TABLE 4. Associations of serum levels of ω-3 polyunsaturated fatty acids with colorectal cancer risk, by sex, Japan Collaborative Cohort Study for the Evaluation of Cancer Risk, 1988–1997

Q*	Men					Women				
	Value†	Cases (no.)	Controls (no.)	OR*,‡	95% CI*	Value†	Cases (no.)	Controls (no.)	OR‡	95% CI
					α-linolenic acid (18:3 ω-3)					
Q1	<0.69	34	56	1.00		<0.71	14	56	1.00	
Q2	0.69–0.849	13	64	0.22	0.09, 0.55	0.71–0.859	20	63	1.97	0.81, 4.79
Q3	0.85–1.069	14	60	0.25	0.10, 0.59	0.86–1.09	30	59	3.07	1.28, 7.33
Q4	≥1.070	22	61	0.39	0.16, 0.91	≥1.10	22	62	2.19	0.87, 5.47
p trend				0.06					0.15	
					Eicosapentaenoic acid (20:5 ω-3)					
Q1	<1.91	25	60	1.00		<1.73	23	57	1.00	
Q2	1.91–2.719	21	60	0.70	0.33, 1.48	1.73–2.384	20	63	0.56	0.25, 1.26
Q3	2.72–3.839	22	60	0.84	0.38, 1.86	2.385–3.329	20	60	0.67	0.31, 1.48
Q4	≥3.840	15	61	0.44	0.18, 1.08	≥3.330	23	60	0.83	0.39, 1.80
p trend				0.13					0.79	
					Docosapentaenoic acid (22:5 ω-3)					
Q1	<0.68	29	57	1.00		<0.665	27	60	1.00	
Q2	0.68–0.829	14	63	0.36	0.15, 0.86	0.665–0.789	24	56	0.83	0.39, 1.75
Q3	0.83–1.019	24	57	0.55	0.24, 1.24	0.790–0.944	19	64	0.62	0.29, 1.34
Q4	≥1.020	16	64	0.30	0.11, 0.80	≥0.945	16	60	0.64	0.30, 1.39
p trend				0.045					0.14	
					Docosahexaenoic acid (22:6 ω-3)					
Q1	<4.23	22	60	1.00		<4.20	19	59	1.00	
Q2	4.23–5.079	23	59	1.01	0.46, 2.20	4.20–5.094	23	61	1.11	0.47, 2.61
Q3	5.08–6.249	29	61	1.17	0.53, 2.62	5.095–5.919	27	59	1.62	0.72, 3.65
Q4	≥6.25	9	61	0.23	0.07, 0.76	≥5.92	17	61	0.80	0.33, 1.93
p trend				0.07					0.86	

* Q, quartile; OR, odds ratio; CI, confidence interval.

† Values are expressed as the weight percentage of total serum lipids.

‡ Odds ratios were derived from a conditional logistic analysis model adjusted for family history of colorectal cancer in first-degree relatives, body mass index, education, smoking and alcohol drinking history, green leafy vegetable intake, and physical exercise. For men, 83 cases and 241 controls and, for women, 86 cases and 240 controls matched on age and participating institution were involved in the analyses.

DISCUSSION

The main strength of our study is its prospective design and the use of biomarkers to evaluate each fatty acid level. Because we collected serum samples and background data from subjects when they were free of cancer, we were able to eliminate any influence of the cancer itself or recall bias on the results. We confirmed our results by repeating the analyses after excluding persons who developed colorectal cancer within the first 2 or 5 years of follow-up, along with their matched controls, to eliminate any potential effects of undiagnosed colorectal cancer cases at baseline.

Our study design is similar to that of the nested case-control study based on data from the Multiple Risk Factor Intervention Trial (MRFIT) (21). Simon et al. examined 108 cancer cases and 215 controls and found no association between any serum fatty acid component and the risk of fatal cancer. Unfortunately, because of the limited number of subjects, they were unable to estimate risk by organ site. This prospective study is the first known to report an association between colorectal cancer risk and specific serum fatty acids.

We found a marginally significant inverse association between serum level of ω-3 PUFAs and the risk of colorectal cancer in men. The odds ratios for the highest versus lowest quartiles of all ω-3 PUFAs examined were less than 1.0 and were statistically significant ($p < 0.05$), except for eicosapentaenoic acid ($p = 0.13$). These findings support the potential preventive effects of fish oil supplements rich in ω-3 PUFAs against colorectal cancer (22, 23), which have been suggested by a number of clinical studies (3–5, 24, 25). The chemopreventive activity of nonsteroidal antiinflammatory drugs on colorectal tumors has been well documented in a number of experimental studies (26–29). Suppression of cyclooxygenase and inhibition of prostaglandin E_2 synthesis by nonsteroidal antiinflammatory drugs is thought to be the

TABLE 5. Associations of serum levels of ω-6 polyunsaturated fatty acids with colorectal cancer risk, by sex, Japan Collaborative Cohort Study for the Evaluation of Cancer Risk, 1988–1997

Q*	Men					Women				
	Value†	Cases (no.)	Controls (no.)	OR*,‡	95% CI*	Value†	Cases (no.)	Controls (no.)	OR‡	95% CI
					Linoleic acid (18:2 ω-6)					
Q1	<22.94	27	60	1.00		<25.19	19	60	1.00	
Q2	22.94–26.34	19	60	0.80	0.39, 1.60	25.19–27.55	15	60	0.86	0.37, 2.02
Q3	26.35–29.75	19	60	0.66	0.30, 1.43	27.56–30.78	24	60	1.61	0.70, 3.70
Q4	≥29.76	18	61	0.57	0.24, 1.38	≥30.79	28	60	1.88	0.78, 4.52
p trend					0.20					0.12
					γ-linolenic acid (18:3 ω-6)					
Q1	<0.17	16	59	1.00		<0.21	28	58	1.00	
Q2	0.17–0.269	24	60	1.60	0.74, 3.46	0.21–0.289	20	61	0.60	0.29, 1.26
Q3	0.27–0.359	17	60	0.98	0.44, 2.21	0.29–0.379	18	57	0.53	0.25, 1.13
Q4	≥0.36	26	62	1.99	0.86, 4.62	≥0.380	20	64	0.62	0.30, 1.31
p trend					0.27					0.23
					Eicosadienoic acid (20:2 ω-6)					
Q1	<0.18	25	52	1.00		<0.17	15	29	1.00	
Q2	0.18–0.199	23	64	0.68	0.33, 1.40	0.17–0.189	20	58	0.69	0.28, 1.72
Q3	0.20–0.219	7	53	0.18	0.06, 0.56	0.19–0.209	22	70	0.52	0.22, 1.22
Q4	≥0.22	28	72	0.71	0.33, 1.53	≥0.21	29	83	0.58	0.25, 1.35
p trend					0.26					0.21
					Dihomo-γ-linolenic acid (20:3 ω-6)					
Q1	<0.84	17	58	1.00		<0.92	19	59	1.00	
Q2	0.84–1.049	22	59	1.27	0.59, 2.73	0.92–1.079	25	58	1.35	0.62, 2.97
Q3	1.05–1.239	22	62	1.13	0.50, 2.55	1.08–1.349	31	62	1.55	0.76, 3.17
Q4	≥1.24	22	62	1.33	0.60, 2.94	≥1.35	11	61	0.53	0.22, 1.31
p trend					0.55					0.46
					Arachidonic acid (20:4 ω-6)					
Q1	<3.71	20	59			<4.20	26	60	1.00	
Q2	3.71–4.619	25	61	1.24	0.55, 2.78	4.20–4.879	22	59	0.67	0.31, 1.46
Q3	4.62–5.269	16	59	0.79	0.32, 1.96	4.88–5.634	16	61	0.49	0.22, 1.10
Q4	≥5.27	22	62	1.16	0.49, 2.75	≥5.635	22	60	0.65	0.30, 1.44
p trend					0.99					0.40
					Docosatetraenoic acid (22:4 ω-6)					
Q1	<0.09	21	56	1.00		<0.085	20	60	1.00	
Q2	0.09–0.099	9	34	0.82	0.31, 2.22	0.085–0.109	27	57	1.47	0.68, 3.15
Q3	0.10–0.119	16	70	0.81	0.35, 1.90	0.110–0.119	13	40	0.87	0.34, 2.21
Q4	≥0.12	37	81	1.58	0.66, 3.78	≥0.12	26	83	0.81	0.35, 1.87
p trend					0.30					0.49

* Q, quartile; OR, odds ratio; CI, confidence interval.

† Values are expressed as the weight percentage of total serum lipids.

