of an enzyme deficiency of aldehyde dehydrogenase 2 (ALDH2),[36,37] which is responsible for detoxifying acetaldehyde in ethanol metabolism. In this regard, a previous study reported no effect modification by genetic polymorphism of ALDH2.[39]

Consistent with a previous study,[4] we found little evidence of a statistical interaction between smoking status and alcohol intake on the development of breast cancer, although we previously reported a substantial association between smoking and premenopausal breast cancer risk in our cohort.[67]

The major strength of our study is its prospective population-based cohort design. Our large sample size and repeated measurement of exposure information over a long follow-up period likely aided the precision of our risk estimate. Differential recall bias was ruled out because exposure information was collected before diagnosis. Low percentages of DCN and DCO suggested that misclassification of disease was unlikely, and if present would have tended to be non-differential between cases and non-cases, which would have attenuated the observed risk toward null.

Several limitations of the study also warrant mention. Because alcohol intake and other epidemiological information were estimated on the basis of self-reported questionnaires, a degree of measurement error was inevitable. The misclassification of alcohol consumption and lack of quantitative evaluation of alcohol intake among occasional drinkers in the questionnaire might have lead to fewer drinkers being classified as having a moderate level of alcohol consumption. In consequence, the impact of a moderate level of alcohol consumption on breast cancer risk could not be clearly evaluated, unlike the case of previous studies.[57] However, our FFQ-based estimates of alcohol consumption have been validated repeatedly.[43,44] The study population in the current study tended to have a low prevalence of alcohol drinkers and this weakened the statistical power to detect the association. Nevertheless, we found a statistically significant positive association between excessive alcohol intake (>150 g ethanol/week) and an increased risk of breast cancer. We could not rule out the possibility of uncontrolled confounding. For instance, our data provided no information on the duration or type of exogenous estrogens used. However, given the internal consistency of our results across different stratifications, residual confounding may be unlikely. Nevertheless, our subgroup analyses showed largely null findings. The lack of effect modification by the use of exogenous estrogens or other factors may be explained by the lack of statistical power in the present study due to the small number of cases. Further, our results may have been affected by selection bias due to unknown receptor status of approximately half of the cases or by chance due to the large number of subgroup analyses. Although our results for ER/PR unknown tumors showed a similar positive trend to the result of overall and ER+ tumors, our results, particularly for ER-negative tumors among past drinkers, should be carefully interpreted.

In conclusion, this population-based prospective study found that alcohol consumption was positively associated with an increased risk of breast cancer in a Japanese population, as it is among Western populations. From a public health point of view, our findings are important because extreme alcohol drinking is avoidable. The impact of alcohol on breast cancer risk was not modified by menopausal status, exogenous estrogen use, intake of dietary isoflavones or folate, BMI, alcohol-induced facial flushing or smoking status. With regard to isoflavones, however, our present data took no account of supplement use, but rather only the intake obtainable from natural food products in the general Japanese diet. Further research needs to determine the generalizability of our results to other populations, with particular attention to the supplementation of isoflavones as a substitute for exogenous hormones, and to clarify the mechanisms of alcohol-mediated carcinogenesis in consideration of tumor receptor status as well as genetic variation.

Acknowledgements

The authors thank all staff members in each study area and in the central offices for their cooperation and technical assistance. They also thank the Iwate, Aomori, Ibaraki, Niigata, Osaka, Kochi, Nagasaki and Okinawa Cancer Registries for their provision of incidence data. R.S. received a research resident fellowship from the Foundation for Promotion of Cancer Research (Japan) for the 3rd term Comprehensive 10-year Strategy for Cancer Control.

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References

1. Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Bouvard V, Altieri A, Cogliano V. Carcinogenicity of alcoholic beverages. *Lancet oncol* 2007;8:292–3.
2. IARC. Preamble to the IARC monographs on the evaluation risks to humans. Available at: http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf, ed. Accessed March 2, 2007.
3. Research WCRFAIfC. Food, nutrition, physical activity, and the prevention of cancer: a global perspective ed. Washington, DC: AICR, 2007.
4. Hamajima N, Hirose K, Tajima K, Rohan T, Calle EE, Heath CW, Jr, Coates RJ, Liff JM, Talamini R, Chantarakul N, Koetsawang S, Rachawat D, et al. Alcohol, tobacco and breast cancer—collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. *Br J Cancer* 2002;87:1234–45.
5. Suzuki R, Orsini N, Mignone L, Saji S, Wolk A. Alcohol intake and risk of breast cancer defined by estrogen and progesterone receptor status—a meta-analysis of epidemiological studies. *Int J Cancer* 2008;122:1832–41.
6. Matsuda T, Marugame T, Kamo K, Katanoda K, Ajiki W, Sobue T. Cancer incidence and incidence rates in Japan in 2002: based on data from 11 population-based cancer registries. *Jpn J Clin Oncol* 2008;38:641–8.
7. National Health and Nutrition Examination Survey. Current status of the nations health and nutrition in Japan, 2004 edn. Tokyo, Japan: Daiich Publisher, 2006.

8. Iwasaki M, Otani T, Inoue M, Sasazuki S, Tsugane S. Body size and risk for breast cancer in relation to estrogen and progesterone receptor status in Japan. *Ann Epidemiol* 2007;17:304–12.
9. Iwasaki M, Otani T, Inoue M, Sasazuki S, Tsugane S. Role and impact of menstrual and reproductive factors on breast cancer risk in Japan. *Eur J Cancer Prev* 2007;16:116–23.
10. The Ministry of Health Law. Dynamic statistics of the population. Available at: http://www.mhlw.go.jp/toukei/saikin/hw/jinkou/geppo/nengai08/index.html. Accessed August 8, 2009.
11. Nagata C, Hu YH, Shimizu H. Effects of menstrual and reproductive factors on the risk of breast cancer: meta-analysis of the case-control studies in Japan. *Jpn J Cancer Res* 1995;86:910–5.
12. Nagata C, Mizoue T, Tanaka K, Tsuji I, Wakai K, Inoue M, Tsugane S. Alcohol drinking and breast cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Jpn J Clin Oncol* 2007;37:568–74.
13. Lin Y, Kikuchi S, Tamakoshi K, Wakai K, Kondo T, Niwa Y, Yatsuya H, Nishio K, Suzuki S, Tokudome S, Yamamoto A, Toyoshima H, et al. Prospective study of alcohol consumption and breast cancer risk in Japanese women. *Int J Cancer* 2005;116:779–83.
14. Fan S, Meng Q, Gao B, Grossman J, Yadegari M, Goldberg ID, Rosen EM. Alcohol stimulates estrogen receptor signaling in human breast cancer cell lines. *Cancer Res* 2000;60:5635–9.
15. Singletary KW, Frey RS, Yan W. Effect of ethanol on proliferation and estrogen receptor-alpha expression in human breast cancer cells. *Cancer Lett* 2001;165:131–7.
16. Reichman ME, Judd JT, Longcope C, Schatzkin A, Clevidence BA, Nair PP, Campbell WS, Taylor PR. Effects of alcohol consumption on plasma and urinary hormone concentrations in premenopausal women. *J Natl Cancer Inst* 1993;85:722–7.
17. Dorgan JF, Baer DJ, Albert PS, Judd JT, Brown ED, Corle DK, Campbell WS, Hartman TJ, Tejpar AA, Clevidence BA, Giffen CA, Chandler DW, et al. Serum hormones and the alcohol-breast cancer association in postmenopausal women. *J Natl Cancer Inst* 2001;93:710–5.
18. Gavaler JS, Rosenblum E. Exposure-dependent effects of ethanol on serum estradiol and uterus mass in sexually mature oophorectomized rats: a model for bilaterally ovariectomized-postmenopausal women. *J Stud Alcohol* 1987;48:295–303.
19. Ginsburg ES, Walsh BW, Shea BF, Gao X, Gleason RE, Barbieri RL. The effects of ethanol on the clearance of estradiol in postmenopausal women. *Fertil Steril* 1995;63:1227–30.
20. Feron VJ, Til HP, de Vrijer F, Woutersen RA, Cassee FR, van Bladeren PJ. Aldehydes: occurrence, carcinogenic potential, mechanism of action and risk assessment. *Mutat Res* 1991;259:363–85.
21. Ristow H, Seyfarth A, Lochmann ER. Chromosomal damages by ethanol and acetaldehyde in *Saccharomyces cerevisiae* as studied by pulsed field gel electrophoresis. *Mutat Res* 1995;326:165–70.
22. Brooks PJ. DNA damage. DNA repair, and alcohol toxicity—a review. *Alcohol Clin Exp Res* 1997;21:1073–82.
23. Seitz HK, Stickel F. Molecular mechanisms of alcohol-mediated carcinogenesis. *Nat Rev* 2007;7:599–612.
24. Dumitrescu RG, Shields PG. The etiology of alcohol-induced breast cancer. *Alcohol* 2005;35:213–25.
25. Yoo KY, Tajima K, Miura S, Takeuchi T, Hirose K, Risch H, Dubrow R. Breast cancer risk factors according to combined estrogen and progesterone receptor status: a case-control analysis. *Am J Epidemiol* 1997;146:307–14.
26. Nichols HB, Trentham-Dietz A, Love RR, Hampton JM, Hoang Anh PT, Allred DC, Mohsin SK, Newcomb PA. Differences in breast cancer risk factors by tumor marker subtypes among premenopausal Vietnamese and Chinese women. *Cancer Epidemiol Biomarkers Prev* 2005;14:41–7.
27. Baglietto L, English DR, Gertig DM, Hopper JL, Giles GG. Does dietary folate intake modify effect of alcohol consumption on breast cancer risk? Prospective cohort study. *BMJ* 2005;331:807.
28. Sellers TA, Vierkant RA, Cerhan JR, Gapstur SM, Vachon CM, Olson JE, Pankratz VS, Kushi LH, Folsom AR. Interaction of dietary folate intake, alcohol, and risk of hormone receptor-defined breast cancer in a prospective study of postmenopausal women. *Cancer Epidemiol Biomarkers Prev* 2002;11:1104–7.
29. Zhang SM, Hankinson SE, Hunter DJ, Giovannucci EL, Colditz GA, Willett WC. Folate intake and risk of breast cancer characterized by hormone receptor status. *Cancer Epidemiol Biomarkers Prev* 2005;14:2004–8.
30. Larsson SC, Bergkvist L, Wolk A. Folate intake and risk of breast cancer by estrogen and progesterone receptor status in a Swedish cohort. *Cancer Epidemiol Biomarkers Prev* 2008;17:3444–9.
31. Nielsen NR, Gronbaek M. Interactions between intakes of alcohol and postmenopausal hormones on risk of breast cancer. *Int J Cancer* 2008;122:1109–13.
32. Suzuki R, Ye W, Rylander-Rudqvist T, Saji S, Colditz GA, Wolk A. Alcohol and postmenopausal breast cancer risk defined by estrogen and progesterone receptor status: a prospective cohort study. *J Natl Cancer Inst* 2005;97:1601–8.
33. Chen WY, Colditz GA, Rosner B, Hankinson SE, Hunter DJ, Manson JE, Stampfer MJ, Willett WC, Speizer FE. Use of postmenopausal hormones, alcohol, and risk for invasive breast cancer. *Ann Intern Med* 2002;137:798–804.
34. Adlercreutz H. Phyto-oestrogens and cancer. *Lancet Oncol* 2002;3:364–73.
35. Wolff PH. Ethnic differences in alcohol sensitivity. *Science* 1972;175:449–50.
36. Shibuya A, Yasunami M, Yoshida A. Genotype of alcohol dehydrogenase and aldehyde dehydrogenase loci in Japanese alcohol flushers and nonflushers. *Hum Genet* 1989;82:14–6.
37. Takeshita T, Morimoto K, Mao X, Hashimoto T, Furuyama J. Characterization of the 3 genotypes of low Km aldehyde dehydrogenase in a Japanese population. *Hum Genet* 1994;94:217–23.
38. Druesne-Pecollo N, Tehard B, Mallet Y, Gerber M, Norat T, Hercberg S, Latino-Martel P. Alcohol and genetic polymorphisms: effect on risk of alcohol-related cancer. *Lancet Oncol* 2009;10:173–80.
39. Choi JY, Abel J, Neuhaus T, Ko Y, Harth V, Hamajima N, Tajima K, Yoo KY, Park SK, Noh DY, Han W, Choe KJ, et al. Role of alcohol and genetic polymorphisms of CYP2E1 and ALDH2 in breast cancer development. *Pharmacogenetics* 2003;13:67–72.
40. Tsugane S, Sobue T. Baseline survey of JPHC study-design and participation rate. Japan Public Health Center-based prospective study on cancer and cardiovascular diseases. *J Epidemiol Jpn Epidemiol Assoc* 2001;11:S24–S29.
41. Otani T, Iwasaki M, Yamamoto S, Sobue T, Hanaoka T, Inoue M, Tsugane S. Alcohol consumption, smoking, and subsequent risk of colorectal cancer in middle-aged and elderly Japanese men and women: Japan Public Health Center-based prospective study. *Cancer Epidemiol Biomarkers Prev* 2003;12:1492–500.
42. Inoue M, Tsugane S. Impact of alcohol drinking on total cancer risk: data from a large-scale population-based cohort study in Japan. *Br J Cancer* 2005;92:182–7.

