Effect of Physical Activity on Breast Cancer Risk: Findings of the Japan Collaborative Cohort Study

Sadao Suzuki,[1] Masayo Kojima,[1] Shinkan Tokudome,[1] Mitsuru Mori,[5] Fumio Sakauchi,[5] Yoshihisa Fujino,[6] Kenji Wakai,[2] Yingsong Lin,[7] Shogo Kikuchi,[7] Koji Tamakoshi,[3] Hiroshi Yatsuya,[4] and Akiko Tamakoshi[7] for the Japan Collaborative Cohort Study Group

[1]Department of Public Health, Nagoya City University Graduate School of Medical Sciences, and Departments of [2]Preventive Medicine/Biostatistics and Medical Decision Making, [3]Nursing, and [4]Public Health, Nagoya University Graduate School of Medicine, Nagoya, Japan; [5]Department of Public Health, Sapporo Medical University School of Medicine, Sapporo, Japan; [6]Department of Preventive Medicine and Community Health, University of Occupational and Environmental Health, Kitakyushu, Japan; and [7]Department of Public Health, Aichi Medical University School of Medicine, Nagakute, Japan

Abstract

Purpose: **This study aimed to examine prospectively the association between physical activity and breast cancer risk in a non-Western population.**
Methods: **We analyzed data from the Japan Collaborative Cohort Study, which included 30,157 women, ages 40 to 69 years at baseline (1988-1990), who reported no previous history of breast cancer, and provided information on their walking and exercise habits. The subjects were followed prospectively from enrollment until 2001 (median follow-up period, 12.4 years). Breast cancer incidence during this period was confirmed using records held at population-based cancer registries. The Cox proportional hazards model was used to estimate the hazard ratio (HR) for the association of breast cancer incidence with physical activity.**
Results: **During the 340,055 person-years of follow-up, we identified 207 incident cases of breast cancer. The most physically active group (who walked for ≥1 hour per day and exercised for ≥1 hour per week) had a lower risk of breast cancer (HR, 0.45; 95% confidence interval, 0.25-0.78) compared with the least active group after adjusting for potential confounding factors. The inverse association of exercise on breast cancer was stronger among those who walked for ≥1 hour per day than those who walked for <1 hour per day (P = 0.042). These results were not significantly modified by menopausal status or body mass index (BMI).**
Conclusions: **Our analysis provided evidence that physical activity decreased the risk of breast cancer. Walking for 1 hour per day and undertaking additional weekly exercise both seemed to be protective against breast cancer, regardless of menopausal status or BMI.** (Cancer Epidemiol Biomarkers Prev 2008;17(12):3396–401)

Introduction

Since the early 1990s, breast cancer has been the most commonly diagnosed cancer, even among Japanese women (1). The continuous increase in breast cancer incidence during recent decades has been an important public health concern in Japan, and there has been growing interest in physical activity as a means of primary prevention. Worldwide, numerous epidemiologic studies have reported associations between physical activity and cancer risk, with most observing a protective effect. Reviews published in 2002 concluded that there was sufficient evidence to support the role of physical activity in preventing breast cancer (2, 3). A systematic review published in 2007 (4) showed a decreased relative risk (<0.8) associated with leisure activities in 8 of 17 cohort studies (5-12), whereas the remaining 9 reported no association (13-21). Three more-recent cohort studies supported the risk reduction (22-24), whereas one found no evidence of a protective effect of physical activity on breast cancer (25). In addition to the 20% to 40% overall risk reduction of breast cancer among the more physically active women (2), the effects of menstrual characteristics, obesity, use of sex hormones, hormone-receptor status, and immune function have also been discussed in previous reports (24, 26, 27). However, these have been based on data from Western populations, and to our knowledge there have been no prospective reports from Asia. Different factors might influence Asian populations, as their characteristics (such as breast cancer incidence, physical activity, and body size) tend to differ from those of Western populations. Here, we analyzed data from a large-cohort study, the Japan Collaborative Cohort (JACC) Study, to examine the relationship between physical activity and breast cancer with a particular emphasis on the interactions with other risk factors, such as menopausal status and obesity.

Materials and Methods

Study Population. The present analysis was based on data from the JACC Study. This prospective cohort study evaluated the cancer risk associated with lifestyle factors

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Requests for reprints: Sadao Suzuki, Department of Public Health, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan. Phone: 81-52-853-8176; Fax: 81-52-842-3830. E-mail: ssuzuki@med.nagoya-cu.ac.jp

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among the Japanese population. At baseline (1988-1990), 110,792 subjects (46,465 men and 64,327 women), ages 40 to 79 y, were enrolled from 45 areas throughout Japan. All of the participants were subsequently followed up for all-cause mortality. Of the women in the baseline cohort, 34,086 lived in the 22 areas where data on both cancer incidence and physical activity were available. The JACC Study has been described in detail elsewhere (28, 29). Informed consent for participation was obtained from all individuals, with the exception of those in a few study areas where informed consent was provided at the group level, after the aims and data confidentiality had been explained to community leaders. The Ethics Board of Nagoya University School of Medicine, Japan, approved the JACC Study protocol.

Physical Activity Assessment. A self-administered questionnaire was used to obtain information on physical activity at baseline (30). The items covered included amount of time spent walking, amount of time spent exercising, and physical activity at the work place. Time spent walking daily was classified into three categories (<30 min, 30-59 min, and ≥1 h), as was time spent exercising (never or seldom, 1-2 h/wk, ≥3 h/wk). The validity of the estimates of time spent participating in sports and leisure activities was examined in a sample of the baseline subjects, suggesting that measuring physical activity level with the single-item question may be appropriate for establishing baseline data that reflect long-term physical activity in a large-scale cohort study (30, 31). We did not analyze the metabolic equivalent intensity, because of a lack of information on the strength of the exercise.

Other Variables. Information on additional potential breast cancer risk factors, such as family history, body mass index (BMI), tobacco and alcohol use, age at menarche, marital status, parity, age at birth of first child, menopausal status, and hormone use, was collected via the baseline questionnaire.

Follow-up and Identification of Breast Cancer Cases. The study participants were followed up from the time of enrollment until 2001, excluding five areas in which they were halted earlier. During this period, population registry data from each municipality were used to ascertain the residential and vital status of the participants. In Japan, the registration of death is required by the Family Registration Law, theoretically providing complete mortality data. Breast cancer incidence was confirmed mainly through the records of the population-based cancer registries in each area. During the study period, only 1,189 (3.9%) of the subjects were lost to follow-up due to moving out of the given study areas. The proportion of death-certificate-only cases was 6.3% (13 of 207). The mortality-to-incidence ratio for breast cancer was 0.26 (50 of 194) in the cohort covered by the cancer registries, which was within the range calculated using the available data from population-based cancer registries in Japan (0.20-0.30; ref. 32). We expect 37.4 breast cancer incidence cases who cannot be found from the cancer registries. The present analysis excluded 246 women who reported a previous diagnosis of breast cancer and 3,683 women who did not provide information on physical activity at baseline. Thus, a total of 30,157 women were included in the present analysis.

Statistical Analysis. For all participants, the person-years of follow-up was calculated as the time from enrollment until the diagnosis of breast cancer, death from any cause, moving out of the study area, or the end of follow-up, whichever occurred first. For the breast cancer cases ascertained by death-certificate-only, the person-years of follow-up were calculated from the time of enrollment until the time of death from breast cancer. Those individuals who died from causes other than breast cancer (n = 2,518) or who moved out of the study areas were treated as censored cases. We used Cox proportional hazards models to estimate the hazard ratios (HR) and 95% confidence intervals (95% CI) for the association of breast cancer incidence with physical activity. We evaluated the relationship using two models: an age-adjusted model (using 5-y age groups), and a multivariable model with adjustments for age, BMI (<22.0 kg/m^2, 22.0-23.9 kg/m^2, 24.0-25.9 kg/m^2, ≥26.0 kg/m^2, or unknown), alcohol drinking (never, past, current, or unknown), age at menarche (<15 y, 15-16 y, ≥17 y, or unknown), education level (attended school until the age of <16 y, 16-18 y, ≥19 y, or unknown), parity (nulliparous, 1 birth, 2-3 births, ≥4 births, or unknown), age at birth of first child (<22 y, 22-23 y, 24-25 y, ≥26 y, or unknown), use of exogenous female hormone (yes, no, or unknown), family history of breast cancer in a first-degree relative (yes, no, or unknown), menopausal status (premenopausal or postmenopausal), and menopausal age for postmenopausal women (<45 y, 45-49 y, ≥50 y, or unknown). In this study, those who provided menopausal age or who were at the average age at menopause, i.e., ≥49 y at baseline, were treated as postmenopausal women, and only those who were <49 y without information of menopausal age were treated as premenopausal women. Each "unknown" category included 5% to 9% of all women. All analyses were stratified by six study areas (Hokkaido and Tohoku, Kanto, Chubu, Kinki, Chugoku, and Kyushu). Trend tests were done for category-based scores, which were assessed by allocating values ranging from 1 to 3 to each individual according to the selected physical activity variables.

To estimate the interaction of time spent walking and time spent exercising, we recategorized the subjects into four groups using the following cutoff points for physical activity: daily walking for <1 h or ≥1 h, and weekly exercising for <1 h or ≥1 h. Furthermore, the HR for the most active group (those who walked for ≥1 h/d and exercised for ≥1 h/wk) compared with the other groups was estimated according to menopausal status and BMI (<24 or ≥24 kg/m^2), and we examined the interaction between physical activity and these factors (Table 5). We used a BMI of 24 kg/m^2 instead of 25 kg/m^2 as a cutoff point for overweight. That was because there were only 47 cases for BMI ≥24 kg/m^2, which were too few to discuss interaction. For instance, we estimated the two HRs for physical activity among women who were premenopausal and postmenopausal at baseline, and then the P value for the interaction term of menopausal status and physical activity was calculated to test the difference between these HRs. We repeated the analysis after excluding the initial 2 y of follow-up, during which 37 cases of breast cancer were diagnosed. All of the P values were two-sided, with $P < 0.05$ indicating statistical significance. All of the analyses were done with SAS version 9.1 (SAS Institute, Inc.).

Table 1. Baseline characteristics associated with age in the JACC Study

Characteristics	Age group				Total
	40-49 y	50-59 y	60-69 y	70-79 y	
Number, *n* (row %)	7,561 (25.1)	9,361 (31.0)	9,098 (30.2)	4,137 (13.7)	30,157 (100.0)
Time spent walking per day					
Never or seldom, *n* (%)	868 (11.5)	1,013 (10.8)	807 (8.9)	403 (9.7)	3,091 (10.2)
Around 30 min, *n* (%)	1,393 (18.4)	1,650 (17.6)	1,794 (19.7)	876 (21.2)	5,713 (18.9)
30-59 min, *n* (%)	1,584 (20.9)	1,989 (21.2)	1,945 (21.4)	956 (23.1)	6,474 (21.5)
≥1 h, *n* (%)	3,716 (49.1)	4,709 (50.3)	4,552 (50.0)	1,902 (46.0)	14,879 (49.3)
Time spent exercising per wk					
Never or seldom, *n* (%)	5,890 (77.9)	7,365 (78.7)	6,591 (72.4)	2,842 (68.7)	22,688 (75.2)
1-2 h, *n* (%)	1,176 (15.6)	1,298 (13.9)	1,412 (15.5)	617 (14.9)	4,503 (14.9)
3-4 h, *n* (%)	338 (4.5)	399 (4.3)	572 (6.3)	306 (7.4)	1,615 (5.4)
≥5 h, *n* (%)	157 (2.1)	299 (3.2)	523 (5.7)	372 (9.0)	1,351 (4.5)

NOTE: Mean (SD) or %, calculated for participants with complete physical activity data.

