Plasma C-Reactive Protein and Risk of Colorectal Cancer in a Nested Case-Control Study: Japan Public Health Center–Based Prospective Study

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Abstract

C-reactive protein is a biomarker indicating inflammation in the body. We measured plasma C-reactive protein to assess whether this biomarker could predict subsequent colorectal cancer incidence. A nested case-control study was conducted within a Japan Public Health Center–based prospective study. During a 11.5-year follow-up, 375 newly diagnosed colorectal cancers were identified in a cohort of 38,373 adults who had returned the baseline questionnaire and provided blood samples. Two controls were selected from the cohort for each case matched by age, sex, study area, date of blood drawn, and fasting time at blood donation. The odds ratio of colorectal cancer for plasma C-reactive protein was estimated using a conditional logistic regression model adjusted for pack-years of smoking, body mass index, alcohol consumption, physical exercise, and family history of colorectal cancer. The highest quartile group of plasma C-reactive protein was significantly associated with colorectal cancer compared with the lowest group (odds ratio, 1.6; 95% confidence interval, 1.1-2.5; P_{trend} = 0.053). The association became clearer after excluding cases of rectal cancer (P_{trend} = 0.041) and limiting colorectal cancer to the intramucosal type (P_{trend} = 0.017). This association was unchanged after deletion of the first 2-year cases. In conclusion, plasma levels of C-reactive protein were associated with a subsequent risk of colon cancer. Inflammation may be involved at the early stage of colon tumor growth. (Cancer Epidemiol Biomarkers Prev 2006;15(4):690–5)

Introduction

Many epidemiologic studies have consistently shown that users of nonsteroidal anti-inflammatory drugs, including aspirin and others, had a lower risk of colorectal cancer than nonusers (1). Inflammation has been one of the candidates for the biological mechanism involved in colorectal cancer development.

Ulcerative colitis is a chronic inflammatory disease of the colon and rectum (2). This disease poses an increased risk of colorectal cancer compared with the general population (3). Inflammation may play an important role in colorectal cancer formation as well as other site neoplasms (4). In fact, various kinds of inflammatory cells, cytokines, and chemokines are involved in carcinogenesis. These inflammatory constituents may result in the initiation or promotion of neoplasms.

C-reactive protein is a well-known acute-phase indicator of inflammation in the body (5). This marker indicates not only an acute-phase response but also a chronic low-level inflammation and is associated with the risk of cardiovascular diseases (6). This indicator correlates well with the proinflammatory cytokines mentioned above (7). Thus, C-reactive protein may be a useful predictor of neoplasms, including colorectal cancer.

However, evidence for the association between C-reactive protein levels before diagnosis and the subsequent risk of colorectal cancer has thus far been sparse and inconsistent (8-10). Furthermore, subanalysis by tumor invasion is needed to clarify whether inflammation leads to an early or late stage of tumor development. To our knowledge, no report has been published that settles this question.

We assessed the association between plasma C-reactive protein and the subsequent risk of colorectal cancer in a nested case-control study within a large prospective cohort study.

Materials and Methods

Study Population. The Japan Public Health Center–based Prospective Study (JPHC study) is an ongoing cohort study investigating cancer, cardiovascular disease, and other lifestyle-related diseases. The first group (cohort I) of the JPHC study started in 1990 and the second group (cohort II) in 1993 (11). Study subjects were mainly residents living in several municipalities in each area administered by a Public Health Center, ages 40 to 59 years for cohort I and 40 to 69 years for cohort II. Moreover, a subcohort of health check-up examinees was added to cohort I whereas two more subcohorts of health check-up examinees and random samples from one city, ages 40 to 69 years, were added to cohort II. The study subjects were identified by the population registry in each municipality. The subcohort of health check-up examinees in cohort I mentioned above were excluded from this report because their cancer incidence data were not available. Thus, we studied a cohort of 65,803 men and 67,520 women. Our study was approved by the institutional review board of the National Cancer Center, Tokyo, Japan.

Questionnaire Survey. Using a self-administered questionnaire, study subjects were asked to provide information about their personal and familial medical histories, smoking, alcohol consumption, frequency of physical exercise, dietary habits, and other lifestyle factors. Their dietary habits were

Received 9/8/05; revised 12/27/05; accepted 2/1/06.