43. Tsubono Y, Kobayashi M, Sasaki S, Tsugane S. Validity and reproducibility of a self-administered food frequency questionnaire used in the baseline survey of the JPHC Study Cohort I. *J Epidemiol Jpn Epidemiol Assoc* 2003;13: S125–S133.
44. Tsugane S, Kobayashi M, Sasaki S. Validity of the self-administered food frequency questionnaire used in the 5-year follow-up survey of the JPHC Study Cohort I: comparison with dietary records for main nutrients. *J Epidemiol Jpn Epidemiol Assoc* 2003;13:S51–S56.
45. Ishihara J, Sobue T, Yamamoto S, Yoshimi I, Sasaki S, Kobayashi M, Takahashi T, Iitoi Y, Akabane M, Tsugane S. Validity and reproducibility of a self-administered food frequency questionnaire in the JPHC Study Cohort II: study design, participant profile and results in comparison with Cohort I. *J Epidemiol Jpn Epidemiol Assoc* 2003;13:S134–S147.
46. Tsubono Y, Takamori S, Kobayashi M, Takahashi T, Iwase Y, Iitoi Y, Akabane M, Yamaguchi M, Tsugane S. A data-based approach for designing a semiquantitative food frequency questionnaire for a population-based prospective study in Japan. *J Epidemiol Jpn Epidemiol Assoc* 1996;6:45–53.
47. The Council for Science and Technology, Ministry of Education C Sports SaT, Japan. Standard tables of food composition in Japan, 4th edn. Tokyo: Printing Bureau, Ministry of Finance, 1982.
48. The Council for Science and Technology, Ministry of Education C Sports SaT, Japan. Standard tables of food composition in Japan, 5th edn. Tokyo: National Printing Bureau, 2005.
49. Willett W. Nutritional epidemiology, 2nd edn. New York: Oxford University Press, 1998.
50. World Health Organization. International classification of diseases for oncology, 3rd edn. Geneva, Switzerland: World Health Organization, 2000.
51. Korn EL, Graubard BI, Midthune D. Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. *Am J Epidemiol* 1997;145:72–80.
52. Collett D. Modeling survival data in medical researched. Chapman & Hall/CRC press LLC, 1999.
53. Rothman KJ. Epidemiology: an introductioned. New York: Oxford University Press, 2002.
54. Greenland S. Re: confidence limits made easy: interval estimation using a substitution method. *Am J Epidemiol* 1999; 149:884, 5–6.
55. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004; 363:157–63.
56. Smith-Warner SA, Spiegelman D, Yaun SS, van den Brandt PA, Folsom AR, Goldbohm RA, Graham S, Holmberg L, Howe GR, Marshall JR, Miller AB, Potter JD, et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. *JAMA* 1998;279:535–40.
57. Allen NE, Beral V, Casabonne D, Kan SW, Reeves GK, Brown A, Green J. Moderate alcohol intake and cancer incidence in women. *J Natl Cancer Inst* 2009;101: 296–305.
58. Etique N, Grillier-Vuissoz I, Flament S. Ethanol stimulates the secretion of matrix metalloproteinases 2 and 9 in MCF-7 human breast cancer cells. *Oncol Rep* 2006; 15:603–8.
59. Tjonneland A, Christensen J, Olsen A, Stripp C, Thomsen BL, Overvad K, Peeters PH, van Gils CH, Bueno-de-Mesquita HB, Ocke MC, Thiebaut A, Fournier A, et al. Alcohol intake and breast cancer risk: the European Prospective Investigation into Cancer and Nutrition (EPIC). *Cancer Causes Control* 2007;18:361–73.
60. Maskarinec G, Verheus M, Steinberg FM, Amato P, Cramer MK, Lewis RD, Murray MJ, Young RL, Wong WW. Various doses of soy isoflavones do not modify mammographic density in postmenopausal women. *J Nutr* 2009;139:981–6.
61. Zhang S, Hunter DJ, Hankinson SE, Giovannucci EL, Rosner BA, Colditz GA, Speizer FE, Willett WC. A prospective study of folate intake and the risk of breast cancer. *JAMA* 1999;281:1632–7.
62. Sellers TA, Kushi LH, Cerhan JR, Vierkant RA, Gapstur SM, Vachon CM, Olson JE, Therneau TM, Folsom AR. Dietary folate intake, alcohol, and risk of breast cancer in a prospective study of postmenopausal women. *Epidemiology* 2001;12:420–8.
63. Tjonneland A, Christensen J, Olsen A, Stripp C, Nissen SB, Overvad K, Thomsen BL. Folate intake, alcohol and risk of breast cancer among postmenopausal women in Denmark. *Eur J Clin Nutr* 2006;60:280–6.
64. Larsson SC, Giovannucci E, Wolk A. Folate and risk of breast cancer: a meta-analysis. *J Natl Cancer Inst* 2007;99:64–76.
65. Feigelson HS, Jonas CR, Robertson AS, McCullough ML, Thun MJ, Calle EE. Alcohol, folate, methionine, and risk of incident breast cancer in the American Cancer Society Cancer Prevention Study II Nutrition Cohort. *Cancer Epidemiol Biomarkers Prev* 2003;12:161–4.
66. Terry MB, Zhang FF, Kabat G, Britton JA, Teitelbaum SL, Neugut AI, Gammon MD. Lifetime alcohol intake and breast cancer risk. *Ann Epidemiol* 2006;16:230–40.
67. Hanaoka T, Yamamoto S, Sobue T, Sasaki S, Tsugane S. Active and passive smoking and breast cancer risk in middle-aged Japanese women. *Int J Cancer* 2005;114: 317–22.

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Appendix

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Cancer Epidemiology 34 (2010) 534–541

Contents lists available at ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.cancerepidemiology.net

10-Year risk of colorectal cancer: Development and validation of a prediction model in middle-aged Japanese men

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ARTICLE INFO

Article history:
Accepted 30 April 2010
Available online 31 May 2010

Keywords:
Prospective study
Epidemiologic method
Risk prediction
Colorectal cancer
Validation
Japanese men

ABSTRACT

Background: To estimate an individual's probability of developing colorectal cancer (CRC) may aid health professionals and individuals in improving lifestyle behaviors or deciding the screening regimens. As fewer studies on cancer risk prediction were seen so far, we initially developed an assessment tool with synthesizing key information from a variety of CRC risk factors through a large population-based cohort study. *Method:* The prediction model was derived from 28,115 men in the Japan Public Health Center-based (JPHC) Prospective Study Cohort II (follow-up: 1993–2005), with risk factors selected by Cox proportion hazard regression. 18,256 men in the JPHC Study Cohort I (follow-up: 1995–2005) were used to evaluate the model's performance. *Results:* 543 and 398 CRCs were diagnosed during the follow-up period in Cohorts II and I, respectively. The prediction model, including age, BMI, alcohol consumption, smoking status, and the daily physical activity level, showed modest discrimination ability for CRC ($C = 0.70$; 95% confidential interval, 0.68–0.72) in Cohort II and well calibrated in Cohort I (Hosmer–Lemeshow $\chi^2 = 14.2$, $P = 0.08$). *Conclusion:* The 10-year CRC risk prediction model may be used to estimate CRC risk in Japanese men. It may also play a role in the promotion of CRC prevention strategies.

1. Introduction

Colorectal cancer (CRC) was the second most commonly diagnosed cancer in the Japanese population in 2002 [1,2]. Approximately 11% of total cancer deaths in men and 14% in women were from CRCs in 2005 [2]. The high morbidity and mortality noted in the Japanese population were similar to those in North American and European counties [3].

Some risk factors for CRC were documented in the revised expert report from the World Cancer Research Fund, including physical activity, alcohol consumption, body and abdominal fatness, and consumption of vegetables and foods containing fiber [4]. A recent meta-analysis confirmed that smoking was significantly associated with CRC incidence and mortality [5]. In epidemiologic studies of the Japanese population, the risk factors of physical activity [6,7], alcohol consumption [8,9], smoking habit [8,9], and body mass index (BMI) [9,10] were consistently identified, whereas consumption of vegetables [11] and foods containing fiber [12] were not. Systematic reviews of large studies in Japan also verified the findings for alcohol consumption [13] and smoking habit [14]. In the Japanese population, however, these risk factors were more prevalent in men than in women, and little evidence of modifying CRC risk by reproductive factors has been found among Japanese women [15,16]. Nevertheless, most of these established risk factors for CRC are modifiable, and their improvement has been incorporated into primary cancer prevention strategies in Japan [17].

Given the high incidence of CRC and its significant cost to society, it is critical to reduce the identified risk factors in order to prevent CRC in a population. An individual's risk probability of developing CRC could be estimated by using information on established factors, which would aid physicians and individuals in improving lifestyle behavior and/or deciding on screening regimens for CRC prevention [17–19]. Moreover, from the public health point of view, risk prediction tools could also be used to effectively disseminate information on cancer prevention.

Several studies estimated the absolute risk probability of developing CRC, although they were based on case–control study [18], expert opinion [20], or specific populations [21,22]. In this paper, we present a CRC risk prediction model in Japanese men, derived and validated by two large cohorts from the Japan Public Health Center-based (JPHC) Prospective Study. We also present a simplified score model that can be easily used to estimate an individual's absolute CRC risk based on lifestyle information.

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doi:10.1016/j.canep.2010.04.021

2. Materials and methods

2.1. Study participants

In the JPHC Study, Cohort I, with participants aged 40–59 years, was launched in 1990 and Cohort II, with participants aged 40–69 years, was added in 1993. A total of 48,448 men were initially identified in 11 public health center-based (PHC) areas throughout Japan. The details of the study design and baseline response have been described elsewhere [23,24]. The study was approved by the Institute Review Board of the National Cancer Center, Tokyo, Japan.

The baseline survey for Cohort II had more comprehensive data on physical activity and the food frequency questionnaire (FFQ) (52 food items) than those and the FFQ (44 food items) for Cohort I. In the 5-year follow-up survey, all investigations including the FFQ (138 food items) were the same for both cohorts. Considering the inconsistency of questionnaires and follow-up periods of the two cohorts, in the present study we used the baseline survey of Cohort II men to derive the risk prediction model of CRC and the 5-year follow-up survey of Cohort I men to validate the model.

Participants who reported a history of cancer or cardiovascular disease, were diagnosed with cancers, or were censored before the start of the follow-up survey were excluded, leaving 28,115 eligible subjects for model derivation in Cohort II and 18,256 for model validation in Cohort I.

2.2. Risk factor measurements

Self-administered questionnaires contained items on demographic characteristics, medical history, smoking habit, alcohol consumption, physical activity, occupation, and other factors, as well as diets by validated FFQs [25,26].

BMI was calculated as weight in kilograms divided by the square of height in meters. Physical activity levels, measured by metabolic equivalent (MET) hours per day, were estimated by multiplying the reported time spent at each activity per day by its assigned MET intensity: heavy physical work or strenuous exercise (4.5), walking or standing (2.0), sedentary (1.5), and sleep or others (0.9) [6,27]. Daily physical activity level was the sum of MET-hour scores across all activities.

Smoking habit was grouped into never, former, and current smokers. Alcohol consumption was categorized into four groups (never, occasional, regular <300 g/week, and regular ≥300 g/week), in which regular drinkers were categorized by multiplying the frequency per week by the usual daily amount of alcohol consumed [8].

Daily food intake was calculated by multiplying the frequency by standard portion size and relative size for each food item in the FFQ. Daily intake of nutrients was calculated using the 5th revised edition of the Standard Tables of Food Composition in Japan [28].

2.3. Follow-up and case assessment

Participants were followed until 31 December 2005. Residence status, movement of households, and survival were confirmed annually using the residential registers. Information on the cause of death was obtained by examining the death certificates provided by the Ministry of Health, Labour, and Welfare. The occurrence of cancer was identified by active patient notification through the major local hospitals in the study areas and data linkage with population-based cancer registries. The site and histology of each cancer were coded using the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3), with C18–C20 for CRC, C180–C189 for colon cancer, and C199 and C209 for rectal cancer.

2.4. Statistical analysis

Person-years of follow-up were counted from the date of survey response (1993 for Cohort II and 1995 for Cohort I) until the date of CRC diagnosis, the date of moving out of a study area, the date of death, or the end of 2005, whichever came first. Persons lost to follow-up were censored on the last confirmed date of their presence in the study area. Extreme values of height (<100 or >199 cm), weight (<20 kg), and BMI (<14 or >40 kg/m^2) were removed from this analysis. Nutrient intakes were categorized into tertiles for all study participants, with the lower tertile as the reference.

2.4.1. Prediction model derived by JPHC Cohort II

Cox proportional hazards models were derived after testing for the assumptions underlying its use. Then the model of predictive risk of developing CRC was fitted, in which the average survival rates at follow-up time points were estimated by baseline hazard function with mean values of potential predictors. Hazard ratios (HR) and 95% confidential interval (CI) of each risk factor were also estimated. Based on the previous publications in Japanese populations and age-adjusted univariate analysis performed for available variables in this study (including more than 30 food items and nutrients), the potential predictors were applied for building the full multivariate model, which including age, BMI, daily physical activity, alcohol consumption, smoking habit, family history of CRC, and diabetes diagnosed, and interested interaction terms with biological plausibility between alcohol and smoking, and physical activity and BMI. PHC areas were treated as strata in the analysis; assessment of likely shrinkage (over-fitting) was evaluated for the reduced models by $[LR-(p-q)-q]/[LR-(p-q)]$, where LR denotes the likelihood ratio χ^2, and p and q denote the regression degrees of freedom for the full model and for a reduced model, respectively [29]. Non-linear relationships (transformations) of age, BMI, or daily physical activity were tested by using multiple fractional polynomial method of two degree [30,31], however, none of which had been statistically significant for leaving in the model.

For each risk factor, the regression coefficients of two cohorts were compared by a 2-tailed Z statistics, $Z=(\beta_{[d]}-\beta_{[v]})/SE$, where $\beta_{[d]}$ and $\beta_{[v]}$ are the regression coefficients of Cohort II and Cohort I, respectively, and SE is the standard error of the difference in the coefficients, calculated as $\sqrt{(SE^2_{\beta_{[d]}} \pm SE^2_{\beta_{[v]}})}$ [32]. The Z statistic was used to test the difference in HR of each risk factor/category between the two cohorts [32]. The individual risk of CRC was estimated based on the baseline hazard function of the Cox regression model derived from Cohort II, which method was same as one developed in Framingham heart study [33], where $P=1-S(t)^{\exp(f[x,M])}$ and $f(x,M)=\beta 1(x1-M1)+\ldots+\beta j(xj-Mj)$. $\beta 1,\ldots,\beta j$ are the regression coefficients, $x1,\ldots,xj$ represent an individual's risk factors, $M1,\ldots,Mj$ are the mean values of the risk factors in the cohort (for category variables, $x1,\ldots,xj$ are the dichotomous value of the created dummy variable for each category, entering 1 if the individual's value fits that certain category and 0 otherwise, and $M1,\ldots,Mj$ are the proportion of the certain category of the variable in the cohort), and $S(t)$ is the average survival rate at time t of subjects with the mean values of the risk factors used in the Cox model. This procedure performed a better validity than prepared by Ederer method [34]. The predicted 10-year risk of CRC, therefore, was estimated by the baseline hazard function of Cohort II with mean values of each predictor at the 10-year follow-up time.

