AEP Vol. 17, No. 4
April 2007: 304–312

whereas a major finding in Western countries was the identification of an inverse association (10, 11, 14). The inverse association in premenopausal women may be attributed to a decrease in circulating estrogen levels, reflecting an increased frequency of anovulatory cycles (41, 42). However, a pooled analysis of seven prospective studies indicated that the inverse association is limited mainly to women with a BMI of 31 kg/m^2 or more (11). Obese women, defined by a BMI of 30 kg/m^2 or more, account for only approximately 3% of Japanese women, but for approximately 33% of US women (6, 7). This is one potential explanation for the lack of an inverse association in the present study.

Obesity leads to a state of relative insulin resistance, chronic hyperinsulinemia, and an increase in IGF-I bioactivity because of insulin-mediated decreases in IGF-binding protein 1 (IGFBP-1) and IGFBP-2. Insulin was shown to be a growth factor for breast cancer cells, and level of C-peptide, a marker of hyperinsulinemia and insulin resistance, predicted breast cancer risk (43). Meta-analysis of IGF-I measured in prospective studies found a positive association with risk for premenopausal, but not postmenopausal, breast cancer (44). Nagata et al. (45) reported that weight and percentage of body fat correlated positively with serum IGF-I levels in premenopausal Japanese women. This might be one reason for the positive association in this study.

An additional potential reason for the positive association of weight and BMI with breast cancer for premenopausal women in this study also should be considered. Among women who were premenopausal at baseline, some portion of breast cancer cases occurred after menopause, given that they were followed up for approximately 10 years on average, during which time some premenopausal women reached menopause. The observed positive association therefore might partly reflect results of postmenopausal women. When we calculated HRs and 95% CIs for breast cancer in patients diagnosed before menopause or age 50 years, given that nearly 95% of our subjects older than 50 years had reached menopause, HRs for BMI were attenuated, particularly in the BMI category of greater than 30 kg/m^2, although a similar result also was found for weight.

Given that the action of estrogen and progesterone on breast cell proliferation appears to be mediated by ER and PR (46, 47), risk factors associated most closely with ER$^+$ and/or PR$^+$ breast cancer may involve mechanisms related to estrogen and progesterone exposure (17–19). Conversely, the cause of ER$^-$ and/or PR$^-$ breast cancer may be independent of hormonal exposure (19). In accord with the present results, several previous studies in Western countries showed that BMI was associated more closely with hormone receptor–positive than –negative breast cancer risk (17–19, 48, 49). This finding indicates that BMI is associated with increased risk for ER$^+$, rather than ER$^-$, breast cancer through hormone-related mechanisms, as mentioned.

With regard to the role of ER status in breast cancer cause, two hypotheses were proposed; namely, that ER status represents different stages in the natural history of the disease and that it represents two distinct forms of breast cancer (16). The present finding that risk-factor profile may differ between these subtypes supports the hypothesis that ER status identifies different types of breast cancer, rather than different stages in the disease process.

The present study has several method advantages. First, we included a considerably larger number of cases (n = 430) than in the largest cohort study conducted in Asian countries to date (n = 161) (21). Second, our prospective design potentially avoids selection bias and recall bias. Finally, we included a large population-based sample with a high response rate (>80%) and low rate of loss to follow-up. Nonetheless, results listed in Table 3 should be interpreted carefully because our data for hormone receptor status were limited: the small number of cases in each subgroup analysis by menopausal status and hormone receptor status limited statistical power, whereas nonstandardized receptor assays may have attenuated the true risk.

In conclusion, our findings suggest that height, weight, and BMI are risk factors for breast cancer among postmenopausal women in Japan. The positive association of weight and BMI might be limited to ER$^+$ breast cancer. Clarification of the role of hormone receptor status in breast cancer cause requires additional studies that include a larger number of cases and investigate not only hormone receptor status, but also detailed information on such tumor characteristics as stage, histologic type, and others.

The authors thank all staff members in each study area and the central offices for their cooperation and technical assistance and the Iwate, Aomori, Ibaraki, Niigata, Osaka, Kochi, Nagasaki, and Okinawa Cancer Registries for their provision of incidence data.

