RESEARCH COMMUNICATION

Dietary Habits and Cancer Mortality Among Middle Aged and Older Japanese Living in Hokkaido, Japan by Cancer Site and Sex

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Abstract

Dietary factors are thought to be closely associated with the development of human cancers and hence numerous studies in this area have already been conducted in the United States and other Western countries. Comparatively few prospective studies have been published in Japan, especially for Hokkaido people. The present investigation was therefore performed to assess links between four leading cancers and some of the Japanese common dietary factors through a cohort study (1984-2002) in Hokkaido by analyzing 1,524 men and 1,634 women separately aged 40 and over. Adjusted Cox proportional hazard regression was used to calculate the relative risk (RR) for each dietary factor. For men, two dietary factors, miso soup (RR=0.2, 95% confidence interval (95%CI)=0.1-0.8) and pickled vegetables (RR=0.2, 95%CI=0.1-0.8) were associated with lower risk for stomach and colorectal cancer respectively. For women, three factors, namely salty confectionary (RR=3.5, 95%CI=1.1-10.9), black tea (RR=3.8, 95%CI=1.1-13.6), and carbonated drink/juice (RR=3.9, 95% CI=1.4-11.1) appeared related to an elevated risk of stomach cancer. However, further analysis simultaneously with all other adjusted factors indicated only carbonated drink/juice (RR=3.1, 95%CI=1.1-8.9) to present a significant risk factor for stomach cancer. One factor, namely wild edible plants (RR=3.3, 95%CI=1.1-9.8), increased the risk for colorectal cancer in women. None of the dietary components were significantly associated with lung or pancreatic cancers. This study also indicated a wide variation in the impact of dietary factors by sex and cancer site, in line with earlier work, poonting to a necessity for careful interpretation. Further epidemiological investigations by sex with more study subjects and confounding factors will be useful for determining the contribution of individual dietary factors to development of human cancers in Hokkaido, Japan.

Key Words: Cohort study - cancers types (stomach-lung-colorectal-pancreatic) - dietary factors - Hokkaido, Japan

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Introduction

Cancer has been the leading cause of death in Japan since 1981, accounting for about 31% of the total deaths in 2000. Among the various cancers, after 1970 the top three sites have been the lung, stomach, and colorectum. Age-adjusted death rates with lung, colorectal and pancreatic cancers demonstrate increasing trend for both men and women, whereas stomach cancer is decreasing (Health and Welfare Statistics Association, 2002). Although studies in United States and Western countries indicate that dietary habits are closely associated with development of cancers, there is only limited evidence from prospective studies in Japanese whose dietary habits is substantially different from Western countries (Tsugane et al, 2001).

Several dietary factors have been postulated as risk factors for human carcinogenesis (Sugimura, 2000; Marchand, 1999; Mirvish, 1983). Most of the studies in Japan have focused on stomach cancer (Masaki et al, 2003; Ngoan et al, 2002; Hoshiyama et al, 2002; Nagata et al, 2002; Kobayashi et al, 2002; Kato et al, 1992; Hoshiyama and Sasaba, 1992; Tajima and Tominaga, 1985), followed by lung cancer (Takezaki et al, 2001a; Ozasa et al, 2001; Ohno et al, 1995), and colorectal cancer (Marchand, 1999; Kono

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et al, 1993; Tajima and Tominaga, 1985). The association of dietary factors with pancreatic cancer has been studied even less or insignificantly than stomach and lung cancers. Surprisingly the epidemiological findings of these dietary studies differed significantly by cancer sites and sex and perhaps for such variation, food carcinogens continue to be a most challenging subject for research into cancer control (Sugimura, 2000). Considering the above-mentioned facts as well as insufficient studies in Hokkaido, the association of 37 dietary factors with lung, stomach, colorectal and pancreatic cancer deaths were investigated by a cohort (1984-2002) study in Hokkaido, Japan. To our knowledge, this was the first cohort (1984-2002) study in Hokkaido and we attempted for the first time to include four leading cancers simultaneously for investigating their association with dietary factors. Hence the findings of this study may be particularly important for Hokkaido.

Materials and Methods

With ethical approval from the Hokkaido Government, this cohort study was initiated by them in 1984-85 and continued until 2002. The study was implemented by the staffs of the 45 health centers located in the Hokkaido Prefecture. It included the subjects aged 40 years and over using the resident registries. In 1984 from the list of 1,363 randomly selected households of 50 areas, a total of 2,883 persons (1,405 men and 1,478 women) were identified as eligible, of which 2,586 (89.7%) responded the baseline survey. Similarly from another list of 339 randomly selected households of 10 new areas in 1985, 679 persons (310 men and 369 women) were identified as eligible for the study, of which 599 (88.2%) responded the survey. Explaining the purposes of the study, informed consent was taken from each subject. Thus in total 3,562 persons were approached, of which 3,185 persons (89.4%) agreed to participate in the study. However, we excluded 27 subjects from the analysis (8 men and 19 women) because of their previous history of cancer. Thus we analyzed 3,158 (1,524 men and 1,634 women) subjects in total.

