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Original Article

Obesity/Weight Gain and Breast Cancer Risk: Findings From the Japan Collaborative Cohort Study for the Evaluation of Cancer Risk

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ABSTRACT

Background: We analyzed data from the Japan Collaborative Cohort Study (36 164 women aged 40–79 years at baseline in 1988–1990 with no previous diagnosis of breast cancer and available information on weight and height) to examine the association between baseline body mass index (BMI)/weight gain from age 20 years and breast cancer risk in a non-Western population.

Methods: The participants were followed prospectively from enrollment until 1999–2003 (median follow-up: 12.3 years). During follow-up, breast cancer incidence was mainly confirmed through record linkage to population-based cancer registries. A Cox proportional hazards model was used to calculate hazard ratios (HRs) and 95% CIs for the association between breast cancer risk and body size.

Results: In 397 644.1 person-years of follow-up, we identified 234 breast cancer cases. Among postmenopausal women, the adjusted HR increased with BMI, with a significant linear trend ($P < 0.0001$). Risk was significantly increased among women with a BMI of 24 or higher (HR: 1.50, 95% CI: 1.09–2.08 for BMI of 24–28.9, and 2.13, 1.09–4.16 for BMI ≥ 29) as compared with women with a BMI of 20 to 23.9. Weight gain after age 20 years and consequent overweight/obesity were combined risk factors for postmenopausal breast cancer risk. This combined effect was stronger among women aged 60 years or older. However, the HRs were not significant in premenopausal women.

Conclusions: Our findings support the hypothesis that weight gain and consequent overweight/obesity are combined risk factors for breast cancer among postmenopausal women, particularly those aged 60 years or older.

Key words: breast cancer; obesity; weight gain; cohort study

INTRODUCTION

Since the early 1990s, breast cancer has been the most frequently diagnosed cancer in Japanese women.[1] Among women, the mortality rate of breast cancer is second only to that of stomach cancer. The recent continuous increase in breast cancer incidence has been an important public health concern in Japan, and the attention devoted to obesity/weight gain as a risk factor for breast cancer has also increased.

Obesity is a well-known risk factor for postmenopausal breast cancer.[2–4] Numerous epidemiologic studies have reported positive associations between obesity and breast cancer risk among white,[5–10] African-American,[11–13] and East Asian women.[14–17] Furthermore, weight gain has been reported as an independent risk factor.[8,9,11,17–21] Several studies have reported an inverse association between body weight in early adulthood and breast cancer incidence.[17,19,20] However, the association has been somewhat inconsistent among

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premenopausal women. Obesity is associated with a decreased risk of breast cancer among white women,[4,10,22–24] although accumulating evidence suggests that the inverse association is limited to women with estrogen receptor- and progesterone receptor-positive tumors.[25–28] Studies of non-white racial/ethnic groups are more limited, and the results are mixed.

To assist in cancer prevention, we analyzed data from a large cohort study—the Japan Collaborative Cohort (JACC) Study—which included 64 327 Japanese women, to examine the association of baseline body mass index (BMI)/weight gain with breast cancer risk, considering menopausal status at baseline. We also investigated the interaction of age on this association.

METHODS

Study population

We analyzed data from the JACC Study, a prospective cohort study that evaluated cancer risk associated with lifestyle factors among the Japanese population. The study has been described in detail previously.[29,30] In brief, the JACC Study was initiated in 1988–1990 and included 110 792 individuals (46 465 men and 64 327 women) aged 40 to 79 years from 45 areas throughout Japan. All participants were subsequently followed for all-cause mortality. In addition, study participants living in 24 areas with cancer registry systems were followed for cancer incidence.

Of the 64 327 women in the baseline cohort, 38 720 lived in the 24 areas where data on cancer incidence were available. The present study excluded 248 women who reported a previous diagnosis of breast cancer and 2308 women who did not provide information on height or weight at baseline. Thus, 36 164 women were included in the present analysis.

Informed consent was obtained from the participants in the form of signatures on the cover pages of the questionnaires, with the exception of those in a few study areas where informed consent was provided at the group level after the aims and data confidentiality had been explained to community leaders. The Ethics Board of Sapporo Medical University approved our study.

Exposure assessment

As a relative indicator of body weight, BMI was calculated as weight in kilograms divided by the square of the height in meters (kg/m^2). Information regarding weight and height was obtained from the self-reported questionnaire. Change in weight from age 20 years to the baseline measurement was calculated as the difference in the reported values at baseline among 20 418 women whose information on weight at age 20 years was available. We did not use BMI for age 20 years because we did not have access to height information at that age.

Information on other potential breast cancer risk factors such as family history of breast cancer, tobacco and alcohol use, age at menarche, marital status, parity, age at first birth, menopausal status, hormone use, and physical activity was collected in the baseline questionnaire. We have no information after baseline, including information on body size or menopausal status.

Follow-up and identification of breast cancer cases

We followed the study participants from enrollment until 1999–2003. During this period, a population registry was used in each municipality to ascertain the residential status and vital status of the participants. In Japan, the Family Registration Law requires registration of all deaths, which theoretically provides complete mortality data. Breast cancer incidence was confirmed mainly through record linkage to population-based cancer registries in each area. To complete the incidence data, we also conducted a systematic review of death certificates and medical records at major local hospitals in some areas.

During the study period, 1799 (5.0%) participants were lost to follow-up due to moving out of their designated study areas. Among the 234 breast cancer cases, no information on diagnosis was available for 13 (5.6%), ie, they were identified with death certification only (DCO). The world standard for DCO in cancer registration is less than 10%. The mortality-to-incidence ratio for breast cancer was 0.262 (58/221) in the cohort covered by cancer registries, which was within the range calculated using available data from population-based cancer registries in Japan (0.20–0.30). We estimated that 36.5 cases of incident breast cancer were not included in the cancer registries.

Statistical analysis

For each cohort subject, person-years of follow-up were counted as time from enrollment to diagnosis of breast cancer, death from any cause, or end of follow-up (1999–2003), whichever occurred first. For breast cancer cases ascertained only by death certificates, person-years of follow-up were calculated from enrollment to death from breast cancer. Those who died from causes other than breast cancer or who moved out of the study areas were treated as censored cases. We used a Cox proportional hazards model to estimate hazard ratios (HRs) and 95% CIs for the association of breast cancer risk with baseline BMI/weight change. Women were divided into 5 categories, using baseline BMI (in accordance with the World Health Organization classification)[31]: less than 18.5, 18.5–19.9, 20–23.9, 24–28.9, and 29 kg/m^2 or higher. Furthermore, BMI was entered directly to evaluate the linear trend of relative weight. The effect of age on the association between BMI and breast cancer risk was examined by analyzing the relationship between age and BMI. Finally, to investigate the combined effect of baseline BMI and weight change from age 20 years, we recategorized the participants into 4 groups using the following cutoff points: baseline BMI less than 24 kg/m^2 and weight gain of less than 10 kg from age 20 years to the baseline measurement.

