RESEARCH COMMUNICATION

Lifestyle-Related Risk Factors for Stomach Cancer in Northeast Thailand

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Abstract

Background: Stomach cancer is not common in Thailand but the life styles of the Thai population are changing to become more Western so that information for planning control programme of stomach cancer is necessary. The highest incidence rates of this neoplasm are found in Eastern Asia, ranging from age-standardized rates of $95.5/10^5$ (men) and $40.1/10^5$ (women) in Yamagata, Japan to $4.1/10^5$ (men) and $2.1/10^5$ (women) in Khon Kaen, Northeast of Thailand. In Thailand, the estimated age-standardized incidence rates in 1993, 1996 were $4.9/10^5$, $4.1/10^5$ in men and $3.0/10^5$, $2.6/10^5$ in women. Risk factors for stomach cancer in Thai population are unclear, but possibly include low intake of vegetables and fruits, alcohol drinking, tobacco smoking and high intake of salt. Objective: To investigate various aspects of dietary factors, smoking, and alcohol drinking in determining risk of stomach cancer in Thai population. Methods: A case-control study was conducted in Khon Kaen, Thailand during 2002-2006, to study the role of these factors in stomach cancer. 101 stomach cancer cases and 202 matched controls (case : control = 1:2) by sex, age (± 3 years) and region were recruited from Srinagarind Hospital and Khon Kaen Regional Hospital, in Khon Kaen Province. All of cases were histologically confirmed. Controls had a variety of diseases, the main ones being disease of the eye. Information on dietary habits, alcohol drinking and smoking were collected by a structured questionnaire, blood samples were collected for further study. Results: The distribution of the general characteristics by case-control status, the distribution of age and sex were similar in cases and controls. In the final analysis, the factors that found to be higher risk but not statistically significant were long-term filter cigarette smoking (OR=1.9, 95%CI: 0.85-4.50), long-term alcohol consumption (OR=1.2, 95%CI: 0.51-2.60) and low intake of vegetables and fruits (OR=1.2, 95%CI: 0.74-1.96). A high intake of vegetable oil (OR=4.5, 95%CI: 1.00.-20.17) was found to be associated with increased risk, and similar tendencies were noted for pork oil (OR=1.4, 95%CI: 0.63-3.01) and jeaw prik (mainly chilly with plara broth) (OR=1.2, 95%CI: 0 .76- 2.01). Conclusion: Our study confirmed protective effects of a high intake of fruits and vegetables against stomach cancer development and showed a high intake of sauces to increase risk of stomach cancer as in other countries in Asia.

Key Words: Case-control - stomach cancer - risk factors - northeast Thailand

Asian Pacific J Cancer Prev, **9**, 71-75

Introduction

Stomach cancer is more common cancer in Thai men than Thai women. The life styles of Thai population are changing as Western styles; therefore it is necessary to find out the information for planning control programmed of stomach cancer. The estimated age-standardized incidence rate of stomach cancer in Thailand were 4.9 per 100,000 for males and 3.0 per 100,000 for females. Chiang Mai had the highest incidence rate were 7.9 per 100,000 and 5.2 per 100,000 both males and females followed by Lampang ASR. were 7.5 and 4.6 per 100,000 in males and females. The lowest rates are in Songkhla ASR. were 2.0 and 1.4 per 100,000 in males and females respectively (Sriplung et al., 2003). The highest incidence rates were found in Eastern Asia, ranging from age standardized rates of $95.5/10^5$ (men) and $40.1/10^5$ (women) in Yamagata, Japan to $4.1/10^5$ (men) and $2.1/10^5$ (women) in Khon Kaen, Northeast of Thailand (Parkin et al., 1997, Sriamporn et al., 2002, Suwanrungruang et al., 2006). In Thailand, the estimated age-standardized incidence rate in 1993/1996 was $4.9/10^5$, $4.1/10^5$ in men

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and $3.0/10^5$, $2.6/10^5$ in women (Deerasamee et al., 1999 ; Sriplung et al., 2003). Risk factors for stomach cancer in Thai population are unclear, but possibly including low intake of vegetables and fruits, alcohol drinking, tobacco smoking and high intake of salt.

The risk of developing cancer in several organs appears to be associated with a dietary factors that is low of fiber and high of calories, protein, fat, and history of family cancer (Huang et al.,1999; Huang et al., 2004). Risk factors for stomach cancer include low intake of vegetable, fruits, alcohol drinking, tobacco smoking and high intake of salt (WCRF, 1997).

As part of a multi-centre study of 'The epidemiological study of host and environmental factors for stomach and colorectal cancers in Southeast Asian Countries', we here examined possible determinants of stomach cancer in the population of Northeast Thailand as a hospital-based case-control study of patients who came to get treatment at Srinagarind Hospital and Khon Kaen Regional Hospital in Khon Kaen, Thailand.

Materials and Methods

Subjects

101 new stomach cancer cases and 202 controls were recruited from Srinagarind Hospital and Khon Kaen Regional Hospital in Khon Kaen Province, Thailand. All of cases were from Northeast. All of stomach cases were not specified sub site 67.33%, 15.84 % antrum, and 13.86% cardia respectively, all of cases were histological confirmed; the most common was adenocarcinoma 69.31%. Stomach cancer cases and controls were recruited in the same period and each case matched by sex, age (± 3 years) and regional. All subjects gave informed consent to their participation in the study. Controls had a variety of diseases, the main ones being disease of the eye. All subjects were interviewed by trained interviewer using a structured questionnaire, the questionnaire composed two sections; demographic socioeconomic status smoking history and food frequency structured by meals.

Table 1. The Distribution of General Characteristics of Stomach Cancer Cases and Controls

Characteristic	Cases (n = 101)	Controls (n = 202)
Sex, n (%)[a]		
Male	57 (56.44)	114 (56.44)
Female	44 (43.56)	88 (43.56)
Age group, n (%)[a]		
≤39	16 (15.84)	29 (14.36)
40-49	23 (22.77)	51 (25.25)
50-59	30 (29.70)	54 (26.73)
60-69	25 (24.75)	59 (29.21)
≥ 70	7 (6.93)	9 (4.46)
Median age y (range)[a]	53(28–70)	53(29–73)
BMI ≥ 25 k/m2, n (%)	3(3.03)	54 (26.73)
Education level, n (%)[a]		
≤ high school	77 (76.24)	171 (84.65)
> high school	24 (23.76)	31 (15.35)
Occupation activity, n (%)		
Heavy labour work	73 (73.00)	150 (74.26)
Moderate work (standing)	14 (14.00)	38 (18.81)
Light work (sitting)	13 (13.00)	14 (6.93)
Income (Baht)		
Median (range)	3000 (333-60000)	3000 (300-60000)

Statistical methods

The association between stomach cancer and some possible risk factors were measured by using odds ratio (OR) and 95% confidence intervals (95% CI) derived from conditional logistic regression to account for the match of cases and controls, all variables were categorized based on percentiles of the distribution in controls.

Body mass index (BMI) was computed as weight (kg) divided by the square of height (m2) which are categorized into two levels (< 25, normal weight and ≥ 25; non-normal; 25 to 29, overweight plus ≥ 30, obese)

Occupation activity is categorized into 3 levels as heavy labour work, moderate work and light work based on working types; heavy labour workers are persons who are labour worker in farms, garden and building constructor, etc. moderate workers are persons who are mostly work by standing or sitting but use power such as sale man, hair stylist, servant and policeman etc. and light workers are persons who are mostly work by sitting and management such as manager and clerk, etc.

Exercises are categorized into two levels (exercise and non-exercise). Exerciser is defined as those who play sports at least 3 times a week, others are non-exercisers Smoking analysis, there were categorized as smokers and nonsmokers Smokers included those who smoked filtered, unfiltered cigarettes and yamuan (a home-made cheroot). Duration of smoking, and average number of cigarettes per year were computed based on all smoking periods reported and dichotomized on the median of the controls. Average number of cigarette was calculated as annual cigarettes smoked (filtered and unfiltered) plus 1.5 times annual yamuan smoked. The 1.5 correction factor was used to allow for the longer size of yamuan compared with the regular cigarettes. The amount of cigarettes was categorized based on the 50th percentile of the controls and dichotomized into low and high levels.