Grant support: Grant-in-Aid for Cancer Research and for the Third-Term Comprehensive 10-Year-Strategy for Cancer Control from the Ministry of Health, Labor, and Welfare of Japan.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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doi:10.1158/1055-9965.EPI-05-0708

assessed by a food-frequency questionnaire of 44 items for cohort I (12) and 52 items for cohort II. A total of 50,456 men (77%) and 55,909 women (83%) filled out and returned the questionnaire.

Blood Collection. Among the study subjects, 15,258 men (23%) and 26,703 women (40%) donated 10-mL samples of venous blood that was drawn into vacutainer tubes containing heparin. Samples were collected at the time of their health check-ups, which extended from 1990 to 1992 for cohort I and from 1993 to 1995 for cohort II, and were divided into plasma and buffy layers, and then preserved at −80°C until analysis.

Follow-up. We followed study subjects until December 31, 2003. When subjects died, we used mortality data from the Ministry of Health, Labor, and Welfare. Those moving to other municipalities were also identified annually through residential registries in their Public Health Center areas. Among study subjects, 9.9% had moved away and 0.2% were lost to follow-up during the study period.

Selection of Cases and Controls. Incidence data on colorectal cancer were collected for the JPHC cancer registry through two data sources: local major hospitals and population-based cancer registries. Indicators of the completeness of colorectal cancer case ascertainment conformed to the international standard (13) as follows: 5.5% of incident cases were notified by death certificates (Death Certificate Notification); 2.2% did not have detailed information except death certificates (Death Certificate Only); and 94.7% were verified by histologic examination (Histologic Verification). We identified 375 cases (196 men and 179 women) of colorectal cancer up to December 31, 2003 from among the 38,373 subjects (14,004 men and 24,369 women) who had returned the baseline questionnaire, did not report diagnosis of any cancer, and provided the blood samples. All 375 cases were pathologically confirmed as adenocarcinoma after excluding 18 cases of unknown pathology and 7 nonadenocarcinoma cases. Of these, 256 subjects had cancer of the colon [International Classification of Diseases for Oncology, third edition (ICD-O-3 code C180-C189); ref. 14] and 119 had cancer of the rectum (ICD-O-3 code C199 and C209). Colon cancers were classified into those of proximal colon (ICD-O-3 code C180-C185) or the distal colon (ICD-O-3 code C186 and C187). Information on tumor depth was available in 370 of the 375 cases, with 120 tumors of the intramucosal type corresponding to Tis in tumor-node-metastasis classification (15) and 250 of the invasive type corresponding to T1 or more. Information on cases diagnosed on the emergence of symptom or colorectal screening was available for only half of the cases in our study, in which 43% of the cases were diagnosed after emergence of symptoms, 45% of the cases by cancer screening, and 11% of cases during follow-up of another disease. Immunochemical fecal occult blood test has been recommended for the general population (i.e., mass screening organized by local governments) whereas colonoscopy screening is not recommended in Japan (16).

For each case, two controls were selected, using incidence density sampling (17), from subjects who had no prior history of colorectal cancer when the case was diagnosed. Controls were matched for each case on sex, age (within 3 years), date of blood drawn (within 3 months), time since last meal (within 4 hours), and study location (Public Health Center area).

Laboratory Assays. Plasma C-reactive protein concentrations were measured using a latex-enhanced high-sensitivity assay on a BN II nephelometer (Dade Behring Marburg GmbH, Marburg, Germany) done by a commercial laboratory (Mitsubishi Kagaku Bio-Clinical Laboratories, Inc., Tokyo, Japan). Samples from matched sets were assayed together. All laboratory personnel were blinded with respect to case or control status. The mean intra-assay coefficient of variation from the quality control samples was 2.7% (n = 10).

