
REVIEW

A Model of Practical Cancer Prevention for Out-patients Visiting a Hospital: the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC)

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Abstract

To promote a cancer prevention program at hospital, we started the hospital-based epidemiologic research program at Aichi Cancer Center (HERPACC) in 1988. Because patients visiting hospitals are very concerned not only about their own health condition but also practical way of disease prevention, we consider outpatients, especially those free of cancer, as ideal targets to make a model program and a practical cancer prevention strategy for general people. To confirm risk and protective effects of lifestyle factors like dietary habits, smoking and drinking, and exercise on cancer in Japanese, we have been undertaking large-scale case-referent comparative studies of main cancer sites (stomach, colorectal, lung, breast and uterine cancers) using the data generated by HERPACC. The risk of respiratory tract cancer was definitely elevated by habitual smoking and that of upper digestive tract cancer by combined habitual smoking and drinking. Frequent intake of raw vegetables and/or fruit in contrast reduced the risk of lung cancer among smokers. Current obesity was positively associated with risk of post-menopausal breast cancer, recently on the increase in Japan. However, all sites of cancer were linearly decreased with frequency of exercise in both males and females. Based on these pieces of evidence and other main results obtained from the HERPACC studies, prevention trials with provision of information about protective and risk factors for main sites of cancers to outpatients have been planned in parallel to continuation of HERPACC.

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Introduction

As worldwide prominent epidemiologists have emphasized (Wynder et al, 1977; Doll et al, 1981; Hirayama, 1990), cancer in adults is one of the lifestyle-related diseases whose risk can be reduced by improvement of our daily lifestyle. If there are specific habits in our lifestyles positively or negatively associated with a targeted cancer, individuals might be usefully divided into three groups by exposure level (and/or genetic susceptibility): high risk (sensitive), low risk (resistant) and average (Fig. 1) (Tajima et al, 1996). For example,

onset age of tobacco-related diseases like lung cancer, in current smokers, among the highest risk group, is relatively young as compared with that in non-smokers, as well as average and/or low risk groups. Individuals in the highest risk group can drop to a lower one after quitting smoking, based on theory with regard to lung cancer prevention.

After World War II, especially in 1955-75, the general dietary condition of Japanese became richer than expected, but unfortunately, most people thereby were exposed to unbalanced over-nutrition conditions with modern daily life. As a result of the massive changes to the Japanese life style, the mortality rates of so-called fat associated

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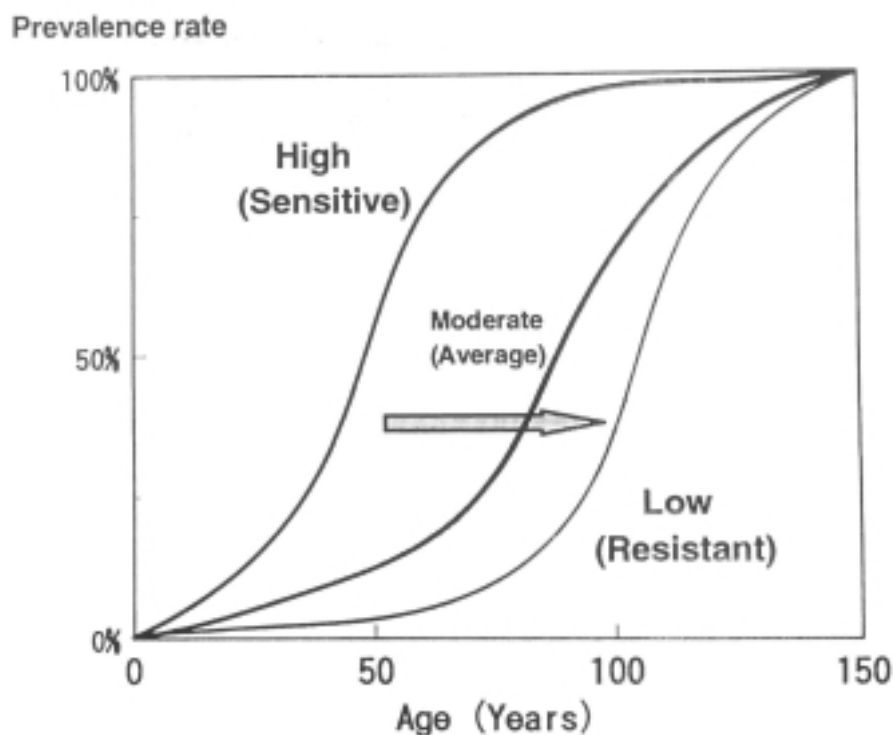


Figure 1. Correlation between exposure level (high, moderate and low) to a risk factor and the age-dependent risk level for related cancer based on hypothetical figures

cancers have exhibited a markedly increasing trend during the last 30 years (Kuroishi et al, 1999). Furthermore, most Japanese engage in little physical activity due to convenient motorized transportation and their sedentary occupations. Recently much epidemiological evidence has been presented that physical activity, including not only leisure sport but also occupational activity, reduces the risk of fat associated cancers, good examples being colon and breast adenocarcinomas (Lee et al, 1990; Thune et

al, 1997; Sesso et al, 1998).

Reacting to the rapid change over time in Japanese lifestyle, epidemiologists should provide information via the mass media that special lifestyle factors may reduce or increase risk of development of cancer in adults. Now many people are interested in a healthy lifestyle as a general prevention strategy for cancers throughout the world. To clarify the positive and negative relations of lifestyle parameters to site-specific cancer risk, we have

Table 1 Annual Number of First-visit Outpatients at Aichi Cancer Center Hospital (1988-1997)

Year	Male			Female		
	Cancer	Non-cancer	Total	Cancer	Non-cancer	Total
1988	493	1,731	2,224	720	4,720	5,440
1989	458	1,674	2,132	664	4,660	5,324
1990	460	1,755	2,215	611	4,822	5,433
1991	440	1,801	2,241	602	4,704	5,306
1992	446	1,558	2,004	563	4,042	4,605
1993	499	1,476	1,975	645	4,211	4,856
1994	497	1,464	1,961	588	3,621	4,209
1995	533	1,457	1,990	538	3,014	3,552
1996	534	1,427	1,961	540	3,253	3,793
1997	575	1,468	2,043	575	3,046	3,621
Total	4,935	15,811	20,746	6,046	40,093	46,139

