Helicobacter pylori infection appears essential for stomach carcinogenesis: Observations in Semarang, Indonesia

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The gastric cancer incidence in Semarang, Indonesia, is exceedingly low: only approximately 1/100th of the level in Japan. To elucidate the reason, we carried out an ecological study recruiting 69 male and 102 female participants from the general populace in January 2005. Positive urea breath tests were 0% for both men and women, and *Helicobacter pylori* (*H. pylori*) IgG antibodies were found in 2% (0–5, 95% confidence interval) of men and 2% (0–4) of women, significantly lower than the 62% (58–65) and 57% (53–60), respectively, in Japan. Furthermore, there were no positive findings with the pepsinogen tests in Semarang, again significant in comparison with the 23% (22–25) and 22% (20–23) in Japan. Variation in smoking levels and consumption of NaCl, vegetables and fruit were found, but not to an extent that would allow explanation of the major differences in gastric cancer incidence. We may conclude that the very low prevalence of *H. pylori* infection and thus chronic atrophic gastritis account for the rarity of stomach cancer in Semarang, Indonesia. (*Cancer Sci* 2005; 96: 873–875)

Since 2002, we have been conducting a collaborative epidemiologic appraisal of host and environmental factors for stomach and colorectal cancer in several South-east Asian countries. Ecological and case-control studies are now being carried out in Hanoi and Ho Chi Minh City, Vietnam; Khon Kaen, Thailand; and Yogyakarta and Semarang, Indonesia, in order to take advantage of the major variation in cancer incidence among these geographical areas and also with data for Japan. Stomach cancer incidence rates in Hanoi, Ho Chi Minh City, Khon Kaen, Yogyakarta and Semarang are approximately 1/2, 1/4, 1/10, 1/50 and 1/100 those prevailing in Japan, respectively: the annual age-adjusted incidence rates for Semarang were $0.6/10^5$ for men and $0.3/10^5$ for women during 1990–1999, and the respective figures for Japan in 1995 were $67/10^5$ and $27/10^5$.[1,2]

Gastric cancer may be caused by environmental or lifestyle risks, host genetic polymorphisms, as well as aging.[3] Many laboratory studies have pointed to roles for carcinogenic substances, including amine pyrolysate products and nitrosamines; however, grilled or barbecued meat and fish are categorized as possible risk factors in humans.[3] A probable risk factor for stomach cancer is salt or salty foods, which act synergistically with *Helicobacter pylori* (*H. Pylori*) infection in the development of stomach cancer in experimental animals[4] and humans.[5] Convincing preventive factors are vegetables and fruit and refrigeration, and a probable preventive factor is vitamin C. The International Agency for Research on Cancer (IARC) has concluded that gastric cancer is a smoke-related malignancy.[6] *H. pylori* is a definite carcinogen,[7–9] and is accepted to be a major factor for chronic atrophic gastritis (CAG),[5] a precursor lesion for stomach cancer.[10]

We here report the results of an ecological study of stomach cancer with reference to *H. pylori* infection and pepsinogen tests as a marker of CAG,[11,12] along with smoking habits and excretion of sodium and potassium[13] as markers of intake of salt or salted foods, and vegetables and fruit, respectively.[14] The study took place in Semarang, located in the central-north of Java island facing the Java sea, and was compared with published values for Japanese people.[15]

Subjects and Methods

In January 2005, we randomly recruited 69 male and 102 female participants from the general populace, mostly Javanese, in the city of Semarang. Mean ages were 57.4 ± 10.9 (SD) for men and 49.2 ± 9.8 for women. Written informed consent was obtained from the study participants and the protocol was approved by the Internal Review Boards of Nagoya City University, Japan, and Diponegoro University and Tugurejo Hospital, Semarang, Indonesia. The subjects were requested to respond to lifestyle questions, including smoking habits, and food frequency questionnaires, and were interviewed by health nurses at a local hospital. Bodyweight and height were measured, and oral mucous membranes, overnight-fasting blood, breath, second morning voiding urine and feces were sampled from each participant.

For the urea breath test (UBT), UBiT-IR300 kits (Otsuka Pharmaceutical, Tokyo, Japan) were used with $\geq 2.5‰$ as positive. Serum antibodies for *H. pylori* were examined by enzyme immunoassay (Kyowa Medics, Tokyo, Japan) and

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Table 1. *Helicobacter pylori*-related markers and pepsinogen (PG) tests in the populace in Semarang compared with Japan

Test	Semarang		Japan	
	Men (n = 69)	Women (n = 102)	Men	Women
Positive urea breath test (%)†	0	0	NA	NA
Positive serum *H. pylori* IgG (%)‡	2 (0–5)§	2 (0–4)	62 (58–65)¶	57 (53–60)
Positive pepsinogen test (%)††	0	0	23 (22–25)‡‡	22 (20–23)

†Positive test was defined as ≥ 2.5‰ by UBiT-IR300 kits. ‡Positive test was defined as ELISA value ≥ 2.3 by enzyme immunoassay. §Age-adjusted prevalence (95% confidence interval). ¶Values are cited from reference number (17). ††Positive test was defined as PGI ≤ 70 ng/mL by chemical luminescence enzyme immunoassay and PGI/PGII ≤ 3.0. ‡‡Values are cited from reference number (12).

Table 2. Smoking rates and urinary excretion of salt and potassium in the populace in Semarang compared with Japan

	Semarang		Japan	
	Men	Women	Men	Women
Smoking rate (%)	55.0 (22.3–87.8)†	0	49.5 (47.2–51.7)‡	18.1 (16.8–19.5)
Salt (g/day)	11.1 (9.8–12.5)	10.4 (9.9–11.0)	12.9 (12.7–13.1)§	11.2 (11.1–11.4)
Potassium (g/day)	2.3 (2.2–2.5)	2.1 (2.1–2.2)	2.5 (2.5–2.5)§	2.4 (2.3–2.4)

†Age-adjusted mean (95% confidence interval). ‡Values were cited from reference number (18). §Values were cited from reference number (15).

ELISA values ≥ 2.3 were defined as positive. Serum pepsinogen (PG) I and PGII were measured by chemical luminescence enzyme immunoassay (Eiken Chemicals, Tokyo, Japan) with cut off points of PGI ≤ 70 ng/mL and PGI/PGII ≤ 3.0,[11] as a non-invasive surrogate for the Sydney classification of CAG.[16] For all of these parameters, age-adjustment was made adopting the world population,[1] as standard, for comparison with Japanese figures.

Second morning voiding urine excretions of sodium, as a marker of intake of salt or salty foods, and potassium, as a marker of consumption of vegetables and fruit, were analyzed by electrode assays, and creatinine was analyzed by an enzymatic method. The daily levels were then estimated with adjustment for creatinine,[13] and compared with the consumption values of Japanese people.[15]

Results

As shown in Table 1, age-adjusted positive rates for UBT were 0% for both men and women in Semarang. *H. pylori* IgG antibodies were found in only 2% (0–5) of men and 2% (0–4) of women, and were significantly lower than the 62% (58–65) and 57% (53–60), respectively, in Japan.[17] Positive findings for the PG tests were 0% in both sexes, again significantly lower than the 23% (22–25) and 22% (20–23) reported for Japanese people.[12]

Smoking rates were rather higher for men in Semarang than in Japan but lower for women (Table 2).[18] Salt excretions were calculated to be 11.1 g/day (9.8–12.5 g/day) for men and 10.4 g/day (9.9–11.0 g/day) for women in Semarang, and only slightly lower than the consumption of 12.9 g/day (12.7–13.1 g/day) for men and 11.2 g/day (11.1–11.4 g/day) for women in Japan.[15] Values for potassium excretions were 2.3 g/day (2.2–2.5 g/day) for men and 2.1 g/day (2.1–2.2 g/day) for women, again close to the consumption of 2.5 g/day (2.5–2.5 g/day) and 2.4 g/day (2.3–2.4 g/day) in Japan.

