博士論文

Rice intake and colorectal cancer in Japanese men and women: the Japan Public Health Center-based prospective Study (JPHC Study)

(多目的コホート研究による日本人男女における米飯摂取と大腸がんの関連に関する研究)

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多目的コホート研究による日本人男女における米飯摂取と大腸がんの関連に関する研究

In partial fulfillment of the requirements
for the degree of
Doctor of Philosophy

A thesis presented

by

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Admission in April 2011

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to

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Tokyo, Japan

2013

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Abstract

Objective: Colorectal cancer (CRC) incidence rate increased rapidly in Japan post-World War II until the mid 1990s, currently ranking among the highest rates in the world. Environmental factors such as physical inactivity, body and abdominal fatness, red and processed meat and excess alcohol consumption may provide some explanation for these changes. We examined the association between rice intake and colorectal cancer risk in comparison to bread, noodles and cereal among Japanese adults enrolled in the Japan Public Health Center-based prospective Study (JPHC Study).

Methods: 73,501 Japanese men (34,559) and women (38,942) were followed up from 1995-1999 (5-year follow-up survey) until the end of 2008 with an average duration of 11 years. During 801,937 person-years of follow-up, we identified 1,276 new colorectal cancer cases (777 and 499 cases for men and women, respectively). Hazard ratios (HRs) and 95% confidence intervals (95% CIs) for cancer were calculated by Cox proportional hazards modeling.

Results: In general, no significant association was observed between the highest and lowest quartile of rice intake and the risk of colorectal cancer and its subsites in men 0.77 (95% CI, 0.56-1.07) and women 1.10 (95% CI, 0.71-1.68), except a non-significant inverse trend observed between rice intake and rectal cancer in men 0.61 (95% CI, 0.35-1.07).

Conclusion: Our findings suggest that the consumption of rice does not have a substantial impact on the risk of colorectal cancer in the Japanese population.

Keywords: Japan; cohort study; colorectal cancer; rice; carbohydrate

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Acknowledgements

If you would have asked me when I graduated from high school what I'd be doing in 10 years, I'm pretty sure the answer would not have been completing a PhD at The University of Tokyo in Japan. What a journey it's been. A wise classmate of mine recently said that a PhD is like climbing Mt. Fuji - it truly is.

I would like to thank my supervisor Dr. Kenji Shibuya for his support over the past few years. In addition to valuable thesis guidance I was able to do an amazing internship at the World Health Organization (WHO) through the Global Leadership Program (GLP). This opportunity fulfilled a childhood dream of mine to work at the WHO. I would also like to thank Dr. Manami Inoue for her endless support from choosing a topic, data, analyses recommendations, endless revisions of manuscripts to completing the dissertation. Without her patient guidance I wouldn't be where I am today.

A special thank you goes to the coauthors of my British Journal of Cancer paper from the National Cancer Center in Japan: Dr. Norie Sawada, Dr. Motoki Iwasaki, Dr. Junko Ishihara, Dr. Shizuka Sasazuki, Dr. Taichi Shimazu, Dr. Taiki Yamaji, and Dr. Shoichiro Tsugane. Their comments helped strengthen my paper, particularly the discussion section and exploring the etiology of colorectal cancer with regards to carbohydrate intake. I additionally received valuable suggestions for analyzing the data in a meaningful way from Dr. Akiko Nanri and Dr. Azusa Hara.

My sincere thanks go to friends and professors in the Department of Global Health Policy past and present for joining in this adventure through discussions, knowledge sharing, good times; particularly Winnie Tseng, Eiko Saito, Dr. Md Mizanur Rahman and Stuart Gilmour. A special bond was formed with the Masters students who graduated in 2013 with whom I volunteered in Fukushima in May 2011.

Finally, I would like to thank my husband Masatada Abe, my parents in Berlin, sister and grandparents in the US as well as dear friends who have believed in me and sent support from all corners of the world. Let's hope the next 10 years are as fulfilling as the previous ones, filled with surprises, guided by a mission to contribute to good health for all.

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List of abbreviations

CI	confidence interval
CI5	Cancer Incidence in Five Continents
CRC	colorectal cancer
CVD	cardiovascular disease
DCO	death certificate only
FFQ	Food Frequency Questionnaire
GI	glycemic index
GL	glycemic load
HR	hazard ratio
HPFS	Health Professionals Follow-up Study
IGF	insulin growth factor
IARC	International Agency for Research on Cancer
JACC Study	Japan Collaborative Cohort Study for Evaluation of Cancer Risk
JPHC Study	Japan Public Health Center-based prospective Study
NHI	National Health Insurance
NHS	Nurses' Health Study
PAF	population attributable faction
PHC	public health center
SMHS	Shanghai Men's Health Study
SWHS	Shanghai Women's Health Study
SEER	Surveillance Epidemiology and End Results

1. INTRODUCTION

1.1. Background

This section highlights trends in Japanese men and women over the past 50 years focusing on cancers of the colon and rectum while comparing these with other common cancers. The second sub-section (1.1.2) discusses environmental factors related to colorectal cancer and sheds light on attributable causes in Japan. The third sub-section (1.1.3) highlights the importance of rice in Japan and Asia and the fourth sub-section (1.1.4) outlines possible pathways in this context.

1.1.1. Trends in colorectal cancer incidence

Colorectal cancer (CRC) is one of the most common cancers globally, third in men and second in women with considerable geographic variation [1, 2]. The majority of cases occur in developed countries with a 10 fold incidence rate difference in Australia/New Zealand and Western Europe compared to Africa and South-Central Asia [1]. However, some Asian populations have undergone a rapid increase approaching levels found in Western countries [2, 3].

The incidence trend for men and women in Japan followed a similar pattern, however rates for women were lower than men. Interestingly, while the IARC Korean data only reflects the past decade, 20 years later than Japan, Korean colorectal incidence also dramatically increased over a short period and is still on the rise based on population representative data from the Korea Central Cancer Registry, National Cancer Center, Korea [1]. The dramatic increase may partially be an artifact of improved colorectal cancer diagnostics. Figure 1 and 2 show only selected countries among those with population-based registries in the Globocan 2008 research using multi country International Agency for Research on Cancer (IARC) data provided by: the Australian Institute of Health and Welfare (Authoritative information and statistics to promote better health and wellbeing), Government of Canada (Statistics Canada), India (Chennai cancer registry), Japan (Miyagi, Osaka and Yamagata cancer registries), Republic of Korea: (National Cancer Center), USA (Surveillance Epidemiology and End Results (SEER) program) [1]. Additionally, in the Scandinavian countries and the Netherlands among men, colorectal cancer trends are also still increasing, while in women the trend began reversing around 2005 [1].

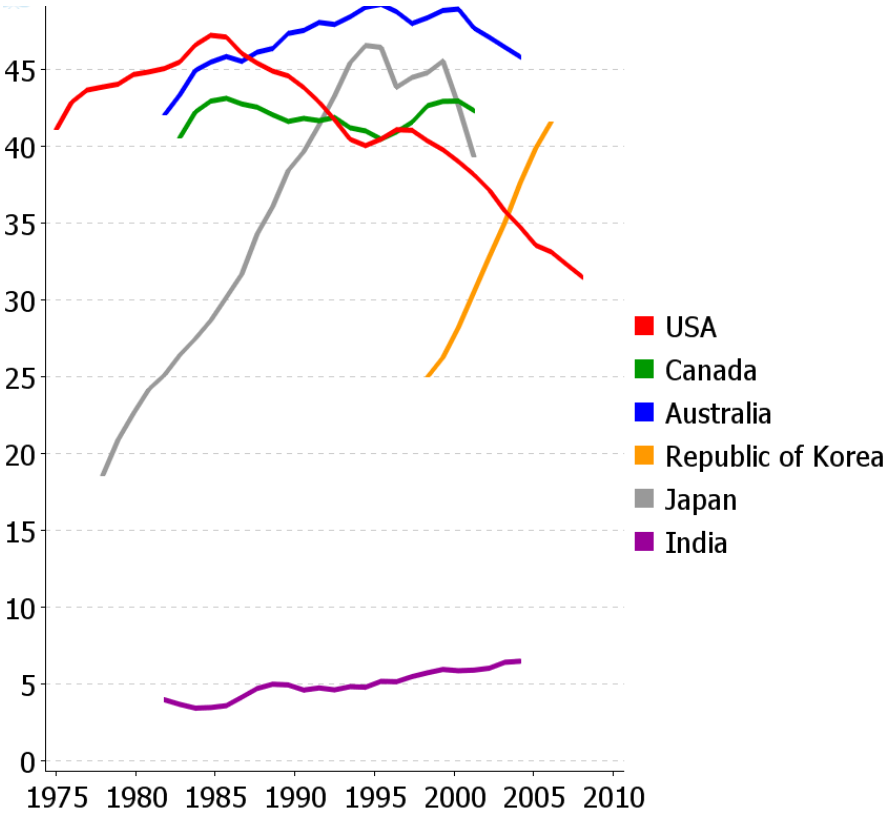

Figure 1: Colorectal cancer incidence trends in selected countries: age-standardized rate (W) per 100,000 for men

Source: Globocan 2008 and International Agency for Research on Cancer [1]

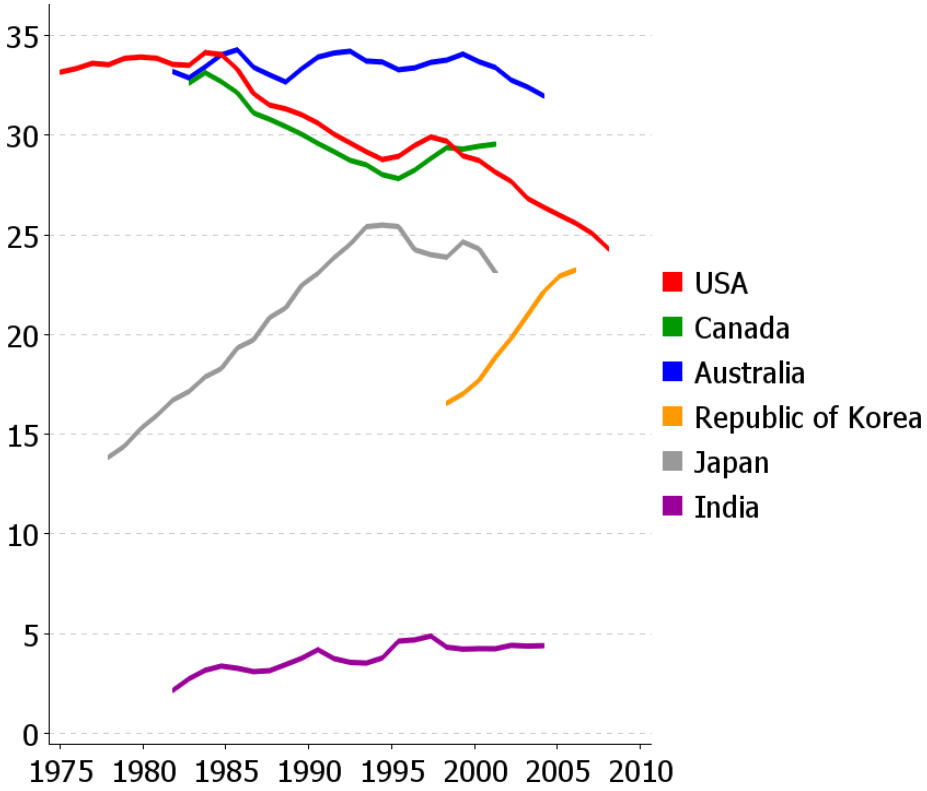

Figure 2: Colorectal cancer incidence trends in selected countries: age-standardized rate (W) per 100,000 for women
Source: Globocan 2008 and International Agency for Research on Cancer [1]

Colorectal cancer incidence in Japan and the USA may be compared in more detail to show differences and similarities. IARC country comparisons demonstrate that colorectal cancer incidence in Japan (Miyagi, Osaka and Yamagata prefectures) increased in men and women in the late 1980s/early 90s, while incidence decreased in the USA [4], represented by nine SEER registries (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah) (Figure 3) [5]. In Japanese men, incidence rates even surpassed those found among American men [4]. Overall, since the early 1980's cancer has been one of the leading causes of death in Japan according to vital statistics (Figure 6 and 7) [6].

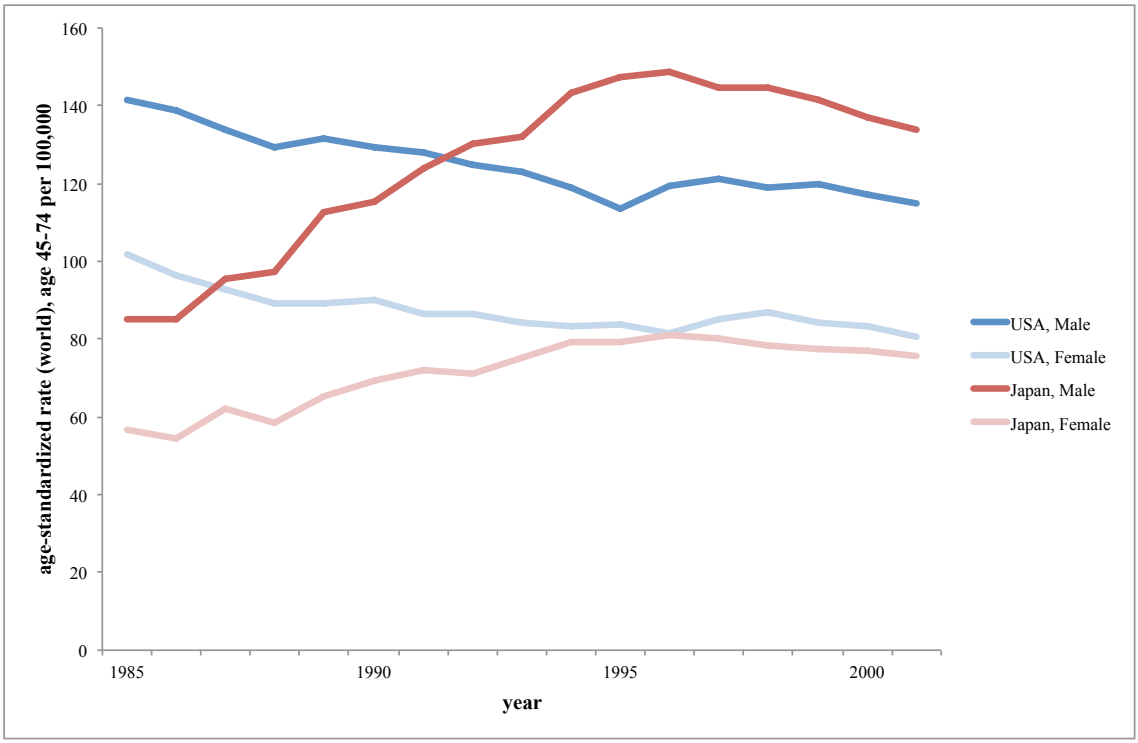

Figure 3: Colorectal cancer incidence trends in Japan and the USA

Source: International Agency for Research on Cancer [4]

In Japan, colorectal cancer has been dramatically increasing since the 1970's [7]. Age-standardized incidence rates of colorectal cancer remain high: e.g. increasing from 16.8 (1975) to 45.5 (2008) per 100,000 among men and 12.9 to 25.7 (1975-2008) in women respectively (Figure 6 and 7) [8], while mortality rates due to colorectal cancer recently started decreasing [9]. Colorectal cancer ranks second highest in Japan rivaled only by stomach cancer in men and breast cancer in women (Figure 4 to 7) [1, 7].