Staffs of the 45 health centers executed baseline survey and collected information for many variables including socio-demographic, medical history, behavioral and dietary habits. Dietary factors included miso soup, bread, egg, mushroom, potato, noodles, instant noodles, soybean curd (fermented soybean) also called tofu in Japanese, seaweed, Japanese pickles, edible wild plants (bracken and butterbur) also called sansai in Japanese, fruits, confectionary items (sweat, salty), drinking back tea, green tea, coffee, cola as well as carbonated drink and juice; eating different kinds of vegetables (green, yellow, white, pale, raw, cooked), fishes (raw, boiled, salted, baked, shell), meats (pork, beef, mutton, chicken, liver, hum and sausages) and milk products (milk, yogurt, butter/margarine, cheese, mayonnaise/dressing). The information about dietary factors was obtained by five categories: never, several times in a year, several times in a month, several times in a week, and everyday. However, for analytical purpose we made two categories (reference category versus comparison category) by combining three groups (never, several times per year, several times per month) under reference category and two groups (several times per week, everyday) under comparison category.

In addition to 37 dietary factors, this study used few more variables form the baseline survey. These were age, sex, health education, health examination, health status and smoking. We used them for adjustment purpose in the Cox proportional model. At baseline survey, health education was determined by asking: "Have you received health education last year?" Similarly screening was ascertained by asking: "Have you completed screening last year?" The answer was recorded either as yes or no for both questions. Health status was obtained by three categories: good, fair, and bad. Smoking was determined by four categories: everyday smoker, sometimes smoker, ex-smoker, and never smoker. Follow-up survey was conducted every year during the study period to know the status of the subjects whether alive, dead, or lost to follow-up (moved outside). If case of death, the date of expiry was recorded and the cause of death was classified according to the International Classification of Disease (ICD) 9th version because during 1980s this version was up-to-date. In case of moving outside from the study area, the date of the last contact was specified and recorded. Information for follow-up surveys was collected either from the study subjects, or their families, or vital statistics. We computed person-years of follow up for each subject. For each cancer site and sex, Cox proportional hazard model was applied to compare the relative risk (RR) of mortality by each dietary factor after adjusting for some potential factors. RR=1.0 indicated reference category (RC). Significant level was reported by P value. Statistical Package for Social Science (SPSS) was used for analysis.

Results

Table 1 presented some relevant information of the study. The mean age of subject at baseline was about 58 years for both men and women. Among the men, 60.3% were current smokers, 23.4% received health education and 61.9% underwent for physical examination. Higher rate of health education (37.6%) and significantly lower rate current smokers (8.4%) was found among the women. During the follow-up period, 797 deaths (494 men and 303 women) were observed, of which 30.6% (155 men and 89 women) were cancer deaths. The mean follow-up period for the deceased was almost half as compared to alive subjects for both men and women. Lung cancer was the leading cause of death among the men, which was followed by stomach, colorectal, and pancreatic cancers respectively. In contrast, stomach cancer was the leading cause of death among the women, which was followed by colorectal, pancreatic, and lung cancers respectively.

We showed the distribution of men by dietary factors and the estimated RRs of mortality with 95% confidence interval (95%CI) for four specific cancers in Table 2. Since

Table 1. Summary Information about Baseline and Follow-up Surveys

Characteristics	Men (n=1524)	Women (n=1634)
Baseline information:		
Mean age ± Standard Deviation (SD)	58.0 ± 11.0	57.6 ± 11.4
Age range (Minimum-Maximum)	57 (40-97)	57 (40-97)
Perceived health status:		
Good	520	362
Fair	722	893
Bad	277	375
Received health education last year (yes/no)	356/1164	610/1013
Received physical examination last year (yes/no)	943/580	1014/616
Smoking:		
Current smoker	919	137
Ex-smoker	227	25
Non-smoker	377	1467
Follow-up information:		
Mean follow-up period for total ± SD	13.8 ± 5.0	14.8 ± 4.5
Mean follow-up period for lost to follow-up ± SD	9.0 ± 4.8	9.4 ± 4.7
Mean follow-up period for the alive ± SD	17.1 ± 0.4	17.1 ± 0.4
Mean follow-up period for the deceased ± SD	8.8 ± 4.7	9.0 ± 5.0
Number of subjects lost to follow-up	104	166
Number of subjects alive	926	1165
Number of deaths from all causes	494	303
Deaths from all types of cancer	155	89
Cancer types:		
Lung cancer	41	10
Stomach cancer	36	15
Colorectal cancer	15	14
Pancreatic cancer	12	13
Others	51	37