Discussion

Our findings of negative or very low prevalence of UBT and *H. pylori* IgG antibodies in both men and women in Semarang, Indonesia are in clear contrast to the case in Japan and, presumably, are directly related to the null PG testing. Smoking was found to be more common for men in Semarang than in Japan, but less common for women. There were only minor differences in estimated intake values for salt, and for vegetables and fruit between people in Semarang and Japan. No evidence was obtained that the marked variation in cancer incidence could be explained on the basis of low consumption of salt or salty foods, or far greater vegetable and fruit consumption. We can assume that refrigeration is less prevalent in Semarang than in Japan. Whether host genetic polymorphisms associated with cellular immunity for chronic inflammation,[19] or differences in *H. pylori* strains regarding infectivity, virulence or inflammatory potency,[5,20] may be important factors in Semarang remains to be clarified. However, the most plausible interpretation of our results is that the rarity of gastric cancer in Semarang is attributable to a low prevalence of *H. pylori* infection along with the non-existence of CAG, the well-established precursor for stomach cancer.[5,7–10]

The precise reason why *H. pylori* prevalence is very low in Javanese people in Semarang and Yogyakarta is unknown.[21] It seems paradoxical given the fact that *H. pylori* is transmitted via fecal–oral, oral–oral or water-borne routes, because most people in Semarang still use well water and the sanitary environment conditions remain basic.[5] The low positivity in Javanese people is, however, compatible with the low prevalence reported for Malay people in Malaysia who share ethnic traits.[22] We should scrutinize whether genetic polymorphisms of Javanese people might confer immunity against *H. pylori* infection. It is also conceivable that specific environmental factors on Java island, including dietary habits, may be effective in preventing *H. pylori* infection.

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While ecological studies are generally regarded as providing low-rank evidence, and the number of recruited subjects was not, strictly speaking, randomly selected and not sufficiently large to be representative of the Semarang populace, our data do provide simple and compelling evidence that the low stomach cancer incidence in Semarang is due to the very low prevalence of *H. pylori* infection and CAG, suggesting that *H. pylori* is a definite and essential factor for the onset of stomach cancer. Further, large scale studies taking into account local medical practice, such as gastric cancer screening and cancer registration, including its completeness and accuracy, now need to be carried out for confirmation.

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COMMENTARY

Comparison of Japanese, American-Whites and African-Americans - Pointers to Risk Factors to Underlying Distribution of Tumours in the Colorectum

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Abstract

Relative incidence rates for colon and rectal cancer vary greatly between populations in the world. While Japanese have historically had low prevalence, immigration to the United States has now resulted in equal if not higher rates than in Caucasian- or African-Americans. Furthermore, recent data from some population-based registries in Japan itself are also pointing to particularly high susceptibility. Of particular interest is the fact that Japanese in both the home country and the US in fact have far higher rates for rectal cancer than the other two ethnic groups. An intriguing question is whether they might also demonstrate variation from Caucasian- and African-Americans in the raltive incidence rates for proximal and distal colon cancers, given the clear differences in risk factors like diabetes, physical exercise, smoking, alcohol consumption, meat and fish intake and calcium exposure which have been shown to operate in these two sites. A comprehensive epidemiological research exercise is here proposed to elucidate ethnic variation in colorectal cancer development, based on cross-cancer registry descriptive and case control approaches. It is envisaged that additional emphasis on screened populations should further provide important insights into causal factors and how primary and secondary prevention efforts can be optimized.

Key Words: Colon cancer - proximal - distal - rectal cancer - registry data - case-control - endoscopy screening

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Introduction

While colon and rectal cancer rates in Caucasian-American, African-American and to some extent, Japanese-American populations appear to be now decreasing, in Japan itself they continue to increase, albeit at remarkably different rates in different registries (see Figure 1). In fact Japanese in some registries, both in the US and in Japan itself, now demonstrate higher rates than either their White or Black counterparts. There is also considerable variation in the relative incidences of colon as opposed to rectal cancer, and a trend has been evident for the ratios of colon to rectal cancers to increase over the last 25 years (see Table 1), as already documented in Japan (Takada et al., 2002).

Risk Factors

There are clear differences in risk and beneficial factors for the two body sites (Table 2). Colon cancer appears more closely associated than rectal cancer with environmental factors leading to obesity, and this association is more pronounced in men than in women (Nakaji et al., 2003). Rectal lesions, in contrast, appearmore linked to alcohol consumption and tobacco smoking (World Cancer Research Fund, 1997; Toyomura et al., 2004), although both alcohol consumption and smoking have been found to be clearly associated with colorectal cancer overall in men (Otani et al., 2003). In one study, age, gender, family history of colon or rectal cancer, height, body mass index, physical activity, folate, intake of beef, pork or lamb as a main dish, intake of processed meat and alcohol were all found to be significantly associated with colon cancer risk, while only age and sex were associated with rectal cancer (Wei et al., 2004)

Division is not only necessary for colon and rectal cancers, but also for subsites within the colon. For all age groups in the US, a proximal migration of colon tumors over time was identified by Mostafa and coworkers (2004), although this might partly be attributable to decrease in the

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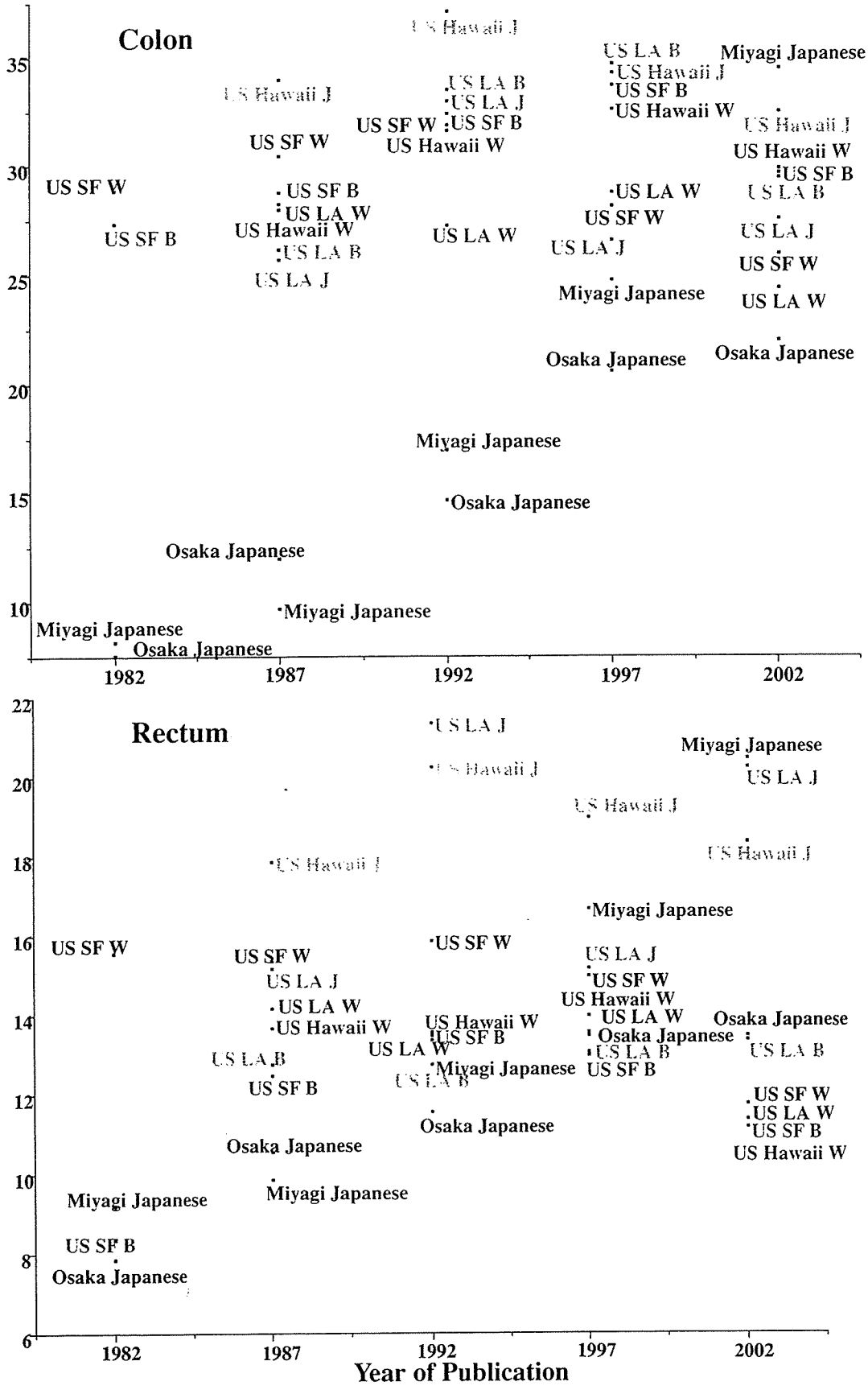