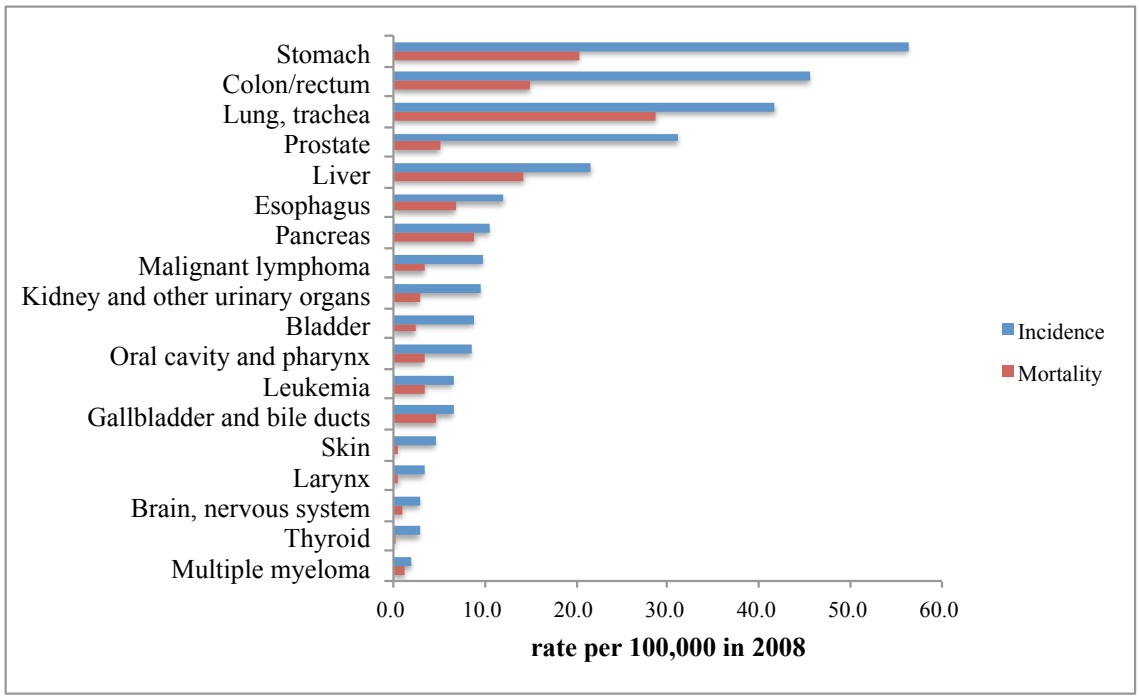

Figure 4: Estimated age-standardized incidence and mortality in Japanese men
Sources: Globocan 2008 [1] and National Cancer Center, Japan [6, 8]

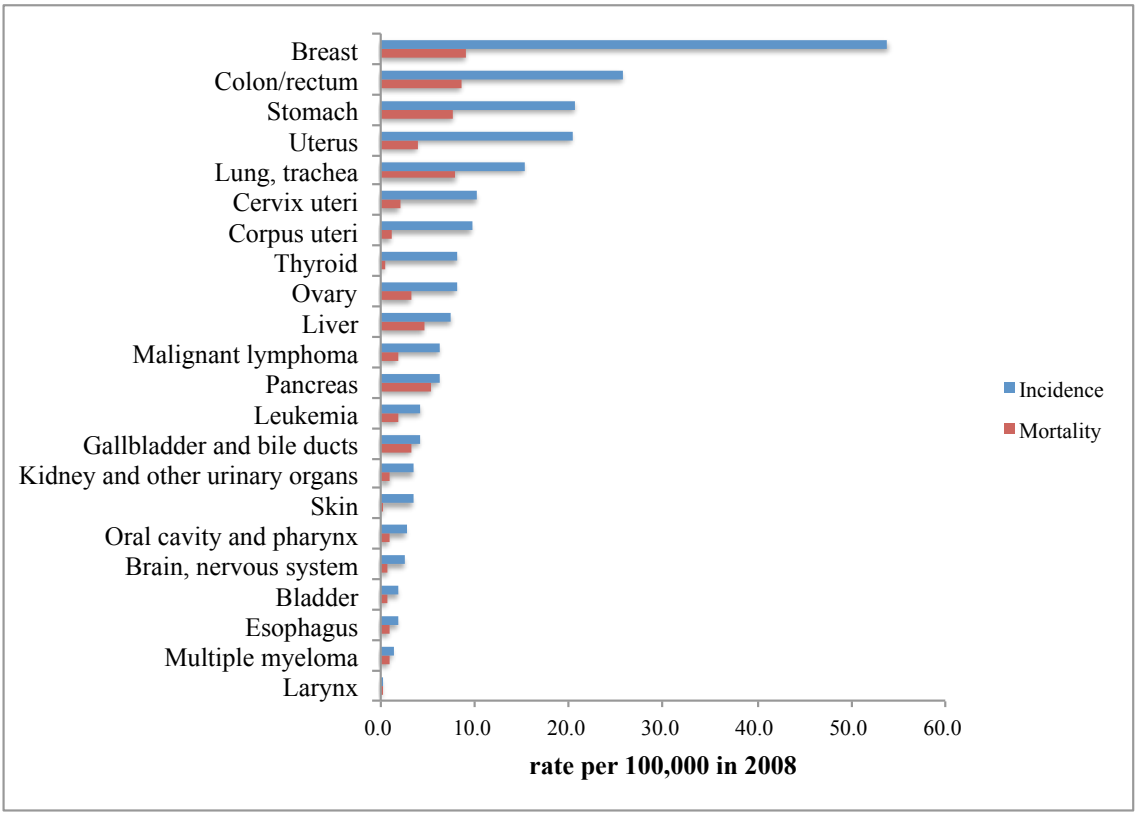

Figure 5: Estimated age-standardized incidence and mortality in Japanese women
Sources, Globocan 2008 [1] and National Cancer Center, Japan [6, 8]

While other cancers, most notably cancer of the stomach in both men and women have been significantly decreasing since the mid 1970's, colorectal cancer continued to increase (Figure 6 and 7). Prominent hormone-associated cancers such as prostate (Figure 6) also continue to increase. Though colorectal cancer is not traditionally considered in this group, recent evidence suggests sex hormones contribute to its development [10].

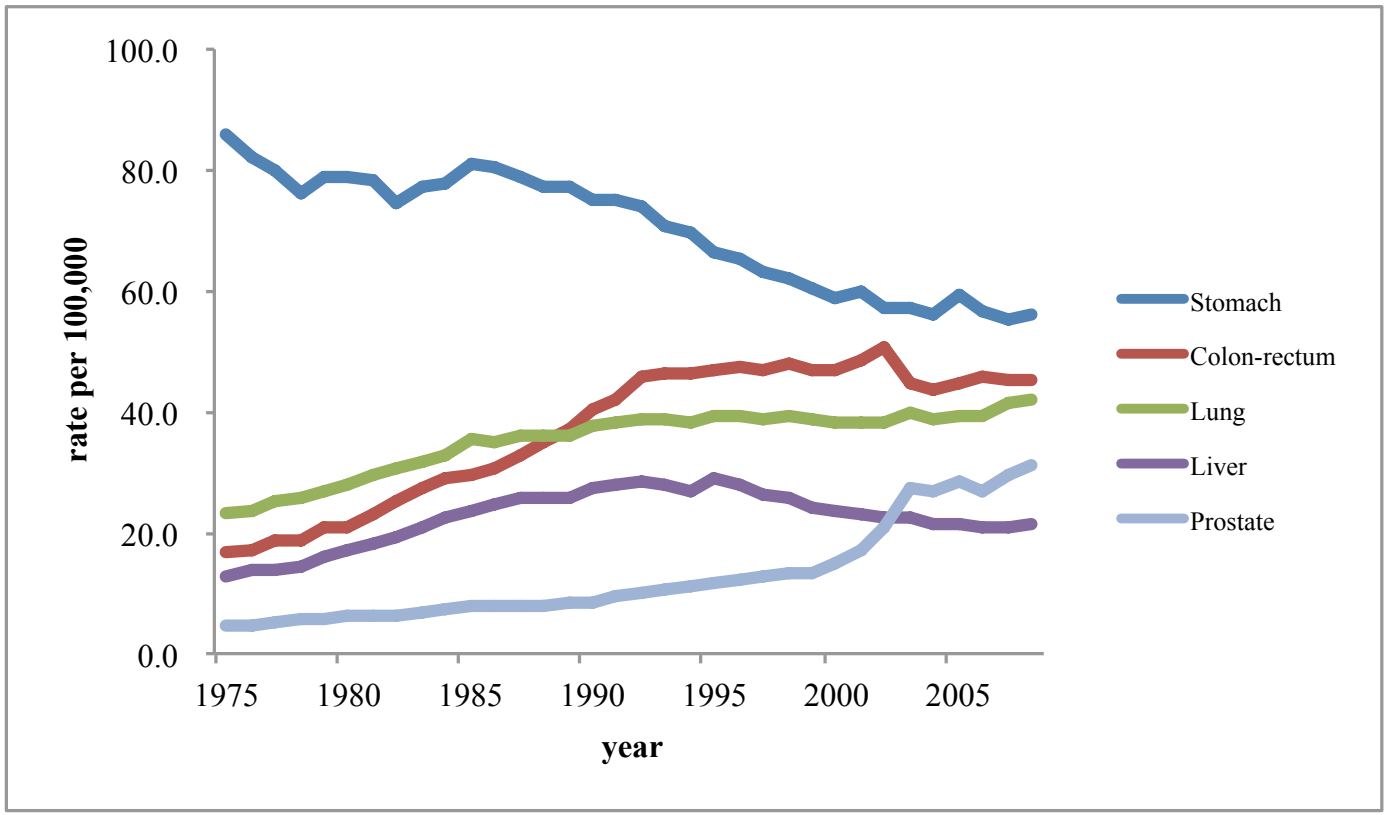

Figure 6: Trends in age-standardized incidence rate in Japanese men (1975-2007)

Source: National Cancer Center, Japan [8]

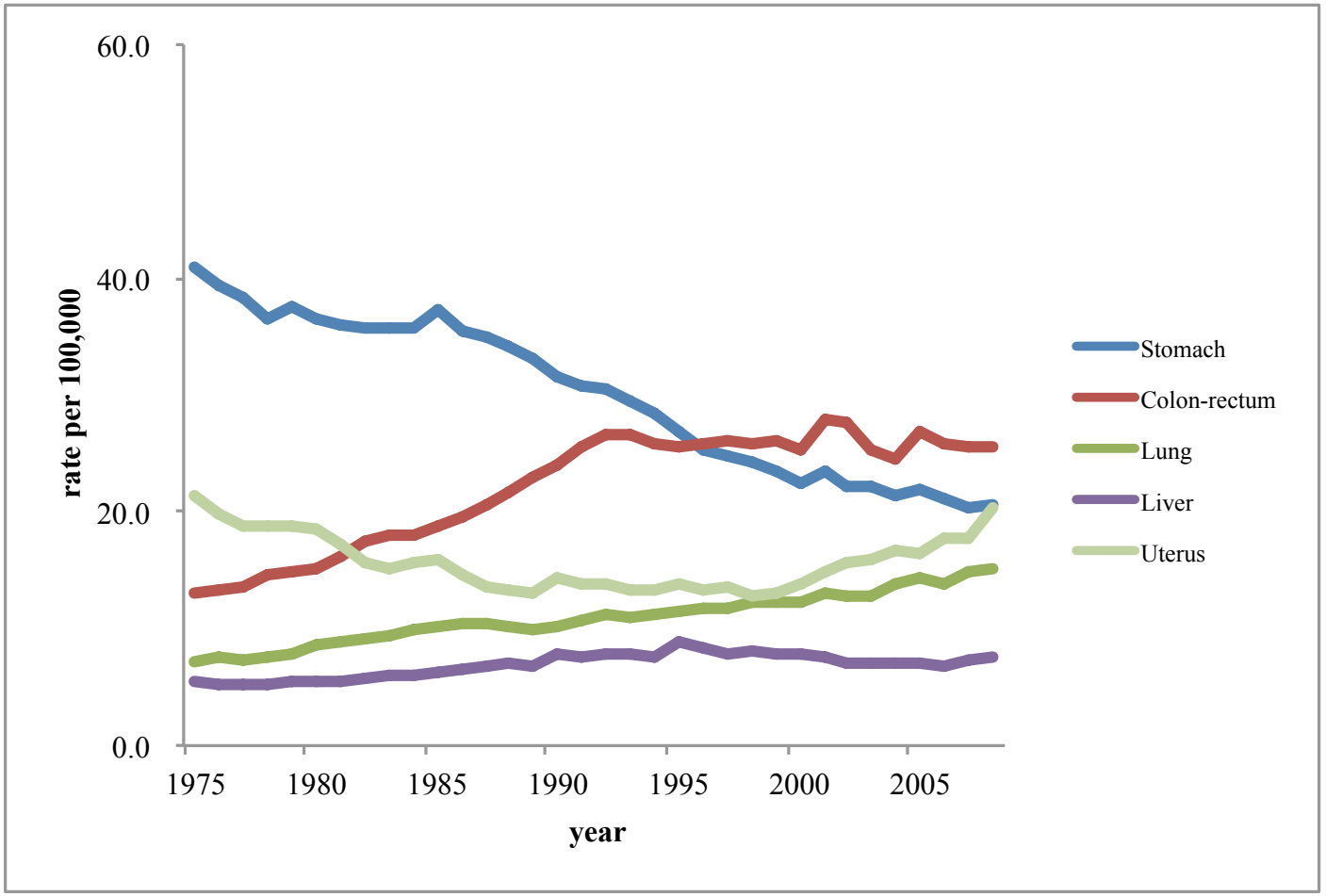

Figure 7: Trends in age-standardized incidence rate in Japanese women (1975-2007)

Source: National Cancer Center, Japan [8]

1.1.2. Environmental exposures

Colon cancer risk is possibly influenced by environmental exposures [11] and therefore in theory preventable if risk factors are removed [12, 13]. Environmental factors such as a more sedentary lifestyle and nutrition, especially western diet may contribute to colorectal cancer incidence [14-18]. The following factors pose an increased risk of developing colorectal cancer (through possible pathways): family history (familial adenomatous polyposis, hereditary nonployposis colorectal cancer); meat and smoking (nitrosamines and heterocylic amines); alcohol [19] (acetaldehyde – effects via reduced folate). In contrast vegetables (antioxidants, folate, maybe fiber); physical activity/low BMI [19, 20] (reduced growth stimulus and transit time); nonsteroidal anti-inflammatory drugs (COX-2 inhibition); hormone replacement therapy [21-23] (maybe prevention of estrogen receptor hypermethlation) show an inverse association. Additionally, questionable decreased risk from calcium/dairy foods (reduced cell proliferation) and multivitamin supplements (maybe folic acid) [18]. The relationship between cereal and colorectal cancer risk is inconclusive [24].

The population attributable faction (PAF), proportion of a disease attributed to exposure to a specific risk factor is a key concept within this context. The PAF in % for colon cancer in Japan in 2005 was relatively low, 51.0 for men and 12.8 for women, (46.6; 6.5 for rectal cancer) [25]. Only half of cases can be explained by the following risk factors in men and just over 10% in women. The highest contributions come from tobacco

smoking (20.4 in men; 4.5 in women), alcohol consumption (32.9; 2.1), and to a lesser extent overweight/obesity (5.2; 4.0) and physical inactivity (3.2; 2.9) [25]. In comparison, liver cancer with a PAF (%) of 92.2 in men and 91.8 in women [25], can be almost fully explained by infection, especially hepatitis C virus and hepatitis B virus (86.4 in men; 90.0 in women) and tobacco smoking [25].

Research among immigrant and local populations may help identify the role of environmental risk factors in carcinogenesis. Colorectal cancer increased among Japanese who moved to the USA, suggesting the possible environmental impact on colon cancer incidence [2]. Some researchers speculate that the recent high colorectal cancer rates in Japan and Korea may be explained by a genetic predisposition, even when consuming a similar diet, caused by Asian's higher sensitivity and susceptibility to gastric and colon cancer [26, 27]. For example, Japanese men in Hawaii had one of the highest colorectal cancer incidence rates (53.5) in the world in the early 1990s [2]. Western diet alone may not explain this large increase.

1.1.3. Importance of rice and contradictory patterns

Rice is the most important staple in Japan typically consumed in the form of white rice [28, 29]. Rice intake may be a surrogate of a traditional Japanese diet and thus might

represent specific dietary patterns, lifestyles and culture. Some typical patterns peculiar to Japanese proposed are “traditional”: rice, fish and miso soup [30, 31] and “rice/snack”: rice, miso soup, cookies [32]. Patterns detecting a negative loading for rice include: “western” [33, 34] and “DFA” (dairy, fruit and low alcohol) [35].

In Japan, descriptive data regarding the association between rice and colorectal cancer is inconsistent. A decreasing trend of rice intake in Japan in recent decades [36] may reflect the current national increasing trends in colorectal cancer incidence, which could suggest an inverse association between rice and colorectal cancer. In contrast, mortality rates of colorectal cancer are high in prefectures in which large amounts of rice are consumed [36-38], suggesting a positive link between rice and colorectal cancer.

There is some, albeit limited, evidence from the 1970s suggesting large quantities of rice may increase the risk of colorectal cancer [16, 39]. However, the evidence for rice and cancer risk in the general population has been sparse and inconsistent from research conducted in the 1980s [26] and recently in 2010 [29] mostly consisting of case-control studies.

The effect of rice on colorectal cancer is inconclusive, especially in Asian populations, consuming a diet high in white rice. Chinese and Korean studies provide important insights, as rice is a staple food in these countries similar to Japan [28]. The Shanghai

Women's Health Study (SWHS) observed no association between rice intake and the risk of colorectal cancer [40]. The Shanghai Men's Health Study (SMHS) reported older men with chronic diseases were more likely to consume a rice and vegetable diet than a diet focused on fruit or meat [41]. The Korean Health and Genome Study reported on dietary patterns and health risk factors finding that the identified rice-vegetable dietary pattern increased risk of hypertension [42].

1.1.4. Potential pathways

In particular, rice, not specifically white rice, may be an important source of dietary fiber. Some studies have confirmed the protective role of dietary fiber in relation to colorectal cancer [24, 43-45], however results remain elusive with other studies finding no association [29, 46, 47]. Burkitt examined Cleave's original hypothesis [48] that refined carbohydrates are an etiological factor related to many diseases, including colorectal cancer [39]. He proposed two possible pathways resulting from refining carbohydrates as a result of economic development: deficient fiber (low-residue diet) leading to fecal arrest and/or excess consumption of refined carbohydrates followed by bacterial changes and subsequently degradation of bile salts to carcinogens and induction of tumors, which may also be a final stage in the former pathway [39]. In a Japanese study 32.2% of cereal fiber intake came from rice and cereals accounted for 21.7% of total dietary fiber intake [29, 46]. Therefore, a large amount of dietary fiber

comes from other sources. While fiber may be protective, it is possible that excessively large quantities of rice, primarily consumed in the form of white rice may increase the risk of colorectal cancer. Colorectal cancer subsite specific results may vary, for example our study suggests that high intakes of rice may be protective of rectal cancer in men, though these results were not statistically significant.