Study Group Members

Members of the JPHC Study Group (principal investigator: S. Tsugane): 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, and A. Okayama, National Cardiovascular Center, Suita; K. Miyakawa, F. Saito, A. Koizumi, Y. Sano, and I. Hashimoto, Iwate Prefectural Ninohe Public Health Center, Ninohe; Y. Miyajima, N. Suzuki, S. Nagasawa, and Y. Furusugi, Akita Prefectural Yokote Public Health Center, Yokote; H. Sanada, Y. Hatayama, F. Kobayashi, H. Uchino, Y. Shirai, T. Kondo, R. Sasaki, Y. Watanabe, and Y. Miyagawa, 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, and F. Shoji, Katsushika Public Health Center, Tokyo; A. Murata, K. Minato, K. Motegi, and T. Fujieda, Ibaraki Prefectural Mito Public Health Center, Mito; K. Matsui, T. Abe, M. Katagiri, and M. Suzuki, Niigata Prefectural Kashiwazaki and Nagaoka Public Health Center, Kashiwazaki and Nagaoka; M. Doi, A. Terao, and Y. Ishikawa, Kochi Prefectural Chuo-higashi Public Health Center, Tosayamada; H. Sueta, H. Doi, M. Urata, N. Okamoto, and F. Ide, Nagasaki Prefectural Kamigoto Public Health Center, Arikawa; H. Sakiyama,

N. Onga, and H. Takaesu, Okinawa Prefectural Miyako Public Health Center, Hirara; F. Horii, I. Asano, H. Yamaguchi, K. Aoki, S. Maruyama, and M. Ichii, 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, and K. Okada, Ehime University, Toon; H. Iso, Osaka University, Suita; Y. Honda and K. Yamagishi, 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 and W. Ajiki, 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; S. Kono, Kyushu University, Fukuoka; K. Suzuki, Research Institute for Brain and Blood Vessels Akita, Akita; Y. Takashima, Kyorin University, Mitaka; E. Maruyama, Kobe University, Kobe; the late M. Yamaguchi, Y. Matsumura, S. Sasaki, and S. Watanabe, National Institute of Health and Nutrition, Tokyo; T. Kadowaki, Tokyo University, Tokyo; Y. Kawaguchi, Tokyo Medical and Dental University, Tokyo; H. Shimizu, Sakihae Institute, Gifu.