Text-Figure 1. Trends in Colon and Rectal Cancer Incidence Rates for Japanese, Blacks and Whites (Data from Cancer Incidence in Five Continents (Vols IV-VIII)

Table 1. Colon/Rectal Cancer Incidence Ratios for Selected Cancer Registries*

Asian Registry	1982	2002	Change	Western Registry	1982	2002	Change
China Hong Kong	1.3:1	1.6:1	++	Australia, NSW	1.7:1	1.6:1	-
China, Shanghai	0.7:1	1.3:1	+++	Colombia, Cali	1.3:1	1.6:1	++
Hawaii, Hawaiians	1.2:1	1.5:1	++	Slovakia	0.7:1	1.1:1	++
India, Bombay	0.8:1	1.2:1	++	Spain Zaragoza	1.1:1	1.4:1	++
Singapore, Chinese	1.0:1	1.3:1	++	Sweden	1.5:1	1.5:1	+/-
Singapore Indian	1.3:1	1.2:1	-	UK S Thames	1.3:1	1.5:1	+
Singapore, Malay	0.7:1	0.9:1	+	UK Scotland	1.6:1	1.7:1	+
Japan, Miyagi	0.9:1	1.7:1	++++	US SF White	1.9:1	2.2:1	++
Japan, Osaka	1.0:1	1.6:1	+++	US SF Black	3.3:1	2.7:1	---

*Values calculated from data in Cancer Incidences in Five Continents 1982 and 2002

incidence of distal cancers coupled with aging of the population (Rabeneck et al., 2003). Among non-Hispanic whites a decline in all sites and stages has been documented, but the decrease was most pronounced for rates of *in situ* and regional/distant tumors in the rectum and sigmoid (Cress et al., 2000). However, in African-Americans proximal cancer rates do appear to be increasing (Troisi et al., 1999). Asians and Pacific Islanders in the US, contrasting with their white and black counterparts, have approximately equal numbers of proximal and distal cancers (Wu et al., 2004). Division of the colorectum anatomically at the junction of the descending and sigmoid colon, and including the rectum above the anal canal with "distal" colorectal cancers demonstrated a predominance of African Americans among those at risk of proximal and a predominance of white males among those at risk of distal lesions (Nelson et al., 1997). In Canada, decreasing rates for colorectal cancer appear limited to tumours located in the distal colon and rectum; the incidence of cancers of the proximal colon has not changed over time (Gibbons et al., 2001). French results also confirm the existence of different trends in colorectal cancer incidence between subsites and sexes (Mitry et al., 2002). In Korea changes in the colon-to-rectal ratio appear mainly be due to an increase in left-sided colon cancer (Kim et al., 2002). It remains to be determined which site is now predominating in different Japanese populations but an earlier study suggested that distal cancer might be most affected by the change in diet in Japan (Tajima et al., 1985)..

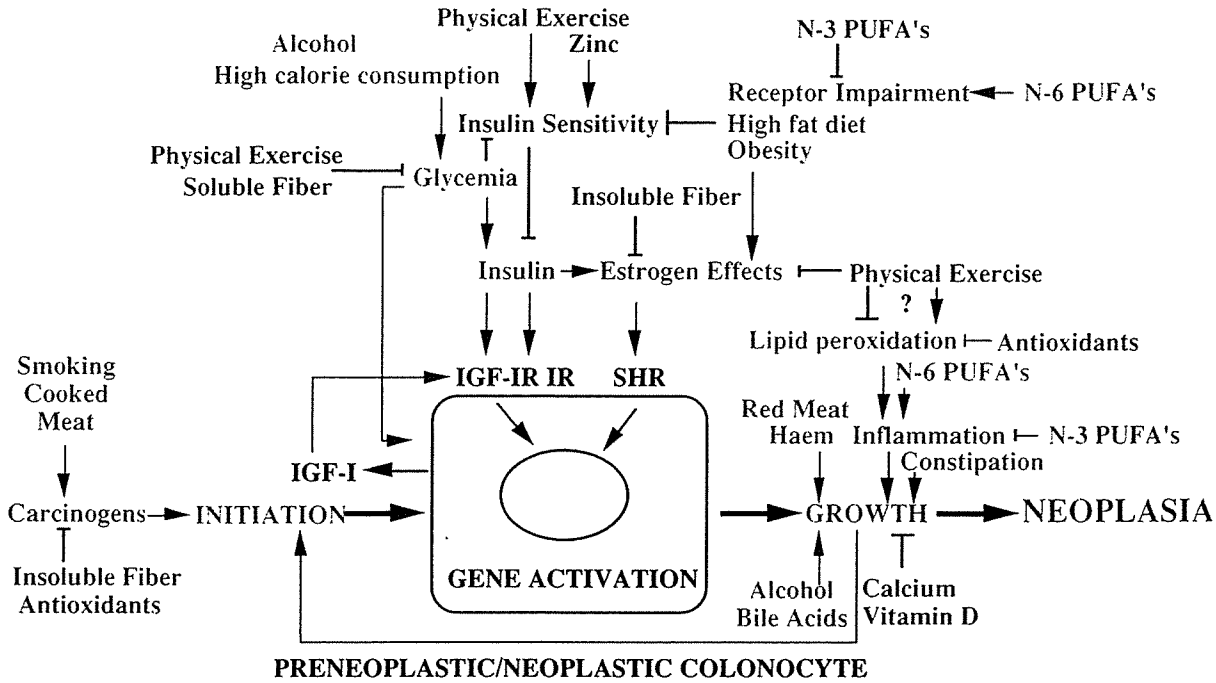
Table 2. Possible Risk and Protective Factors for Cancer of the Proximal and Distal Colon and Rectum

Factor	Proximal	Distal	Rectum
Risk			
Smoking	?	+	++
Alcohol	?	+	+
Western Diet	+	++	?
Asian Diet	+?	--	?
Red Meat	?	+	+
NIDDM	++	+	+
Constipation	+	++	?
Cholecystectomy	++	?	?
Protective			
Physical Activity	-	-	-?
Fibre Intake	-	-	?
Calcium	?	--	--
Vitamin D	?	--	--
Fish	-	-	-

+, ++ promotion -,-- inhibition +?/-? possible effect, ? unclear

A summary of data regarding separation of the different sites within the colorectum for risk factors is also provided in Table 2 and possible modes of action are illustrated in Figure 2. Cigarette smoking may be significantly associated with an increased risk of adenomas, regardless of the location, but most pronouncedly for rectal lesions in one study (Toyomura et al., 2004). In another in China, increasing tertiles of smoking duration in ever smokers was also associated with increased rectal cancer risk (Ho et al., 2004). 'Irritable bowel' (soft or loose feces) might be associated with distal subsites of colorectal cancer, independently or combined with habitual smoking (Inoue et al., 1995). Regarding the impact of alcohol, an increased risk of colorectal cancer was found in current drinkers (Ho et al., 2004), and daily consumption of any type was associated with increased risks of cancer of the distal colon and the rectum but not the proximal colon (Sharpe et al., 2002). Similar findings have been documented for adenomas in Japan (Toyomura et al., 2004). However, in 8 cohort studies a positive alcohol association was evident for cancer of the proximal colon, distal colon and rectum (Cho et al., 2004).