Same as fiber and colorectal cancer, rice may be a surrogate of starch. Intake of starch is greater than fiber and resistant starch may be more important in the production of short-chain fatty acids and stool quantity [29], thus possibly affecting the colon and rectum. The type and serving condition of food probably determine the role of starch in colorectal carcinogenesis [29], which may be enhanced via hyperinsulinemia assumed to be a mechanism in obesity-related carcinogenesis [49]. However resistant starch may be protective [29]. An international study found starch compared to non-starch polysaccharides was more strongly correlated with colorectal cancer incidence [50] while case–control studies in Western populations found no association [45]. Past research astutely noted that primary carcinogenic "triggers" may vary by population susceptibility, both genetic and environmental [26].

1.2. Rationale and objectives of the present study

1.2.1. Rice, diabetes and colorectal cancer

The association between rice intake and diabetes has been established in Japanese women [28], as has the relationship between diabetes and colon cancer in the Japanese men [51]. An international meta-analysis found an association between diabetes and increased risk of colorectal cancer in men and women [52]. The possible link between rice and colorectal cancer should therefore be further explored.

1.2.2. Glycemic index, glycemic load and colorectal cancer

The glycemic index and glycemic load and cancer risk [53, 54], specifically colorectal cancer [40, 55-67] has received more attention than intake of rice and colorectal cancer risk. While rice is certainly not equivalent to these two composite measurements of carbohydrate intake, it can be assumed that it contributes the greatest portion toward the glycemic index and glycemic load in Japan, certainly in the past. In the Shanghai Women's Health Study, rice contributed 69% of total carbohydrates and 80% of the total glycemic load [40].

The glycemic index is a measure of how quickly blood glucose levels rise after eating. More specifically, it is a ranking of the quality of carbohydrates based on postprandial blood glucose response [59, 60, 68, 69]. For example the GI of glucose is 100. In general, refined starches have a high GI [70]. The glycemic load on the other hand reflects both the quality and quantity of carbohydrates [57, 59, 68]. To obtain the GL the GI must be divided by 100 and the result gets multiplied by net carbohydrates in grams: GI/100 x Net Carbohydrates [71]. The GL of a cup (186g) of white rice is 33. In comparison the GL of 1 slice (30g) of white bread and 1 cup (140g) of spaghetti are 10 and 16 and respectively [71]. Exploring individual food items such as bread and pasta in addition to the GI and GL is important. Even though both are heavily consumed in Italy the odds ratios were different [56]. This would be partially masked when only looking at the glycemic index or load. Low GI diets may lower insulin output and ensuing chronic diseases such as cancer [72, 73].

Many studies which investigated the association between glycemic index/load and colorectal cancer drew on the hypothesis that circulating insulin may lead to colorectal cell proliferation [55, 56]. Glycemic effects from diets containing large amounts of refined starch may contribute to high levels of circulating insulin and insulin-like growth factor [59], which may be associated with an increased risk of colorectal cancer [55, 56]. Colorectal cancer risk is associated with non-insulin dependent diabetes mellitus [74, 75]. Normal and malignant colonic mucosa contains insulin and insulin

growth factor (IGF) that can stimulate development of colorectal cells and tumor growth [76-78].

Several studies found a high glycemic load increased the risk of colorectal cancer [56-60, 69, 79], but two of these were case control studies subject to selection and recall bias. One study suggested that refined carbohydrates play a detrimental role in the etiology of colorectal cancer with odds ratios of high vs. low glycemic index 1.7 (95% CI, 1.4-2.1) and glycemic load 1.8 (95% CI, 1.5-2.2) [56].

Subsite analysis was conducted in some studies; specifically proximal colon cancer risk was associated with a high glycemic index [58]. The Health Professionals Follow-up Study (HPFS) in men found glycemic load and sugar intake particularly affected the risk of rectal cancer [57, 60]. A positive association between glycemic load, carbohydrate intake and distal colon cancer risk was suggested [55].

Other studies showed no evidence that high glycemic load increases the risk of colorectal cancer [40, 55, 57, 61, 62, 64, 66, 67, 80, 81]. An example of a prominent study finding no association in women is the Nurses Health Study (NHS I) [57]. High levels of carbohydrate and sugar intake did not support an increased risk of colorectal cancer in at least one study [55]. Both the HPFS and NHS I found no significant risk for colorectal cancer based on carbohydrate, glycemic load, glycemic index and sugar after

stratifying by proximal and distal colon cancer [57]. However, a non-significant trend between increased carbohydrate intake and increasing risk of colorectal cancer in men was observed, but not in women [57]. An inverse association between intake of carbohydrates and proximal colon cancer was observed in women [57].

1.2.3. Objectives

The originality of this work lies in the main exposure it considers - the main staple food item in the Japanese diet rice. In nutrition research it is important to first consider food items, then nutrients and finally composite measures such as the glycemic index and load. Researching individual food items is difficult and potentially finding non-significant results makes meaningful discussion a challenge. Nevertheless the aim of this study was to tackle this challenge. Therefore, we for the first time analyzed a large-scale prospective population-based cohort to understand the association between colorectal cancer and rice intake in the Japanese population. The study aims to:

(1) Assess colorectal cancer risk by quartile of rice, bread, noodle, and carbohydrate intake;

(2) Evaluate effect modification of main risk factors and rice on colorectal cancer; and

(3) Compare risk differences by colorectal cancer subsite and gender

1.3. Organization of the thesis

The thesis is organized in five chapters. The first chapter provides the background information on colorectal cancer and rice intake in Japan as well as outlining the rationale and objectives of the study. Chapter 2 describes the methods and materials. Chapter 3 presents results, hazard ratios and 95% confidence intervals of colorectal cancer incidence risk according to quartiles of rice and other grain-based foods. Chapter 4 considers the results, revisits contradictory patterns of rice intake and colorectal cancer in Japan and sex differences. The chapter also provides information on strengths and limitations of the study. Chapter 5 summarizes the entire dissertation, gives policy recommendations, ideas for future research and completes this work.

2. METHODS

The methods chapter describes the design and history of the Japan Public Health Center–based prospective Study (JPHC). Further, the study population is introduced. Details are provided on exposure variables (2.2.) and follow-up identification of colorectal cancer cases (2.3.). In the final section (2.4.), approaches to statistical analysis are described.

2.1. Study design and population

The JPHC Study is a 30-year on-going cohort study focusing on cancer, cardiovascular and other lifestyle-related diseases. The details of the study design have been described elsewhere [82-85]. In brief, the JPHC Study originated in the late 1980s, as Japan was under-going demographic transition and life expectancy tremendously increased. Lifestyle changed from previous Japanese cohorts such as Takeshi Hirayama's "Lifestyle and Mortality" cohort (1965-1982) [86]. The country also underwent a major shift from infectious to non-communicable diseases in the second half of the twentieth century. The purpose of the JPHC Study was therefore to collect scientific data to contribute to evidence-based disease prevention guidelines with the specific objective of elucidating and clarifying risk and preventive factors of cancer and cardiovascular diseases [84].

The groundwork was laid from 1989-1991 in a cross-sectional study carried out in five public health center (PHC) areas by the Epidemiology Division of the National Cancer Center Research Institute [85]. In late 1989 cohorts of 40 to 59 year olds were formed in these five PHC districts. Specialist committees from the National Cancer Center and National Cardiovascular Center worked to cooperatively develop a multipurpose cohort.

Financing was requested by the Ministry of Health and Welfare and provided as an extension to the cancer research grant by the Ministry of Finance. In 1992 the "Koseisho Multipurpose Prospective Cohort Study" was established, now "Japan Public Health Center-based Prospective Study on Cancer and Cardiovascular Diseases" (JPHC Study) [85].

The five initial 1989 cohorts made up the core, cohort I, including public health centers in Ninohe, Iwate; Yokote, Akita; Saku, Nagano; Chubu, Okinawa; and Katsushika, Tokyo, established in 1990. Cohort II established in 1993 included residents belonging to PHCs in Mito, Ibaraki; Nagaoka, Niigata; Chuo-higashi, Kochi; Kamigoto, Nagasaki; Miyako, Okinawa; and Suita, Osaka. Most areas aside from Suita, Osaka and Katsushika, Tokyo were not urban centers. Figure 8 presents the geographic distribution of the areas and number of study participants in each PHC area. From the map, it is easy to see the study includes a wide representation of Japanese adults from the northern (Akita) to southern (Okinawa) end of the archipelago (Figure 8).

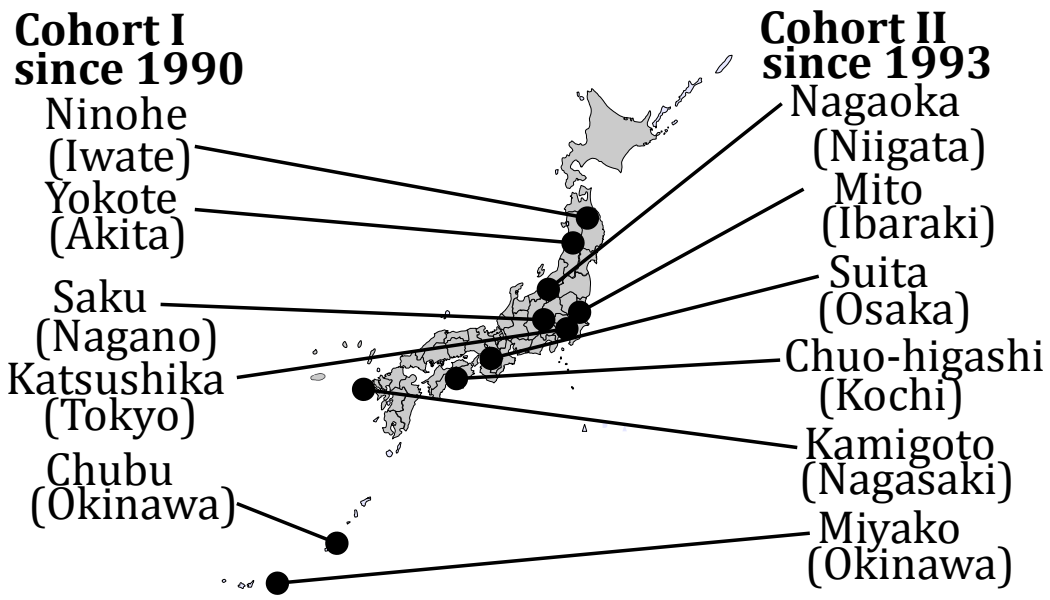

Figure 8: Map of participating Japanese Public Health Centers

Source: adapted from standard JPHC Study method slides

140,020 residents—all 40-59 or 40-69 (cohort II) year olds living the city and town in 11 PHC areas were included. At baseline, a self-administered questionnaire on lifestyle was administered, blood samples were taken and health checkup data collected. A robust follow-up system capturing mortality, migration and incidence of cancer and cardiovascular diseases was implemented. Follow-up surveys were administered at five and ten years [84].

Study participants responding to the 5-year follow-up questionnaire 1995 to 1999, ages 45–74 years were included in the present study. The 5-year follow-up survey was used as baseline because this survey included a more detailed self-administered food

frequency questionnaire (FFQ). Figure 9 visually depicts the systematic process to define the study sample. One public health center area, Katsushika, Tokyo, was excluded because cancer incidence information was not available. We started with a population-based cohort of 133,323 participants. We excluded non-Japanese participants (n=51), late reports of emigration occurring before the starting point (n=187), ineligibility due to incorrect birth date (n=7), and duplicate enrollments (n=4). After the exclusion of 11,583 subjects who had died, moved out of the study area, or were lost to follow-up before the starting point, 121,492 eligible participants remained. From these, 98,505 responded to the questionnaire, yielding a response rate of 81.1% (Figure 9). The study received approval from the institutional review board of the National Cancer Center, Tokyo, Japan (No. 13-021).

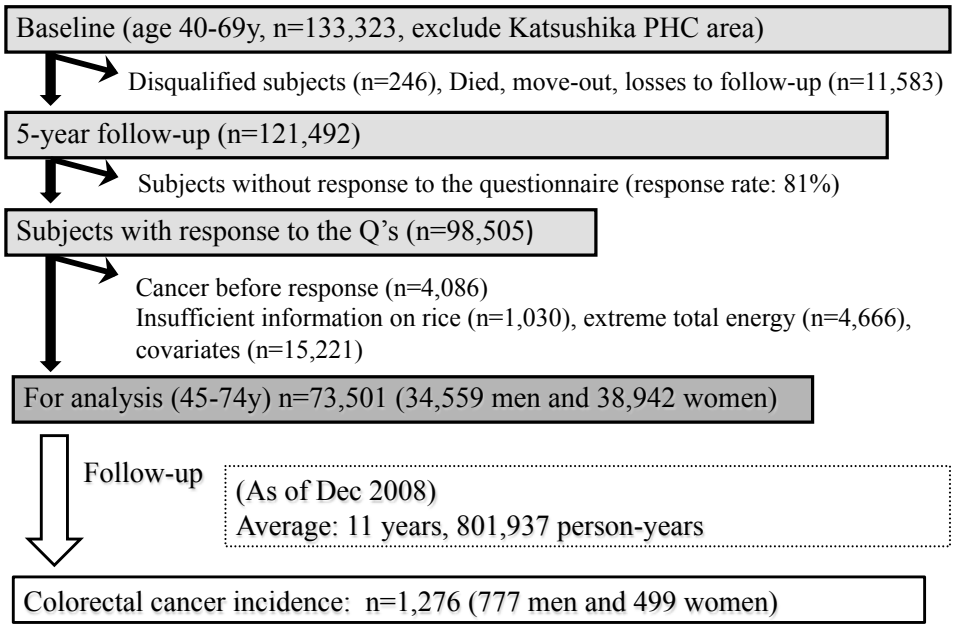

Figure 9: Study sample

Source: adapted from standard JPHC Study method slides

2.2. Exposure variables

2.2.1. Dietary assessment of main exposure variables

The JPHC Study questionnaire included data on demographics, lifestyle, occupation, height, weight, smoking, alcohol consumption, physical activity, working hours, and stress. The validated Food Frequency Questionnaire (FFQ) used in the follow-up survey was designed to estimate dietary intake of 138 food and beverage items and was validated for the estimation of various nutrients and food groups in Japan using JPHC Study subjects [87].

Participants were asked about their usual eating habit during the past year. Specifically, they denoted frequency of consumption of individual food items as well as representative sizes relative to standard portions. Details regarding carbohydrate related food items collected in the JPHC Study were described previously [28]. Briefly, for rice (japonica rice; round and short grain), participants selected from nine options ranging from < 1 bowl per day to ≥10 bowls per day and rice-bowl portion size: small (110 grams), medium (140 grams), and large (170 grams). The FFQ did not specify the type of rice, but it can be assumed that the vast majority of participants predominantly consumed white rice [28]. The FFQ also included one bread item and four noodle items (Japanese, buckwheat, Okinawan, and Chinese noodles). Response choices for

frequency including bread and noodle items were never, 1–3 times per month, 1 to 2 times per week, 3 to 4 times per week, 5 to 6 times per week, once a day, 2 to 3 times per day, 4 to 6 times per day, and ≥7 times per day [14, 28, 88]. Participants were asked to denote the portion from the following options: small (50% less than normal), medium (standard portion), and large (50% greater than a regular portion) [14, 28, 88]. Daily intake of food items was calculated by multiplying frequency by standard portion and relative size.

FFQ validity was assessed using 14 or 28 day dietary records (DR) in 335 randomly subsampled subjects in five of the JPHC Study areas where Spearman's correlation coefficients between DR and FFQ were 0.67 for rice, 0.67 for bread, and 0.42 for noodles in men and 0.55, 0.63, and 0.43 in women [28, 89-91]. Regarding reproducibility of estimations, Spearman's correlation coefficients for intake of rice, bread, and noodles were 0.79, 0.70, and 0.49 in men and 0.69, 0.67, and 0.57 in women between the FFQs administered 1 year apart [28, 89-91].

2.2.2. Other covariates

Other covariates used in the analysis were included due to previously established or probable associations with colorectal cancer. These were: age [92-94], obesity [19, 20, 95], tobacco consumption [19, 83, 95, 96], alcohol consumption [19, 83, 95, 97],

physical activity [95, 98], past history of type 2 diabetes [51], screening examinations for colorectal cancer [99, 100], menopausal status and hormone use (women) [21-23, 101], intake of red meat [27, 102], total energy [95], calcium [103, 104], magnesium [105], vitamin B6 [106], vitamin B12 [106], folate [107, 108], vitamin D [104, 109], n-3 PUFAs [88], and fiber [43, 68, 110]. Age at 5-year follow-up was used. Body mass index was calculated as weight (kg) / height $(m)^2$ at starting point of this study (5-year follow-up survey). Participants were asked about their tobacco consumption pattern: smoking never, past, or current. Current smokers additionally noted the number of cigarettes smoked per day. Alcohol consumption was categorized as: hardly ever, 1 to 3 days a month, 1 to 2 days a week, 3 to 4 days a week, 5 to 6 days a week, or drinking every day. Subsequently, participants denoted their most usual combination of alcohol consumption in one day from the following choices: Japanese sake ("go" 180 ml, 23 grams of ethanol), shochu/awamori ("go" 180 ml, 36 grams of ethanol), beer (large bottle 633 ml, 23 grams of ethanol), whiskey (glass 30 ml, 13 grams of ethanol), wine (glass 100 ml, 6 grams of ethanol). The options on the questionnaire included: I do not drink, less than 0.5, 1, 2, 3, 4, 5-6, 7 or more of the respective "go", bottle or glass.