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

Characteristics	BMI at baseline				
	<18.5	18.5–19.9	20–23.9	24–28.9	≥29
Number, *n* (row%)	2373 (6.6%)	3654 (10.1%)	18231 (50.4%)	10737 (29.7%)	1169 (3.2%)
Height (cm)	152.0 ± 7.0	151.0 ± 5.8	151.3 ± 5.5	150.7 ± 5.6	149.3 ± 6.4
BMI	17.4 ± 1.0	19.3 ± 0.4	22.0 ± 1.1	25.8 ± 1.3	31.0 ± 2.0
Weight at age 20 years (kg)	46.5 ± 6.1	47.8 ± 5.7	49.6 ± 6.2	51.0 ± 6.6	52.2 ± 6.8
Weight change[a] (kg)	−6.3 ± 5.9	−3.7 ± 5.4	1.1 ± 6.3	7.8 ± 7.0	17.1 ± 8.3
Age at inclusion (years)	61.3 ± 10.8	58.5 ± 10.7	57.1 ± 10.0	57.9 ± 9.3	58.3 ± 9.3
Age at menarche (years)	15.2 ± 1.8	15.0 ± 1.8	14.9 ± 1.8	14.8 ± 1.8	14.9 ± 1.9
Age at first birth (years)	25.4 ± 3.5	25.2 ± 3.3	25.0 ± 3.2	24.9 ± 3.2	25.0 ± 3.5
Age at menopause (years)	48.2 ± 4.9	48.5 ± 4.5	48.8 ± 4.6	48.7 ± 4.8	48.5 ± 5.1
Years of education	16.5 ± 2.2	16.6 ± 2.1	16.7 ± 2.1	16.3 ± 2.0	16.0 ± 2.1
Nulliparous, *n* (%)	144 (6.6%)	175 (5.2%)	700 (4.1%)	404 (4.0%)	53 (4.9%)
Not married, *n* (%)	69 (3.4%)	61 (1.9%)	227 (1.4%)	111 (1.2%)	20 (2.0%)
Exogenous female hormone use, *n* (%)	124 (6.2%)	160 (5.2%)	792 (5.1%)	471 (5.2%)	61 (6.1%)
Family history of breast cancer, *n* (%)	30 (1.3%)	42 (1.2%)	269 (1.5%)	167 (1.6%)	13 (1.1%)
Current smoker, *n* (%)	162 (7.6%)	201 (6.2%)	779 (4.7%)	470 (4.8%)	81 (7.7%)
Current drinker, *n* (%)	453 (20.4%)	790 (23.1%)	4250 (24.8%)	2444 (24.2%)	223 (20.5%)

BMI, body mass index.
Mean (SD) or %, calculated from subjects with no missing data for any variable.
[a]Difference in body weight at age 20 years and baseline.

We evaluated the association using age-adjusted and multivariable models with adjustment for age (using 10-year age groups), tobacco smoking (never, past, current, or unknown), alcohol consumption (never, past, current, or unknown), age at menarche (<15, 15–16, ≥17 years, or unknown), education level (attended school until age <16, 16–18, ≥19 years, or unknown), parity (nulliparous, 1, 2–3, ≥4 births, or unknown), age at first birth (<22, 22–23, 24–25, ≥26 years, or unknown), menopausal status (premenopausal at baseline, <45, 45–49, or ≥50 years), use of exogenous female hormone (yes, no, or unknown), first-degree family history of breast cancer (yes, no, or unknown), and physical activity categories[32] (4 groups using the following cutoff points of physical activity: daily walking <1 h and exercise time <1 h a week, or unknown). All analyses were performed with regard to menopausal status and stratified by 6 study areas (Hokkaido and Tohoku, Kanto, Chubu, Kinki, Chugoku, and Kyushu).

We repeated the analysis after excluding the first 2 years of follow-up, during which 38 cases of breast cancer were diagnosed. All *P* values were 2-sided, and a *P* value less than 0.05 was considered to indicate statistical significance. All regression analyses were performed using the PROC PHREG procedure of SAS Version 9.1 (SAS Institute, Cary, NC, USA). Study areas were not incorporated in the Cox model with other potential confounders but were adjusted for using the strata option in the PHREG procedure.

RESULTS

Average age and BMI (SD) at baseline of the 36164 women were 57.8 (10.0) years and 22.9 (3.1) kg/m^2, respectively. In 397644.1 person-years of follow-up (median follow-up time, 12.3 years), we identified 234 breast cancer cases. Table 1 shows the distribution of risk factors for breast cancer in association with BMI. Women with a BMI less than 18.5 were older and more likely to be nulliparous and unmarried. The 2 extreme BMI groups had higher percentages of smokers and lower percentages of drinkers. Groups with higher BMI at baseline had increased weights at age 20 years and greater weight gain from age 20 years to baseline. However, the difference in weight at age 20 years between the 2 extreme BMI groups was relatively small (46.5 kg vs 52.2 kg), and weight change from age 20 years (−6.3 kg vs 17.1 kg) was a stronger contributor to body size at baseline. The average (SD) overall change in weight during the period was 2.7 (8.2) kg.

Table 2 shows breast cancer risk associated with baseline BMI in relation to menopausal status. After adjustment for potential confounding factors, neither a significant HR nor a linear trend was observed among the 8131 premenopausal women. In contrast, among 28033 postmenopausal women, the adjusted HR increased with BMI and showed a significant linear trend ($P < 0.0001$). Furthermore, significantly increased risk was observed among women with a BMI of 24 or higher (HR: 1.50, 95% CI: 1.09–2.08 for BMI of 24–28.9; 2.13, 1.09–4.16 for BMI ≥29) as compared with those with a BMI of 20 to 23.9. The adjusted HRs per 5-kg/m^2 increment in BMI among pre- and postmenopausal women were 0.95 (95% CI: 0.60–1.50) and 1.68 (95% CI: 1.34–2.01), respectively.

To observe the effect of age on the association between BMI and breast cancer risk among postmenopausal women, we calculated the HR for a 5-kg/m^2 increment in BMI in younger (40–59 years) and older (60–79 years) age groups. The older group had a higher HR (2.00, 95% CI: 1.48–2.70) than the younger group (1.37, 95% CI: 0.96–1.96) for a

Table 2. Hazard ratios for breast cancer associated with BMI in the JACC Study

BMI	Cases	Person-years	Age-adjusted		Multivariate[a]	
			Hazard ratio	95% CI	Hazard ratio	95% CI
Premenopausal women						
<18.5	3	4799	0.89	(0.28–2.89)	0.82	(0.25–2.68)
18.5–19.9	6	10327	0.83	(0.35–1.97)	0.78	(0.33–1.84)
20–23.9	39	55363	1.00	Reference	1.00	Reference
24–28.9	13	25975	0.71	(0.38–1.33)	0.76	(0.40–1.43)
≥29	1	2453	0.54	(0.07–3.97)	0.62	(0.08–4.58)
P for trend			0.97		0.82	
Postmenopausal women						
<18.5	7	19412	0.71	(0.33–1.55)	0.64	(0.30–1.40)
18.5–19.9	7	28831	0.47	(0.22–1.02)	0.46	(0.21–1.00)
20–23.9	77	146684	1.00	Reference	1.00	Reference
24–28.9	71	93372	1.47	(1.06–2.03)	1.50	(1.09–2.08)
≥29	10	10427	2.00	(1.03–3.89)	2.13	(1.09–4.16)
P for trend			<0.0001		<0.0001	

BMI, body mass index.
[a]Adjusted for age, height, age at menarche, age at menopause (among postmenopausal women only), years of education, parity, marital status, use of exogenous female hormone, first-degree family history of breast cancer, smoking status, alcohol drinking, physical activity, and study area.