Results

The average age at baseline was 57.6 ± 10.1 years, and the median follow-up time was 12.4 years. During the 340,055 person-years of follow-up, we identified 207 incident cases of breast cancer. The annual incidence of breast cancer in the cohort per 1,000 women was 0.61. Table 1 shows the distributions of physical activity according to age. Time spent walking was distributed similarly in the four age groups, with ~50% of the subjects walking for ≥1 hour per day. By contrast, for time spent exercising and physical activity at the work place, the older the subjects, the more physically active they tended to be. Regardless of the age group, more than two thirds of the participants never or seldom exercised.

Table 2 presents the risk of breast cancer in relation to physical activity. After adjusting for potential confounding factors, the HR was marginally decreased among those who walked for ≥1 hour per day (HR, 0.73; 95% CI, 0.53-1.01). However, those who exercised for ≥3 hours per week were not statistically decreased (HR, 0.85; 95% CI, 0.51-1.40). The *P* value for the linear trend of time spent walking was 0.043, which indicated that the dose-response effect of time spent walking and breast cancer risk was significant. The adjusted HR for those who walked for ≥1 hour compared with the rest of the women was significantly different (HR, 0.70; 95% CI, 0.53-0.93), although that for those who exercised for ≥3 hours per week was not significant (HR, 0.83; 95% CI, 0.59-1.16).

To investigate the joint effect of walking and exercise, we recategorized the data using the following cutoff points for physical activity: daily walking for <1 hour and exercising for <1 hour per week. Table 3 shows the mean values and distributions of risk factors for breast cancer according to the walking and exercise time categories. The subjects who walked and exercised more tended to be older and to drink more alcohol. The BMI values did not significantly differ between categories (range, 22.7-22.8 kg/m^2).

Table 4 shows the HRs of breast cancer associated with the joint effect of time spent walking and time spent exercising. The most physically active group (those who walked for ≥1 hour per day and exercised for ≥1 hour per week) had a lower risk of breast cancer (HR, 0.45; 95% CI, 0.25-0.78) compared with the least active group after adjusting for potential confounding factors. A significant interaction (P = 0.042) was observed between time spent walking and time spent exercising, meaning that the combined effect of exercise and walking on breast cancer was significant.

The HR of the most physically active group compared with the rest of the women was estimated for the subgroups according to menopausal status and BMI in Table 5, to examine the effects modification of these factors on the association between physical activity and breast cancer onset. The marginal inverse association was

Table 2. HR of breast cancer associated with physical activity in the JACC study

Physical activity	Cases	Person-years	Age adjusted	Multivariate*
			HR (95% CI)	HR (95% CI)
Time spent walking per day				
<30 min	69	96,752	1.00 (Reference)	1.00 (Reference)
30−59 min	56	71,411	1.14 (0.71 − 1.84)	1.13 (0.80 − 1.61)
≥1 h	82	171,892	0.70 (0.51 − 0.97)	0.73 (0.53 − 1.01)
P for trend			0.021	0.043
Time spent exercising per week				
Never or seldom	161	255,829	1.00 (Reference)	1.00 (Reference)
1−2 h	29	51,043	0.87 (0.59 − 1.30)	0.83 (0.56 − 1.23)
≥3 h	17	33,183	0.87 (0.53 − 1.45)	0.85 (0.51 − 1.40)
P for trend			0.45	0.33

*Adjusted for age, BMI, alcohol drinking, age at menarche, education level, parity, age at birth of first child, use of exogenous female hormone, family history of breast cancer in a first-degree relative, menopausal status, and menopausal age for postmenopausal women.

Table 3. Baseline characteristics associated with physical activity in the JACC study

Characteristics	Time spent exercising <1 h/wk		Time spent exercising ≥1 h/wk	
	Time spent walking per day		Time spent walking per day	
	<1 h	≥1 h	<1 h	≥1 h
Number, *n* (row %)	11,864 (39.3)	10,824 (35.9)	3,414 (11.3)	4,055 (13.4)
BMI, mean ± SD (kg/m^2)	22.8 ± 3.2	22.7 ± 3.0	22.8 ± 3.0	22.7 ± 2.9
Age at baseline, mean ± SD, y	57.5 ± 10.3	56.8 ± 9.6	58.5 ± 10.3	59.2 ± 10.4
Age at menarche, mean ± SD, y	14.8 ± 1.8	14.9 ± 1.8	14.8 ± 1.8	14.9 ± 1.8
Age at birth of first child, mean ± SD, y	25.2 ± 3.3	25.0 ± 3.3	25.1 ± 3.2	24.9 ± 3.1
Age at menopause, mean ± SD, y	48.7 ± 4.8	48.6 ± 4.6	48.8 ± 4.7	48.9 ± 4.5
Age of the end of education, mean ± SD, y	16.6 ± 2.1	16.5 ± 2.1	16.9 ± 2.2	16.7 ± 2.1
Postmenopausal, *n* (%)	8,946 (75.4)	8,176 (75.5)	2,657 (77.8)	3,225 (79.5)
Nulliparous, *n* (%)	612 (5.2)	387 (3.6)	142 (4.2)	163 (4.0)
Not married, *n* (%)	223 (2.0)	120 (1.2)	65 (2.1)	42 (1.1)
Exogenous female hormone use, *n* (%)	580 (5.4)	474 (4.8)	191 (6.2)	207 (5.7)
Family history of breast cancer,* *n* (%)	191 (1.6)	159 (1.5)	63 (1.9)	65 (1.6)
Current smoker, *n* (%)	606 (5.6)	556 (5.7)	133 (4.3)	183 (5.0)
Current drinker, *n* (%)	2,594 (23.1)	2,447 (24.0)	906 (27.9)	1,122 (29.4)

NOTE: Mean (SD) or %, calculated for participants with complete physical activity data.
*In a first-degree relative.

observed in each subgroup, and no significant interaction was observed. This suggests that the inverse association was not modified by these factors. Similar results were found after excluding the initial 2 years of follow-up, during which 37 cases of breast cancer were diagnosed.

Discussion

Our prospective analysis of the relationship between physical activity and breast cancer in Japanese women revealed a significant inverse association. In particular, the combined effect of walking and exercise was stronger than that expected based on the individual effects. Moreover, the combined protective effect of walking and exercise was not modified significantly by menopausal status or BMI. This suggests that physical activity has a protective effect regardless of menopausal status or weight. Previous studies of Western populations have provided convincing evidence of an inverse association between physical activity and breast cancer risk (2, 3), as supported by a recent systematic review (4). Adding more recent cohort studies (22-25), 10 of 21 showed a significantly decreased breast cancer risk associated with physical activity. Despite the comparatively lower incidence of breast cancer in Japan (1), an inverse association between physical activity and breast cancer incidence has also been observed, which was consistent with the findings of previous case-control studies in Japan (33-35).

The present study showed an interactive effect of walking and exercise. This could be explained in several ways. For instance, multiple types of exercise might work more effectively than a single type of exercise, the effect of physical activity might be quadratic, or walkers might tend to exercise more intensely. Whatever the reason, our results indicate that walking for ≥1 hour per day should initially be recommended, and additional weekly exercise should be undertaken to improve the protective effect against breast cancer.

In the present study, menopausal status and BMI did not affect the relationship between physical activity and breast cancer. Of the two, the modifying effect of menopausal status is the more controversial. Among the previous cohort studies that have analyzed this association according to menopausal status, only two have observed a significantly decreased breast cancer risk among premenopausal women (11, 22), and the evidence is weaker among premenopausal women (5, 10, 17). This difference might be partly due to the way in which menopause has been treated in the analyses. All of the studies, including the present one, reporting a protective effect of physical activity among premenopausal women have used only baseline menopausal status and have not updated this measure. By contrast, a study that found no association did update the menopausal status (19), and menopause was included as one of its end points.

Compared with menopausal status, the effect modification of BMI on the association between physical

Table 4. HR of breast cancer associated with physical activity in the JACC study

Physical activity		Cases	Person-years	Age adjusted	Multivariate*
Time spent walking (h/d)	Time spent exercising (h/wk)			HR (95% CI)	HR (95% CI)
<1	<1	93	130,279	1.00 (Reference)	1.00 (Reference)
≥1	<1	68	125,550	1.18 (0.79 - 1.77)	1.13 (0.75 - 1.69)
<1	≥1	32	37,885	0.76 (0.56 - 1.04)	0.82 (0.60 - 1.12)
≥1	≥1	14	46,342	0.42 (0.24 - 0.74)	0.45 (0.25 - 0.78)
P for interaction				0.035	0.041

*Adjusted for age, BMI, alcohol drinking, age at menarche, education level, parity, age at birth of first child, use of exogenous female hormone, family history of breast cancer in a first-degree relative, menopausal status, and menopausal age for postmenopausal women.

Table 5. HR of breast cancer among the most physically active group compared with the rest of the women by subgroup of menopausal status and BMI in the JACC study

Subgroup	Age adjusted	Multivariate*
	HR (95% CI)	HR (95% CI)
Menopausal status		
Premenopausal	0.14 (0.02 – 0.97)	0.13 (0.02 – 0.91)
Postmenopausal	0.53 (0.29 – 0.96)	0.53 (0.29 – 0.96)
P for interaction	0.524	0.528
BMI (kg/m^2)		
<24	0.43 (0.20 – 0.91)	0.42 (0.19 – 0.90)
≥24	0.45 (0.18 – 1.10)	0.44 (0.18 – 1.09)
P for interaction	0.940	0.949

*Adjusted for age, BMI, alcohol drinking, age at menarche, education level, parity, age at birth of first child, use of exogenous female hormone, family history of breast cancer in a first-degree relative, menopausal status, and menopausal age for postmenopausal women.

activity and breast cancer risk has been more consistent, as previous studies have failed to show general effects (5, 6, 8-10, 13, 14, 16, 18, 19, 21). These findings suggest that the effect of physical activity is independent of menopausal status (despite the possibility of a less precise effect among premenopausal women) and BMI. Therefore, the recommendation to undertake physical activity to prevent breast cancer does not need to be altered according to differences in these factors.

A major strength of the present study is its prospective design, which might avoid the recall bias that is possible in case-control studies. Moreover, information on other risk factors for breast cancer was included, and potential confounding factors were controlled for in the analyses when examining the association.