2.4.2. Prediction model validated by JPHC Cohort I

Discrimination, the ability of a predictive model to separate those who experience an event from those who do not, was

Table 1

Full and reduced predicative models for estimation of developing colorectal cancer events in Cohort II men, Japan Public Health Center-based Prospective Study, 1993–2005.

Variables retained	Full model			Reduced 1[a]			Reduced 2[b]		
	β	S.E.(β)	P-Value	β	S.E.(β)	P-Value	β	S.E.(β)	P-Value
CRC[c]									
Age, year	0.079	0.006	<0001	0.080	0.006	<0001	0.080	0.006	<0001
BMI, kg/m^2	0.001	0.061	0.98	0.047	0.016	<0.01	0.047	0.016	<0.01
Physical activity, MET-h/d	−0.055	0.049	0.27	−0.019	0.006	<0.01	−0.019	0.006	0.01
Family history of CRC (yes)	−0.085	0.382	0.82	−0.087	0.382	0.82	–	–	–
Diabetes (yes)	0.103	0.160	0.52	0.095	0.160	0.55	–	–	–
Alcohol consumption[d]									
Never	0.052	0.244	0.83	−0.163	0.210	0.44	−0.163	0.210	0.44
Regular (<300 g/w)	0.393	0.230	0.09	0.359	0.192	0.06	0.358	0.192	0.06
Regular (≧300 g/w)	0.584	0.273	0.03	0.657	0.195	0.001	0.659	0.195	0.001
Smoking									
Former	−0.165	0.196	0.40	0.070	0.133	0.60	0.071	0.133	0.59
Current	−0.225	0.330	0.50	0.237	0.119	0.05	0.239	0.119	0.04
Smoking × alcohol	0.078	0.056	0.17	–	–	–	–	–	–
BMI × physical activity	0.002	0.002	0.46	–	–	–	–	–	–
d.f.	12			10			8		
Likelihood ratio x^2	239.8			237.3			241.2		
Shrinkage	–			0.96			0.97		
C-Index	0.703			0.699			0.699		
Colon cancer									
Age, year	0.084	0.008	<0001	0.085	0.008	<0001	0.085	0.008	<0001
BMI, kg/m^2	0.037	0.079	0.64	0.048	0.021	0.02	0.049	0.021	0.02
Physical activity, MET-h/d	−0.028	0.063	0.66	−0.019	0.008	0.02	−0.020	0.008	0.01
Family history of CRC (yes)	0.438	0.384	0.25	0.437	0.384	0.26	–	–	–
Diabetes (yes)	0.330	0.188	0.08	0.323	0.188	0.09	–	–	–
Alcohol consumption[d]									
Never	0.077	0.323	0.81	−0.133	0.276	0.63	−0.140	0.276	0.61
Regular (<300 g/w)	0.493	0.305	0.11	0.431	0.253	0.09	0.419	0.254	0.10
Regular (≧300 g/w)	0.651	0.363	0.07	0.657	0.257	0.01	0.655	0.258	0.01
Smoking									
Former	−0.006	0.258	0.98	0.180	0.173	0.30	0.186	0.173	0.28
Current	−0.012	0.433	0.98	0.341	0.157	0.03	0.347	0.157	0.03
Smoking × alcohol	0.057	0.073	0.44	–	–	–	–	–	–
BMI × physical activity	0.000	0.003	0.90	–	–	–	–	–	–
d.f.	12			10			8		
Likelihood ratio x^2	165.7			165.1			166.0		
Shrinkage	–			0.94			0.95		
C-Index	0.710			0.710			0.708		
Rectal cancer									
Age, year	0.072	0.009	<0001	0.071	0.009	<0001	0.067	0.009	<0001
BMI, kg/m^2	−0.054	0.098	0.58	0.033	0.025	0.19	–	–	–
Physical activity, MET-h/d	−0.097	0.078	0.22	−0.018	0.010	0.07	−0.020	0.008	0.02
Diabetes (yes)	−0.357	0.311	0.25	−0.078	0.240	0.75	–	–	–
Alcohol consumption[d]									
Never	0.027	0.374	0.94	−0.401	0.291	0.17	−0.094	0.361	0.80
Regular (<300 g/w)	0.261	0.349	0.45	0.083	0.259	0.75	0.365	0.335	0.28
Regular (≧300 g/w)	−0.536	0.514	0.30	0.488	0.268	0.07	0.745	0.281	0.01
Smoking									
Former	−0.3%	0.305	0.19	0.088	0.181	0.63	–	–	–
Current	0.504	0.415	0.22	0.088	0.181	0.63	–	–	–
Smoking × alcohol	0.109	0.087	0.21	–	–	–	–	–	–
BMI × physical activity	0.003	0.003	0.31	–	–	–	–	–	–
d.f.	11			9			5		
Likelihood ratio χ^2	82.9			80.0			75.7		
Shrinkage	–			0.89			0.94		
C-Index	0.698			0.678			0.678		

[a] Removed interactions.
[b] Further removed family history and diabetes diagnosed for CRC and colon cancer; diabetes diagnosed, BMI, and smoking habit for rectal cancer.
[c] CRC, colorectal cancer; MET, metabolic equivalent.
[d] Occasional alcohol consumption was as the reference.

assessed using the *C* statistic, the area under the receiver operating characteristic curve [32]. The overall *C* statistics and its 95% CIs were calculated by logistic regressions. Calibration is another measure of performance of a prediction model that tests how closely predicted outcomes agree with actual outcomes [32,35].

The calibration was conducted in Cohort I, using the β coefficients, the mean of each risk factor, and the average survival rate at 10-year from the original Cohort II. Participants in Cohort I were divided into 10 deciles of individual predicted risk, and in each decile the expected events were the sum of individual predicted

Table 2
Characteristics of risk factors, person-years of follow-up, and colorectal cancer events in men, Japan Public Health Center-based Prospective Study, 1993–2005[a].

Risk factor	Cohort II[b]						Cohort I[c]					
	Participants, mean (SD), %	No. of participants	Person-years of follow-up	No. of events			Participants, mean (SD), %	No. of participants	Person-years of follow-up	No. of events		
				CRC	Colon	Rectum				CRC	Colon	Rectum
Age, year	52.9(8.8)	28,115	310,059	543	329	214	54.7 (6.0)	18,256	184,496	389	239	150
BMI, kg/m^2	23.4 (2.9)	28,115	310,059	543	329	214	23.6 (2.8)	18,256	184,496	389	239	150
Physical activity, MET-h/d	28.7(7.3)	27,284	300,982	523	314	209	26.8 (7.0)	17,112	173,159	361	219	142
Alcohol consumption												
Never	23.5	6,355	68,967	96	60	36	23.2	4,192	41,652	83	51	32
Occasional	7.7	2,087	23,652	26	15	11	8.6	1,565	16,013	22	10	12
Regular: <300 g/w	48.1	13,038	143,999	248	155	93	35.4	6,403	65,130	108	64	44
Regular: ≧300 g/w	20.8	5,623	62,184	146	85	61	32.9	5,948	60,187	171	111	60
Smoking status												
Never	23.6	6,579	74,342	111	64	47	36.1	6,483	66,178	110	68	42
Former	23.9	6,657	73,238	142	89	53	16.2	2,901	29,256	78	57	21
Current	52.5	14,601	159,481	284	174	110	47.7	8,555	85,836	195	112	83

[a] CRC, colorectal cancer; MET, metabolic equivalent.
[b] Cohort II (follow-up: 1993–2005) was used to develop the prediction model.
[c] Cohort I (follow-up: 1995–2005) was to evaluate the prediction model's performance.

risk [36]. The Hosmer–Lemeshow χ^2 test was applied to analyze the difference between the observed and estimated risk by groups of deciles [37]. The ratio of observed and expected CRC events (the sum of individual predicted risk probability in a certain risk category) was used to test the model predictive capability for each risk factor in Cohort I. The 95% CIs for O/E ratio was calculated as $(O/E) \times \exp[\pm 1.96\sqrt{(1/O)}]$; the prediction model underestimated the CRC risk if the O/E ratio was >1, while it overestimated the risk if the O/E ratio was <1 [36].

2.4.3. Simple point score model

A simple point score model (risk sheet) for CRC was developed based on the original prediction model, with the transference of continuous variables of age, BMI, and physical activity into category variables [38,39]. The β coefficients were newly fitted by the Cox model with each of category variables. The first step was to round regression coefficients to scores, and in this analysis, we multiplied coefficients by three, and round them [38,40]. Further, the risk score of each participant was assigned by summing the points from each risk factor present. The score sheets provide comparison 10-year absolute risks for persons of the same age from average and low-risk CRC.

All analyses were conducted using SAS version 9.01 (SAS Inc., Cary, NC, USA).

3. Results

As of December 2005, newly diagnosed cases of CRC were 543 in Cohort II and 389 in Cohort I. In total, 310,059 and 184,496 person-years were observed in the average follow-up periods of 11.0 and of 10.1 years in Cohorts II and I, respectively.

Comparisons of model constructions among the full predictive model and the models with reduced variables were shown in Table 1, in which the reduced multivariate model with age, BMI, physical activity, smoking habit and alcohol consumption was the optimal one (the global test for model non-proportionality, $P = 0.984$, 0.597, and 0.093 for CRC, colon, and rectal cancer, respectively). Numbers of participants, person-years of follow-up, and CRC events, as well as the risk factors of CRC are listed in Table 2. The respective β coefficients and HRs for CRC risk factors obtained from Cox regression of Cohorts II and I, with baseline survival rate at 10-years, are shown in Table 3. Risk factors showed similar relationships to CRC, colon, and rectal cancer.

In the discriminatory analysis of Cohort II, the C statistics were 0.70 (95% CI, 0.68–0.72) for CRC, 0.71 (95% CI, 0.68–0.74) for colon cancer, and 0.68 (95% CI, 0.64–0.71) for rectal cancer, showing a good ability to distinguish cases from non-cases. In Cohort I, the C statistics were 0.64 (95% CI, 0.61–0.67) for CRC, 0.66 (95% CI: 0.62–0.70) for colon cancer, and 0.62 (95% CI: 0.57–0.66) for rectal cancer, showing a modest ability to distinguish cases from non-cases.

In the calibration analysis, χ^2 was 14.2 ($P = 0.08$) for CRC, 11.0 ($P = 0.20$) for colon, and 11.2 ($P = 0.19$) for rectum cancer, showing that the actual rates of CRC in Cohort I were similar to the rates predicted by the Cohort II function (Fig. 1). The overall O/E ratios were 1.09 (95% CI, 0.98–1.23) for CRC, 1.19 (95% CI, 1.03–1.37) for colon cancer, and 0.94 (95% CI, 0.78–1.12) for rectal cancer. Agreement between the predicted and the observed number of events was good in most risk factor categories with several exceptions (e.g., underestimation for CRC in the "never" alcohol consumption category and overestimation for rectal cancer in the age group of 45–49) (Table 4).

In addition, when participants who had a history of diabetes (1991 in Cohort II and 1332 in Cohort I) or a family history of CRC in first-degree relatives (475 in Cohort II and 157 in Cohort I) were excluded, the same predictive risk factors were identified, and similar discrimination and calibration values were observed for CRC, colon, and rectal cancer, respectively, in Cohort I (data not shown).

The simple point score model (risk sheet) was developed for CRC in Cohort II (Fig. 2), for which the C statistic was 0.69 (95% CI, 0.67–0.71). In Fig. 2, the average and the lowest risk probability by age groups in Cohort II are also shown. Correspondingly, validation was performed in Cohort I for the simple point score model: the C statistic was 0.61 (95% CI, 0.58–0.64) for CRC, with similar O/E ratios and 95% CIs in each category of risk factors (data not shown).

4. Discussion

We developed a CRC risk prediction model with established risk factors of age, BMI, alcohol consumption, smoking status, and physical activity level for middle-aged Japanese men. The prediction model was well calibrated in an external cohort. We also presented a simple point score model (risk sheet) for CRC risk estimation.

Cancer is a multifactorial disease involving a variety of factors in the development of clinical manifestations. This recognition has

Table 3
β-Coefficients and hazard ratios with 95% confidence intervals of colorectal cancer risk factors in men, Japan Public Health Center-based Prospective Study, 1993–2005[a].

Risk factor	Cohort II[b,d]						Cohort I[c,d]					
	CRC		Colon		Rectum		CRC		Colon		Rectum	
	β	HR (95% CI)	β	HR (95% CI)	β	HR (95%CI)	β	HR (95% CI)	β	HR (95% CI)	β	HR (95% CI)
Age, year	0.080	1.08 (1.07–1.10)	0.085	1.09 (1.07–1.11)	0.067	1.07 (1.05–1.09)	0.063	1.07 (1.05–1.09)	0.062	1.06 (1.04–1.09)	0.065	1.07 (1.04–1.10)
BMI, kg/m^2	0.047	1.05 (1.02–1.08)	0.049	1.05 (1.01–1.09)	–	–	0.003	1.00 (0.97–1.04)	0.013	1.01 (0.97–1.06)	–	–
Physical activity, MET-h/d	−0.019	0.98 (0.97–0.99)	−0.020	0.98 (0.97–1.00)	−0.020	0.98 (0.97–1.00)	−0.017	0.98 (0.97–1.00)	−0.027	0.97 (0.95–0.99)	−0.006	0.99 (0.97–1.02)
Alcohol consumption												
Never	−0.163	0.85 (0.56–1.28)	−0.140	0.87 (0.51–1.49)	−0.149	0.86 (0.48–1.55)	0.314	1.37 (0.88–2.14)	0.474	1.61 (0.88–2.92)	−0.028	0.97 (0.51–1.87)
Occasional		1.00		1.00		1.00		1.00		1.00		1.00
Regular: <300 g/w	0.358	1.43 (0.98–2.09)	0.419	1.52 (0.93–2.50)	0.309	1.36 (0.80–2.31)	0.072	1.07 (0.69–1.67)	0.182	1.20 (0.67–2.16)	−0.197	0.82 (0.43–1.55)
Regular: ≥300 g/w	0.659	1.93 (1.32–2.83)	0.655	1.93 (1.16–3.19)	0.745	2.11 (1.21–3.65)	0.679	1.97 (1.30–3.00)	0.858	2.36 (1.35–4.14)	0.348	1.42 (0.76–2.63)
Smoking status												
Never		1.00		1.00				1.00		1.00		
Former	0.071	1.07 (0.83–1.39)	0.186	1.21 (0.86–1.69)	–	–	0.438	1.55 (1.15–2.09)	0.605	1.83 (1.27–2.64)	–	–
Current	0.239	1.27 (1.01–1.60)	0.347	1.41 (1.04–1.92)	–	–	0.323	1.38 (1.08–1.77)	0.222	1.25 (0.91–1.72)	–	–
Baseline survival function at 10-year, St(10)	0.9882		0.9928		0.9954		0.9835		0.9890		0.9942	

[a] CRC, colorectal cancer; HR, hazard ratio; CI, confidential interval; MET, metabolic equivalent.
[b] Cohort II (follow-up: 1993–2005) was used to develop the prediction model.
[c] Cohort I (follow-up: 1995–2005) was to evaluate the prediction model's performance.
[d] The HR of each risk factor/category was not significantly different between Cohort II and Cohort I ($P > 0.05$) for the model of CRC, colon, and rectal cancer, respectively.