Statistical Analysis. Adjusted means for cases and controls were calculated using least square means in analysis of covariance by the PROC GLM procedure in SAS software. Percentages of baseline characteristics were unadjusted crude values. We used the extensions of the Mantel-Haenszel procedure (18) with matched pairs for comparison of the baseline characteristics and the baseline plasma C-reactive protein concentrations between cases and controls using the PROC FREQ procedure with CMH option. We also tested the linear trend of covariates by quartiles of plasma concentration of C-reactive protein using the extensions of the Mantel-Haenszel procedure (18). The odds ratio (OR) and 95% confidence interval (95% CI) for baseline concentrations of plasma C-reactive protein, divided into quartiles based on control distribution, were calculated by a conditional logistic regression model adjusted for pack-years of smoking (continuous), body mass index (BMI; continuous), alcohol consumption (continuous), physical exercise (less than once a week, or once a week or more), and family history of colorectal cancer as well as using matched pairs. The linear trend of OR was tested using the logarithmic-transformed median value of C-reactive protein in each category because the measurements were log-normally distributed. P values for the trend were evaluated using the two-sided test with 0.05 as the significant level. We estimated the OR of cancer cases stratified by site or depth of tumor as well as the OR of all colorectal cancer cases. All statistical analyses were done with SAS software (version 9.1, SAS Institute, Inc., Cary, NC).

Results

Pack-years of smoking or alcohol consumption were higher in cases than in matched controls (Table 1). Other characteristics, including dietary factors, did not substantially differ between the two groups. The higher the quartiles of plasma C-reactive protein were in controls, the older they were, the more they smoked, and the higher their BMI (Table 2). Plasma C-reactive protein was higher in colon cancer cases than in matched controls (0.55 mg/L in cases versus 0.45 mg/L in controls; P = 0.023; Table 3). Distal colon cases differed more from controls than proximal colon cases did.

Table 1. Baseline characteristics of cases and controls

Characteristics	Cases (n = 375)	Controls (n = 750)	P
Men, n (%)	196 (52)	392 (52)	—
Age (y), mean*	56.7	56.6	0.35
Pack-years of smoking, mean†	14.0	12.2	0.028
BMI (kg/m^2), mean†	23.6	23.4	0.22
Alcohol consumption (g/wk), mean†	123.5	90.1	<0.0010
Physical exercise, n (%)‡	82 (22)	129 (18)	0.060
Vitamin supplement use, n (%)	59 (17)	107 (16)	0.54
Family history of colorectal cancer, n (%)	9 (2.4)	8 (1.1)	0.086
Total energy intake (kcal/d), mean§	1,648	1,664	0.55
Folate intake (μg/d), mean§	312	310	0.81
Dietary fiber intake (g/d), mean§	7.8	7.8	0.75
Calcium intake (mg/d), mean§	446	445	0.91
Vitamin D intake (μg/d), mean§	6.0	5.9	0.46
Red meat intake (g/d), mean§	15.4	15.0	0.57
Processed meat intake (g/d), mean§	3.5	3.4	0.92
Vegetable intake (g/d), mean§	127	123	0.32
Fruit intake (g/d), mean§	93.6	96.2	0.58

*Adjusted for sex.
†Adjusted for sex and age.
‡Number (percentage) of subjects doing physical exercise once a week or more.
§Adjusted for sex, age, and cohort.

Table 2. Association between plasma C-reactive protein and covariates among controls at baseline

Variables	Quartiles of plasma C-reactive protein				
	Lowest (<0.24 mg/L)	Second (0.24-0.45 mg/L)	Third (0.46-0.95 mg/L)	Highest (≥0.96 mg/L)	P_{trend}
Men, *n* (%)	86 (46)	104 (55)	101 (54)	101 (54)	0.16*
Age (y), mean†	56.0	55.6	57.0	57.9	0.0024†
Pack-years of smoking, mean‡	9.2	12.1	13.1	14.4	0.0018‡
BMI, mean‡	22.3	23.2	23.9	24.3	<0.0010‡
Alcohol consumption, mean‡	78.4	84.8	91.4	108.1	0.076‡
Physical exercise, *n* (%)	36 (20)	34 (18)	29 (16)	30 (16)	0.11‡
Vitamin supplement use, *n* (%)	24 (14)	27 (16)	22 (14)	34 (21)	0.26‡
Family history of colorectal cancer, *n* (%)	2 (1.1)	1 (0.5)	2 (1.1)	3 (1.6)	0.54‡

*Adjusted for age.
†Adjusted for sex.
‡Adjusted for sex and age.