REFERENCES

1. The Research Group for Population-based Cancer Registration in Japan. Cancer incidence and incidence rates in Japan in 1998: Estimates based on data from 12 population-based cancer registries. Jpn J Clin Oncol. 2003;33:241–245.
2. Minami Y, Tsubono Y, Nishino Y, Ohuchi N, Shibuya D, Hisamichi S. The increase of female breast cancer incidence in Japan: Emergence of birth cohort effect. Int J Cancer. 2004;108:901–906.
3. Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB. Cancer Incidence in Five Continents, vol VIII. IARC Scientific Publications no.155. Lyon: International Agency for Research on Cancer; 2002.
4. Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002 Cancer Incidence, Mortality and Prevalence Worldwide, IARC CancerBase No. 5, version 2.0. Lyon: IARC; 2004.
5. Ministry of Health, Labour and Welfare. Kokumin Eiyo no Genjou Results of National Nutrition Survey, 2002 [Japanese]. Tokyo: Daiichi Shuppan; 2004.
6. Yoshiike N, Seino F, Tajima S, Arai Y, Kawano M, Furuhata T, et al. Twenty-year changes in the prevalence of overweight in Japanese adults: The National Nutrition Survey 1976-95. Obes Rev. 2002;3:183–190.
7. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999-2000. JAMA. 2002;288:1723–1727.
8. Bergstrom A, Pisani P, Tenet V, Wolk A, Adami HO. Overweight as an avoidable cause of cancer in Europe. Int J Cancer. 2001;91:421–430.
9. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004;363:157–163.
10. Friedenreich CM. Review of anthropometric factors and breast cancer risk. Eur J Cancer Prev. 2001;10:15–32.
11. van den Brandt PA, Spiegelman D, Yaun SS, Adami HO, Beeson L, Folsom AR, et al. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. Am J Epidemiol. 2000;152:514–527.
12. Lahmann PH, Hoffmann K, Allen N, van Gils CH, Khaw KT, Tehard B, et al. Body size and breast cancer risk: Findings from the European Prospective Investigation into Cancer and Nutrition (EPIC). Int J Cancer. 2004;111:762–771.
13. Vatten LJ, Kvinnsland S. Body height and risk of breast cancer. A prospective study of 23,831 Norwegian women. Br J Cancer. 1990;61:881–885.
14. Ursin G, Longnecker MP, Haile RW, Greenland S. A meta-analysis of body mass index and risk of premenopausal breast cancer. Epidemiology. 1995;6:137–141.
15. Yasui Y, Potter JD. The shape of age-incidence curves of female breast cancer by hormone-receptor status. Cancer Causes Control. 1999;10:431–437.
16. Habel LA, Stanford JL. Hormone receptors and breast cancer. Epidemiol Rev. 1993;15:209–219.
17. Althuis MD, Fergenbaum JH, Garcia Closas M, Brinton LA, Madigan MP, Sherman ME. Etiology of hormone receptor-defined breast cancer: A systematic review of the literature. Cancer Epidemiol Biomarkers Prev. 2004;13:1558–1568.
18. Potter JD, Cerhan JR, Sellers TA, McGovern PG, Drinkard C, Kushi LR, et al. Progesterone and estrogen receptors and mammary neoplasia in the Iowa Women's Health Study: How many kinds of breast cancer are there? Cancer Epidemiol Biomarkers Prev. 1995;4:319–326.
19. Huang WY, Newman B, Millikan RC, Schell MJ, Hulka BS, Moorman PG. Hormone-related factors and risk of breast cancer in relation to estrogen receptor and progesterone receptor status. Am J Epidemiol. 2000;151:703–714.
20. Yoo KY, Tajima K, Miura S, Takeuchi T, Hirose K, Risch H, et al. Breast cancer risk factors according to combined estrogen and progesterone receptor status: A case-control analysis. Am J Epidemiol. 1997;146:307–314.
21. Goodman MT, Cologne JB, Moriwaki H, Vaeth M, Mabuchi K. Risk factors for primary breast cancer in Japan: 8-Year follow-up of atomic bomb survivors. Prev Med. 1997;26:144–153.
22. Wu MH, Chou YC, Yu JC, Yu CP, Wu CC, Chu CM, et al. Hormonal and body-size factors in relation to breast cancer risk: A prospective study of 11,889 women in a low-incidence area. Ann Epidemiol. 2006;16:223–229.
23. Kuriyama S, Tsubono Y, Hozawa A, Shimazu T, Suzuki Y, Koizumi Y, et al. Obesity and risk of cancer in Japan. Int J Cancer. 2005;113:148–157.
24. Lawson JS, Field AS, Champion S, Tran D, Ishikura H, Trichopoulos D. Low oestrogen receptor alpha expression in normal breast tissue underlies low breast cancer incidence in Japan. Lancet. 1999;354:1787–1788.
25. Nomura Y, Kobayashi S, Takatani O, Sugano H, Matsumoto K, McGuire WL. Estrogen receptor and endocrine responsiveness in Japanese versus American breast cancer patients. Cancer Res. 1977;37:106–110.
26. Matsumoto K, Kitamura Y, Sugano H. Hormone receptors and Japanese breast cancer. Acta Pathol Jpn. 1982;32(Suppl 1):S145–S154.
27. Watanabe S, Tsugane S, Sobue T, Konishi M, Baba S. Study design and organization of the JPHC Study. J Epidemiol. 2001;11(Suppl):S3–S7.
28. Tsugane S, Sasaki S, Tsubono Y. Under- and overweight impact on mortality among middle-aged Japanese men and women: A 10-y follow-up of JPHC Study cohort I. Int J Obes. 2002;26:529–537.
29. Lin DY, Wei LJ, Ying Z. Checking the Cox model with cumulative sums of martingale-based residuals. Biometrika. 1993;80:557–572.
30. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. Am J Epidemiol. 1993;138:923–936.
31. Wei LJ, Lin DY, Weissfeld L. Regression analysis of multivariate incomplete failure time data by modeling marginal distribution. J Am Stat Assoc. 1989;84:1065–1073.
32. Chie WC, Li CY, Huang CS, Chang KJ, Lin RS. Body size as a factor in different ages and breast cancer risk in Taiwan. Anticancer Res. 1998;18:565–570.
33. Tung HT, Tsukuma H, Tanaka H, Kinoshita N, Koyama Y, Ajiki W, et al. Risk factors for breast cancer in Japan, with special attention to anthropometric measurements and reproductive history. Jpn J Clin Oncol. 1999;29:137–146.
34. Hirose K, Tajima K, Hamajima N, Inoue M, Takezaki T, Kuroishi T, et al. A large-scale, hospital-based case-control study of risk factors of breast cancer according to menopausal status. Jpn J Cancer Res. 1995;86:146–154.
35. Shu XO, Jin F, Dai Q, Shi JR, Potter JD, Brinton LA, et al. Association of body size and fat distribution with risk of breast cancer among Chinese women. Int J Cancer. 2001;94:449–455.