‡ Odds ratios were derived from conditional logistic analysis model adjusted for family history of colorectal cancer in first-degree relatives, body mass index, education, smoking and alcohol drinking history, green leafy vegetable intake, and physical exercise. For men, 83 cases and 241 controls and, for women, 86 cases and 240 controls matched on age and the participating institution were involved in the analyses.

main mechanism for this activity. ω-3 PUFAs are thought to influence the carcinogenic process via their effects on the synthesis of prostaglandins and thromboxanes (1) through a mechanism similar to that of nonsteroidal antiinflammatory drugs. Increased intake of eicosapentaenoic and docosahexaenoic acids might also promote apoptosis in cells of the normal human colonic mucosa (30).

We found no significant association between ω-3 PUFAs and the risk of colorectal cancer in women. α-linolenic and linoleic acid were associated with colorectal cancer inci-

dence in the opposite direction for men and women. MUFAs showed a marginally significant positive association for men only. On the basis of the available data, we cannot suggest a plausible explanation for the gender difference in the association between fatty acids and colorectal cancer risk. Genetic and hormonal factors, nutritional status, and disease are all thought to influence fatty acid metabolism (31). In addition, it has been suggested that female sex hormones play a role in the etiology of colorectal cancer (32, 33). Interestingly, the odds ratios for the highest versus lowest quartiles were less than 1.0 for all of the ω-3 PUFAs examined in women when those women who developed colorectal cancer within the first 5 years of follow-up were excluded. It is possible that physical disorders or medications not evaluated in the present analyses might have influenced the results. Unfortunately, we did not collect data on use of nonsteroidal antiinflammatory drugs and other medications that might have interfered with the association between ω-3 PUFAs and colorectal cancer risk. Further investigation of diet and metabolism will therefore be necessary to clarify these gender interactions. In addition, we did not observe an obvious dose response between serum levels of ω-3 PUFAs and colorectal cancer risk. Additional studies should thus examine whether an optimal level of ω-3 PUFAs is associated with colorectal cancer prevention.

The risks of colorectal cancer are reported to vary by subsite (34, 35). The available data showed no obvious differences between the separate risk of colon cancer and the combined risk of colorectal cancer regarding the association with fatty acids. Although we were unable to estimate the independent risks by subsite in our study because of the limited number of cases, they should be confirmed in future studies with larger sample sizes.

Some limitations that affected interpretation of our results must be noted. First, our subjects were selected from among the participants of a large cohort study. As Kato et al. (36) discussed previously, subjects in cohort studies tend to be homogeneous and health conscious, which might reduce the between-person variation in food consumption and other health-related factors and make detection of associations between individual fatty acids and disease risk more difficult. Moreover, the subjects in the present study were limited to those who donated blood samples: only 36.6 percent of the total cohort. In fact, those who did not donate blood samples were more likely to be highly educated, to consume alcohol daily, and to exercise less compared with those who donated blood samples, regardless of gender. In addition, compared with nonparticipants, male participants tended to be older and female participants tended to be younger. The differences in the background characteristics of the subjects should be considered to generalize our findings. Second, because this was a multicenter study (12), the procedures used to collect blood were not uniform. However, we confirmed that no area had a greatly different distribution of fatty acid levels. In addition, we matched cases and controls by participating institution; therefore, any bias due to differences between areas should have been accounted for.

Third, we used serum samples that were stored at −80°C for 11–14 years to evaluate the levels of fatty acids. Iso et al. (37) examined 31 serum samples taken from subjects in the present cohort in 1990 and again in 1998. They reported an increase in the composition of saturated fatty acids (29.2 percent vs. 30.3 percent) and 20:3 (dihomo-γ linolenic acid) (0.85 percent vs. 0.98 percent), a decline in the composition of MUFAs (22.9 percent vs. 22.4 percent), and no changes in the other fatty acids over this 8-year time interval. Zeleniuch-Jacquotte et al. (11) reported that storage for up to 12 years at −80°C effectively protected PUFAs from oxidation. However, the long-term effects of storage for up to 14 years have not been confirmed. Fourth, although we used the fatty acid composition of serum total lipids as a biomarker, several alternative methods are available for biologic assessment of fat intake. Adipose tissue and the erythrocyte membrane reflect long- and medium-term fatty acid intake, respectively, whereas serum reflects only short-term (weeks to months) intake (10). Although measuring these alternative biomarkers is more expensive and invasive, they might be a better index for use in predicting colorectal cancer. Therefore, our results should be confirmed by using these media. Fifth and finally, we evaluated the fatty acids and background characteristics of the subjects only once, at baseline. These measurements might not accurately reflect the long-term habits of the subjects. Thus, repeated measurements should be considered to reduce measurement errors (11).

ACKNOWLEDGMENTS

This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (2; 14031222) 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 (61010076, 62010074, 63010074, 1010068, 2151065, 3151064, 4151063, 5151069, 6279102, and 11181101).

The authors express their appreciation to Dr. Kunio Aoki, Professor Emeritus, Nagoya University School of Medicine and the former chairman of the JACC Study Group; and to Dr. Haruo Sugano, the former director of the Cancer Institute of the Japanese Foundation for Cancer Research, who greatly contributed to initiating the study.

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Perceived Psychologic Stress and Colorectal Cancer Mortality: Findings From the Japan Collaborative Cohort Study

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Objective: The purpose of this research was to examine the relationship between perceived psychologic stress and colorectal cancer mortality in a prospective large-scale study. **Methods:** Between the years 1988 and 1990, 32,153 men and 45,854 women aged 40 to 79 years were enrolled. Participants completed a self-administered questionnaire that addressed demographic, lifestyle, and psychosocial characteristics. Subjects were subsequently followed for mortality until the end of 1999. Perceived psychologic stress was assessed using the question "Do you feel stress during your daily life?" The 4 possible responses, ranging from "little or none" (1) to "extreme" (4), were dichotomized as low (1 or 2) or high (3 or 4) stress. Relative risks (RRs) with 95% confidence intervals (CIs) for colon and rectal cancer according to the perceived level of stress were estimated using Cox's proportional hazard model. **Results:** During the follow-up period (average, 9.6 years), 193 colon cancer deaths (96 men and 97 women) and 127 rectal cancer deaths (88 men and 39 women) were confirmed within the study group. Women who reported high stress had a 1.64-fold higher risk of colon cancer mortality (multivariate-adjusted RR, 1.64; 95% CI, 1.01–2.66) compared with those reporting low stress. There was no significant association between perceived stress and female rectal cancer or male colon and rectal cancer mortality. **Conclusions:** Perceived psychologic stress was weakly associated with increased mortality from colon cancer in women. No positive or inverse association was found in men. Further studies are needed to confirm our results. **Key words:** colorectal carcinoma, psychosocial factors, perceived stress, cohort study.

BMI = body mass index; **CI** = confidence interval; **HPA axis** = hypothalamic–pituitary–adrenocortical axis; **ICD-10** = 10th Revision of the International Classification of Diseases; **OR** = odds ratio; **RR** = relative risk; **SAM system** = sympathetic–adrenal–medullary system.

INTRODUCTION

The human body responds to stress through the autonomic nervous system, the hypothalamic–pituitary–adrenocortical (HPA) axis and the cardiovascular, metabolic, and immune systems. However, the physiological systems that are activated by stress can themselves cause damage (1). According to Rosch (2), the idea that cancer might be related to stress or emotional factors is as old as the history of medicine. Many clinical and laboratory studies, as well as anecdotal reports, support the hypothesis that stress can significantly influence susceptibility and resistance to cancer, and can affect the course of the disease (2–4). However, epidemiologic studies have produced inconsistent results, largely owing to inappropriate study design and the difficulties measuring psychologic variables (5). Dalton et al. (6) reviewed the data from previous epidemiologic studies and found no association between major life events and cancer risk, and inconsistent conclusions were obtained with respect to depression and personality factors. The authors attributed these inconclusive results to methodologic weaknesses in the studies such as inadequacies in sample size, length of follow up, the detection of cancer cases, and control for confounding factors. This highlights the need for well-designed large prospective studies of the association between cancer risk and psychologic variables.

Colorectal cancer is the second leading cause of cancer-related death in most developed countries (7). Epidemiologic studies have revealed that several lifestyle factors such as a diet rich in fat but poor in vegetables and fiber combined with low physical activity increase the risk of colorectal cancer (8). Alcohol intake (9) and constipation (10,11) have also been suggested to increase the risk. The colon and rectum are known to be particularly sensitive to psychologic stress (12–15), and lifestyle factors and behaviors that are associated with colorectal cancer risk are also influenced by psychologic stress (1,16). Some case–control studies have reported a positive association between colorectal cancer risk and psychosocial stress factors such as job-related stress (17,18) and stressful life events (19,20). However, because having cancer itself is a stressful event, it is difficult for patients to accurately evaluate previous stressful events and their psychologic status without recall bias. Such biases could be avoided by examining the relationship between these factors in a prospective study.

Stress can be defined as a nonspecific response of the body to a demand from the environment or as a process of adapta-

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This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (2; No. 14031222) 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, and 11181101).