age and smoking were significantly associated with cancer deaths (data not shown), these factors are finally adjusted in the Cox proportional model. Perceived health status, health education and health examination are excluded from the final model since they were not significantly associated with cancer deaths. Cox model showed that none of the dietary factors was significantly associated with lung and pancreatic cancers. Though some decreased risk of lung cancer death was found for those subjects who consumed raw fish, backed fish, raw green-yellow vegetables, tofu, and green tea more frequently. Only one factor namely miso soup significantly decreased the risk of stomach cancer (RR=0.2, 95%CI=0.1-0.8). It should be noted that miso soup consumption in Japan is very common because about 99% men and women consume it several times in a week or everyday. Though not significant, some factors like raw fish, boiled fish, wild edible plants, meat, yogurt, butter/margarine, potato, salty confectionary revealed elevated risk of stomach cancer. In contrast, shellfish and raw green-yellow vegetables revealed lower risk of stomach cancer. Only the consumption of Japanese pickle was found significantly protective (RR=0.2, 95%CI=0.1-0.8) for colorectal cancer. Some other factors such as boiled fish, cooked green-yellow vegetables, fruit, butter/margarine, coffee, sweat, and salty confectionary showed decreased risk of colorectal cancer, whereas meat and liver indicated increased risk. For pancreatic cancer, raw white-pale vegetables, seaweed, mushroom, and bread showed decreased risk and salty confectionary showed increased risk.

Like men, the distribution of women by dietary factors and the estimated RRs with 95%CI for four specific cancers are presented in Table 3. None of the dietary factors was significantly associated with lung cancer, though some elevated risk was observed for raw fish consumption and decreased risk was found for mayonnaise/dressing and seaweed consumption. For stomach cancer, three factors such as black tea (RR=3.8, 95%CI=1.1-13.6), carbonated drink/juice (RR=3.9, 95%CI=1.4-11.1), and salty confectionary (RR=3.5, 95%CI=1.1-10.9) significantly increased the risk of mortality. Slightly elevated risk of stomach cancer mortality was observed for boiled fish, shellfish, mayonnaise/dressing, and bread consumption. In contrast, reduced risk was found for cooked vegetables, seaweed, and coffee consumption. Wild edible plant

Table 2. Estimated RRs and 95%CI for Men According to Dietary Consumption (adjusted for age and smoking)

	[a]Reference/ Comparison group	Men				
		Total RR (95% CI)	Lung RR (95% CI)	Stomach RR (95% CI)	Colorectal RR (95% CI)	Pancreatic RR (95% CI)
Raw fish	1030/493	1.0 (0.7-1.4)	0.7 (0.3-1.3)	1.6 (0.8-3.14)	1.1 (0.4-3.1)	0.6 (0.2-2.3)
Boiled fish	602/921	0.9 (0.6-1.2)	0.9 (0.5-1.7)	1.4 (0.7-2.8)	0.5 (0.2-1.4)	0.6 (0.2-1.8)
Backed fish	304/1219	1.1 (0.7-1.6)	0.6 (0.3-1.1)	1.0 (0.5-2.4)	1.6 (0.4-7.2)	-
Salty fish	735/786	0.9 (0.6-1.2)	0.8 (0.5-1.5)	0.9 (0.5-1.8)	0.7 (0.2-2.0)	1.4 (0.4-4.3)
Shellfish	1237/281	0.7 (0.4-1.0)	0.9 (0.4-2.1)	0.3(0.1-1.0)	0.3 (0.0-2.3)	-
Raw GYV	469/1051	0.8 (0.6-1.2)	0.7 (0.4-1.3)	0.6 (0.3-1.1)	1.8 (0.5-6.2)	0.7 (0.2-2.1)
Raw WPV	405/1115	1.0 (0.7-1.4)	1.3 (0.6-2.8)	0.8 (0.4-1.5)	1.4 (0.4-5.1)	0.4 (0.1-1.2)
Cooked GYV	236/1285	0.9 (0.6-1.4)	0.8 (0.4-1.9)	0.8 (0.3-2.0)	0.5 (0.1-1.4)	-
Cooked WPV	223/1293	1.0 (0.6-1.6)	0.9 (0.4-2.1)	0.8 (0.3-1.8)	0.6 (0.2-2.1)	-
Wild plants	1227/299	1.1 (0.7-1.6)	1.0 (0.5-2.2)	1.8 (0.9-3.7)	2.9 (0.0-2.2)	0.9 (0.2-3.9)
Fruit	162/1360	1.0 (0.6-1.6)	0.8 (0.3-2.2)	1.1 (0.4-3.0)	0.4 (0.1-1.5)	-
Meat (except chicken)	606/915	1.1 (0.8-1.6)	1.1 (0.6-2.0)	1.4 (0.7-2.8)	2.0 (0.6-6.3)	1.4 (0.4-4.8)
Chicken	979/542	1.1 (0.8-1.5)	1.2 (0.6-2.2)	0.9 (0.5-1.9)	1.0 (0.3-2.8)	0.6 (0.2-2.3)
Liver	1439/83	1.4 (0.8-2.6)	0.9 (0.2-3.7)	1.7 (0.5-5.6)	2.9 (0.6-12.7)	1.7 (0.2-13.2)
Ham, sausage	1135/388	1.0 (0.7-1.4)	1.1 (0.5-2.3)	1.0 (0.5-2.1)	0.5 (0.1-2.2)	0.7 (0.2-3.3)
Egg	195/1327	1.4 (0.8-2.3)	1.0 (0.4-2.5)	2.5 (0.6-10.3)	2.0 (0.3-15.3)	-
Milk	509/1014	1.0 (0.7-1.4)	1.1 (0.6-2.1)	1.1 (0.5-2.2)	0.7 (0.3-2.0)	1.4 (0.4-5.2)
Yogurt	1304/212	0.8 (0.5-1.3)	1.3 (0.6-2.8)	1.6 (0.8-3.6)	0.7 (0.3-2.0)	0.5 (0.1-4.2)
Butter/margarine	986/531	0.9 (0.6-1.2)	1.1 (0.6-2.1)	1.7 (0.9-3.2)	0.3 (0.1-1.3)	1.0 (0.3-3.2)