Our study had some limitations that should be considered when interpreting the results. First, because we used only a simple questionnaire at baseline, neither metric equivalent nor updated values were available to evaluate physical activity. In general, assessing physical activity in epidemiologic studies is difficult, which might explain the heterogeneous results observed across studies of its association with breast cancer (36). Although it is possible that the reported levels might have overestimated or underestimated the actual physical activity, the information was collected before diagnosis and should not have differed according to the end point status. Thus, the misclassification of physical activity in the present study for both reasons is nondifferential. It means the estimated HRs tend to be close to the null, and true HRs should be smaller due to the misclassification. In addition, because more than two thirds of the women in our cohort never or seldom exercised, we expect less serious misclassification. Second, updated information on menopausal status was lacking, which could modify the relationship between physical activity and breast cancer. Thus, from an etiologic viewpoint, the misclassification of menopausal status at the onset of breast cancer should be important. However, from the viewpoint of cancer prevention, the menopausal status at cancer onset is comparatively less important, and the HR could be naturally interpreted for premenopausal women at baseline. Third, misclassification of menopausal status at baseline should also be considered. However, the point estimate of the HR among premenopausal women was smaller than that among postmenopausal women, which could not be explained from misclassification. In addition, the results were not essentially changed when we removed women who were 47 to 50 years old from the premenopausal group. More studies are needed of premenopausal women in larger subjects.

In summary, our analysis provided evidence that physical activity decreased the risk of breast cancer among Japanese women. Another encouraging finding of this study is that the effect of physical activity on breast cancer risk is not modified by menopausal status and BMI. We recommend walking for 1 hour per day along with additional weekly exercise to protect against breast cancer, regardless of menopausal status and BMI.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Appendix 1. The Japan Collaborative Cohort Study Group

The present members of the JACC Study and their affiliations are as follows: Dr. Akiko Tamakoshi (present chairman of the study group), Aichi Medical University School of Medicine; Dr. Mitsuru Mori, Sapporo Medical University School of Medicine; Dr. Yutaka Motohashi, Akita University School of Medicine; Dr. Ichiro Tsuji, Tohoku University Graduate School of Medicine; Dr. Yosikazu Nakamura, Jichi Medical School; Dr. Hiroyasu Iso, Institute of Community Medicine, University of Tsukuba; Dr. Haruo Mikami, Chiba Cancer Center; Dr. Yutaka Inaba, Juntendo University School of Medicine; Dr. Yoshiharu Hoshiyama, University of Human Arts and Sciences Graduate School; Dr. Hiroshi Suzuki, Niigata University Graduate School of Medical and Dental Sciences; Dr. Hiroyuki Shimizu, Gifu University School of Medicine; Dr. Hideaki Toyoshima, Nagoya University Graduate School of Medicine; Dr. Shinkan Tokudome, Nagoya City University Graduate School of Medical Sciences; Dr. Yoshinori Ito, Fujita Health University School of Health Sciences; Dr. Shuji Hashimoto, Fujita Health University School of Medicine; Dr. Shogo Kikuchi, Aichi Medical University School of Medicine; Dr. Kenji Wakai, Nayoga University Graduate School of Medicine; Dr. Akio Koizumi, Graduate School of Medicine and Faculty of Medicine, Kyoto University; Dr. Takashi Kawamura, Kyoto University Center for Student Health; Dr. Yoshiyuki Watanabe and Dr. Tsuneharu Miki, Kyoto Prefectural University of Medicine Graduate School of Medical Science; Dr. Chigusa Date, Faculty of Human Environmental Sciences, Mukogawa Women's University; Dr. Kiyomi Sakata, Wakayama Medical University; Dr. Takayuki Nose, Tottori University Faculty of Medicine; Dr. Norihiko Hayakawa, Research Institute for Radiation Biology and Medicine, Hiroshima University; Dr. Takesumi Yoshimura, Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health, Japan; Dr. Akira Shibata, Kurume

University School of Medicine; Dr. Naoyuki Okamoto, Kanagawa Cancer Center; Dr. Hideo Shio, Moriyama Municipal Hospital; Dr. Yoshiyuki Ohno (former chairman of the study group), Asahi Rosai Hospital; Dr. Tomoyuki Kitagawa, Cancer Institute of the Japanese Foundation for Cancer Research; Dr. Toshio Kuroki, Gifu University; and Dr. Kazuo Tajima, Aichi Cancer Center Research Institute.

The past investigators of the study group were listed in ref. 28 except for the following eight members (affiliations are those at the time they participated in the study): Dr. Takashi Shimamoto, Institute of Community Medicine, University of Tsukuba; Dr. Heizo Tanaka, Medical Research Institute, Tokyo Medical and Dental University; Dr. Shigeru Hisamichi, Tohoku University Graduate School of Medicine; Dr. Masahiro Nakao, Kyoto Prefectural University of Medicine; Dr. Takaichiro Suzuki, Research Institute, Osaka Medical Center for Cancer and Cardiovascular Diseases; Dr. Tsutomu Hashimoto, Wakayama Medical University; Dr. Teruo Ishibashi, Asama General Hospital; and Dr. Katsuhiro Fukuda, Kurume University School of Medicine.

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RESEARCH COMMUNICATION

Sex and Seasonal Variations of Plasma Retinol, α-Tocopherol, and Carotenoid Concentrations in Japanese Dietitians

Jin Xiang[1a], Teruo Nagaya[2], Xin-En Huang[1b], Kiyonori Kuriki[3], Nahomi Imaeda[4], Yuko Tokudome[5], Juichi Sato[6], Nakako Fujiwara[7], Shinzo Maki[8], Shinkan Tokudome[2]*

Abstract

Aim: To clarify sex and seasonal variations of plasma antioxidant concentrations among middle-aged Japanese. Subjects and Methods: We investigated sex and seasonal variations of plasma antioxidant concentrations, including retinol, α-tocopherol, and carotenoids (α-carotene, β-carotene,β-cryptoxanthin, lutein and lycopene), in 55 middle-aged dietitians (46 women and 9 men) in Aichi Prefecture, Central Japan, who took no supplements from autumn 1996 to summer 1997. Reversed-phase high performance liquid chromatography was used to measure plasma antioxidant concentrations in overnight-fasting blood samples. Results: Plasma levels of α-tocopherol, α-/β-carotene, β-cryptoxanthin and lutein were significantly influenced by sex, being significantly higher for women than men in each corresponding season; retinol and lycopene, however, showed no such difference. For women, winter values of α-tocopherol, α-/β-carotene, lutein and lycopene were significantly lower than corresponding summer values, and had reached their annual lowest. Retinol failed to show any significant seasonal variation, whereas the winter value of β-cryptoxanthin had reached its annual highest. For men, β-cryptoxanthin exhibited significant seasonal changes and was also highest in winter. Winter values of α-tocopherol, α-/β-carotene and lycopene were lower compared with other seasons, but not statistically significant, probably due to the small sample size. Conclusions: The findings indicate that sex and seasonal variations of plasma antioxidant concentrations should be taken into account in nutritional epidemiologic studies.

Key Words: Sex - season - variation - plasma antioxidants - retinol - α-tocopherol - carotenoids

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Introduction

According to epidemiologic observations, many antioxidants are inversely associated with the risk or prevalence of chronic diseases (Goodman, 1984; Cutler, 1991; Mobarhan et al., 1991; Byers et al., 1992). Antioxidants are thought to play an important role in disease prevention, in particular, such as vitamin E in the prevention of heart disease (Rimm et al., 1993; Stampfer et al., 1993), and retinoids, tocopherols and carotenoids in the prevention of cancer (Moon et al., 1976; Suda et al., 1986; Bertram et al., 1991; Knekt et al., 1991; Rimm et al., 1993).

Plasma concentrations of antioxidants may fluctuate according to host and environmental factors. Sex (Shibata et al., 1989), smoking/drinking habits (Stryker et al., 1988) and season (Cantilena et al., 1992) have also been observed to impact on plasma antioxidant levels. However, in the Asian countries, including Japan, where host and environmental factors are known to be fundamentally different from those in the Western world, few studies have been conducted to investigate the effects of sex and seasonal changes on plasma antioxidant concentrations.

Here we examined the influence of sex (a host factor) and season (an environmental factor) on variations in plasma antioxidant levels in Japanese dietitians living in Aichi Prefecture, Central Japan who participated in our previous nutritional studies (Tokudome et al., 2001; Imaeda et al., 2002; Kuriki et al., 2002; Tokudome et al., 2002).

Materials and Methods

Study Subjects

One hundred and six middle-aged dietitians (85 women, 21 men), who were members of the Aichi

*[1a]Dept of Science Research, [1b]Dept of Chemotherapy, Jiangsu Cancer Hospital and Research Institute, Nanjing, China, [2]Dept of Public Health, Nagoya City University Graduate School of Medical Sciences, Mizuho-ku, Nagoya 467-8601, [3]Aichi Cancer Center, Chikusa-ku, Nagoya, [4]Nagoya Women's University, Mizuho-ku, Nagoya, [5]Nagoya University of Arts and Sciences, Nisshin, [6]Dept of General Medicine, Nagoya University Hospital, Showa-ku, Nagoya, [7]Aichi Kiwami College of Nursing, Ichinomiya, [8]Aichi Prefectural Dietitians' Association, Kita-ku, Nagoya, Japan *For correspondence: tokudome@med.nagoya-cu.ac.jp*

Prefectural Dietitians' Association residing in Aichi Prefecture, Central Japan voluntarily participated in this study, as reported elsewhere (Tokudome et al., 2001). In brief, 97 subjects were enrolled after excluding those with chronic diseases. Among them, 86 whose four-season blood samples (Autumn 1996 - Summer 1997) were available, entered the current investigation. Information on demographic characteristics, drinking and smoking habits, regular exercise, and intake of supplements, including vitamins, was obtained from a self-administered questionnaire. Finally, 55 subjects (46 women and 9 men) who regularly took no supplements were eligible for in-depth analysis.

This protocol was approved by the Ethics Committee of the Nagoya City University Graduate School of Medical Sciences, and written informed consent was secured from each study participant.

Methods

Overnight-fasting venous blood was sampled using a tube with EDTA-2Na, and separated into plasma, buffy coat, and RBC clot. The samples were stored at -80° C until analysis.

Seven plasma antioxidants, including retinol, α-tocopherol and five carotenoids (α-/β-carotene, β-cryptoxanthin, lutein and lycopene) were assessed by reverse-phase high performance liquid chromatography (HPLC) according to a modification of Talwar's method (Talwar et al., 1998). At the time of analysis, samples were thawed at room temperature. As an internal standard, 0.1 ml retinol acetate and 0.1 ml tocopherol acetate were added to 0.1 ml plasma. The total volume was raised to 1.3 ml with distilled water. After protein was precipitated by adding 0.9 ml ethanol, fat-soluble substances were extracted twice with 1.2 ml hexane.