Received for publication February 8, 2004; revision received July 21, 2004.
DOI: 10.1097/01.psy.0000151742.43774.6d

0033-3174/05/6701-0072

tion in reaction to psychologic, physical, or chemical stimuli. There are unlimited sources of stress, and responses vary greatly between individuals and in different situations (16,21). The way in which an individual perceives a situation determines their specific response to stressful stimuli (1). Common physiological responses to stress are alterations of the sympathetic–adrenal–medullary (SAM) system and the HPA axis. Both the autonomic nervous system and the HPA axis can, in turn, influence the immune system, and persistent suppression of the immune system increases the risk of cancer. More specifically, dysfunction of the autonomic nervous system might cause irregular bowel movements, which have recently been identified as a possible risk factor for colon cancer (22).

We therefore propose that individuals who experience high levels of perceived stress during their daily life are at a greater risk of mortality from colorectal cancer. To test this hypothesis, we evaluated the perceived levels of psychologic stress in healthy Japanese adults. The subjects were then followed prospectively to examine the association between psychologic stress and colorectal cancer death. Adjustments were made during analysis of the data for possible confounding factors.

MATERIALS AND METHODS

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk

All data were taken from the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study), which was a nationwide multicenter collaborative study sponsored by the Ministry of Education, Culture, Sports, Science and Technology of Japan (Monbukagakusho). The methods of the JACC Study have been described in detail elsewhere (23). Briefly, the original study population consisted of 110,792 Japanese adults aged 40 to 79, who were enrolled between the years 1988 and 1990 in 45 areas throughout Japan. Most of the subjects were recruited from the general population or when undergoing routine health checks in the municipalities. On enrollment, participants completed a self-administered questionnaire that assessed demographic characteristics, lifestyle habits, and medical history, as well as psychologic attitudes toward life. Written informed consent for participation was obtained individually from subjects, with the exception of those in a few study areas in which informed consent was provided at the group level after the aim of the study and confidentiality of the data had been explained to community leaders. The study protocol was approved by the Ethics Committee of Medical Care and Research of Fujita Health University School of Medicine, Japan.

The focus of this study was the association between psychologic stress and colorectal cancer. We therefore excluded 73 individuals who reported a history of colorectal cancer, along with all of the respondents from the six areas in which the questionnaire did not include the psychologic evaluation section (n = 23,330). In addition, those who neglected to address this section (n = 7511) and those who did not answer the specific question about psychologic stress (n = 1867) were excluded; 10.7% of the eligible participants refused to answer this question. A total of 78,007 subjects (32,153 men and 45,854 women) were therefore included in the final analysis.

Evaluation of Perceived Psychologic Stress

Perceived psychologic stress was assessed in this study through responses to the question "Do you feel stress during your daily life?" Four possible answers were provided: little or none (1), moderate (2), high (3), and extreme (4). For the purposes of the analysis, these responses were dichotomized and subjects who chose response 1 or 2 were categorized as having high stress levels, whereas those that chose response 3 or 4 were categorized as having low stress levels.

Identification of Colorectal Cancer Cases and Follow Up of the Cohort

Subjects were followed for mortality until the end of 1999. The Family Registration Law in Japan requires registration of death. Therefore, mortality was determined using municipal resident registration records, and causes of death were confirmed using death certificates, with permission from the Ministry of Public Management, Home Affairs, Post and Telecommunications. The end point of the study was defined as death from colon cancer (International Classification of Diseases, 10th Revision [ICD-10]: C18) or rectal cancer (ICD-10: C20). Subjects who moved out of the study area or died from causes other than colorectal cancer were treated as censored cases. During the study period, only 3.3% (n = 2600) of the participants were lost from the follow up as a result of change of residence. We calculated the risk period for each subject as the interval between the date of questionnaire administration and whichever of the following occurred first: the date of death or the date of moving from the study area or December 31, 1999.

Statistical Analysis

Although colon and rectal cancers are often considered together, several differences have been identified in their etiologies (24). We therefore separately evaluated the risk of colon cancer and rectal cancer by sex. All analyses were performed using the SAS statistical package, release 8.2 (SAS Inc., Cary, NC).

First, to explore the background characteristics of psychologic stress, we calculated the means and proportions of the baseline variables for each level of perceived psychologic stress by gender. Mean values were compared using analysis of covariance with adjustment for age. The relationships between the baseline categorical variables and psychologic stress were examined using logistic regression, with adjustment for age, by gender; significant interactions between gender and baseline variables in relation to psychologic stress were further examined through logistic regression models. Then, to determine the impact of perceived psychologic stress on colorectal cancer mortality, age-adjusted relative risks (RR) with 95% confidence intervals (CIs) for colon and rectal cancers according to the perceived level of stress were estimated using Cox's proportional hazard model. We calculated the RRs for "high" versus "low" stress levels and tested for linear trends in the associations by including the responses as continuous variables. To adjust for the influence of possible confounding factors, multivariate adjusted models were computed. The first model included the following age and lifestyle factors, which are known to influence colorectal cancer risk: body mass index (BMI) calculated as weight (kg)/height (m^2) and categorized as "≥25 kg/m^2" or "<25 kg/m^2;" history of colorectal cancer in parents or siblings ("yes" or "no"); current smoking status ("smoker" or "nonsmoker"); intake frequency of alcohol ("≥5 days per week" or "<5 days per week"); sleep duration per night ("<7 hours" or "≥7 hours"); intake frequency of green leafy vegetables ("daily" or "not daily"); time spent walking per day ("≤30 minutes" or ">30 minutes"); and severe constipation (bowel movement frequency "once every 4 days or less" or "once every 3 days or more"). All of the variables of the baseline characteristics were then added to the second model, which included the following sociologic factors: age at leaving full-time education ("≥20 years" or "<20 years"); marital status ("married" or "unmarried"); having children ("yes" or "no"); and being in full-time employment ("yes" or "no").

For each covariate, missing values were treated as an additional category in the variables and were included in the models. In all cases, two-sided probability (p) values <.05 were considered to be statistically significant.

RESULTS

During the follow-up period (average, 9.6 years; standard deviation, 2.0 years; total of 749,354 person-years), a total of 7685 deaths (4563 men and 3122 women) were recorded, which included 193 deaths from colon cancer (96 men and 97 women) and 127 deaths from rectal cancer (88 men and 39 women).

Table 1 presents the baseline characteristics of the study population for each level of perceived psychologic stress.

TABLE 1. Background Characteristics at Baseline of the Participants by Perceived Stress by Gender

		Men			Women			
		Perceived stress		Age-adjusted OR for having high stress (95% CI)	Perceived stress		Age adjusted OR for having high stress (95% CI)	*p* value for gender interaction
		Low (n = 24,816)	High (n = 7337)		Low (n = 36,634)	High (n = 9220)		
Sociodemographic characteristics								
Age	Mean	58.7	53.3		58.4	54.8		
	SD	10.1	9.5		10.0	9.7		
≥65 years	%	29.3	13.6	0.38 (0.35–0.41)	29.0	17.6	0.52 (0.49–0.56)	<.0001
Age of final education completed >20 years	%	9.8	16.8	1.89 (1.75–2.03)	4.6	7.7	1.60 (1.46–1.75)	.005
Married	%	93.5	93.9	1.14 (1.05–1.24)	82.3	85.3	1.12 (1.06–1.19)	NS
Having children	%	72.6	72.7	1.02 (0.96–1.08)	72.2	70.0	0.90 (0.86–0.95)	.002
Being in full-time employment	%	30.7	51.7	1.66 (1.55–1.78)	11.7	20.4	1.45 (1.38–1.52)	<.0001
Medical and life-style characteristics								
BMI (kg/m^2)	Mean	22.6	22.8		23.0	22.9		
	SD	2.9	5.2		3.8	3.2		
>25	%	18.1	19.9	1.05 (0.98–1.12)	23.3	22.0	0.92 (0.87–0.97)	.0009
Having family history of colorectal cancer	%	2.2	2.2	0.98 (0.82–1.17)	2.5	2.9	1.15 (0.998–1.32)	NS
Current smoker	%	50.0	53.0	1.04 (0.99–1.10)	4.3	6.1	1.43 (1.30–1.58)	<.0001
Daily alcohol drinker	%	50.8	51.0	0.95 (0.90–1.00)	5.0	5.8	1.19 (1.08–1.31)	.0002
Hours of sleep (hours/day)	Mean	7.6	7.2		7.2	6.9		
	SD	1.1	1.1		1.1	1.1		
<7 hours	%	14.2	23.4	1.85 (1.73–1.97)	24.9	35.8	1.65 (1.57–1.73)	.0006
Daily consuming green leafy vegetables	%	29.3	26.1	0.90 (0.85–0.95)	33.9	32.6	0.96 (0.92–1.01)	.04
Daily walking time <30 min	%	25.7	33.4	1.43 (1.35–1.51)	23.8	25.7	1.10 (1.05–1.16)	<.0001
Severe constipation; bowel movements less than once per 4 days	%	1.1	1.1	1.22 (0.94–1.58)	3.8	5.7	1.56 (1.41–1.74)	.04

OR = odds ratio estimated using logistic regression analysis; CI = confidence interval; SD = standard deviation; NS = not significant; BMI = body mass index.