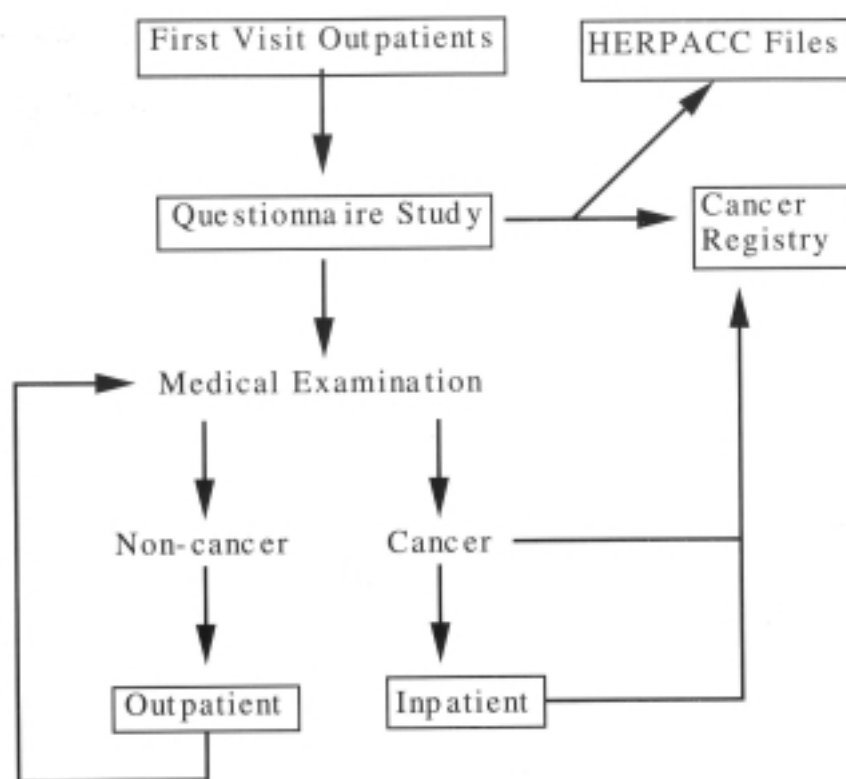


Figure 2. Flow chart of systematic data collection in the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC)

undertaken large-scale case-referent comparative studies for main sites of cancer with the use of data from the hospital-based epidemiologic research program at Aichi Cancer Center (HERPACC), Japan. We have already assessed the risk impact of general dietary habits, habitual smoking and drinking, beverage habits and regular physical exercise for health.

In the present report, we review risk and protective factors for main site of cancers obtained from the HERPACC studies and recommend a model program and practical cancer prevention strategy for patients at cancer hospitals.

Data Collection and Analysis

Since 1988, we have conducted HERPACC studies comprising a self-administered questionnaire completed by all the first visit outpatients to the Aichi Cancer Center Hospital (ACCH). All questionnaires were collected after checking by a trained interviewer for incomplete responses. The data were processed using the computer system of the Aichi Cancer Center Research Institute (ACCRI). The questionnaire included items on occupation, smoking and drinking habits, dietary habits, sleeping habits, and physical exercise. Further details of this questionnaire study can be obtained from a previous

paper (Inoue et al, 1996).

Of all the first-visit outpatients, totaling 74,280 between January 1988 and December 1997, 6,422 patients (8.6%) were excluded due to interviewer absence or a visit only for consultation. The questionnaire was finally administered to 67,885 patients and 66,893 (98.6%) returned adequate responses (Table 1). The data collected were linked with hospital-based cancer registry files as a master file of the HERPACC study (Fig 2). Our final analysis was based on data from 10,981 cancer patients (16.4% with 4,935 men and 4,093 women) first diagnosed within 6 months after first visit as having cancer by histological examination and 55,904 cancer free referents (15,811 men and 40,093 women).

For statistical analysis, logistic regression was used to obtain odds ratios (ORs) and 95% confidence intervals (95% CI) as estimates of relative risk. Eligible referents were not matched, because our previous study showed that a large number based on outpatients gave a steadier estimate than matched (Hamajima et al, 1994). To clarify independent risk factors for each site of cancer, we carried out multivariate analyses using a model including main factors: age at first hospital-visit, habitual smoking and drinking, beverage and dietary intake and body mass index (BMI). All calculations were performed using SAS (SAS Institute) LOGISTIC procedures.

Features of Lifestyles in General Patients

There is great variation between men and women in smoking and drinking habits in Japan, both being much higher in men (Table 2 and Figure 3). Most dietary items in fact also showed a significant difference in the proportional distribution between men and women (Inoue et al, 1997). The proportion was higher in men than in women for the traditional Japanese foods, rice and fish, but not for vegetables and fruit. In both sexes, considerable discrepancy was apparent with the age group. Direction of the trend with age did not appreciably differ between the sexes for most dietary items. To evaluate the methodological issues in using first-visit outpatients as referents in epidemiological studies, the features of general lifestyles of non-cancer outpatients at ACCH were

compared with those of the general population. Differences in the features of selected aspects of lifestyle between non-cancer outpatients and general population after adjustment for sex and age were very small. Therefore, it was concluded that it is feasible to use non-cancer outpatients as referents in large-scale hospital-based epidemiologic studies.

Protective and Risk Factors for Main Cancer Sites

1) Stomach cancer

Gastric cancer incidence and mortality have markedly decreased in Japan over the last 50 years (Kuroishi et al, 1999). However, they still rank among the highest in the

Table 2 Proportional frequency (percent) of first-visit outpatients# by habitual smoking, alcohol drinking, other beverage consumption, and dietary intakes by age group (From Inoue et. al., 1997)