Clearly there must be effects of nutrition and in Korea, a Western dietary pattern was found to be associated with colon cancer risk, especially in females with distal colon cancer, while a traditional diet appeared linked to proximal lesions (Kim et al., 2005). Similarly, Japanese-style foods may decrease the risk of distal colon cancer, but increase the likelihood of proximal tumour development (Inoue et al., 1995). A moderately positive association between higher western pattern scores and risk of colon or distal colon adenomas has also been documented (Wu et al., 2004). One important component of the Western diet is red meat intake and there is evidence that this is an important determinant of colon cancer risk (Kono, 2004; Norat et al., 2005). In one study, highest versus lowest tertile meat consumption appeared significantly linked with both colon and rectal



Influences of major risk and beneficial factors on preneoplastic and neoplastic cells. PUFAs, polyunsaturated fatty acids; IGF-IR, insulin like growth factor I receptor; IR, insulin receptor; SHR, steroid hormone receptor; NSAIDs, non-steroid anti-inflammatory drugs; ——► , enhancing stimulus; ——┤ , inhibitory effect.

Figure 2. Mechanisms Whereby Risk and Protective Factors Could Impact on Colon and Rectal Cancer Development

cancer, independent of the sex (Ye et al., 2003), but in another substantial increase was only apparent for distal colon cancer (Chao et al., 2005; Larsson et al., 2005). Increased risk may be related to the cooking temperature and close contact of the food to the heating source, higher risks being observed for heavily browned surfaces when meats were barbecued or iron-pan cooked (Navarro et al., 2004). Dietary haem iron that is present in red meat is associated with an increased risk of proximal colon cancer, especially among women who drink alcohol (Lee et al., 2004), and it has been argued that the association between consumption of red meat and the risk of colon cancer is mainly due to its haem content, and is largely independent of any included dietary fat (Sesink et al., 2000).

Given the conclusion of protective effects of fruit and vegetables in the World Cancer Research Fund publication of 1997, recent cohort data offering little support for associations between intakes and colorectal cancer risk are surprising, although legume fiber did appear to have benefit (Lin et al., 2005). One problem is the considerable confounding by other dietary and lifestyle factors (Michels et al., 2005). With high intake of nuts and seeds a significant inverse association was observed in subgroup analyses for colon cancer in women (Jenab et al., 2004). In an earlier survey of 13 colon and rectum case-control studies (Howe et al.,1992), twelve demonstrated an inverse association with fiber, similar for both left and right sides of the colon. An international comparison of starch consumption similarly revealed a strong inverse link with colorectal cancer incidence (Cassidy et al., 1986). The drop in consumption of fiber by Japanese in the post-war period has in fact been found to be followed after a time-lag by increase in colon cancer (Tsuji et al., 1996).

Another protective factor may be consumption of raw or cooked fish, primarily in the colon but also to some extent in the female rectum (Yang et al., 2003). This was recently extended to total omega-3 polyunsaturated fatty acids (Kojima et al., 2005). A focus on distal adenomas, however, did not provide support for the hypothesis that a higher intake of marine n-3 fatty acids or a higher n-3/n-6 ratio reduces the risk (Oh et al., 2005).

Although one major study did not generate evidence in favour of an association of calcium and vitamin D intake and colorectal cancer risk (Lin et al., 2005), 800 mg of calcium per day confered an approximately 25% reduction in another (Flood et al., 2005). High levels of calcium intake were found to reduce risk of rectal cancer in women but not men (Slattery et al., 2004). In the same study, similar reduction in rectal cancer risk among women was observed for vitamin D, low-fat dairy products and sunshine exposure. An inverse association for milk has also been documented, but limited to cancers of the distal colon and rectum (Cho et al., 2004a). Furthermore, benefit from higher 25-hydroxyvitamin D 25(OH)D concentrations was observed for cancers of the distal colon and rectum, but not the proximal colon (Feskanich et al., 2004). Regarding mechanisms of action, reports of increased apoptosis (Miller et al., 2005) and reduced proliferation (Kallay et al., 2005) are of obvious relevance.

There have been a number of reports of increased risk

of proximal colonic cancer after cholecystectomy (Vernick et al., 1980; Alley and lee, 1983; Paul et al., 1993) and recently a decrease linked to a CYP7A1 polymorphism rendering less activity of the enzyme converting cholesterol to bile acids has provided compelling evidence (Hagiwara et al., 2005), in line with the proposed promoting role of bile acids and metabolic activity of colonic bacteria (Zuccato et al., 1993). Some data have been documented supporting the hypothesis that cholecystectomy may be a risk factor for right-sided colon cancer, but indicating that it may exert a protective influence against rectal cancer (Caprilli et al., 1989).

A great deal of interest has been concentrated on possible links between type II diabetes and associated obesity on the one hand and colorectal cancer on the other (see Moore et al., 1998 for review) and in Japan the time trends for the two diseases are in line with an important contribution (Kuriki et al., 2004).Waist circumference has been found to be a stronger predictor of colon cancer risk than BMI, central obesity being linked to an increased risk of cancer of both the proximal and distal colon (Moore et al., 2004). While NIDDM was associated with modestly increased risk of sigmoid colon adenomas in Japan (Kono et al., 1998), statistically significant elevation in relative risk was limited to the proximal colon in the US (Limburg et al., 2005). Of interest in this context is the finding that dietary zinc, protective against diabetes, is linked with a decreased risk in both proximal and distal colon sites (Lee et al., 2004). Diet with a high dietary glycemic load may increase the risk of colorectal cancer in women (Higginbotham et al., 2004) but this could not be confirmed for distal adenomas (Oh et al., 2004).

There may be a role for estrogen and reproductive factors like age at menarche, particularly in distal colon cancer (Yoo et al., 1999). An inverse association was detected between the number of full-term pregnancies and the risk of colon cancer in female subjects, as well as the age at menarche (Ghadirian et al., 1998). In this context, the possibility of protective effects of phytoestrogens, possibly due to competitive binding to estrogen receptors needs to be taken into account (Lechner et al., 2005).

There is considerable evidence in the literature that physical activity is associated with reduced risk of colon but not rectal cancer in both males and females (for review see Moore et al., 1998). The same conclusion was drawn from a major meta-analysis (Samad et al., 2005). However, a significant inverse association has been reported for moderate/heavy occupational activity in the distal colon and rectum but not in the proximal colon (Colbert et al., 2001). One possible mechanism whereby physical exercise might be protective is through effects on insulin actions (Moore et al., 1998a; 1998b). Another is on constipation, which has been shown to have a positive association with risk of colon cancer (Ghadirian et al., 1998), especially in the distal region in black women (Roberts et al., 2003). However, a meta-analysis (Sonnenberg and Muller, 1993), as well as a case control study focused on middle-aged adults (Jacobs and White, 1998), suggested the colon rather than the rectum to be the site of greatest impact of this factor.

