populations, what are the plausible explanations? Japanese have a high prevalence of the slow-metabolizing variant of the aldehyde dehydrogenase gene (8). The variant induces increased and persisting blood levels of acetaldehyde after alcohol ingestion (10). The modifying effect of the aldehyde dehydrogenase variant on the association between alcohol drinking and colorectal cancer risk was suggested in an earlier Japanese study (32); however, it has recently been challenged by large-scale studies (33, 34). Therefore, it remains unclear whether the seemingly stronger association among Japanese is explained by a genetic difference in the efficiency of metabolizing alcohol among regular drinkers. Alternatively, the clearer contrast in risk between drinkers and nondrinkers in Japanese may be ascribed to more precise classification of the nonexposure reference group, which presumably included a higher proportion of lifetime abstainers who were genetically unable to metabolize acetaldehyde.

Nongenetic factors may contribute to the heterogeneity in risk among populations. Folate deficiency is hypothesized to enhance the adverse effect of alcohol (35), and if Japanese alcohol drinkers have a higher prevalence of folate deficiency than their Western counterparts, a stronger association may emerge. However, in the present study as well as the pooled analysis of Western studies (22), there was only limited evidence suggesting a modifying effect of dietary folate on the alcohol-colorectal cancer association. Thus, folate probably does not explain the difference in the strength of association between the Japanese and Western studies. Instead, we found a pronounced association with alcohol intake in men with the lowest body mass indices, a finding compatible with results from the pooled analysis of Western studies (22).

This differential association by body composition has been interpreted on the basis of the insulin hypothesis: Alcohol drinking improves insulin resistance (36), which is increased in obese people (37) and may be related to increased risk of colorectal cancer (38) or colon cancer (39); thus, the carcinogenic potential of alcohol could be partially cancelled through its favorable effects on insulin resistance among obese persons. However, such a favorable action of alcohol may not benefit lean persons, whose risk of developing cancer through an insulin-mediated pathway may be minimal. The apparently stronger alcohol-colorectal cancer association in Japanese is thus attributable, at least in part, to their lower body mass index relative to that of Westerners. Nevertheless, our finding for obese men, showing a significant increase in risk with alcohol intake—a finding that was not observed in the pooled analysis among Western populations (22)—suggests that other characteristics of Japanese may intensify the effects of alcohol in colorectal carcinogenesis.

We also found a significant association with an alcohol intake of $\geq$23 g/day in women. Although the data did not allow us to assess risk for specific categories of greater alcohol intake, the hazard ratio associated with a 15-g/day increase in alcohol consumption in women was comparable to that for men (HRs were 1.13 for women and 1.11 for men). As previously suggested (22, 31), the effects of alcohol drinking on colorectal cancer risk may be similar in magnitude for men and women.

There were several strengths in the present study. First, we analyzed data from cohort studies that used validated questionnaires to collect data on alcohol consumption. Second, each study controlled for a common set of variables that are known or suggested to cause or prevent colorectal cancer, and all investigators confirmed that additional adjustment for physical activity did not alter their results. Third, with a large number of habitual drinkers in men, we were able to examine the risk of moderate drinking with reasonable statistical power. This point should be important from a public-health point of view; even a small increase in risk for an exposure category with a large number of drinkers leads to a considerable increase in the total number of cases, as for the present case in men (but not in women). Lastly, we estimated hazard ratios with and without exclusion of ex-drinkers from the reference category, by which we could infer the influence of ex-drinking on the association between alcohol drinking and colorectal cancer.

Our study also had some limitations. First, we used only baseline information on alcohol drinking, and thus we could not assess the effects of lifetime alcohol consumption or changes in drinking habits during follow-up on colorectal cancer risk. Second, random variation related to exposure measurement might have attenuated the associations. Third, although investigators in each study adjusted their results extensively for factors associated with colorectal cancer risk, we cannot exclude the possibility that our estimates were distorted because of residual confounding.

In summary, this pooled analysis of data from large prospective studies carried out in Japan confirmed that alcohol drinking is associated with increased risk of colorectal cancer in a dose-response manner in men and women. Although moderate drinking is associated with decreased risk of overall mortality (40), the present finding in men, showing a statistically significant 42 percent increase in colorectal cancer risk with an alcohol intake of 23–45.9 g/day, calls for attention. If the present association is causal, one fourth of all cases of colorectal cancer among Japanese men are attributable to an alcohol intake of $\geq$23 g/day. Moderation of alcohol drinking is an important aspect of the prevention of colorectal cancer. Further research is required to elucidate the roles of genetic and environmental factors that modify the alcohol-colorectal cancer association.