Physical activity was measured using a composite ranked score to calculate metabolic equivalent (METS) task-hours per day from physical labor and extreme sports: none, less than 1 hour, 1 hour or more; time sitting (3 hours or less, 3 to 8 hours, 8 hours or more), or time walking or standing (less than 1 hour, 1 to 3 hours, 3 hours or more).

Each combination was given a weight to calculate METS. Past history of type 2 diabetes was self-reported at the time of the 5-year follow-up questionnaire. Screening examinations for colorectal cancer were self-reported in the health check question: "If you have had any tests in the past one year, please mark all of them" (fecal occult blood test, barium enema, or colonoscopy). Menopausal status (premenopausal or natural or induced postmenopausal) and use of exogenous female hormones were self-reported by women.

Red meat was calculated as a composite of the individual food items in this food group: steak, grilled beef, stir-fried pork, deep fried pork, stewed pork Western and Japanese style, pork in soup and pork liver. The following options for individual items were given, translated from the Japanese questionnaire on the Study's English questionnaire: I do not eat it, 1 to 3 times a month, 1 to 2 times a week, 3 to 4 times a week, 5 to 6 times a week, once daily, 2 to 3 times daily, and 4 to 6 times daily. Total energy and nutrient intakes were estimated using the food item consumption reported on the FFQ and the Standard Tables of Food Composition in Japan (4^{th} revised edition) for energy and nutrients [91, 111].

2.3. Follow-up and identification of colorectal cancer cases

Subjects were followed from the 5-year follow-up survey (around 1995 and 1998 respectively) through December 31, 2008. Residential registers in each municipality in the study areas annually confirmed residence status and survival of participants. Data on those who no longer resided in the study area were confirmed by the municipal office of the area they moved to. Persons who were lost to follow-up were censored on the last confirmed date of presence in the study area. Deaths were identified through death certificate information provided with permission by the Japanese Ministry of Health, Labour and Welfare [14].

Colorectal cancer incidence cases were identified by active patient notification from major local hospitals in the study areas and population-based cancer registries. We coded colorectal cancer cases as C18-C20 according to the International Classification of Diseases for Oncology, third edition [112]. In our cancer registry system, the proportion of cases for which information was available from death certificates only (DCO) was 2.7%. A DCO below 5% is a good quality indicator. The reason for the low DCO in our study was the type of cancer assessed and the link with population-based registries and hospitals. We conducted site-specific analyses: for colon (C18.0– C18.5 for proximal colon and C18.6–C18.7 for distal colon) and rectal (C19 and C20) cancer [112]. In detail, the outcome variables were composites of the following ICD-O-3

codes: C18.0 cecum, C18.1 appendix, C18.2 ascending colon (right), C18.3 hepatic flexure of colon, C18.4 transverse colon, C18.5 splenic flexure of colon, C18.6 descending colon (left), C18.7 sigmoid colon, C18.8 overlapping lesion of colon, C18.9 colon, C19.9 rectosigmoid junction, and C20.9 rectum [112]. The earliest date of diagnosis was used when a subject had multiple primary colon or rectal cancers with the exception of simultaneous cancers in which case the most advanced was used [14].

2.4. Statistical analysis

We excluded participants who had been diagnosed with or reported as having cancer before the starting point (n=4,086) or subjects with missing information for main exposure variables: i.e. rice, bread, noodle intake (n=1,030) or who reported extreme total energy intakes (upper 2.5% or lower 2.5%; n=4,666) or missing data. 88,722 participants were enrolled in our analysis. Subjects with missing values for covariates were excluded (n=15,221). Resulting in a final sample of 73,501 men (n=34,559) and women (n=38,942).

We calculated person-years of follow-up for each participant from the starting point to the date of colorectal cancer diagnosis, date of emigration from the study area, date of death, or end of the follow-up (31 December 2008), whichever came first. Using Cox proportional hazards models, we calculated hazard ratios (HR) and 95% confidence

intervals for developing colorectal cancer for rice categories in quartiles by gender, with the lowest consumption category as the reference. The median value of each quartile was included in the trend analysis. We stratified by anatomic sub-sites: colon, rectal, proximal and distal colon cancer.

We employed three Cox proportional hazards models. First, we adjusted for only age and PHC area. Second, we adjusted for potential confounding variables: age (continuous); public health center area (10); body mass index (<25, 25-26.9, 27-29.9, ≥30 kg/m^2); cigarette smoking (never, past, or current: 1-19, 20-29, ≥30 cigarettes per day); alcohol consumption (for men—none; drinker: <150, 150–299, 300–449, or ≥450 grams of ethanol per week; for women—none; drinker: <150 or ≥150 grams of ethanol per week); quartile of physical activity in metabolic equivalent (METS) task-hours per day; history of type 2 diabetes (yes or no); screening examinations for colorectal cancer (fecal occult blood test, barium enema, or colonoscopy); menopausal status (premenopausal or natural or induced postmenopausal) and use of exogenous female hormones (yes or no) in women. Total energy (kcal per day, continuous) and crude intake by quartile of red meat (grams per day) were also included in the model. Crude intake by quartiles of: rice (grams per day), bread (grams per day), noodles (grams per day) were mutually adjusted for. Median intake in grams per day by quartile was used for the analysis. Median was deemed more appropriate [40, 54] in this study as there was large variation in in the width of each category. Crude values were used for

individual food items to provide true intake values allowing for meaningful conclusions to be drawn for public health policies. Intake of cereal (grams per day) was analyzed in a separate model without adjustment for rice, bread and noodles due to collinearity.

Finally, in the full model, we additionally adjusted for energy-adjusted intake of log-transformed nutrients using median intake by quartile: calcium (milligrams per day), magnesium (milligrams per day), vitamin B6 (milligrams per day), vitamin B12 (micrograms per day), folate (micrograms per day), vitamin D (micrograms per day), n-3 polyunsaturated fatty acids, (grams per day) and fiber (grams per day). Dietary factors were adjusted by total energy using the residual method [14, 113-115]. We employed the approach suggested by Willett [116], to compute "energy-adjusted" nutrients by regressing the absolute nutrient on the total caloric intake and added a constant to eliminate zero and negative values. We first calculated the mean logarithmic energy for men 7.64 and women 7.48 and then log-transformed the nutrients to do a series of regression analyses. We obtained the coefficient of energy (slope) for each particular nutrient for each sex separately in our study: e.g., for calcium 1.15 and 1.28 for men and women, respectively. The last item, the constant: e.g., for calcium was -2.69 for and -3.37 for men and women, respectively. Finally, we calculated the nutrient residuals from the log-transformed energy adjusted nutrients. The equations to calculate energy-adjusted log-transformed values are as follows:

Calories=(mean log-transformed energy)*(slope: coefficient energy)+(intercept:

constant); Model 2=Nutrient residual + Calories [116].

Example from current study: calcium men=(7.636054)*(1.149215)+(-2.685951) and calcium women=(7.481789)*(1.279657)+(-3.373055).

In total, five outcome variables were examined: colorectal cancer, colon cancer, rectal cancer, proximal colon cancer, and distal colon cancer. Four main exposure variables: rice, bread, noodle and cereal intake by quarter were compared in three models: age-area only, Model 1 and Model 2. Results were presented separately for men and women. Therefore a total of 120 individual models were employed for the main analysis presented in Tables 1-8. All analyses were performed with Stata SE 12.1 (StataCorp, College Station, TX) [117].

3. RESULTS

The results chapter describes the characteristics of the study population by quartile of rice intake (3.1). This chapter also provides information on the main findings of the study regarding colorectal cancer incidence and risk defined as hazard ratios by quartile of rice intake primarily (3.2) and secondarily for comparative purposes: bread, noodle and cereal intake (3.3). Additional analyses were carried out according to quartile of rice intake for possible effect modification (3.4) and subgroup analysis by latitude (3.5).

3.1. Characteristics of study participants

During 801,937 person-years of follow-up, we identified 1,276 new colorectal cancer cases (777 for men, 499 for women). The JPHC Study sample represents public health centers primarily from non-metropolitan areas in Japan. Table 1 shows that BMI slightly decreased with quartile of rice intake in men (Table 1), while there was no consistent pattern among women (Table 2). Regular alcohol consumption was highest in the lowest rice intake group in men and women, while smoking was higher in the highest and the second highest rice intake groups in men compared to the lower intake (Table 1), but highest in the lowest rice intake group in women (Table 2). METS increased with intake of rice in both sexes though not as consistently in women. Total energy followed the same pattern. In contrast, bread and noodle intake were highest in the lowest quarter of rice intake. Cereal intake increased proportional to rice intake.

Table 1: Characteristics of study participants at the 5-y follow-up survey according to quartiles of rice intake among men in the JPHC Study

	Men (*n*=34,559)				
Variable	Q1 (low)	Q2	Q3	Q4 (high)	P value
Rice (n)	8823	15444	5647	4645	
Rice (g/d) median (range)	122 (0-136)	183 (137-183)	244 (190-243)	305 (273-592)	<0.0001
Rice (g/d)[2]	92±42	176±16	238±10	330±43	<0.0001
Age (y)	56.78±7.90	57.00±7.96	55.16±7.06	55.56±6.92	<0.0001
BMI (kg/m^2)	23.70±2.94	23.63±2.89	23.53±2.78	23.47±2.71	<0.0001
Alcohol intake (%)[3]	74.45	71.52	72.36	70.89	<0.0001
Current smoker (%)	45.49	45.49	53.16	51.00	<0.0001
METs (MET-h/d)	31.54±6.39	32.47±6.72	33.76±7.03	35.04±7.04	<0.0001
History of type 2 diabetes (%)	10.11	10.17	6.94	5.47	<0.0001
CRC screening (%)[4]	31.15	32.54	31.82	33.86	0.009
Dietary intake[5]					
Total energy (kcal/d)	1941.65±602.74	2091.79±598.31	2356.88±595.60	2638.17±571.54	<0.0001
Calcium (mg/d)	549±249	491±210	441±180	389±154	<0.0001
Magnesium (mg/d)	282±62	275±54	264±47	254±43	<0.0001
Vitamin B6 (mg/d)	1.55±0.38	1.50±0.32	1.43±0.27	1.35±0.25	<0.0001
Vitamin B12 (μg/d)	10.6±5.1	9.8±4.3	9.3±3.9	8.4±3.5	<0.0001
Folate (μg/d)	384±153	372±139	344±120	317±110	<0.0001
Vitamin D (μg/d)	11.5±6.5	10.9±6.1	10.6±5.7	9.8±5.7	<0.0001
n-3 PUFAs (g/d)	3.31±1.26	3.03±1.06	2.77±0.93	2.47±0.84	<0.0001
Fiber (g/d)	12.1±5.0	11.4±4.3	10.6±3.8	10.0±3.4	<0.0001
Bread (g/d)	32±43	20±34	20±32	16±24	<0.0001
Noodles (g/d)	130±130	116±113	118±108	111±102	<0.0001
Cereals (g/d)	285±147	326±123	387±119	468±118	<0.0001
Red meat (g/d)	48±47	48±45	49±43	47±40	0.10

[1] JPHC, Japan Public Health Center-based; Q, quartile; MET, metabolic equivalent task; CRC, colorectal cancer; n-3 PUFA, n-3 polyunsaturated fatty acid; food items and nutrients reported according to the Standard Composition Table (basis for the nutrient calculation). Subjects with missing data were excluded (BMI: *n*=2195; smoking status: *n*=4122; alcohol consumption: *n*=6698; MET: *n*=2944; menstruation: *n*=2898; hormone use: *n*=2674; n-3 PUFA: *n*=98) total excluded: *n*=15,221.

[2] Values are mean ± standard deviation (all such values) unless stated otherwise.

[3] Alcohol consumption ≥ 1g ethanol/wk.

[4] CRC screening included fecal occult blood test, barium enema, or colonoscopy.

[5] All mean total intakes of nutrient are energy adjusted.

Table 2: Characteristics of study participants at the 5-y follow-up survey according to quartiles of rice intake among women in the JPHC Study

	Women (*n*=38,942)				
Variable	Q1 (low)	Q2	Q3	Q4 (high)	P value
Rice (n)	14837	5339	15430	3336	
Rice (g/d) median (range)	96 (0-122)	143 (136-144)	183 (147-183)	244 (190-487)	<0.0001
Rice (g/d)[2]	90±40	140±3	183±2	263±46	<0.0001
Age (y)	55.89±7.69	57.39±7.83	56.80±7.71	55.74±7.10	<0.0001
BMI (kg/m^2)	23.34±3.18	23.67±3.21	23.52±3.10	23.44±3.16	<0.0001
Alcohol intake (%)[3]	23.44	15.08	15.44	16.37	<0.0001
Current smoker (%)	7.27	4.44	4.50	5.25	<0.0001
METs (MET-h/d)	31.77±5.50	32.18±5.97	32.26±5.90	32.95±6.05	<0.0001
History of type 2 diabetes (%)	4.17	5.69	3.77	2.76	<0.0001
CRC screening (%)[4]	29.59	33.28	34.65	30.64	<0.0001
Postmenopausal status (%)	73.38	78.72	76.58	73.80	<0.0001
Hormone use (%)	3.09	2.73	2.47	2.28	0.003
Dietary intake[5]					
Total energy (kcal/d)	1735.26±531.93	1877.97±547.63	1945.83±538.03	2217.16±532.49	<0.0001
Calcium (mg/d)	596±229	543±185	492±168	400±144	<0.0001
Magnesium (mg/d)	272±53	270±44	260±43	241±39	<0.0001
Vitamin B6 (mg/d)	1.41±0.31	1.41±0.26	1.37±0.24	1.25±0.22	<0.0001
Vitamin B12 (μg/d)	9.6±4.30	9.3±3.96	9.1±3.6	8.1±3.6	<0.0001
Folate (μg/d)	414±147	408±135	383±126	329±110	<0.0001
Vitamin D (μg/d)	10.9±5.8	10.8±5.6	10.7±5.3	9.6±4.9	<0.0001
n-3 PUFAs (g/d)	3.25±0.99	3.07±0.88	2.92±0.83	2.51±0.76	<0.0001
Fiber (g/d)	13.8±4.6	13.4±4.0	12.4±3.8	10.9±3.3	<0.0001
Bread (g/d)	41±52	22±29	22±30	23±36	<0.0001
Noodles (g/d)	96±97	91±87	91±86	94±88	<0.0001
Cereals (g/d)	254±117	284±101	306±99	393±111	<0.0001
Red meat (g/d)	42±40	44±42	43±40	40±35	0.006

[1] JPHC, Japan Public Health Center-based; Q, quartile; MET, metabolic equivalent task; CRC, colorectal cancer; hormone use, current use of exogenous female hormones (%); n-3 PUFA, n-3 polyunsaturated fatty acid; food items and nutrients reported according to the Standard Composition Table (basis for the nutrient calculation). Subjects with missing data were excluded (BMI: *n*=2195; smoking status: *n*=4122; alcohol consumption: *n*=6698; MET: *n*=2944; menstruation: *n*=2898; hormone use: *n*=2674; n-3 PUFA: *n*=98) total excluded: *n*=15,221.

[2] Values are mean ± standard deviation (all such values) unless stated otherwise.

[3] Alcohol consumption ≥ 1g ethanol/wk.

[4] CRC screening included fecal occult blood test, barium enema, or colonoscopy.

[5] All mean total intakes of nutrient are energy adjusted.

3.2. Colorectal cancer incidence by quartiles of rice intake

Age-adjusted colorectal cancer incidence (per 1000) in men and women ranged from 20.62 (highest quarter of rice) to 24.10 (lowest) and from 11.20 to 12.05, respectively. Table 3 and 4 present hazard ratios (HRs) and 95% CIs by sex for colorectal cancer incidence according to quartile of rice, bread, noodle and cereal intake among Japanese men and women. There was no statistically significant association between rice intake and colorectal cancer risk among men for the HRs estimated in Model 2 for the highest compared to the lowest quartile of rice in men: 0.77 (95% CI: 0.56-1.07). The trend analysis, analyzed by scores, was not statistically significant. In women, no association was found for rice intake and colorectal cancer risk.

Further stratified analyses show site-specific results for colon and rectal cancer in Tables 5 and 6, respectively and proximal and distal colon cancers in Tables 7 and 8, respectively. We noted a non-significant inverse association between the quartiles of rice intake and the risk of rectal cancer in men (Table 5). In women, a non-significant trend of risk increase in colon cancer by quartile of rice intake (Table 6) and proximal colon cancer (Table 8) was found, but not in men. Distal colon cancer showed no association with rice in both sexes (Tables 7 and 8).