[a]Reference group = took never + took several times per year + took several times per month.
Comparison group = took several times per week+ took everyday.
"-" : Not estimated due to 0 case in either of the two group; * P<0.05
GYV: green & yellow vegetables; WPV: white/pale vegetables

Table 2. Estimated RRs and 95%CI for Men According to Food Consumption (adjusted for age and smoking) (continued)

	[a]Reference/ Comparison group	Men				
		Total RR (95% CI)	Lung RR (95% CI)	Stomach RR (95% CI)	Colorectal RR (95% CI)	Pancreatic RR (95% CI)
Cheese	1317/203	1.0 (0.7-1.7)	1.6 (0.8-3.4)	1.2 (0.5-3.0)	-	0.6 (0.1-4.4)
Mayonnaise/ dressing	756/764	0.9 (0.7-1.3)	1.0 (0.5-1.8)	1.1 (0.6-2.2)	1.2 (0.4-3.2)	0.5 (0.2-1.8)
Tofu	167/1355	1.2 (0.7-2.1)	0.6 (0.3-1.3)	3.6 (0.5-26.0)	1.5 (0.2-11.2)	1.3 (0.2-9.9)
Miso soup	16/1506	0.4 (0.1-1.1)	-	0.2 (0.1-0.8)*	-	-
Seaweed	488/1035	0.9 (0.6-1.2)	1.1 (0.6-2.2)	0.9 (0.4-1.7)	1.2 (0.4-3.7)	0.5 (0.2-1.4)
Green tea	246/1274	1.0 (0.7-1.6)	0.6 (0.3-1.2)	1.1 (0.4-2.5)	1.3 (0.3-5.9)	-
Black tea	1420/99	0.6 (0.3-1.3)	0.6 (0.1-2.5)	0.4 (0.1-2.7)	0.9 (0.1-6.9)	-
Cola	1342/180	0.5 (0.3-1.1)	0.5 (0.1-2.2)	0.3 (0.0-1.9)	-	-
Coffee	927/595	0.8 (0.6-1.2)	0.7 (0.4-1.4)	1.0 (0.5-2.0)	0.3 (0.1-1.4)	0.6 (0.2-2.2)
Carbonated drink/Juice	1009/508	0.9 (0.6-1.3)	1.1 (0.5-2.1)	0.8 (0.4-1.8)	0.6 (0.2-2.1)	0.2 (0.0-1.8)
Japanese pickle	121/1401	0.8 (0.5-1.5)	1.0 (0.3-3.3)	0.9 (0.3-3.1)	0.2 (0.1-0.8)*	-
Potato	275/1248	1.2 (0.8-1.9)	1.0 (0.4-2.2)	2.2 (0.7-7.1)	0.8 (0.2-2.7)	1.1 (0.2-4.8)
Sweat confectionary	572/950	1.0 (0.7-1.4)	1.1 (0.6-2.1)	0.8 (0.4-1.6)	0.4 (0.2-1.2)	1.1 (0.3-3.7)
Salty confectionary	986/533	1.1 (0.8-1.6)	1.3 (0.7-2.3)	1.4 (0.7-2.6)	0.3 (0.1-1.2)	2.5 (0.8-8.0)
Mushroom	928/594	0.8 (0.6-1.1)	0.9 (0.5-1.6)	0.9 (0.4-1.7)	0.9 (0.3-2.6)	0.3 (0.1-1.4)
Bread	1124/397	0.8 (0.5-1.2)	0.7 (0.3-1.6)	1.3 (0.7-2.7)	0.5 (0.1-2.2)	0.3 (0.0-2.3)
Instant noodle	1326/194	0.9 (0.6-1.5)	1.3 (0.7-2.3)	0.5 (0.1-2.0)	1.3 (0.3-5.7)	0.7 (0.1-5.7)
Noodle	808/715	1.0 (0.7-1.3)	1.1 (0.4-2.9)	0.8 (0.4-1.6)	0.6 (0.2-1.8)	0.4 (0.1-1.5)