Significant gender interactions were observed for all variables, with the exceptions of marital status and family history. Regardless of sex, subjects who reported high stress were more likely to be married than those who reported low stress, although this trend was only weakly significant. Stress was more strongly associated with younger age, higher education levels, having a full-time job, and having fewer hours of sleep per day in men compared with women. Daily consumption of green leafy vegetables was negatively associated with stress in men, but not in women. Having children and having a BMI $\geq$25 kg/m^2 were both inversely associated with stress in women, but not men. In addition, smoking, daily alcohol consumption, and severe constipation were all positively associated with stress in women alone.

Next, the impacts of perceived psychologic stress on colon and rectal cancer mortalities were estimated by gender, using Cox's proportional hazard model (Table 2). In men, there was no significant association between perceived psychologic stress and colon or rectal cancer mortality; the age-adjusted RRs were 1.01 (95% CI, 0.58–1.75) for colon cancer and 0.93 (95% CI, 0.52–1.66) for rectal cancer. These results were almost unchanged by adjustment for possible confounding factors. In women, a marginally significant association was found between the dichotomized levels of perceived psychologic stress and colon cancer mortality. Women who reported high psychologic stress had a 1.61-fold higher mortality risk (95% CI, 1.00–2.61) compared with those who reported low stress. This risk increased slightly after adjustment for lifestyle factors (multivariate adjusted RR_1, 1.64; 95% CI, 1.01–2.66). Even after adjusting for all of the baseline characteristics, including sociologic factors, the association between stress and female colon cancer remained significant (RR_2, 1.63; 95% CI, 1.002–2.640). The RR for rectal cancer mortality associated with perceived high psychologic stress in women was also greater than unity, although this relationship was not statistically significant (age-adjusted RR, 1.28; 95% CI, 0.59–2.81; multivariate adjusted RR_1, 1.27; 95% CI, 0.58–2.80; RR_2, 1.27; 95% CI, 0.58–2.81). No linear trend was observed between response to the stress question and colon or rectal cancer mortality in either men or women.

DISCUSSION

We found a weak but significant positive association between perceived psychologic stress and the risk of female colon cancer mortality. An increased risk of rectal cancer mortality was also observed in women, although the association was not statistically significant. No positive or inverse association was found between perceived psychologic stress and colon and rectal cancer mortality in men.

The strength of our study lies in the fact that we evaluated the baseline characteristics of all subjects when they were free from cancer and then followed them prospectively. In addition, our subjects were members of the general population recruited from a total of 45 different communities from across Japan. This study design significantly limited the influence of both recall and selection biases, which are unavoidable in case–control studies.

Iso et al. examined the relationship between perceived stress and mortality from cardiovascular diseases in the same initial population as the present study using a similar ques-

TABLE 2. Relative Risk (RR) for Colorectal Cancer Mortality According to the Level of Perceived Stress, Derived From Cox's Proportional Hazard Models by Gender

	Men			Women		
	Perceived stress			Perceived stress		
	Low (n = 24,816)	High (n = 7337)		Low (n = 36,634)	High (n = 9220)	
Person-years	233,849	70,320		355,038	90,147	
Colon cancer death	n = 80	n = 16	*p* value for trend‡	n = 75	n = 22	*p* value for trend‡
RR (95% CI)						
Age-adjusted RR	1.00 (reference)	1.01 (0.58–1.75)	.74	1.00 (reference)	1.61 (1.00–2.61)	.15
Multivariate RR_1*	1.00 (reference)	0.96 (0.55–1.67)	.59	1.00 (reference)	1.64 (1.01–2.65)	.15
Multivariate RR_2†	1.00 (reference)	0.95 (0.55–1.66)	.58	1.00 (reference)	1.63 (1.00–2.64)	.15
Rectal cancer death	n = 74	n = 14	*p* value for trend‡	n = 31	n = 8	*p* value for trend‡
RR (95% CI)						
Age-adjusted RR	1.00 (reference)	0.93 (0.52–1.66)	.69	1.00 (reference)	1.28 (0.59–2.81)	.76
Multivariate RR_1*	1.00 (reference)	0.95 (0.53–1.70)	.67	1.00 (reference)	1.27 (0.58–2.80)	.75
Multivariate RR_2†	1.00 (reference)	0.96 (0.53–1.73)	.61	1.00 (reference)	1.27 (0.58–2.81)	.75

* Multivariate RR_1 adjusted for following lifestyle factors: age, obesity, family history of colorectal cancer, smoking, drinking, daily consuming of green vegetables, walking, and constipation.

† Multivariate RR_2 adjusted for the lifestyle factors and following social factors: education, marital status, having children and being in a fulltime employment.

‡ *p* value for trend: the linear trends in the associations of stress levels and cancer risk were tested by entering the stress levels ranged from 1 to 4 as continuous variables in the models.

CI = confidence interval.

tionnaire (25). Their analysis revealed positive associations between perceived stress and increased stroke mortality in women, and between perceived stress and chronic heart disease in both sexes. Lifestyle factors that are associated with colorectal cancer risk—such as obesity, low physical activity, excessive alcohol consumption, and low vegetable intake—are also known risk factors for cardiovascular diseases. However, even when we adjusted for these factors in our analysis, the independent association between colon cancer mortality and perceived psychologic stress persisted in women. These observations indicate that for both female colon cancer and cardiovascular diseases, psychologic stress is possibly an independent risk factor separate from other lifestyle factors.

Colorectal cancer and psychologic stress were not positively associated among the male subjects in our study. Numerous epidemiologic studies have reported an increased prevalence of stress-related disorders—including acute stress disorder, posttraumatic stress disorder, and major depressive disorder—among women compared with men. However, we cannot conclude from our data alone that men are less susceptible than women to the effects of stress in relation to colorectal cancer risk. We observed significant gender interactions between most of the background characteristics examined and perceived stress levels. High stress was more strongly associated in men than in women with having a full-time job, and spending less time sleeping and walking. Having children and obesity were both inversely associated; by contrast, smoking and daily alcohol consumption were positively associated with stress in women alone. Although we adjusted for all of these variables in our multivariate analysis, it remains possible that a combination of perceived psychologic stress and differences in background characteristics might increase the risk of female colon cancer. We should also note that limitations of the questionnaire might provide an alternative explanation for the gender differences observed in the present study. The single question that was used to assess perceived stress levels might not have accurately reflected the psychologic burden of male subjects. Further studies will be necessary to clarify gender differences in the relationship between perceived psychologic stress and colorectal cancer risk.

Female sex hormones might have a role in the association between stress and colon cancer risk. It has been suggested that colon cancer might share etiologic factors with breast cancer in women (26,27). A number of studies have shown protective effects of parity on cancers of the colon, breast, and reproductive organs (28); modifications of hormone profiles caused by pregnancy and their effects on bile acid metabolism might be the main mechanisms of these associations (29,30). Recently, Helgesson et al. examined a cohort of 1462 Swedish women aged 38 to 60 years and followed these subjects for 24 years (31). The authors reported that stress associated with daily activities, which was measured using a four-item self-administered questionnaire, was associated with a twofold increase in the risk of subsequent breast cancer compared with individuals that reported no stress. Although the possible mechanisms of this association have not been addressed, the interaction between psychologic stress and female sex hormones in relation to cancer risk is worthy of further investigation.

Some limitations to the interpretation of our data should be noted. First, the end point of the study was death from colon or rectal cancer, so the risks reported here relate to fatal colon and rectal cancers only, not cancers that respond to curative treatments. Moreover, these data do not allow a discussion of whether perceived psychologic stress influences the development or progression of colorectal cancers. Second, perceived stress was assessed only on the basis of the response to a single question: "Do you feel stress during your daily life?" Stress is clearly a complex phenomenon, the measurement of which is controversial, and it is not possible to capture full data on this subject using any available tools at present. However, it is generally agreed that the reliability of a test increases with the number of questions (32). Our findings should therefore be confirmed using more sophisticated methods to assess psychologic stress from a range of perspectives, including general and specific types of stress that are related to different environments such as the home and workplace.

Third, although we observed a significant association between the dichotomized levels of stress and the risk of female colon cancer, there was no linear trend between the four separate responses to the stress question and colon cancer mortality. These data do not allow us to determine whether there is an acceptable level of perceived stress or whether the results are the result of limitations of the questionnaire.