Table 3: Hazard Ratio (HR) and 95% CI of colorectal cancer according to quartiles of rice, bread, noodle and cereal intake among men in the JPHC Study

	Men					
				Age-area	Model 1	Model 2
	No. cases	Person-years	Incidence rate[1]	HR (95% CI)	HR (95% CI)	HR (95% CI)
Rice						
Q1	217	90336.74	24.10	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	338	161548.73	21.40	0.84 (0.70-0.99)	0.90 (0.75-1.08)	0.88 (0.73-1.06)
Q3	128	62110.34	22.89	0.87 (0.69-1.09)	0.96 (0.76-1.23)	0.91 (0.71-1.18)
Q4	94	52997.71	20.62	0.69 (0.53-0.88)	0.85 (0.64-1.13)	0.77 (0.56-1.07)
P trend				0.007	0.369	0.179
Bread						
Q1	326	138252.72	24.76	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	194	91057.57	23.18	0.99 (0.83-1.18)	1.05 (0.88-1.26)	1.05 (0.88-1.26)
Q3	114	61917.40	20.30	0.89 (0.72-1.10)	0.98 (0.79-1.23)	0.97 (0.78-1.21)
Q4	143	75765.81	19.69	0.88 (0.72-1.08)	1.01 (0.81-1.26)	0.98 (0.78-1.23)
P trend				0.192	0.988	0.751
Noodle						
Q1	210	106032.54	19.98	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	170	73397.31	23.97	1.23 (1.00-1.50)	1.26 (1.02-1.54)	1.26 (1.02-1.54)
Q3	203	97244.08	22.99	1.17 (0.96-1.42)	1.18 (0.97-1.44)	1.18 (0.96-1.44)
Q4	194	90319.58	23.85	1.18 (0.97-1.44)	1.20 (0.97-1.49)	1.18 (0.95-1.47)
P trend				0.211	0.223	0.301
Cereal						
Q1	193	86168.81	22.00	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	200	90071.01	22.90	1.05 (0.86-1.28)	1.12 (0.92-1.38)	1.11 (0.90-1.36)
Q3	196	94350.91	22.62	0.99 (0.81-1.21)	1.11 (0.89-1.37)	1.08 (0.87-1.36)
Q4	188	96402.78	22.36	0.92 (0.75-1.14)	1.11 (0.86-1.42)	1.07 (0.81-1.40)
P trend				0.332	0.547	0.780

[1] Age-adjusted incidence rate (per 1000)

Model 1: Multivariate adjusted for age (y, continuous), area (10), alcohol consumption (none; drinker: <150, 150-299, 300-449, or ≥450g ethanol/wk for men), smoking status (never, past, current: 1-19, 20-29, ≥30 cigarettes/day), BMI (<25, 25-26.9, 27-29.9, ≥30 kg/m^2), quartile of metabolic equivalent tasks (hours/day), history of diabetes mellitus (yes or no) colorectal screening (yes or no), total energy intake (kcal/d, continuous), and red meat intake (g/d, quartile). Crude intake of rice, bread and noodles (g/d, quartile) were also mutually adjusted for. Separate model for energy-adjusted cereal: without rice, bread and noodles.

Model 2 Additionally adjusted for intakes (according to g/d, quartile) of energy-adjusted calcium, magnesium, vitamin B6, vitamin B12, folate, vitamin D, n-3 polyunsaturated fatty acids, and fiber.

Table 4: Hazard Ratio (HR) and 95% CI of colorectal cancer according to quartiles of rice, bread, noodle and cereal intake among women in the JPHC Study

	Women					
				Age-area	Model 1	Model 2
	No. cases	Person-years	Incidence rate[1]	HR (95% CI)	HR (95% CI)	HR (95% CI)
Rice						
Q1	174	161613.12	12.05	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	71	59833.11	12.51	1.04 (0.79-1.38)	1.07 (0.81-1.43)	1.10 (0.82-1.48)
Q3	216	174650.78	13.68	1.06 (0.87-1.31)	1.12 (0.90-1.39)	1.18 (0.92-1.50)
Q4	38	38846.61	11.20	0.90 (0.62-1.28)	0.98 (0.67-1.44)	1.10 (0.71-1.68)
P trend				0.976	0.600	0.312
Bread						
Q1	155	117202.34	13.89	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	137	112631.23	13.76	1.03 (0.81-1.29)	1.05 (0.83-1.33)	1.05 (0.83-1.33)
Q3	108	100095.85	12.45	0.98 (0.76-1.26)	1.03 (0.79-1.33)	1.04 (0.80-1.35)
Q4	99	105014.20	10.68	0.89 (0.68-1.15)	0.96 (0.72-1.28)	1.01 (0.75-1.36)
P trend				0.303	0.695	0.986
Noodle						
Q1	129	98660.89	13.71	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	125	117114.14	12.09	0.88 (0.69-1.13)	0.90 (0.70-1.16)	0.90 (0.70-1.16)
Q3	113	113433.45	11.54	0.84 (0.65-1.09)	0.88 (0.68-1.15)	0.88 (0.67-1.14)
Q4	132	105735.13	14.53	1.02 (0.80-1.31)	1.11 (0.85-1.46)	1.12 (0.85-1.47)
P trend				0.554	0.229	0.230
Cereal						
Q1	116	99398.97	12.37	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	130	108611.76	13.18	1.05 (0.82-1.35)	1.11 (0.86-1.43)	1.15 (0.88-1.49)
Q3	130	112772.49	13.08	1.04 (0.81-1.34)	1.14 (0.87-1.49)	1.19 (0.90-1.58)
Q4	123	114160.40	12.59	0.98 (0.76-1.27)	1.14 (0.84-1.54)	1.21 (0.87-1.70)
P trend				0.794	0.464	0.309

[1] Age-adjusted incidence rate (per 1000)

Model 1: Multivariate adjusted for age (y, continuous), area (10), alcohol consumption (none; drinker: <150 or ≥150 g/ethanol/wk for women), smoking status (never, past, current: 1-19, 20-29, ≥30 cigarettes/day), BMI (<25, 25-26.9, 27-29.9, ≥30 kg/m^2), quartile of metabolic equivalent tasks (hours/day), history of diabetes mellitus (yes or no) colorectal screening (yes or no), menopausal status (yes or no, women only), use of exogenous female hormones (yes or no, women only), total energy intake (kcal/d, continuous), and red meat intake (g/d, quartile). Crude intake of rice, bread and noodles (g/d, quartile) were also mutually adjusted for. Separate model for energy-adjusted cereal: without rice, bread and noodles.

Model 2 Additionally adjusted for intakes (according to g/d, quartile) of energy-adjusted calcium, magnesium, vitamin B6, vitamin B12, folate, vitamin D, n-3 polyunsaturated fatty acids, and fiber.

Table 5: Hazard Ratio (HR) and 95% CI of colon and rectal cancer according to quartiles of rice, bread, noodle and cereal intake among men in the JPHC Study

	Men							
	Colon				Rectum			
	No. cases	Age-area HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	No. cases	Age-area HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Rice								
Q1	140	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	77	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	226	0.87 (0.70-1.07)	0.95 (0.76-1.18)	0.93 (0.74-1.17)	112	0.78 (0.58-1.05)	0.82 (0.60-1.10)	0.79 (0.58-1.08)
Q3	87	0.91 (0.69-1.20)	1.05 (0.78-1.41)	1.01 (0.73-1.39)	41	0.78 (0.53-1.16)	0.82 (0.54-1.24)	0.76 (0.49-1.18)
Q4	65	0.72 (0.53-0.98)	0.93 (0.66-1.33)	0.88 (0.58-1.32)	29	0.62 (0.40-0.97)	0.71 (0.43-1.16)	0.61 (0.35-1.07)
P trend		0.067	0.902	0.685		0.039	0.171	0.085
Bread								
Q1	219	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	107	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	127	0.98 (0.78-1.22)	1.05 (0.84-1.32)	1.05 (0.84-1.31)	67	1.01 (0.74-1.37)	1.05 (0.77-1.44)	1.06 (0.78-1.45)
Q3	76	0.90 (0.69-1.17)	1.02 (0.78-1.34)	1.01 (0.77-1.32)	38	0.86 (0.59-1.25)	0.92 (0.62-1.35)	0.91 (0.62-1.33)
Q4	96	0.91 (0.71-1.67)	1.07 (0.81-1.39)	1.04 (0.79-1.38)	47	0.83 (0.58-1.18)	0.91 (0.62-1.34)	0.86 (0.58-1.28)
P trend		0.440	0.682	0.810		0.254	0.564	0.390
Noodle								
Q1	138	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	72	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	128	1.44 (1.13-1.83)	1.47 (1.16-1.88)	1.48 (1.16-1.89)	42	0.85 (0.58-1.24)	0.86 0.59-1.27)	0.85 (0.58-1.25)
Q3	131	1.17 (0.92-1.48)	1.19 (0.93-1.53)	1.21 (0.94-1.55)	72	1.16 (0.84-1.61)	1.15 (0.82-1.62)	1.11 (0.79-1.56)
Q4	121	1.15 (0.90-1.47)	1.19 (0.91-1.55)	1.21 (0.92-1.58)	73	1.24 (0.89-1.72)	1.21 (0.85-1.72)	1.12 (0.78-1.61)
P trend		0.744	0.614	0.543		0.089	0.169	0.366
Cereal								
Q1	131	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	62	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	137	1.07 (0.84-1.36)	1.15 (0.90-1.47)	1.14 (0.89-1.47)	63	1.01 (0.71-1.43)	1.08 (0.75-1.54)	1.05 (0.73-1.50)
Q3	130	0.97 (0.76-1.25)	1.09 (0.84-1.43)	1.09 (0.83-1.43)	66	1.02 (0.71-1.45)	1.13 (0.77-1.64)	1.07 (0.73-1.59)
Q4	120	0.88 (0.68-1.14)	1.06 (0.78-1.45)	1.06 (0.76-1.47)	68	1.02 (0.71-1.45)	1.19 (0.77-1.82)	1.08 (0.68-1.72)
P trend		0.210	0.860	0.918		0.925	0.440	0.759

Model 1: Multivariate adjusted for age (y, continuous), area (10), alcohol consumption (none; drinker: <150, 150-299, 300-449, or ≥450g ethanol/wk for men), smoking status (never, past, current: 1-19, 20-29, ≥30 cigarettes/day), BMI (<25, 25-26.9, 27-29.9, ≥30 kg/m^2), quartile of metabolic equivalent tasks (hours/day), history of diabetes mellitus (yes or no) colorectal screening (yes or no), total energy intake (kcal/d, continuous), and red meat intake (g/d, quartile). Crude intake of rice, bread and noodles (g/d, quartile) were also mutually adjusted for. Separate model for energy-adjusted cereal: without rice, bread and noodles.

Model 2: Additionally adjusted for intakes (according to g/d, quartile) of energy-adjusted calcium, magnesium, vitamin B6, vitamin B12, folate, vitamin D, n-3 polyunsaturated fatty acids, and fiber.

Table 6: Hazard Ratio (HR) and 95% CI of colon and rectal cancer according to quartiles of rice, bread, noodle and cereal intake among women in the JPHC Study

	Women							
	Colon				Rectum			
		Age-area	Model 1	Model 2		Age-area	Model 1	Model 2
	No. cases	HR (95% CI)	HR (95% CI)	HR (95% CI)	No. cases	HR (95% CI)	HR (95% CI)	HR (95% CI)
Rice								
Q1	121	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	53	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	45	0.97 (0.68-1.37)	1.00 (0.70-1.43)	1.02 (0.71-1.46)	26	1.20 (0.74-1.93)	1.22 (0.74-1.99)	1.29 (0.78-2.13)
Q3	157	1.11 (0.87-1.42)	1.17 (0.90-1.52)	1.21 (0.90-1.61)	59	0.96 (0.65-1.41)	1.01 (0.67-1.51)	1.12 (0.72-1.77)
Q4	33	1.12 (0.75-1.67)	1.24 (0.81-1.89)	1.33 (0.82-2.16)	5	0.39 (0.15-0.98)	0.41 (0.16-1.07)	0.51 (0.18-1.43)
P trend		0.378	0.188	0.156		0.148	0.258	0.726
Bread								
Q1	118	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	37	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	92	0.92 (0.70-1.21)	0.95 (0.72-1.25)	0.95 (0.72-1.25)	45	1.36 (0.88-2.11)	1.36 (0.87-2.13)	1.37 (0.88-2.15)
Q3	81	0.99 (0.75-1.32)	1.06 (0.79-1.44)	1.08 (0.79-1.46)	27	0.95 (0.58-1.57)	0.95 (0.56-1.60)	0.97 (0.58-1.65)
Q4	65	0.78 (0.57-1.07)	0.88 (0.63-1.24)	0.93 (0.65-1.32)	34	1.21 (0.75-1.97)	1.18 (0.70-1.99)	1.25 (0.72-2.17)
P trend		0.168	0.593	0.824		0.814	0.936	0.757
Noodle								
Q1	93	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	36	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	91	0.92 (0.68-1.23)	0.92 (0.69-1.24)	0.92 (0.69-1.24)	34	0.81 (0.51-1.30)	0.85 (0.53-1.37)	0.85 (0.53-1.36)
Q3	87	0.93 (0.69-1.26)	0.96 (0.71-1.31)	0.95 (0.70-1.30)	26	0.64 (0.38-1.07)	0.70 (0.41-1.18)	0.69 (0.41-1.17)
Q4	85	0.94 (0.70-1.27)	1.01 (0.73-1.40)	1.02 (0.73-1.42)	47	1.21 (0.78-1.89)	1.38 (0.85-2.24)	1.39 (0.84-2.28)
P trend		0.843	0.763	0.752		0.155	0.067	0.071
Cereal								
Q1	78	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	38	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	99	1.21 (0.89-1.62)	1.27 (0.94-1.72)	1.30 (0.95-1.78)	31	0.74 (0.46-1.19)	0.78 (0.48-1.26)	0.83 (0.51-1.37)
Q3	97	1.18 (0.87-1.60)	1.29 (0.94-1.78)	1.33 (0.95-1.87)	33	0.76 (0.47-1.22)	0.84 (0.51-1.39)	0.91 (0.54-1.55)
Q4	82	1.00 (0.73-1.38)	1.16 (0.80-1.67)	1.21 (0.80-1.81)	41	0.93 (0.59-1.46)	1.09 (0.63-1.87)	1.24 (0.68-2.28)
P trend		0.773	0.604	0.538		0.982	0.580	0.340

Model 1: Multivariate adjusted for age (y, continuous), area (10), alcohol consumption (none; drinker: <150 or ≥150 g/ethanol/wk for women), smoking status (never, past, current: 1-19, 20-29, ≥30 cigarettes/day), BMI (<25, 25-26.9, 27-29.9, ≥30 kg/m^2), quartile of metabolic equivalent tasks (hours/day), history of diabetes mellitus (yes or no) colorectal screening (yes or no), menopausal status (yes or no, women only), use of exogenous female hormones (yes or no, women only), total energy intake (kcal/d, continuous), and red meat intake (g/d, quartile). Crude intake of rice, bread and noodles (g/d, quartile) were also mutually adjusted for. Separate model for energy-adjusted cereal: without rice, bread and noodles.

Model 2: Additionally adjusted for intakes (according to g/d, quartile) of energy-adjusted calcium, magnesium, vitamin B6, vitamin B12, folate, vitamin D, n-3 polyunsaturated fatty acids, and fiber.

Table 7: Hazard Ratio (HR) and 95% CI of proximal and distal colon cancer according to quartiles of rice, bread, noodle and cereal intake among men in the JPHC Study

	Men							
	Proximal colon				Distal colon			
	No. cases	Age-area HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	No. cases	Age-area HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Rice								
Q1	57	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	76	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	96	0.91 (0.65-1.26)	0.98 (0.70-1.38)	0.94 (0.66-1.34)	114	0.80 (0.60-1.07)	0.89 (0.66-1.21)	0.92 (0.67-1.26)
Q3	34	0.83 (0.53-1.28)	0.96 (0.61-1.53)	0.88 (0.53-1.45)	49	0.95 (0.65-1.38)	1.10 (0.74-1.64)	1.15 (0.74-1.77)
Q4	36	0.89 (0.57-1.37)	1.17 (0.70-1.95)	1.00 (0.55-1.81)	26	0.55 (0.35-0.87)	0.72 (0.43-1.21)	0.77 (0.42-1.39)
P trend		0.503	0.638	0.903		0.041	0.491	0.737
Bread								
Q1	91	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	108	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	63	1.18 (0.86-1.63)	1.26 (0.90-1.75)	1.24 (0.89-1.73)	60	0.93 (0.68-1.28)	1.02 (0.74-1.41)	1.02 (0.74-1.41)
Q3	31	0.91 (0.61-1.38)	1.01 (0.66-1.54)	0.98 (0.64-1.50)	42	0.99 (0.69-1.42)	1.15 (0.79-1.67)	1.15 (0.79-1.67)
Q4	38	0.94 (0.64-1.38)	1.07 (0.70-1.63)	1.01 (0.66-1.57)	55	1.03 (0.74-1.44)	1.24 (0.86-1.79)	1.24 (0.85-1.81)
P trend		0.590	0.930	0.877		0.792	0.223	0.238
Noodle								
Q1	60	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	68	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	54	1.43 (0.99-2.07)	1.45 (1.00-2.11)	1.48 (1.02-2.14)	64	1.43 (1.02-2.02)	1.47 (1.04-2.07)	1.46 (1.04-2.07)
Q3	60	1.23 (0.86-1.76)	1.25 (0.86-1.81)	1.27 (0.88-1.85)	66	1.19 (0.85-1.68)	1.21 (0.85-1.71)	1.20 (0.85-1.71)
Q4	49	1.06 (0.73-1.56)	1.10 (0.73-1.65)	1.12 (0.73-1.70)	67	1.29 (0.92-1.81)	1.31 (0.91-1.89)	1.32 (0.90-1.92)
P trend		0.876	0.978	0.964		0.324	0.355	0.350
Cereal								
Q1	53	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	66	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	56	1.08 (0.74-1.57)	1.15 (0.78-1.69)	1.13 (0.76-1.67)	73	1.12 (0.80-1.56)	1.22 (0.86-1.72)	1.23 (0.87-1.74)
Q3	63	1.13 (0.78-1.65)	1.26 (0.85-1.88)	1.22 (0.80-1.85)	62	0.92 (0.65-1.31)	1.05 (0.72-1.54)	1.08 (0.73-1.60)
Q4	51	0.88 (0.59-1.31)	1.04 (0.65-1.67)	0.98 (0.59-1.65)	64	0.95 (0.67-1.35)	1.17 (0.76-1.79)	1.22 (0.77-1.93)
P trend		0.464	0.920	0.882		0.542	0.654	0.564

Model 1: Multivariate adjusted for age (y, continuous), area (10), alcohol consumption (none; drinker: <150, 150-299, 300-449, or ≥450g ethanol/wk for men), smoking status (never, past, current: 1-19, 20-29, ≥30 cigarettes/day), BMI (<25, 25-26.9, 27-29.9, ≥30 kg/m^2), quartile of metabolic equivalent tasks (hours/day), history of diabetes mellitus (yes or no) colorectal screening (yes or no), total energy intake (kcal/d, continuous), and red meat intake (g/d, quartile). Crude intake of rice, bread and noodles (g/d, quartile) were also mutually adjusted for. Separate model for energy-adjusted cereal: without rice, bread and noodles.