Samples were mixed and centrifuged for 15 min. The hexane layer was gathered and evaporated under a nitrogen atmosphere. The residue was reconstituted with tetrahydrofuran making up to 0.3 ml with a mobile phase, and 0.2 ml was injected into Shimadzu HPLC with a Nucleosil C18 column. The mobile phase, which consisted of methanol, acetonitrile and tetrahydrofuran in the ratio of 75 : 20 : 5, flowed at 0.6 ml/min. Using an SPD-M10 Avp Shimadzu diode array detector, retinol and retinol acetate were detected at 325 nm, α-tocopherol and tocopherol acetate at 292 nm, α-/β-carotene, β-cryptoxanthin and lutein at 450 nm, along with lycopene at 473 nm.

Laboratory accuracy and precision in the measurements of seven plasma antioxidants (retinol, α-tocopherol, and five carotenoids) were maintained and assessed by using pooled plasma. Concentrations of antioxidants in the plasma were calculated with the aid of commercially available lyophilized serum from NIST (the National Institute of Standards and Technology). Two pooled plasma samples were analyzed at the beginning and the end of each run. Coefficients of variation for the antioxidants ranged from 3.3% (α-tocopherol) to 13.7% (β-crytoxanthin) for the same day determination, and from 5.0% (retinol) to 14.6% (β-crytoxanthin) for day-to-day reproducibility.

Table 1. Baseline Demographic and Lifestyle Characteristics of 55 Japanese Dietitians Not Taking Supplements

Characteristics	Women (n=46)		Men (n=9)		p value[a]
Age(y) mean(SD)	46.4 (7.8)		47.7 (10.2)		0.67
BMI(kg/m²)[b] n (%)					0.11
<19.8	12	26.1	1	11.1	
19.8-24.2	30	65.2	5	55.6	
>24.2	4	8.7	3	33.3	
Smoking habit					<0.001
Current	1	2.2	2	22.2	
Ceased	1	2.2	3	33.3	
Never	44	95.7	4	44.4	
Drinking habit					<0.05
Current	9	19.6	6	66.7	
Ceased	1	2.2	0	0	
Never	36	78.3	3	33.3	
Regular exercise					0.3
With	29	63.0	4	44.4	
Without	17	37.0	5	55.6	

[a]By Chi-square test or Student t-test, [b]Categorization was made according to obesity assessment standards set by Japan Obesity Association.

Table 2. Plasma Concentrations of Retinol, α-Tocopherol, and Carotenoids in Japanese Dietitians Not Taking Supplements

		Women (n=46)	Men (n=9)
Retinol (umol/L)	Autumn	2.12 (1.18-3.60)	2.33 (1.47-2.86)
	Winter	2.25 (0.77-3.45)	2.41 (1.82-2.75)
	Spring	2.16 (1.23-4.18)	2.80 (1.86-2.97)
	Summer	2.25 (1.34-3.88)	2.37 (1.66-3.11)
α-Tocopherol (umol/L)	Autumn	31.8 (18.4-65.3)[e]	21.8 (18.2-39.1)
	Winter	28.2 (17.0-49.0)[c,b,e]	21.7 (18.3-41.6)
	Spring	33.3 (23.2-68.9)[e]	27.2 (19.2-42.9)
	Summer	33.1 (21.6-60.1)[e]	26.0 (18.4-41.9)
α-Carotene (umol/L)	Autumn	0.30 (0.11-0.71)[b]	0.20 (0.10-0.72)
	Winter	0.25 (0.09-0.58)[b,e]	0.13 (0.08-0.40)
	Spring	0.26 (0.11-0.63)[b,e]	0.14 (0.07-0.59)
	Summer	0.36 (0.12-1.17)[e]	0.16 (0.09-1.04)
β-Carotene (umol/L)	Autumn	1.33 (0.42-2.53)[e]	0.60 (0.27-2.08)
	Winter	1.10 (0.21-3.12)[c,b,e]	0.55 (0.26-1.60)
	Spring	1.27 (0.47-3.16)[e]	0.67 (0.13-1.61)
	Summer	1.40 (0.48-3.74)[e]	0.60 (0.30-1.92)
β-Crypto-xanthin (umol/L)	Autumn	0.55 (0.10-1.70)[a,b,e]	0.24 (0.11-0.56)
	Winter	1.06 (0.14-3.20)[c,b]	0.73 (0.13-2.10)[d]
	Spring	0.49 (0.10-2.02)[b,e]	0.18 (0.11-0.57)
	Summer	0.39 (0.08-1.07)[e]	0.22 (0.08-0.32)
Lutein (umol/L)	Autumn	0.85 (0.36-1.21)[a,e]	0.50 (0.32-0.74)
	Winter	0.73 (0.30-1.09)[c,b,e]	0.53 (0.31-0.70)
	Spring	0.81 (0.39-1.66)[e]	0.61 (0.31-0.76)
	Summer	0.87 (0.37-1.71)[e]	0.57 (0.26-1.50)
Lycopene (umol/L)	Autumn	0.49 (0.12-1.49)[b]	0.53 (0.10-1.08)
	Winter	0.32 (0.11-1.67)[c,b]	0.33 (0.10-0.71)
	Spring	0.51 (0.09-1.83)[b]	0.49 (0.11-0.70)
	Summer	0.71 (0.18-2.17)	0.55 (0.12-0.97)

*Medians; ranges (minimum-maximum) in parentheses. Significantly different: [a]from women in winter, p<0.01, [b]from women in summer, p<0.05, [c]from women in spring, p<0.05, [d]from men in summer, p<0.05, [e]between women and men in the same season, p<0.05

Statistical analysis

The normality of distribution of seasonal antioxidant measurements in each sex group was determined by the Shapiro-Wilk test. If not normally distributed, distribution-free (non-parametric) methods were adopted for further statistical analyses. The Kruskal-Wallis test was adopted for an analysis of variance with the seasons by sex, and the Wilcoxon 2-sample test for variance between men and women. Procedures of FREQ, UNIVARIATE, or NPAR1WAY in the SAS package were used for statistical calculations (SAS Institute, Inc., 1990). Differences were considered to be statistically significant at $p<0.05$.

Results

Baseline demographic and lifestyle characteristics of 55 Japanese dietitians (46 women and 9 men) who took no supplements are summarized in Table 1. There were no statistical differences between women and men in age, BMI or physical exercise. However, smoking and drinking rates were significantly higher in men.

The Shapiro-Wilk test showed that few distributions of plasma antioxidant values in each sex and season appeared normally distributed. Therefore, non-parametric methods were adopted for statistical analyses. Table 2 shows sex- and season-specific medians and ranges of respective antioxidants. Retinol and lycopene did not significantly differ between men and women. α-Tocopherol was significantly higher in women than men in all seasons, and reached its highest in spring for all subjects. The Kruskal-Wallis test showed that there were statistically significant seasonal variations in α-/β-carotene, β-cryptoxanthin, lutein and lycopene in women, as well as β-cryptoxanthin in men. Both α-carotene and β-carotene were higher in women than men in each corresponding season. A higher level was noted in women in summer, and in men in autumn or spring. The concentrations of β-cryptoxanthin were higher in women than men in each corresponding season with the highest value appearing in winter for both groups. Lutein was highest in summer in women, while it was highest in spring in men. Women showed higher lutein than men, irrespective of the season.

Discussion

Plasma levels of α-tocopherol, α-/β-carotene, β-cryptoxanthin and lutein were significantly higher for women than men in each corresponding season; but no sex difference was observed for retinol and lycopene. For women, winter concentrations of α-tocopherol, α-/β-carotene, lutein and lycopene were significantly lower than their corresponding summer values, and were the lowest of the entire year. Retinol demonstrated no significant seasonal variation; however, the winter level of β-cryptoxanthin was found to be the highest of the whole year. For men, β-cryptoxanthin showed significant seasonal changes and was also highest in winter. Winter concentrations of α-tocopherol, α-/β-carotene and lycopene tended to be lower compared with other seasons. Plasma concentrations of α-tocopherol, α-/β-carotene, β-cryptoxanthin and lutein in women were higher than in men throughout the year.

The present findings are in harmony with the observations of healthy Japanese students, university staff and general local inhabitants (Ito et al., 1990), a Spanish clinical staff (Olmedilla et al., 1994), and the US general population (Krasinski et al., 1989), as well as in a US hospital-based study (Stacewicz-Saquntzakis et al., 1987). That may be explained by the fact that Japanese women consume more fruit and vegetables (Inoue et al., 1997), smoke less and drink less alcohol than Japanese men (Tsubono et al., 1997; Health Promotion and Nutrition Division 1998). It has been proven that fruit and vegetables are major sources of these micronutrients (Resources Council 1982; Willett, 1990; Resources Council 1992; Tokudome et al., 1998), while smoking and drinking risked diminishing the reserves of antioxidants (Russell-Briefel et al., 1985; Stryker et al., 1988). Interestingly, however, our results are also consistent with the reports that the retinol level in men may be slightly higher than in women (Stacewicz-Saquntzakis et al., 1987; Krasinski et al., 1989; Ito et al., 1990; Olmedilla et al., 1994). Although it is still impossible to fully elucidate the mechanism underlying why plasma antioxidant concentrations differ by sex, this variation should be taken into account in the assessment as well as the planning of any nutritional epidemiologic research; otherwise it could impose a bias due to the sex predominance in the study population.

In the present study, the seasons did not significantly affect retinol in either men or women. However, there were statistically significant seasonal changes of α-tocopherol, α-/β-carotene, β-cryptoxanthin, lutein and lycopene in women; but statistical power did not appear sufficient to detect such seasonal variations in men. For all study subjects, higher α-tocopherol occurred in spring, and higher β-cryptoxanthin in winter, whereas, α-/β-carotene and lycopene tended to be higher in summer or in autumn. This could be attributable to dietary variations by season, since all study participants come from central Japan (longitude around 136°~137° E., latitude around 35° N.), where there are distinct seasonal changes in the temperature and hours of sunlight. It is noteworthy that from September to later October Japanese enjoy an abundance of agricultural products, including fruit, and green and yellow vegetables. Our previous study of the same dietitian cohort showed that the dietary intakes of selected vitamins and minerals measured by weighed diet records were greater in autumn and winter than those in spring and summer (Tokudome et al., 2002). Similar seasonal changes have also been observed by Olmedilla (Olmedilla et al., 1994), and in studies on α-carotene (Van Staveren et al., 1986; Ziegler, 1989; Rautalahti et al., 1993). In the case of retinol, seasonal variations are not as remarkable as with other micronutrients, compatible with other studies (Olmedilla et al., 1994; Cooney et al., 1995); however, the reason remains obscure, suggesting that adjustments for seasonal effects should be allowed at least for α-tocopherol and the above-mentioned carotenoids in nutritional epidemiologic studies.

In conclusion, although mechanisms of sex and seasonal variations in plasma retinol, α-tocopherol and five carotenoids need to be further elucidated in different ethnic groups and areas, such changes in blood antioxidant levels should also be taken into account to determine any associations with disease prevention and health promotion in nutritional epidemiologic research.