Table 3. Multivariate hazard ratios for breast cancer associated with baseline BMI and weight change among postmenopausal women in the JACC Study

Weight change from age 20 years	Baseline BMI <24		Baseline BMI ≥24	
	Hazard ratio	95% CI	Hazard ratio	95% CI
Premenopausal women				
Loss, unchanged, or gain of <10 kg	1.00	Reference	0.94	(0.35–2.55)
Gain of ≥10 kg	0.53	(0.07–3.96)	1.88	(0.85–4.16)
Postmenopausal women				
Loss, unchanged, or gain of <10 kg	1.00	Reference	1.34	(0.69–2.58)
Gain of ≥10 kg	0.99	(0.24–4.19)	2.55	(1.47–4.42)

BMI, body mass index.
Adjusted for age, height, age at menarche, years of education, parity, marital status, use of exogenous female hormone, first-degree family history of breast cancer, smoking status, alcohol drinking, physical activity, and study area.

5-kg/m^2 increment of BMI, after adjustment for potential confounders.

An effect of weight gain between age 20 years and baseline on breast cancer risk was observed only among postmenopausal women. The HR (95% CI) for 1 increment of weight gain was 1.04 (1.01–1.07). Among premenopausal women it was 0.99 (0.94–1.04) and not significant.

The combinatorial effect of baseline BMI and weight change between age 20 years and baseline was examined to evaluate the effect of these factors separately (Table 3). In premenopausal women, no significant HR or association was found. Conversely, in postmenopausal women, only those with a baseline BMI of 24 or higher and weight gain of at least 10 kg from age 20 years to baseline had a significant HR (2.55, 95% CI: 1.47–4.42), as compared with those with a baseline BMI of less than 24 and a weight gain of less than 10 kg from age 20 years to baseline. These findings indicate that weight gain after age 20 years and consequent overweight/obesity are combined risk factors for breast cancer among postmenopausal women. This combined effect was particularly strong in older women (HR: 4.08, 95% CI: 1.88–8.88). In addition, weight at age 20 years was not a significant predictor of breast cancer after adjustment for height at baseline and other potential confounders among premenopausal and postmenopausal women in this study. Furthermore, similar results were obtained after excluding the 33 breast cancer cases that occurred during the first 2 years of follow-up (data not shown).

DISCUSSION

To our knowledge, this is the first prospective report from Japan on the association between obesity/weight gain and breast cancer risk by age group. Our findings revealed a significant association between BMI/weight gain and postmenopausal breast cancer risk, particularly among older women. For postmenopausal women, especially those aged 60 years or older, weight gain after age 20 years and consequent

overweight/obesity were identified as combined risk factors for breast cancer, after adjusting for potential confounders. In other words, being overweight or obese at baseline was a much greater risk factor among women who were postmenopausal, were aged 60 years or older, and had gained at least 10 kg from age 20 years to baseline.

Our results for postmenopausal women are consistent with those obtained in a number of studies worldwide. The adjusted HR per 5-kg/m^2 increment in BMI in the present study (1.68) was slightly higher than the summary risk ratios from a meta-analysis[4] of studies conducted in the Asia-Pacific (1.31), North America (1.15), and Europe and Australia (1.09). Breast cancer prevention via weight control is expected to be more effective among postmenopausal women in the Asia-Pacific region. With regard to cancer pathogenesis, the increased risk in overweight/obese postmenopausal women is due to the fact that adipose tissue is the major source of estrogenic hormones after menopause.[33,34] Furthermore, our results conform with those of an earlier report showing that adult weight gain might be better than cross-sectional BMI as an adiposity index.[35]

In contrast, we did not observe any significant association between BMI/weight change and breast cancer risk among premenopausal women. In our cohort, age at baseline was 40 years or older; thus, follow-up did not completely cover the premenopausal period. A previous study reported an inverse association between BMI and breast cancer risk among white women. One hypothesis is that young overweight women are more likely to have anovulatory cycles with less cumulative exposure to endogenous estrogen.[36,37] Another hypothesis is that there is greater clearance of estrogen by the liver in young overweight women.[38] These hypotheses are strengthened by results from studies suggesting that the inverse associations are limited to women with tumors that are estrogen receptor- and progesterone receptor-positive.[25–28] Thus, the heterogeneity of pathologic types among premenopausal breast cancer weakens the association and possibly explains the inconsistent results among non-white racial/ethnic groups. This heterogeneity of cancer etiology in relation to BMI and receptor type makes cancer prevention in premenopausal women difficult and of less practical importance. Further investigations of cancer pathogenesis are needed among non-white racial/ethnic groups.

A major advantage of the present study was its prospective design, which may avoid the possibility of recall bias inherent to case-control studies. Moreover, information on other breast cancer risk factors was included, and potential confounding factors were controlled in analyses of the association.

This study has some limitations that should be considered when interpreting our results. First, because we did not have updated information on menopausal status, which would modify the association between BMI/weight change and breast cancer, the possibility of misclassification of menopausal status at breast cancer onset should be considered. Such misclassification would be problematic in premenopausal women, since recently menopausal women would be misclassified as premenopausal during the follow-up period. Such misclassification could partly explain the inconsistent results from several studies of the association between body size and breast cancer among premenopausal women. Studies of younger women with updated information on menopausal status should be initiated among premenopausal women. However, this limitation is a minor concern for postmenopausal women. Changes during follow-up, especially those related to lifestyle, might alter the results. However, many risk factors, such as marriage status, number of children, and family history of breast cancer, would be unlikely to change after age 40. To our knowledge, substantial changes in risk factors for breast cancer related to BMI have not been reported.

Second, because we used simple questionnaires at baseline only, we have data at only 2 time points, ie, age 20 years and baseline. We did not have data on the time period of weight gain, which would provide useful information for recommendations. Lack of information on weight gain around menopause would also weaken the association among premenopausal women. Furthermore, weight at age 20 years is retrospective information and may be systematically biased among women at extremes of body size. However, these data were obtained before breast cancer diagnosis, and therefore any misclassification is not likely to be differential.

The accuracy of cancer identification in the present study was not ideal. We estimated that 36.5 cases of incident breast cancer were not included in our follow-up, and this number is not inconsiderable. However, these cases would be independent of body size; thus, estimated HRs would tend toward the null.

In summary, our findings support the hypothesis that a weight gain of 10 kg or more and consequent overweight/obesity (BMI ≥24) are combined risk factors for breast cancer among Japanese postmenopausal women, particularly those aged 60 years or older. Thus, to prevent breast cancer, weight gain after age 20 years should be avoided and weight control should be increasingly emphasized with increasing age. The association between body size and premenopausal breast cancer was not clear in the present study and varies across studies; thus, optimal weight for breast cancer prevention cannot be specified at this time.

ONLINE ONLY MATERIALS

Abstract in Japanese.

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Conflicts of interest: None declared.

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Multilocus sequence typing of DNA from faecal specimens for the analysis of intra-familial transmission of *Helicobacter pylori*

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This study used multilocus sequence typing (MLST) of total DNA extracted from faecal specimens to genotype *Helicobacter pylori* to analyse intra-familial transmission. Faecal DNA was extracted and amplified by nested PCR. The products were analysed by direct sequencing and the allele type was determined using an MLST website. Mother-to-child transmission was suspected in at least two of three families, and father-to-child transmission was suspected in one family.

INTRODUCTION

Infection by the Gram-negative microaerophilic rod *Helicobacter pylori* is associated with the development of chronic gastritis, peptic ulcers and gastric adenocarcinoma in humans (Kusters *et al.*, 2006). It is thought that one of the modes of transmission of *H. pylori* is between family members, and therefore the presence of infected family members is an important risk factor in children (Konno *et al.*, 2008). However, there have been few studies that have proven intra-familial infection using isolated family strains (Konno *et al.*, 2005; Nahar *et al.*, 2009). It is difficult to isolate *H. pylori* from the gastric mucosa of children, as endoscopic analysis is not often undertaken. Therefore, the genotypes of paediatric *H. pylori* strains have not been analysed fully in comparison with those of other adult family members.