In conclusion, perceived psychologic stress was weakly associated with increased mortality from colon cancer in women but not in men. Future studies should attempt to clarify these results in terms of gender differences and their relevance to other types of cancer. In addition, it will be important to explore the most appropriate methods of measuring stress in the context of its role as a possible risk factor for cancer.

The authors express their sincere appreciation to Dr. K Aoki, Professor Emeritus, Nagoya University School of Medicine, and the former chairman of the JACC Study Group, and Dr. H Sugano, the former Director of the Cancer Institute of the Japanese Foundation for Cancer Research, who greatly contributed to the initiation of the study.

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Impact of menstrual and reproductive factors on breast cancer risk in Japan: Results of the JACC study

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(Received October 4, 2004/Revised November 9, 2004/Accepted November 19, 2004/Online publication January 19, 2005)

The incidence of breast cancer among Japanese women, a traditionally low-risk population, has increased substantially. To evaluate the association of reproductive factors with breast cancer risk, we examined 38 159 Japanese women, aged 40–79 years, who responded to a questionnaire on reproductive and other lifestyle factors from 1988 to 1990 in the Japan Collaborative Cohort Study. During an average 7.6 years of follow-up, we documented 151 incidents of breast cancers. Cox proportional hazards modeling was employed to estimate relative risks (RR) and 95% confidence intervals (CI). There was a significant decline in the risk of breast cancer with increasing parity among parous women (trend $P = 0.01$). Women with four or more parities had a 69% lower risk than uniparous women, a reduced risk was also evident among menopausal women. Breast cancer risk tended to rise with increasing age at first delivery (trend $P = 0.05$), the association being very apparent among menopausal women (trend $P = 0.02$). Compared to the women who had their first delivery before age 25, those who delayed this event until after age 34 had an RR of 2.12 (95% CI: 0.72–6.21) and 3.33 (1.07–10.3) among the overall subjects and the menopausal, respectively. There was no apparent association of breast cancer risk with age at menarche or menopause. Our study concerning reproductive risk factors suggests that breast cancer in Japan is similar to that in Western countries, and that reproductive factors, particularly the number of parity and age at first delivery, might be important in the etiology of breast cancer among Japanese women. (*Cancer Sci* 2005; 96: 57–62)

Historically, Japanese women have a lower risk of breast cancer compared to occidental women. The age-adjusted incidence rate to the world standard population of breast cancer in 1998 among Japanese women was 33.8/100 000,[1] about one-third the incidence in white women in the USA (99.0/100 000 from 1997 to 2001).[2] However, the incidence of breast cancer among Japanese women has been increasing at an alarming rate over the last two decades, with a 1.88-fold increase from 1978 to 1998 (age-adjusted incidence rate to the world standard population: 17.9–33.8, respectively).[1,3] Since the latter half of 1990s breast cancer has been the leading site of cancer incidence among Japanese women. The increase was more pronounced among younger women. The ratios of the age-specific rate in 1998 to that in 1987 were 2.36 and 1.89 for age groups 45–49 and 60–64, respectively.

The epidemiology of breast cancer has been studied extensively, especially in regards to its association with reproductive and menstrual factors.[4–22] The results of several studies have been published, most of which were conducted in high-risk Western countries, using a case-control design dealing with the issue. These studies suggested that some aspects of reproductive history including parity, age at first delivery, and age at menarche, could affect the development of breast cancer. During this period of the marked increase in breast cancer incidence, there have been socio-economic changes in Japan, giving rise to major alterations in various reproductive patterns and menstrual characteristics. Nagata *et al.*[5] performed a meta-analysis of eight case-control studies conducted from 1948 to 1993 in Japan on the effect of reproductive factors on the risk of breast cancer. Their findings suggested that breast cancer in Japan was similar with respect to reproductive risk factors to that in high-incidence areas. The Japanese living environment including socio-economic and life-style factors is still changing. We report here on the effects of reproductive and menstrual factors on the risk of breast cancer to identify factors that might have contributed to the change in breast cancer incidence, using data obtained from a large sample of Japanese women participating in the Japan Collaborative Cohort Study for Evaluation of Cancer Risk; the JACC Study designed prospectively.

Materials and Methods

The JACC study. The Japan Collaborative Cohort Study for Evaluation of Cancer Risk, the JACC Study (sponsored by the Ministry of Education, Culture, Sports, Science, and Technology of Japan), is a nationwide multicenter collaborative study to prospectively evaluate the various risks and/or protective factors on cancer mortality and incidence. Study methods and ethical issues have been described in detail elsewhere.[23] Briefly, our study was initiated in 1988, and enrollment continued until the end of 1990. A total of 45 areas were involved in this prospective study, which were selected from seven of the eight districts in Japan, thus covering almost the entire country. We enrolled 127 477 apparently healthy inhabitants in these areas who completed the survey questionnaire. Two strategies were applied to obtain informed consent for participation: by individuals signing the cover page of the questionnaire in the majority of study areas, and by explaining the aim of the study and confidentiality of the data to community leaders in a few areas. Of the 127 477 enrolled, 110 792 (46 465 men and 64 327 women), aged 40–79 years, were followed. Of the 64 327 women, 38 720 women lived in 24 study areas where cancer registries were available. Among those, we excluded from analysis 561 subjects who had a history of breast cancers at baseline or within one year of follow-up time, leaving 38 159 women enrolled in the present study.

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 doi: 10.1111/j.1349-7006.2004.00010.x

The present study protocol was approved by the Ethics Committee of the Nagoya University Graduate School of Medicine, Nagoya, Japan.

Data collection. A self-administered questionnaire was used to assess the baseline characteristics of participants. It covered medical history and included lifestyle-related items such as diet, physical activity, drinking and smoking, and the family history of several medical conditions, including cancer. For women, information was obtained on menstrual factors (age at menarche and age at menopause), and reproductive variables (number of pregnancies, number of parity, and age at first delivery).

Follow-up and identification of breast cancer cases. We used population registries in local municipalities to determine the vital and residential status of the subjects. Registration of death is required by the Family Registration Law in Japan and is enforced throughout the country. For logistical reasons, we discontinued the follow-up of subjects who moved out of their study areas.

We ascertained the incidence of cancer by consulting the records of population-based cancer registries, supplemented by a systematic review of death certificates. In some areas, medical records were also reviewed in local major hospitals. The follow-up was conducted from the time of the baseline survey through to the end of 1997. During this study period, only 3.4% ($n = 1322$) of the participants were lost at follow-up because of relocation.

The mortality to incidence ratio for breast cancer was 0.15 in the cohort covered by cancer registries. This figure is lower than with those in acceptably accurate population-based cancer registries in Japan (0.20–0.30),[24] and indicates that a reasonably high proportion of breast cancer cases were identified. The proportion of Death Certificate Only registrations was 5.9% (9 of 151 cases).

Finally, the mean 7.6-year follow-up analyses verified 151 incident cases of colon cancer among 38 159 women. Because of missing values for certain reproductive variables, the total number of cases and person-years of follow-up varied somewhat among analyses (age at menarche: 134 cases during 268 785 person-years of follow-up; gravida: 139 cases during 271 245 person-years of follow-up; parity: 140 cases during 267 332 person-years; age at first delivery: 120 cases during 229 784 person-years age at menopause: 96 cases during 189 681 person-years of follow-up).

Statistical analysis. In the present study, variables of interest were age at menarche, gravida, parity, age at first delivery, and age at menopause. For each participant, the person-years of follow-up were calculated from the date of filling out the baseline questionnaire to the development of breast cancer, death from any cause, moving out of the study area, or the end of the follow-up period, whichever occurred first. Nine of 151 breast cancer cases were discovered only by death certificate, and their person-years of follow-up were calculated from the date of enrollment to death from breast cancer. We used PROC PHREG in SAS software for Cox proportional hazards modeling to compute relative risks (RR), adjusting for age at enrollment. In another multivariate analysis, study area (Hokkaido and Tohoku, Kanto, Chubu, Kinki, Chugoku, Kyushu), smoking status (never, past, current), alcohol consumption (none, past, present), exercise: 'How long do you take exercise or sports in a week?' (≥5, 3–4, 1–2 h per week, seldom), green leafy vegetable intake (3–7, 1–2 days per week, seldom), meat intake (3–7, 1–2 days per week, seldom), family history of breast cancer, and body mass index (weight in kilograms/[height in meters]^2) were further adjusted. All other reproductive and menstrual factors, were also adjusted. These variables were assessed by the baseline questionnaire and were selected as covariates because they were known or suspected to modify the risk of breast cancer. In the analysis, all categorical variables were entered as dummy variables. Missing values for each covariate were treated as an additional category in the variable and were included in the model. A linear trend of association was assessed by the regression model assigning a score (0, 1, 2, ...) to the levels of each independent variable.