Alcohol drinking, there were two categories for alcohol drinking: drinkers and nondrinkers. Drinkers, was defined as who have consumed at least one type of all alcoholic beverages (beer, sato, white alcohol, mekong and other whiskies) and consumed within range of ever day to once a month . Those who did not drink or have consumed all alcoholic beverages with frequently less than one time a month were categorized as nondrinkers.

Dietary intake within a previous year (vegetables, fruits, fish/shellfish: fresh/sea water, meat and fried meat), there were categorized two levels as low and high. Frequencies of each dietary intake, and an amount of intake per year were computed based on each type of dietary intakes reported and dichotomized on the median of controls.

Results

In this matched case-control study, the distributions of age, sex and residence were the same in cases and controls. There were 135 males and 118 females, median

Table 2. Smoking Habit and Alcohol Drinking (Males Only)

Type (frequency per yr)	Cases (n=101)	Controls (n=202)	OR_c (95% CI)	OR_{adj} (95% CI)
Smoking				
Duration and type of cigarette, n[c] (%)				
Nonsmokers	5 (8.8)	22 (19.3)	1.0	1.0
Filtered (>20 years)	19 (33.9)	30 (26.3)	1.4 (0.71-2.88)	1.5 (0.73-3.12)
Unfiltered (> 7 years)	1 (2.6)	1 (1.2)	2.3 (0.13-37.86)	1.7 (0.07-37.72)
Amount of cigarettes per yr,n[c] (%)				
Nonsmokers	5 (8.9)	22 (19.3)	1.0	1.0
Low (1-3650)	20 (35.7)	53 (46.5)	1.3 (0.46-3.77)	1.7 (0.54-5.48)
High (>3650)	31 (55.4)	39 (34.2)	2.7 (0.97-7.94)	3.4 (1.04-10.92)
			P for trend: 0.01	*P for trend: 0.01*
Type of cigarette, n[c] (%)				
Filtered	12 (92.3)	20 (95.2)	1.0	1.0
Unfiltered	1 (7.7)	1 (4.8)	1.7 (0.09-30.62)	1.2 (0.05-25.59)
Alcohol drinking, n[c] (%)				
Non drinker	22 (38.6)	53 (46.1)	1.0	1.0
Ever drinker	35 (61.4)	62 (53.9)	1.3 (0.69-2.55)	1.4 (0.68-2.66)
Duration				
Nondrinkers	22 (38.6)	53 (46.5)	1.0	1.0
Short (1-21 years)	17 (29.8)	31 (27.2)	1.3 (0.61-2.87)	1.2 (0.48-2.85)
Long (> 21 years)	18 (31.6)	30 (26.3)	1.4 (0.67-3.13)	1.5 (0.67-3.29)

Stomach cancer; OR, odds ratio; 95% CI, 95% confidence interval.[c]Missing cases, Adjusted for age

age is 53 year. The majority were educated lower than high school. Most of subjects were hard labour workers, the median income per month for both cases and controls are similar (3,000 baht per month) (Table 1).

Smoking habits in male cases and controls, and the odds ratio (OR) were found to be associated with an increased risk but not statistically significant (OR=1.2, 95%CI: 0.74-1.95). There was strong association between high consumptions of cigarettes smoking and stomach cancer with statistically significant (OR=3.4, 95%CI: 1.04-10.92, P-value 0.01). There was a higher risk of stomach cancer but not statistically significant in smoker with long-term of filtered cigarettes (OR= 1.5, 95%CI: 0.73-3.12). There was no evidence of a dose-response effect with respect to duration of smoking. Alcohol consumption every day and consumption period were increased risk of stomach cancer but not statistically significant (OR=1.2, 95%CI: 0.48-2.85 (short period), and OR=1.5, 95%CI: 0.67-3.29 (long period)) (Table 2).

Low consumption of vegetables and fruits are associated with an increased risk of stomach cancer (OR=1.2, 95%CI: 0.72-2.07) but not statistically significant. This study showed increased consumption of meat and grilled meat are protective factors (OR=0.6, 95%CI: 0.35-1.02 and OR=0.6, 95%CI: 0.39-1.17) (Table 3).

Preference for spicy food was associated with stomach cancer risk in this population. This study found that a high intake of vegetable oil was high risk for stomach cancer (OR=5.4, 95%CI: 1.05-27.39, P-value 0.03), pork oil (OR=1.4, 95%CI: 0.58-3.48) and Jeaw Prik (mainly chilly with plara broth) (OR=1.2, 95%CI: 0.76- 2.18) were found to be associated with an increased risk but not statistically significant . For red and dry chilli were protective factors

Table 3. Amount of Food Intake Associated with Stomach Cancer

Types (frequency per yr)	Cases (n=101)	Controls (n=202)	OR_c (95% CI)	OR_{adj} (95% CI)
Vegetable/Fruits, n[c] (%)				
High (535-1098)	45 (45.0)	100 (49.7)	1.0	1.0
Low (234-534)	55 (55.0)	101 (50.3)	1.2 (0.74-1.96)	1.2 (0.72-2.07)
Vegetable Only, n[c] (%)				
High (295-606)	46 (45.5)	98 (48.5)	1.0	1.0
Low (120-294)	55 (54.5)	104 (51.5)	1.1 (0.6-1.8)	1.19 (0.68-1.90)
Fruit Only, n[c] (%)				
High (247-588)	44 (44.0)	94 (46.8)	1.0	1.0
Low (72-246)	56 (56.0)	107 (53.2)	1.1 (0.68-1.81)	1.1 (0.66-1.83)
Fish/Shellfish:Fresh/Seawater,n[c] (%)				
High (420-1459)	49 (49.0)	101 (50.0)	1.0	1.0
Low (30-419)	51 (51.0)	101 (50.0)	1.0 (0.64–1.68)	1.0 (0.62-1.66)
Meat, n[c] (%)				
Low (0-241)	62 (62.0)	102 (50.5)	1.0	1.0
High (242-858)	38 (38.0)	100 (49.5)	0.6 (0.38-1.02)	0.6 (0.35-1.02)
Grill Meat n[c] (%)				
Low (0-154)	62 (62.0)	102 (50.5)	1.0	1.0
High (155-674)	38 (38.0)	100 (49.5)	0.7 (0.45–1.19)	0.6 (0.39–1.17)

Stomach cancer; OR, odds ratio; 95% CI, 95% confidence interval. [a]Odds ratio from a conditional logistic regression model including the matching factors and the individual characteristic listed. [c]Missing cases

Table 4. Cooking and Food Preparation by Case-control Status

Type of Food Preparation	Cases (n=101)	Controls (n=202)	OR_c (95% CI)	OR_{adj} (95% CI)
Vegetable oil	98 (98.0)	185 (91.5)	4.5 (1.00-20.17)	5.4 (1.05-27.39)
			P for Trend 0.03	*P for Trend 0.02*
Pork oil	12 (12.0)	18 (8.9)	1.4 (0.63-3.01)	1.4 (0.58-3.48)
Coconut oil	28 (28.0)	55 (27.3)	1.0 (0.60-1.77)	1.0 (0.59-1.77)
Green chilli	60 (60.0)	119 (58.9)	1.0 (0.64-1.70)	1.0 (0.63-1.71)
Red chilli	85 (85.0)	182 (90.1)	0.6 (0.32-1.27)	0.6 (0.28-1.31)
Dry chilli	70 (70.0)	158 (78.2)	0.6 (0.38-1.16)	0.6 (0.34-1.20)
Jeaw prik (mainly chilly with plara broth)	49 (49.5)	89 (44.1)	1.2 (0.76-2.01)	1.2 (0.76-2.18)
Jeaw prik (no plara broth, mainly chilli with fish sauce)	29 (29.3)	74 (36.6)	0.7 (0.42-1.20)	0.6 (0.35-1.15)
Sea salt	12 (11.9)	14 (6.9)	2.2 (0.95-5.27)	2.1 (0.89-5.22)
			P for Trend 0.05	*P for Trend 0.001*

*Adjusted for age

of a high intake (OR=0.6,95%CI: 0.28-1.31, OR=0.6, 95%CI: 0.34-1.20) but not statistically significant. A high consumption of sea salt was high risk (OR=2.1, 95%CI: 0.89-5.22) (Table 4).