The highest quartile of plasma C-reactive protein compared with the lowest was significantly associated with colorectal cancer (OR, 1.6; 95% CI, 1.1-2.5; P_{trend} = 0.053; Table 4). There was a positive association only in colon cancer (P_{trend} = 0.041) but not in rectal cancer (P_{trend} = 0.82). OR by colon subsite did not substantially differ between cancer of the proximal colon (OR, 1.0, 1.1, 1.0, 1.6) and cancer of the distal colon (OR, 1.0, 1.2, 1.4, 1.6). The intramucosal type, but not the invasive type, of colon cancer was associated with plasma C-reactive protein (Table 5). OR was 2.6 (95% CI, 1.1-6.2) for the highest group versus the lowest group (P_{trend} = 0.017) in the intramucosal type. In contrast, no association was observed in the invasive type. Differences among subsite colons were not evident due to a small number of cases. The association in the intramucosal cancer was unchanged after reanalysis that excluded the first 2-year cases (data not shown).

Furthermore, we did the same analyses by sex or age at diagnosis. ORs (95% CIs) for 1 SD increase of logarithmic transformed C-reactive protein concentrations were 1.6 (1.1-2.5) for men and 1.1 (0.67-1.9) for women in analyses of intramucosal colon cancer, and 1.0 (0.73-1.5) for men and 1.1 (0.82-1.5) for women in analyses of invasive colon cancer. The median age at diagnosis was 65 years. One-SD incremental ORs of intramucosal colon cancer were 1.5 (0.99-2.2) for the group <65 years of age and 1.9 (0.96-3.9) for the group 65 years or older. ORs of invasive colon cancer were 1.3 (0.95-1.8) for the group <65 years of age and 0.84 (0.61-1.2) for the group 65 years or older.

Discussion

Plasma C-reactive protein was associated with the risk of colon cancer. This result was consistent with one previous study but not with another. Erlinger et al. (8) showed a significant association between baseline C-reactive protein levels and the subsequent risk of colon cancer in a nested case-control study within the CLUE II cohort, a prospective study conducted to find clues to prevent cancer and heart disease. Their report as well as the present study found an association only in colon cancer. In contrast, Zhang et al. (9) reported no association between baseline C-reactive protein levels and the risk of colorectal cancer in the Women's Health Study, a randomized, double-blind, placebo-controlled, 2 × 2 factorial trial using low-dose aspirin and vitamin E for the primary prevention of cancer and cardiovascular disease. Although their study was an intervention trial using aspirin (a preventive agent against colorectal neoplasms), their analysis was justified because their analysis was conducted with a careful adjustment for trial assignments as well as other covariates. They also reported that the association did not differ between the assigned groups. Moreover, Ito et al. (10) recently reported no association in a nested case-control study from analyzing the risk of colorectal cancer incidence and death. Inconsistency among these four studies, including ours, may be explained by age at blood draw, range of C-reactive concentration, and tumor invasion levels. First, mean ages were older for study subjects of Erlinger et al. (64 years; ref. 8) and Ito et al. (62 years; ref. 10) than those of Zhang et al. (55 years; ref. 9) and ours (57 years). Second, two studies covered a higher range, from <1 to ≥3 mg/L [Erlinger et al. (8) and Zhang et al. (9)], whereas two other studies covered a lower range, from <0.25 to ≥1 mg/L [Ito et al. (10) and our study]. Finally, three studies, except ours, examined only the risk of invasive cancer whereas we examined also the risk of intramucosal cancer. Here, we may assume that the higher range of C-reactive protein is associated with the risk of colon cancer only in older subjects as in the study of Erlinger et al. (8). In younger subjects, C-reactive protein, regardless of the range in blood, may be associated with only the risk of intramucosal colon cancer as in ours.