Males								
Variable(category)	<30	30-39	40-49	50-59	60-69	>69	Trend	
habitual smoking								
(current smoker)	56.8	57.0	52.6	44.0	39.1	24.8	-	*
(ex-smoker)	9.8	18.2	26.8	30.0	45.0	57.0	+	*
(never-smoker)	33.5	24.8	20.6	26.0	15.9	18.2	-	*
habitual alcohol drinking								
(current drinker)	59.1	73.5	73.8	68.2	60.4	43.8	-	*
(ex-drinker)	4.7	3.4	3.7	4.5	7.6	12.0	+	*
(never-drinker)	36.2	23.1	22.5	27.3	32.0	44.2	+	
beverages								
green tea (every day)	56.4	72.3	80.4	85.0	84.7	85.6	+	*
coffee (every day)	60.7	76.7	76.7	61.1	50.1	44.4	-	*
black tea (every day)	12.5	6.8	7.5	4.2	5.6	3.5	-	*
dietary items								
type of breakfast (rice)	50.3	44.7	50.4	63.2	61.6	61.6	+	*
soybean paste soup (every day)	53.0	55.8	65.6	70.8	68.3	68.5	+	*
bean curd (>2times/wk)	23.0	24.3	33.7	40.6	49.0	51.8	+	*
pickled vegetables (>2times/wk)	4.7	7.8	12.5	17.7	22.5	26.5	+	*
fresh vegetables (every day)	27.8	30.7	32.3	37.0	47.1	54.9	+	*
fruit (every day)	13.2	15.1	21.3	30.2	43.8	55.3	+	*
green vegetables (>2times/wk)	27.7	31.1	35.1	38.7	45.8	49.0	+	*
milk (>2times/wk)	30.1	34.5	32.5	38.9	46.9	60.4	+	*
eggs (>2times/wk)	67.6	66.2	59.1	61.6	64.1	66.2		
dried/salted fish (>2times/wk)	3.7	6.8	8.0	12.8	13.9	17.1	+	*
cooked/raw fish (>2times/wk)	9.1	17.6	25.8	39.8	33.9	42.6	+	*
chicken (>2times/wk)	25.3	16.3	12.1	14.1	17.8	23.4		
beef (>2times/week)	24.0	14.6	10.3	9.0	8.0	8.6	-	*
pork (>2times/week)	30.1	14.8	10.7	8.6	7.7	6.3	-	*

#: Between January 1991 and December 1992, Aichi Cancer Center Hospital. *: p<0.001

Table 2 (continued)

Females								
Variable(category)	<30	30-39	40-49	50-59	60-69	>69	Trend	
habitual smoking								
(current smoker)	19.3	19.2	12.5	8.4	6.0	7.5	-	*
(ex-smoker)	6.1	7.3	3.0	3.2	5.1	3.5	+	*
(never-smoker)	74.6	73.5	84.6	88.4	88.9	89.0	-	*
habitual alcohol drinking								
(current drinker)	37.4	35.8	31.8	23.6	14.8	8.5	-	*
(ex-drinker)	1.9	1.1	1.2	1.6	1.7	1.6	+	*
(never-drinker)	60.7	63.2	67.0	74.7	83.5	90.0	+	
beverages								
green tea (every day)	65.2	73.8	81.3	84.8	87.3	82.0	+	*
coffee (every day)	50.1	69.2	67.6	50.7	36.3	23.1	-	*
black tea (every day)	14.3	9.1	7.3	6.2	5.2	4.2	-	*
dietary items								
type of breakfast (rice)	31.6	29.7	42.6	53.8	54.7	58.8	+	*
soybean paste soup (every day)	41.4	56.6	59.0	62.0	59.9	60.1	+	*
bean curd (>2times/wk)	23.5	44.2	44.7	51.4	53.0	50.0	+	*
pickled vegetables (>2times/wk)	5.1	8.0	11.0	18.1	24.1	23.2	+	*
fresh vegetables (every day)	28.3	37.4	40.2	42.6	46.1	44.6	+	*
fruit (every day)	22.9	33.9	44.4	54.8	61.7	65.3	+	*
green vegetables (>2times/wk)	41.5	52.5	56.3	60.7	59.2	61.6	+	*
milk (>2times/wk)	39.0	47.0	43.2	51.6	54.3	59.5	+	*
eggs (>2times/wk)	68.7	74.8	72.3	65.5	61.8	64.9	-	*
dried/salted fish (>2times/wk)	3.5	5.2	7.4	12.4	11.9	11.9	+	*
cooked/raw fish (>2times/wk)	13.0	22.4	27.4	37.2	38.7	41.3	+	*
chicken (>2times/wk)	20.3	18.1	20.7	22.3	24.1	24.2	+	
beef (>2times/week)	13.3	10.6	11.3	10.0	8.9	7.0	-	*
pork (>2times/week)	17.3	19.3	20.6	13.6	9.5	9.2	-	*

#: Between January 1991 and December 1992, Aichi Cancer Center Hospital. *: p<0.001

world. It is supposed that the declining trend of gastric cancer not only in Japan but also other Asian countries has been caused by marked changes in the manner of general lifestyle accompanying introduction of refrigerators for fresh food reservation (Tominaga, 1987). Another factor possibly related to the recent decrease in gastric cancer incidence might be reduction in risk of helicobacter pylori infection in highly epidemic countries.

From the HERPACC study (Inoue et al, 1994), habitual smoking is associated with increased risk of gastric cancer in men (OR=2.6), being more prominent in the cardiac site (OR=4.4), especially in those who are drinkers (OR=4.7) (Table 3). With regard to histological type of gastric cancer, habitual smoking is more likely to be associated with differentiated adenocarcinoma development (Inoue et al, 1999). A Western-style breakfast decreases the risk of antrum site gastric cancer, while consumption of greasy food increases the risk of cardiac site tumors.

Fresh vegetables decrease the risk of both sub-sites of gastric cancer.

Independent of the gender, a positive family history of gastric cancer was found to be associated with a moderate increase in risk of gastric cancer (OR=1.5), while no link was observed with a family history of cancer other sites (Inoue et al, 1998). Furthermore, investigation of combined effects of gastric cancer family history (GCFH) and other factors like smoking habit and raw vegetables showed habitual smoking interacted in a synergistic fashion regarding risk of cardiac site gastric cancer in males (OR=15.9), while frequent intake of fresh vegetables decreased risk of antrum site gastric cancer in both sexes (OR=0.43) (Huang et al, 1999).