[a]Reference group = took never + took several times per year + took several times per month.
Comparison group = took several times per week+ took everyday.
"-" : Not estimated due to 0 case in either of the two group; * P<0.05

significantly increased the risk of colorectal cancer mortality (RR=3.3, 95%CI=1.1-9.8). Milk consumption showed decreased risk and raw white-pale vegetables and chicken showed increased risk of colorectal cancer. Meat (all except

Table 3. Estimated RRs and 95%CI for Women According to Food Consumption (adjusted for age, health status, health education, health screening & smoking)

	[a]Reference/ Comparison group	Women				
		Total RR (95% CI)	Lung RR (95% CI)	Stomach RR (95% CI)	Colorectal RR (95% CI)	Pancreatic RR (95% CI)
Raw fish	1278/354	1.4 (0.9-2.3)	3.0 (0.8-10.7)	2.0 (0.7-5.8)	1.2 (0.3-4.5)	1.3 (0.4-4.9)
Boiled fish	684/948	1.7 (1.1-2.7)*	1.6 (0.4-6.3)	3.0 (0.8-10.5)	1.2 (0.4-3.7)	1.2 (0.4-3.6)
Backed fish	307/1326	1.3 (0.8-2.4)	1.1 (0.2-5.3)	1.6 (0.4-7.0)	0.9 (0.2-3.1)	1.3 (0.3-6.6)
Salty fish	785/845	1.1 (0.7-1.7)	1.6 (0.4-5.5)	1.5 (0.5-4.2)	1.6 (0.5-5.0)	0.9 (0.3-2.7)
Shellfish	1361/269	1.4 (0.8-2.4)	0.7 (0.1-5.2)	2.1 (0.7-6.6)	1.9 (0.5-6.9)	1.2 (0.3-5.3)
Raw GYV	468/1164	0.9 (0.6-1.4)	1.9 (0.4-8.9)	1.8 (0.5-6.3)	1.0 (0.3-3.4)	1.0 (0.3-3.4)
Raw WPV	373/1259	1.1 (0.7-1.9)	1.5 (0.3-7.4)	1.4 (0.4-5.1)	4.9 (0.6-38.3)	1.3 (0.3-4.7)
Cooked GYV	168/1466	1.2 (0.6-2.7)	1.1 (0.1-8.5)	0.4 (0.1-1.4)	-	-
Cooked WPV	163/1468	0.9 (0.5-1.9)	1.1 (0.1-8.6)	0.4 (0.1-1.4)	-	1.1 (0.1-9.1)
Wild plants	1310/318	1.3 (0.8-2.0)	1.7 (0.4-6.4)	1.0 (0.3-3.5)	3.3 (1.1-9.8)*	0.7 (0.2-3.1)
Fruits	79/1555	1.1 (0.4-2.9)	-	-	0.5 (0.1-3.8)	0.6 (0.1-4.6)
Meat (except chicken)	762/868	1.1 (0.7-1.7)	1.3 (0.4-4.5)	0.9 (0.3-2.5)	1.0 (0.3-3.0)	2.7 (0.8-8.9)
Chicken	1055/577	1.0 (0.6-1.5)	0.5 (0.1-2.5)	0.9 (0.3-2.7)	1.7 (0.6-5.2)	2.2 (0.7-6.7)
Liver	1570/61	0.9 (0.2-3.8)	-	2.6 (0.3-19.9)	-	-
Ham, sausage	1189/445	0.8 (0.5-1.4)	0.4 (0.1-3.1)	0.7 (0.2-2.6)	1.4 (0.4-4.5)	0.6 (0.1-2.6)
Egg	211/1420	1.3 (0.7-2.5)	-	1.2 (0.3-5.2)	2.3 (0.3-17.9)	2.4 (0.3-18.5)
Milk	542/1092	0.8 (0.5-1.2)	1.5 (0.3-7.4)	1.0 (0.4-3.0)	0.5 (0.2-1.3)	1.2 (0.4-4.1)
Yogurt	1293/330	0.7 (0.4-1.3)	0.5 (0.1-4.0)	0.3 (0.0-2.3)	0.4 (0.1-2.8)	0.9 (0.2-3.9)
Butter/margarine	1092/535	1.1 (0.7-1.7)	0.7 (0.2-3.5)	0.6 (0.2-2.3)	1.3 (0.4-4.3)	1.3 (0.4-4.4)

[a]Reference group = took never + took several times per year + took several times per month.
Comparison group = took several times per week+ took everyday.
"-" : Not estimated due to 0 case in either of the two group; * P<0.05
GYV: green & yellow vegetables; WPV: white/pale vegetables