It is known that age at diagnosis or menopausal status might modify the association between reproductive factors and breast cancer risk. Unfortunately, as we had no information on menopausal status at diagnosis, we could not help performing the same analysis as above among the menopausal women at baseline. Furthermore, we described the menstrual and reproductive factors by age at 10-year intervals to identify any such trends in Japan. These data were analyzed using PROC ANOVA with contrast linear statement in SAS software.

The 95% confidence intervals (CI) were presented for all RR. All P-values were based on two-sided tests, in which $P < 0.05$ was considered statistically significant.

Results

Association of age at menarche, gravida, parity, and age at first delivery with the risk of breast cancer. Table 1 presents the age-adjusted and multivariate RR for breast cancer by age at menarche, gravida, parity, and age at first delivery among all subjects. There was no association between breast cancer risk and age at menarche. The multivariate RR of breast cancer for women with any pregnancy compared with those with no pregnancy was above unity [RR (95% CI): 1.64 (0.52–5.19)], whereas a significant declining trend in risk was observed only for women with any pregnancy. Similarly, the multivariate RR of breast cancer for parous women compared with nulliparous was near unity [RR (95% CI): 0.95 (0.38–2.32)]; whereas only among parous women, the multivariate RR by the number of parity compared to those with one delivery were 0.78 (0.42–1.44) for two deliveries, 0.68 (0.36–1.31) for three, and 0.31 (0.13–0.76) for four and more. There was a significantly declining trend for the association between the number of parity and the risk of breast cancer (P-value for trend = 0.01). Only among parous women, was there a borderline significant increase in the risk of breast cancer with rising age at first delivery (P-value for trend = 0.05), with the highest risk occurring in women who had their first delivery at age 35 or older (RR = 2.12).

Association of reproductive and menstrual factors with the risk of breast cancer among menopausal women at baseline. The associations of age at menarche, parity, and age at first delivery with breast cancer risk were almost equal to those observed among overall subjects (Table 2). The positive association of age at first delivery with breast cancer risk was clear among menopausal women. A significantly increasing trend was observed, and the RR for women who had their first delivery at age 35 or older rose to 3.33. With reference to age at menopause, compared to women whose menopause occurred at age 45 or less, the point estimates tended to be above unity but no consistent trend in risk emerged (P-value for trend = 0.15).

Among the premenopausal women at baseline, whose menopausal status at diagnosis was unknown, the associations of menarche and parity with breast cancer were similar to those among the postmenopausal women at baseline. Meanwhile, no association of age at first delivery with breast cancer was observed among the premenopausal women.

Description of menstrual and reproductive factors by generation. We describe the above-mentioned reproductive and menstrual factors by age at 10-year intervals among the present study participants in Table 3, although it is necessary to consider survival bias in the interpretation of the results. Both age at menarche and the number of parity declined with decreasing age at baseline (P-value for trend < 0.01). Age at first delivery increased with decreasing age at baseline (P-value for trend

 doi: 10.1111/j.1349-7006.2004.00010.x

Table 1. Adjusted relative risk (RR) for breast cancer by age at menarche, gravida, parity, and age at first delivery, JACC study, 1988–1997

	Person-years†	No. cases†	RR (95%CI)‡	RR (95%CI)§
Age at menarche				
≤12	17 524	9	1.00	1.00¶
13–14	99 163	51	1.02 (0.50–2.09)	1.05 (0.51–2.15)
15–16	102 068	51	1.03 (0.50–2.13)	1.15 (0.55–2.41)
≥17	50 030	23	0.97 (0.43–2.15)	1.27 (0.56–2.85)
P-value for trend			0.89	0.45
Gravida				
No pregnancy	13 237	5	1.00	1.00††
Any pregnancy	258 008	134	1.35 (0.55–3.31)	1.64 (0.52–5.19)
1	13 512	9	1.00	1.00††
2	57 263	43	1.11 (0.54–2.28)	1.11 (0.52–2.38)
3	74 961	35	0.69 (0.33–1.44)	0.69 (0.32–1.50)
≥4	112 272	47	0.63 (0.31–1.29)	0.63 (0.29–1.33)
P-value for trend			0.01	0.01
Parity				
Nulliparous	13 307	8	1.00	1.00††
Parous	254 025	132	0.85 (0.42–1.74)	0.95 (0.38–2.32)
1	18 984	17	1.00	1.00‡‡
2	96 954	59	0.69 (0.40–1.18)	0.78 (0.42–1.44)
3	86 679	45	0.58 (0.33–1.01)	0.68 (0.36–1.31)
≥4	51 408	11	0.23 (0.11–0.50)	0.31 (0.13–0.76)
P-value for trend			<0.01	0.01
Age at first delivery (only parous women)				
<25	105 682	48	1.00	1.00§§
25–<30	105 347	51	1.05 (0.71–1.56)	1.02 (0.67–1.56)
30–<35	15 527	17	2.45 (1.41–4.26)	1.99 (1.09–3.66)
35–	3 228	4	2.77 (0.99–7.67)	2.12 (0.72–6.21)
P-value for trend			<0.01	0.05

†Number of cases and person-years do not always add up to the total because of missing information for the risk factors. ‡Adjusted for age at baseline. §Adjusted for age at baseline, study area (Hokkaido and Tohoku, Kanto, Chubu, Kinki, Chugoku, Kyushu), smoking status (never, past, current), alcohol consumption (none, past, regular), exercise (≥5, 3–4, 1–2 days/week, seldom), meat intake (3–7, 1–2 days/week, seldom), green leafy vegetable intake (3–7, 1–2 days/week, seldom), family history of breast cancer (Y/N), and BMI at baseline (<18.5, 18.5–<22, 22–<25, 25–kg/m²). ¶Additionally adjusted for menopausal status and the number of parity. ††Additionally adjusted for menopausal status and age at menarche. ‡‡Additionally adjusted for menopausal status, age at menarche, and age at first delivery. §§Additionally adjusted for menopausal status, age at menarche, and the number of parity.

< 0.01). Age at menopause among the subjects aged 60–69 years at baseline was significantly higher than among those aged 70–79 years at baseline. The well-known risk factors were pronounced among the younger generation.

Discussion

This prospective study in Japan, a low-risk country, demonstrated some degree of reproducibility of the most established menstrual and reproductive breast cancer risk factors among occidentals. We found that multiparity was associated with decreased risk of breast cancer, and that late age at first delivery was related to increased risk, similar to that found in most epidemiological studies conducted in Western[8–13,15–17] and Asian countries.[6] We, however, did not find that early age at menarche was associated with breast cancer risk. The effects of these reproductive factors did not differ among postmenopausal subjects at baseline.

The biological mechanisms underlying pregnancy and breast cancer risk has been proposed both in epidemiological and experimental studies,[25–27] although contradictory results have also been reported.[28,29] According to the proposed multistep process of carcinogenesis,[30] undifferentiated mammary gland cells might be initiated by carcinogens and after promotion give rise to a breast tumor several years later. The mammary gland epithelium could reach full differentiation at the first full-term pregnancy, and differentiated cells do not divide or proliferate under normal conditions and are less susceptible to the effects of carcinogens. In other words the earlier the first full-term pregnancy, the earlier the mammary gland cells undergo differentiation. Furthermore, the first full-term pregnancy changes long-term hormonal levels including decreased prolactin, higher sex hormone-binding globulin, and lower estrogen.[31–33] These changes may provide further protection against breast cancer. Meanwhile, a transient increase in the risk of breast cancer after childbirth has been reported.[10,15–17] In our present study, women who had a first birth at 30 years or older had a significantly high risk of breast cancer compared with those under 25 years old. Women who did not have a first birth until age 30 might already have had cells that had undergone early stages of malignant transformation, and pregnancy could have stimulated the growth of these mutated cells. In our study, the association of age at first delivery with breast cancer risk was strengthened among postmenopausal women at baseline, but the association was not observed among premenopausal women at baseline aged 40 or older. This fact is inconsistent with the results of the studies

Table 2. Adjusted relative risk (RR) for breast cancer by age at menarche, parity, age at first delivery, and age at menopause among menopausal women, JACC study, 1988–1997