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RESEARCH COMMUNICATION

Development of a Semi-quantitative Food Frequency Questionnaire for Dietary Studies - Focus on Vitamin C Intake

Le Tran Ngoan[1]*, Nguyen Cong Khan[2], Le Bach Mai[2], Nguyen Thi Thanh Huong[3], Nguyen Thi Thu[1], Nguyen Thi Lua[1], Lai Thi Minh Hang[1], Nguyen Ngoc Bich[1], Nguyen Van Hieu[1], Ha Van Quyet[1], Le Thi Tai[1], Do Duc Van[1], Malcolm A Moore[4], Shinkan Tokudome[5], Takesumi Yoshimura[6]

Abstract

The present work aimed to provide a basis for examination of intake of selected food items determined with a semi-quantitative food frequency questionnaire (SQFFQ) and planned-food selection (PFS). From February to July of 2003, ninety one cancer patients and 90 matched (sex and age ± 5 years) non-cancer patients were directly interviewed by trained interviewers using the designed questionnaire at the inpatient-department of Viet Duc hospital, Ha Noi City, Viet Nam. Study subjects consumed more SQFFQ-food items than PFS-food items, so that the latter method might not accurately reflect dietary habits regarding estimation of nutrient intake, especially vitamins. Because these are beneficial factors acting against cancer development at many sites, the absence of food items selected by SQFFQ may result in a poor database regarding possible confounding factors. For futher clarification we then focused on vitamin C contributions of Vietnamese food and analyzed data of the National Nutritional Household Survey in 2000: 7,686 households throughout the country (vitamin C intake status) and 158 households with 741 persons of the population of Hanoi city (individual food items contributing to vitamin C). Direct interview using a validated questionnaire with an album of current Vietnamese food items-recipes and weighing checks was conducted to obtain information regarding all types of food intake over the last 24-hours. Contribution analysis using the Nutritive Composition Table of Vietnamese Foods, revision 2000, and stepwise regression analysis was applied. Average intake adjusted by ages of vitamin C per person per day was estimated. In total, the study subjects were found to currently consume 184 food items. Average intake of vitamin C was 72.5 mg per person per day at the national level: 57.9% from leafy vegetables, 33.4% from fresh fruits, and 6.4% from non-leafy vegetables. For vitamin C contribution, the highest 25 food items contributed to a cumulative 95.3% of vitamin C intake with a cumulative R2=0.99.

Key Words: Dietary influence - semi-quantitative food frequency questionnaire - vitamin C - sources - Viet Nam

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Introduction

The relation of diet to cancer has long been highlighted (Bulkley, 1914) and during the 1980s about 35% of human cancers were estimated to be due to dietary factors (Doll & Peto, 1981). However, our knowledge of mechanisms linking diet to cancer are still limited, largely because quantitation is very difficult. We earlier found that frequent intake of fried foods increased the risk of developing stomach cancer as much as four fold, based on follow-up of 25 selected food items in 586 Japanese foodstuffs (Ngoan et al., 2002; Tokudome et al., 1998).

To select food items for epidemiological studies on dietary habits and cancer there are two generally applied methods: semi-quantitative food frequency questionnaire (SQFFQ); and the other is a planned-food selection (PFS). These two methods have major differences in principles and ways of choosing food items, including the designed questionnaires. Selection of food items by SQFFQ is based on nutrient contributions by food intake whereas by PFS it is based on the investigator's hypothesis for a possible relationship with specific food items. Very few studies have been performed to address advantages and disadvantages of these two methods. Therefore the present work was performed focusing on the diet of Viet Nam.

It has been hypothesized that vitamin C may reduce the risk of developing stomach cancer by about 50% (Balansky et al., 1986). Vitamin C contribution by daily

*[1]Hanoi Medical University, [2]National Nutrition Institute, [3]Quang Binh Department of Health, Hanoi City, Viet Nam, [4]UICC-ARO, [5]Nagoya City University, Nagoya, [6]Fukuoka Institute of Health and Environmental Sciences, Fukuoka, Japan *For Correspondence: Dept. of Occupational Health, Hanoi Medical University, Ton That Tung Street, Hanoi, Viet Nam. Fax 84-4-8525115, E-mail: letngoan@hmu.edu.vn*

Table 1. Proportions of Study Subjects Consuming Food Selected by the SQFFQ

	Food item (English: Vietnamese)	Intake#		
Rice and cereals				
1/1	Standard polished rice: gao te may	100	100	2028
2/6	Bread: banh mi	80	77	44
3 /3	Rice - soup noodles: banh pho	71	83	68
4/4	Rice noodles: bun	83	85	47
5/5	Wheat noodles: mi tom	75	72	94
6/2	Glutinous rice: gao nep cai	89	85	53
7/*	Rice noodle: mi gao	53	52	42
Beans, tofu				
8/26	Black bean dried: dau den	67	68	32
9/*	Green beans (peas): dau xanh	86	73	37
10/27	Dried peanut seed: lac hat	82	85	56
11/43	Monordica (red): gac	40	44	2
12/25	Tofu: dau phu	97	97	126
Vegetables				
13/28	Water spinach: rau muong	98	93	140
14/29	Mustard greens: cai xanh	91	89	28
15/30	Sauropus, sp. Leaves: rau ngot	88	90	16
16/36	Malabar night shade: rau mong toi	83	82	15
17/31	Tomato: ca chua	92	93	43
18/37	Chinese cabbage: cai thia	53	58	9
19/38	Radish garden while: cu cai trang	62	64	5
20/39	Cabbage, common: cai bap	93	92	36
21/35	Winter melon: bi xanh	89	90	10
22/32	Gourd, sponge gourd: muop	89	83	9
23/33	Mungobean sprouts: gia dau xanh	82	80	36
24/40	Bamboo shoot: mang chua	62	67	8
25/41	Banana flowers: nu chuoi	27	36	2
26/42	Dried seaweed: rau cau kho	1	2	0.1
27/*	Kohlrabi: su hao	97	93	22
28/*	Cauliflower: su lo	61	72	7
29/*	Carrot: ca rot	50	65	7
30/*	Lettuce: rau diep	74	72	22
Fats and oils				
31/58	Plant oils: dau an	58	78	194
32/59	Pork fat: mo lon	64	49	154
33/*	Chicken fat: mo ga	10	10	6
Meats and eggs				
34/7	Pork lean: thit lon nac	62	72	140
35/8	Pork medium fat: ba chi	63	67	174
36/13	Grouse field chicken: thit ga	95	97	48
37/9	Beef meat grade II: thit bo loai 2	70	83	46
38/10	Pork, ribs no bone: suon lon	84	89	47
39/14	Pork, leg no bone: chan gio lon	64	72	26
40/19	Duck grade I: thit vit	71	74	12
41/22	Pork liver: gan lon	64	54	11
42/23	Chicken liver: gan ga	20	24	5
43/24	Dog meat: thit cho san	55	62	6
44/12	Hen egg: trung ga	72	82	99
45/11	Duck egg: trung vit	73	79	64
Fishes				
46/17	Carp; amur: ca tram	61	54	23
47/18	Scad, anchovy: ca nuc	36	34	27
48/21	major carp: ca troi	42	44	14
49/20	Mackerel, king fish: ca thu	15	21	5
50/*	Mullet, harder: ca diec	17	13	3
51/*	Carp: ca chep	52	64	17
52/*	Fish snack dead: ca qua	45	45	9
53/*	Climbing perch: ca ro dong	26	30	6
54/*	African carp: ca ro phi	35	28	6
55/*	Hyphophthalmichthys: ca me	40	35	9
56/*	Snail large edible: oc nhoi	45	43	4
57/*	Shrimp fields river: tom dong	73	75	26
58/*	Crab, fresh water: cua dong	61	67	35
Fruits				
59/52	Guava common: oi	35	31	4
60/51	Sugar apple, sweetsop: na	75	80	24
61/45	Orange, sweet: cam	79	75	15
62/44	Pomelo, pummelo: buoi	49	46	6

	Food item (English: Vietnamese)	Intake#		
63/46	Lemon: chanh	48	52	15
64/49	Papaya ripe: du du chin	53	57	4
65/54	Tangerine, orange: quit	64	57	11
66/53	Mandarin: quat chin	7	12	3
67/47	Banana: chuoi	65	65	21
68/*	Banana-dward: chuoi tieu	60	67	39
69/48	Watermelon: dua hau	80	81	14
70/50	Pear: le	34	34	2
71/55	Star apple, cainito: vu sua	21	17	1
72/*	Litchi: vai	78	88	16
73/*	Jack fruit: mit	60	56	5
74/*	Longan: nhan	88	82	7
75/*	Plum: man	22	26	2
76/*	Apple: tao ta	43	46	11
77/*	Apple: tao tay	49	40	10
Milk and snacks				
78/15	Milk cow: sua bo tuoi	14	30	28
79/16	Soybean milk: sua dau nanh	26	53	61
80/56	Biscuits, plain: bich quy	62	62	80
81/57	Sugar crude, brown: duong cat	85	80	167
Salted food items				
82/60	Fish sauce: nuoc mam ca	98	96	503
83/*	Fermented soybean past: tuong	37	39	31
84/61	Soya bean sauce: xi dau	17	33	15
85/*	Glutamate seasoning: mi chinh	89	90	496
86/63	Seasoning salt: bot canh	91	98	554
87/*	Salted eggplant: ca muoi	60	60	24
88/*	Shredded meat: ruoc thit lon	39	43	29
89/*	Salted-dried fishes: ca kho	45	35	8
90/*	Shrimp sauces: mam tom dac	40	42	15
91/*	Salted cucumber: dua chuot muoi	9	10	3
92/*	Salted onion (Welsh): hanh muoi	45	56	10
93/34	Rape bird salted: dua cai sen	70	63	54
94/*	Other pickled vegetables: dua khac	14	22	14
95/*	Salted peanuts: lac rang muoi	48	54	45
96/*	Mince lean pork meats: gio lua	88	82	21
97/*	Mince fat pork meats: cha lon	80	73	21
98/*	Bacon: thit muoi	0	0	0
99/*	Ham: giam bong	2	3	0.4
100/*	Chinese pork sausage: lap xuong	17	15	4
101/*	Chinese braised pork: thit kho tau	50	56	21
102/*	Deep-boiled fishes: ca kho	76	82	39
103/*	Fermented beef meat: nem chua	33	39	10
Fried food				
104/*	Garlic, onion: hanh, toi	70	71	76
105/*	Fish: ca	84	88	42
106/*	Meat: thit	62	64	30
107/*	Potato, taro: khoai cu	39	30	15
108/*	Tofu: dau phu	92	89	88
109/*	Rice papers: nem ran	70	66	17
110/*	Eggs: trung	79	81	64
111/*	Special sauce: n-uoc hµng	36	45	23
112/*	Tempura: tam bot ran	24	33	4
Broiled food				
113/*	Fresh fish: ca tuoi	18	12	1
114/*/*	Dry cuttle fish: muc nuong	39	39	3
116/*	Cattle meat: gia suc	37	34	5
117/*	Poultry meat: gia cam	23	31	3
118/*	Potato, taro: khoai cu	44	24	6
119/*	Babecu: quat cha	58	60	11
Drinking habits				
120/*	Powder coffee: ca phe hoa tan	20	25	5
121/*	Coffee filter: ca phe phin	23	21	16
122/*	Tea: tra	72	62	1278
123/62	Beer: bia	62	61	93
124/*	Imported alcohol: ruou ngoai	16	10	2
125/*	Domestic alcohol: ruou noi	55	47	238
126/*	Imported wine: ruou vang ngoai	10	6	1
127/*	Domestic wine: ruou vang noi	20	19	6

#Percentage of Cases consuming, % of controls consuming and mean intake *salted/fried/broiled foods food consumption could conceivably be a strong inhibitor against various types of carcinogens. We therefore further examined vitamin C contributions by Vietnamese foodstuffs in our SQFFQ.