Multilocus sequence typing (MLST) analysis has become the most common method for genetic analysis of bacterial strains. MLST has been applied previously for the root causal analysis of outbreaks (Chalmers *et al.*, 2008), hospital infections (Walker *et al.*, 2012) and intra-familial infections (Staples *et al.*, 2012). An *H. pylori* MLST database is available online, consisting of seven housekeeping genes (http://pubmlst.org/helicobacter/), with over 2000 alleles detected at each locus. The genetic identity of various pathogenic strains can be analysed by MLST, which is tied in with information on the geographical sources of *H. pylori*, exposing major events in the history of human settlement (Achtman *et al.*, 1999; Falush *et al.*, 2001, 2003; Linz *et al.*, 2007; Moodley *et al.*, 2009; Wirth *et al.*, 2004).

After *H. pylori* organisms reach the anaerobic environment of the intestine, the micro-organisms are unable to grow and change morphology to their coccoid forms, which are non-culturable (Shirai *et al.*, 2000). However, the DNA of *H. pylori* has been reported to be detected by PCR using faecal specimens from infected patients (Scaletsky *et al.*, 2011) and animals (Oshio *et al.*, 2009). Here, we compared the MLST of faecal DNA specimens for the detection of intra-familial *H. pylori* infection.

Abbreviations: MLST, multilocus sequence typing; ST, sequence type.

METHODS

Participants. Children aged 0–12 years attending seven elementary schools, three nursery schools and six kindergartens in Sasayama city, Hyogo, Japan, were recruited into an epidemiological study. The Sasayama Study, for *H. pylori* infection in children, was carried out from November 2010 to March 2011. Stool samples were collected from 783 children, and 15 samples gave positive results. Family members of the 15 stool antigen-positive children were asked to provide stool samples, and 35 people belonging to 12 families provided samples.

The Sasayama Study was undertaken in accordance with the Declaration of Helsinki with approval from the Ethics Committees of Kyorin University, Tokyo; Hyogo College of Medicine, Hyogo; and Aichi Medical University School of Medicine, Aichi. Informed consent was obtained from the parents of children and from participants.

Stool antigen test. The collected stool specimens were kept at −80 °C until use. A TestMate Pylori Antigen enzyme immunoassay

(Wakamoto) was used for selection of *H. pylori*-positive faeces according to the manufacturer's guidelines. Briefly, 30 mg faecal specimen was diluted with 1 ml diluent. Faecal solution (50 µl) was added to each well and mixed with the reagent. Absorbance at 450 nm/630 nm was measured using a spectrophotometer, and the cut-off value of the test was taken as 0.100.

DNA extraction. Total DNA of *H. pylori* antigen-positive faeces was extracted using a QIAamp Stool kit (Qiagen) according to the manufacturer's instructions. Briefly, 200 mg frozen faeces was used for each extraction, and 200 µl DNA solution in Buffer AE (Qiagen) was eluted at the final step. *H. pylori* 16S rRNA gene-targeted primers were used for detection of *H. pylori* DNA by real-time PCR (Osaki *et al.*, 2006) and confirmed the *H. pylori* antigen-positive faecal samples.

MLST. The primers used for MLST are shown in Table 1. Gene fragments containing the *efp*, *mutY*, *ppa* and *trpC* genes were amplified from *H. pylori*-positive specimens by nested PCR. For the first reaction, 10 µl 2× Ampdirect Plus buffer (Shimadzu), 0.1 µl BIOTAQ Hot Start DNA Polymerase (Bioline), 2 µl primer mix (10 pmol μl^{-1} each), 6.9 µl distilled water and 1 µl DNA sample made a reaction volume of 20 µl. The Ampdirect Plus buffer neutralizes inhibitory substances in biological samples, and, as a result, increases PCR detection. The reaction mixture was incubated in a TP600 thermal cycler (Takara). Ex-*Taq* (Takara) was used in the second PCR. The amplification program consisted of one cycle at 94 °C for 10 min (first PCR) or 1 min (second PCR) and followed by 40 cycles of 94 °C for 20 s, 50–58 °C for 45 s and 72 °C for 45 s, with a final cycle at 72 °C for 7 min. The PCR products were separated using a 2 % agarose gel, stained by ethidium bromide and visualized under UV light. If two bands were visualized on the gel, only the band identical in size to the control band was collected.

The products were analysed by direct sequencing. Sequencing reactions were performed in a Bio-Rad DNA Engine Dyad PTC-220 Peltier thermal cycler using an ABI BigDye Terminator v3.1 Cycle Sequencing kit with AmpliTaq DNA polymerase (FS Enzyme; Applied Biosystems), according to the protocol supplied by the manufacturer. Single-pass sequencing was performed on each template using one of the second-PCR primers (forward or reverse, Table 1). The fluorescently labelled fragments were purified from the unincorporated terminator nucleotides by ethanol precipitation. The samples were resuspended in distilled water and subjected to electrophoresis in an ABI 3730xl sequencer (Applied Biosystems). The direct sequencing results obtained were submitted to the MLST website, and the closest allele typing of each gene was determined.

Using the allelic profile of the four genes, the sequence type (ST) of each faecal sample was also determined through the MLST website by the nearest match.

RESULTS AND DISCUSSION

Fifteen stool antigen-positive children were found in the Sasayama Study. Family members of the 15 children were asked to provide stool samples, and 35 people from 12 families provided samples. We selected three families for MLST analysis according to the following; the proband child was diagnosed with *H. pylori* twice by a positive stool antigen test at 0 and 3 months, and the child had two stool antigen-positive family members. The remaining nine families did not match these conditions. All stool antigen-positive faeces were also positive for *H. pylori* DNA by PCR with no false-positive results.

MLST profiles of the *H. pylori* DNA extracted from faeces were determined in the three families in which there was an *H. pylori*-positive child and two family members (Table 2). In family A, *H. pylori* DNA and antigens were detected from the child and the parents but not from the sibling. The first faecal DNA sample of child A had four genes identical to its father. The second sample had the same *mutY* allele as its parents and the same *efp* allele as its mother.

In families B and C, *H. pylori* DNA and antigens were detected in the children, mothers and grandfathers but not

Table 1. Primers used in this study

Locus	PCR	Name	Primer*	Amplicon (bp)	Reference
efp	First	efp_for1	GGCAATTTGGATGAGCGAGCTC	558	MLST website
		efp_rev1	CTTCACCTTTTCAAGATACTC		MLST website
	Second	efp_for2	GGGCTTGAAAATTGAATTGGGCGG	500	MLST website
		efp_rev2	GTATTGACTTTAATGATCTCACCC		MLST website
mutY	First	mutY_for4	TTATGAAGTCTCTATATCAGCGAAGT	529	This study
		mutY_rev 4	TACCTAAACAATAAGGATTGAAAGG		This study
	Second	mutY_for 5	ATATCAGYGAAGTGATGAGC	516	This study
		mutY_rev 5	CCYAAACAATAAGGRTTKGAA		This study
ppa	First	ppa_for1-1	GAARTKAGCCATGACGCTRA	698	MLST website
		ppa_rev 4	GGGTTAARATCGTTAAATTGTAG		MLST website
	Second	ppa_for 1-2	AGCCATGACGCTRAKYCTTT	490	This study
		ppa_rev 1-2	CTCTTTGTTTTCAAACCCCTTG		This study
trpC	First	trpC_for8	AGCATCGCCCTCTAAAGGTT	618	This study
		trpC_rev 6	AAGCCCGCACACTTTATTTTC		This study
	Second	trpC_for 9	TCGCCCTCYAAAGGTTTRAT	564	This study
		trpC_rev 9	TCAAATCCTTTTCTTTCATYA		This study

*Y=C or T; K=G or T; R=A or G.