	Person-years†	No. cases†	RR (95%CI)‡	RR (95%CI)§
Age at menarche				
≤12	7 544	5	1.00	1.00¶
13–14	56 763	32	0.85 (0.33–2.18)	0.86 (0.33–2.23)
15–16	78 204	35	0.68 (0.26–1.74)	0.74 (0.29–1.93)
≥17	43 671	18	0.62 (0.23–1.70)	0.79 (0.29–2.18)
P-value for trend			0.20	0.60
Parity				
Nulliparous	7 275	5	1.00	1.00††
Parous	171 672	86	0.73 (0.30–1.79)	1.17 (0.37–3.73)
1	12 798	10	1.00	1.00‡‡
2	58 715	37	0.83 (0.41–1.68)	0.86 (0.41–1.84)
3	57 496	31	0.69 (0.34–1.40)	0.79 (0.36–1.77)
≥4	42 662	8	0.22 (0.09–0.57)	0.34 (0.12–0.98)
P-value for trend			<0.01	0.05
Age at first delivery (only parous women)				
<25	73 184	29	1.00	1.00§§
25–<30	69 160	32	1.16 (0.70–1.92)	1.13 (0.66–1.92)
30–<35	10 654	12	2.90 (1.48–5.69)	2.20 (1.04–4.65)
35–	2 233	4	4.60 (1.62–13.1)	3.33 (1.07–10.3)
P-value for trend			<0.01	0.02
Age at menopause				
≤45	37 140	14	1.00	1.00¶¶
46–<50	50 790	22	1.15 (0.59–2.24)	1.25 (0.61–2.57)
50–<55	91 837	55	1.59 (0.89–2.86)	1.69 (0.90–3.17)
≥55	9 914	5	1.37 (0.49–3.82)	1.20 (0.38–3.74)
P-value for trend			0.11	0.15

†Number of cases and person-years do not always add up to the total due to missing information for the risk factors. ‡Adjusted for age at baseline. §Adjusted for age at baseline, study area (Hokkaido and Tohoku, Kanto, Chubu, Kinki, Chugoku, Kyushu), smoking status (never, past, current), alcohol consumption (none, past, regular), exercise (≥ 5, 3–4, 1–2 days/week, seldom), meat intake (3–7, 1–2 days/week, seldom), green leafy vegetable intake (3–7, 1–2 days/week, seldom), family history of breast cancer (Y/N), and BMI at baseline (<18.5, 18.5–<22, 22–<25, 25-kg/m²). ¶Additionally adjusted for the nunber of parity and age at menopause. ††Additionally adjusted for age at menarche and at menopause. ‡‡Additionally adjusted for age at menarche, age at menopause, and age at first delivery. §§Additionally adjusted for age at menarche, age at menopause, and the number of parity. ¶¶Additionally adjusted for age at menarche and the number of parity.

conducted in Western countries reporting that late age at first full-term pregnancy had a greater effect on the risk of breast cancer diagnosis at early age or before menopause.[12] Further investigation is necessary to determine whether our findings are a result of the lack of reproductive information, such as the final term of pregnancy, the number of abortions and breast feeding, or are linked to the hormonal milieu or lifestyle peculiar to Japanese, or are merely attributable to chance.

We also found that multiparity was associated with a decreased risk of breast cancer independent of the effect of age at first delivery, although these two variables were inversely correlated (correlation of coefficient = –0.27, $P < 0.001$). This result is consistent with the possibility that cellular differentiation of the mammary gland initiated by the first birth might mask or overcome the short-term promoting effect of subsequent pregnancy for multiparous women,[14] and that every new pregnancy might differentiate the remaining undifferentiated cells, which are caused by inconsistency in the process of differentiation.[30] Alternatively, parity could be a surrogate for other exposures relevant to breast cancer risk. Physical activity associated with large families has been suggested as such an exposure.[34,35] In our previous study,[36] the women with more children were likely to take more time to exercise at baseline. However, the protective effect of multiparity was unchanged after adjustment for physical activity other than smoking, alcohol intake, and diet. The independently protective effect of multiparity on breast cancer observed in our study may be due to some yet unidentified factors specific to the women such as social or psychological factors. More research on the effect of a large family on important lifestyle factors is needed.

It has been hypothesized that early menarche induces an early proliferation of mammary gland cells through early exposure to high hormonal levels. Several studies showed that early age at menarche had a greater effect on breast cancer risk.[5–9,18–22] However, there was no association between age at menarche and breast cancer risk in our study. In the study by Clavel-Chapelon *et al.*[9] reporting the adverse effect of early menarche, age at menarche was 13.3 and 12.7 years old on average for the 1930 and 1950 cohorts, respectively, whereas mean ages at menarche for the corresponding cohorts in our study were 15.1 and 13.9 years old. Our inconsistent finding may be a result of the difference of age at menarche as well as the small number of breast cancer cases.

Late age at menopause is known to be a risk factor for breast cancer.[20–22] In our study, the women who reached menopause at a late age were likely to have a higher risk of breast cancer, although no consistent trend was observed. The higher breast cancer risk in women with a late menopause is most likely explained by both the longer duration and higher level of exposure to estrogen and progesterone experienced by these women. They also may experience a larger number of anovulatory cycles resulting in a lack of cyclic progesterone. The effect of hormonal milieu on breast cancer during anovulatory cycle is less clear.

The study by Nagata *et al.*,[5] which is a meta-analysis of eight case-control studies on the effect of reproductive factors on the risk of breast cancer in Japan, reported that late age at first delivery and early age at menarche were significantly associated with risk of breast cancer. They also found that parity is one of the independent risk factors of breast cancer. Concerning age at first delivery and parity, our findings were consistent with theirs. However, our prospective study observed no association between age at menarche and risk of breast cancer. Seven of

Table 3. Mean (SD) values of menstrual and reproductive factors according to age, JACC study, 1988–1997

	Age at baseline (years)				
	40–49	50–59	60–69	70–79	
Age at menarche (year)	13.9 ± 1.42	15.1 ± 1.79	15.3 ± 1.80	15.6 ± 1.69	<0.01†
The number of parity	2.31 ± 0.86	2.36 ± 0.96	2.80 ± 1.31	3.68 ± 1.96	<0.01†
Age at first birth (year)	25.2 ± 3.06	25.1 ± 3.12	24.9 ± 3.30	25.0 ± 3.71	<0.01†
Age at menopause (year)	–	–	49.1 ± 4.53	48.5 ± 4.55	<0.01‡

†*P*-value for trend; ‡*P*-value for difference.

 doi: 10.1111/j.1349-7006.2004.00010.x

eight case-control studies had been conducted mainly in urban areas and six of them had used hospital controls, whereas our study areas were population-based and nationwide. Inconsistency in the effect of age at menarche may be a result of the difference in study area or subject.

There are both strengths and limitations in our study. The strengths include its prospective design. Data on exposure were collected before diagnosis and prior to any breast cancer deaths, which could preclude recall bias. Moreover, as data on the many kinds of exposure known or suspected to modify the risk of breast cancer were collected in the present study, we could elucidate the independent effects of reproductive factors by multivariate adjustment. However, the lack of reproductive information such as the final term of pregnancy and breast feeding is one of the limitations of our study. The second limitation arises from the validity of self-reported reproductive histories. Some reproductive exposures occurred long before enrollment or any diagnosis of disease. However, previous studies on the validity of self-reported reproductive histories have shown good agreement between the respondents of reproductive events and their medical records.[37,38] Thirdly, Familial history of breast cancer is considered one of the important risk factors for breast cancer. In our study, familial history of first-degree relatives was also significantly associated with breast cancer incidence. However, we examined neither familial history of the relatives beyond the first-degree of relationship nor the germinal mutation in the *BRCA1* or *BRCA2* genes. Breast cancer cases in this study include the hereditary breast and ovarian cancer syndrome. Unfortunately, our study is not also able to distinguish between estrogen receptor-positive and negative breast cancers. Finally, our results might include chance findings because the participants were not drawn demographically from Japan as a whole. Also, the number of incidents of cancer cases of the breast was small compared to those in Western studies.

The present study suggested that breast cancer in Japan is similar to that in Western countries in terms of menstrual and reproductive risk factors. In Japan, the westernization of lifestyles has progressed rapidly since the early 1960s. Changes in lifestyle and behavior related to socio-economic development including food intake pattern and birth-control behavior, might have resulted in earlier age at menarche, later age at first delivery, fewer children, and later age at menopause. These changes observed in our study reflect substantial generational differences in menstrual and reproductive factors. Breast cancer has already become the most common malignancy among women in Japan. The recent increase in beast cancer risk is more pronounced in premenopausal than postmenopausal women. Therefore, it is necessary to further examine the change in reproductive factors, their effect on breast cancer, and the interactive effects between reproductive factors and lifestyle factors such as obesity and fat intake among Japanese women, most of whom have lived largely westernized lifestyle since childhood, in consideration of the difference between premenopausal and postmenopausal breast cancers.

Acknowledgments

The authors wish to express their appreciation to Dr Kunio Aoki, Professor Emeritus, Nagoya University School of Medicine and former chairman of the JACC Study Group, and to Dr Haruo Sugano, former Director of the Cancer Institute of the Japanese Foundation for Cancer Research, both of whom contributed greatly to the initiation of the study.

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This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (2) (No. 14031222) 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, and 11181101).

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 doi: 10.1111/j.1349-7006.2004.00010.x

Int. J. Cancer: **113,** 509 (2005)

Letter to the Editor

Is the Proportion of Infection-Related Cancers Much Greater than Generally Appreciated?