Table 3. Estimated RRs and 95%CI for Women According to Food Consumption (adjusted for age, health status, health education, health screening & smoking) (continued)

	[a]Reference/ Comparison group	Women				
		Total RR (95% CI)	Lung RR (95% CI)	Stomach RR (95% CI)	Colorectal RR (95% CI)	Pancreatic RR (95% CI)
Cheese	1419/208	1.1 (0.6-2.2)	1.1 (0.1-8.8)	1.2 (0.3-5.4)	1.5 (0.3-6.8)	1.7 (0.4-7.9)
Mayonnaise/ dressing	632/1001	0.9 (0.6-1.4)	0.5 (0.2-1.9)	2.7 (0.8-9.5)	1.0 (0.3-3.2)	1.1 (0.4-3.5)
Soybean curd	135/1498	1.4 (0.6-3.4)	-	1.1 (0.1-8.5)	0.9 (0.1-6.9)	-
Miso soup	19/1612	-	-	-	-	-
Seaweed	449/1184	1.0 (0.6-1.5)	0.4 (0.1-1.3)	0.5 (0.2-1.5)	0.8 (0.2-2.5)	1.2 (0.3-4.3)
Green tea	358/1273	1.0 (0.6-1.6)	0.7 (0.2-2.9)	0.7 (0.2-1.9)	1.2 (0.3-4.4)	0.5 (0.2-1.6)
Black tea	1506/124	1.0 (0.4-2.4)	2.1 (0.3-17.5)	3.8 (1.1-13.6)*	-	-
Cola	1521/106	0.9 (0.3-2.4)	2.4 (0.3-19.8)	-	2.2 (0.3-17.8)	-
Coffee	992/641	0.6 (0.4-1.1)	2.1 (0.5-8.0)	0.3 (0.1-1.4)	0.7 (0.2-2.8)	0.2 (0.0-1.8)
carbonated drink/Juice	1126/502	1.5 (0.9-2.3)	1.8 (0.5-6.6)	3.9 (1.4-11.1)*	0.8 (0.2-3.0)	0.2 (0.0-1.8)
Japanese pickle	116/1518	1.6 (0.6-3.9)	-	-	-	0.5 (0.1-2.6)
Potato	238/1394	1.3 (0.7-2.5)	0.7 (0.2-3.5)	0.6 (0.2-2.3)	-	1.8 (0.2-14.4)
Sweat confectionary	523/1111	1.4 (0.9-2.2)	0.6 (0.2-2.2)	2.3 (0.6-8.3)	1.0 (0.3-3.0)	2.2 (0.6-8.0)
Salty confectionary	876/755	1.1 (0.7-1.7)	0.6 (0.2-2.2)	3.5 (1.1-10.9)*	0.6 (0.2-1.8)	1.1 (0.4-3.4)
Mushroom	985/648	1.18 (0.8-1.8)	1.1 (0.3-4.0)	1.0 (0.4-2.8)	1.3 (0.4-3.8)	2.4 (0.8-7.5)
Bread	1134/497	0.9 (0.5-1.5)	0.3 (0.0-2.5)	2.4 (0.9-6.5)	-	1.9 (0.6-5.9)
Instant noodle	1460/172	0.6 (0.2-1.4)	-	1.5 (0.3-6.4)	0.8 (0.1-6.2)	-
Noodle	869/764	1.2 (0.8-1.8)	1.8 (0.5-6.3)	3.0 (1.0-9.4)	0.9 (0.3-2.7)	1.3 (0.4-3.8)

[a]Reference group = took never + took several times per year + took several times per month.
Comparison group = took several times per week+ took everyday.
"-" : Not estimated due to 0 case in either of the two group; * P<0.05

chicken), chicken, and mushroom showed elevated risk for pancreatic cancer though none of the dietary factors associated significantly. From Table 2 and 3 it can be concluded that the level of protectiveness or risk level of dietary factors varied by sex. Some factors which showed some protectiveness in men failed to show their protectiveness in women and vice versa. Black tea may be an example in this regard.

Discussion

To our knowledge, this was the first cohort study in Hokkaido which aimed to study the association of leading cancers with several food items commonly consumed by the Japanese. Hokkaido differs from most other parts of Japan because of its cold climate. It is also believed that people of Hokkaido consume more fat such as meat, liver, ham, sausage, cheese, milk, and other dairy products than the people of other parts. But none of the fatty foods analyzed by our study was significantly associated with cancer. The smoking rate is also at the highest level in Hokkaido for both-sexes as compared to other parts of Japan, though smoking was found as risk factor only for men. Although our study examined 26 to 37 dietary factors to find their relationships with lung, stomach, colorectal and pancreatic cancers, only six factors (2 factors in men and 4 factors in women) showed significant association with either stomach or colorectal cancers. Surprisingly lung and pancreatic cancers failed to show any significant association with any of the dietary factors. Among the six significant factors, four factors were significantly associated with stomach cancer, of which were miso soup was protective for men and black tea, carbonated drink/juice, and salty confectionary were risk factors for women. For colorectal cancer, two significant factors were Japanese pickles (protective factor) for men and wild edible plants (risk factor) for women. None of six factors significantly associated with both stomach and colorectal cancers. Though boiled fish showed significant association for all-cancers, this significance level disappeared for any of the four specific cancers.