2) Colorectal cancer

Colorectal cancer is less common in Japan than in West

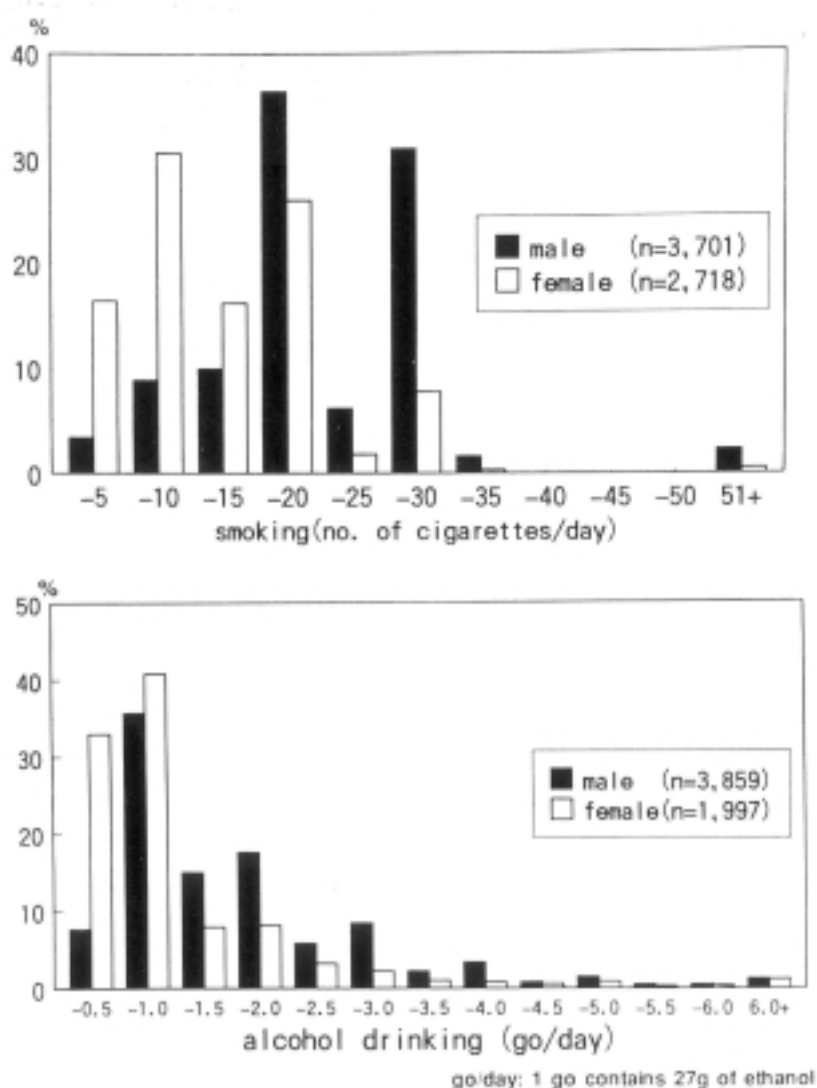


Figure 3. Distribution of daily consumption of cigarettes (number of cigarettes per day) among current smokers and alcohol intake (go/day: 1 go contains 27g of ethanol) among current drinkers

Table 3 Combined effects of habitual smoking and drinking on each subsite of gastric cancer in males. (From Inoue et. al., 1994).

Type of habit ¹	Subsite				
	% exposed subjects among controls	Total ² (n=420) OR (95% CI) ³	Cardia (n=79) OR (95% CI)	Middle (n=133) OR (95% CI)	Antrum (n=170) OR (95% CI)
Smoke(-) and Drink(-)	8.8	1.00	1.00	1.00	1.00
Smoke(-) and Drink(+)	14.3	0.54 (0.26-1.12)	0.85 (0.13-5.48)	0.44 (0.16-1.21)	0.67 (0.22-1.99)
Smoke(+) and Drink(-)	24.8	1.50 (0.83-2.70)	3.05 (0.67-13.9)	0.74 (0.33-1.67)	2.19 (0.94-5.11)
Smoke(+) and Drink(+)	52.1	1.97* (1.14-3.42)	4.70*(1.10-20.2)	1.28 (0.62-2.63)	2.32*(1.03-5.21)

¹Smoke(+): Current smoker or Ex-smoker; Smoke(-): Non-smoker, Drink(+): Current drinker or Ex-drinker; Drink(-): Non-drinker. ²Subsite in 38 cases could not be determined because of multiple, diffuse, or advanced disease. ³OR: odds ratio, 95% CI: 95% * Statistically significant (p<0.05)

Table 4 Summary table of risk trend of dietary habits for colorectal cancer by subsite. (From Inoue et al., 1995).

	Subsite					
	Proximal colon		Distal colon		Rectum	
	Female	Male	Female	Male	Female	Male
Western-style breakfast	+	NC	+	+	-	NC
Japanese-style foods	NC	NC	-	?	+	NC
Fruit	NC	NC	-	+	NC	-
Vegetables	NC	?	NC	+	NC	NC
Meat	+	?	NC	NC	NC	-

+, increase; NC, no change; - decrease; ?, undetermined. Bold symbols indicate statistical significance.

ern countries, but it has been increasing in recent years (Parkin et al, 1997). This trend has been observed most markedly for distal lesions. With regard to this subsite-specificity; the drastic increment of average intake of total fat per capita among Japanese, especially in 1955-1977, has been positively correlated with the increase in distal colon cancer, rather than proximal colon cancer (Tajima et al, 1985b). Differences in the etiology of colorectal cancer by sub-site have been reviewed in one previous study, which suggested that environmental factors were related more strongly to distal colon cancer and host-specific factors to proximal colon cancer (McMichal et al, 1985). On the other hand, risk factors for rectal cancer were different from those for colon cancer, having similarities with the gastric cancer case (Tajima et al, 1985a).

In a recent report of case-referent studies, risk trends for dietary habits relevant to colorectal cancer were presented in relation to the main dietary factors (Inoue et al, 1995). Habitual smoking increased the risk for rectal cancer in both sexes. Japanese-style foods decreased the risk for distal colon cancer but increased the risk for proximal colon cancer in women (Table 4). It was also suggested that irritable bowel habit (soft or loose feces) might be associated with distal colorectal cancer. With regard to the relation between reproductive factors and women's colon cancer, age at menarche and first full-term pregnancy were significantly higher for distal than for proximal colon cancer cases (Yoo et al, 1999). These evidences suggested that the risk factors for colorectal cancer differ by sub-site among the relatively low-risk Japanese population.