Family history of cancer was strong association with an increased risk for stomach cancer (OR=2.3, 95%CI: 1.32-3.94, P-value 0.00). Both of cases and controls BMI were lower than 25 k/m2 ; 81.06%, median 21.3 then BMI more than 25 k/m2 was a protective factors same as exercise was a protective factors but not statistically significant (OR=0.7, 95% CI: 0.33-1.33) (Table 5).

Discussion

For this study we found stomach cancer risks were associated with many factors such as; high of tobacco smoking, alcohol drinking, vegetable oil, pork oil, Jaew Prik with plara's broth, sea salt will increased risk of stomach cancer.

In men, tobacco smoking may be related to the risk of stomach cancer, the higher risk of stomach cancer among low and high amount of cigarettes; OR=3.4, trend P-value 0.01. and alcohol drinking was increased risk (Chow et al.,1999; Nishio et al., 2006; Sjodahl et al.,2007).

The role of different dietary factors is promoting and preventing stomach cancer have resulted in broad consensus that fresh fruits and vegetables are protective factors, while preserved, salt and pickled foods enhance risk (WCRF, 1997) same as previous study (Sriamporn et al., 2002). High consumption of meat and grilled meat were protective factors, contrast other study cause of high and low consumption are not difference when compare with other study. Most of spice and food plant in Thailand may have chemopreventive activities and may be reduced incidence of stomach cancer (Bhamarapravati et al., 2003; Suwanrungruang et al., 2006) same as this study, we found that chillis are protective factors; OR=0.6 but not statistically significant. The salt intake and consumption of fermented foods, salt intake especially sea salt has a strong associated an increased risk for stomach cancer after adjusted with age groups; OR=3.6, tend P-value 0.00 (Hoshiyama and Sasaba, 1992; Nazario et al.,1993; Lee et al., 1995; WCRF,1997; Sriamporn et al., 2002; Sun et al., 2002; Kurosawa et al.,2006)

In summary, the present case-control study of stomach cancer confirmed cigarette smoking habit and high number of cigarettes, alcohol drinking and period of drunk, low consumption of fruits and vegetables were risk factors of stomach cancer in Northeast, Thailand. High intake of oils and salt especially sea salt and relative of first degree family history of cancer were found to be associated with increased risk (Huang et al.,1999; Huang et al., 2004; Barber et al.,2006).

The majority of the causes of cancer; such as tobacco smoking, alcohol drinking, fat, salt, obesity etc. are associated with life-style, that is personal choices and not environmental causes.

Acknowledgements

This research was a part of the project "(The epidemiological study of host and environmental factors for stomach and colorectal cancers in Northeast, Thailand)" which was approved by the research ethics committee, Faculty of Medicine, Khon Kaen University, Reference No. HE450818. The study was supported in part by grants from the The MONKASHO (The Japanese Ministry of Education, Culture, Sports, Science, and

Table 5. Characteristics Associated with Stomach Cancer

Characteristics	Cases (n=101)	Controls (n=202)	OR_c (95% CI)	OR_{adj} (95% CI)
Family history of cancer, n (%)	39 (39.0)	45 (22.3)	2.2[b] (1.31–3.78)	2.3[b] (1.32–3.94)*
			P for Trend 0.001	*P for Trend 0.001*
BMI ≥ 25 k/m², n (%)	3 (3.03)	54 (26.7)	0.1[b] (0.02–0.29)	0.1[b] (0.02–0.29)*
			P for Trend 0.001	*P for Trend 0.001*
Exercise , n (%)	17 (16.8)	25 (12.4)	0.7 (0.35–1.36)	0.7 (0.33–1.33)**

Stomach cancer; ORc, Crude Odd Ratio; ORadj, Adjusted Odd Ratio for *age,**sex. 95% CI, 95% confidence interval. [a]Odds ratio from a conditional logistic regression model including the matching factors and the individual characteristic listed. [c]Missing cases

Technology). We are grateful for all the help from Srinagarind Hospital, Khon Kaen Regional Hospital and Cancer Unit staff especially Ms.Sujinant Horasith who assisting in the interviewing part.

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Changes of Mental Stress Biomarkers in Ultramarathon

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Key words
- ultramarathon
- serotonin
- tryptophan
- β-endorphin

Abstract

We investigated the possible influence of an exhaustive physical exercise on mental stress biomarkers (serotonin, tryptophan, and β-endorphin) along with dopamine, noradrenalin and free fatty acids in an ultramarathon race in which 45 km was run on the first day and 90 km on the second. We obtained serum samples at 6 different time points during and after the race from 18 Japanese male runners who completed the marathon. Overall changes of serum serotonin and tryptophan concentrations were statistically significant according to ANOVA for repeated measurements ($p < 0.05$). Serum serotonin levels elevated rapidly on the first day with the post hoc Tukey's test. Tryptophan concentrations inversely decreased during the race, possibly because of utilization for synthesis of serotonin. Levels of β-endorphin appeared to increase on the first and second days, but were not statistically significant. In conclusion, serum serotonin, tryptophan and β-endorphin appeared to be used for mental stress markers in physical exercise.

March 10, 2008

DOI 10.1055/s-2008-1038490
Published online April 17, 2008
Int J Sports Med 2008; 29: 867 – 871 © Georg Thieme Verlag KG Stuttgart · New York · ISSN 0172-4622

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Introduction

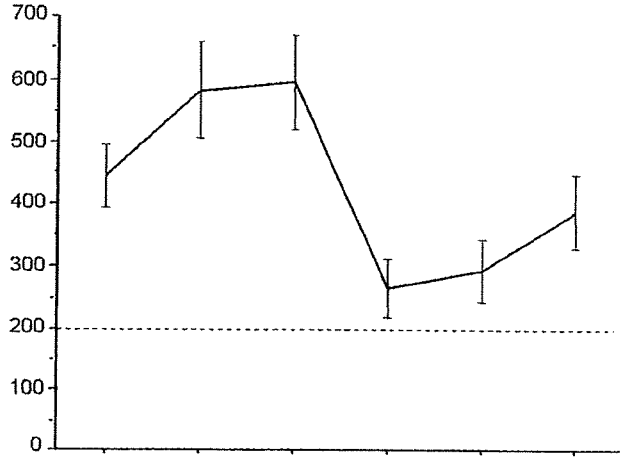
Mild to moderate exercise is believed to be beneficial for physical and mental well-being, possibly through reducing risks of diseases such as hypertension, cardiovascular disease, stroke, diabetes mellitus, and cancer along with diverting mental stress and resulting in an euphoric state. Conversely, it has been suggested that exhaustive physical exercise causes mental stress and central fatigue [7]. Although there have been a few reports [3,4,8] concerning changes of serum mental state markers in exhaustive running races, they only scrutinized variations during the races.

In the present study, we investigated changes in both serum serotonin, which is believed to stabilize the mental state even in exhaustive condition, and tryptophan (Trp) (precursor of serotonin), and β-endorphin (so called "inner morphine") not only during but also after a two-day marathon. We also measured serum concentrations of free fatty acids (FFA) deployed from adipose tissue, released into the circulation, and utilized as energy in exercise to investigate influences of serum FFA on serotonin synthesis, and to compare with dopamine (DA) and noradrenalin (NA) produced in the adrenal glands. When a stress stimulates the organs, these hormones are secreted into the circulation. They are also secreted in the brain. DA is especially important because it mediates signals from β-endorphin.

[illegible]

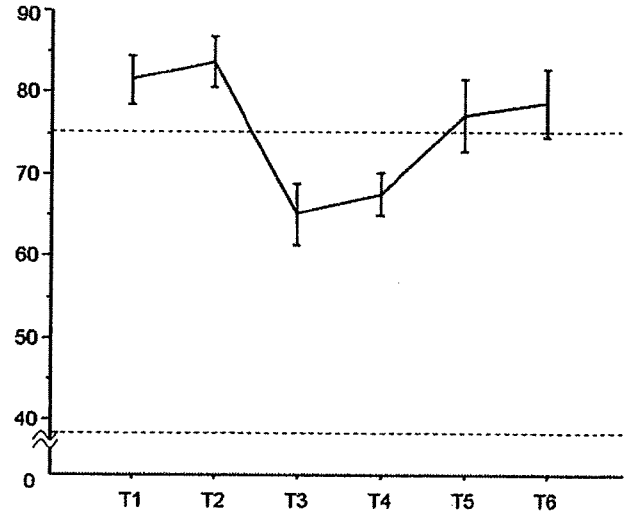
A noncompetitive two-day marathon, as described elsewhere [16], was held in Gifu Prefecture, Japan, on July 24 – 25, 2004. In brief, the race covered a total of 130 km distance running and mountaineering over 2 days. On the first day, at 11 : 00 a. m., the participants began a full-length 45-km marathon to be completed within 6.5 hours. On the second day, at 3 : 30 a. m., they resumed the race, covering approximately 90 km, including climbing a mountain approximately 1100 m high, then returning to the starting point within 15.5 hours.