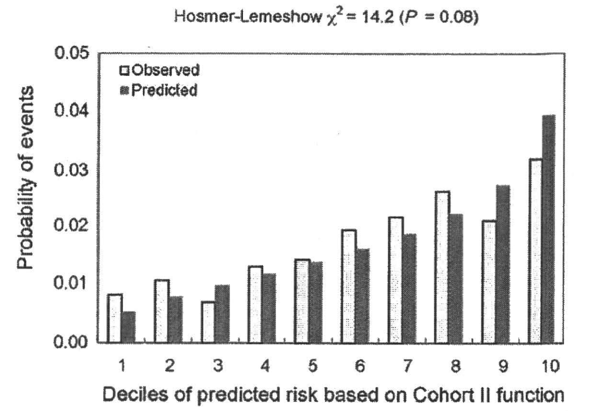

Fig. 1. The 10-year observed and predicted colorectal cancer events in Cohort I men, Japan Public Health Center-based Prospective Study, 1993–2005.

led the development of risk assessment tools that attempt to synthesize the values of numerous variables into a single statement about the risk of developing a cancer [41]. In this prediction model, age, alcohol consumption, and daily physical activity level were identified as the most important CRC risk factors, consistent with other reports [4,18,20]. Although body weight was also a potential predictor in this analysis, BMI was arbitrarily selected in the model building as a relevant comprehensive risk factor of CRC [10,18,20].

Dietary factors such as consumption of red meat, green vegetables, fibers, dairy, calcium supplement use, or intake of folate were not identified in this population, although they were previously reported as possibly related to CRC risk [4,18,42]. Moreover, no dietary food combinations, including total meat (pork, beef, bacon, ham, and sausage) [42], processed meat (bacon, ham, and sausage) [42,43], total white meat (fish and poultry) [42], ratio of red meat to vegetable, or ratio of red meat to white meat [44] were risk predictors of CRC in this study population. Although in recent years the dietary pattern in the Japanese population has tended toward the western pattern, the traditional dietary habits were substantially maintained, especially in older people [45]. This may account for the lack of foods or dietary nutrients serving as significant factors for predicting CRC in men. Alternatively, it might be possible that data in this study population were insufficient to support a quantitative statement about the exact magnitude of risk from these diets.

A previous CRC risk prediction model was developed by means of larger case–control studies and included CRC screening during the previous 3 years and number of relatives with CRC [18]. In our study, sigmoidoscopy/colonoscopy and fecal occult blood test were not available in the Cohort II questionnaire, although these are known as indicators for the secondary prevention for CRC [46]. The personal history of diabetes was reported as a possible risk factor of CRC [26]. In the present study, however, diabetes showed statistical significance for colon cancer in the univariate analysis but not in the multivariate analysis. In addition, few participants reported a family history of CRC, such that this factor could not be considered for entering into the prediction model. In the analysis for participants without history of diabetes or family history of CRC, a similar predictive ability for CRC was observed. This may indicate that these two factors were not powerful enough for prediction of CRC in this population. Nevertheless, most CRC risk factors included in this prediction model represent lifestyle choices that can be modified with the aim of preventing the disease.

Several validation studies on cancer risk prediction models also showed modest discriminatory accuracy as measured by *C*

Table 4
10-Years of observed and expected colorectal cancer events, ratios and 95% confidential intervals in Cohort I men, Japan Public Health Center-based Prospective Study, 1993–2005[a].

	CRC					Colon					Rectum				
	Observed	Expected	*O/E* ratio	95%	CI	Observed	Expected	*O/E* ratio	95	%CI	Observed	Expected	*O/E* ratio	95%	CI
Overall	322	294	1.09	0.98	1.23	215	181	1.19	1.03	1.37	107	114	0.94	0.78	1.12
Age, years															
45–49	45	39.0	1.15	0.84	1.58	35	22.8	1.53	1.02	2.31	10	16.4	0.61	0.38	0.99
50–54	62	53.2	1.17	0.89	1.53	41	31.8	1.29	0.91	1.82	21	21.4	0.98	0.64	1.50
55–59	95	76.1	1.25	1.00	1.56	55	46.7	1.18	0.88	1.57	40	29.5	1.36	0.95	1.95
60–64	112	119.9	0.93	0.78	1.12	78	75.9	1.03	0.82	1.29	34	44.7	0.76	0.57	1.02
65–69	8	6.2	1.30	0.59	2.86	6	4.0	1.52	0.57	4.07	2	2.3	0.87	0.24	3.14
BMI, kg/m^2															
<25	230	200.9	1.14	1.00	1.31	153	123.6	1.24	1.04	1.48	–	–	–	–	–
≧25	92	93.5	0.98	0.80	1.21	62	57.6	1.08	0.83	1.39	–	–	–	–	–
Physical activity, MET-h/d															
<22.0	118	109.3	1.08	0.89	1.30	92	67.8	1.36	1.07	1.72	33	41.9	0.79	0.58	1.07
22.0–<28.9	95	101.4	0.94	0.77	1.14	70	62.4	1.12	0.87	1.44	34	39.4	0.86	0.63	1.18
≧28.9	83	83.6	0.99	0.80	1.23	57	50.9	1.12	0.85	1.47	33	33.1	1.00	0.71	1.40
Alcohol consumption															
Never	66	42.5	1.55	1.15	2.10	48	26.0	1.84	1.26	2.71	18	16.5	1.09	0.67	1.77
Occasional	19	17.7	1.07	0.67	1.71	9	10.6	0.85	0.47	1.56	10	6.4	1.57	0.72	3.42
Regular: <300 g/w	95	103.0	0.92	0.76	1.12	59	65.5	0.90	0.71	1.15	36	37.9	0.95	0.69	1.31
Regular: ≧300 g/w	137	129.6	1.06	0.89	1.26	96	78.2	1.23	0.98	1.53	41	53.1	0.77	0.59	1.01
Smoking status															
Never	87	91.6	0.95	0.77	1.17	58	52.7	1.10	0.84	1.44	–	–	–	–	–
Former	69	48.9	1.41	1.07	1.87	52	31.5	1.65	1.16	2.34	–	–	–	–	–
Current	160	149.7	1.07	0.91	1.25	103	94.6	1.09	0.89	1.33	–	–	–	–	–

[a] CRC, colorectal cancer; *O/E*, observed/expected; CI, confidential interval; MET, metabolic equivalent.

Step 1: Assign a score

Age, year	Score
40-44	0
45-49	1
50-54	3
55-59	4
60-64	5
65-69	6

BMI, Kg/m^2	Score
<25	0
≥ 25	1

BMI, Body Mass Index

Smoking habit	Score
No	0
Former	0
Current	1

Alcohol consumption	Score
No	0
Occasional	0
Regular <300 g/w	1
Regular ≥300 g/w	2

Physical activity, MET-h/day	Score
<24.7	0
24.7-<34.6	-1
≥34.6	-1

MET, metabolic equivalent

Step 2: Add sum of scores

Risk factors	Score
Age	
BMI	
Smoking habit	
Alcohol consumption	
Physical Activity	
Total	

Step 3: Determine absolute risk of colorectal cancer

Total score	10-year risk, %
-1	0.2
0	0.3
1	0.5
2	0.7
3	0.9
4	1.3
5	1.8
6	2.4
7	3.3
8	4.6
9	5.9
10	7.4

Reference standard of 10-year absolute risk of colorectal cancer, %

Age	Average risk	Lowest risk
40-44	0.5	0.1
45-49	0.9	0.2
50-54	1.4	0.3
55-59	1.9	0.5
60-64	2.7	0.7
65-69	3.0	0.7

Fig. 2. Simple point score model (risk sheet) for evaluation of 10-year risk of colorectal cancer incidence in men.

statistics, including 0.61 for CRC [36], 0.60–0.63 for breast cancer [47,48], and 0.60–0.69 for lung cancer [49,50]. Similarly, the modest ability to predict CRC in this study suggested that in future studies stronger risk predictors need to be found [18], for instance, dietary nutrient intake or genotypes.

The overall predicted number of CRC events was close to the actual number, with several exceptions in the validation. The differences between the observed and the predicted CRC events in Cohort I may be due to a different distribution of participants with higher risk in the two cohorts. For example, more elderly men and smokers were in Cohort II than in Cohort I, while more heavy alcohol drinkers were in Cohort I than in Cohort II. The discrepancies in the questionnaires used in the two cohorts also may partly account for the difference [36].

The validation in this study was done in an external cohort (Cohort I); however, risk factor profiles and measurement were similar to those of the population for model development (Cohort II). Therefore, the generalizability of the prediction model needs to be tested in other populations to provide more external validations. Another limitation of this study was that the simple point score model (risk sheet) for estimation of CRC risk included not only simple frequency components (age, body weight, and smoking) but also those based on calculation (alcohol consumption by gram per week and physical activity by MET-hour per day). This may make it inconvenient for an individual to use the sheet directly. In addition, because the 5-year follow-up measurement was used as the baseline for Cohort I in this analysis, the smaller relevant population might reduce its validation capability.

In summary, the CRC risk prediction model was developed based on a large cohort study; it showed modest discrimination power and was well calibrated in another large cohort. This model may be used by clinicians, public health professionals, and individuals to estimate the CRC risk for Japanese men, which could play a role in the promotion of CRC prevention strategies. Further validation in other populations, with the addition of more established factors, is necessary.

Conflict of interest statement

None declared.

Acknowledgments

This study was supported by a Grant-in-Aid for Cancer Research (19 shi-2) and for the Third Term Comprehensive 10-year Strategy for Cancer Control (H21-Sanjigan-Ippan-003) from the Ministry of Health, Labour and Welfare of Japan and Grants-in-Aid for Scientific Research for Young Scientists (A) (19689014) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan and Japan Society for the Promotion of Science.

We thank all staff members in each study area for their painstaking efforts to conduct the baseline survey and follow-up. Members of the JPHC Study Group (principal investigator: S. Tsugane) include: S. Tsugane, M. Inoue, T. Sobue, and T. Hanaoka, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo; J. Ogata, S. Baba, T. Mannami, A. Okayama, and Y. Kokubo, National Cardiovascular Center, Suita; K. Miyakawa, F. Saito, A. Koizumi, Y. Sano, I. Hashimoto, T. Ikuta, and Y. Tanaba, Iwate Prefectural Ninohe Public Health Center, Ninohe; Y. Miyajima, N. Suzuki, S. Nagasawa, Y. Furusugi, and N. Nagai, Akita Prefectural Yokote Public Health Center, Yokote; H. Sanada, Y. Hatayama, F. Kobayashi, H. Uchino, Y. Shirai, T. Kondo, R. Sasaki, Y. Watanabe, Y. Miyagawa, Y. Kobayashi, and M. Machida, Nagano Prefectural Saku Public Health Center, Saku; Y. Kishimoto, E. Takara, T. Fukuyama, M. Kinjo, M. Irei, and H. Sakiyama, Okinawa Prefectural Chubu Public Health Center, Okinawa; K. Imoto, H. Yazawa, T. Seo, A. Seiko, F. Ito, F. Shoji, and R. Saito, Katsushika Public Health Center, Tokyo; A. Murata, K. Minato, K. Motegi, and T. Fujieda, Ibaraki Prefectural Mito Public Health Center, Mito; T. Abe, M. Katagiri, M. Suzuki, and K. Matsui, Niigata Prefectural Kashiwazaki and Nagaoka Public Health Center, Kashiwazaki and Nagaoka; M. Doi, A. Terao, Y. Ishikawa, and T. Tagami, Kochi Prefectural Chuo-higashi Public Health Center, Tosayamada; H. Doi, M. Urata, N. Okamoto, F. Ide, and H. Sueta, Nagasaki Prefectural Kamigoto Public Health Center, Arikawa; H. Sakiyama, N. Onga, H. Takaesu, and M. Uehara, Okinawa Prefectural Miyako Public Health Center, Hirara; F. Horii, I. Asano, H. Yamaguchi, K. Aoki, S. Maruyama, M. Ichii, and M. Takano, Osaka Prefectural Suita Public Health Center, Suita; S. Matsushima and S. Natsukawa, Saku General Hospital, Usuda; M. Akabane, Tokyo University of Agriculture, Tokyo; M. Konishi, K. Okada, and I. Saito, Ehime University, Toon; H. Iso, Osaka University, Suita; Y. Honda, K. Yamagishi, S. Sakurai, and N. Tsuchiya, Tsukuba University, Tsukuba; H. Sugimura, Hamamatsu University, Hamamatsu; Y. Tsubono, Tohoku University, Sendai; M. Kabuto, National Institute for Environmental Studies, Tsukuba; S. Tominaga, Aichi Cancer Center Research Institute, Nagoya; M. Iida, W. Ajiki, and A. Ioka, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka; S. Sato, Osaka Medical Center for Health Science and Promotion, Osaka; N. Yasuda, Kochi University, Nankoku; K. Nakamura, Niigata University, Niigata; S. Kono, Kyushu University, Fukuoka; K. Suzuki, Research Institute for Brain and Blood Vessels Akita, Akita; Y. Takashima and M. Yoshida, Kyorin University, Mitaka; E. Maruyama, Kobe University, Kobe; M. Yamaguchi, Y. Matsumura, S. Sasaki, and S. Watanabe, National Institute of Health and Nutrition, Tokyo; T. Kadowaki, Tokyo University, Tokyo; M. Noda and T. Mizoue, International Medical Center of Japan, Tokyo; Y. Kawaguchi, Tokyo Medical and Dental University, Tokyo; H. Shimizu, Sakihae Institute, Gifu.