Materials and Methods

Development of a database semi-quantitative food frequency questionnaire

Based on the national household survey of food consumption in 2000, the analysis was performed with surveyed data for Hanoi. A total of 158 households (5 clusters multiplying around 30 households per cluster) living in Hanoi participated in a 24- hour recall survey during September 2000. The unit of survey was the household. A 24-hour recall survey was also carried out on one weekday. Direct interviews were done in the households by 2 investigators from the National Institute of Nutrition (NIN). The total time of interview for each subject was around 45 minutes.

Based on the Vietnam Food Composition Tables, the following 17 nutrients were selected: energy, protein, fat, carbohydrate, dietary fibber, vitamins (including carotene, vitamin A, C, B1, and B2), and minerals (including calcium, phosphorus, iron and zinc). In total, 184 kinds of foodstuff were consumed by the subjects. The nutrient intake from food was computed by multiplying the food intake (in grams) with nutrient content per gram of food as listed in the Nutritive Composition Tables of Vietnamese food (revision 2000).

According to the contribution analysis and also multiple regression analysis, we choose all food/recipes with up to 90% cumulative contribution for these 17 nutrients, then foods/ recipes having apparently similar nutrient contents were grouped. Afterwards, all foods/ recipes with up to 90% cumulative contributions and 0.9 cumulative multiple regression co-efficient were included in the SQFFQ. The number of food items was 63 (see Table 1).

Planned-food selection

Our planned food items for further estimation of salt intake, cooking methods and drinking habit were rice and cereals (1), beans (1), vegetables (4), oils (1), fishes (9), fruits (7), salted food (18), fried food (9), broiled food (7), and beverages (7). A total of 127 food items are included in the same questionnaire, with the overlap noted (Table 1). From each patient, information regarding of frequent intake, size of intake unit and number of intake unit per year was obtained.

Direct interviews of cancer and non-cancer patients

From February to July of 2003, ninety one cancer patients and 90 matched (Sex and age ± 5) non-cancer patients were directly interviewed by trained interviewers at the inpatient-department of Viet Duc hospital. No missing data were found among the 181 completed questionnaires for 127 food items.

Assessment of vitamin C intake sources

We analyzed data of the National Nutritional Household Survey in 2000: 7,686 households throughout the country (vitamin C intake status) and 158 households with 741 persons of the population of Hanoi city (individual food items contributing to vitamin C intake). Direct interviews using a validated questionnaire with an album of current Vietnamese food items-recipes and weighing check were conducted to obtain information regarding all types of food intake during the last 24-hour. Contribution analysis using the Nutritive Composition Table of Vietnamese Foods, revision 2000 and stepwise regression analysis was applied (National Institute of Nutrition, 2000; Tokudome et al., 1998). Average intake adjusted by age of vitamin C per person per day was estimated. Correlation analysis as Pearson Correlation Coefficients and a regression formula was calculated for the average amount intake of foods and vitamin C intake for the eight regions of Viet Nam.

Results

In total, 12 food groups and beverages are used by Vietnamese people at present. All 63 food items that were chosen by the method of SQFFQ were consumed by all patients. Ordinary polished rice intake by all study subjects was about 5.5 intake units per day. Among 64 food items that were chosen by the method of planned-food selection, no-one consumed bacon, a salted food (see Table 1).

The proportion of cancer patients who consumed 63 food items selected by SQFFQ was ranked from 1 to 100%, with a mean of 64% that was higher than the 47% for 64 food items selected by PFS, ranked from zero to 97%. Similarly, the proportions of non-cancer patients who consumed 63 food items selected by SQFFQ were ranked from 2 to 100% and the mean of 66% was higher than the 47% found for 64 food items selected by PFS, ranked from zero to 93%.

Average amount intake of vitamin C was 72.5 mg per person per day at the national level. In total, the study subjects currently consumed 184 food items. The contributions of 53 items accounting for 97.7% of the total intake are listed in Table 2. Approximate proportions of vitamin C contribution were 57.9% for leafy vegetables, 33.4% for fresh fruits, and 6.4% for nopn-leafy vegetables. The highest 25 items contributed a cumulative 95.3% of intake with a cumulative R2=0.99 (see Figure 1).

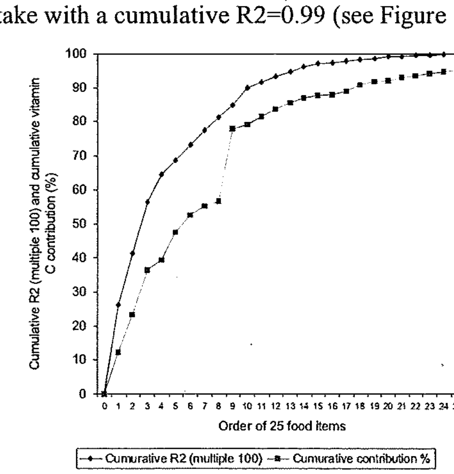

Figure 1. Cumulative R2 and Vitamin Contribution

Table 2. Vitamin C Contributions of Individual Items

	English name	Vietnamese name	Code*	(%)
Fruits				
1	Guava common	oi	5040	10.98
2	Sugarapple, sweetsop	na	5034	8.24
3	Orange, sweet	cam	5002	5.01
4	Pomelo, pummelo	buoi	5001	2.90
5	Lemon	chanh	5003	1.98
6	Papaya ripe	du du chin	5017	1.29
7	Tangerine, orange	quit	5047	0.69
8	Banana	chuoi (cac loai)	5006-07	0.63
9	Mandarin	quat chin	5046	0.51
10	Watermelon	dua hau	5011	0.28
11	Apple	tao (cac loai)	5050-51	0.27
12	Dragons eyes	thanh long	5044	0.19
13	Pear	le	5023	0.14
14	Starapple, cainito	vu sua	5054	0.08
15	Cucumber	dua chuot	4027	0.08
16	Persimmon kaki	hong do	5020	0.05
17	Carambola, Star fruit	khe	4045	0.04
18	Ohia, Malaya roseapp	gioi	5018	0.04
	Sub – total for fruit	33.40		
Leaves				
19	Water spinach, water convol	rau muong	4082	21.40
20	Mustard greens	cai xanh	4016	13.09
21	Sauropus (Leaves)	rau ngot	4085	12.31
22	Malabar night shade	rau mong toi	4079	2.71
23	Jute potherb	rau day	4069	2.36
24	Chinese cabbage	cai thia	4015	1.87
25	Cabbage, common	cai bap	4010	1.23
26	Onion, Welsh (leaves)	hanh la	4038	0.97
27	Amaranth, White	rau ren trang	4073	0.60
28	Mungobean sprouts,	gia dau xanh	4036	0.52
29	Celery, Chinese	can tay	4018	0.37
30	Sweat marjoram	rau kinh gioi	4076	0.17
31	Parsley, curley	rau mui tau	4081	0.13
32	Basil sweat leaves, raw	rau hung	4074	0.07
33	Dill	thia la	4099	0.05
34	Limnophila aromatic	rau ngo	4084	0.02
35	Lettuce	rau xa lach	4089	0.01
36	Balm - mint	tia to	4100	0.01
37	Polygonum odoratum	rau ram	4087	0.01
	Sub – total for leaves	57.90		
Tubers				
38	Tomato	ca chua	4005	2.13
39	Radish garden while, raw	cu cai trang	4021	1.55
40	Winter melon	bi xanh	4002	0.85
41	Gourd, sponge gourd	muop	4054	0.77
42	Bamboo shoot	mang chua	4050	0.32
43	Chili pepper	ot vang to	4061	0.16
44	Balsam - pear	muop dang	4055	0.14
45	Aubergine	ca tim	4009	0.11
46	Cow - peas, yard long	dau dua	4030	0.11
47	Potato, White	khoai tay	2014	0.08
48	Banana flowers	banana flower	4043	0.04
49	Momordica	gac	4034	0.04
50	Carrots	ca rot	4007	0.04
51	Taro tuber	khoai so	2013	0.03
52	Ginger root fresh	gung tuoi	13003	0.02
53	Pumpkin squash	bi dao	4003	0.01
	Sub – total for tubers	6.40		

* Nutritive composition table of Vietnamese foods, revision 2000. Total contribution of vitamin C is 97.7% by 53 food items

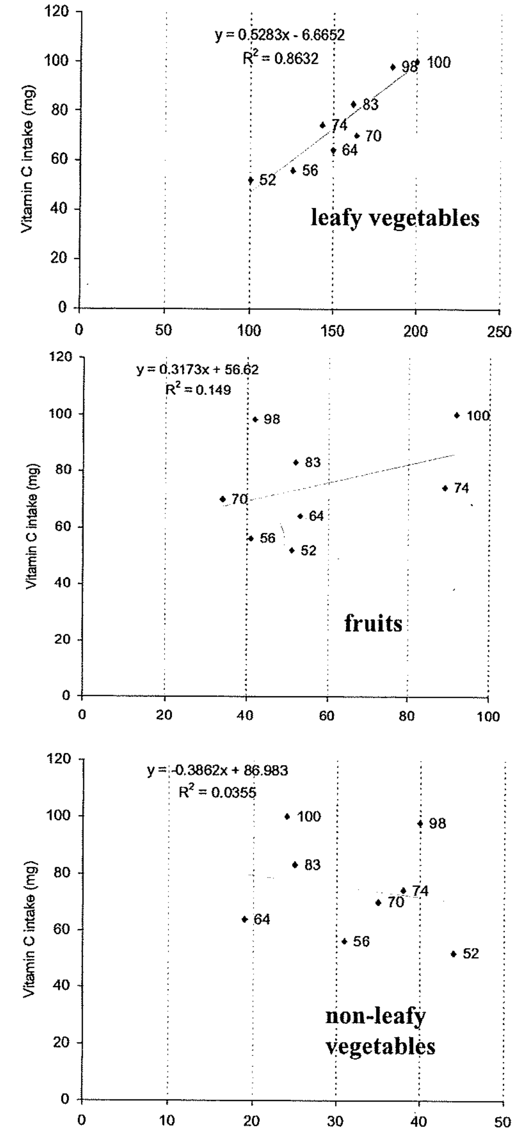

Figure 2. Correlations Between Vitamin C Intake and Consumption of Foodstuffs

A significant strong positive relationship between the average amount intake of vitamin C was found across the eight regions of Viet Nam (R2= 0.86) with average intake of leafy vegetables but not with average intake of fruit (R2= 0.15) or non-leafy vegetables (R2= 0.04) (see Figure 2).