We asked 41 nonprofessional Japanese male athletes to join, 24 of whom agreed. From them we received written informed consent for their completion of dietary and lifestyle questionnaires, measurements of anthropometric characteristics,



T1	ns	ns	<0.05	ns	ns
T2		ns	<0.05	<0.05	<0.05
T3			<0.05	<0.05	<0.05
T4				ns	ns
T5					ns
T6					

Fig. 1 Changes of serum serotonin concentrations (nM) ± SE. Horizontal broken line (– –) indicates lower limit of the reference value. P values of ANOVA (post hoc Tukey's method). SE: standard error; ns: not statistically significant.



T1	ns	<0.05	<0.05	ns	ns
T2		<0.05	<0.05	ns	ns
T3			ns	ns	ns
T4				ns	ns
T5					ns
T6					

Fig. 2 Changes of serum tryptophan concentrations (μmol/L) ± SE. Horizontal broken lines (– –) indicate upper and lower limits of the reference values. P value of ANOVA (post hoc Tukey's method). SE: standard error; ns: not statistically significant.

and sampling of blood and urine. The protocol was approved by the Institutional Review Board of the Nagoya City University Graduate School of Medical Sciences and by the chairman and organizing committee of the race.

Anthropometric measurements and sampling of venous blood and urine were performed at 6 time points: i.e., three spot blood samples before the race (T1: baseline), immediately after the goal on the first day (T2), and immediately after the goal on the second day (T3), and three fasting blood samples on the morning one day after the race (T4), on the morning three days after the race (T5), and on the morning five or six days after the race (T6). Sampled blood was stored at – 80 °C until assayed for serotonin, Trp, β-endorphin and other serum markers. Serum serotonin levels were determined by EIA kit (Immunotech S.A., Marseille, France), β-endorphin by EIA kit (Phoenix Pharmaceutical, Inc., Burlingame, USA), and serum Trp concentrations were measured by HPLC method at Kitasato Junior College of Health and Hygienic Sciences. FFA, DA, and NA were also measured at SRL laboratory in Japan. FFA was measured by EIA, and DA and NA by HPLC method.

Data are expressed as mean with standard deviation or standard error. We adopted analysis of variance (ANOVA) for repeated measurements, followed by post hoc Tukey's test for multiple comparisons of 6 time points. For this analysis, we used StatView version 5.0 computer software (SAS Institute, Inc., USA).

Eighteen of the 24 runners completed the race. All were non-smokers. In terms of anthropometric measures, their average age was 53.9 ± 12.0 years (mean ± SD), and body mass index (BMI) was 21.4 ± 1.6 kg/m^2. Average completion time for the two-day race was 18.4 ± 3.0 hours, ranging from 11.8 to 21.8 hours (data not shown).

Changes of the mean concentrations of serum serotonin with standard error (SE) are presented in **Fig. 1**. They steeply elevated at T2, and then reached the maximum levels at T3. They rapidly decreased below the baseline value at T4, and gradually recovered to the baseline in the follow-up period. They were within the reference range (200 to 2600 nM) [15] throughout the study period.

Serum Trp levels increased but were not statistically significant at T2, and then significantly decreased below the baseline value at T3 (**Fig. 2**). They recovered during the follow-up period. Serum Trp levels were above the upper limit of the reference range (37 to 75 μmol/L) [15] at T5 and T6.

Serum β-endorphin concentrations elevated at T2 and reached the highest level at T3; however, the differences were not statistically significant. They gradually decreased to the baseline in the follow-up period. They were within the reference range (0.12 to 2.0 ng/ml) [15] throughout the study period.

Serum FFA concentrations were elevated during the race (T1 to T3), and reached the peak level at T3 throughout the study period. They decreased to the reference range (0.25 to 0.6 mEq/L) [15] at T5 and T6 (**Fig. 3**). They were statistically significant except between T1 vs. T6, T2 vs. T4, and T5 vs. T6.

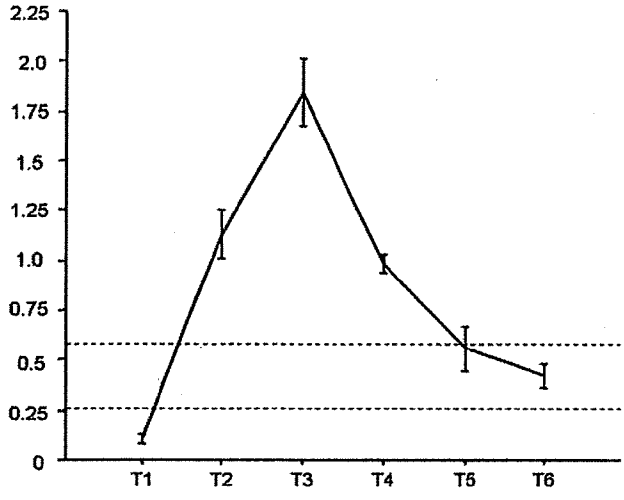


Fig. 3 Changes of serum FFA concentrations (mEq/L) ± SE. Horizontal broken lines (– –) indicate upper and lower limits of the reference values. P values of ANOVA (post hoc Tukey's method). SE: standard error; ns: not statistically significant.

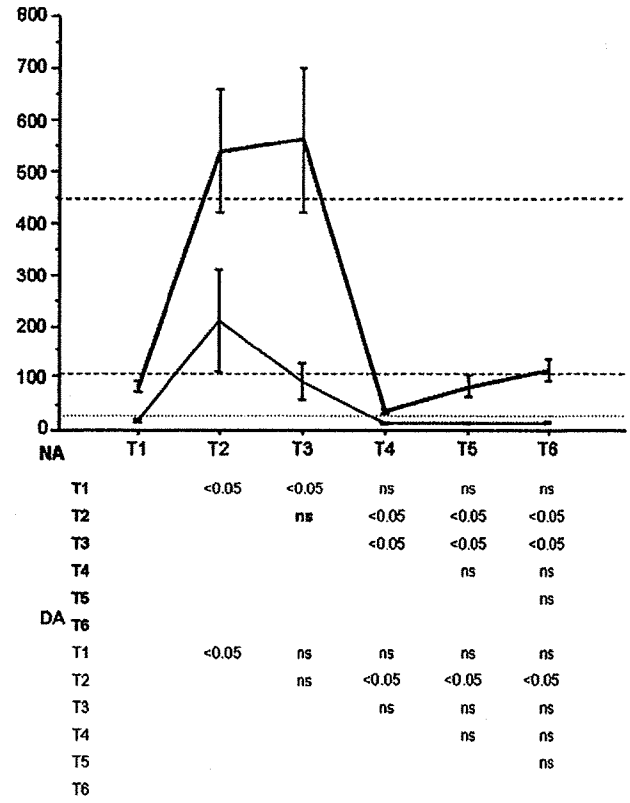


Fig. 4 Changes of serum noradrenalin (NA: bold line) and dopamine (DA) concentrations (pg/ml) ± SE. Horizontal broken lines (– –) for NA indicate upper and lower limits of the reference values and dotted line (.....) for DA the upper limit. P values of ANOVA (post hoc Tukey's method). SE: standard error: ns: not statistically significant.

Changes of serum DA and NA concentrations were demonstrated together in **Fig. 4**. They were higher than the upper limit of the reference range (< 25 pg/ml for DA, 100 to 450 pg/ml for NA) [15] during the race period (T2 and T3). Changes of serum NA concentrations were statistically significant between T1 vs. T2 and T3, T2 vs. T4, T5, and T6, and T3 vs. T4, T5 and T6. Changes of serum DA levels were statistically significant between T1 vs. T2 and T2 vs. T4, T5 and T6.