Because chronic inflammatory disease had an increased risk of colorectal cancer (3), we hypothesized that colonic inflammation increases the risk of colon cancer, which our results showed. However, C-reactive protein indicating systemic inflammation is not always correlated to colonic inflammation. Fecal calprotectin, a marker of bowel inflammation, is not correlated to serum C-reactive protein but to BMI and low exercise levels (19). Obesity may increase the C-reactive protein concentration. A recent study reported that plasma C-reactive protein levels were associated with high BMI and other indicators of obesity (20). Moreover, several dietary intervention trials found that weight loss reduced C-reactive protein in obese individuals (21). Therefore, circulating C-reactive protein may reflect two conditions: inflammation and obesity, both of which are risk factors of colon cancer (3, 22). Considering the role as an indicator of

Table 3. Plasma C-reactive protein of cases and controls

	Plasma C-reactive protein (mg/L)		*P*
	Cases	Controls	
Colorectal cancer, *n*	375	750	
Median [interquartile range]	0.52 [0.28-1.2]	0.45 [0.24-0.96]	0.065
Colon cancer, *n*	256	512	
Median [interquartile range]	0.55 [0.27-1.4]	0.45 [0.25-0.96]	0.023
Proximal colon cancer, *n*	123	246	
Median [interquartile range]	0.52 [0.26-1.3]	0.45 [0.25-0.89]	0.27
Distal colon cancer, *n*	125	250	
Median [interquartile range]	0.67 [0.31-1.4]	0.46 [0.25-1.0]	0.039
Rectal cancer, *n*	119	238	
Median [interquartile range]	0.44 [0.31-0.93]	0.46 [0.20-0.96]	0.96

Table 4. ORs and 95% CIs of colorectal cancer for plasma C-reactive protein

	Quartiles of plasma C-reactive protein				
	Lowest (<0.24 mg/L)	Second (0.24-0.45 mg/L)	Third (0.46-0.95 mg/L)	Highest (≥0.96 mg/L)	P_{trend}
Colorectal cancer					
Cases/controls	64/171	97/179	88/178	106/169	
OR (95% CI)	1.0 (reference)	1.5 (0.99-2.2)	1.3 (0.85-2.0)	1.6 (1.1-2.5)	0.053
Colon cancer					
Cases/controls	46/110	59/129	59/120	80/120	
OR (95% CI)	1.0 (reference)	1.1 (0.71-1.9)	1.2 (0.73-2.0)	1.6 (0.99-2.7)	0.041
Proximal colon cancer					
Cases/controls	26/54	29/64	26/57	37/54	
OR (95% CI)	1.0 (reference)	1.1 (0.57-2.2)	1.0 (0.49-2.1)	1.6 (0.79-3.3)	0.18
Distal colon cancer					
Cases/controls	17/54	28/60	31/59	42/63	
OR (95% CI)	1.0 (reference)	1.2 (0.53-2.6)	1.4 (0.63-3.3)	1.6 (0.77-3.5)	0.16
Rectal cancer					
Cases/controls	18/61	38/50	29/58	26/49	
OR (95% CI)	1.0 (reference)	2.4 (1.2-4.9)	1.4 (0.63-3.2)	1.4 (0.63-3.3)	0.82

NOTE: ORs were estimated using matched pairs with adjustment for pack years of smoking (continuous), BMI (continuous), alcohol consumption (g/wk ethanol; continuous), physical exercise (less than once a week, or once a week or more), and family history of colorectal cancer.

obesity, a difference in the association of C-reactive protein between colon and rectal cancer in our study may be plausible because BMI and physical inactivity are more strongly associated with colon cancer than rectal cancer (23). However, C-reactive protein is not just a surrogate marker of obesity because, if so, it would be also associated with invasive colon cancer.

Plasma C-reactive protein was associated with the intramucosal rather than the invasive type of colon cancer. This association persisted after the first 2-year cases. This did not present a carcinoma-related inflammation, but rather indicated that the inflammation was associated with carcinogenesis rather than with tumor invasion. This finding was consistent with a report that nonsteroidal anti-inflammatory drugs reduced the risk of adenoma recurrence, an early lesion of colorectal cancer (24), although, to our knowledge, there has been no study showing an association between C-reactive protein and the risk of colorectal adenoma. Additionally, an animal study showed that inflammation converted human colonic adenoma cells to adenocarcinoma cells in nude mice (25). However, the finding of no association with invasive colon cancer was inconsistent with a report that nonsteroidal anti-inflammatory drugs also prevented invasive colorectal cancer (1). One possible reason for such a disparity may be due to the fact that nonsteroidal anti-inflammatory drugs had apoptotic as well as anti-inflammatory effects on the inhibition of cell proliferation (26).