Table 2. MLST of faecal DNA in three families

Family	Family member*	Allele type for:			
		efp	*mutY*	*ppa*	*trpC*
A	Index child (1st)	1908†	703	1934	454
	Index child (2nd)	181	703	838	181
	Father	1908†	703	1934	454
	Mother	181	703	945	ND
	Sibling‡	–	–	–	–
B	Index child (1st)	1807	1540	502	1468
	Index child (2nd)	1807	1540	502	457
	Mother	1908	1540	502	1468
	Grandfather	1908	703	945	181
	Father‡	–	–	–	–
	Sibling‡	–	–	–	–
C	Index child (1st)	1908	2019	938	457
	Index child (2nd)	1908	703	1934	457
	Mother	1908	703	1934	1239
	Grandfather‡	–	–	–	–
	Father‡	–	–	–	–
	Sibling‡	–	–	–	–

ND, Not determined.

*1st and 2nd indicate the first and second samples taken, with an interval of 3 months between the first sample collection and the second.

†There were three differences from the 1908 allele sequence.

‡These family members were *H. pylori* negative.

from the faeces of siblings and fathers. The first faecal DNA sample from child B had identical allele types for the *mutY*, *ppa* and *trpC* loci but a different allele for the *efp* locus compared with those of the mother. The second sample from child B had identical *mutY* and *ppa* genes but different *trpC* and *efp* genes compared with its mother. The first faecal DNA sample from child C had the same *efp* gene only as its mother, but the second sample had identical alleles for *efp*, *mutY* and *ppa*.

The candidates for *H. pylori* sequence typing were defined from the database by combinations of MLST loci (Table 3). According to these data, in family A, the first sample of the child was shown to be same as that of its father and the second sample to be the same as its mother. In families B and C, the two isolates from the children were identified to be the same as those of their mothers.

We determined the source from whom the original strain was transmitted to the child. The implication was therefore that *H. pylori* was transmitted from mother to child in families B and C. In family A, *H. pylori* may have been transmitted either from the father and/or the mother. The results also implied that *H. pylori* strains from the grandfather were probably not the source of infection. In the Sasayama Study (from 2010 to 2011), no siblings of *H. pylori*-positive children were positive for faecal *H. pylori* antigen or the 16S rRNA gene. In this study, the infection rate was also very low. This may show that intra-familial transmission of *H. pylori* is rare.

Seven loci (*atpA*, *efp*, *mutY*, *ppa*, *trpC*, *ureI*, *vacA* and *yphC*) of housekeeping genes are available for MLST analysis of *H. pylori* isolates. These are widely used markers for genomic diversity within *H. pylori* populations (Yamaoka, 2009). For the MLST analysis using faecal specimens, we used PCR to examine the above seven loci. It was difficult to obtain amplification products of *H. pylori* DNA >600 bp from faecal DNA due to the presence of either other bacterial DNA or substances inhibitory for PCR amplification. In addition, it may have been that the levels of *H. pylori* DNA were relatively low in the gut or that the DNA was damaged.

For the identification of allele types of *atpA*, *ureI* and *yphC*, fragments of ~600 bp (actually sizes of 627 bp, 535–585 bp and 504–631 bp, respectively) were needed to be amplified using available primers, so we instead selected the four shorter-length fragments (*efp*, *mutY*, *ppa* and *trpC*) for MLST using faecal samples.

In another study, we also showed that in one family the MLST profile of the child's *H. pylori* isolate from gastric mucus was identical to that of his mother's strain but not to that of the father's strain (data not shown). *H. pylori* MLST may therefore be useful as a tool for detection of the source of intra-familial infection.

Mother-to-child transmission occurs in early childhood and has been thought to be the most probable route of transmission of *H. pylori* in various countries including Bangladesh (Nahar *et al.*, 2009) and Japan (Konno *et al.*, 2008). In our study, mother-to-child transmission was suspected in two or three of the three cases analysed, whilst father-to-child transmission was suspected in one case. Furthermore, grandparent-to-child transmission was not detected. Our study indicated that parents can be a potential source of *H. pylori* infection in children.

The alleles of *trpC* belonged to different ST types in family C, and the *ppa* allele was different in two samples. One possible explanation is that multiple strains with different alleles had colonized the child or, less likely, that these genes had mutated in the 3-month study period.

It was reported by Raymond *et al.* (2004) that analysis of the isolates from family members indicated natural mixed infection in the family. Identical alleles were found in some strains isolated from the children and parents, demonstrating that strains had circulated within the family.

It is well known that high genetic diversity is a hallmark of *H. pylori*. Kennemann *et al.* (2011) reported very few mutations in an isolate cultured for 3 months after infection of a human volunteer, highlighting the importance of mixed infections for genetic diversification of *H. pylori* through recombination. As it has been reported that *H. pylori* strains exhibit diverse genotypes after long-term infection from childhood to adulthood (Kraft, *et al.*, 2006),

Table 3. Results of MLST

Family	Member*	Candidates for MLST (STs)†	Family member with similar STs
A	Child (1st)	**960/1660/2250/2265**	Father
	Child (2nd)	**181**	Mother
	Father	**960/1660/2250/2265**	
	Mother	**181**/664/960/975/978/1143/1145/1262/1264/1403/1445/1733	
B	Child (1st)	**489/1108/1346/1466/1565/1929**/2145	Mother
	Child (2nd)	**489**/669/**1108**/1290/**1466/1929**/2145	Mother
	Mother	**489/1108/1346/1466/1565/1929**/2265	
	Grandfather	181/960/1228/2265	
C	Child (1st)	669/870/1290/**2250/2265**	Mother
	Child (2nd)	669/1290/2207/**2265**	Mother
	Mother	960/1809/**2250/2265**	
	Grandfather	402/2269	

*1st and 2nd indicate the first and second samples taken, with an interval of 3 months between the first sample collection and the second.
†STs that were the same in each family are indicated in bold.

it is likely that intra-familial transmission of *H. pylori* can be determined by a molecular technique such as MLST.

In conclusion, these results demonstrated that MLST of faecal *H. pylori* DNA is a useful tool for the detection of intra-familial transmission.

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ORIGINAL PAPER

A prospective cohort study of shift work and the risk of death from pancreatic cancer in Japanese men

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Abstract
Purpose There is mounting evidence that shift work involving night work increases cancer risk. We examined the relationship between working rotating shifts and the risk of death from pancreatic cancer on the basis of data from the Japanese Collaborative Cohort Study (JACC Study).
Methods The present analysis was restricted to 22,224 men who were 40–65 years of age at baseline (1988–1990) and who reported working full time or were self-employed in the JACC Study. The subjects were followed through 31 December 2009. Information on occupation and lifestyle factors was collected using a self-administered questionnaire. The Cox proportional hazards model was used to estimate the relative risk (RR) and 95 % confidence interval (CI) for the risk of death from pancreatic cancer in relation to shift work.
Results During the follow-up period, 127 pancreatic cancer deaths were observed. Overall, we found no statistically significant increase in the risk of death from pancreatic cancer associated with rotating shift work. As compared to day-shift workers, the RRs were 0.83 (95 % CI 0.43–1.60) for rotating shift workers and 0.61 (95 % CI 0.22–1.60) for fixed night-shift workers, after adjustment for potential confounding factors. The multivariable-adjusted RR was 1.34 (95 % CI 0.66–2.75) among rotating shift workers in the analysis restricted to men who reported working full time at baseline.
Conclusions Our data did not support the hypothesis that shift work is significantly associated with the risk of death from pancreatic cancer in this cohort of Japanese men.