Model 2: Additionally adjusted for intakes (according to g/d, quartile) of energy-adjusted calcium, magnesium, vitamin B6, vitamin B12, folate, vitamin D, n-3 polyunsaturated fatty acids, and fiber.

Table 8: Hazard Ratio (HR) and 95% CI of proximal and distal colon cancer according to quartiles of rice, bread, noodle and cereal intake among women in the JPHC Study

	Women							
	Proximal colon				Distal colon			
	No. cases	Age-area HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	No. cases	Age-area HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Rice								
Q1	66	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	42	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	24	0.91 (0.57-1.45)	0.92 (0.57-1.48)	0.94 (0.57-1.53)	21	1.41 (0.83-2.39)	1.48 (0.85-2.56)	1.52 (0.87-2.66)
Q3	89	1.11 (0.80-1.54)	1.11 (0.78-1.58)	1.18 (0.80-1.73)	61	1.34 (0.89-2.01)	1.46 (0.94-2.25)	1.52 (0.94-2.47)
Q4	24	1.39 (0.86-2.26)	1.45 (0.86-2.45)	1.66 (0.90-3.05)	5	0.55 (0.22-1.41)	0.64 (0.24-1.70)	0.68 (0.24-1.95)
P trend		0.208	0.196	0.139		0.884	0.571	0.480
Bread								
Q1	69	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	41	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	57	0.98 (0.69-1.40)	1.01 (0.71-1.45)	1.02 (0.71-1.46)	33	0.92 (0.58-1.46)	0.96 (0.60-1.54)	0.95 (0.60-1.52)
Q3	48	1.05 (0.72-1.52)	1.11 (0.75-1.64)	1.14 (0.77-1.70)	28	0.92 (0.57-1.51)	1.01 (0.61-1.68)	0.99 (0.59-1.66)
Q4	29	0.66 (0.42-1.03)	0.74 (0.46-1.19)	0.81 (0.49-1.34)	27	0.82 (0.49-1.36)	0.96 (0.55-1.67)	0.93 (0.52-1.66)
P trend		0.089	0.255	0.501		0.466	0.936	0.845
Noodle								
Q1	55	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	32	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	52	0.88 (0.60-1.29)	0.89 (0.60-1.31)	0.89 (0.60-1.31)	34	0.99 (0.61-1.61)	1.01 (0.62-1.64)	1.01 (0.62-1.65)
Q3	44	0.78 (0.52-1.17)	0.81 (0.53-1.22)	0.80 (0.53-1.22)	37	1.18 (0.73-1.91)	1.23 (0.75-2.02)	1.22 (0.74-2.01)
Q4	52	0.95 (0.65-1.40)	1.02 (0.67-1.56)	1.04 (0.68-1.61)	26	0.86 (0.51-1.45)	0.94 (0.53-1.65)	0.95 (0.54-1.69)
P trend		0.939	0.754	0.685		0.599	0.865	0.916
Cereal								
Q1	40	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	32	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	66	1.56 (1.05-2.31)	1.63 (1.09-2.44)	1.70 (1.13-2.57)	29	0.87 (0.53-1.45)	0.93 (0.56-1.56)	0.96 (0.56-1.62)
Q3	43	1.01 (0.65-1.56)	1.09 (0.69-1.72)	1.16 (0.72-1.87)	46	1.41 (0.89-2.23)	1.56 (0.95-2.55)	1.60 (0.95-2.69)
Q4	54	1.26 (0.83-1.91)	1.43 (0.88-2.34)	1.58 (0.92-2.71)	22	0.69 (0.40-1.20)	0.80 (0.42-1.52)	0.84 (0.42-1.68)
P trend		0.766	0.442	0.313		0.376	0.789	0.859

Model 1: Multivariate adjusted for age (y, continuous), area (10), alcohol consumption (none; drinker: <150 or ≥150 g/ethanol/wk for women), smoking status (never, past, current: 1-19, 20-29, ≥30 cigarettes/day), BMI (<25, 25-26.9, 27-29.9, ≥30 kg/m^2), quartile of metabolic equivalent tasks (hours/day), history of diabetes mellitus (yes or no) colorectal screening (yes or no), menopausal status (yes or no, women only), use of exogenous female hormones (yes or no, women only), total energy intake (kcal/d, continuous), and red meat intake (g/d, quartile). Crude intake of rice, bread and noodles (g/d, quartile) were also mutually adjusted for. Separate model for energy-adjusted cereal: without rice, bread and noodles.

Model 2: Additionally adjusted for intakes (according to g/d, quartile) of energy-adjusted calcium, magnesium, vitamin B6, vitamin B12, folate, vitamin D, n-3 polyunsaturated fatty acids, and fiber.

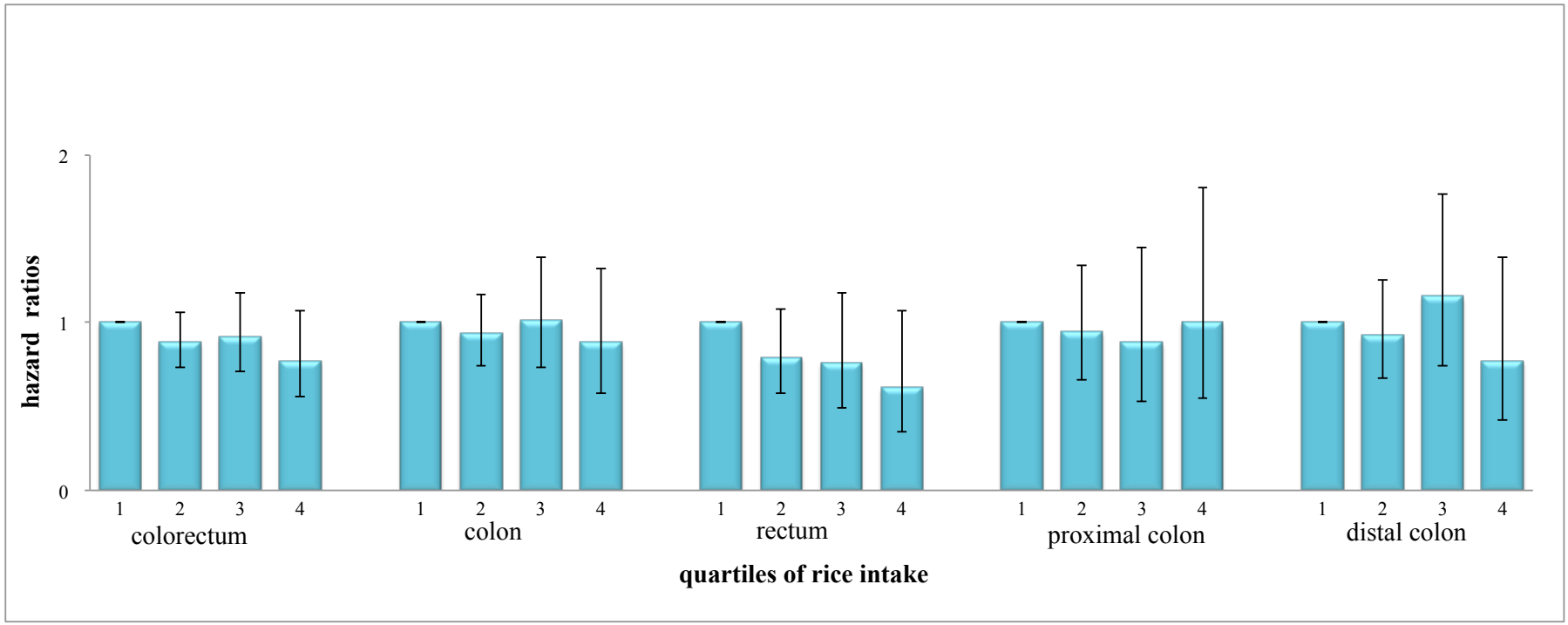

Figure 10: Overview of Hazard Ratio (HR) and 95% CI of colorectal cancer according to quartiles of rice among men in the JPHC Study

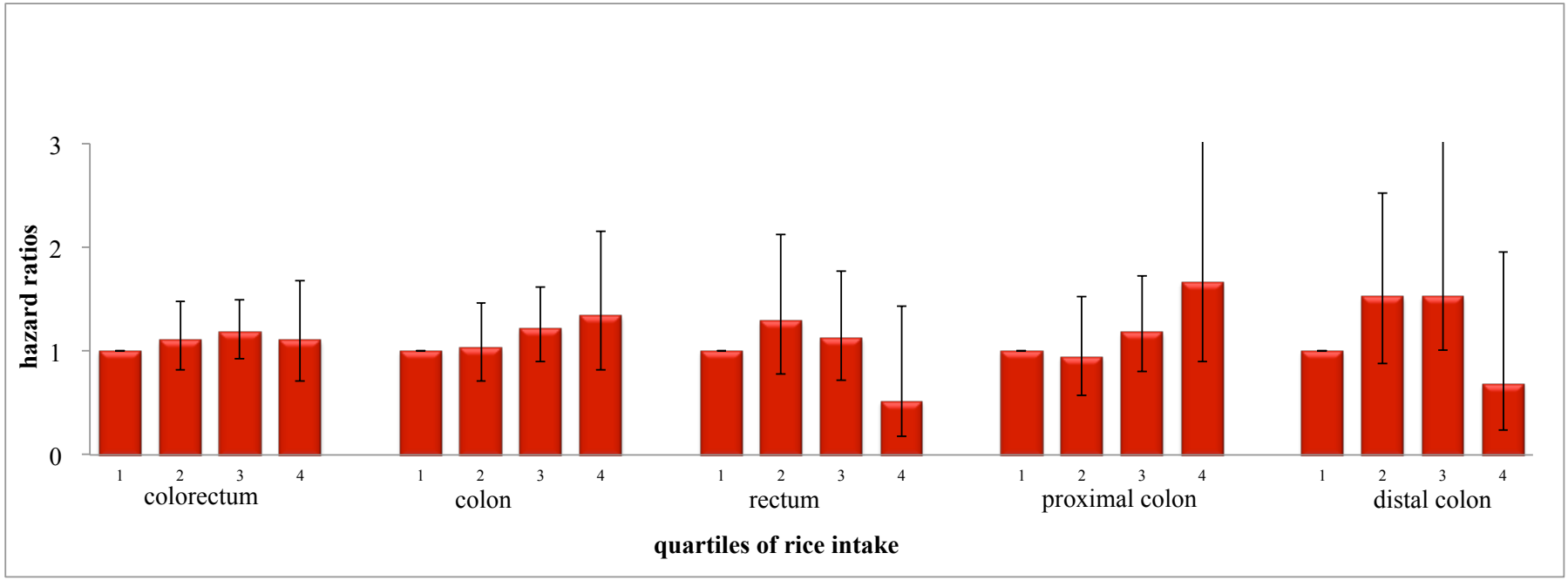

Figure 11: Overview of Hazard Ratio (HR) and 95% CI of colorectal cancer according to quartiles of rice by sex among women in the JPHC Study

Additional analyses by excluding intra mucosal/non-invasive cases did not change the results substantially (data not shown).

3.3. Colorectal cancer incidence by quartiles of bread, noodles and cereals

As shown in Tables 3-8, no significant association was found between the intake of bread and risk of colorectal cancer in men and women. Among women and colorectal cancer risk according to quartile of noodle and cereal intake there was also a lack of significant association. Among women, only the second lowest quartile of cereal intake in all three models showed a significant risk of proximal cancer 1.56 (95% CI, 1.05-2.31), 1.63 (95% CI, 1.09-2.44) and 1.70 (95% CI, 1.13-2.58) (Table 8).

3.4. Effect modification for major confounders

Additionally, effect modification was tested for rice and all covariates, aside from nutrients. No terms were significant for men, whereas we found a significant effect modification between rice and smoking, alcohol consumption, and BMI among women (*P* for interaction with rice was 0.004 for smoking, 0.02 for alcohol consumption and 0.02 for BMI) (Table 9).

Table 9: Effect modification in fully adjusted model according to intake of rice

	Men			Women		
Rice (categorical) with	HR	95% CI	*P*	HR	95% CI	*P*
Age	0.99	(0.98-1.00)	0.25	1.00	(0.99-1.02)	0.43
Smoking status						
Never	1.00			1.00		
Ever	0.98	(0.90-1.06)	0.59	0.69	(0.54-0.89)	0.004
Alcohol consumption						
Never	1.00			1.00		
Ever	0.97	(0.92-1.02)	0.27	0.79	(0.65-0.96)	0.02
Body Mass Index						
<25	1.00			1.00		
≥25	1.03	(0.99-1.06)	0.14	1.05	(1.01-1.09)	0.02
Metabolic equivalent tasks						
Quartile 1	1.00			1.00		
>Quartile 1	1.00	(0.94-1.07)	0.90	1.00	(0.92-1.08)	0.98
Past history of diabetes						
No	1.00			1.00		
Yes	1.13	(0.87-1.48)	0.35	1.21	(0.82-1.78)	0.33
CRC screening						
No	1.00			1.00		
Yes	0.94	(0.80-1.11)	0.49	0.90	(0.75-1.09)	0.29
Menopausal status						
No	−			1.00		
Yes	−	−	−	0.92	(0.72-1.17)	0.48
Exogenous hormone use						
No	−			1.00		
Yes	−	−	−	2.11	(0.92-4.89)	0.08

P for interaction

Hazard ratios of rice consumption among women were checked in models for smoking, alcohol and BMI. For both smoking and alcohol it was not possible to obtain the values for each quartile of rice as the number of cases in the smoking and regular alcohol consumption categories were too small especially in the highest quartile of rice intake. For BMI none of the results were significant.

Subgroup analyses stratifying by gender and smoking (never vs ever) and alcohol (non-regular vs. regular), BMI (<25 vs. ≥25), METS (Q1&Q2 vs. Q3&Q4), past history of diabetes mellitus (no vs. yes), were performed individually, but showed no significant colorectal cancer incidence risk difference by quartiles of rice consumption in these subcategories (data not shown).

3.5. Subgroup analyses by latitude according to intake of rice

Further subgroup analyses were carried out in addition to possible confounding factors. Table 10 presents the HRs and 95% CIs for colorectal cancer risk by quartile of rice stratified by latitude. For this sub-analysis the North/East public health centers were grouped together (Nihohe, Iwate; Yokote, Akita; Nagaoka, Niigata; Mito, Ibaraki; and Saku, Nagano) and compared with those in the South/West (Miyako, Okinawa; Chubo, Okinawa; Kamigoto, Nagasaki; Chuo-higashi, Kochi; and Suita, Osaka). Overall, results were not significant and did not differ by latitudinal grouping. Age-area only adjusted models had significant *P* trends in the South/West region with the highest vs. lowest quartile of rice 0.97 (95% CI, 0.65-1.46; *P* trend 0.05) and 1.07 (95% CI, 0.71-1.61; *P* trend 0.01) for men and women respectively.