36. Albanes D. Caloric intake, body weight, and cancer: A review. Nutr Cancer. 1987;9:199–217.
37. Stoll BA. Breast cancer risk in Japanese women with special reference to the growth hormone-insulin-like growth factor axis. Jpn J Clin Oncol. 1992;22:1–5.
38. Juul A, Bang P, Hertel NT, Main K, Dalgaard P, Jorgensen K, et al. Serum insulin-like growth factor-I in 1030 healthy children, adolescents, and adults: Relation to age, sex, stage of puberty, testicular size, and body mass index. J Clin Endocrinol Metab. 1994;78:744–752.
39. Trichopoulos D, Lagiou P, Adami HO. Towards an integrated model for breast cancer etiology: The crucial role of the number of mammary tissue-specific stem cells. Breast Cancer Res. 2005;7:13–17.
40. Hirose K, Tajima K, Hamajima N, Takezaki T, Inoue M, Kuroishi T, et al. Effect of body size on breast-cancer risk among Japanese women. Int J Cancer. 1999;80:349–355.
41. International Agency for Research on Cancer. IARC Handbooks of Cancer Prevention Volume 6 Weight Control and Physical Activity. Lyon: IARC; 2002.
42. Potischman N, Swanson CA, Siiteri P, Hoover RN. Reversal of relation between body mass and endogenous estrogen concentrations with menopausal status. J Natl Cancer Inst. 1996;88:756–758.
43. Bruning PF, Bonfrer JM, van Noord PA, Hart AA, de Jong Bakker M, Nooijen WJ. Insulin resistance and breast-cancer risk. Int J Cancer. 1992;52:511–516.
44. Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: Systematic review and meta-regression analysis. Lancet. 2004;363:1346–1353.
45. Nagata C, Shimizu H, Takami R, Hayashi M, Takeda N, Yasuda K. Dietary soy and fats in relation to serum insulin-like growth factor-1 and insulin-like growth factor-binding protein-3 levels in premenopausal Japanese women. Nutr Cancer. 2003;45:185–189.
46. Pike MC, Spicer DV, Dahmoush L, Press MF. Estrogens, progestogens, normal breast cell proliferation, and breast cancer risk. Epidemiol Rev. 1993;15:17–35.
47. Clemons M, Goss P. Estrogen and the risk of breast cancer. N Engl J Med. 2001;344:276–285.
48. Yoo K, Tajima K, Park S, Kang D, Kim S, Hirose K, et al. Postmenopausal obesity as a breast cancer risk factor according to estrogen and progesterone receptor status (Japan). Cancer Lett. 2001;167:57–63.
49. Macinnis RJ, English DR, Gertig DM, Hopper JL, Giles GG. Body size and composition and risk of postmenopausal breast cancer. Cancer Epidemiol Biomarkers Prev. 2004;13:2117–2125.

Role and impact of menstrual and reproductive factors on breast cancer risk in Japan

Motoki Iwasaki, Tetsuya Otani, Manami Inoue, Shizuka Sasazuki, Shoichiro Tsugane and for the Japan Public Health Center-based Prospective Study Group

The aim of this study was to clarify the role and impact of menstrual and reproductive factors in relation to breast cancer and its hormone receptor-defined subtype, overall and separately among premenopausal and postmenopausal women in a low-risk population, using data from the Japan Public Health Center-based Prospective study. A total of 55 537 women aged 40–69 years completed a self-administered questionnaire, which included items about menstrual and reproductive history. During 1990–2002, 441 newly diagnosed cases of breast cancer were identified. Early age at menarche for premenopausal women, late age at natural menopause, nulliparity and low parity for both premenopausal and postmenopausal women, and late age at first birth for postmenopausal women were significantly associated with an increased risk of breast cancer. No overall significant associations were seen between the use of exogenous female hormones or breast feeding and breast cancer risk. Age at menarche and age at natural menopause were somewhat more closely associated with the risk of progesterone receptor-negative than positive breast cancer although no difference was observed for estrogen receptor status. Risks associated with parity, number of births and age at first birth did not significantly differ by hormone receptor-defined breast cancer. Our findings suggest that menstrual and reproductive factors may play an important role in the development of breast cancer among low-risk populations, similarly as they do in Western populations, and that risk factors might differ by hormone receptor status. *European Journal of Cancer Prevention* **16:116–123 © 2007 Lippincott Williams & Wilkins.**

European Journal of Cancer Prevention 2007, 16:116–123

Keywords: breast cancer, hormone receptor, menstrual factors, reproductive factors, prospective study

Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan

Correspondence to Motoki Iwasaki, MD, PhD, Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
Tel: +81 3 3542 2511 ext. 3389; fax: +81 3 3547 8578;
e-mail: moiwasak@gan2.res.ncc.go.jp

Sponsorship: This study was supported by Grants-in-Aid for Cancer Research, for the Third Term Comprehensive Ten-Year Strategy for Cancer Control, and for Research on Risk of Chemical Substances from the Ministry of Health, Labour and Welfare of Japan, and Grants-in-Aid for Scientific Research on Priority Areas (17015049) and for Young Scientists (B) (17790378) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan and Japan Society for the Promotion of Science.