Keywords Pancreatic cancer · Shift work · Cohort study · Risk

Introduction

Pancreatic cancer is the fifth leading cause of cancer-related death in Japan, with 26,780 deaths in 2010. The etiology of pancreatic cancer remains largely unknown, although cigarette smoking and longstanding type-II diabetes have been shown to be associated with an increased risk [ ]. The lack of effective pancreatic cancer screening tools coupled with the dismal prognosis for this form of cancer make it crucial to identify modifiable risk factors that can be incorporated into a prevention strategy.

Approximately 15–20 % of the working population in industrialized countries engages in night-shift work, drawing significant interest in the effect of such work patterns on health, including on the formation of cancers. Exposure to light at night may suppress the production of melatonin, a hormone involved in circadian rhythms and sleep [ ]. Disruption of circadian rhythms has been shown to promote

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carcinogenesis in animal studies [3–5]. Although the findings are not entirely consistent, epidemiologic studies have indicated that shift work is significantly associated with increased risks of breast, colorectal, and prostate cancers [6–13]. Furthermore, in the Nurses' Health Study, women who had worked 30 or more years on rotating night shifts had a 36 % elevated risk of breast cancer compared with women who had never worked rotating night shifts [9]. Recent studies have also indicated that women with morning preference who engage in nigh shifts may have a higher risk compared with women with evening preference [14, 15]. This finding suggests that extended periods of working rotating night shifts and chronotype may be important factors in determining cancer risk.

On the basis of sufficient evidence from animal studies and limited evidence from epidemiologic studies, the working group of IARC concluded in 2007 that "shift work that involves circadian disruption is probably carcinogenic to humans" [16]. There have been experimental data showing that disruption of circadian rhythms in mice is associated with accelerated growth of pancreatic cancer [5], but the association between shift work and pancreatic cancer risk in humans remains unclear. To test the hypothesis that rotating shift work might be associated with an increased risk of pancreatic cancer, we analyzed data from a prospective cohort study of middle-aged and elderly Japanese individuals.

Methods

Study cohort: the JACC Study

The JACC Study started in 1988, enrolling 110,585 people (46,395 men and 64,190 women) from 45 areas throughout Japan. Participants were 40–79 years of age at baseline. Informed consent was obtained by having the study subject sign the cover of the questionnaire, except in a few study areas where it was provided at the group level after the aim of the study and confidentiality of the data had been explained to community leaders. At enrollment, participants completed a self-administered questionnaire addressing demographic characteristics, family history of cancer, medical history, occupation, and lifestyle factors. Pre-coded options for response to occupation were employed, working part-time job, self-employed, housewife, no occupation, or others. The cohort participants were followed until 31 December 2009. Because of logistical problems, follow-ups were discontinued before 31 December 2009, in 10 areas. During the follow-up period, we verified the vital status of participants using resident-registry data from the municipalities. Mortality was ascertained from the causes of death recorded on death certificates. Pancreatic cancer was classified according to the 10th revision of the International Classification of Disease, malignant neoplasm of the pancreas (ICD10, C25). The ethics committee at the Aichi Medical University School of Medicine approved the JACC Study.

Subjects for the present analysis

Our analysis was restricted to men who were 40–65 years of age at baseline and who reported working full time or were self-employed at baseline. After excluding men with missing data on occupation and those who had a history of cancer at baseline, 22,224 men remained for inclusion in the present analysis.

Exposure data

We collected information on shift work based on the question: "Which form of work schedule have you engaged in for your longest occupation?" Men were asked to indicate the most regular schedule they had undertaken among three work schedules: fixed daytime work, fixed nighttime work, or rotating shift work.

We also collected information on covariates, including age, height, weight, medical history, family history of cancer, smoking (current smoker, former smoker, or nonsmoker), alcohol consumption (current drinker, former drinker, or nondrinker), job type (office work, manual work, or other), physical activity at work (sitting, alternate sitting and standing, or standing with/without moving), workplace (indoor, outdoor, or both), level of perceived stress (low, moderate, high, or very high), educational level, and marriage status. Body mass index (BMI) was calculated from height and weight reported by the subjects.

Statistical analysis

We computed person-years of follow-up for each cohort participant from baseline to 31 December 2009, or to the date of pancreatic cancer death, death from any cause, or loss to follow-up, whichever occurred first. The Cox proportional hazards model was used to estimate RRs and 95 % CIs for the association between shift work and the risk of death from pancreatic cancer. In the multivariable analyses, we adjusted for potential confounding factors, including age (continuous), BMI (<20, 20–22.4, 22.5–24.9, $\geqq 25.0$), history of diabetes (yes, no), alcohol drinking (never, past, current), cigarette smoking (never, past, current <20 cigarettes per day, current $\geqq 20$ cigarettes per day), sleep time (continuous), and perceived stress (low, moderate, high).

All analyses were conducted using SAS 9.1 (SAS Institute, Cary, NC, USA). p Values for statistical tests were two-tailed and considered to be statistically significant if they were <0.05.

Table 1 Baseline characteristics of the study subjects according to work schedule in the JACC Study

	Daytime work (n = 18,781)	Fixed nighttime work (n = 1,083)	Rotating shift work (n = 2,360)
Age (years)	52.2 ± 7.4	52.0 ± 7.2	50.4 ± 7.2
Body mass index (kg/m^2)	22.9 ± 3.7	23.2 ± 2.8	23.1 ± 2.7
History of diabetes (%)	4.9	3.5	4.3
Current smokers (%)	54.6	54.5	57.5
Current drinkers (%)	77.7	72.4	75.4
High perceived stress in daily life (%)	24.4	23.6	33.2
Job type (%)			
Office work	20.0	6.6	14.1
Manual work	52.0	64.4	48.9
Sleep time (h)	7.4 ± 1.0	7.3 ± 1.0	7.1 ± 1.0

Results

We recorded 127 pancreatic cancer deaths during an average follow-up period of 18 years. Daytime workers, fixed nighttime workers, and rotating shift workers accounted for 84.5, 4.9, and 10.6 % in the baseline cohort, respectively. Table 1 shows baseline characteristics of the cohort participants according to work schedule. Compared to daytime workers, rotating shift workers tended to be younger, were more likely to smoke, and were more likely to perceive high stress in daily life. The average sleep time tended to be shorter in rotating shift workers than in daytime workers.

Overall, we found no statistically significant increase in the risk of pancreatic cancer death associated with rotating shift work (Table 2). After adjustment for other potential confounding factors, the RR was 0.83 (95 % CI 0.43–1.60) among rotating shift workers in comparison with daytime workers. However, the multivariable-adjusted RR was 1.34 (95 % CI 0.66–2.75) among rotating shift workers in the analysis restricted to those who reported working full time at baseline.