Table 10: Hazard Ratio (HR) and 95% CI of colorectal cancer according to quartiles of rice intake by latitude in the JPHC Study

	Men							Women						
		Age-area		Model 1		Model 2			Age-area		Model 1		Model 2	
	N	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	N	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
NE														
Q1	112	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)	94	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
Q2	176	0.87	(0.71-1.06)	0.78	(0.63-0.95)	0.79	(0.64-0.97)	34	0.97	(0.79-1.19)	0.74	(0.50-1.10)	0.73	(0.49-1.10)
Q3	97	0.81	(0.67-0.98)	0.94	(0.77-1.16)	0.96	(0.77-1.20)	157	0.84	(0.69-1.02)	1.06	(0.81-1.40)	1.05	(0.77-1.42)
Q4	77	0.82	(0.64-1.04)	0.88	(0.66-1.16)	0.91	(0.66-1.26)	28	0.85	(0.66-1.10)	0.86	(0.55-1.36)	0.87	(0.51-1.46)
P			0.36		0.83		0.94			0.15		0.94		0.95
SW														
Q1	105	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)	80	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
Q2	162	1.37	(1.11-1.68)	1.20	(0.96-1.50)	1.20	(0.95-1.51)	37	1.39	(1.11-1.74)	1.49	(0.99-2.25)	1.63	(1.07-3.49)
Q3	31	0.81	(0.61-1.06)	0.95	(0.71-1.27)	0.94	(0.69-1.28)	59	0.91	(0.70-1.18)	1.11	(0.78-1.60)	1.30	(0.88-1.94)
Q4	17	0.97	(0.65-1.46)	1.05	(0.67-1.63)	1.02	(0.63-1.64)	10	1.07	(0.71-1.61)	1.19	(0.60-2.37)	1.52	(0.73-3.19)
P			0.05		0.38		0.39			0.01		0.56		0.17

NE=North/East: Nihohe, Iwate; Yokote, Akita; Nagaoka, Niigata; Mito, Ibaraki; and Saku, Nagano

SW=South/West: Miyako, Okinawa; Chubo, Okinawa; Kamigoto, Nagasaki; Chuo-higashi, Kochi; and Suita, Osaka

N=number of cases, *P* trend

4. DISCUSSION

4.1. Summary of findings

This is the first population-based study on the association between rice intake and colorectal cancer in Japan. Overall, we found that rice intake was not associated with colorectal cancer in both men and women. Similarly, bread, noodle and total cereal intake were not associated with colorectal cancer in the JPHC Study.

Among possible effect modifying variables rice and smoking, alcohol consumption, and BMI among women were significant. The subgroup analysis of main exposure factors was based on previous findings of the JPHC Study [19, 51, 83] suggesting possible differences in smoking, alcohol, BMI, METS, and past history of diabetes mellitus. For example Inoue et al. 2012 found ever smoker (RR 1.35 in men and 1.38 in women), alcohol drinker (1.64; 1.08), and BMI ≥25 (1.24; 1.17) differed from their respective counterparts [25]. However these subgroups showed no significant difference in risk of colorectal cancer according to quartile of rice intake between groups. Subgroup analysis was also performed by public health center in latitude groups, as latitude itself may be a risk of cancer [118]. These showed no significant differences.

4.2. Study contribution to contradictory patterns

Non-significant results are challenging to meaningfully discuss. However they are interesting and equally important to results showing strong associations. The present study contributes to the literature gap by addressing the contradictory patterns in Japan: trends of declining rice consumption [36] concurrent with increasing colorectal cancer incidence [8], while ecological observations suggest prefectures with high colorectal cancer mortality also consume lots rice [36-38]. The JPHC Study data were and continue to be robustly collected to account for possible biases as best as possible. While it is not possible to extrapolate these results to other countries, this study shows no consistent direction for the association of rice intake and colorectal cancer in Japanese men and women. The inconsistent pattern may not be completely overcome. However, the discussion below based on the findings seeks to disentangle the seemingly contradictory patterns by elaborating on gender and subsite differences.

Rice may represent dietary patterns, lifestyles and/or culture as mentioned in the introduction extending the discussion beyond rice intake in grams in relation to colorectal cancer risk. However, because factor or principal component analysis was not conducted in this study, it is not appropriate to draw conclusions based on this line of discussion. Some key findings in this field are worth noting: A previous JPHC Study paper identified a traditional Japanese diet as fish, miso soup, pickled vegetables, rice, salted fish and roe, (negative loading for bread and butter) and alcohol for men was

significantly associated with increased risk of gastric cancer [30]. The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study) noted a "rice/snack": rice, miso soup, cookies, orange juice (negative vegetables) suggesting a borderline positive association with stomach cancer among male Tokyoites [32]. The Ohsaki National Health Insurance grouped rice with a negative loading as part of the DFA (dairy, fruit and low alcohol diet), while the rice was not part of the "Japanese dietary pattern"[35]. A study in the southern part of the country characterized negative rice loading in combination with high bread, margarine and coffee loading as a "western" pattern [33, 34]. These two studies did not detect a traditional Japanese diet, but suggested high intake of white rice could deteriorate glucose metabolism and partially explain high prevalence of type 2 diabetes in Japan.

Rice may partially represent dietary patterns, however inconsistencies and differences exist, even within Japan as shown by the different patterns detected. Age, place of residence and occupation could be linked with rice consumption patterns and culture. With older Japanese presumably consuming more rice, those living in rural areas and possibly those in more agriculturally or traditionally oriented jobs.

Methodologically, JPHC Study data is superior to ecological observations. Survival analysis using cox proportional hazard models was used and combined with individual level rice intake in grams per day. Detailed colorectal cancer coding according to the

ICD-O-3 permitted stratified analysis by anatomical subsite. Japanese national nutritional data does not include proximal and distal colon cancer. The present study found some albeit non-significant subsite differences. There was an indication for a positive trend in proximal colon cancer in women, compared with distal colon cancer where no such relationship was suggested (Figure 10 and 11). Detailed comparisons between men and women were possible due to the large sample size and significant number of cases.

4.3. Sex differentials

In the present study all analyses were performed separately for men and women. Overall, age-standardized colorectal cancer incidence rates in the JPHC Study were twice as high in men compared to women, similar to 2007 Japan rates 63.4 and 35.9 per 100,000 respectively [119]. Our non-significant results hint at an inverse trend between rice intake and rectal cancer among men (Figure 10), mirror the findings of a Japanese case-control study in the southern part of the country suggesting that rice consumption is inversely associated with distal colon and rectal cancers [29]. A limitation to the aforementioned study however was the lack of stratification by sex, probably due to the relatively small number of cases.

The difference in risk by sex has also been indicated in previous studies, some studies indicated that diet-associated risk was more prominent in the proximal (right) colon cancer in women [26, 120, 121] while distal colon [26] and rectal cancer were more common among men [2, 17]. The current study accords with the aforementioned observation, suggesting a non-significant positive trend between increased rice intake and colorectal cancer incidence in women (Figure 11), specifically proximal colon cancer.

The sex differences found in the present study and international studies on diet and non-communicable diseases may offer some insights. There are biological differences between men and women relating to genetics [122] and metabolism for example. The behavioral differences might be equally important but are rarely considered in medical studies. Biological and social differences combined may have a cumulative affect on research, health at the individual level, systems and policy [122]. In general, chronic diseases such as cancer and CVD are more common among men, also true in the present study, while chronic disorders such as migraines are more common among women [122]. Health behavior, occupation safety are two examples affecting men's and women's health differently [122]. Specifically regarding colorectal cancer, McMichael and Potter suggested that the sex difference risk of proximal colon cancer may be due to behavioral differences such as diet and physical activity [121]. Consumption in the present study differs, with men consuming more rice and higher total energy for

example. Health behavior, alcohol and smoking, also greatly differed between men and women with 70-75% of men (Table 1) consuming more than 1g of alcohol per week compared to 15-24% of women (Table 2). However the same authors argued that sex differences in disease risk are probably due to biological differences according to specific physiology and organ functions [120].

Regarding the contradictory patterns of rice and colorectal cancer in Japan in relationship to the present study's results, a tentative non-significant inverse association was observed in men, specifically rectal cancer (Figure 10), whereas the non-significant results hinted at a positive association among women, particularly concerning cancer of the colon, proximal colon (Figure 11). National ecological trends appear contradictory, however when disentangled by subsite and sex these contradictions may represent the true association between rice and colorectal cancer risk in Japan.

A Japanese study in Miyagi prefecture found similar to our study, that colon cancer was more pronounced compared with rectal cancer from 1959-1997 [123]. Descriptive epidemiology in Caucasian populations showed that colorectal cancer incidence rates among women were higher under age 55, but this trend reversed in the older group [26, 94] to which the majority of our study belonged.

In-depth gender and colorectal cancer subsite specific research is needed to draw more precise conclusions. McMichael and Potter's 1985 hypothesis paper also emphasizes the importance of three pillars in conducting diet and colon cancer epidemiology: sex, age and anatomical subsite [26]. Their study for example found that total dietary energy intake in tertiles showed a moderate dose response to colon cancer risk among women while the relationship was weak among men [26].

4.4. Strengths and limitations of the study

The present study has several strengths [14]. Firstly, a large sample of individual level data from a general population with a high response rate and low loss to follow-up reduced selection bias. Within an average of 11 years of follow-up a sufficient number of cases were identified for analysis. Secondly, due to the prospective nature of the study, consumption data was collected before the diagnosis of colorectal cancer, reducing the possibility of recall bias. Thirdly, we used colorectal cancer incidence as an endpoint rather than death, as this more directly measures colorectal cancer risk [2]. Finally, Japan provided a most suitable setting for examining the association between rice and colorectal cancer, due to the food item in question being the most important staple in Japanese cuisine.

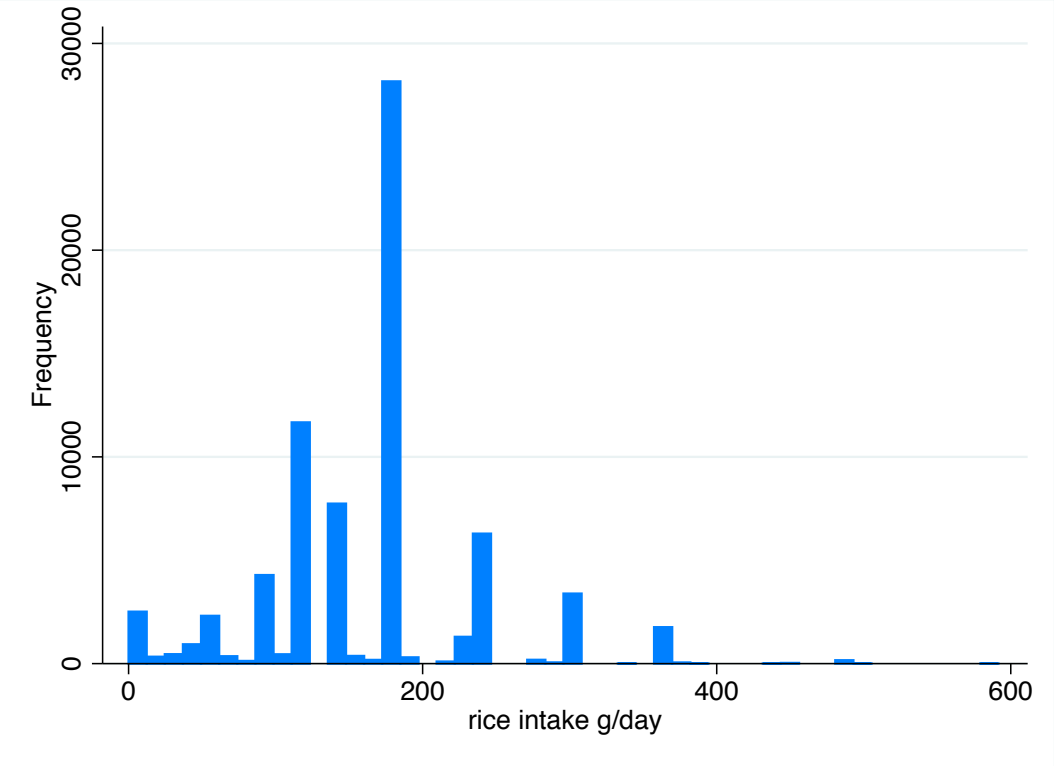

Figure 12 Rice intake for JPHC Study

There are however, several limitations in the present study. Firstly, while the FFQ has been validated and reflects long-term dietary intake in Japan [89], measurement error may persist. Also, changes in dietary habits during the study period may have led to misclassification of individual intake, which could distort results. At the time of data collection, however, we could not know the outcome of each participant, case or non-case. Therefore, the misclassification would be random across the study subjects, which would attenuate the true risk, if any. Secondly, despite adjusting for possible confounding factors in the analysis, including several nutrient and food items, remaining residual confounding may exist [14]. We could not adjust for additional geographic elements i.e. urban vs. rural; detailed family history of cancer; household

clustering effect; additional micronutrients and genetic markers. Each of these factors individually and cumulatively could affect the findings in relation to risk of colorectal cancer. Thirdly, we built quartiles of rice, which were imbalanced in the number of subjects due to several big peaks in the distribution. Especially, 15,000 men and 18,000 women had the same value of 182.7g, which could not be split (Figure 12). Finally, improvements in colorectal cancer diagnostics changed the quality of cancer registration, which may influence colorectal cancer incidence and mortality [123-126].

5. CONCLUSION

Our analysis of the Japan Public Health Center-based prospective Study suggests that the consumption of rice after adjusting for possible confounders does not have a substantial impact on the risk of colorectal cancer in Japanese men and women, particularly those living in non-metropolitan areas. Similarly, bread, noodle and overall cereal intake had little or no significant affect on risk of colorectal cancer in the JPHC Study.

The present study showed no substantial risk of colorectal cancer based on the consumption of carbohydrates: rice, bread, noodles and total cereal in Japan. Therefore, no specific policy conclusions may be drawn from this study. It is worthy to note that previous studies found an association between the glycemic index, glycemic load and colorectal cancer risk, which are heavily correlated with carbohydrate consumption, especially rice in the context of Japan and other Asian countries. However even among and within Asian countries the staple food varies, for example in parts of India nan (bread) is the staple [127]. Even when comparing rice, intakes vary. In Bangladesh for example 60-70% of carbohydrate intake comes from rice [128]. Studies concluding that diets with a high glycemic index or glycemic load may be detrimental to the development of chronic diseases are misleading with the results remaining elusive. This study cannot concur with suggestions to curb diets to achieve lower glycemic index and load.

More meta-analyses and pooled studies, especially in the Asian context are needed to confidently interpret these results. The Asian Cohort Consortium for example could pool results from the Shanghai Women's Health Study, Shanghai Men's Health Study, the JPHC Study etc., for a larger total sample and enable direct country comparison within the region. Larger pooled data would allow for even more differentiated/ stratified analyses such exploring the association between the very highest group of rice and bread intake and colorectal cancer. In the JPHC Study stratified analyses for individual noodle food items could be performed. Soba for example represents a healthy food while the fat and salt content in ramen are high. Intriguing though it may be to explore factors outside of the western diet to explain the cause of colorectal cancer incidence increase in Japan after WWII, our study barely found a significant association. After careful analysis of the exposure and outcome, rice intake and the risk of colorectal cancer, from age-area only adjusted to two appropriate multivariable adjusted models, the findings basically remained unchanged - no substantial association either between rice or non-rice cereals or total cereal intake with the risk of colorectal cancer in the JPHC Study sample. The pattern for Japanese men and women by colorectal subsite was slightly different, but in line with previous research on different dietary exposures and the risk of colorectal cancer. For men, a slight inverse non-significant trend between rice intake and colorectal cancer, specifically rectal cancer became apparent. While for women a non-significant association between rice and risk of colon, particularly proximal colon cancer was observed.

Colorectal cancer incidence remains high globally, especially in Japan. To date only about half can be explained by risk factors such as tobacco smoking, alcohol consumption, high body mass index and physical inactivity in men and only around 10% in women [25]. Colorectal cancer is partially an environmental disease, which would make a portion of new cases theoretically preventable by avoiding established risk factors. More research on possible genetic risk and gene-environment interactions is needed. This study, within the Japanese non-metropolitan setting, has shown that there is overall no substantial risk of developing colorectal cancer and subsites based on consumption of rice, neither a hazard, nor a protective factor. In a way this is a relief, Japanese should continue to enjoy their staple carbohydrate consumed with many different dishes. In the meantime, we as researchers can look to other potential risk factors

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Appendix A: Food Frequency Questionnaire (relevant pages)

Health Promotion Questionnaire

If you found an error in your name or address, please correct it with a red pen.

The Ministry of Health and Welfare: The Japan Public Health Center-based prospective Study on Cancer and Cardiovascular Disease Research Group

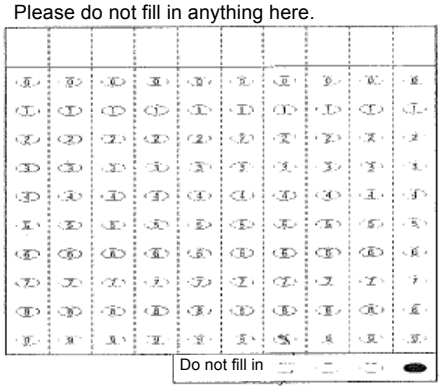
National Cancer Center

National Cardiovascular Center

We may call to ask you some questions regarding the contents of what you have filled in. Please provide your phone number below if you do not mind.

☎ ——

Please do not fill in anything here.



Before starting the questionnaire

The Epidemiology Research Group of the Ministry of Health, Labor and Welfare is working on research on “How do I prevent adult illnesses such as cancer, stroke, myocardial infarction, etc.?” In this context, we carried out the “Health Promotion Questionnaire” from 1990 to 1991 targeting people who were born from 1930 through 1949 who live in the cities, towns and villages of five health center districts throughout the nation.

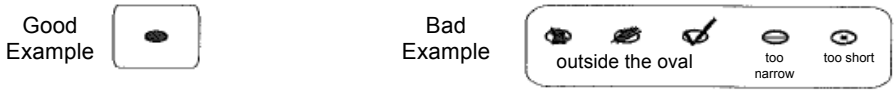
Five years have passed since the survey, and we are carrying out a second questionnaire to find out whether there have been any changes in lifestyle or health status of people during this interval, and also details about the state of your dietary life. We would like to ask your cooperation now that you understand the background of this survey.