References

[1] Matsuda T, Marugame T, Kamo K, Katanoda K, Ajiki W, Sobue T. Cancer incidence and incidence rates in Japan in 2002: based on data from 11 population-based cancer registries. Jpn J Clin Oncol 2008;38:641–8.
[2] The Editorial Board of the Cancer Statistics in Japan, ed. Cancer statistics in Japan 2007. Tokyo: Foundation for Promotion of Cancer Research (FPCR), 2007
[3] Shibuya K, Mathers CD, Boschi-Pinto C, Lopez AD, Murray CJ. Global and regional estimates of cancer mortality and incidence by site. II. Results for the global burden of disease 2000. BMC Cancer 2002;2:37.
[4] Wiseman M. The second World Cancer Research Fund/American Institute for Cancer Research expert report. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Proc Nutr Soc 2008;67:253–6.
[5] Botteri E, Iodice S, Bagnardi V, Raimondi S, Lowenfels AB, Maisonneuve P. Smoking and colorectal cancer: a meta-analysis. JAMA 2008;300:2765–78.
[6] Lee KJ, Inoue M, Otani T, Iwasaki M, Sasazuki S, Tsugane S. Physical activity and risk of colorectal cancer in Japanese men and women: the Japan Public Health Center-based prospective study. Cancer Causes Contr 2007;18:199–209.
[7] Isomura K, Kono S, Moore MA, Toyomura K, Nagano J, Mizoue T, et al. Physical activity and colorectal cancer: the Fukuoka colorectal cancer study. Cancer Sci 2006;97:1099–104.
[8] Otani T, Iwasaki M, Yamamoto S, Sobue T, Hanaoka T, Inoue M, et al. Alcohol consumption, smoking, and subsequent risk of colorectal cancer in middle-aged and elderly Japanese men and women: Japan Public Health Center-based prospective study. Cancer Epidemiol Biomarkers Prev 2003;12:1492–500.
[9] Shimizu N, Nagata C, Shimizu H, Kametani M, Takeyama N, Ohnuma T, et al. Height, weight, and alcohol consumption in relation to the risk of colorectal cancer in Japan: a prospective study. Br J Cancer 2003;88:1038–43.
[10] Otani T, Iwasaki M, Inoue M. Body mass index, body height, and subsequent risk of colorectal cancer in middle-aged and elderly Japanese men and women: Japan public health center-based prospective study. Cancer Causes Contr 2005;16:839–50.
[11] Tsubono Y, Otani T, Kobayashi M, Yamamoto S, Sobue T, Tsugane S. No association between fruit or vegetable consumption and the risk of colorectal cancer in Japan. Br J Cancer 2005;92:1782–4.
[12] Otani T, Iwasaki M, Ishihara J, Sasazuki S, Inoue M, Tsugane S. Dietary fiber intake and subsequent risk of colorectal cancer: the Japan Public Health Center-based prospective study. Int J Cancer 2006;119:1475–80.
[13] Mizoue T, Inoue M, Wakai K, Nagata C, Shimazu T, Tsuji I, et al. Alcohol drinking and colorectal cancer in Japanese: a pooled analysis of results from five cohort studies. Am J Epidemiol 2008;167:1397–406.

[14] Mizoue T, Inoue M, Tanaka K, Tsuji I, Wakai K, Nagata C, et al. Tobacco smoking and colorectal cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. Jpn J Clin Oncol 2006;36:25–39.
[15] Akhter M, Inoue M, Kurahashi N, Iwasaki M, Sasazuki S, Tsugane S. Reproductive factors, exogenous female hormone use and colorectal cancer risk: the Japan Public Health Center-based Prospective Study. Eur J Cancer Prev 2008;17:515–24.
[16] Tamakoshi K, Wakai K, Kojima M, Watanabe Y, Hayakawa N, Toyoshima H, et al. A prospective study of reproductive and menstrual factors and colon cancer risk in Japanese women: findings from the JACC study. Cancer Sci 2004;95:602–7.
[17] Tsugane S. What we know about associations between diet and cancer. JMAJ 2008;51:7.
[18] Freedman AN, Slattery ML, Ballard-Barbash R, Willis G, Cann BJ, Pee D, et al. Colorectal cancer risk prediction tool for white men and women without known susceptibility. J Clin Oncol 2008.
[19] Parkin DM, Olsen AH, Sasieni P. The potential for prevention of colorectal cancer in the UK. Eur J Cancer Prev 2009;18:179–90.
[20] Colditz GA, Atwood KA, Emmons K, Monson RR, Willett WC, Trichopoulos D, et al. Harvard report on cancer prevention volume 4: Harvard cancer risk index. Risk Index Working Group, Harvard Center for Cancer Prevention. Cancer Causes Contr 2000;11:477–88.
[21] Selvachandran SN, Hodder RJ, Ballal MS, Jones P, Cade D. Prediction of colorectal cancer by a patient consultation questionnaire and scoring system: a prospective study. Lancet 2002;360:278–83.
[22] Imperiale TF, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF. Using risk for advanced proximal colonic neoplasia to tailor endoscopic screening for colorectal cancer. Ann Intern Med 2003;139:959–65.
[23] Tsugane S, Sobue T. Baseline survey of JPHC study–design and participation rate. Japan public health center-based prospective study on cancer and cardiovascular diseases. J Epidemiol 2001;11:S24–9.
[24] Iwasaki M, Otani T, Yamamoto S, Inoue M, Hanaoka T, Sobue T, et al. Background characteristics of basic health examination participants: the JPHC study baseline survey. J Epidemiol 2003;13:216–25.
[25] Sasaki S, Kobayashi M, Ishihara J, Tsugane S. Self-administered food frequency questionnaire used in the 5-year follow-up survey of the JPHC study: questionnaire structure, computation algorithms, and area-based mean intake. J Epidemiol/Jpn Epidemiol Assoc 2003;13:S13–22.
[26] Inoue M, Iwasaki M, Otani T, Sasazuki S, Noda M, Tsugane S. Diabetes mellitus and the risk of cancer: results from a large-scale population-based cohort study in Japan. Arch Intern Med 2006;166:1871–7.
[27] Inoue M, Iso H, Yamamoto S, Kurahashi N, Iwasaki M, Sasazuki S, et al. Daily total physical activity level and premature death in men and women: results from a large-scale population-based cohort study in Japan (JPHC study). Ann Epidemiol 2008;18:522–30.
[28] Technology. CfSa, Ministry of Education C., Sports, Science and Technology the Government of Japan, ed. Standard tables of food composition in Japan, the fifth revised and enlarged edition. Tokyo: Printing Bureau, Ministry of Finance, 2005.
[29] Harrell Jr FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361–87.
[30] Royston P, Ambler G, Sauerbrei W. The use of fractional polynomials to model continuous risk variables in epidemiology. Int J Epidemiol 1999;28:964–74.
[31] Sauerbrei W, Meier-Hirmer C, Benner A, Royston P. Multivariable regression model building by using fractional polynomials: description of SAS, STATA and R programs. Comput Stat Data Anal 2006;50:3464–85.
[32] Liu J, Hong Y, D'Agostino Sr RB, Wu Z, Wang W, Sun J, et al. Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study. JAMA 2004;291:2591–9.
[33] D'Agostino Sr RB, Grundy S, Sullivan LM, Wilson P. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA 2001;286:180–7.
[34] Therneau TM, Grambsch GP. Expected survival. Modeling survival data: extending the Cox model. Springer; 2004. p. 280.
[35] D'Agostino RB, Nam BH. Evaluation of the performance of survival analysis models: discrimination and calibration measures. In: Balakrishnan NRC, ed. Handbook of statistics, vol. 23. London, England: Elsevier, 2004.
[36] Park Y, Freedman AN, Gail MH, Pee D, Hollenbeck A, Schatzkin A, et al. Validation of a colorectal cancer risk prediction model among white patients age 50 years and older. J Clin Oncol 2009;27:694–8.
[37] Lemeshow S, Hosmer Jr DW. A review of goodness of fit statistics for use in the development of logistic regression models. Am J Epidemiol 1982;115:92–106.
[38] Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837–47.
[39] Wu Y, Liu X, Li X, Li Y, Zhao L, Chen Z, et al. Estimation of 10-year risk of fatal and nonfatal ischemic cardiovascular diseases in Chinese adults. Circulation 2006;114:2217–25.
[40] Steyerberg EW. Clinical prediction models: a practical approach to development, validation, and updating. Springer; 2009.
[41] Kannel WB, McGee DL. Composite scoring–methods and predictive validity: insights from the Framingham Study. Health Serv Res 1987;22:499–535.
[42] Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, Willett WC. Intake of fat, meat, and fiber in relation to risk of colon cancer in men. Cancer Res 1994;54:2390–7.
[43] Cross AJ, Leitzmann MF, Gail MH, Hollenbeck AR, Schatzkin A, Sinha R. A prospective study of red and processed meat intake in relation to cancer risk. PLoS Med 2007;4:e325.
[44] McCullough ML, Feskanich D, Stampfer MJ, Giovannucci EL, Rimm EB, Hu FB, et al. Diet quality and major chronic disease risk in men and women: moving toward improved dietary guidance. Am J Clin Nutr 2002;76:1261–71.
[45] Kim MK, Sasaki S, Sasazuki S, Tsugane S. Prospective study of three major dietary patterns and risk of gastric cancer in Japan. Int J Cancer 2004;110:435–42.
[46] Lee KJ, Inoue M, Otani T, Iwasaki M, Sasazuki S, Tsugane S. Colorectal cancer screening using fecal occult blood test and subsequent risk of colorectal cancer: a prospective cohort study in Japan. Cancer Detect Prev 2007;31:3–11.
[47] Chen J, Pee D, Ayyagari R, Graubard B, Schairer C, Byrne C, et al. Projecting absolute invasive breast cancer risk in white women with a model that includes mammographic density. J Natl Cancer Inst 2006;98:1215–26.
[48] Barlow WE, White E, Ballard-Barbash R, Vacek PM, Titus-Ernstoff L, Carney PA, et al. Prospective breast cancer risk prediction model for women undergoing screening mammography. J Natl Cancer Inst 2006;98:1204–14.
[49] Rosner BA, Colditz GA, Webb PM, Hankinson SE. Mathematical models of ovarian cancer incidence. Epidemiology 2005;16:508–15.
[50] Cronin KA, Gail MH, Zou Z, Bach PB, Virtamo J, Albanes D. Validation of a model of lung cancer risk prediction among smokers. J Natl Cancer Inst 2006;98:637–40.

The Journal of Nutrition
Nutrition and Disease

High Dietary Intake of Magnesium May Decrease Risk of Colorectal Cancer in Japanese Men[1,2]

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Abstract

Magnesium maintains genomic stability and is an essential cofactor for DNA synthesis and repair. Magnesium intake has been reported to be inversely associated with colorectal cancer (CRC) risk in Western populations. This study examined the association between dietary intake of magnesium and CRC risk in Japanese men and women aged 45–74 y. Data from 40,830 men and 46,287 women, at the 5-y follow-up of the Japan Public Health Center-based Prospective Study, who responded to a 138-item FFQ were used in this analysis. A total of 689 and 440 CRC events were observed during the mean follow-up of 7.9 and 8.3 y for men and women, respectively. When adjusted for potential confounders, the hazard ratio and 95% CI in the highest quintile of magnesium intake compared with the lowest quintile in men were 0.65 (95% CI, 0.40–1.03) for CRC (P-trend = 0.04), 0.48 (95% CI, 0.26–0.89) for colon cancer (P-trend = 0.01), and 0.97 (95% CI, 0.47–2.02) for rectal cancer (P-trend = 0.93). Borderline inverse associations were also observed in men who consumed alcohol regularly (P-trend = 0.07) or had a BMI <25 kg/m^2 (P-trend = 0.06). There were similar inverse associations for invasive colon cancer and distal colon cancer. There were no significant associations between magnesium intake and cancer risk in women. Higher dietary intake of magnesium may decrease the risk of CRC in Japanese men. J. Nutr. 140: 779–785, 2010.

Introduction

Magnesium maintains genomic stability and is an essential cofactor in almost all enzymatic systems involved in DNA synthesis and repair (1). Magnesium deficiency may increase membrane dysfunctions and susceptibility toward oxidative stress (1). Studies on supplemental magnesium in animals have demonstrated a reduced incidence of induced colon tumors by means of inhibition of oncogene expression in colon cancer cell

[1] Supported by a Grant-in-Aid for Scientific Research on Priority Areas (17015049) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

[2] Author disclosures: E. Ma, S. Sasazuki, M. Inoue, M. Iwasaki, N. Sawada, R. Takachi, and S. Tsugane, no conflicts of interest.

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proliferation (2–4). Prospective studies (5–8) in human populations of the association between magnesium intake and risk of colorectal cancer (CRC)[4] found inverse associations between magnesium intake and risk of colon cancer (5,6,8) and rectal cancer (6). In particular, 2 studies (6,8) indicated that magnesium intake may prevent colon cancer risk by improving insulin sensitivity in overweight or type 2 diabetes populations.

Calcium also has a beneficial effect against colon cancer and may share several metabolic pathways with magnesium (9–11). A recent large case-control study indicated that total magnesium consumption was linked to a significantly lower risk of colorectal adenoma, especially in those individuals with a low ratio of calcium:magnesium intake and a higher vitamin D intake (12).

Fewer observational studies of the association between magnesium intake and CRC incidence are available. In the Asian population, the association of dietary intake of magnesium with the incidence of CRC risk has not, to our knowledge, been investigated to date. In this article, we present an analysis for CRC, colon, and rectal cancer, which is based on data obtained through the Japan Public Health Center (JPHC)-based Prospective Study.