Pointers for Future Research

Clearly there are a number of different factors which are active in different sites within the colorectum and presumably these reflect physiological variation. The major difference between the proximal and distal colon is that the former is far more active in absorbing water from the feces, while the latter has a greater role for storage before defecation through the rectum. Why should there be the observed variation in sub-site dependence of cancer development? Can we find plausible explanations as to the underlying mechanisms? One approach might be to take advantage in racial and geographical variation in incidence rates. For example the available data for colon and rectal cancers in Japan and the different racial groups in the US suggest that cancer registries are in a good position to clarify the situation regarding sub-site distributions of colorectal cancers in Japanese in Japan, Hawaii and the West Coast, as well as both Caucasian- and African-Americans. There is considerable variation between incidence rates among the racial groupings (see Figure 3), with striking separation on a racial basis, Japanese in the US continuing to group together with their counterparts in Japan itself. Elucidation of what might be the responsible factors is necessary for generation of effective programs for primary and secondary prevention and for this purpose cross-registry collaboration is essential. A number of concrete approaches can be envisaged marrying descriptive with analytical epidemiology.

1) Determination of Change in Sub-Site and Stage Distribution, as well as Age at Diagnosis and Size, of Colon and Rectal Cancers Over Time.

Access data from Japanese and American (Hawaii, California) Registries for the period 1976 to the present and make comparisons, taking into minor variation in diagnostic criteria.

2) Determination of the Sub-Site and Stage Distribution, as well as Age of Diagnosis and Size, of Lesions Detected by Colonoscopy Following a Positive ImmunoFOBT Test or Other Screening Result.

Access data from screening centers in Japan and where possible in the US to ascertain the influence of different screening modalities and diagnostic procedures.

3) Develop Consistent Food Frequency/Lifestyle Questionnaires for Use in Japan and the United States to Determine Risk and Beneficial Factors.

In order to allow full comparability of case-control studies between registries and countries, questionnaires need to be collated for consistency, as for example with the South-East Asia-Japan Project being conducted by Tokudome et al (2004).

4) Using Physician-Diagnosed or Screened Cases, Conduct Case-Control Studies of Risk Factors for Separate Colorectal Subsites as well as ChemopreventionTrials, feo example with NSAIDs.

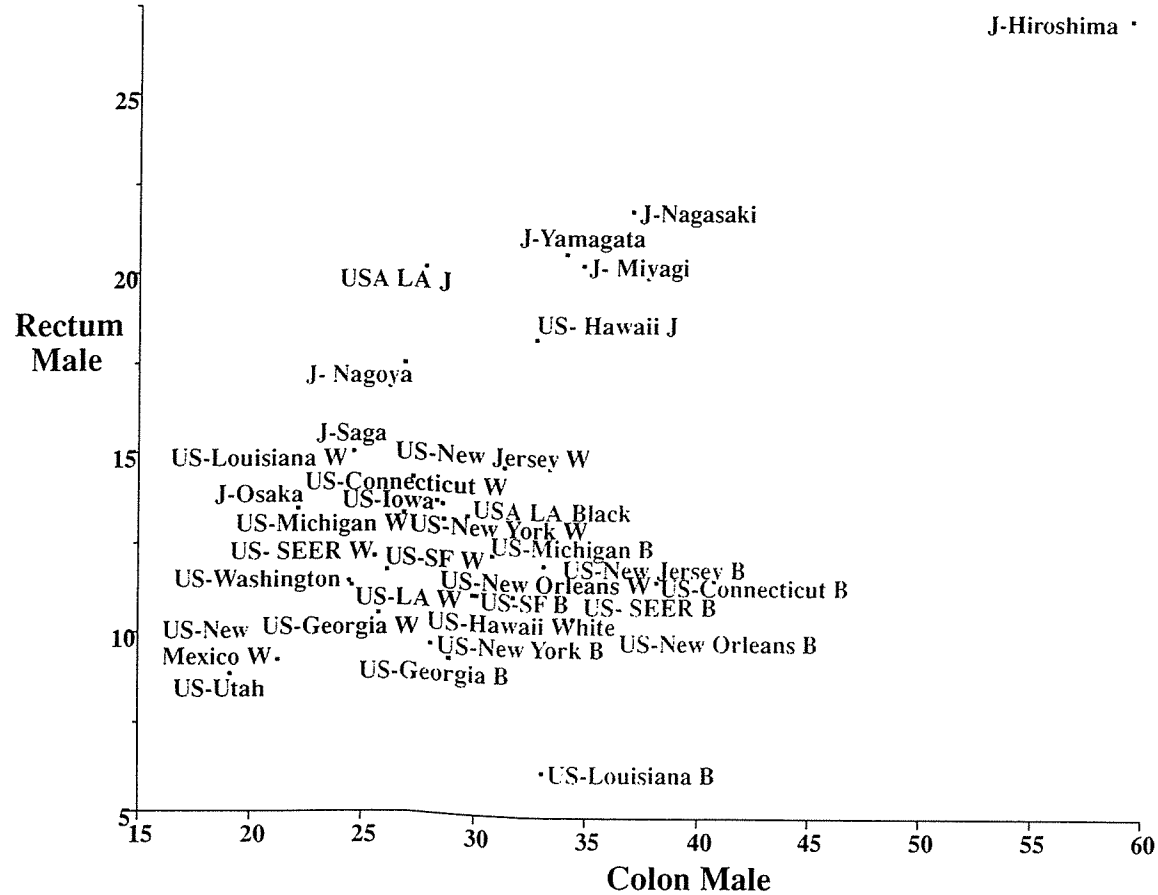


Figure 3. Colon-Rectal Cancer Ratios for Male Japanese, Blacks and Whites (Data from Parkin et al., 2002).

As collaborative efforts, comprehensive case-control studies focusing on colorectal physiology, diet, fecal characteristics, anthropomorphic parameters, diabetes, physical exercise, smoking and alcohol consumption as risk factor for separate subsites within the colon and rectum might be conducted in tandem by scientists in the US and Japan. On the Japanese side the HERPACC program of Aichi Cancer Center (Tajima, 2000) and the Fukuoka Colorectal Cancer Study (Kono et al., 2004) are concrete examples of research projects already underway which might be persuaded to participate in collaborative exercises.

While organization of cross-registry and cross-country research presents ergonomic problems because of distant locations, these are no more unsurmountable that the difficulties involved in setting up major cohort-based projects. Benefits might include the ability to effectively focus on ethnic variation in gene polymorphisms which could be participating in genetic-environmental interactions. Elucidation of what determines risk is essential to provide the basis for mechanism-based cancer prevention - international cooperation among scientists is a core tool for this purpose.

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Relationship between body mass index and the risk of ovarian cancer in the Japanese population: Findings from the Japanese Collaborate Cohort (JACC) study.

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Aim: The incidence of ovarian cancer in Japan has increased since the 1970s. The many studies that have assessed the relationship between body mass index (BMI) and the risk of ovarian cancer have produced contradictory results. Here we investigated this relation using data from the Japan Collaborative Cohort Study for the Evaluation of Cancer Risk, which was initiated in 1988. Methods: A self-administered questionnaire on dietary habits and other risk factors for cancer was completed by 36 456 Japanese women. After 7.6 years of follow up, 38 cases of ovarian cancer were available for analysis. Cox proportional-hazards models were used to compute relative risks and to adjust for confounders. Results: Compared to women with BMI of 18.5-24.9 kg/m(2), the relative risk of ovarian cancer was 2.24 (95% CI = 1.10-4.21) for BMI of 25.0-29.9 and 1.78 (95% CI = 0.24-13.34) for BMI of >/= 30 kg/m(2). A test for trend revealed that this finding was statistically significant (P = 0.014). Conclusion: The results of this study suggest that being overweight is independently

associated with a higher risk of developing ovarian cancer in the Japanese population.

PMID: 16176517 [PubMed - in process]

1: Asian Pac J Cancer Prev. 2005 Jul-Sep;6(3):412-9.