3) Lung cancer

It was well established that cigarette smoking is the major cause of lung cancer. A survey conducted by the World Health Organization on lung cancer found that 97% of the respondents agreed that at least 80% of all lung cancer cases were due to tobacco (Koo et al, 1990). It was estimated in Japan that 67% of lung cancer cases among men are attributable to cigarette smoking

(Tominaga, 1988). Hirayama emphasized three important parameters: 1) age of starting smoking; 2) number of cigarettes smoked per day; 3) period of smoking, which independently influence the risk for lung cancer (personal communication).

In the case-referent study based on HERPACC, the current smokers showed an increased risk of lung cancer (OR=6.61) which was dependent on the number of cigarettes smoked per day and declined markedly with later age of taking up the smoking habit (Gao et al, 1993). The ex-smokers showed a 3.56-fold increased risk of lung cancer and the ORs gradually decreased with years passed since cessation of smoking. On the other hand, the OR for lung cancer decreased to 0.41 and 0.56 with high amounts and frequency of fruit and raw vegetable intake among currently smoking men (Table 5). Especially lettuce and cabbage showed protective effects against lung cancer, the OR decreasing by a half. In general heavier smokers take less fruit and raw vegetables compared with nonsmokers so that their overall lifestyle predisposes to lung cancer.

4) Breast cancer

The incidence rates of breast cancer in most Asian countries are much lower than in Western countries, but it has been estimated that breast cancer will be the most common cancer among Japanese women by the year 2000 (Parkin et al, 1997; Kuroishi et al, 1999). The age distribution of breast cancer in Japanese women is entirely different from that in the United States, even though age-specific elevation of risk in pre-menopausal women is somewhat similar. Since the drop in the age-specific incidence curve for breast cancer follows behind the average age of menopause (around 50 years old), it was hypothesized that the etiologic factors for pre-menopausal breast cancer seem to be different from those for post-menopausal breast cancer.

Our large-scale case-referent study of risk factors for breast cancer revealed that the current body mass index (BMI: weight(G)/height(M)²) was positively associated

Table 5 Odds Ratios (ORs) for Lung Cancer According to Intake Frequency of Fruit, Raw and Green Vegetables by Smoking Status. (From Gao et al., 1993).

	Current smokers		Ex-smokers		Non-smokers	
	Case/Cont.	OR ^{a)} (95% CI)	Case/Cont.	OR ^{b)} (95% CI)	Case/Cont.	OR (95% CI)
Fruit						
>2 times/wk	98/42	1.00	33/33	1.00	4/15	1.00
3-4 times/wk	40/27	0.66(0.36-1.23)	24/20	1.25(0.58-2.67)	3/12	0.94(0.17-5.02)
Every day	42/46	0.41(0.24-0.72)	26/51	0.53(0.27-1.04)	5/29	0.65(0.15-2.77)
Raw vegetables						
>2 times /wk	83/39	1.00	27/27	1.00	2/13	1.00
3-4 times/wk	51/29	0.91(0.50-1.66)	18/29	0.90(0.38-2.17)	1/14	0.46(0.04-5.75)
Every day	47/47	0.56(0.32-0.99)	38/48	0.81(0.41-1.59)	10/29	2.24(0.43-11.71)
Green vegetables						
>2 times/wk	16/64	1.00	43/53	1.00	5/24	1.00
3-4 times/week	46/30	0.94(0.53-1.65)	30/27	1.35(0.70-2.63)	6/16	1.80(0.67-6.91)
Every day	17/21	0.48(0.23-1.00)	10/21	0.69(0.29-1.63)	1/16	0.30(0.03-2.81)

a) Adjusted by smoking index (daily number of cigarettes x smoking years)

b) Adjusted by period since quitting smoking

with post menopausal breast cancer (OR=2.08 for highest quintile vs. lowest), but did not affect the risk in pre-menopausal women (Hirose et al, 1995 and 1999). Estimates of risk were below unity for BMI at around age 20 in after stratifying BMI at around age 20, gaining BMI in later life was positively associated with increased risk, regardless of volumes in early life (Fig. 4). A protective effect of physical activity against breast cancer was observed among both pre- and post-menopausal women. Current smoking and drinking elevated the risk of breast cancer in the pre-menopausal period.

In a case-referent analysis of impact of family history on the risk of developing breast cancer (Hirose et al, 1997), risk of breast cancer was found to be greater when a sister(s) had breast cancer (OR=3.51) than when the mother had (OR=1.47). For women having a family member with ovarian cancer, the risk for breast cancer diagnosed under age 40 was extremely high (OR=5.04). These results suggested that a family history of breast cancer, especially among sisters, elevated the risk of developing breast cancer, especially among women with a high BMI.

5) Uterus cancer

The incidence rate of cervical cancer (CC) is around twice as high in Asian countries, including Japan, as in Europe or North America (Parkin et al, 1997). In contrast, the incidence rate ratio of endometrial cancer (EC) vs. CC in Asia is extremely low compared with that for Western countries (Figure 5). Recently in Japan the CC

incidence and mortality rates have been remarkably decreasing, mirroring gradual increase. Therefore there is considerable interest in differences in risk factors between CC and EC in Japan.

From the analysis of subsite-specific risk factors by case-referent study, habitual smoking and experience of pregnancy increased the risk of CC, while decreasing the risk of EC (Hirose et al, 1996). Greater BMI, daily intake of fruit and more frequent consumption of fish decreased the risk of CC, whereas predisposed to EC. We observed similar risk and protective factors for breast cancer (Table 6), but the effect of being overweight (BMI>25) was more prominent in the EC case (Hirose et al, 1999). Daily intake of milk decreased the risk of CC. The observed risk reduction in both CC and EC, as shown for breast cancer, by regular exercise and dietary control for health is noteworthy in terms of prevention strategy for the general population.