ACKNOWLEDGMENTS

This work was supported by a grant (Third Term Comprehensive 10-Year Strategy for Cancer Control) from the Ministry of Health, Labour and Welfare, Japan.

The authors gratefully acknowledge the assistance of Izumi Suenega and Kie Nagao.

Members of the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan: *National Cancer Center, Tokyo*—Shoichiro Tsugane (Principal Investigator), Manami Inoue, Shizuka Sasazuki, Motoki Iwasaki, Tetsuya Otani (until 2006), Norie Kurahashi (since 2007), and Taichi Shimazu (since 2007); *Tohoku University, Sendai*—Ichiro Tsuji (since 2004) and Yoshitaka Tsubono

(in 2003); *Miyagi Cancer Research Institute, Miyagi*—Yoshikazu Nishino; *Nagoya University, Nagoya*—Kenji Wakai; *Aichi Cancer Center, Nagoya*—Keitaro Matsuo (since 2006); *Gifu University, Gifu*—Chisato Nagata; *International Medical Center of Japan, Tokyo*—Tetsuya Mizoue; *Saga University, Saga*—Keitaro Tanaka.

Conflict of interest: none declared.

REFERENCES

1. Parkin DM, Whelan SL, Ferlay J, et al, eds. Cancer incidence in five continents. Vol 8. (IARC Scientific Publication no. 155). Lyon, France: International Agency for Research on Cancer, 2002.
2. Statistics and Information Department, Minister's Secretariat, Japan Ministry of Health, Labour and Welfare. Age-adjusted death rates by prefecture: special report on vital statistics 2000. (In Japanese). Tokyo, Japan: Japan Health and Welfare Statistics Association, 2002.
3. Longnecker MP, Orza MJ, Adams ME, et al. A meta-analysis of alcoholic beverage consumption in relation to risk of colorectal cancer. Cancer Causes Control 1990;1:59–68.
4. Bagnardi V, Blangiardo M, La Vecchia C, et al. A meta-analysis of alcohol drinking and cancer risk. Br J Cancer 2001; 85:1700–5.
5. Moskal A, Norat T, Ferrari P, et al. Alcohol intake and colorectal cancer risk: a dose-response meta-analysis of published cohort studies. Int J Cancer 2007;120:664–71.
6. Baan R, Straif K, Grosse Y, et al. Carcinogenicity of alcoholic beverages. Lancet Oncol 2007;8:292–3.
7. International Agency for Research on Cancer. Consumption of alcoholic beverages and ethyl carbamate (urethane). (Meeting summary). (IARC monographs on the evaluation of carcinogenic risks to humans, vol 96). Lyon, France: International Agency for Research on Cancer, 2007. (http://monographs.iarc.fr/ENG/Meetings/vol96-summary.pdf). (Accessed May 1, 2007).
8. Takeshita T, Morimoto K, Mao X, et al. Characterization of the three genotypes of low Km aldehyde dehydrogenase in a Japanese population. Hum Genet 1994;94:217–23.
9. International Agency for Research on Cancer. Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide. (IARC monographs on the evaluation of carcinogenic risks to humans, vol 71). Lyon, France: International Agency for Research on Cancer, 1999.
10. Agarwal DP, Goedde HW. Pharmacogenetics of alcohol metabolism and alcoholism. Pharmacogenetics 1992;2:48–62.
11. Mizoue T, Tanaka K, Tsuji I, et al. 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.
12. Shimizu N, Nagata C, Shimizu H, 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.
13. Otani T, Iwasaki M, Yamamoto S, 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.
14. Wakai K, Kojima M, Tamakoshi K, et al. Alcohol consumption and colorectal cancer risk: findings from the Japan Collaborative Cohort Study. J Epidemiol 2005;15(suppl 2):173S–9S.
15. Akhter M, Kuriyama S, Nakaya N, et al. Alcohol consumption is associated with an increased risk of distal colon and rectal cancer in Japanese men: The Miyagi Cohort Study. Eur J Cancer 2007;43:383–90.
16. 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(suppl):24S–9S.
17. Tamakoshi A, Yoshimura T, Inaba Y, et al. Profile of the JACC Study. J Epidemiol 2005;15(suppl 1):4S–8S.