Comparison of Japanese, american-whites and african-americans - pointers to risk factors to underlying distribution of tumours in the colorectum.

Moore MA, Sobue T, Kuriki K, Tajima K, Tokudome S, Kono S.

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Relative incidence rates for colon and rectal cancer vary greatly between populations in the world. While Japanese have historically had low prevalence, immigration to the United States has now resulted in equal if not higher rates than in Caucasian- or African-Americans. Furthermore, recent data from some population-based registries in Japan itself are also pointing to particularly high susceptibility. Of particular interest is the fact that Japanese in both the home country and the US in fact have far higher rates for rectal cancer than the other two ethnic groups. An intriguing question is whether they might also demonstrate variation from Caucasian- and African-Americans in the raltive incidence rates for proximal and distal colon cancers, given the clear differences in risk factors like diabetes, physical exercise, smoking, alcohol consumption, meat and fish intake and calcium exposure which have been shown to operate in these two sites. A comprehensive epidemiological research exercise is here proposed to elucidate ethnic variation in colorectal cancer development, based on cross-cancer registry descriptive and case control approaches. It is envisaged that additional emphasis on screened populations should further provide important insights into causal factors and how primary and

Dr. Franco Cavalli

I am writing a letter of invitation letter to the 4th Regional Asian Pacific Organization of Cancer Prevention (APOCP) suggested by Dr. Tajima, K.

We are going to hold the 4th Regional Conference of APOCP in Nagoya, Japan, during January 20th -21st 2006.

We are very much pleased if you could attend the conference and give a plenary lecture.

We would like to provide you accommodations, exempt registration fees and prepare you some honorarium for the plenary lecture at the conference. But we are very much pleased If you could use UICC money to travel to Japan.

For your information, attached please find homepage of our conference along with affiliated Annual Meeting of Japanese Epidemiological Society and 5th Japan Korea Epidemiology Seminar.

JEA and JK Epidemiology Seminar
http://www.med.nagoya-cu.ac.jp/kouei.dir/jea/index.html

The 4th APOCP
http://www.med.nagoya-cu.ac.jp/kouei.dir/apocp/index.htm

Our Office: Department of Health Promotion and Preventive Medicine
http://www.med.nagoya-cu.ac.jp/kouei.dir/

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secondary prevention efforts can be optimized.

PMID: 16236010 [PubMed - in process]

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Diagnostic accuracy of glycohemoglobin A1c (HbA1c) for postprandial hyperglycemia was equivalent to that of fasting blood glucose

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Abstract

Objectives: To compare the sensitivity, specificity, and total accuracy of an HbA1c of ≥6.5% in the detection of hyperglycemia (PPHG) relative to those of a fasting blood glucose (FBG) of ≥7.0 mmol/L.

Methods: A total of 6,010 subjects (2,987 men and 3,023 women) living or working in Kasugai, Japan, underwent a medical checkup at Kasugai City Medical Care Center between April 2001 and March 2002. For the 91 subjects who had either a FBG of ≥7.0 mmol/L or an HbA1c of ≥6.5%, a 75-g oral glucose tolerance test was performed to confirm or exclude PPHG. We calculated the true- and false-positive odds ratios to evaluate the sensitivity and specificity of HbA1c relative to FBG, and compared the overall accuracy by calculating the conditional relative odds ratio (CROR).

Results: Among the 91 subjects, the true- and false-positive odds ratios were 0.43 (95% CI 0.26–0.69) and 0.40 (0.13–1.27) (Fisher's exact test, $P < .090$), respectively; the CROR was 1.07 (95% CI 0.30–3.75).

Conclusions: Although the HbA1c test was marginally more specific but less sensitive than the FBG test, at the given cutoff points the accuracies of two tests were equivalent.

Keywords: Screening; HbA1c; Fasting blood glucose; Diabetes; Postprandial hyperglycemia; McNemar odds ratio

1. Introduction

A diabetes survey conducted in 2002 revealed that there were 7.40 million people with diabetes in Japan, with prevalence increasing with age [1]. It is considered that the onset of type 2 diabetes, which accounts for the majority of diabetes cases among Japanese, can be prevented or its progression can be arrested by improving a patient's lifestyle [2–8]. Thus, diabetes screening for early detection and treatment is often conducted in workplaces and communities in Japan; however, postprandial hyperglycemia (PPHG) may not be detected by fasting blood glucose (FBG) concentrations.

Glycohemoglobin A1c (HbA1c) is widely used as an indicator of glycemic control, because it reflects blood glucose concentrations for 1–2 months prior to blood testing and is not affected by the diet just prior to blood sampling [9–16]. HbA1c is measured not only in the treatment of diabetic patients but also for diagnosis of the disease. It is one of the basic health-checkup items and is accepted as an important indicator in the diagnosis of diabetes by the Japan Diabetes Society [17]. In addition, some reports have suggested that HbA1c is an appropriate screening test because of its high sensitivity [18–25]. Others, however, have doubted the efficacy of such a test [26–31]. Despite the importance of evaluating HbA1c accuracy for diabetes, this has seldom been discussed in detail [18,19,25,26].

In the present study, we compared the accuracy of a FBG of ≥7.0 mmol/L to that of an HbA1c of ≥6.5% [17] for PPHG using a large database comprising a general population of those who visited our facility for a medical checkup.

2. Subjects and methods

During April 2001 and March 2002, 6,184 individuals (3,107 men and 3,077 women) underwent a complete routine

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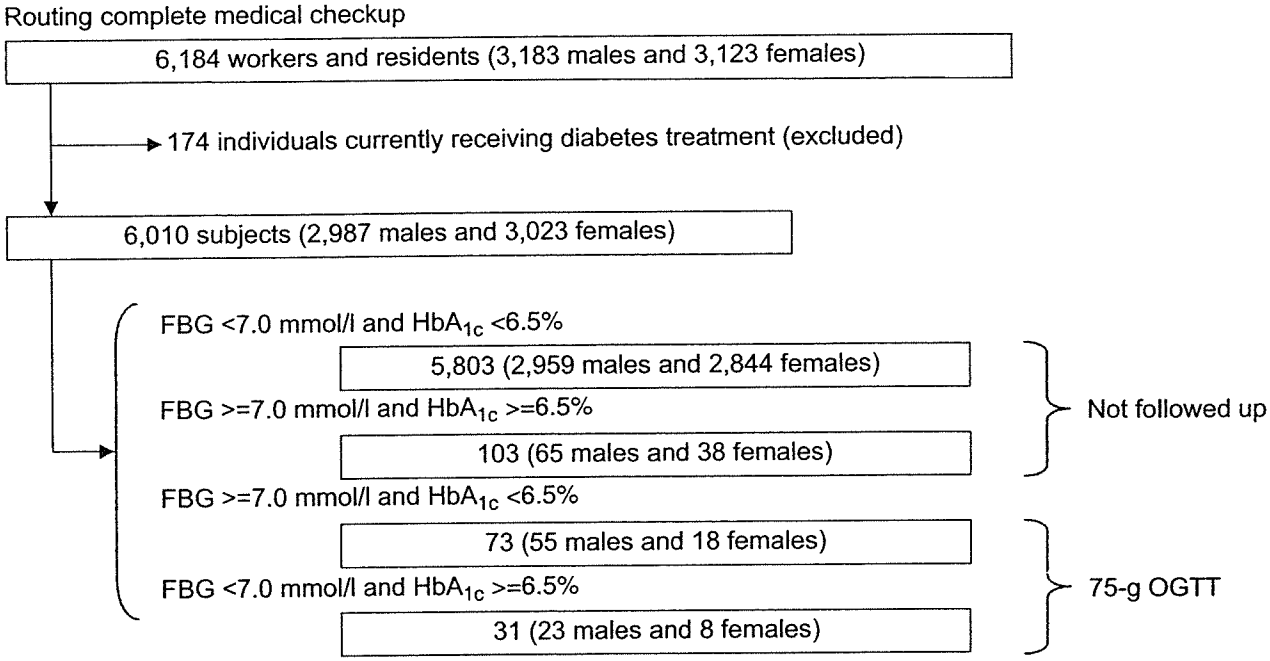