We observed typical changes in serum serotonin and Trp concentrations in this study. Serum serotonin levels significantly increased during the race, but rapidly decreased after the race. On the other hand, serum Trp concentrations significantly decreased below the baseline on the second day. Interestingly, serum serotonin and Trp levels varied almost inversely during the race. Like serotonin, serum β-endorphin concentrations elevated during the race, although the changes were not statistically significant. These three serum biomarkers along with FFA, DA and NA seem useful for assessing mental stress during and after physical exercise.

Serum serotonin is peripherally produced from serum free-Trp (fTrp) in enterochromaffin cells of the intestinal membranes. When released into blood vessels [13], platelets absorb it and store it in their cytosol. Peripheral serotonin is considered to work for blood coagulation with platelets. Serum FFA concentrations rapidly elevate during vigorous exercise. Circulating FFA usually binds to albumin, and this combination is much stronger than the Trp-albumin combination [9]. When fTrp increases in the blood, the increased ratio of serum fTrp/branched chain amino acids makes fTrp pass more easily through the blood brain barrier (BBB). Then fTrp is converted to serotonin in neurons in Raphe nuclei, which spread widely to the brain through nerve fibers. Thus, brain serotonin increases in an exercise such as this marathon. Serotonin transporter (SERT) reportedly exists on the membranes of endothelial cells of the brain capillary [10], and SERT is found on both the brain and capillary side of cells. Therefore, serotonin possibly passes through the BBB via SERT between the capillary and brain, and serum serotonin concentrations increase during the race.

Although serum serotonin has been suggested to be a causal substance of central fatigue in exhaustive exercise [17], another report indicated that its concentrations elevated in non-exhaustive exercise such as stepping movement [14]. Thus, it is still controversial whether or not elevated serum serotonin levels in exercise really indicate central fatigue. In the present study, serum serotonin (also β-endorphin) concentrations on the first day (T2) were as high as those on the second day, despite twice the running distance on the second day. The elevations of serum serotonin and β-endorphin were possibly due to a stress reaction to physical exercise stimulus, and not to brain fatigue.

Serum fTrp is one of the essential amino acids and also the precursor of peripheral and central serotonin [13]. In the present study, serum Trp levels elevated at the baseline, because the participants took food and beverage *ad libitum* to keep their physical and nutritional condition in order to prepare for the following longer distance running. On the second day of the race, its

levels rapidly decreased but were within the reference range. There is a report suggesting a fairly significant inverse correlation between brain serotonin and plasma Trp levels [12], which may be due to Trp consumption as energy in organs, including liver and muscles, in a race, and peripheral as well as central serotonin synthesis as seen in the inverse trends from T2 to T3 of serotonin and Trp in the present study. Naturally, serum Trp concentrations might indicate the balance between intake of amino acids and consumption.

β-endorphin is one of the internal opioids, a 31-amino acid peptide, and is primarily produced from pro-opiomelanocortin (POMC) in the anterior pituitary gland [4]. When various stress stimuli (including mental stress) attack the human body, corticotropin releasing factors (CRF) are secreted into the pituitary portal system from CRF-producing cells in the hypothalamus. Secreted CRF stimulates the POMC-producing cells and β-endorphin is released into the circulation [17]. A previous report suggested that long distance running was a potential stress stimulus for this chemical substance, and that the duration of an exercise, not its workload, is possibly critical in stimulating β-endorphin release [11]. Elevated serum β-endorphin concentrations induced by physical exercise have been linked to several psychological alterations, including "exercise-induced euphoria" and modified pain perception [7]. Although the differences were not statistically significant partly due to the small number of study subjects, and essentially to small changes of β-endorphin as a potent opioid, we observed obviously elevated serum β-endorphin, as well as serotonin, levels as a typical response to physical exercise. β-endorphin was found to activate μ-receptor on γ-aminobutylic acid (GABA) intermediating neuron, to regulate GABA regulatory output, and deregulate DA-producing cells in tegmentum mesencephali [6]. Therefore, we considered that elevated serum DA levels may have induced the "euphoric" feeling experienced by the runners in the present study. However, we could not validate the findings because we did not use a mental stress questionnaire for the runners. As mentioned above, β-endorphin and DA may closely cooperate to control our mental state in physical exercise.

The changes of serum NA concentrations were observed just like those of serotonin. Although serum serotonin concentrations were within the reference range throughout the study period, serum NA concentrations were above the reference level (at T2 and T3) during the marathon. In the postrace period, they were just below the lower normal limit. These facts indicated that serum NA levels were elevated in the exhaustive physical exercise, and drastically fell afterwards. In a previous report on animals [5], there were no responses to a physical stress stimulation on serotonin neurons, but excitement was observed in NA neurons by the same stress stimulation. Thus, the changes of serum NA concentrations in our study were specifically influenced and more varied than serotonin concentrations by the physical stress of the marathon.

In conclusion, serum serotonin concentrations increased probably due to the exhausting physical exercise of the marathon, whereas serum Trp levels inversely decreased. Serum β-endorphin values were enhanced, possibly owing to the physical exercise. Thus, these substances in addition to FFA, DA and NA seemed to be adopted for mental stress biomarkers in physical exercise. Further studies, however, are warranted to examine whether peripheral concentrations of serotonin and β-endorphin are directly parallel to the brain levels.

Acknowledgements

This study was supported, in part, by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. We appreciate the runners having willingly participated in our study and the chairman and organizing committee of the Maranic race. We thank Ms. Fujii, T., Ms. Kubo, Y., Ms. Nakanishi, N., Ms. Ito, Y., Ms. Higuchi, K., Ms. Mori, M., and Ms. Watanabe, M. for their technical assistance.

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J Epidemiol 2008; 18(2) 77-83

Original Article

Active Smoking, Passive Smoking, and Breast Cancer Risk: Findings from the Japan Collaborative Cohort Study for Evaluation of Cancer Risk

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Received July 27, 2007, and accepted December 13, 2007.

ABSTRACT

Background: Evidence is lacking regarding the relationship between cigarette smoking and breast cancer in Japanese women. We examined the association between breast cancer incidence and active and passive smoking in the Japan Collaborative Cohort Study for Evaluation of Cancer Risk.

Methods: Our study comprised 34,401 women aged 40-79 years who had not been diagnosed previously with breast cancer and who provided information on smoking status at baseline (1988-1990). The subjects were followed from enrollment until December 31, 2001. Cox proportional-hazards models were used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for the association between breast cancer incidence and tobacco smoke.

Results: During 271,412 person-years of follow-up, we identified 208 incident cases of breast cancer. Active smoking did not increase the risk of breast cancer, with a HR for current smokers of 0.67 (95% CI: 0.32-1.38). Furthermore, an increased risk of breast cancer was not observed in current smokers who smoked a greater number of cigarettes each day. Overall, passive smoking at home or in public spaces was also not associated with an increased risk of breast cancer among nonsmokers. Women who reported passive smoking during childhood had a statistically insignificant increase in risk (HR: 1.24; 95% CI: 0.84-1.85), compared with those who had not been exposed during this time.

Conclusion: Smoking may not be associated with an increased risk of breast cancer in this cohort of Japanese women.

Key words: Smoking, Breast Neoplasms, Risk, Cohort Studies.

INTRODUCTION

Breast cancer is a complex, multifactorial disease with a strong interaction between genetic and environmental factors.[1] The role of cigarette smoking in breast cancer etiology has been investigated extensively over several decades, because it is one of the few potentially modifiable environmental factors that contributes to the development of this malignancy.[2,3] However, despite a large number of epidemiologic studies being carried out, it remains controversial whether cigarette smoking is associated with an increased risk of breast cancer. While the majority of studies have shown a weak positive or null association,[4] the association appears to be strongest in premenopausal women[5] or in women who started smoking at an early age or smoked before their first full-term pregnancy.[6] A positive association

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with passive smoking has also been reported in some studies,[7-10] but was not observed consistently in other studies.[11-14] A recent review suggested that studies with detailed assessment of exposure to passive smoking were more likely to show a stronger positive association between passive smoking and breast cancer risk.[4]

Only a small number of epidemiologic studies have examined the relationship between smoking and breast cancer in Asian countries,[11,15-17] in which the incidence of breast cancer is generally lower than in Western countries. A recent systematic review, based on studies in Japanese women, concluded that smoking possibly increased the risk of breast cancer in the Japanese population.[18] However, definitive evidence is still lacking as only one of the three cohort studies included in that review found a positive association in pre-menopausal women.