18. Tsuji I, Nishino Y, Tsubono Y, et al. Follow-up and mortality profiles in the Miyagi Cohort Study. J Epidemiol 2004;14(suppl 1): 2S–6S.
19. Department of Epidemiology and Preventive Medicine, Gifu University School of Medicine. Profile of Takayama cohort. In: Interim report of Takayama Study. Gifu, Japan: Gifu University School of Medicine, 2005:1–8.
20. World Health Organization. International classification of diseases for oncology. Third Edition. Geneva, Switzerland: World Health Organization, 2000.
21. World Health Organization. International classification of diseases and related health problems. Tenth Revision. Geneva, Switzerland: World Health Organization, 1990.
22. Cho E, Smith-Warner SA, Ritz J, et al. Alcohol intake and colorectal cancer: a pooled analysis of 8 cohort studies. Ann Intern Med 2004;140:603–13.
23. Marugame T, Yamamoto S, Yoshimi I, et al. Patterns of alcohol drinking and all-cause mortality: results from a large-scale population-based cohort study in Japan. Am J Epidemiol 2007; 165:1039–46.
24. Ogawa K, Tsubono Y, Nishino Y, et al. Validation of a food-frequency questionnaire for cohort studies in rural Japan. Public Health Nutr 2003;6:147–57.
25. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
26. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. Am J Public Health 1998;88:15–19.
27. Hillman RS, Steinberg SE. The effects of alcohol on folate metabolism. Ann Rev Med 1982;33:345–54.
28. Homann N, Tillonen J, Salaspuro M. Microbially produced acetaldehyde from ethanol may increase the risk of colon cancer via folate deficiency. Int J Cancer 2000;86:169–73.
29. Sanjoaquin MA, Allen N, Couto E, et al. Folate intake and colorectal cancer risk: a meta-analytical approach. Int J Cancer 2005;113:825–8.
30. Cho E, Smith-Warner SA, Spiegelman D, et al. Dairy foods, calcium, and colorectal cancer: a pooled analysis of 10 cohort studies. J Natl Cancer Inst 2004;96:1015–22.
31. Ferrari P, Jenab M, Norat T, et al. Lifetime and baseline alcohol intake and risk of colon and rectal cancers in the European Prospective Investigation into Cancer and Nutrition (EPIC). Int J Cancer 2007;121:2065–72.
32. Murata M, Tagawa M, Watanabe S, et al. Genotype difference of aldehyde dehydrogenase 2 gene in alcohol drinkers influences the incidence of Japanese colorectal cancer patients. Jpn J Cancer Res 1999;90:711–19.
33. Matsuo K, Wakai K, Hirose K, et al. A gene-gene interaction between *ALDH2* Glu487Lys and *ADH2* His47Arg polymorphisms regarding the risk of colorectal cancer in Japan. Carcinogenesis 2006;27:1018–23.
34. Yin G, Kono S, Toyomura K, et al. Alcohol dehydrogenase and aldehyde dehydrogenase polymorphisms and colorectal cancer: The Fukuoka Colorectal Cancer Study. Cancer Sci 2007; 98:1248–53.
35. Giovannucci E. Alcohol, one-carbon metabolism, and colorectal cancer: recent insights from molecular studies. J Nutr 2004;134(suppl):2475S–81S.

36. Facchini F, Chen YD, Reaven GM. Light-to-moderate alcohol intake is associated with enhanced insulin sensitivity. Diabetes Care 1994;17:115–19.
37. Colditz GA, Willett WC, Stampfer MJ, et al. Weight as a risk factor for clinical diabetes in women. Am J Epidemiol 1990;132:501–13.
38. La Vecchia C, Negri E, Decarli A, et al. Diabetes mellitus and colorectal cancer risk. Cancer Epidemiol Biomarkers Prev 1997;6:1007–10.
39. Inoue M, Iwasaki M, Otani T, et al. Diabetes mellitus and the risk of cancer: results from a large-scale population-based cohort study in Japan. Arch Intern Med 2006;5;166: 1871–7.
40. Tsugane S, Fahey MT, Sasaki S, et al. Alcohol consumption and all-cause and cancer mortality among middle-aged Japanese men: seven-year follow-up of the JPHC Study Cohort I. Am J Epidemiol 1999;150:1201–7.