Fig. 1. Research subjects and selection process. *Abbreviations:* FBG, fasting blood glucose; OGTT, oral glucose tolerance test.

medical checkup at the Kasugai City Medical Care Center. Most of them were healthy workers and residents of Kasugai City (population ≈ 290,000). Out of these 6,184 individuals, 174 individuals currently undergoing diabetes treatment were excluded from the study, leaving 6,010 subjects (2,987 men and 3,023 women) in whom both FBG and HbA1c were examined. A FBG of ≥7.0 mmol/L or an HbA1c of ≥6.5% was considered positive; if either examination proved positive, a 75-g oral glucose tolerance test (OGTT) was performed for a PPHG diagnosis (Fig. 1). In the present study, a 2-hour 75-g OGTT of ≥11.1 mmol/L was used as the reference of PPHG for comparing the accuracy of an HbA1c of ≥6.5% with that of a FBG of ≥7.0 mmol/L.

To compare the two tests, we followed up only those subjects whose test results were discordant (i.e., FBG ≥ 7.0 mmol/L and HbA1c < 6.5%, or FBG < 7.0 mmol/L and HbA1c ≥ 6.5%). We examined both the true- and false-positive odds ratios to evaluate the sensitivity and specificity of HbA1c relative to FBG. Their accuracies were compared by calculating the conditional relative odds ratio (CROR) [32].

FBG concentrations were measured with an enzyme test of hexokinase [33] using an automated analyzer (7170S, Hitachi, Osaka, Japan). HbA1c concentrations were measured with high-performance liquid chromatography (Hi Auto A1c, Arkray, Kyoto, Japan). These methods have been recommended by the Committee on Glycohemoglobin Standardization of the Japan Diabetes Society [34,35]. All

Table 1
Characteristics of the 6,010 subjects, all living or working in Kasugai, Japan

Characteristic	Men	Women
Sample size, no.	2,987	3,023
Age, years	58.7 ± 11.4	57.9 ± 9.5
Height, cm	166.2 ± 6.3	153.7 ± 5.7
Weight, kg	63.4 ± 9.1	52.2 ± 7.4
Body mass index, kg/m^2	22.9 ± 2.8	22.1 ± 2.9
Body fat, %	21.6 ± 5.0	28.0 ± 5.7
FBG, mmol/L	5.4 ± 0.9	5.2 ± 0.8
HbA1c, %	5.3 ± 0.6	5.1 ± 0.5

Values are mean ± SD. *Abbreviations:* FBG, fasting blood glucose; HbA1c, glycohemoglobin A1c.

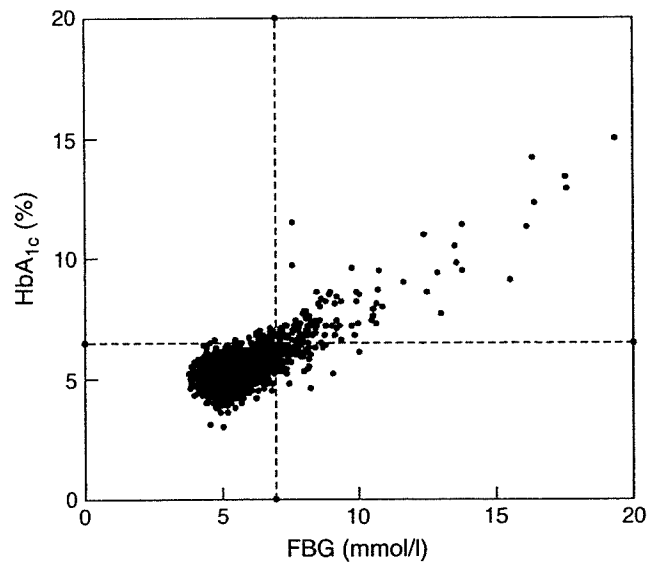

Fig. 2. Correlation between HbA_{1c} and FBG concentrations. HbA_{1c}, glycohemoglobin Alc; FBG, fasting blood glucose.

Table 2
Distribution of results for several cutoff levels of HbA1c under the fixed cutoff point for FBG ≥ 7.0 mmol/L

Cutoff level of HbA1c	HbA1c ≥ cutoff level and FBG < 7.0 mmol/L	HbA1c < cutoff level and FBG ≥ 7.0 mmol/L	HbA1c ≥ cutoff level and FBG ≥ 7.0 mmol/L	HbA1c < cutoff level and FBG < 7.0 mmol/L
≥ 6.1%, no.	121	33	143	5,713
≥ 6.2%, no.	84	44	132	5,750
≥ 6.3%, no.	64	54	122	5,770
≥ 6.4%, no.	41	68	108	5,793
≥ 6.5%, no.	31	73	103	5,803
≥ 6.6%, no.	23	80	96	5,811
≥ 6.7%, no.	16	83	93	5,818

Abbreviations: PPHG, postprandial hyperglycemia.

statistical analyses were performed using SAS software (release 8.2; SAS Institute, Cary, NC, USA).

3. Results

The ages, body mass indices, and body fat percentages of the male and female subjects were 58.7 ± 11.4 and 57.9 ± 9.5 years (means ± SD), 22.9 ± 2.8 and 22.1 ± 2.9 kg/m^2, and 21.6 ± 5.0% and 28.0 ± 5.7%, respectively; their respective FBG concentrations were 5.4 ± 0.9 and 5.2 ± 0.8 mmol/L, and their HbA1c concentrations were 5.3 ± 0.6% and 5.1 ± 0.5% (Table 1). As shown in Fig. 2, a positive correlation ($r = .73$, $P < .0001$) was observed between the FBG and HbA1c concentrations.

The distribution of the test results for several cutoff levels of HbA1c with a fixed cutoff point for FBG ≥ 7.0 mmol/L is shown in Table 2. When the cutoff point for HbA1c was set at ≥6.5%, 104 subjects showed discordant test results. We followed up only these 104 subjects, and did not follow up the remaining 5,906 subjects (of whom 103 had positive and 5,803 had negative results).

The results of a 75-g OGTT were obtained from 91 of 104 (87.5%) subjects, as indicated in Table 3 and Fig. 3. Of these 91 subjects, 77 were diagnosed as having PPHG and 14 were not. Among the 77 PPHG subjects, 23 had HbA1c ≥ 6.5% and FBG < 7.0 mmol/L, and 54 had FBG ≥ 7.0 mmol/L and HbA1c < 6.5%. Therefore, the true-positive odds ratio of HbA1c to FBG was 23/54 = 0.43 (95% CI 0.26–0.69). On the other hand, among the 14 subjects who did not have PPHG, 4 had HbA1c ≥ 6.5% and FBG < 7.0 mmol/L, and 10 had FBG ≥ 7.0 mmol/L and HbA1c < 6.5%, for a false-positive odds ratio of 4/10 = 0.40 (95% CI 0.13–1.27) (Fisher's exact test, $P < .090$). The relative accuracy of HbA1c to FBG, with the given cutoff values assessed using the CROR, was 0.426/0.400 = 1.07 (95% CI 0.30–3.75).