Prevention Strategy in a Cancer Hospital

There is now very little a question that a healthy lifestyle with well-regulated dietary habits, avoidance of cigarette smoking and regular exercise can reduce the risk of cancer. To evaluate variation in characteristic living patterns of our outpatients in ACCH and their relation to those of the public at large we systematically compared major factors and confirmed that these did not substantially differ (Inoue et al, 1997). While the optimal exercise level to prevent cancer has yet to be determined, our HERPACC study on

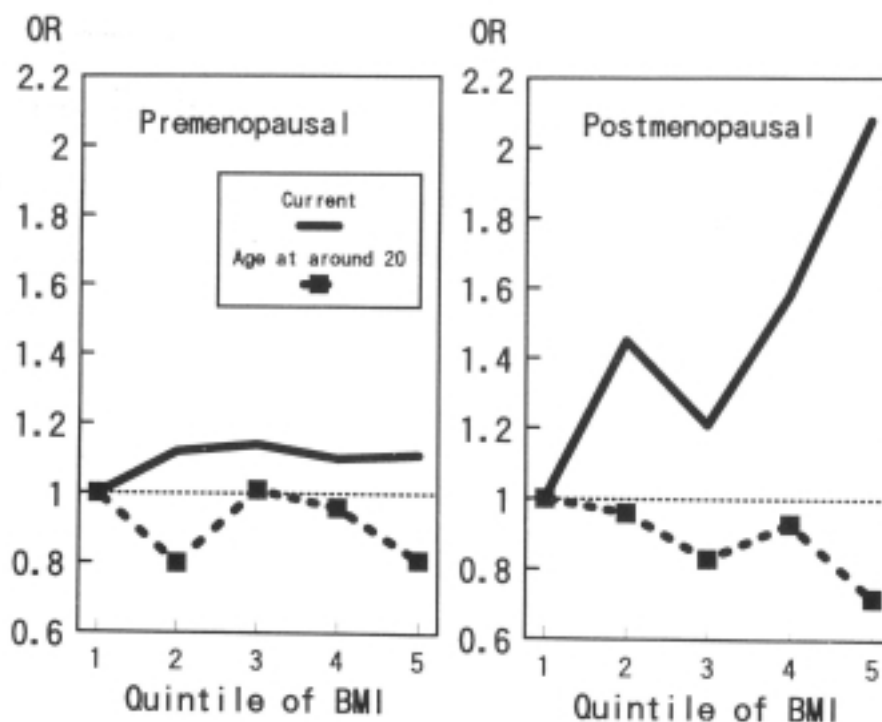


Figure 4. Age-adjusted odds ratios of pre- and postmenopausal breast cancer according to the level of body mass index.

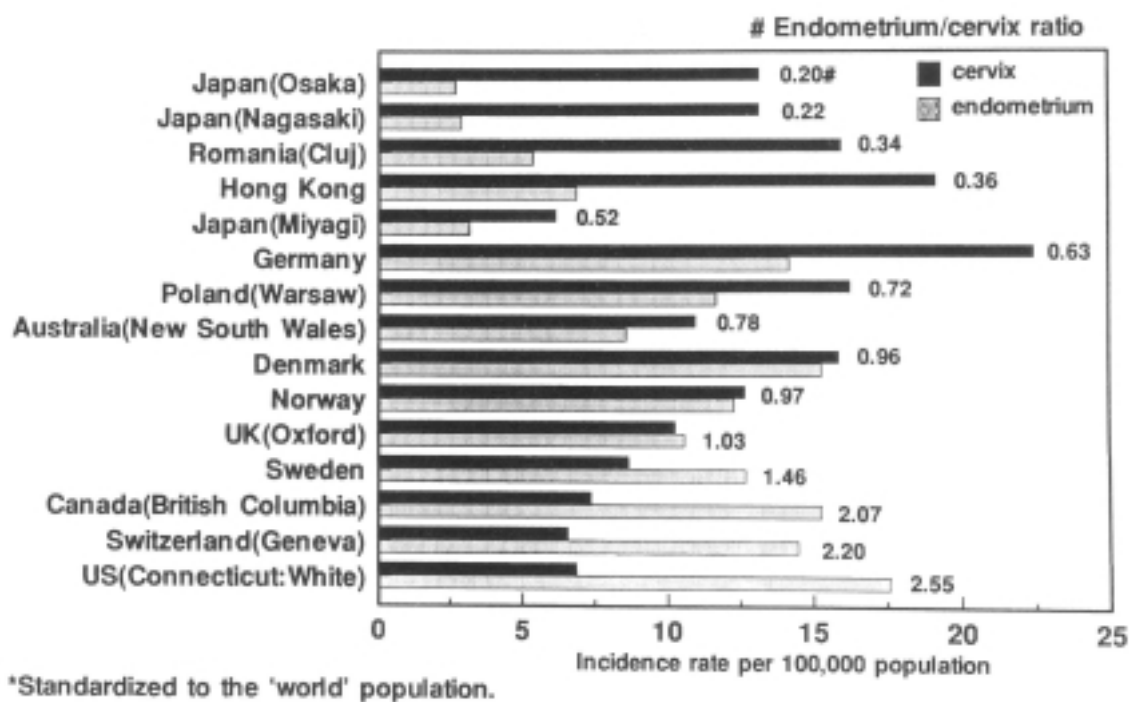


Figure 5. Age-adjusted incidence rates and ratios of cervical and endometrial cancers in 13 countries around the world (1983-1987).

Table 6 Summary of Reproductive and Anthropometric Factors for Three Cancers in Women. From Hirose et al., 1999.

Factor	Breast	Endometrium	Ovary
Marriage (no vs. yes)	++	+	-
Age at menarche (>14 vs. <13)	--		+
Age at menopause (>54 vs. >47)	+	+	+
Menstrual regularity at age 20-29yrs (regular vs. irregular)	--		
Delivery (>2 times vs. never)	--	--	-
Age at first full-term Pregnancy (>26 vs. <24)	++	+	
Breast feeding (>11 mo vs. never) ^{a)}	--	+	-
Height (>157 cm vs. <152cm)	++	+	
Weight (>54 kg vs. <50kg)	++	++	+
BMI			
Current (>24 vs. <21)	++	++	
at age 20 (>22 vs. <21)	--	-	-
Change of BMI after 20 yrs (0 vs. 0-2.5)	--		
Change of BMI after 20 yrs (>2.5 vs. 0-2.5)	++	++	+

^{a)} Among parous women. Å{- : OR>1.15, OR<0.85 Å{- : statistically significant (P<0.05).

exercise for health showed risk reduction for most main sites of cancer development (Figure 6) (Tajima et al, 1999). The important hypothetical mechanisms are that regular exercise activates natural killer cells, lowers insulin-related growth factors and restricts storage of carcinogens in fat tissue (McCarty et al, 1997; McTiernan et al, 1998; Tanaka et al, 1999). Though prospectively observed exposure data will no doubt become available for Japanese women in the future, case-referent studies also provide valuable evidence and in the present investigation clear evidence was obtained that the risk of main sites of cancer in Japanese is markedly decreased by being fit and healthy.