We conducted an additional analysis that excluded all deaths within the first 2 years of follow-up to remove the potential effect of underlying diseases at baseline on the risk of death from pancreatic cancer. The risk estimation remained unchanged; the RR was 0.84 (95 % CI 0.44–1.62).

Discussion

In this cohort study of Japanese men, we evaluated the hypothesized association between shift work and the risk of death from pancreatic cancer. Overall, there was no significant association between rotating shift work and the risk of death from pancreatic cancer. The major strength of our study is that it is a prospective study, which precludes the recall bias that plagues case–control studies. Furthermore, we collected detailed information on lifestyle factors, allowing us to control for other confounding factors, such as cigarette smoking, history of diabetes, sleep time, and perceived stress level.

Epidemiologic studies are not entirely consistent in showing a positive association between shift work and cancer risk [6–13]. Several different mechanisms have been proposed in studies that observed a positive link. The principal mechanism involves a melatonin pathway. The biological function of melatonin is wide-ranging, and affects sleep, circadian rhythm, sexual maturation and reproduction, and aging [2]. As for cancer, melatonin has been shown to inhibit tumor growth through a direct antiproliferative effect, an enhancement of immune function, the scavenging of free radicals, and the modulation of the expression of tumor suppressor genes [2]. Longstanding exposure to light at night may be associated with a suppression of melatonin [17], which may in part contribute to the increased risk observed among shift workers. In addition to the melatonin pathway, metabolic disturbances, such as impairment of insulin sensitivity, may also explain some of the adverse late effects of prolonged shift work [18].

Although the mechanisms underlying the association between shift work and cancer risk are biologically plausible and are supported by experimental evidence, convincing data from epidemiologic studies are still lacking. To our knowledge, our study was the first prospective cohort study to address shift work and the risk of death from pancreatic cancer in Japanese individuals. The null finding should be interpreted in light of several limitations. First, given the small number of pancreatic cancer deaths observed in our study, especially in the category of those working fixed night or rotating shift schedules, we were limited to detecting statistically significant associations. Second, one possible explanation for the null finding is

Table 2 Association between rotating shift work and the risk of death from pancreatic cancer in the JACC Study

	Person-years	Deaths	RR1	95 % CI	RR2	95 % CI
Daytime work	322,341	111	1.00		1.00	
Fixed nighttime work	19,565	5	0.67	0.27–1.64	0.61	0.22–1.60
Rotating shift work	41,042	11	0.88	0.47–1.64	0.83	0.43–1.60

RR relative risk, *CI* confidence interval

RR1: adjusted for age (continuous)

RR2: adjusted for age (continuous), body mass index (<20, 20.0–22.4, 22.5–24.9, ≧25.0), history of diabetes (yes, no), alcohol drinking (never, past, current), cigarette smoking (never, past, current <20 cigarettes per day, current ≧20 cigarettes per day), perceived stress (low, moderate, high), and sleep time (continuous)

selection bias. However, we consider that the effect of the so-called health worker effect is minimal in our cohort study, because the prevalence of shift work at baseline was similar to that reported in a 1991 survey, and the mortality of cohort participants was also similar to that of the general Japanese populations. Third, the assessment of shift work was crude, with only one question to obtain exposure data. We lacked information on the duration of shift work, which is important to more accurately quantify the amount of exposure. Other epidemiologic studies had similar measurement problems in accurately defining and assessing relevant exposures. For example, the exact nature of work schedule/patterns is difficult to define; most studies did not differentiate between continuous and intermittent shifts. Fourth, although we adjusted for cigarette smoking, history of diabetes, sleep time, and perceived stress level, it is still possible that our risk estimates could have been affected by other unknown confounding factors, including hormone and stress levels. Unfortunately, these data were not available in the present study. Finally, the null result may be due, in part, to the variations in individuals' capacities to adjust to their irregular work schedules and their tolerance to disruptions of their normal circadian rhythms. Such variations could be accounted for by genetic variations in circadian genes [19]. A previous study has reported that the variant Per3 genotype was significantly associated with an increased risk of breast cancer among premenopausal women [20], suggesting the importance of interaction between genetic variants and environmental factors in cancer development.

In conclusion, our data did not support the hypothesis that shift work is significantly associated with the risk of death from pancreatic cancer in this cohort of Japanese men. Further studies are needed to address the role of shift work in the development of pancreatic cancer by improving exposure measurement and incorporating relevant biomarkers.

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Conflict of interest The authors declare that they have no conflict of interest.

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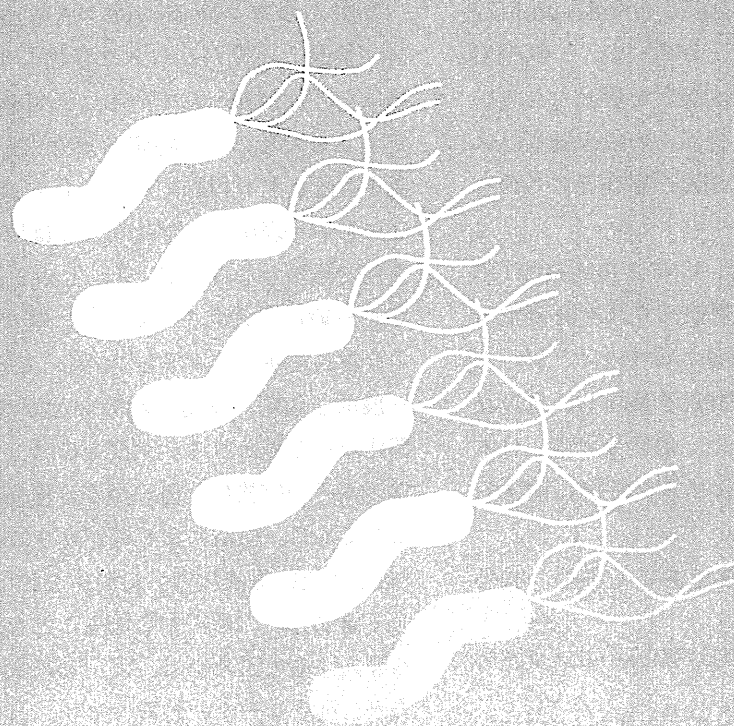

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胃がんリスク評価－ABC分類の問題点と対策

菊地 正悟

はじめに

所謂ABC分類は、*Helicobacter pylori*(以下*H. pylori*)抗体と血清pepsinogen(ペプシノゲン、ペプシノーゲンとも、以下PG)値とを用いて、個々人の胃がんリスクを評価する方法である[1]。*H. pylori*抗体による*H. pylori*感染の有無と、PG値による胃粘膜萎縮の有無とを組み合わせて2×2＝4つに分類する(**表1**)。*H. pylori*抗体価は能書記載(感染診断)のカット・オフ値が、PG値は三木らの基準(PG Ⅰ≦70ng/mL and PG Ⅰ / PG Ⅱ≦3.0)[2]が用いられることが多いが、一部(PG Ⅰ≦70ng/mL and PG Ⅰ / PG Ⅱ≦4.0)を萎縮としているところもある。この方法は、胃がんの将来的なリスクを評価するものであって、胃がんの存在そのものを推定するものではない。

日本ヘリコバクター学会では、今年から従来の「ペプシノーゲン検討委員会」が「胃がんリスク評価推進委員会」と改称され、血清PG検査だけでなく、胃がんリスク評価についても現在ある課題を検討し、有用な形でその普及を図ることとなった。他学会では、日本消化器がん検診学会に、「胃がんリスク評価に関する附置研究会」が設置されている。