If you are willing to participate this time, please read the “Instructions on How to Filli in the Questionnaire” below and answer the questions beginning on the following page.

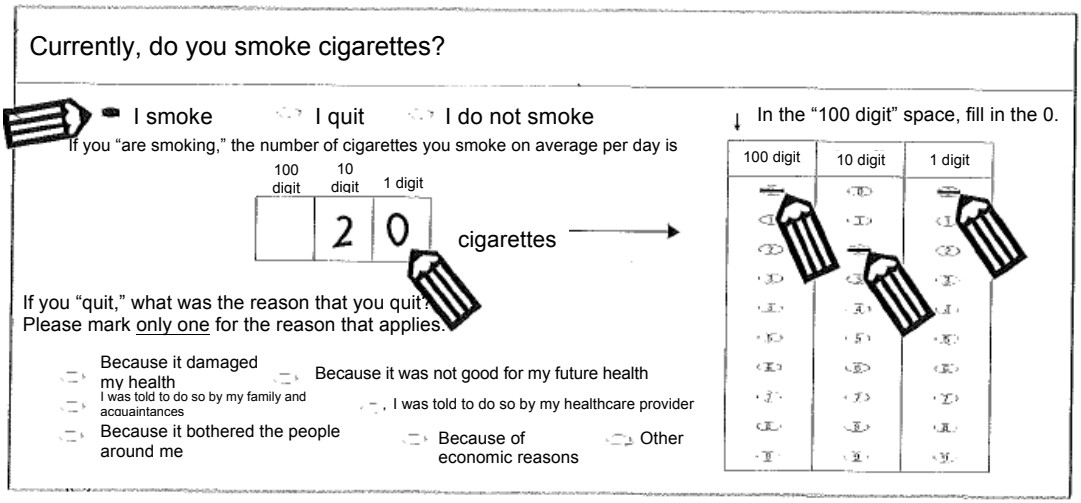
Instructions on How to Fill in the Questionnaire

1. As much as possible, please fill in this questionnaire by yourself.
2. Please fill in the given space (the oval circles) that apply with a black pencil, or enter a number of letter in the box. If you choose “Other” in the multiple choice selections, please fill in specific details in the parentheses.
3. Please use an HB, B or H graphite pencil.
4. Please do not use a fountain pen or ballpoint pen.
5. If you have any corrections, please erase them entirely with an eraser.
6. Please do not fill in anything in the blank spaces.

(example for filling in the mark)



For example, please fill it in as shown below if you currently smoke cigarettes, and you smoke 20 cigarettes on average per day.

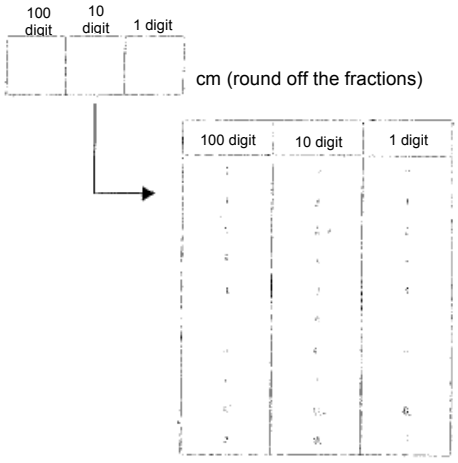


What month is it today?

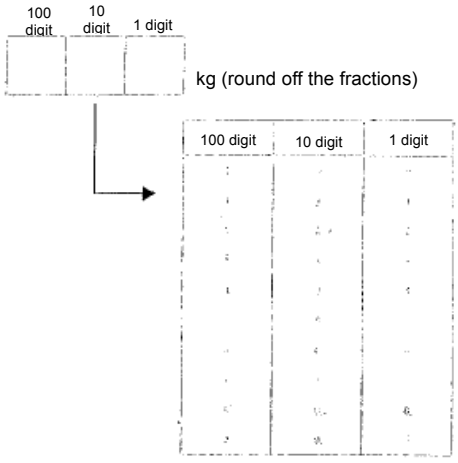
○January ○February ○March ○April ○May ○June
○July ○August ○September ○October ○November ○December

What is your gender? ○Male ○Female

About how tall are you currently?



About how much do you weigh currently?



We are going to ask you about “rice (cooked rice).”

About what size rice bowl do you eat with?
○Small rice bowl ○Normal rice bowl ○Donburi large rice bowl

About how many bowls do you eat in 1 day, combining breakfast, lunch and dinner?
○Less than 1 bowl ○1 bowl ○2 bowls ○3 bowls 4 bowls
○5 bowls ○6 bowls ○7 - 9 bowls ○10 bowls or more

Do you eat vitamin-enriched rice?
○No ○Yes

Do you mix in wheat or millet or Japanese hie?
○I do notmix it in ○I sometimes mix it in ○I always mix it in

We are going to ask you about “miso soup.”

About how frequently do you eat it?
○I hardly ever eat it ○1 - 3 days a month ○1 - 2 days a week ○3 - 4 days a week
○5 - 6 days a week ○I eat it every day

About how many cups do you eat in 1 day, combining breakfast, lunch and dinner?
○Less than 1 cup ○1 cup ○2 cups ○3 cups ○4 cups
○5 cups ○6 cups ○7 - 9 cups ○10 cups or more

How do you season it?
○Fairly diluted ○Normal ○Fairly thick

Currently, do you smoke cigarettes?

I smoke I quit I do not smoke

If you "are smoking," the number of cigarettes you smoke on average per day is

100 digit | 10 digit | 1 digit

cigarettes →

100 digit	10 digit	1 digit

If you "quit," what was the reason that you quit?
Please mark only one for the reason that applies.

- Because it damaged my health
- Because it was not good for my future health
- I was told to do so by my family and acquaintances
- I was told to do so by my healthcare provider
- Because it bothered the people around me
- Because of economic reasons
- Other

How frequently do you drink?

- I hardly ever drink
- 1 - 3 days a month
- 1 - 2 days a week
- 3 - 4 days a week
- 5 - 6 days a week
- I drink every day

Please choose the most usual combination that you drink in one day.

(Example) If normally after drinking one large bottle of beer you drink 2 go of Japanese sake, in the "Beer" area fill in "1 bottle" and in the "Japanese Sake" area fill in "2 go," and in the "Shochu or Awamori," "Whiskey," and "Wine" areas, fill in "I do not drink."

Japanese Sake 1 go (180ml)	I do not drink	less than 0.5 go	1 go	2 go	3 go	4 go	5 - 6 go	7 go or more
Shochu or Awamori 1 go (180ml)	I do not drink	less than 0.5 go	1 go	2 go	3 go	4 go	5 - 6 go	7 go or more
*Beer Large bottle (633ml)	I do not drink	less than 0.5 bottle	1 bottle	2 bottles	3 bottles	4 bottles	5 - 6 bottles	7 bottles or more
Whiskey Single (30ml)	I do not drink	less than 0.5 glass	1 glass	2 glasses	3 glasses	4 glasses	5 - 6 glasses	7 bottles or more
Wine Glass (100ml)	I do not drink	less than 0.5 glass	1 glass	2 glasses	3 glasses	4 glasses	5 - 6 glasses	7 bottles or more

*Please make the conversion at medium bottle or 500ml can, 0.8 of a bottle; small bottle or 350ml can, 0.6 of a bottle

In the past 5 years (from January 1, 1990 to present), have you been told by your healthcare provider that you have the following illness(es), and you had the following surgery(ies)? Please mark all that apply.

Disease

Stroke	Myocardial Infarction	Angina Pectoris	Diabetes
Gout	Cataracts	Gall Stones	Urethral Stones or Kidney Stones
Stomach Ulcers	Duodenal Ulcers	Stomach Polyps	Colon Polyps Chronic Hepatitis or Cirrhosis of the Liver
Stomach Cancer	Colon Cancer	Liver Cancer	Lung Cancer
Breast Cancer	Uterine Cancer	Other Cancer → Site [ ]	

Mark Not Necessary

Surgery

Stomach	Colon	Gall Stones	
Ovaries	Lung	Mammary glands	other → Site [ ]

Mark Not Necessary

Questions about Your Dietary Life

Now some questions about your diet will follow.

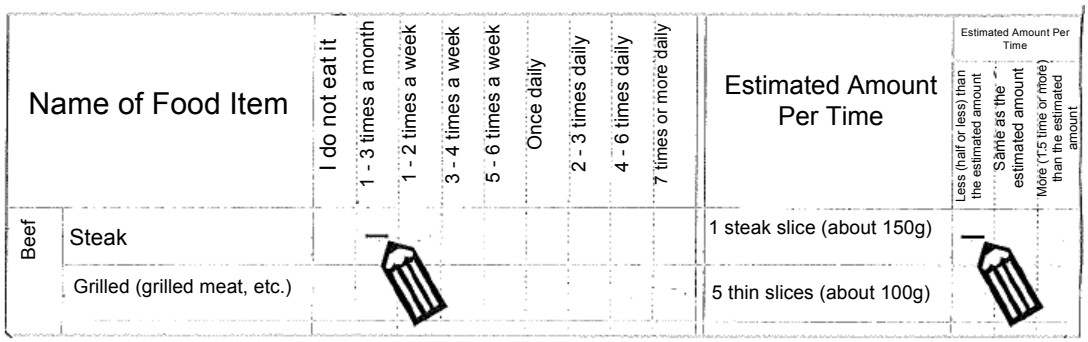
Recalling your diet over the past one year, please answer with average frequencies and amounts.

If you answer all the items, a detailed nutritional calculation of your normal dietary life can be made, so we will be able to report to each of you individually at a later date whether you have a nutritional balance, or whether your vitamins are enough, etc.

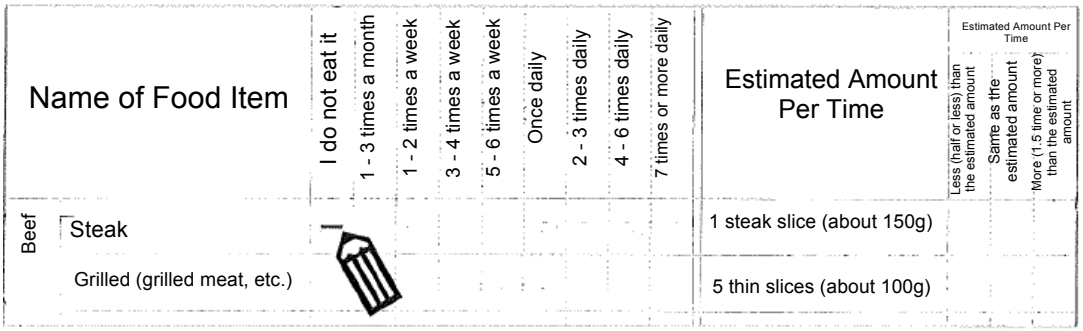
There are a lot of questions, and it this may be difficult for you, but we ask you to please complete it to the end.

Example

If you eat beef steak about 2 times a month, and the amount you eat per time is about half a steak, then fill it in as follows.



If you hardly ever eat beef steak (less than once a month), fill it in as follows.



Do not fill in anything in the estimated amount.

Recalling your diet over the past one year, please fill in average frequencies and amounts.

Name of Food Item		I do not eat it	1 – 3 times a month	1 – 2 times a week	3 – 4 times a week	5 – 6 times a week	Once daily	2 – 3 times daily	4 – 6 times daily	Estimated Amount Per Time	Estimated Amount Per Time		
											Less (half or less) than the estimated amount	Same as the estimated amount	More (1.5 time or more) than the estimated amount
Beef	Steak									1 steak slice (about 150g)			
	Grilled (grilled meat, etc.)									5 thin slices (about 100g)			
	Stewed (curry or stew, etc.)									3 pieces 2 - 3cm-diced (about 50g)			
Pork	Stir-Fried (vegetable stir-fry, etc.)									3 thin slices (about 60g)			
	Fried (port cutlet, etc.)									1 pork cutlet (about 100g)			
	Stewed (curry or stew, etc.)									3 pieces 2 - 3cm-diced (about 50g)			
	Boiled (boiled kakuni or Okinawan name: rafty, etc.)									2 slices (about 60g)			
	Soups (pork soup or Okinawan name: chumi soup, etc.)									2 thin slices (about 40g)			
	Pork liver (Nirareba stir-fry, etc.)									2 slices (about 40g)			
Chicken	Grilled (yakitori, etc.)									2 skewers of yakitori (about 70g)			
	Fried (karaage, etc.)									3 pieces (about 50g)			
	Chicken liver (yakitori, etc.)									1 skewer of yakitori (about 30g)			
Roast Ham										1 normal slice (about 15g)			
Wieners and Sausages										2 pieces (about 30g)			
Bacon										1 strip (about 20g)			
Canned Luncheon Meet										1/8 can (about 40g)			
Milk										1 200cc-glass			
Eggs										1 medium (about 50g)			
Cheese										1 slice of sliced cheese (about 20g)			
Yogurt										1 container (about 120g)			
Salted cod, salted mackerel, salted salmon										1 slice of fish meat (about 70g)			
Dried fish (open dried flavor)										1 piece (about 50g)			

Recalling your diet over the past one year, please fill in average frequencies and amounts.

Bread types (including pastries also)									1 piece of 6 slices (about 60g)			
Udon									1 donburi bowlful (about 250g)			
Soba									1 donburi bowlful (about 200g)			
Okinawa soba									1 donburi bowlful (about 200g)			
Ramen									1 donburi bowlful (about 220g)			
Mochi cakes									1 commercially marketed cake (about 50g)			
Japanese confections (Daifuku, manju)									1 confection (about 70g)			
Cakes									1 slice small cake (about 70g)			

Do not fill in

Usually per day, about how many hours do you move your body including work?			
In physical labor and extreme sports?	None	Less than 1 hour	1 hour or more
Time sitting?	3 hours or less	3 - 8 hours	8 hours or more
Time walking or standing?	Less than 1 hour	1 - 3 hours	3 hours or more

About how often do you have the opportunity to play sports or exercise outside of work?				
Hardly ever	1 - 3 times a month	1 - 2 times a week	3 - 4 times a week	Almost every day

Do not fill in

We are asking these only of women.

Currently, do you take female hormone medications? ○ I do not take them ○ I do take them

Currently, do you have menses (menstruation)?

○ I do ○ I have had menopause naturally ○ I have had menopause surgically, etc.

For persons who have had menopause, at what age did you have menopause?

○ Age 39 or under ○ Age 40 - 44 ○ Age 45 - 49 ○ Age 50 - 54 ○ Age 55 - 59 ○ Age 60 or over

Who filled this in?	○ Self ○ Representative

This is the end. We would appreciate it if you would check once more that you have not omitted anything. Thank you very much for your cooperation spending a long time on this.

Appendix B: Ethical Approval

独立行政法人国立がん研究センター研究倫理審査様式集 20130401

（様式６-1）

2013 年　8 月　6 日

研究倫理審査委員会結果通知書

独立行政法人国立がん研究センター理事長　殿

独立行政法人国立がん研究センター研究倫理審査委員会委員長

研究計画に関する申請あるいは報告について、当センターの規程に基づき（ 審査 ・ 判断 ）を行い、以下のとおり判定した。

研究課題番号	13-021		
研究課題名	多目的コホート研究(JPHC Study)		
研究責任者	がん予防・検診研究センター　センター長 津金昌一郎		
適用となる倫理指針	☐ 臨床研究に関する倫理指針　☑ 疫学研究に関する倫理指針 ☐ ヒトゲノム・遺伝子解析研究に関する倫理指針		
研究実施計画書等に関する情報	（申請の種別が①②③の場合に記載） 研究実施計画書の作成日：2013 年　7 月　22 日　第　2　版（バージョン） 説明同意文書の作成日：　年　月　日　第　版（バージョン）		
申請/報告の種別	☐ ①研究計画の新規申請　☑ ②研究計画の変更申請 ☐ ③実施状況報告　☐ ④安全性情報に関する報告 ☐ ⑤倫理指針に関する重大な不適合等に関する報告 ☐ ⑥その他 ＿＿＿＿＿＿		
審査方法・判断方法	☐ 通常（合議）審査（委員会開催日：　年　月　日） ☑ 迅速審査（適用条件：規程 14 条 1 号 1 項軽微な変更） ☐ 研究倫理審査委員会委員長決裁 ☐ あらかじめ指名する者による審査不要の判断※		
委員会判定日（上記※の場合を除く）	2013 年 8 月 6 日	判定	☑承認　☐条件付き承認　☐却下 ☐保留（継続審査）　☐差し戻し ☐非該当　☐その他 ＿＿＿＿＿＿
付帯条件・勧告			
判定が承認以外の場合の理由、その他の意見			
備考	研究計画は、倫理的及び科学的並びに実施可能性からみて、問題ないと判断されるので、承認する。		

（様式６-２）

２０１３年０８月２０日

研究許可申請に関する指示・決定通知書

研究責任者（申請者）　殿

独立行政法人国立がん研究センター理事長

貴殿から申請のあった上記の研究について、以下のとおり決定したので、通知する。

判定	☑ 許可　☐ 不許可　☐ 差し戻し　☐ 非該当 ☐ その他 ＿＿＿＿＿＿
当センターにおける研究期間	自：1990 年　4 月　1 日 至：2024 年　3 月　31 日