Though our study failed to show any significant association of dietary factors with lung cancer, Takezaki et al (2001a) found many significant factors for squamous cell and small cell carcinomas in Japan, of which some of them were risk factors and some of them were protective factors. For men, the identified risk factors were carrot, pumpkin, egg, miso soup, and coffee, whereas the protective factors included fruits, green vegetables, pickled vegetables, and cooked/raw fish. For women, dried/salty fish was found as risk factor and green tea was found as protective factor. Similarly some risk as well as protective factors were identified by other studies (Darby et al, 2001; Ozasa et al, 2001; Ohno et al, 1995). However the studies (Takezaki et al, 2001a; Ozasa et al, 2001) including the present one showed dietary variation in relation to lung cancer between men and women. Sometimes one dietary factor which showed protectiveness for men lung cancer may act as risk factor for women lung cancer. Ham & sausages may be an example in this regard (Ozasa et al, 2001).

Several studies (Masaki et al, 2003; Hoshiyama et al, 2002; Kobayashi et al, 2002; Nagata et al, 2002; Ngoan et al, 2002; McCullough et al, 2001; Galanis et al, 1998; Gao et al, 1999; Ward and Lopez-Carrillo, 1999; Ji et al, 1998; Hoshiyama and Sasaba, 1992; Kato et al, 1992; Tajima and Tominaga, 1985) identified many dietary factors such as fresh fruits, vegetables (yellow, green, white and pickled), eggs, meat, soybean products, beans, green tea, salted foods, seaweed, liver, and so on, which revealed significant association with stomach cancer. Though most of the dietary items were investigated by our study, only four factors were significant for stomach cancer. One significant factor was miso soup which revealed the protectiveness against stomach cancer in men. Hirayama (1987) also found the significantly protective effect of miso soup in a large-scale cohort study. However, our finding did not support the findings of some previous studies (Ngoan et al, 2002; Galanis et al, 1998; Hoshiyama and Sasaba, 1992; Kato et al, 1992; Tajima and Tominaga, 1985). The cohort study of Ngoan et al (2002) found even higher risk of stomach cancer in men, though the association was insignificant. Similarly cohort studies of Galanis et al (1998) and Kato et al (1992) and a case-control study of Tajima and Tominaga (1985) did not find any significant relationship between stomach cancer deaths and miso soup. The case-control study of Hoshiyama and Sasaba (1992) found significantly higher risk for stomach cancer due to miso soup consumption and they argued that an excess use of salt in miso soup may be risky. Since we could not estimate the RR for women, it is not possible to compare our results with other studies. However, the finding of decreased stomach cancer death due to miso soup consumption should be validated by further studies.

The significant relationship between salty confectionary and stomach cancer (RR=3.5, 95%CI=1.1-10.9) by our study was also partially supported by the findings of other studies (Takezaki et al, 2001; Ward and Lopez-Carrillo, 1999; Ji et al, 1998; Lee et al, 1995; Tsugane et al, 1994; Tajima and Tominaga, 1985). Consumption of salted snakes/crackers in Mexico (Ward and Lopez-Carrillo, 1999), salted food, fish, and salted meat in China (Takezaki et al, 2001b; Ji et al, 1998), and salted side-dishes in Korea (Lee et al, 1995) significantly elevated the risk of stomach cancer deaths. These studies revealed that salty foods act as risk factors not only in Japan but other countries also. Sugimura (2000), Tsugane et al (1994) and Mirvish (1983) explained the possible mechanisms of elevated risk of stomach cancer due to the consumption of salty foods. According to Mirvish (1983) high salt concentration is likely to be a promoting factor for stomach (gastric) cancer induction and might also facilitate carcinogen absorption by the stomach. It is also possible that salt usage mainly reflects the intake of salted fish and meat products which contain nitrosamide precursors. These precursors are correlated primarily with gastric cancer. Sugimura (2000) in his review reported that high doses of salt disrupt the mucin layer covering and protecting gastric

epithelium and further damage epithelial cells by generation of high osmotic pressure. This is in turn stimulates proliferation of stem cells of gastric epithelium providing favorable conditions for mutation occurrence. Prolonged damage results in chronic atrophic gastritis and intestinal metaplasia, both of which are understood to precursor lesions of intestinal type gastric cancer.