The sustained increase in breast cancer incidence in Japanese women over recent decades has become a major public health concern in Japan.[19] Clarifying the relationship between smoking and breast cancer may provide insights into strategies aimed at preventing this malignancy. In order to better understand the association between active and passive smoking and breast cancer risk, we analyzed data from a large cohort study of mainly postmenopausal women in Japan.

METHODS

Study Population

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC) is a prospective cohort study designed to evaluate cancer risk associated with lifestyle factors in the Japanese population. A full description of the JACC Study is available elsewhere.[20,21] Briefly, the study was established in 1988-1990, with 110,792 people (46,465 men and 64,327 women), aged 40 to 79 years, being enrolled from either the general population or from subjects who had municipal health check-ups in 45 areas throughout Japan. All the participants were followed up for all-cause mortality. In addition to mortality, the incidence of cancer was recorded in subjects living in 24 areas in which cancer registry systems were established.

Of the 64,327 women in the original cohort, 38,593 women lived in the 24 areas where data on incidence were available. We excluded women who reported a previous diagnosis of breast cancer (n=161) and women who gave no information on smoking status in the baseline questionnaire (n=4031), leaving 34,401 women eligible for the present analysis. The average age at enrollment was 58.0 years.

We obtained informed consent by requesting the subjects to sign the cover page of the questionnaire. In some areas, informed consent was obtained at a group level, after the purpose of the study and confidentiality of the data had been explained to community leaders. The Ethics Board at Nagoya University School of Medicine approved the study in 2000.

Data Collection

At baseline, we used a self-administered questionnaire to obtain information on demographic characteristics, tobacco and alcohol use, physical activity and other lifestyle factors. Questions on active cigarette smoking comprised smoking status (never, past or current), age at which smoking started, the number of cigarettes smoked per day, years of smoking, and smoking cessation. Information on passive smoking was collected in nonsmokers by recording the response to the following three questions. Firstly, "In the past, were you exposed to tobacco smoke at home?" Women who responded that they had been exposed to environmental tobacco smoke (ETS) were also asked to report the frequency of this passive exposure as either sometimes, 1-2 days/week, 3-4 days/week, or almost every day. Secondly, "In the past, were you exposed to tobacco smoke in public spaces?" Women who answered 'yes' to this question also reported the frequency of this passive exposure. Thirdly, "Were you exposed to tobacco smoke from family members in your childhood?" The subjects were categorized as having been exposed to passive smoking if they reported ever being exposed to tobacco smoke at home or in public spaces.

Information on other potential risk factors for breast cancer, such as alcohol drinking, age at menarche, parity, age at the birth of her first child, and age at menopause, was also collected in the baseline questionnaire.

Follow-up and Identification of Breast Cancer Cases

Follow-up was conducted from enrollment until December 31, 2001. During this period, population registries in the municipalities were used to ascertain the residential and vital status of the participants. In Japan, registration of death is required by Family Registration Law and theoretically provides complete mortality data. Breast cancer incidence was confirmed mainly through linkage of records to the population-based cancer registry in each area. To complete the incidence data, we also conducted a systematic review of death certificates and reviewed medical records in local major hospitals in some areas.

During the study period, 2.7 percent of the subjects were lost to follow-up due to having left the study areas. The proportion of cancer cases with death certificate only was 5.3 percent (11 of 208 cases). The mortality to incidence ratio for breast cancer was 0.15 in the cohort covered by cancer registries. This value was lower than that available from population-based cancer registries in Japan (between 0.20 and 0.30).[22]

Statistical Analysis

For each participant in the cohort, the person-years of follow-up were counted as either the time from enrollment to the diagnosis of breast cancer, death from any cause, or the end of

follow-up (December 31, 2001), whichever occurred first. For breast cancer cases ascertained only by death certificates, the person-years of follow-up were calculated from enrollment to death from breast cancer. Women who died of causes other than breast cancer or moved out of the study areas were treated as censored cases. We used Cox proportional-hazards models to estimate the hazard ratio (HR) and 95% confidence interval (CI) for the association between breast cancer incidence and tobacco smoke. The analyses on the association between passive smoking and breast cancer risk were limited to nonsmokers. Potential confounding factors included in the multivariable models were age (continuous), study area (Hokkaido and Tohoku, Kanto, Chubu, Kinki, Chugoku, Kyushu), body mass index (BMI; <20.0, 20.0-24.9, 25.0-29.9, or ≥30.0 kg/m^2), alcohol consumption (never, past, or current), daily walking (seldom or never, 30, 30-59, 60 minutes), parity (nulliparous or 1, 2 or 3, or ≥4 births), age at the birth of her first child (<22, 22-25, or ≥26 years), menopausal status (premenopausal or postmenopausal), age at menarche (<15, 15-16, or ≥17 years), use of sex hormones (yes/no) and family history of breast cancer in a first-degree relative (yes/no). These variables were selected as covariates as they are known to, or alternatively have been suspected of modifying the risk of breast cancer. We also conducted analyses limited to post-menopausal women only, as the mean age of the study cohort was 58 years and 66 percent of the women reported their age at menopause in the baseline questionnaire.

All P values were 2-sided, with P<0.05 indicating statistical significance. All the analyses were performed with SAS® package version 9.1 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

During 271,412 person-years of follow-up, we identified 208 incident cases of breast cancer. Table 1 shows the distributions of risk factors for breast cancer grouped according to smoking status. Current, ex-, and nonsmokers represented 1.6%, 5.3%, and 93.1% of the cohort population, respectively. Smokers and nonsmokers differed in their alcohol consumption, age at the birth of her first child, age at menopause, and use of sex hormones. Compared with nonsmokers, current smokers tended to drink more alcohol, had given birth at a younger age, became menopausal at an earlier age, and were more likely to be on hormone therapy. There were no significant differences in the other risk factors between current and past smokers.

Table 2 summarizes the risk of breast cancer in relation to current and past smoking. After adjustment for potential confounding factors, the relative risk was slightly increased in ex-smokers (HR: 1.27). However, this association was not statistically significant. Cigarette smoking did not increase the risk of breast cancer incidence, with the HR for current smokers being 0.67 (95% CI: 0.32-1.38). In addition, no increased risk was observed for current smokers who smoked a greater number of cigarettes per day.

Overall, passive smoking at home or in public spaces was not associated with an increased risk of breast cancer in nonsmokers (Table 3). Passive smoking at home appeared to decrease the risk, although this association was not statistically significant. Women who reported passive smoking during childhood had a statistically insignificant increase in the risk of developing breast cancer (HR: 1.24 ; 95% CI: 0.84-1.85), compared with women not exposed to passive smoking during this time.

No significant increase in breast cancer incidence in relation to active smoking was observed in the analyses limited to post-menopausal women only, with the HR being

Table 1. Distribution of risk factors for breast cancer in women in the JACC Study, grouped according to smoking status at baseline (1988-1990).

Risk factors	Smoking status at baseline			P*
	Never (n=32023)	Current (n=1814)	Past (n=564)	
Age (year)**	57.8	56.4	60.9	<0.01
Body mass index (kg/m^2)	22.9	22.7	23.3	0.06
Family history of breast cancer (%)	1.4	1.6	1.2	0.46
Alcohol consumption (g/day)	8.1	20.0	13.6	<0.01
Age at menarche (yr)	14.9	14.9	14.9	0.68
Age at the birth of her first child (year)	25.1	24.8	24.7	<0.01
Age at menopause (yr)***	48.7	47.9	48.4	<0.01
Use of sex hormones (%)	4.9	7.4	3.1	<0.01

Data presented are means otherwise specified.

*: The significance of differences in baseline characteristics between current and nonsmokers was tested using the χ^2 test or Student's t test, where appropriate.

**: The number of women in each 10-year age group were as follows: 40-49, 8345; 50-59, 10772; 60-69, 10412; 70-79, 4872.

***: Sixty six percent of the women reported their age at menopause at baseline.

Table 2. Hazard ratios and 95% confidence intervals for breast cancer in relation to active smoking in the JACC Study.