Materials and Methods

Study participants. The JPHC Study was initiated in 1990 and includes 11 public health center (PHC)-based areas throughout Japan. The study population was defined as all registered Japanese living in these PHC areas (13). In 1990, 5 PHC areas (Cohort I) were selected based on variation in the mortality rate of stomach cancer according to a previous ecological study; in 1993, 6 PHC areas (Cohort II) were added, which were selected according to geographical distribution and feasibility (14). The baseline survey was sent to a total of 140,420 participants, with an overall response rate of 79% in Cohort I and 84% in Cohort II (14). Previous reports (14,15) explained the details of the study design and baseline profiles. The study was approved by the Institutional Review Board of the National Cancer Center, Tokyo, Japan.

Participants in Katsushika, Tokyo, were excluded from this analysis because of the lack of cancer incident data. Participants who responded to the 5-y follow-up survey of the JPHC study, a total of 46,034 men and 52,484 women aged 45–74 y, were used for this analysis. The 5-y follow-up survey conducted between 1995 and 1998 for 2 subcohorts (overall response rate was 81.3%) contained a self-administrated questionnaire on demographic characteristics, medical history, smoking habit, alcohol consumption, physical activity, occupation, and other factors, as well a 138-item FFQ to assess dietary intake.

Dietary intake assessment. In the FFQ, participants were asked how often they consumed individual food items and the representative size of their portions relative to the size of a standard portion. The 9 response choices for frequency were never, 1–3 times/mo, 1–2 times/wk, 3–4 times/wk, 5–6 times/wk, 1 time/d, 2–3 times/d, 4–6 times/d, and ≥7 times/d. Response choices for portion size were small (50% smaller than standard), medium (same as standard), and large (50% larger than standard). The details of the FFQ were described in a previous report (16). Daily food intake was calculated by multiplying the frequency by the standard portion size and the relative portion size for each food item in the FFQ; daily intake of nutrients was calculated by using the 5th revised and enlarged edition of the *Standard Tables of Food Composition in Japan* (17). The validity of dietary intake of magnesium estimated from the FFQ was evaluated in a subsample of cohorts by comparing the estimated intake with that in dietary records (18). Spearman correlation coefficients between energy-adjusted intakes estimated from the FFQ and dietary records for magnesium were 0.45–0.46 in men and 0.42–0.45 in women (18). In addition, although the FFQ had questions on supplement use, intake of magnesium and other nutrients from supplements was not included in this analysis because no comprehensive database for supplements was available (16).

Follow-up and case ascertainment. Participants were followed until 31 December 2005. Residence status, relocation, and survival were confirmed annually by checking the residential registers. Under Japanese laws, resident and death registrations are required and inspection of resident registries is available to anyone (13). Information on the cause of death was obtained by examining the death certificates provided by the Ministry of Health, Labor, and Welfare, and the occurrence of cancer was identified by notification of active cancer patients through the major local hospitals in the study areas and by data linkage with population-based cancer registries. When local hospitals could not cover a sufficiently high proportion of cancer patients, the population-based registry (prefecture wide) was used as a supplemental data source (19). Death certificate notification and death certificate only have been clearly defined as indices of completeness and validity. In our cancer registry system, the proportion of cases with death certificate notification was 5.1%, in which information available from death certificates only was 2.4% for CRC. The site and histology of each cancer were coded according to the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) (codes C18–C20). Analyses of site-specific cancers were conducted: C18 for colon cancer (C180–C185 for proximal colon cancer and C186–C189 for distal colon cancer) and C199 and C209 for rectal cancer. In addition, CRC cases were further classified according to the depth of tumor invasion, i.e. invasive cancer [over a mucosal layer (malignant, primary site)] and noninvasive cancer [within a mucosal layer (carcinoma in situ)].

Statistical analysis. Exclusion of participants included those who reported a history of any cancer (1396 men and 1975 women) or had no nutrition data (567 men and 480 women). We also excluded participants who reported extreme values of height (<100 or >199 cm) and weight (<20 kg), did not provide information on dietary intake of magnesium, or reported extreme values (< or >2.5%) of total energy intake (lowest and highest cutoffs were 5192 and 14,150 kJ in men, respectively, and 3523 and 15,414 kJ in women, respectively) to remove some unreliable data and thus compute reasonable energy-adjusted nutrients. These exclusions left 40,830 men and 46,287 women eligible for this analysis.

Person-years of follow-up were counted from the date of the survey until the date of CRC diagnosis, the date of moving out of a study area, the date of death, or the end of 2005, whichever came first. Persons lost to follow-up were censored on the last confirmed date of their presence in the study area. On the basis of the sex-specific distribution of all study participants, dietary intakes of magnesium and other nutrients were adjusted for total energy intake with the residual model (20). BMI was categorized into 4 levels (<25, 25–<27, 27–<30, ≥30 kg/m^2) (21). Metabolic equivalent (MET) hours of physical activities were estimated by multiplying the reported time spent at each physical activity per day by its assigned MET intensity (22,23). Smoking habit categories consisted of never, former, and current smoking. Alcohol consumption was categorized into 4 groups (never; occasional; regular, <300 g/wk; and regular, ≥300 g/wk), in which regular drinker was calculated by multiplying the frequency per week by the usual daily intake of alcohol (15).

Hazard ratios (HR) and 95% CI for the development of CRC were explored by Cox proportional hazards regression analyses. In an analysis for site-specific events, cancer events in the other sites were considered censored cases (21). Testing of the associations between magnesium intake and CRC risk was first conducted with adjustment for age (continuous) and PHC, in which magnesium intake was categorized into a quintile category for analysis, with the lower quintile serving as the reference. On the basis of this model, other potential confounders were added, including alcohol consumption, smoking status, physical activities (MET-h/d) (continuous), CRC screening test (colonoscopy, barium enema, or fecal occult blood test), BMI, diabetes mellitus, vitamin supplement use, and menopausal status (for women). Further adjustment included dietary intake of total energy, energy-adjusted saturated fat, zinc, fiber, vitamin B-6, folate, and calcium (all in quintile categories).

[4] Abbreviations used: CRC, colorectal cancer; HR, hazard ratio; JPHC, Japan Public Health Center; MET, metabolic equivalent; PHC, public health center; TRP, transient receptor potential.

Stratified analysis was performed for alcohol consumption (never or occasional, regular), smoking status (never, ever), BMI (<25, ≥25 kg/m^2), and menopausal status (no, yes, for women). Tests for linear trend across quintiles were performed by using the median value of magnesium intake as a continuous variable. All *P*-values reported were 2-sided and the significance level was set at <0.05. All analyses were conducted with SAS version 9.1 (SAS Institute). Values in the text are means ± SD unless noted otherwise.

Results

As of December 2005, there were 689 newly diagnosed cases of CRC for men (172 proximal and 249 distal colon cancers, with 290 invasive cases; and 268 rectal cancers, with 224 invasive cases) and 440 for women (168 proximal and 127 distal colon cancers, with 230 invasive cases; and 145 rectal cancers, with 127 invasive cases). A total of 340,811.8 and 397,340.6 person-years were observed with a mean follow-up of 7.9 y for men and 8.3 y for women, respectively.

Magnesium intakes were 284.4 ± 105.3 mg/d in men and 279.4 ± 104.6 mg/d in women. Men and women who consumed more magnesium tended to be older, less likely to smoke and drink alcohol and more likely to undergo CRC screening and to have a higher prevalence of diabetes. For nutrients (except for total energy at the highest quintile of magnesium intake), both men and women who reported a higher intake of magnesium were more likely to have a higher intake of calcium, zinc, folate, fiber, vitamin B-6, and vitamin D; the men were more likely to have a higher intake of saturated fat, but women were not. In addition, the ratio of calcium:magnesium intake and the use of vitamin supplements in women were relatively higher than those in men (**Table 1**). The age- and PHC-adjusted model and other multivariate models for HR related to magnesium intake for CRC risk showed similar results (**Table 2**). With adjustment for all potential risk factors and relevant nutrient intakes, the HR and 95% CI in the highest quintile of magnesium intake in men, compared with the lowest quintile in men, were 0.65 (95% CI, 0.40–1.03; *P*-trend = 0.04) for CRC, 0.48 (95% CI, 0.26–0.89; *P*-trend = 0.01) for colon cancer, and 0.97 (95% CI, 0.47–2.02; *P*-trend = 0.93) for rectal cancer. Magnesium intake was inversely associated with risk of invasive colon cancer and distal colon cancer and tended to be negatively associated with risk of invasive CRC (*P* = 0.06), but it was not associated with risk of rectal cancer. Magnesium intake was not associated with CRC risk in women.

Compared with the lowest tertile, the highest tertile of magnesium intake was marginally associated with a reduction in CRC risk in men who consumed alcohol regularly (*P*-trend = 0.07) and in those with a BMI <25 kg/m^2 (*P*-trend = 0.06) (**Table 3**). There were no clear associations between combined BMI and alcohol consumption with CRC risk and the test for interaction was not significant in men. The restricted analysis was applied to postmenopausal women, nonsmoking women, women with a BMI <25 or ≥25 kg/m^2, and women who did not consume alcohol regularly. Associations were nonsignificant, similar to results obtained using data from all women (data not shown).

In addition, when participants who had diabetes (2674 men and 1497 women) or used vitamin supplements (4137 men and 6895 women) were excluded, associations observed for CRC, colon cancer, and rectal cancer were similar to those for total men or total women (data not shown). Moreover, when participants with CRC diagnosed within 2 y of follow-up were removed from the analysis, similar results were observed for both men and

Discussion

In this large population-based prospective study, we found significant inverse associations among dietary intake of magnesium and risk of CRC and colon cancer in men. These inverse associations were most evident for colon cancer.

Magnesium is abundant in vegetables, rice and wheat, soy and soy products, fish, and milk and other dairy products in the Japanese diet (24,25). The National Nutrition Survey in Japan in 2006 showed that intakes of magnesium among respondents >20 y of age were 274 ± 99 mg/d in men and 245 ± 92 mg/d in women (25), which is similar to our results. The daily intake of magnesium in our study was also similar to those reported in other populations (5,6,8). The interquintile range of total magnesium was 245–351 mg/d in the Iowa Women's Health Study (5) and 209–255 mg/d in the Swedish Mammography Cohort (6), both of which observed inverse associations between magnesium intake and colon cancer risk in women. The Netherland Cohort Study (8), with magnesium intakes of 286–373 mg/d in men and 256–326 mg/d in women, found weak, nonsignificant, inverse associations between total magnesium intake and CRC and colon cancer risk in both men and women and in participants with a BMI >25 kg/m^2. Compared with intakes in our study and others (5,6), the Women's Health Study (7) had a relatively higher intake of magnesium of 279–392 mg/d and did not observe any significant associations. This study pointed out that high magnesium intake may be related to reduction of CRC risk only among populations with relatively low intakes of magnesium and, therefore, populations who have sufficient intake of magnesium may obtain little benefit from increased intake.

The absorption of magnesium is directly or indirectly affected by calcium (26,27), whereas the absorption of calcium is closely related to and regulated by vitamin D (16,28). Ionized magnesium (Mg^{2+}) is a chronic regulatory agent, as opposed to ionized calcium (Ca^{2+}), because Mg^{2+} shares the transient receptor potential (TRP) channels with Ca^{2+} in the paracellular pathway, the epithelial Ca^{2+} (TRPV5/6) and Mg^{2+} (TRPM6/7) channels (27). In particular, the TRPM7 receptor possesses a higher affinity for Mg^{2+} than Ca^{2+} and is expressed and implicated in cellular Mg^{2+} homeostasis (12,27,29). Facilitated by these channels, a high calcium intake may interfere with magnesium absorption and vice versa. On the other hand, magnesium absorption is vitamin D independent, but repletion of vitamin D is associated with increments in magnesium absorption (26). The interactions among magnesium, and calcium, as well as vitamin D are important in intestinal magnesium transport and absorption (26,27). Our previous study (15) reported the potential inverse association between dietary intake of calcium and CRC risk as well as the potential effect modification between calcium and vitamin D against CRC risk in Japanese men. Another American study (12) identified inverse associations between total magnesium intake and colorectal adenoma in total participants and participants with a low ratio of calcium: magnesium intake (<2.78); magnesium intake (301.4 ± 128.6 mg/d in adenoma cases and 321.2 ± 122.1 mg/d in controls) in this study was also greater than that in our study. The American study (12) also indicated that the absorption of magnesium might be significantly elevated when vitamin D intake was high and that the ratio of calcium:magnesium intake was low, because the absorption of magnesium could be significantly depressed when the calcium concentration was high (26). In our previous study (15), the amount of dietary intake of calcium was considered to be relatively lower; accordingly, the ratio of

TABLE 1 Characteristics of study population according to magnesium intake at 5-y follow-up (JPHC-based Prospective Study)[1]