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Dear Sir,

Etiologic fractions of malignancies differ by population, depending on the age and sex distribution, time and place, which is of interest with reference to cancer prevention and control. In a famous exercise in the 1980s, Doll and Peto[1] estimated values for differences in cancer causes in the US, which have long been cited throughout the world, including Japan. They argued that 30% of malignant tumors were attributable to smoking, with 35% caused by an inappropriate diet. The proportion considered due to infections was no more than 10%.

Smoking is the single most potent causal factor for various malignancies, and it may also play significant roles in promotion of lesions triggered by other carcinogens and infections.[1–3] Thus, anti-smoking campaigns and strategies remain crucial for cancer prevention and control. The second major fraction, attributable to dietary factors such as excess energy intake, high or imbalanced consumption of fats/oils, and associated with physical inactivity and obesity, may be greater in elderly people than in the younger generation.[4] The diet clearly has characteristics of a double-edged sword, and research is slowly but surely elucidating the interactions that need to be targeted for primary and secondary prevention. The major malignant tumors that will still remain are generally infection-linked.

In fact, laboratory and epidemiologic studies have provided clear evidence that many malignant tumors can be ascribed to the influence of chronic infections by microorganisms, including parasites, bacteria and viruses. In addition to the obvious case of hepatocellular carcinomas caused by hepatitis B and C viruses, *Helicobacter pylori* is a definite and necessary factor for stomach cancer,[2,5] human papillomaviruses are causal for cervical cancer and possibly some proportion of head and neck and anogenital malignancies,[2,6] nasopharyngeal cancer and certain type of lymphomas are provoked by the Epstein-Barr virus and adult T-cell leukemia is due to human T-lymphotropic virus type I.

In Japan, during 1993–1997, the infection-related malignancies in the liver, stomach and cervix, as well as adult T-cell leukemia, have been estimated from cancer registration data to account for approximately 35% of the total in males and 30% in females.[7] If we include head and neck and anogenital malignant tumors, the percentages would be elevated to around 45% in males and 40% in females, respectively.

The fraction due to chronic infections may be greater in developing countries. We can enumerate several examples without difficulty, including hepatitis B virus-related hepatocellular carcinoma in Qidong and Haimen, China, liver flukes (*Opisthorchis viverrini*)-associated cholangiocarcinoma in Khon Kaen, Thailand, Epstein-Barr virus-related lymphoma in Indonesia, parasite (*Schistosoma haematobium*)-associated bladder cancer in Egypt and HIV-related Kaposi sarcoma worldwide.[2,5]

Analyses of host factors, including genetic polymorphisms, and interactions between host and environmental factors are clearly of continuing importance in the postgenome era. However, in practical terms for the present, because of the possibility of applying prophylactic vaccination and immunoglobulin therapy or prescribing antibiotics, infection-related malignancies would appear to be more controllable than tobacco-associated malignant tumors and much more readily preventable than aging- and lifestyle-related cancers. The fact that the etiologic burden may be much greater than generally perceived needs more emphasis in cancer prevention and control efforts.

Yours sincerely,

Shinkan TOKUDOME*, Sadao SUZUKI, Masayo KOJIMA and Akihiro HOSONO

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Received 29 June 2004; Accepted after revision 27 July 2004
DOI 10.1002/ijc.20592
Published online 28 September 2004 in Wiley InterScience (www.interscience.wiley.com).

American Journal of Epidemiology Advance Access published September 25, 2006

American Journal of Epidemiology

DOI: 10.1093/aje/kwj321

Human Genome Epidemiology (HuGE) Review

Meta- and Pooled Analysis of *GSTT1* and Lung Cancer: A Huge-GSEC Review

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Received for publication July 20, 2005; accepted for publication April 1, 2006.

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Lung cancer is the most common malignancy in the Western world, and the main risk factor is tobacco smoking. Polymorphisms in metabolic genes may modulate the risk associated with environmental factors. The glutathione *S*-transferase theta 1 gene (*GSTT1*) is a particularly attractive candidate for lung cancer susceptibility because of its involvement in the metabolism of polycyclic aromatic hydrocarbons found in tobacco smoke and of other chemicals, pesticides, and industrial solvents. The frequency of the *GSTT1* null genotype is lower among Caucasians (10–20%) than among Asians (50–60%). The authors present a meta- and a pooled analysis of case-control, genotype-based studies that examined the association between *GSTT1* and lung cancer (34 studies, 7,629 cases and 10,087 controls for the meta-analysis; 34 studies, 7,044 cases and 10,000 controls for the pooled analysis). No association was observed between *GSTT1* deletion and lung cancer for Caucasians (odds ratio (OR) = 0.99, 95% confidence interval (CI): 0.87, 1.12); for Asians, a positive association was found (OR = 1.28, 95% CI: 1.10, 1.49). In the pooled analysis, the odds ratios were not significant for either Asians (OR = 0.97, 95% CI: 0.83, 1.13) or Caucasians (OR = 1.09, 95% CI: 0.99, 1.21). No significant interaction was observed between *GSTT1* and smoking on lung cancer, whereas *GSTT1* appeared to modulate occupational-related lung cancer.

disease susceptibility; epidemiology; genes; genetic predisposition to disease; *GSTT1*; lung neoplasms; meta-analysis

Abbreviations: CI, confidence interval; GSEC, Genetic Susceptibility to Environmental Carcinogens; GST, glutathione *S*-transferase; *GSTT1*, glutathione *S*-transferase theta 1 gene; OR, odds ratio.

Editor's note: This paper is also available on the website of the Human Genome Epidemiology Network (http://www.cdc.gov/genomics/hugenet/).

GENE

The glutathione *S*-transferase (GST) supergene family consists of phase II detoxifying enzymes catalyzing several reduced glutathione-dependent reactions with compounds containing an electrophilic center (1). The GST family comprises at least eight classes of GST isoenzymes: alpha, mu, pi, sigma, theta, kappa, omega, and zeta (2). Genetic polymorphisms have been described in all these classes (3). The soluble GSTs exist as dimeric proteins of approximately 25 kDa; they are highly expressed, constituting up to 4 percent of the total soluble proteins (4).

Two theta-class GSTs, GSTT1 and GSTT2, have been identified in the human liver, and the corresponding genes are localized in the same region on human chromosome 22, specifically in the subband 22q11.2 (5, 6). GSTT1 enzymes show important differences in their catalytic activity compared with other GSTs: they have lower glutathione binding activity, with increased catalytic efficiency (7, 8). Theta is considered the most ancient of the GSTs, and theta-like GSTs are found in almost all organisms investigated (2). The encoded GSTT1 human subunit is about 25,300 Da (9); the gene is 8.1 kb long (10).

Among the GST substrates, there are several environmental carcinogens found in food, air, or medications, such as polycyclic aromatic hydrocarbons, found in combustion products, diet, and tobacco smoke (11). Polycyclic aromatic hydrocarbons are activated by members of the phase 1 cytochrome P-450 supergene family to epoxide-containing metabolites (e.g., benzo[*a*]pyrene-7,8-diol-9,10-oxide), which are substrates for the mu, alpha, and pi GST classes. *GSTT1* is an interesting candidate gene for lung cancer susceptibility because of its involvement in the metabolism of chemicals such as methylating agents, pesticides, and industrial solvents (2). In vitro studies suggest that both GSTT1 and GSTM1 enzymes protect cells from the toxic products of phase 1 detoxification reactions (12, 13).

However, GSTT1-catalyzed reactions can also increase the toxicity of some compounds, such as dichloromethane (2). GSTs also conjugate isothiocyanates, which are potent inducers of enzymes that detoxify environmental mutagens (14). The conjugation process diverts the isothiocyanates from the enzyme induction pathway into excretion (15), leading to elimination of these anticarcinogenic substances (16) and thus decreasing their potential chemopreventive effect (17).

GENE VARIANTS

The most common polymorphism in *GSTT1* consists of a deletion of the whole gene, resulting in the lack of active enzyme (18). Complete deletion at the *GSTT1* locus (19) was hypothesized by observing the phenotypic variation in glutathione-related detoxification of halomethanes by human erythrocytes, resulting in "conjugator" and "nonconjugator" phenotypes (20). Recently, another less common polymorphism (*Thr104Pro*) in the *GSTT1* gene was described that also results in a nonconjugator phenotype (21).

The frequency of the *GSTT1* deletion varies among different populations (22). In particular, the prevalence of the *GSTT1* null genotype is lower among Caucasians (10–20 percent) compared with Asians (50–60 percent) (23). The frequency of the *GSTT1* null polymorphism in the controls included in the present meta- and pooled analyses is similar to what was previously published (22): 18.7 percent (meta-analysis) and 19.0 percent (pooled analysis) in Caucasians; 53.8 percent and 53.6 percent, respectively, in Asians; and