Blood samples were collected before cancer diagnosis, supporting the idea that plasma levels indicated a cancer-free status. C-reactive protein was measured only once. However, this biomarker has small intra-individual but large inter-individual variations. A prior study showed that study individuals tended to have relatively stable C-reactive protein values over a 6-month period for which C-reactive protein was measured every 3 weeks for eight time points (27). Moreover, few diurnal variations within each individual were shown (28). Thus, a one-point measurement could indicate an individual's chronic status of inflammation. If intra-individual

Table 5. ORs and 95% CIs of colon cancer by invasive type for plasma C-reactive protein

	Quartiles of plasma C-reactive protein				
	Lowest (<0.24 mg/L)	Second (0.24-0.45 mg/L)	Third (0.46-0.95 mg/L)	Highest (≥0.96 mg/L)	P_{trend}
Intramucosal type					
Colon cancer					
Cases/controls	18/51	19/49	24/43	33/39	
OR (95% CI)	1.0 (reference)	1.0 (0.47-2.3)	1.6 (0.65-4.2)	2.6 (1.1-6.2)	0.017
Proximal colon cancer					
Cases/controls	7/20	9/21	9/14	10/13	
OR (95% CI)	1.0 (reference)	1.1 (0.28-4.6)	3.0 (0.48-18)	2.5 (0.45-14)	0.27
Distal colon cancer					
Cases/controls	8/30	10/24	14/28	23/25	
OR (95% CI)	1.0 (reference)	1.1 (0.30-3.7)	2.0 (0.52-7.4)	3.4 (1.0-11)	0.029
Invasive type					
Colon cancer					
Cases/controls	27/56	39/77	35/76	45/78	
OR (95% CI)	1.0 (reference)	1.1 (0.58-2.1)	1.1 (0.56-2.0)	1.2 (0.64-2.4)	0.55
Proximal colon cancer					
Cases/controls	18/31	19/42	17/42	26/40	
OR (95% CI)	1.0 (reference)	1.0 (0.42-2.4)	0.77 (0.32-1.9)	1.3 (0.56-3.2)	0.51
Distal colon cancer					
Cases/controls	9/24	18/34	17/31	18/36	
OR (95% CI)	1.0 (reference)	1.1 (0.35-3.3)	1.3 (0.41-3.9)	0.86 (0.29-2.6)	0.72

NOTE: ORs were estimated using matched pairs with adjustment for pack-years of smoking (continuous), BMI (continuous), alcohol consumption (g/wk ethanol; continuous), physical exercise (less than once a week, or once a week or more), and family history of colorectal cancer.

variations were to produce measurement errors, it would attenuate the association and thus could not explain for our findings. OR was sufficiently adjusted for covariates to avoid confounding, although residual confounding could not be completely excluded. Although BMI, which is correlated with C-reactive protein, was statistically adjusted, it is possible that we were not able to rule out residual confounding accompanied by BMI, if C-reactive protein may play a role indicating obesity as well as local inflammation as mentioned above. Moreover, we were not able to adjust for the history of nonsteroidal anti-inflammatory drugs use because when obtaining information on medications for heart disease or headaches, we did not ask respondents to specify the kinds taken. Exogenous hormone use is associated with C-reactive protein (9) and is related to the risk reduction of colorectal cancer (29). In our study, 10% of female cases and 12% of female controls had experience of exogenous hormone use as oral contraceptives or hormone replacement therapy. Two percent of cases or controls used exogenous hormone at baseline. Although we repeatedly calculated multivariate-adjusted ORs between C-reactive protein and the risk of colorectal cancer with further adjustment of exogenous hormone use in women, the results did not differ from those without exogenous hormone use. In addition, our results should be cautiously interpreted in terms of their generalizability due to the low percentage of blood samples donated. Health check-up examinees in our previous report had a different socioeconomic status with a lifestyle profile favorable to good health compared with non-examinees (30). Thus, our present results may be applicable only to health-conscious populations.