	Quintiles of energy-adjusted magnesium intakes, range (median), *mg/d*				
	Q1 (lower)	Q2	Q3	Q4	Q5
Men	<238 (216)	238–<267 (254)	267–<294 (280)	294–<327 (308)	≥327 (355)
Participants, *n*	8166	8166	8166	8166	166
Age, *y*	55.4 ± 7.6	55.9 ± 7.7	56.6 ± 7.7	57.5 ± 7.8	58.7 ± 7.8
BMI, *kg/m²*	23.6 ± 3.3	23.5 ± 3.1	23.5 ± 3.0	23.6 ± 3.1	23.6 ± 3.2
Current smoker, %	52.8	47.1	45.4	41.2	37.0
Regular alcohol consumption, %	79.2	70.6	65.7	62.9	55.4
Physical activity, *MET-h/d*	26.5 ± 7.1	26.3 ± 7.0	26.3 ± 6.9	26.3 ± 6.9	26.0 ± 6.9
Diabetes melitus, %	5.7	5.8	6.2	7.7	10.9
Colonscopy or barium enema or fecal occult blood test, %	25.8	31.6	33.6	35.4	36.1
Vitamin supplement use, %	8.1	9.5	10.4	11.0	11.5
Nutrient intakes[2]					
Total energy, *kJ/d*	2159.6 ± 644.9	2173.6 ± 633.9	2186.4 ± 636.1	2188.4 ± 635.6	2148.5 ± 648.7
Saturated fat, *g/d*	15.4 ± 7.0	17.0 ± 6.2	17.4 ± 6.1	17.6 ± 5.9	17.5 ± 5.8
Dietary fiber, *g/d*	7.6 ± 2.3	9.7 ± 2.4	11.3 ± 2.7	13.2 ± 3.1	17.1 ± 4.9
Calcium, *mg/d*	336.5 ± 142.2	447.6 ± 178.1	514.9 ± 204.5	576.2 ± 217.1	679.5 ± 233.4
Calcium:magnesium	1.6 ± 0.6	1.8 ± 0.7	1.8 ± 0.7	1.9 ± 0.7	1.9 ± 0.6
Zinc, *mg/d*	7.9 ± 1.5	8.6 ± 1.2	8.8 ± 1.1	9.0 ± 1.1	9.5 ± 1.2
Folate, *μg/d*	250.9 ± 77.6	318.9 ± 83.5	365.8 ± 88.1	424.7 ± 102.7	544.2 ± 158.3
Vitamin B-6, *mg/d*	1.3 ± 0.3	1.4 ± 0.2	1.5 ± 0.2	1.7 ± 0.3	1.9 ± 0.3
Vitamin D, *μg/d*	7.2 ± 4.6	9.2 ± 5.4	10.3 ± 5.8	11.5 ± 6.6	13.0 ± 8.1
Women	<237 (219)	237–<262 (250)	262–<286 (274)	286–<316 (299)	≥316 (342)
Participants, *n*	9257	9257	9258	9257	9258
Age, *y*	55.4 ± 8.1	56.2 ± 8.0	57.0 ± 7.8	57.8 ± 7.6	58.9 ± 7.5
BMI, *kg/m²*	23.5 ± 3.6	23.4 ± 3.5	23.4 ± 3.4	23.5 ± 3.5	23.7 ± 3.7
Current smoking, %	7.3	5.6	4.5	4.3	4.6
Regular alcohol consumption, %	14.1	13.0	13.1	11.8	10.9
Physical activity, *MET-h/d*	25.4 ± 6.0	25.6 ± 6.0	25.9 ± 5.9	25.8 ± 5.9	25.7 ± 5.9
Diabetes melitus, %	2.7	2.8	3.3	4.0	5.5
Postmenopausal, %	63.0	68.3	72.9	77.0	79.8
Colonscopy or barium enema or fecal occult blood test, %	23.8	29.6	32.4	34.7	35.2
Vitamin supplement use, %	14.3	14.5	15.6	14.9	15.2
Nutrient intake[2]					
Total energy, *kJ/d*	1844.8 ± 594.8	1856.9 ± 559.8	1894.5 ± 550	1899.8 ± 540.8	1838.3 ± 554.1
Saturated fat, *g/d*	18.6 ± 6.3	17.9 ± 5.3	17.4 ± 5.1	16.8 ± 5.1	16.3 ± 5.3
Dietary fiber, *g/d*	9.4 ± 2.4	11.5 ± 2.4	13.1 ± 2.6	15.0 ± 2.9	18.8 ± 4.5
Calcium, *mg/d*	412.1 ± 172.2	516.3 ± 193.9	570.3 ± 199.4	618.2 ± 198.0	705.6 ± 213.5
Calcium:magnesium	1.9 ± 0.8	2.1 ± 0.8	2.1 ± 0.7	2.1 ± 0.7	2.0 ± 0.6
Zinc, *mg/d*	7.9 ± 1.0	8.1 ± 0.8	8.2 ± 0.8	8.3 ± 0.8	8.7 ± 0.9
Folate, *μg/d*	280.0 ± 76.6	351.4 ± 80.7	403.7 ± 91.5	459.6 ± 102.0	579.9 ± 157.2
Vitamin B-6, *mg/d*	1.2 ± 0.2	1.3 ± 0.2	1.5 ± 0.2	1.6 ± 0.2	1.8 ± 0.3
Vitamin D, *μg/d*	7.3 ± 4.4	9.3 ± 5.2	10.5 ± 5.8	11.2 ± 6.1	12.2 ± 7.5

[1] Values are mean ± SD or %.
[2] Energy-adjusted intake.

with those reported in Western studies (5,6,12). On the other hand, vitamin D intake in our study was higher than that reported in this American study (3.4 ± 2.2 μg/d in adenoma cases and 3.7 ± 2.5 μg/d in controls). Our findings also provided a reasonable explanation that a higher intake of magnesium in persons at the lower ratio of calcium:magnesium intake level may have a reduction in their CRC risk through the balance of nutrients including magnesium and calcium.

We think that the lack of an inverse relationship in women may be due to the different risk profiles in men and women in the Japanese population. In Japanese men, physical activity was associated with decreased risk of CRC, whereas obesity, diabetes, and C-peptide were associated with increased risk of CRC (13,21,22,30). In Japanese women, however, these associations were not significant and were weaker than in Western populations (31). Therefore, magnesium likely did not have a protective effect in women via an improvement in insulin sensitivity. In addition, the increased level of female hormones as the increment of internal fattiness may reduce CRC risk (31). The difference between men and women in CRC risk may also be explained by differences in alcohol consumption. About 75% of Japanese men and only 20% of Japanese women consume alcohol; this rate of alcohol consumption in Japanese men is higher than that in other populations (16,32). Alcohol may increase CRC risk by disturbing DNA synthesis and methylation in the one-carbon metabolism pathway (32,33). Animal studies suggest that marginal magnesium deficiency is more likely to result in pathological signs in the presence of increased oxidative

TABLE 2 HR and 95% CI of CRC according to magnesium intake (JPHC-based Prospective Study, 1995–2005)[1]

	Quintiles of energy-adjusted magnesium intake					
	Q1 (lower)	Q2	Q3	Q4	Q5	*P*-trend
Men						
CRC cases, *n*	163	131	118	136	141	
HR (95% CI)	1.00	0.79 (0.59–1.04)	0.66 (0.47–0.92)	0.71 (0.48–1.04)	0.65 (0.40–1.03)	0.04
Invasive CRC						
Cases, *n*	118	102	85	102	107	
HR (95% CI)	1.00	0.82 (0.59–1.13)	0.65 (0.44–0.96)	0.69 (0.44–1.07)	0.59 (0.34–1.02)	0.06
Colon cancer						
Cases, *n*	105	74	82	78	82	
HR (95% CI)	1.00	0.68 (0.47–0.98)	0.71 (0.47–1.09)	0.62 (0.37–1.01)	0.48 (0.26–0.89)	0.01
Proximal colon cancer						
Cases, *n*	42	31	33	33	33	
HR (95% CI)	1.00	0.78 (0.44–1.40)	0.85 (0.43–1.66)	0.84 (0.39–1.84)	0.55 (0.21–1.46)	0.25
Distal colon cancer						
Cases, *n*	63	43	49	45	49	
HR (95% CI)	1.00	0.61 (0.38–0.97)	0.62 (0.36–1.08)	0.49 (0.25–0.93)	0.43 (0.19–0.95)	0.02
Invasive colon cancer						
Cases, *n*	68	56	55	54	57	
HR (95% CI)	1.00	0.72 (0.46–1.12)	0.72 (0.43–1.20)	0.60 (0.33–1.10)	0.44 (0.21–0.92)	0.02
Rectal cancer						
Cases, *n*	58	57	36	58	59	
HR (95% CI)	1.00	0.97 (0.62–1.51)	0.54 (0.31–0.97)	0.86 (0.47–1.59)	0.97 (0.47–2.02)	0.93
Invasive rectal cancer						
Cases, *n*	50	46	30	48	50	
HR (95% CI)	1.00	0.95 (0.58–1.54)	0.54 (0.29–1.01)	0.80 (0.41–1.57)	0.85 (0.38–1.90)	0.81
Women						
CRC						
Cases, *n*	60	93	89	93	105	
HR (95% CI)	1.00	1.72 (1.12–2.63)	1.46 (0.89–2.39)	1.37 (0.78–2.39)	1.15 (0.60–2.21)	0.69
Invasive CRC						
Cases, *n*	49	75	75	72	86	
HR (95% CI)	1.00	1.64 (1.03–2.61)	1.49 (0.87–2.55)	1.36 (0.74–2.49)	1.19 (0.58–2.44)	0.94
Colon cancer						
Cases, *n*	39	59	61	63	73	
HR (95% CI)	1.00	1.72 (1.01–2.94)	(0.86–2.92)	1.49 (0.75–2.97)	1.29 (0.57–2.89)	0.92
Proximal colon cancer						
Cases, *n*	21	32	41	37	37	
HR (95% CI)	1.00	1.46 (0.71–3.01)	1.64 (0.73–3.68)	1.38 (0.56–3.44)	0.85 (0.28–2.53)	0.41
Distal colon cancer						
Cases, *n*	18	27	20	26	36	
HR (95% CI)	1.00	2.03 (0.92–4.49)	1.39 (0.53–3.61)	1.55 (0.54–4.45)	2.01 (0.60–6.71)	0.44
Invasive colon cancer						
Cases, *n*	31	46	50	46	57	
HR (95% CI)	1.00	1.63 (0.90–2.95)	1.59 (0.81–3.14)	1.43 (0.66–3.09)	1.34 (0.54–3.32)	0.86
Rectal cancer						
Cases, *n*	21	34	28	30	32	
HR (95% CI)	1.00	1.70 (0.83–3.46)	1.24 (0.53–2.88)	1.16 (0.45–2.99)	0.93 (0.31–2.86)	0.59
Invasive rectal cancer						
Cases, *n*	18	29	25	26	29	
HR (95% CI)	1.00	1.65 (0.78–3.49)	1.32 (0.55–3.20)	1.27 (0.47–3.43)	1.00 (0.31–3.25)	0.77

[1] Adjusted for age (continuous) and PHC, BMI (<25, 25–<27, 27–<30, ≥30 kg/m^2), smoking status (never, former, current), alcohol consumption (never; occasional; regular, <300 g/wk; regular, ≥300 g/wk), screening test (no, yes), vitamin supplement use (no, yes), diabetes (no, yes), menopausal status (no, yes, for women), physical activities (continuous), total energy intake, energy-adjusted intakes of saturated fat, dietary fiber, calcium, zinc, folate, vitamin D, and vitamin B-6 (all in quintiles).

or chronic inflammatory stress (1), which may have been caused by alcohol consumption. Significant associations in our study suggest that magnesium intake may provide a prominent benefit for men who regularly consume alcohol.

The Netherland Cohort Study reported that higher total magnesium intake reduced CRC risk in overweight women as a result of decreased insulin resistance (8). However, in our study, we did not observe significant associations in either overweight

TABLE 3 HR and 95% CI of CRC according to magnesium intake with stratified by risk factors in men (JPHC-based Prospective Study, 1995–2005)[1]

	Tertiles of energy-adjusted magnesium intake			
	T1 (lower)	T2	T3	*P*-trend
No or occasional alcohol consumption				
Cases, *n*	46	52	83	
Age- and PHC-adjusted HR (95% CI)	1.00	0.71 (0.47–1.06)	0.83 (0.56–1.22)	0.43
Multivariate HR (95% CI)	1.00	0.71 (0.42–1.20)	0.97 (0.49–1.93)	0.66
Regular alcohol consumption				
Cases, *n*	201	152	142	
Age- and PHC-adjusted HR (95% CI)		0.80 (0.65–0.99)	0.79 (0.63–0.99)	0.04
Multivariate HR (95% CI)	1.00	0.81 (0.61–1.07)	0.69 (0.47–1.03)	0.07
No smoking				
Cases, *n*	66	65	65	
Age- and PHC-adjusted HR (95% CI)	1.00	0.78 (0.55–1.11)	0.65 (0.45–0.92)	0.02
Multivariate HR (95% CI)		0.82 (0.51–1.32)	0.68 (0.36–1.29)	0.35
Smoking	201			
Cases, *n*	1.00	137	149	
Age- and PHC-adjusted HR (95% CI)	1.00	0.75 (0.60–0.94)	0.81 (0.64–1.01)	0.06
Multivariate HR (95% CI)	1.00	0.85 (0.63–1.14)	0.86 (0.57–1.31)	0.21
BMI <25 kg/m^2				
Cases, *n*	171	155	156	
Age- and PHC-adjusted HR (95% CI)	1.00	0.79 (0.64–0.99)	0.74 (0.59–0.93)	0.01
Multivariate HR (95% CI)	1.00	0.90 (0.66–1.21)	0.68 (0.45–1.04)	0.06
BMI 25 kg/m^2				
Cases, *n*	79	53	75	
Age- and PHC-adjusted HR (95% CI)	1.00	0.65 (0.45–0.92)	0.79 (0.57–1.11)	0.26
Multivariate HR (95% CI)	1.00	0.71 (0.44–1.13)	1.17 (0.64–2.15)	0.78

[1] Multivariate HR are adjusted for age (continuous), PHC, BMI (<25, 25–<27, 27–<30, ≥30 kg/m^2), smoking status (never, former, current), alcohol consumption (never; occasional; regular, <300 g/wk; regular, ≥300 g/wk), diabetes (no, yes), screening test (no, yes), vitamin supplement use (no, yes), physical activities (continuous), total energy intake, energy-adjusted intakes of saturated fat, dietary fiber, calcium, zinc, folate, vitamin D, and vitamin B-6 (all in quintiles).

men or women. In contrast, we found an inverse association between magnesium intake and CRC risk in men with a BMI < 25 kg/m^2. The Japanese population has a higher proportion of lean people (BMI ≥ 27 kg/m^2 was ~11.5% in men and 13.4% in women) compared with populations in Western countries (8,32). This may be a reason for the different findings between Japanese women and Western women regarding the modified risk associations by BMI. Interestingly, the incidence of diabetes in the Japanese population is also higher in lean people, in contrast to Western populations (34). Given their relatively moderate magnesium status, it is possible that lean people might benefit substantially from magnesium intake through improvement of insulin sensitivity in the Japanese population. Diabetes was a risk factor of colon cancer in the Japanese population (13), however, the limited number of participants with diagnosed diabetes during follow-up restricted further analysis.