Data from various sources for vitamin C intake in Viet Nam are summarized in Table 3.

Discussion

Study subjects were found to consume more SQFFQ-food items than PFS, that is, 64% verses 47% of cancer patients and 66% verses 47% of non-cancer patients who have consumed these food items. These results suggest that information obtained by PFS might not reflect the real dietary habits of study subjects regarding estimation of nutrient intake, especially proteins and vitamins. Because these latter are beneficial factors against developing cancer at many sites, therefore, an absence of

Table 3. Average Intake of Vegetables and Fruits (g) and Vitamin C (mg) in Viet Nam by Time Period

Population Time	Source	Study subjects	Method	Veg/fruits (g)	Vit C (mg)
All populations	WHO 1990	Estimation	Estimation	400	100
Viet Nam, 2000,	Present study	7,686 households	24-hour recall + double methods*	241	72.5
Viet Nam 1996	(Giay et al., 1996)	4,216 households	24 - hour recall**	166	19-55
Viet Nam, 1987-89	(Mai et al., 2001)	12,000 households	24 - hour recall**	196	53
HCM City, 1999	(Kieu et al., 2002)	300 individuals	24 - hour recall**	235	76
Hanoi City, 1996	(Anh et al., 2001)	299 individuals	24 - hour recall**	197	66

NS, not stated; HCM, Ho Chi Minh City. * Double methods: food record and weighing check before cooking, processing, and preserving for meal at the level of 1 gram; ** Face to face direct interviews

food items that are selected by PFC may result a poor database regarding possible confounding factors. It was earlier confirmed that FFQ results are in good accord with 3day-weighed diet records (Tokudome et a., 2005).

Regarding principles and methods of SQFFQ-food selection, semi-quantitative food frequency questionnaire covers about 90% or more nutrients intake. This information will be a basic of dietary habit of the study population. Validity and reproducibility with the SQFFQ has been verified in Japan (Date et al., 2005) and the same approach has also been applied in Korean (Kim et al., 2004). Reproducibility and validity of a food frequency questionnaire among Vietnamese in Ho Chi Minh City have also been reported (Kusama et al., 2005). However, by following these principles and methods, some possible planned-food items will not be selected. Therefore, additional food items that are chosen by PFS in the designed questionnaire should be considered as following the researcher's hypothesis.

A database of SQFFQ for vitamin C was developed in the present study and some 25 food items contributing up to 95.3% of total vitamin C intake were selected. A similar approach for calcium intake was very recently reported (Khan et al., 2008).

From 1987 to 2000, Vietnamese intake of vitamin C was found to range from 19 to 76 mg per day, and therefore lower than the 100 mg per day recommended by the WHO to prevent against cancer in humans (World Health Organization, 1990). Similarly it was earlier found that large numbers of Vietnamese subjects demonstrate very low serum concentrations of beta-carotene and tocopherol (Kieu et al., 2002b). In both urban and rural groups, more than 50% and 20% of children showed beta-carotene and tocopherol levels in the range of severe deficiency (Ta et al., 2003). Viet Nam is a tropical country and produces abundant vegetables and fruits, but people consume less than 400 gram of vegetables and fruits resulting a low vitamin C and other antioxidant intake. In fact, wild vegetables may contribute significantly to the overall micronutrient intakes, mostly carotene, vitamin C and calcium intakes (Ogle et al., 2001). Health education to promote consumption of vegetables and fruits should be conducted. Paradoxically, a low fat intake and low serum cholesterol may also be a problem in some sections of the populace (Anh et al., 2001).

Here we found two variables of the cumulative R2 and cumulative vitamin C contribution are parallel in the same direction, Figure 1. Therefore, variable of the cumulative R2 should be an indicator in selecting food items for our study on the relation of diet to cancer (Tokudome et al., 1998). Due to the fact that fruits are only available in season and may be expensive at other times, Vietnamese usually only prepare fruits for people suffering from health problems. By this custom, there was a weak correlation between the average amount intakes of fruits with the average amount intake of vitamin C. A similar observation was seen for non-leafy vegetables because these are also seasonal in Viet Nam. To improve vitamin C intake, leafy vegetables are the best way because these food items are produced in all four seasons in Viet Nam.

In recognition of the continuing shift in dietary patterns in Viet Nam, largely dependent on the socieconomic groups (Dien et al., 2004) new guidelines have been prepared for Recommended Dietary Allowances (RDAs) (Khan and Hoan, 2008). In adults in Vietnam, undernutrition may still be a public health problem in rural areas whereas overnutrition has started to become noteworthy in the urban context (Hanh et al., 2001). A consensus on the need for regional collaboration and harmonization of RDAs was recently reached by participants from Indonesia, Malaysia, Philippines, Singapore, Thailand and Vietnam (Barba and Cabrera, 2008) and it is to be hope that further research will provide the evidence base for rational nutrition planning in this region of the world.

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RESEARCH COMMUNICATION

Gastric and Colo-rectal Cancer Mortality in Viet Nam in the Years 2005-2006

Le Tran Ngoan[1]*, Nguyen Thi Diep Anh[1], Nguyen Thi Thanh Huong[2], Nguyen Thi Thu[1], Nguyen Thi Lua[1], Lai Thi Minh Hang[1], Nguyen Ngoc Bich[1], Nguyen Van Hieu[1], Ha Van Quyet[1], Le Thi Tai[1], Do Duc Van[1], Nguyen Cong Khan[3], Le Bach Mai[3], Shinkan Tokudome[4], Takesumi Yoshimura[5]

Abstract

Background: The International Collaborative Epidemiological Study of Host and Environmental Factors for Stomach and Colorectal Cancers in Southeast Asian Countries (SEACs) has been conducted in Viet Nam from 2003 to 2008 on a case-control basis. For further effective primary prevention, we examined gastric and colorectal cancer mortality nationwide ineight regions of Viet Nam in 2005-06. Methods: Both demographic data and lists of all deaths in 2005-06 were obtained from all 10,769 commune health stations in Viet Nam. Five indicators included name, age, sex, date of death and cause of death was collected for each case. We selected only communes having the list of deaths with clear cause for each case and crude mortality rate for all causes from 300-600/100,000 as published by the Ministry of Health for a reasonable accuracy and completeness. Obtained data for all causes, all cancers, stomach and colorectal cancer deaths as well as demographic information were processed using Excel software and exported to STATA 8.0 for estimation of world age-standardized cancer mortality rates per 100,000. Results: Data were available for 1,246 gastric cases, (819 male and 427 female) with age-standardized mortality rates from 12.7 to 31.3 per 100,000 in males and from 5.9 to 10.3 per 100,000 in females in the 8 regions of the country. For colorectal cancers, 542 cases (268 male and 274 female) gave mortality rates from 4.0 to 11.3 per 100,000 in males and from 3.0 to 7.8 per 100,000 in females. Discussion: Stomach cancer mortality in males in the region of North East in the North Viet Nam (2005-06) was higher than that in Japan (2002) (31.3 versus 28.7 per 100,000) while colorectal cancer in Viet Nam was lower. While prevalence of *Helicobacter pyloris* infection in Viet Nam was from 70-75% in both males and females, the stomach cancer rate in males was significantly higher than in females, 31.3 versus 6.8 per 100,000, suggesting an influence of other environmental risk factors. Whether protective factors are operating against colorectal cancer in Viet Nam now needs to be explored.

Key Words: Cancer mortality - stomach - colorectal - population-based-routine-death registration - Viet Nam

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Introduction

The International Collaborative Epidemiological Study of Host and Environmental Factors for Stomach and Colorectal Cancers in Southeast Asian Couintries (SEACs) has been conducted in Viet Nam from 2003 to 2008 on a case-control basis. Viet Nam is divided into eight regions, the North East, North West, Red River Delta (Three regions in the North), North central coast, South Central Coast, and Central Highland (Three regions in Central Viet Nam), North-East South and Mekong River Delta (Two regions in the South).

The vast majority of stomach cancers are due to environmental factors and therefore are amendable to control (Doll & Peto, 1981). Incidences are relatively high in Viet Nam (Ngoan et al., 2002) but might be expected to differ within the country (Ngoan et al., 2001a). Estimated incidence of colorectal cancers in Viet Nam increased from 9.3 to 11.8 per 100,000 in males and from 6.4 to 8.3 per 100,000 in females between 1990 and 2002 as published by IARC in GLOBOCAN. Estimated mortality in 2002 was 5.6 and 5.2 per 100,000 in males and females, respectively (IARC, 2002). However, the GLOBOCAN data for Viet Nam were estimated based on incidence data for Hanoi and Ho Chi Minh cities only, and therefore might not reflect the real problem for the whole country because over 75% of Vietnamese live in rural areas (General Statistics Office, 1999; Vietnam-

[1]*Hanoi Medical University,* [2]*Quang Binh Department of Health,* [3]*National Nutrition Institute, Hanoi City, Viet Nam,* [4]*Nagoya City University, Nagoya,* [5]*Fukuoka Institute of Health and Environmental Sciences, Fukuoka, Japan *For Correspondence: Dept. of Occupational Health, Hanoi Medical University, Ton That Tung Street, Hanoi, Viet Nam. Fax. 84-4-8525115, E-mail: letngoan@hmu.edu.vn*

Central-Census-Steering-Committee, 1991). For this reason, we here tried to generate a comprehensive picture for stomac and colorectal cancers in the eight regions of Viet Nam to facilitate epidemiological studies in our country.

Materials and Methods

The socialist Republic of Viet Nam introduced a national mortality system in 1992. This unique system relied on commune-level officials providing basic demographic data and information on the cause of death. The information collected is recorded in an official book referred to as the A6. The data from the A6 was collated by the District-level Health Service who in turn forward the information to the Provincial and Central-level governments. The data comprises all cancer mortality records at the commune-level. Based on this system, descriptive cancer epidemiology was designed for the present study. Both demographic data and list of all deaths in 2005-06 were obtained from all 10,769 commune health stations. Five indicators included name, age, sex, date of death and cause of death was collected for each case. These process of this unique system in collecting cancer data has been introduced elf where (Ngoan, 2006; Ngoan et al., 2007).