Now we are recommending the six fundamental rules of lifestyle for cancer prevention to all the first-visit outpatients in our hospital. The first, no smoking is absolutely recommended because cigarette smoking is the strongest risk factor for many sites of cancer, especially, those in the pharynx, larynx, lung and esophagus. The second, overindulgence in alcohol is harmful for health and more than 40-50mg a day is definitely detrimental in terms of esophageal, liver and colon cancer. The third, sufficient intake of green-yellow (G-Y) vegetables and

fruit everyday can reduce risk in all organ sites, because they contain abundant of vitamins and minerals which protect against carcinogenic agents. The fourth, restriction of animal fat intake appears very important for colon, breast and prostate cancers. The fifth, restriction of salt intake to less than 10g a day is recommended because stomach cancer in Japanese is highly associated with salty foods. Finally, regular exercise is strongly recommendable to prevent not only cancer but also other chronic diseases like cardio-vascular disease and diabetes mellitus.

On this basis, prevention trials at hospital are now planned for outpatients who are concerned about information on protective and risk factors for cancer. In general they are motivated to visit hospital to maintain their own health and improve their lifestyles. Actually an obesity control trial has already started for breast cancer prevention in women with a body mass index (BMI) over 25 and a tobacco control program with nicotine patch usage is also running for male smokers in the ACCH, parallel to continuation of the HERPACC studies in general.

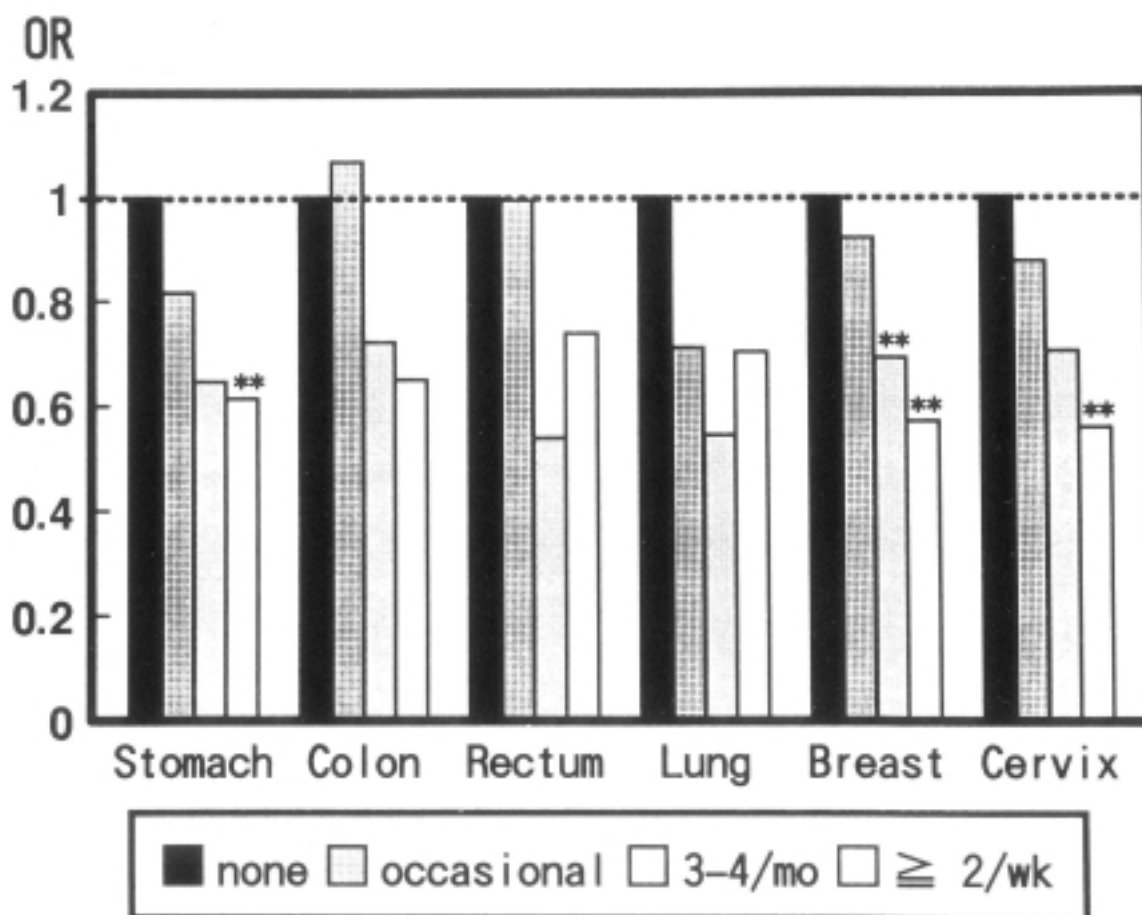


Figure 6. Trends in Odds ratios# for six main sites of cancer in categorical frequency groups of regular exercise (HERPACC study in 1988-1995, 40-69 year old females)

Adjusted by selected lifestyle factors corresponding with those in Table 2

*, **: Statistically significant ($p < 0.05$, $P < 0.01$)

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References

- Doll R, Peto R (1981). The causes of cancer, Oxford Medical Publication, Oxford, pp 1256-1260.
- Gao C-M, Tajima K, Kuroishi T, Hirose K, Inoue M (1993). Protective effects of raw vegetables and fruit against lung cancer among smokers and ex-smokers: A case-control study in the Tokai area of Japan. *Jpn J Cancer Res*, **84**, 594-600.
- Hamajima N, Hirose K, Inoue M, et al (1994). Case-control studies: matched controls or all available controls? *J Clin Epidemiol*, **47**, 971-5.
- Hirayama T (1990). Life-style and mortality: A large-scale census-based cohort study in Japan. Karger, Basel, pp 28-59.
- Hirose K, Tajima K, Hamajima N, et al (1995). A large-scaled, hospital-based case-control study of risk factors of breast cancer according to menopausal status. *Jpn J Cancer Res*, **86**, 146-154.
- Hirose K, Tajima K, Hamajima N, et al (1999). Comparative case-referent study of risk factors among hormone-related female cancers in Japan. *Jpn J Cancer Res*, **90**, 255-261.
- Hirose K, Tajima K, Hamajima N, et al (1997). Impact of family history on the risk of breast cancer among the Japanese. *Jpn J Cancer Res*, **88**, 1130-6.
- Hirose K, Tajima K, Hamajima N, et al (1996). Subsite(cervix/endometrium)-specific risk and protective factors in uterus cancer. *Jpn J Cancer Res*, **87**, 1001-9.
- Hirose K, Tajima K, Hamajima N, et al (1999). Effect of body size on breast-cancer risk among Japanese women. *Int J Cancer*, **80**, 349-355.