Under the given conditions, the HbA1c test detected only 27 positive subjects, but the FBG test found 64. As indicated in Table 2, when the cutoff point for HbA1c was lowered to 6.3%, 64 positive subjects were detected by the HbA1c test, and 54 by the FBG test, among the subjects having discordant results. Out of the 54 subjects with HbA1c < 6.3% and FBG ≥ 7.0 mmol/L, 42 were diagnosed as PPHG and 10 as non-PPHG, and 2 were unknown. If the diagnostic accuracy did not change—and this is speculative—then the sensitivity and the specificity should be close to each other when the discordant number is close. Thus, we can hypothesize a close sensitivity (42/52 = 80.7%) for the 64 subjects with HbA1c ≥ 6.3% and FBG < 7.0 mmol/L, and we would find 51.6 PPHG cases by lowering the HbA1c cutoff point to 6.3%, which is 24.1 more cases than when the current accepted cutoff point is used (51.6 − 31 × 24/27 = 24.1).

4. Discussion

For the diagnosis of PPHG, blood glucose concentrations before and 2 hours after the oral administration of 75 g of glucose are used as the reference standard. In the setting of a medical checkup, however, it is difficult to administer the OGTT to all subjects. If diabetes is diagnosed based only on the FBG concentration, PPHG may not be detected [36–38]. It is possible to reduce the false-negative rate with markers reflecting daily blood glucose concentrations.

HbA1c, 1,5-anhydro-D-glucitol [39,40], and fructosamine [41,42] are widely used as indicators of the glycemic control of diabetic patients, but their assay methods have not yet

Table 3
Results of 2-hour 75g-OGTT obtained from 104 subjects

Test results	75g-OGTT ≥ 11.1 mmol/L (PPHG)	75g-OGTT < 11.1 mmol/L (non-PPHG)	Not examined	Total
HbA1c ≥ 6.5% and FBG < 7.0 mmol/L, no.	23	4	4	31
HbA1c < 6.5% and FBG ≥ 7.0 mmol/L, no.	54	10	9	73
Total, no.	77	14	13	104

Abbreviations: OGTT, oral glucose tolerance test; PPHG, postprandial hyperglycemia.

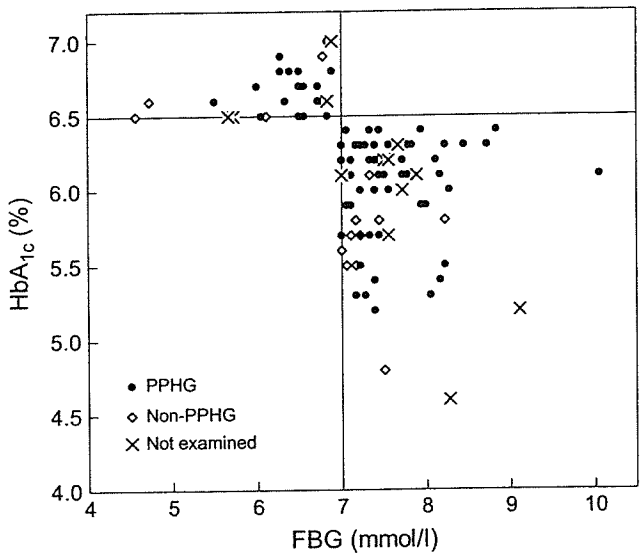

Fig. 3. HbA_{1c} and FBG concentrations versus the status of PPHG. HbA_{1c}, glycolhemoglobin A1c; FBG, fasting blood glucose, PPHG, postprandial hyperglycemia.

been standardized. In contrast, HbA1c (which is the glycated metabolite of HbA_0 and continues to exist in the blood for the life span of red blood cells after their formation [12–14]) is often used, because the assay method has been standardized based on the recommendation of the Committee of the Japan Diabetes Society for the Diagnostic Criteria of Diabetes Mellitus in Japan. Because FBG and HbA1c target different aspects of blood sugar metabolism and because in fact the correlation between HbA1c and FBG is not especially high ($r = .73$), if the accuracy of HbA1c is sufficiently high, we can expect it to be effective in the detection of PPHG. That is why we examined the accuracy of HbA1c relative to that of FBG for PPHG.

In the present study, we used the CROR method [32] to compare the accuracy levels of the two tests. This method is applied to the comparison of two tests with fixed cutoff values. It is different from the method using receiver-operating characteristic curves in which the cutoff values are integrated out. The CROR method is excellent for two main reasons. First, it allows us to follow up and compare only subjects who have discordant test results. For example, in the present study, instead of having to follow up all 6,010 subjects, we could limit follow-up to just 104. Second, the CROR is conditioned on individual levels using the McNemar odds ratio. Thus, the relative odds ratio is adjusted for potential confounders and should be less biased.

The true-positive odds ratio is the ratio of positive odds for HbA1c to those for FBG among PPHG subjects. Thus, if the ratio is 1, both tests have equivalent true-positive rates (sensitivities), and a higher true-positive odds ratio results in a more sensitive HbA1c test. In the present study, we obtained a true-positive odds ratio of 0.43 (95% CI 0.26–0.69), indicating that an HbA1c of ≥6.5% is less sensitive than a FBG of ≥7.0 mmol/L. The false-positive odds ratio, on the other hand, is the ratio of false-positive odds for HbA1c to those for FBG among non-PPHG subjects. Accordingly, if the ratio is 1, each test has an equivalent false-positive rate (i.e., the same specificity), so that a higher false-positive odds ratio results in a less specific HbA1c test. We obtained a false-positive odds ratio of 0.40 (95% CI 0.13–1.27) (Fisher's exact test, $P < .090$), indicating that the specificity of an HbA1c of ≥6.5% is marginally higher than that of a FBG of ≥7.0 mmol/L. This suggests that an HbA1c cutoff of ≥6.5% has a lower sensitivity and higher specificity than a FBG of ≥7.0 mmol/L, using a 75-g OGTT as the reference standard. The CROR is the ratio of these two odds ratios, which is equivalent to the relative accuracy of the two tests. In the present study, the CROR of 1.07 (95% CI 0.30–3.75) indicated that the accuracies of the two tests are equivalent at the given cutoff points.

An HbA1c of ≥6.5% detects fewer positives than a FBG of ≥7.0 mmol/L because it has a more conservative cutoff point, and not because the HbA1c test is less accurate. If the cutoff point for HbA1c is reduced, we expect more positives (consisting of true and false positives). As shown in Table 2, when the cutoff point for HbA1c is lowered to 6.3%, the criterion of HbA1c ≥ 6.3% and a FBG < 7.0 mmol/L will detect 64 positives, and that of HbA1c < 6.3% and a FBG ≥ 7.0 mmol/L will find 54. If the accuracy of HbA1c is not influenced by a cutoff level, we can expect that an HbA1c of ≥6.3% will detect as many PPHG patients as a FBG of ≥7.0 mmol/L with a similar false-positive rate. We estimated that reducing the HbA1c cutoff point to 6.3% would allow the detection of 24 new PPHG cases from 6,010 individuals, or ~4.0 per 1,000 population. We therefore suggest that lowering the cutoff point for HbA1c to 6.3% might improve the detection of new patients. Note, however, that this estimation is valid only if the diagnostic accuracy of HbA1c does not vary with the cutoff point. More false-positives will occur if the accuracy of HbA1c decreases as the cutoff point is reduced. In this case, the cutoff point of ≥6.3% is a good threshold to avoid lowering accuracy. Further investigations on the relation between the cutoff point and accuracy of HbA1c are needed, for which the CROR method will be useful and effective.

The first strength of the present study is, as we have noted, the use of the CROR method [32]. This method produces a less biased estimate, and one that is adjusted for potential confounders. Second, the 75-g OGTT satisfies the three principles of a reference standard [43], that it is (i) applied to all included subjects, (ii) an independent assessment of test and standard, and (iii) a standardized protocol. Finally, because the subjects were healthy workers and residents, the results should be externally valid when we apply them to the general population.

The present study does have several weaknesses. First, the low number of false-positive subjects for both tests resulted in a wide confidence interval for the relative false-positive odds ratio. Despite a sample size of >6,000 subjects, we obtained only a marginal relative false-positive odds ratio