	Person-years	No. of cases	Hazard ratios (95% confidcence intervals)	
			Age-adjusted	Multivariate*
Nonsmokers	338113	196	1.00 (reference)	1.00 (reference)
Ex-smokers	5002	4	1.41 (0.53-3.80)	1.27 (0.46-3.48)
Current smokers	17945	8	0.75 (0.37-1.53)	0.67 (0.32-1.38)
0-10 (cigarettes/day)	9291	5	0.92 (0.38-2.24)	0.84 (0.34-2.06)
≧ 11	7766	3	0.64 (0.21-2.01)	0.55 (0.17-1.75)

*: Hazard ratios adjusted for age, area, body mass index, family history of breast cancer, alcohol drinking, daily walking, age at menarche, age at the birth of her first child, menopause status at baseline, number of births, and use of sex hormons.
Women who had missing data on number of cigarettes smoked per day were excluded.

Table 3. Hazard ratios and 95% confidence intervals for breast cancer in relation to passive smoking among nonsmokers in the JACC Study.

	Person-years	No. of cases	Hazard ratios (95% confidcence intervals)	
			Age-adjusted	Multivariate*
Passive smoking at home				
No	93043	63	1.00 (reference)	1.00 (reference)
Yes				
Sometimes	38314	17	0.65 (0.38-1.10)	0.59 (0.33-1.05)
Almost everyday	107269	51	0.68 (0.47-0.99)	0.71 (0.48-1.05)
Passive smoking in public spaces				
No	142414	83	1.00 (reference)	1.00 (reference)
Yes				
Sometimes	73607	37	0.84 (0.57-1.24)	0.77 (0.51-1.15)
Almost everyday	36335	20	0.93 (0.57-1.53)	0.84 (0.51-1.40)
Passive smoking during childhood				
No	79623	37	1.00 (reference)	1.00 (reference)
Yes	255172	141	1.21 (0.84-1.74)	1.24 (0.84-1.85)

*: Hazard ratios adjusted for age, area, body mass index, family history of breast cancer, alcohol drinking, daily walking, age at menarche, age at the birth of her first child, menopausal status at baseline, number of births and use of sex hormones.
Women who had missing data in each category were excluded.

1.20 (95% CI: 0.52-2.80) for current smokers.

We also conducted an analysis using nonsmokers who had not been exposed to passive smoking either at home or in public spaces as a reference group. The risk estimates for current and past smoking in this group were essentially unchanged (data not shown).

DISCUSSION

We examined the relationship between cigarette smoking and breast cancer in a large Japanese cohort comprised mainly of postmenopausal women. Our findings indicated that neither active nor passive smoking were associated with an increased risk of breast cancer in our study cohort.

We found no indication of an increased risk for breast cancer in current smokers. Previous studies have provided conflicting results on the association between active smoking and breast cancer risk, with the majority of studies showing no significant association, or only a modest, positive association.[2,3] The Nurses' Health Study concluded that smoking did not increase the risk of breast cancer.[14] When adjusted for alcohol drinking, no association was observed between cigarette smoking and breast cancer risk in a collaborative reanalysis of individual data from 53 epidemiologic studies.[3] In contrast, a pooled analysis including both case-control and cohort studies published before December 2004 reported an approximately 40 percent increase in the risk of breast cancer in active tobacco smokers.[4] However, cohort studies are more likely to show no association, or to yield modest risk estimates compared with case-control studies. This suggests that recall bias or selection bias inherent in case-control studies may influence the association between breast cancer and active smoking.

We have interpreted our finding of a lack of association between active smoking and breast cancer risk from both a biological and methodological perspective. Firstly, it has been suggested that considerable heterogeneity exists in the

etiology of breast cancer.[23] Breast cancer can be classified according to estrogen receptor and/or progesterone receptor expression, with each type having different clinical, pathological and molecular features.[24] The positive association between breast cancer and smoking may be diluted or masked in studies that treat breast cancer as a single outcome, as we did in our analyses. Secondly, given that the majority of the women in our cohort were nonsmokers at baseline and only the small number of current smokers developed breast cancer during follow-up, it was difficult to detect a statistically significant relationship between smoking and breast cancer risk. Thirdly, concern has been raised previously that studies showing no significant positive associations included many women in the reference group who had been exposed to passive smoking but who had never smoked.[4] This may explain, in part, the lack of association we observed in our study. However, even when we included women who had never been exposed to either active or passive smoking as the reference group, we observed no increased risk of breast cancer in current smokers. Fourthly, the majority of the women in our cohort were postmenopausal. We therefore conducted an analysis limited to postmenopausal women only and found no significant associations. Accordingly, we consider that our finding of a lack of a significant association between active smoking and breast cancer risk is applicable to postmenopausal Japanese women. However, the lack of information on menopausal status at diagnosis of breast cancer did not allow us to carry out a detailed analysis. Our result is consistent with that of another large cohort study conducted in Japan,[16] in which no significant association was obtained between smoking and breast cancer incidence in postmenopausal women. However, the possibility remains that smoking may be associated with an increased risk of breast cancer in premenopausal women, as that cohort study showed a 3.9-fold increase in breast cancer risk for premenopausal Japanese women.[16] In contrast to the inconsistent results for premenopausal women, the majority of studies have shown that cigarette smoking was not associated with an increased risk of breast cancer in postmenopausal women.[3,4]

In the present study, passive smoking at home or in public places was not associated with an increased risk of breast cancer in nonsmokers. Evidence supporting a positive association between passive smoking and breast cancer risk has been derived mainly from case-control studies.[4] However, three large cohort studies conducted in the United States did not confirm the positive findings of these case-control studies.[12-14] In the Nurses' Health Study, passive smoking was unrelated to breast cancer risk.[14] Similarly, a large, prospective study reported no association between ETS from a smoking spouse or from other sources and the risk of death from breast cancer.[12] In contrast, a recent Japanese cohort study reported a significant 2.6-fold increased risk of breast cancer for passive smoking in premenopausal women.[16] Moreover, a review by the California Environmental Protection Agency concluded that regular ETS exposure was related to breast cancer diagnosed in younger women who were primarily premenopausal.[25] The interpretation of these contradictory results is difficult, given the heterogeneity of breast cancer etiology, variation in study design and the precision of ETS measurement. However, active smoking is not an established risk factor for breast cancer, and the amount of exposure is lower from ETS than from active smoking. In addition, previous studies that examined this association were of small sample size and retrospective. On the basis of these facts, we consider it unlikely that passive smoking plays a major role in the development of breast cancer, although it may be related to breast cancer in certain high-risk populations.

The strength of our study was its prospective design, which avoided recall bias inherent in case-control studies. Information on other risk factors for breast cancer was available and potential confounding factors were controlled for in the analyses examining the association between smoking and breast cancer.

The limitations of our study merit consideration. As mentioned earlier, due to the small number of breast cancer cases who were current smokers, we were unable to conduct a detailed analysis examining the association between breast cancer and factors such as age when smoking was started, frequency, and duration. Previous studies suggested that early childhood may be a critical period of risk, and that there may be an increased risk with starting smoking at an earlier age and long duration of smoking.[26] Another limitation of our study was that we did not collect information on menopausal status at diagnosis of breast cancer, hormonal receptor status or genetic polymorphisms, all of which can be used to define breast cancer risk more accurately.[27,28] Finally, the validity of our findings on passive smoking may be a concern given the relatively high percentage of missing data (24.8%) regarding this exposure. Random errors are more likely in this situation and therefore the real association may have been underestimated. Further improvements in the measurement of passive smoking are therefore needed in order to provide more accurate risk estimates for passive smoking and breast cancer.

In conclusion, our results suggest that smoking is not associated with the risk of breast cancer in this cohort of Japanese women.

ACKNOWLEDGMENT

This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Culture, Sports, Science and Technology of Japan. The JACC Study has also been supported by Grants-in-Aid for Scientific Research from the same ministry (Nos. 61010076, 62010074,

63010074, 1010068, 2151065, 3151064, 4151063, 5151069, 6279102, 11181101, 17015022, and 18014011). The study sponsor has no involvement in the study design, data collection, analysis and interpretation of data.