Our study identified black tea as a significant risk factor for women stomach cancer. It is difficult to explain why black tea consumption increased the risk of stomach cancer? Possibly black tea consumption is not directly related with stomach cancer but the lifestyles (not studied here) associated with it may increase the risk of stomach cancer in women. Surprisingly the RR was less than unity for men. The prospective study of Galanis et al (1998) and case-control study of Tajima and Tominaga (1985) did not find any significant association between black tea consumption and stomach cancer in Japan. A prospective study in Netherlands also failed to show any significant association between tea and stomach cancer (Goldbohm et al, 1996). The variations by studies and gender have caused difficulties to draw any conclusion regarding tea consumption and cancer. Perhaps for these reasons in a review Yang and Wang (1993) concluded that no-clear cut conclusion could be drawn about the relationship between tea consumption and human cancer. They argued that the effect of black tea consumption on cancer is likely to depend on the causative factors of the specific cancer and therefore a protective effect observed on a certain cancer with a specific population may not be observable with a cancer of different etiology.

Frequent consumption of carbonated drink/juice significantly increased the risk of stomach cancer among women but not for men. The finding is unique to our study. The possible factors to be considered are still unknown, but it may be possible that the chemical agents which, is used for coloring the carbonated drink/juice may contain some carcinogenic elements. It may also be possible that people who drink carbonated drink/juice tend to get fatty and thus may have some cholesterol problems. Anyway further studies are required to validate our finding.

When we further included salty confectionary, carbonated drink/juice, and black tea simultaneously in the Cox model with all adjusted factors for women (not shown in result), the significant associations with stomach cancer disappeared for salty confectionary (RR=2.9, 95%CI=0.9-9.2, P=0.072) and black tea (RR=3.0, 95%CI=0.8-11.2, P=0.095) except carbonated drink/juice (RR=3.1, 95%CI=1.1-8.9, P=0.033).

The Japanese have long used the young buds and seeds of a variety of native wild plants (such as bracken fern, butterbur) as human foods or folk medicines (herbal remedy). Though the nature of carcinogen contained in bracken fern has long been uncertain, the review of Hirono (1993) indicated that some of the wild plants are carcinogenic to experimental animals. In our study consumption of wild plants significantly increased the risk of colorectal cancer for women but not for men. However, slightly elevated risk was observed in men. Hirono (1993) in his review mentioned some of the possible carcinogens contained in these plants. These are pyrrolizidine alkaloids, petasitenine, senkirkine, and symphytine. Because of their existence in the wild plants, the author emphasized to avoid the use of plants either as foods or medicines. The author argued that that most of the human cancers are induced by environmental causes and the possibility of cancer development by a certain carcinogen is increased when modifiers, such as the habitual use of a specific food or medicine provide favorable conditions for that development.

The consumption of Japanese pickles, which contain many kinds of vegetables, significantly decreased the risk of colorectal cancer is another finding of our study which needs further investigations, because it contradicts with the results of other studies (Kono et al, 1993; Tajima and Tominaga, 1985). Tajima and Tominaga (1985) identified pickled hakusai (vegetables) as a significant risk factor for rectum cancer though it was insignificant for colon cancer. However, other pickles except pickled hakusai was insignificant for both colon and rectum cancer. According to Takahashi et al (1979), Japanese pickles contained materials except carrots that are mutagenic to Salmonella.

As there was no significant association of dietary factors with pancreatic cancer, it can be said that dietary factors are not so important for pancreatic cancer like stomach cancer. However, further studies are needed to examine the association between dietary factors and pancreatic cancer. It deserves further investigations as pancreatic cancer is increasing in Japan.

A major limitation of the study was the small number of cases, particularly among the women. This may limit the statistical power in some of the exposure categories. Though we compared the results of the study with the results of other studies, these may not be directly comparable because of variations in study samples (small to large), study type and adjusting factors. This study was also limited by the dietary intake information. Therefore the results for many of the dietary items should be interpreted with cautions. Another limitation was not to consider the Helicobacter Pylori infection in our study, which is very common in Japan and regarded as one of the main causes of stomach cancer mortality. It was also significantly associated with salty foods such as miso soup and pickled vegetables (Tsugane et al, 1994).

Although there were some limitations, this study leads us to conclude that the associations of dietary factors with different cancers are always inconsistent, which may differ by place to place and study to study and therefore it may be wise to confine the results of the study only in the respective study area. Some dietary factors may adversely affect the stomach cancer in women as compared to men. Lung cancer and pancreatic cancer may be less affected by dietary factors than stomach and colorectal cancers. Some factors which may show some protectiveness for some of the specific cancers in men, may act as risk factors or act normally in case of women. So analysis by sex may be more informative

than the combined analysis for both-sexes. Our study also indicated that even in the same sex, one factor may show protectiveness for some of the specific cancers but for others it may act as a risk factor or as normal factor. Because of these variations, analysis for total cancer may not be so much meaningful in Japanese context. However, further epidemiological research with more study subjects (to increase the power) and confounding factors may be useful in Hokkaido to assess the consistency of the associations between dietary factors and different cancers by sites.

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