To date, 94.6% (10,184 commune health stations) of the 10,769 communes (from the 638 of 671 districts within the 64 provinces) have forwarded the required data and we currently have approximately 93,719 cancer deaths occurred at all 638 districts for the 2 year period. Number of person-years was 76,726,873 in 2005 and 77,902,688 in 2006 (Ngoan et al., 2007). Because data obtained from number of 10,184 commune health stations, level of accuracy and completeness might be varied among them. Because crude mortality rate of all causes has been estimated from 300 to 600 per 100,000 published by the Ministry of Health (Ministry of Health, 2007), we categorized that communes were eligible when communes having the list of deaths with clear cause for each case and crude mortality rate for all causes from 300 – 600/100,000 for a reasonable accuracy and completeness. Gastric and colorectal cancer cases were coded following ICD-10 as C16 and C18-21.

For 2005-06, we identified 13,460 cases of stomach cancer among 93,719 all cancers nationwide and 4,646 cases of colorectal cancers.

Results

Stomach Cancers

Available data for the present analysis was 1,246 cases, male 819 and female 427. Age-standardized stomach cancer mortality rates were from 12.7 to 31.3 per 100,000 in males and from 5.9 to 10.3 per 100,000 in females (see Table 1). For the age group of 40-49, cancer mortality rates various from 5.9 to 33.1 per 100,000 in males and from 4.2 to 15.6 per 100,000 in females. Among males, the ratio of highest to lowest rates was 2.46 (31.3 versus 12.7 per 100,000) but it was only 1.75 in females. Male to female ratios in the region of North East in the North

Table 1. Registered Numbers and Stomach Cancer Mortality Rates per 100,000 (ASR) by Sex in Eight Regions of Viet Nam

Region	Male			Female		
	No	Crude rate	ASR	No	Crude rate	ASR
Red river delta	274	22.1	27.7	145	11.2	10.1
North-East	120	18.3	31.3	43	6.3	6.8
North-West	29	11.5	19.8	13	4.9	7.5
North central	144	16.3	21.9	77	8.4	8.1
Central coast	50	14.9	18.9	24	6.9	5.9
Central plateau	32	11.0	22.8	18	6.0	10.3
South-East	64	7.5	12.7	46	5.2	6.8
Mekong delta	106	9.6	15.0	61	5.3	6.8

Table 2. Registered Numbers and Colorectal Cancer Mortality Rates per 100,000 (ASR) by Sex in Eight Regions of Viet Nam

Region	Male			Female		
	No	Crude rate	ASR	No	Crude rate	ASR
Red river delta	68	5.5	6.9	75	5.8	5.2
North-East	20	3.1	4.4	34	5.0	5.0
North-West	7	2.8	4.7	9	3.4	5.0
North central	29	3.3	4.0	34	3.7	3.0
Central coast	18	5.4	7.7	13	3.7	4.1
Central plateau	9	3.1	6.0	7	2.3	3.7
South-East	34	4.0	6.3	24	2.7	3.4
Mekong delta	83	7.5	11.3	78	6.8	7.8

Viet Nam was 4.60 for all ages but it was 7.88 for the age of 40-49.

A comparison of rates with other communities in Asia (data from GLOBOCAN) is given in Figure 1.

Colorectal Cancers

The registered number was 542 cases, male 268 and

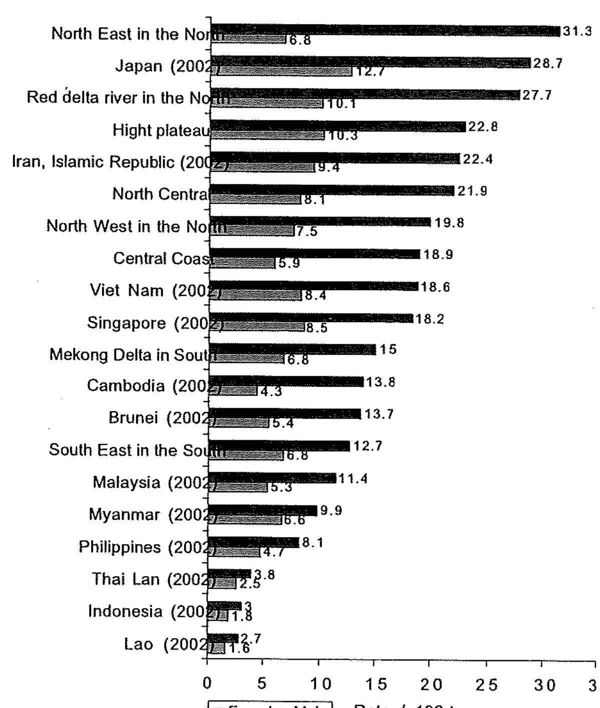

Figure 1. Age-standardized Stomach Cancer Mortality

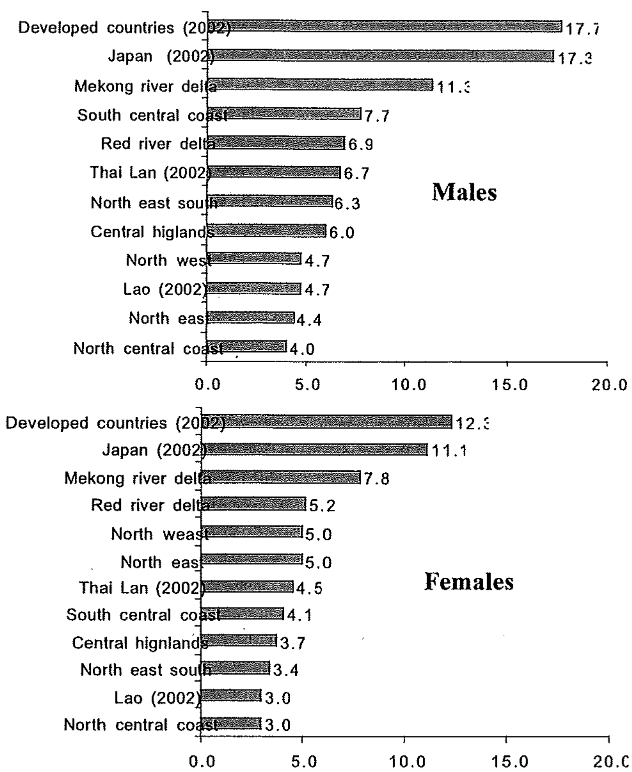

Figure 2. Age-standardized Colorectal Cancer Mortality

female 274 in 2005-06 from eligible commune populations within eight regions of Viet Nam, giving a male to female ratio of 0.98. In the eight regions, age-standardized colorectal cancer mortality rates were from 4.0 to 11.3 per 100,000 in males and from 3.0 to 7.8 per 100,000 in females (Table 2). The highest mortality rates were seen in both males (11.3 per 100,000) and females (7.8 per 100,000) in the region of Mekong River Delta in the South Viet Nam. The age specific rate per 100,000 were sharply increased from the age group 50-59 with a peak at 80+ as high as 346.6 and 275.3 per 100,000 in males and females, respectively.

A comparison of rates with other communities in Asia (data from GLOBOCAN) is given in Figure 2.

Discussion

The present results showed considerable variation in stomach and colorectal cancer mortality among the regions of Viet Nam but overall the values were very high for stomach and somewhat lower than in other countries for the large bowel.

We earlier reported low stomach cancer survival, with only 23.8% for one year and 0.8% for five years (Ngoan et al., 2007a). Stomach cancer mortality in males in the region of North East in the North Viet Nam (2005-06) was here found to be higher than that in Japan (2002), (31.3 versus 28.7 per 100,000). While the prevalence of Hp infection in Viet Nam is from 70-75% in both males and females, with especially high values in large urban areas, such as the city of Hanoi (Hoang et al., 2005), stomach cancer in males was significantly higher than females, 31.3 versus 6.8 per 100,000, suggesting the existence of other environmental risk factors, like possibly smoking. Because salt strongly enhances and promotes chemical gastric carcinogenesis and *H pylori* infection in both humans and animals, there may be an association between work, salt intake, and the development of stomach cancer among workers in particular (Ngoan and Yoshimura, 2003). The finding of very low incidence of stomach malignancy in Yogyakarta (Tokudome et al., 2005) and Semarang (Tokudome et al., 2006), Indonesia, appears to be due to the rarity of *H pylori*. Similar results have been reported in Malaysia, whereby the incidence of gastric carcinoma was found to be much higher in Chinese in Penang compared to Malays in Kelantan, where the *H. pylori* infection rate is exceptionally low (Gurjeet et al., 2005). Whether some dietary factor may be playing a role remains unclear. While the absolute rates for stomach mortality were higher for the Red River Delta than for other areas, we earlier found better cancer survival in Hanoi than in Phu Tho province, pointing to a need for greater efforts in early detection and treatment in rural areas (Ngoan et al., 2007).

The higher rates for colorectal cancer in the Mekong delta than in the Red River delta might suggest that there is an influence of Ho Chi Minh city as opposed to Hanoi. We earlier found differences in female but not male incidence rates (Ngoan et al., 2001) and a case-control comparison of the two major cities would appear warranted. Lower incidences in Ho Chi Minh city were also found for cancers of the nasopharynx, stomach, lung and female breast, while that of cervical cancer was significantly higher than in Hanoi (Ngoan et al., 2001).

We now need to extend our studies to other cancers, for example to cervical cancer, For females, cancer death in the cervix is uncommon in Hanoi but it is a very common site in Ho Chi Minh (Ngoan et al., 2002). major risk factors for HPV DNA detection were indicators of sexual habits, most notably the presence of HSV-2 antibodies, nulliparity and the current use of oral contraceptives. Women in Hanoi showed the lowest HPV prevalence ever reported so far, and as expected, HPV prevalence closely correlated with ICC incidence rates. (Pham et al., 2003). Although cervical HPV infection is extremely common, particualrly among female sex workers in southern Vietnam, prevalence varies by education level, sexual activity, habits of regular partners, and HIV status (Hernandez and Vu Nguyen, 2008). There is also significant increase in risk of cervical cancers linked to to multi parity and illiteracy (Ngoan and Yoshimura, 2001b). However, a lay health worker outreach program with Vietnamese women has produced significant increases in Pap testing (Mock et al., 2006) and initial responses to the HPV vaccine for girls in Vietnam appear favorable. Beliefs regarding negative social consequences for girls who engage in premarital sex are prevalent but unassociated with HPV vaccine acceptability (Dinh et al., 2007).

Another important cancer in Viet Nam is the hepatocellular carcinoma, with slightly higher rates in Ho Chi Minh city than in Hanoi (Ngoan et al., 2001). This could partly be explained by herbicide exposure(Ngoan and Yoshimura, 2001a) as well as a high age-dependent incidence of liver cancer among carriers of HBsAg (+) in a general population (Ngoan and Yoshimura, 2001c). Universal infant HBV vaccination should reduce chronic HBV prevalence in Vietnam but it was estimated that the HBV-related liver disease burden will continue to rise (Nguyen et al., 2008).

In conclusion, the present study obtained data nationwide from the eight regions of Viet Nam and showed major variation which might provide clues to risk factors and how to target prevention efforts. Future investigations should also explore links to cardiovascular disease mortality, which is also high (Hoang et al., 2006) so that both primary prevention and secondary treatment initiatives can be coordinated for all of the non-communicable diseases, including diabetes associated with colorectal cancer and stroke correlating with stomach cancer.

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