous case-control studies[51,52]. It is possibly because potato consumption is a marker for "meat and potatoes" meals or of the fat-laden condiments with which potatoes are commonly consumed and this population cannot be ruled out[53]. Consumption of potato products, such as potato chips which contain a high percentage of fat as well as salt, has become increasingly popular. This may be also a reason of this association. Further investigation needs to be done to clarify such relationship.

In some epidemiologic studies, fish intake is associated with protection against colorectal cancer[54] while smoking, frequent consumption of egg and dairy products are associated with development of this disease[55-57]. In the multi-factorial logistic regression analysis performed in our study, however, none of

these potential variables affected the role of colorectal cancer as a risk factor.

Although it is well known that the change in bowel movement may be a relatively earlier sign of colorectal cancer, there was no significant difference in bowel movement found in our study. A person will seek for medical treatment when he has abnormalities in bowel movement.

An artificial neural network using backpropagation algorithm can discriminate any arbitrary analog spatial patterns [31, 58]. This algorithm raises the overfit problem as the number of processing units in the hidden layers increases [59]. To evaluate the behavior of the artificial neural network, we applied the data to the artificial neural networks with different numbers of the processing units in the hidden layer.

The popular methods to evaluate artificial neural networks

are using ROC curve [32] and correct positive (negative) classification rate [60]. Using matched data, we employed the ROC curve which is not affected by the prevalence of the disease.

The result showed that increasing the number of the input variables and the number of the processing units in the hidden layer led to poor discriminant function for the applying data. It suggests that there is no advantage of using 16 variables for predicting colorecal cancer compared with using 5 variables even when an artificial neural network is applied.

From an epidemiological standpoint, our findings have confirmed the risk factors of colorectal cancer suggested by numerous case-control studies, and suggests comprehensive health education should be useful in the prevention of colorectal cancer among healthy population.

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