ここでは、①ABC分類の名称に関する議論、②必要とされる背景、③リスク評価の精度(判定基準と精度の評価)に関する問題、④検診システムを構築する上でのデータ管理の問題、⑤除菌歴に関する問題、について検討する。日本ヘリコバクター学会会員諸兄には、釈迦に説法になってしまうところも多々あるかと思われるが、お許しをいただきたい。

表1 *H. pylori*抗体とPG値による胃がんのリスク評価分類(除菌歴のない人が対象)

	*H. pylori*抗体	PG値判定*	
A群	(−)	(−)	胃がんリスク低い
B群	(+)	(−)	胃がんリスク中等度
C群	(+)	(+)	胃がんリスク高い
D群	(−)	(+)	胃がんリスク高い

*PG Ⅰ≦70ng/mLかつPG Ⅰ /PG Ⅱ≦3.0を陽性、PG Ⅰ≦70ng/mLかつPG Ⅰ /PG Ⅱ≦4.0を陽性とするところも。C群とD群を合わせてC群とすることもある。

1) 胃がんリスク評価の名称

胃がんリスク評価には、「ABC検診」、「胃がんリスク検診」、「胃がんリスク分類」、「ABC分類」など、様々な呼称が使われている。将来の胃がんリスクを推定するものなので、特定の疾患(主にがん)の早期発見を目的とする「検診」という用語は必ずしも適切ではないという理由で、学会などでは用いないようにする方向で議論がなされている。しかし、「検診」という言葉が一般に普及していること、すでに「○○検診」という言葉を使って実施しているところもあることから、一般的な使用、実施の現場などでは「○○検診」でも問題ないと思われる。重要なのは、一般の人、特に受診者やその家族に、何がわかる検査なのかを周知することである。血清による胃がんリスク評価の実施主体(企業、健康保険組合、自治体など)、受託機関や関連する学会は、この周知を図ることも重要である。新しく導入するところでは、「○○分類」や「○○評価」の方が、説明しやすいと思われる。

2) リスク評価が必要とされる背景

これまでの研究で感染者と持続感染歴のない未感染者で20倍以上の胃がんリスクの違い(リスク比)があることが示されている[3,4]。*H. pylori*除菌後にも胃がんの発生は少なくなく、特に萎縮の進んだ例ではリスクが高いようである[5]。これまでの研究で示されてきた

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リスク比3～6倍という数字は、自然除菌による血清抗体価陰性化例が、非感染例として扱われることによる過小評価と考えられる。10年以上観察した前向き研究においても、採血時にすでに血清抗体が陰性化していた自然除菌例から発生した胃がんを未感染例からの発生と数えることによって過小評価されている。この影響は、病原性の強い東アジア型の*H. pylori*株の感染している地域で大きい[6]。

*H. pylori*の感染歴の有無で20倍以上胃がんのリスクが違うとすると、未感染者の胃がんリスクはかなり低いことになる。未感染者に関しては、現行の胃がん検診を実施することは、マイナス面が大きいことは明らかであり、実施すべきではない。

胃がん検診が開始された1960年頃は、がん年齢である40歳以上の人口のほとんどが、*H. pylori*感染者か自然除菌後であったと考えられる。胃がんのハイリスク者が人口のほとんどである状況のもとでは、現行の胃がん検診は理にかなった対策であった。当初、有効性の評価がなされないままに導入されてはいるが、後に症例対照研究で有効性が示されている。

図1に、最近のわが国の*H. pylori*感染有病率（prevalence）の推定値[7]を示す。胃がん検診の対象年齢の40歳以上の*H. pylori*陽性率は、40歳代で28％、50歳代で43％、60歳代で54％、70歳代で71％と推定される。このように、検診対象年齢で*H. pylori*陽性率が50％を割り込む状況においては、年齢区分した全対象に現行の胃がん検診を行うことは、非効率である。感染歴を有する者が50％である場合には、1人の胃がんを救命するのに必要な検診対象者数は100％であった時の2倍になる[8]。

すでに報告したように、わが国の胃がん罹患率、死亡率は、胃がん検診が始められた頃に比べ、年齢別にみるとかなり低下している（**表2**）[9]。これは、*H. pylori*陽性率が低下しているためである。

このような状況のもとでは、対象年齢の下限を引き上げて胃がん罹患率の高い年齢だけを対象にするか、*H. pylori*感染歴のない胃がん低リスク群と感染歴のある高リスク群に対象を篩い分けて高リスク群だけに胃がん対策を行う必要がある。

対象年齢を引き上げても、胃がん低リスク群が対象にかなりの割合で含まれてしまい、その割合は年々増加するので、あまり効率的な方法ではない。低リスクと高リスクの篩い分けの方が効率的である。尿素呼気試験（UBT）、便中抗原検査、血清/尿中抗体検査などの*H. pylori*の感染診断単独では、自然除菌例が低リスク群に入ってしまう。そこで、血清PG検査を同時に行って、実際に胃がんリスクの高い自然除菌例を高リスク群と判定するようにしたのが、胃がんリスク評価である。この方法では、*H. pylori*抗体陽性群の中でも、PG値によって胃がんリスクをある程度評価できる（**表1**のB群とC群の分類）ことが明らかになっている[1]。UBTなどと血清PG検査を組み合わせる方法もあるが、採血だけで済む血清抗体とPG検査の組み合わせが標準的な方法である。

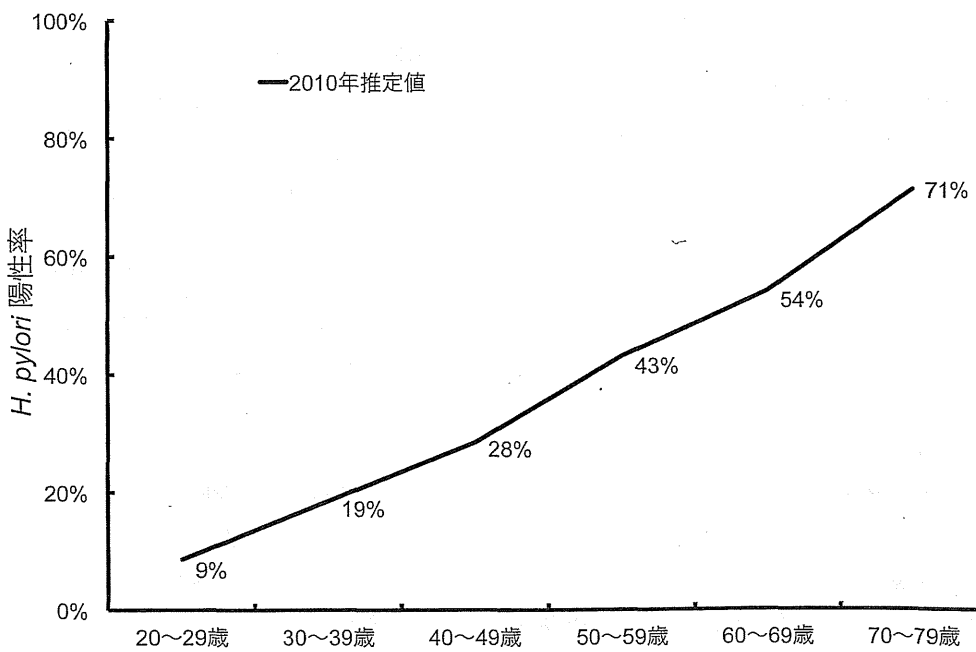

図1　2010年のわが国の*H. pylori*感染率の推定。文献7より引用（抜粋）