- Huang X-E, Tajima K, Hamajima N, et al (1999). Effect of life style on the risk of subsite-specific gastric cancer in those with and without family history. *J Epidemiol*, **9**, 40-45.
- Inoue M, Tajima K, Yamamura Y, et al (1999). Influence of habitual smoking on gastric cancer by histologic subtype. *Int J Cancer*, **81**, 39-43.
- Inoue M, Tajima K, Hirose K, et al (1997). Epidemiological features of first-visit outpatients in Japan: comparison with general population and variation by sex, age, and season. *J Clin Epidemiol*, **50**, 69-77.
- Inoue M, Tajima K, Hirose K, et al (1994). Life-style and subsite of gastric cancer - joint effect of smoking and drinking habits. *Int J Cancer*, **56**, 494-9.
- Inoue M, Tajima K, Hirose K, et al (1995). Subsite-specific risk factors for colorectal cancer: a hospital-based case-control study in Japan. *Cancer Causes Control*, **6**, 14-22.
- Inoue M, Tajima K, Kobayashi S, et al (1996). Protective factor against progression from atrophic gastritis to gastric cancer - Data from a cohort study in Japan. *Int J Cancer*, **66**, 309-314.
- Inoue M, Tajima K, Yamamura Y, et al (1998). Family history and subsite of gastric cancer: data from a case-referent study in Japan. *Int J Cancer*, **78**, 801-5.
- Koo L, Ho JHC (1990). Worldwide epidemiological pattern of lung cancer in non-smokers. *Int J Epidemiol*, **19**, s14-23.
- Kuroishi T, Nishikawa Y, Tominaga S, Aoki K (1999) Cancer mortality statistics in 33 countries (1953-1992). *Gann Monogr Cancer Res*, **47**, 153-217.
- Kuroiwa A and Yan H (1999), Moderate exercise: Is it effective for prevention of cancer? In Exercise for Preventing Common Diseases. Eds Tanaka H and Shindo M pp 98-108, Springer Verlag, Tokyo.
- Lee IM, Paffenbarger RS, Hsieh CC (1991). Physical activity and risk of developing colorectal cancer among college alumni. *J Natl Cancer Inst*, **83**, 1324-9.
- McMichael AJ, Potter JD (1985). Host-specific carcinogenesis: certain bile-acid metabolism profiles that selectively increase the risk of proximal colon cancer. *J Natl Cancer Inst*, **75**, 185-191.
- McTiernan A, Ulrich C, Slate S et al (1998). Physical activity and cancer etiology: association and mechanisms. *Cancer Causes Controls*, **9**, 487-509.
- Parkin DM, Whelan SL, Ferley J, Raymond L, Young J (1997). *Cancer Incidence in Five Continents, Vol 7*. Lyon, France, International Agency for Research of Cancer.
- Sesso HD, Paffenbarger RS, Lee IM (1998). Physical activity and breast cancer risk in the college alumni health study (United State). *Cancer Causes Control*, **9**, 433-9.
- Tajima K, Sonoda S (1996). Ethnoepidemiology, a new paradigm, for studying cancer risk factors and prevention strategy. *Gann Monogr Cancer Res*, **44**, 3-12.
- Tajima K, Hirose K, Nakagawa N, Kuroishi T, Tominaga S (1985). Urban-rural difference in the trend of colo-rectal cancer mortality with special reference to the subsites of colon cancer in Japan. *Jpn J Cancer Res*, **76**, 717-728.
- Tajima K, Hirose K, Inoue M, Takezaki T, Hamajima N (1999), Exercise and cancer prevention: Study from Hospital-based Epidemiologic research Program at Aichi Cancer Center (HERPACC). In Exercise for Preventing Common Diseases. Eds Tanaka H and Shindo M pp98-108, Springer Verlag, Tokyo.
- Tajima K, Tominaga S (1985). Dietary habits and gastro-intestinal cancers: a comparative case-control study of stomach and large intestinal cancers in Nagoya, Japan. *Jpn J Cancer Res*, **76**, 705-716.
- Thune I, Brenn T, Lund E, et al (1997). Physical activity and the risk of breast cancer. *N Engl J Med*, **336**, 1269-75.
- Tominaga S (1988). Smoking and cancer. *Asian Med J*, **31**, 209-215.
- Wynder EL, Gori GB (1977). Contribution of the environment to cancer incidence: An epidemiologic exercise. *J Natl Cancer Inst*, **58**, 825-832.
- Yoo K-Y, Tajima K, Inoue M, et al (1999). Reproductive factors related to the risk of colorectal cancer by subsite: A case-control analysis. *Br J Cancer*, **79**, 1901-6.

Personal profile: **Kazuo Tajima**

Kazuo Tajima was born in Hiroshima, Japan in 1947. After graduating Ohsaka University, Medical School, he trained orthopedics for a year in the University, general surgery for 5 years (1973-77) in the Serei Mikatabara Hospital in Hamamatsu and surgical pathology for 2 years (1977-79) in the Aichi Cancer Center Hospital in Nagoya. Since March 1979, he has committed to studies of cancer epidemiology as a research staff of Division of Epidemiology at the Aichi Cancer Center Research Institute. In 1985-86, he has also taken a course, Master of Public Health, at the Johns Hopkins University in Baltimore.

His main interests are large-scale hospital-based epidemiology for cancer prevention and ethnoepidemiological studies on main sites of cancers in the Pan Pacific areas. During the last 20 years, he has vigorously conducted international cooperative studies on HTLV-I and its related diseases in Asia and South America. He is also nominated as a treasurer of the Asian Pacific Federation of Organizations for Cancer Research and

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