In conclusion, plasma C-reactive protein may predict colon carcinogenesis but not tumor invasion. Should future trials of lifestyle intervention or chemoprevention against colorectal cancer be conducted, populations with a high inflammatory status assessed by C-reactive protein levels might be the target of choice.

Appendix A. Japan Public Health Center–Based Prospective Study Group

Members of the Japan Public Health Center–based Prospective Study Group are S. Tsugane, M. Inoue, T. Sobue, T. Hanaoka (National Cancer Center, Tokyo); J. Ogata, S. Baba, T. Mannami, A. Okayama (National Cardiovascular Center, Suita); K. Miyakawa, F. Saito, A. Koizumi, Y. Sano, I. Hashimoto (Iwate Prefectural Ninohe Public Health Center, Ninohe); Y. Miyajima, N. Suzuki, S. Nagasawa, Y. Furusugi (Akita Prefectural Yokote Public Health Center, Yokote); H. Sanada, Y. Hatayama, F. Kobayashi, H. Uchino, Y. Shirai, T. Kondo, R. Sasaki, Y. Watanabe, Y. Miyagawa (Nagano Prefectural Saku Public Health Center, Saku); Y. Kishimoto, E. Takara, T. Fukuyama, M. Kinjo, M. Irei, H. Sakiyama (Okinawa Prefectural Chubu Public Health Center, Okinawa); K. Imoto, H. Yazawa, T. Seo, A. Seiko, F. Ito, F. Shoji (Katsushika Public Health Center, Tokyo); A. Murata, K. Minato, K. Motegi, T. Fujieda (Ibaraki Prefectural Mito Public Health Center, Mito); K. Matsui, T. Abe, M. Katagiri, M. Suzuki (Niigata Prefectural Kashiwazki and Nagaoka Public Health Center, Kashiwazaki and Nagaoka); M. Doi, A. Terao, Y. Ishikawa (Kochi Prefectural Chuo-higashi Public Health Center, Tosayamada); H. Sueta, H. Doi, M. Urata, N. Okamoto, F. Ide (Nagasaki Prefectural Kamigoto Public Health Center, Arikawa); H. Sakiyama, N. Onga, H. Takaesu (Okinawa Prefectural Miyako Public Health Center, Hirara); F. Horii, I. Asano, H. Yamaguchi, K. Aoki, S. Maruyama, M. Ichii (Osaka Prefectural Suita Public Health Center, Suita); S. Matsushima, S. Natsukawa (Saku General Hospital, Usuda); M. Akabane (Tokyo University of Agriculture, Tokyo); M. Konishi, K. Okada (Ehime University, Matsuyama); H. Iso, Y. Honda (Tsukuba University, Tsukuba); H. Sugimura (Hamamatsu University, Hamamatsu); Y. Tsubono (Tohoku University, Sendai); M. Kabuto (National Institute for Environmental Studies, Tsukuba); S. Tominaga (Aichi Cancer Center Research Institute, Nagoya); M. Iida, W. Ajiki (Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka); S. Sato (Osaka Medical Center for Health Science and Promotion, Osaka); N. Yasuda (Kochi Medical School, Nankoku); S. Kono (Kyushu University, Fukuoka); K. Suzuki (Research Institute for Brain and Blood Vessels Akita, Akita); Y. Takashima (Kyorin University, Mitaka); E. Maruyama (Kobe University, Kobe); the late M. Yamaguchi, Y. Matsumura, S. Sasaki, S. Watanabe (NIH and Nutrition, Tokyo); and T. Kadowaki (Tokyo University, Tokyo).

Acknowledgments

We thank the staff members in each study area for their painstaking efforts to conduct the baseline and follow-up surveys; Iwate, Aomori, Ibaraki, Niigata, Osaka, Kochi, Nagasaki, and Okinawa cancer registries for providing their incidence data; and Tomohiro Shintani, Hidehito Takenaka, and Kyoko Suzuki for their valuable technical assistance.

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Cancer Epidemiol Biomarkers Prev 2006;15:690-695.