Our study has several limitations. First, this analysis was based on a single measurement of intake of dietary nutrients obtained through the self-administered FFQ; therefore, inevitable misclassification of magnesium intake might attenuate the true relationship with CRC risk (6). Second, magnesium intake from drinking water was not considered and intake of magnesium supplements could not be computed; hence, the total magnesium intake of each participant from different sources may be underestimated in this study. However, a Japanese study (35) on trace element levels in drinking water reported that the magnesium concentration was only 3.83 ± 3.29 mg/L in 34 municipalities. Furthermore, the observed similar inverse associations in participants who did not report supplemental magnesium intake indicate that it is unlikely that data fo individuals who consumed magnesium supplements could hav caused notable fluctuations of this study's results (12,24) Nevertheless, further studies with detailed information o drinking water and supplement use may be helpful in examinin these associations (36). Third, we could not rule out th possibility of biases from unmeasured confounders, althoug the multivariate analysis showed results similar to those from th age- and PHC-adjusted analyses. Because relevant data wer unavailable in this population, we could not test the associatio between the potential relevant genotype(s) and CRC risk and th interaction effect with magnesium intake related to CRC risk (12).

One advantage of this study is that the quality of the cance registry in this population was satisfactory according to an international comparison (37). In addition, participants in this large-scale population-based prospective study had a higher compliance rate, with only 0.7% men and 0.8% women lost to follow-up up to the end of the analysis.

It should be noted that many findings in this study were borderline or not significant; thus, further evidence is needed. In Japan, the recommended dietary allowances for magnesium intake are 370, 350, and 310 mg/d for men aged 30–49, 50–69, and >70 y, respectively, and 280, 290, and 270 mg/d for women aged 30–49, 50–69, and >70 y, respectively (38). In summary, higher dietary intake of magnesium may reduce CRC risk in Japanese men. Increased intake of magnesium-rich foods is recommended if other studies, including randomized controlled trials, confirm our findings.

Acknowledgments

S.T, S.S., and M.I. designed the research; E.M., S.S., M.I., R.T., and N.S. analyzed data; and E.M. and S.S. wrote the paper. All authors read and approved the final manuscript.

Literature Cited

1. Hartwig A. Role of magnesium in genomic stability. Mutat Res. 2001;475:113–21.
2. Wang A, Yoshimi N, Tanaka T, Mori H. Inhibitory effects of magnesium hydroxide on c-myc expression and cell proliferation induced by methylazoxymethanol acetate in rat colon. Cancer Lett. 1993;75:73–8.
3. Mori H, Morishita Y, Mori Y, Yoshimi N, Sugie S, Tanaka T. Effect of magnesium hydroxide on methylazoxymethanol acetate-induced epithelial proliferation in the large bowels of rats. Cancer Lett. 1992;62:43–8.
4. Wang A, Yoshimi N, Tanaka T, Mori H. The inhibitory effect of magnesium hydroxide on the bile acid-induced cell proliferation of colon epithelium in rats with comparison to the action of calcium lactate. Carcinogenesis. 1994;15:2661–3.
5. Folsom AR, Hong CP. Magnesium intake and reduced risk of colon cancer in a prospective study of women. Am J Epidemiol. 2006;163:232–5.
6. Larsson SC, Bergkvist L, Wolk A. Magnesium intake in relation to risk of colorectal cancer in women. JAMA. 2005;293:86–9.
7. Lin J, Cook NR, Lee IM, Manson JE, Buring JE, Zhang SM. Total magnesium intake and colorectal cancer incidence in women. Cancer Epidemiol Biomarkers Prev. 2006;15:2006–9.
8. van den Brandt PA, Smits KM, Goldbohm RA, Weijenberg MP. Magnesium intake and colorectal cancer risk in the Netherlands Cohort Study. Br J Cancer. 2007;96:510–3.
9. Bostick RM, Potter JD, Sellers TA, McKenzie DR, Kushi LH, Folsom AR. Relation of calcium, vitamin D, and dairy food intake to incidence of colon cancer among older women. The Iowa Women's Health Study. Am J Epidemiol. 1993;137:1302–17.
10. Cho E, Smith-Warner SA, Spiegelman D, Beeson WL, van den Brandt PA, Colditz GA, Folsom AR, Fraser GE, Freudenheim JL, et al. Dairy foods, calcium, and colorectal cancer: a pooled analysis of 10 cohort studies. J Natl Cancer Inst. 2004;96:1015–22.
11. Zheng W, Anderson KE, Kushi LH, Sellers TA, Greenstein J, Hong CP, Cerhan JR, Bostick RM, Folsom AR. A prospective cohort study of intake of calcium, vitamin D, and other micronutrients in relation to incidence of rectal cancer among postmenopausal women. Cancer Epidemiol Biomarkers Prev. 1998;7:221–5.
12. Dai Q, Shrubsole MJ, Ness RM, Schlundt D, Cai Q, Smalley WE, Li M, Shyr Y, Zheng W. The relation of magnesium and calcium intakes and a genetic polymorphism in the magnesium transporter to colorectal neoplasia risk. Am J Clin Nutr. 2007;86:743–51.
13. Inoue M, Iwasaki M, Otani T, Sasazuki S, Noda M, Tsugane S. Diabetes mellitus and the risk of cancer: results from a large-scale population-based cohort study in Japan. Arch Intern Med. 2006;166:1871–7.
14. Tsugane S, Sobue T. Baseline survey of JPHC study: design and participation rate. Japan Public Health Center-based Prospective Study on Cancer and Cardiovascular Diseases. J Epidemiol. 2001;11:S24–9.
15. Iwasaki M, Otani T, Yamamoto S, Inoue M, Hanaoka T, Sobue T, Tsugane S. Background characteristics of basic health examination participants: the JPHC Study Baseline Survey. J Epidemiol. 2003;13:216–25.
16. Ishihara J, Inoue M, Iwasaki M, Sasazuki S, Tsugane S. Dietary calcium, vitamin D, and the risk of colorectal cancer. Am J Clin Nutr. 2008;88:1576–83.
17. Council for Science and Technology; Ministry of Education, Culture, Sports, Science and Technology, Japan. Standard tables of food composition in Japan. 5th revised and enlarged ed. Tokyo: National Printing Bureau; 2005.
18. Ishihara J, Inoue M, Kobayashi M, Tanaka S, Yamamoto S, Iso H, Tsugane S. Impact of the revision of a nutrient database on the validity of a self-administered food frequency questionnaire (FFQ). J Epidemiol. 2006;16:107–16.
19. Watanabe S, Tsugane S, Sobue T, Konishi M, Baba S. Study design and organization of the JPHC study. Japan Public Health Center-based Prospective Study on cancer and cardiovascular diseases. J Epidemiol. 2001;11:S3–7.
20. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. Am J Epidemiol. 1986;124:17–27.
21. Otani T, Iwasaki M, Inoue M. Body mass index, body height, and subsequent risk of colorectal cancer in middle-aged and elderly Japanese men and women: Japan public health center-based prospective study. Cancer Causes Control. 2005;16:839–50.
22. Lee KJ, Inoue M, Otani T, Iwasaki M, Sasazuki S, Tsugane S. Physical activity and risk of colorectal cancer in Japanese men and women: the Japan Public Health Center-based prospective study. Cancer Causes Control. 2007;18:199–209.
23. Inoue M, Iso H, Yamamoto S, Kurahashi N, Iwasaki M, Sasazuki S, Tsugane S. Daily total physical activity level and premature death in men and women: results from a large-scale population-based cohort study in Japan (JPHC study). Ann Epidemiol. 2008;18:522–30.
24. Akizawa Y, Koizumi S, Itokawa Y, Ojima T, Nakamura Y, Tamura T, Kusaka Y. Daily magnesium intake and serum magnesium concentration among Japanese people. J Epidemiol. 2008;18:151–9.
25. Ministry of Health, Labor, and Welfare/Society for the Information on Health and Nutrition. The National Health and Nutrition Survey in Japan, 2005. Tokyo: Daiichi Shuppan Publishing Co., Ltd.; 2009. p. 88–97.
26. Hardwick LL, Jones MR, Brautbar N, Lee DB. Magnesium absorption: mechanisms and the influence of vitamin D, calcium and phosphate. J Nutr. 1991;121:13–23.
27. Hoenderop JG, Bindels RJ. Epithelial Ca2+ and Mg2+ channels in health and disease. J Am Soc Nephrol. 2005;16:15–26.
28. Wei MY, Garland CF, Gorham ED, Mohr SB, Giovannucci E. Vitamin D and prevention of colorectal adenoma: a meta-analysis. Cancer Epidemiol Biomarkers Prev. 2008;17:2958–69.
29. Schmitz C, Perraud AL, Johnson CO, Inabe K, Smith MK, Penner R, Kurosaki T, Fleig A, Scharenberg AM. Regulation of vertebrate cellular Mg2+ homeostasis by TRPM7. Cell. 2003;114:191–200.
30. Otani T, Iwasaki M, Sasazuki S, Inoue M, Tsugane S. Plasma C-peptide, insulin-like growth factor-I, insulin-like growth factor binding proteins and risk of colorectal cancer in a nested case-control study: the Japan public health center-based prospective study. Int J Cancer. 2007;120:2007–12.
31. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet. 2008;371:569–78.
32. Mizoue T, Tanaka K, Tsuji I, Wakai K, Nagata C, Otani T, Inoue M, Tsugane S. Alcohol drinking and colorectal cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. Jpn J Clin Oncol. 2006;36:582–97.
33. Matsuo K, Ito H, Wakai K, Hirose K, Saito T, Suzuki T, Kato T, Hirai T, Kanemitsu Y, et al. One-carbon metabolism related gene polymorphisms interact with alcohol drinking to influence the risk of colorectal cancer in Japan. Carcinogenesis. 2005;26:2164–71.
34. Sakurai M, Miura K, Takamura T, Ishizaki M, Morikawa Y, Nakamura K, Yoshita K, Kido T, Naruse Y, et al. J-shaped relationship between waist circumference and subsequent risk for Type 2 diabetes: an 8-year follow-up of relatively lean Japanese individuals. Diabet Med. 2009;26:753–9.
35. Kikuchi H, Iwane S, Munakata A, Tamura K, Nakaji S, Sugawara K. Trace element levels in drinking water and the incidence of colorectal cancer. Tohoku J Exp Med. 1999;188:217–25.
36. Wiklund L, Pousette J, George M. Magnesium intake, drinking water, and risk of colorectal cancer. Author reply. JAMA. 2005;293:2599.
37. Parkin DM, Bray F. Evaluation of data quality in the cancer registry: principles and methods Part II. Completeness. Eur J Cancer. 2009;45:756–64.
38. Ministry of Health, Labor, and Welfare, Japan, editor. Dietary reference intakes for Japanese, 2005. Tokyo: Daiichi Shuppan Publishing Co., Ltd.; 2005.

Identification of a Functional Genetic Variant at 16q12.1 for Breast Cancer Risk: Results from the Asia Breast Cancer Consortium

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Abstract

Genetic factors play an important role in the etiology of breast cancer. We carried out a multi-stage genome-wide association (GWA) study in over 28,000 cases and controls recruited from 12 studies conducted in Asian and European American women to identify genetic susceptibility loci for breast cancer. After analyzing 684,457 SNPs in 2,073 cases and 2,084 controls in Chinese women, we evaluated 53 SNPs for fast-track replication in an independent set of 4,425 cases and 1,915 controls of Chinese origin. Four replicated SNPs were further investigated in an independent set of 6,173 cases and 6,340 controls from seven other studies conducted in Asian women. SNP rs4784227 was consistently associated with breast cancer risk across all studies with adjusted odds ratios (95% confidence intervals) of 1.25 (1.20−1.31) per allele ($P = 3.2\times10^{-25}$) in the pooled analysis of samples from all Asian samples. This SNP was also associated with breast cancer risk among European Americans (per allele OR = 1.19, 95% CI = 1.09−1.31, $P = 1.3\times10^{-4}$, 2,797 cases and 2,662 controls). SNP rs4784227 is located at 16q12.1, a region identified previously for breast cancer risk among Europeans. The association of this SNP with breast cancer risk remained highly statistically significant in Asians after adjusting for previously-reported SNPs in this region. *In vitro* experiments using both luciferase reporter and electrophoretic mobility shift assays demonstrated functional significance of this SNP. These results provide strong evidence implicating rs4784227 as a functional causal variant for breast cancer in the locus 16q12.1 and demonstrate the utility of conducting genetic association studies in populations with different genetic architectures.

Citation: Long J, Cai Q, Shu X-O, Qu S, Li C, et al. (2010) Identification of a Functional Genetic Variant at 16q12.1 for Breast Cancer Risk: Results from the Asia Breast Cancer Consortium. PLoS Genet 6(6): e1001002. doi:10.1371/journal.pgen.1001002

Editor: Greg Gibson, Georgia Institute of Technology, United States of America

Received February 1, 2010; **Accepted** May 25, 2010; **Published** June 24, 2010

Funding: Genotyping assays and statistical analyses for this research were supported primarily through NIH grants R01CA124558, R01CA64277, R01CA70867, R01CA90899, and R01CA100374 (WZ), R01CA118229 (X-OS), and R01CA122756 (QC). Participating studies (Principal Investigator, grant support) in the consortium are as follows: the Shanghai Breast Cancer Study (WZ, R01CA64277), the Shanghai Breast Cancer Survival Study (X-OS, R01CA118229), the Shanghai Endometrial Cancer Study (X-OS, R01CA92585, contributing only controls to the consortium), the Nashville Breast Health Study (WZ, R01CA100374), the Tianjin Study (KC, the National Natural Science Foundation of China Grant No. 30771844), the Nanjing Study (HS, IRT0631, China), the Taiwan Biobank Study (C-YS, DOH97-01), the Hong Kong Study (USK, Research Grant Council, Hong Kong SAR, China, HKU 7520/05 M and 76730 M), the Multiethnic Cohort Study (BEH, CA63464; L. Kolonel, CA54281; and CAH, CA132839), the Nagano Breast Cancer Study (ST, Grants-in-Aid for the Third Term Comprehensive Ten-Year Strategy for Cancer Control from the Ministry of Health, Labor and Welfare of Japan, and for Scientific Research on Priority Areas (17015049) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan), the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (KT, Grants-in-Aid for Scientific Research on Priority Areas (17015052) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan H. Tanaka, Grants-in-Aid for the Third Term Comprehensive Ten-Year Strategy for Cancer Control from the Ministry of Health, Labor and Welfare of Japan, H20-002). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

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