The authors thank Dr. Kunio Aoki, Professor Emeritus, Nagoya University School of Medicine and the former chairman of the JACC Study Group, and Dr. Haruo Sugano, the former Director of the Cancer Institute of the Japanese Foundation for Cancer Research, for their major contribution to the initiation of the JACC study.

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Cancer Causes Control (2008) 19:931–937
DOI 10.1007/s10552-008-9154-5

ORIGINAL PAPER

A prospective study of educational background and breast cancer among Japanese women

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Received: 7 January 2008 / Accepted: 21 March 2008 / Published online: 4 April 2008

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Abstract

Objective This prospective cohort study examined the association between educational level and breast cancer incidence in Japan.

Method A baseline survey was conducted between 1988 and 1990 among 110,792 residents of 45 areas, aged 40–79 years. Data were restricted to 24 areas where incidence registry data were available, and to subjects which provided information on educational level (32,646). The subjects were assigned to three groups according to their level of education (<16, 16–18, 18<). During 13 years of follow-up (328,931 person-year), 169 cases of breast cancer were newly diagnosed.

Results Women with a high level of education had an increased risk of breast cancer (HR = 1.93, 95 percent confidence interval (95% CI): 1.18, 3.16, in women with the highest educational level) compared with women with the lowest educational level. Adjustment for lifestyle and reproductive factors did not substantially change the results. In addition, when analyses were stratified by age subgroups, the educational difference in breast cancer incidence was more evident among the younger than the elder subgroup.

Conclusion The present results suggested that cancer prevention strategies should recognize women with a higher educational level as a high risk group for breast cancer.

Keywords Epidemiology · Breast cancer · Education · Cohort study · Japan

Introduction

Socioeconomic status is recognized as a powerful indicator of health. People with a high socioeconomic status generally have better health in terms of both morbidity and mortality. Breast cancer, however, is more common among women with a high than a low socioeconomic status [1–13]. This atypical association is regarded as partly due to differences in reproductive and maternal behavior among women in these groups [1, 6, 10, 11]. For example, delayed child bearing and fewer children among women with a high socioeconomic status may increase the risk of breast cancer.

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The profile of breast cancer risk may differ between countries, particularly between Western and Asian countries. Evidencing this, Japanese women have historically had a lower risk of breast cancer than Western women [14]. Nevertheless, despite differences in the association of socioeconomic status with reproductive behavior between sociocultural conditions, no prospective evidence for the association between socioeconomic status and breast cancer in non-white populations has been reported.

Here, we prospectively examined the association of educational background, a major proxy of socioeconomic status, with breast cancer among Japanese women with adjustment for reproductive factors. In addition, given findings that the association between socioeconomic status and breast cancer is weakening in some western countries [7, 12, 15], we also examined whether this is true in Japan.

Materials and methods

Details of the Japan Collaborative Cohort Study for the Evaluation of Cancer Risk (JACC Study), which was sponsored by the Ministry of Education, Science, Sports, and Culture of Japan, have been described previously [16, 17]. Briefly, a baseline survey was conducted through 45 areas of Japan from 1988 to 1990 among 110,792 residents (46,465 men and 64,327 women) who ranged in age from 40 to 79 years at recruitment. In 22 of 45 areas, all residents living in a given target area were regarded as study subjects. In an additional 20 areas, those who had undertaken a basic health examination conducted under the Health and Medical Service Law for the Aged were invited to participate in the study. In two further areas, the study subjects consisted of health examinees plus volunteers. In one final area, subjects were defined based on a health check-up for atomic bomb survivors. Response rates were obtainable from 17 of the 22 areas which included all living residents as subjects, and showed an average response rate of 83%. The vital status of each participant was checked annually using data held at regional research centers, with permission received from the Ministry of Public Management, Home Affairs, Post, and Telecommunications of Japan to review the population registration entries. The incidence of cancer was determined by linkage with cancer registries in 24 of the 45 study areas. Details concerning the completeness of the survey for incidence of cancer have been reported previously. Briefly, the mortality-incidence ratio among the areas was 0.15 to 0.53 in women [18]. A diagnosis of cancer of the breast was defined by code 'C50' according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD–10).

We previously reported that the mortality-to-incidence ratio for breast cancer was 0.15 in the cohort covered by cancer registries [19]. This ratio is lower than those in acceptably accurate population-based cancer registries in Japan (0.20–0.30) [20], indicating that a reasonably high proportion of breast cancer cases were identified.

Follow-up surveys on incidence were conducted until the end of 2001, excluding five areas in which they were halted earlier. Informed consent procedures were approved by the Ethics Committee of Nagoya University, Japan.

Data retrieval for analysis

Analysis was restricted to subjects from the 24 areas from which incidence data were available (38,720 women). Subjects in whom cancer had been diagnosed in any site before baseline were excluded ($n = 747$). Further, all subjects in one area which used a slightly different version of the questionnaire without questions on educational level were excluded ($n = 2,547$), as were those in other areas who did not provide information on education ($n = 2,780$). Finally, data from 32,646 women were used for analysis. During 13 years of follow-up (328,931 person-years), 169 cases of breast cancer were newly diagnosed.

Exposure data

The subjects were assigned to three groups according to their level of education: those who attended school beyond the age of 18 years (equivalent to university); those who attended school until 16–18 years (equivalent to high school); and those who attended school until 15 years or less (equivalent to junior high school or less).

The self-administered questionnaire also inquired about other baseline characteristics that could be potentially related to mortality, including smoking status (never, former, or current smoker); alcohol intake (non-habitual drinker, former habitual drinker, or habitual drinker of ethanol at 1–22, 23–45, and ≥46 g per day); history of hypertension or diabetes; attendance at a breast cancer screening program; self-examination of breasts; degree of perceived stress in daily life (frequent, occasional, very occasional, or never); hours of walking (<0.5, 0.5, 0.6–0.9, and ≥1.0 h per day); hours of exercise (<1, 1–2, 3–4, and ≥5 h per week); and body height and weight. Information on reproductive behavior was also provided, including number of pregnancies, number of deliveries, age at first delivery, age at menarche, and age at menopause.

Statistical analysis

Cox proportional hazards regression analysis [21] was used to estimate the hazard ratio (HR) of education level for breast cancer incidence after adjustment for the potential confounding factors listed above, by stratification of areas using the 'strata' statement of the procedure. The model, included age divided into 5-year groups and body mass index (BMI) divided into four groups (<22, 22–23.9, 24–25.9, and ≥26). The model included lifestyle-related factors, which may potentially relate to cancers and more general health outcomes. The model then additionally included reproductive factors, which are regarded as risk factors for breast cancer. Subjects were further divided into two groups before analysis, those aged less than 18 years or 18 years or more in 1949, when the Japanese educational system underwent significant reform following World War II. Before 1949, it was not possible to classify schools into levels such as "primary school," "junior high school," and "high school" as an index of educational level, as the Japanese educational system was highly complex and inconsistent. Further, skipping of grades and leaving school early were common before this date. Linear trends of association were assessed by the regression model, which assigned a score (0, 1, 2) to each educational level. All calculations were performed using the SAS statistical software package [22].

Results

Selected baseline characteristics of the study subjects by educational level are listed in Table 1. Women who were educated to a high level were less likely to smoke and more likely to consume alcohol, and more likely to attend a breast cancer screening program and conduct breast self-examination. They were also less likely to have experienced pregnancy and delivery, and to have had earlier menarche and later menopause.

Table 2 shows that women with a high level of education had an increased risk of breast cancer (the age-adjusted HR = 1.93; 95% CI: 1.18, 3.16, in women with the highest educational level) compared with women with the lowest educational level. This difference was also significant on trend analysis (p for trend = 0.010). No substantial change in the results was seen with Models 2 and 3, which included additional factors potentially associated with breast cancer.

Table 2 also shows HRs of educational level for breast cancer incidence stratified by age subgroup. The association between educational level and breast cancer was not confirmed among subjects aged 18 years or above in 1949. In contrast, a greater difference in incidence between educational groups was observed among those aged less than 18 in 1949. The age-adjusted HR of breast cancer incidence in women with the highest educational level was 2.44 (95% CI: 1.21, 4.92; $p = 0.013$) compared with those with the lowest educational level.