Members of the Japan Public Health Center-based Prospective Study Group: S. Tsugane (principal investigator), M. Inoue, T. Sobue and T. Hanaoka, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo; J. Ogata, S. Baba, T. Mannami and A. Okayama, National Cardiovascular Center, Suita; K. Miyakawa, F. Saito, A. Koizumi, Y. Sano and I. Hashimoto, Iwate Prefectural Ninohe Public Health Center, Ninohe; Y. Miyajima, N. Suzuki, S. Nagasawa and Y. Furusugi, Akita Prefectural Yokote Public Health Center, Yokote; H. Sanada, Y. Hatayama, F. Kobayashi, H. Uchino, Y. Shirai, T. Kondo, R. Sasaki, Y. Watanabe and Y. Miyagawa, Nagano Prefectural Saku Public Health Center, Saku; Y. Kishimoto, E. Takara, T. Fukuyama, M. Kinjo, M. Irei and H. Sakiyama, Okinawa Prefectural Ishikawa (Chubu) Public Health Center, Ishikawa; K. Imoto, H. Yazawa, T. Seo, A. Seiko, F. Ito and F. Shoji, Katsushika Public Health Center, Tokyo; A. Murata, K. Minato, K. Motegi and T. Fujieda, Ibaraki Prefectural Kasama (Mito) Public Health Center, Mito; K. Matsui, T. Abe, M. Katagiri and M. Suzuki, Niigata Prefectural Kashiwazaki and Nagaoka Public Health Center, Kashiwazaki and Nagaoka; M. Doi, A. Terao and Y. Ishikawa, Kochi Prefectural Tosayamada (Chuo-higashi) Public Health Center, Tosayamada; H. Sueta, H. Doi, M. Urata, N. Okamoto and F. Ide, Nagasaki Prefectural Arikawa (Kamigoto) Public Health Center, Arikawa; H. Sakiyama, N. Onga and H. Takaesu, Okinawa Prefectural Miyako Public Health Center, Hirara; F. Horii, I. Asano, H. Yamaguchi, K. Aoki, S. Maruyama and M. Ichii, 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 and K. Okada, Ehime University, Matsuyama; H. Iso, Osaka University, Suita; Y. Honda and K. Yamagishi, 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 Centre Research Institute, Nagoya; M. Iida and W. Ajiki, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka; S. Sato, Osaka Medical Center for Health Science and Promotion, Osaka; N. Yasuda, Kochi University, Kochi; S. Kono, Kyushu University, Fukuoka; K. Suzuki, Research Institute for Brain and Blood Vessels Akita, Akita; Y. Takashima, Kyorin University, Mitaka; E. Maruyama, Kobe University, Kobe; the late M. Yamaguchi, Y. Matsumura, S. Sasaki and S. Watanabe, National Institute of Health and Nutrition, Tokyo; T. Kadowaki, Tokyo University, Tokyo; Y. Kawaguchi, Tokyo Medical and Dental University, Tokyo.

Received 20 November 2005 **Accepted** 15 February 2006

Introduction

Although Japan has a relatively low risk for female breast cancer (Parkin *et al.*, 2002), the incidence rate has gradually increased over the last 30 years (The Research Group for Population-based Cancer Registration in Japan, 2003; Minami *et al.*, 2004). Interestingly, the age-specific breast cancer incidence rate in Japan shows a unique pattern: rates after the age of 50 years decrease or flatten with increasing age (The Research Group for Population-based Cancer Registration in Japan, 2003), while those in Western countries continue to increase after menopause (Yasui and Potter, 1999). As this drop in age-specific

0959-8278 © 2007 Lippincott Williams & Wilkins

incidence occurs around the average age of natural menopause, the etiology of premenopausal breast cancer seems to differ from that of postmenopausal cancer. In addition, the age-specific incidence rate differs by estrogen and progesterone receptor (ER/PR) status; that of ER-positive (ER +)/PR-positive (PR +) breast cancer shows an approximately constant rate of increase in the postmenopausal period, whereas that of ER-negative (ER−)/PR + and ER-/PR-negative (PR−) cancer decreases or remains unchanged after menopause (Yasui and Potter, 1999). This observation may suggest that the large international variation in breast cancer incidence rate is due to differences in risk for different hormone receptor subtypes.

The epidemiology of breast cancer has been widely studied in a large number of populations, particularly among high-risk Caucasians (Kelsey *et al.*, 1993). Although previous studies in Western countries have consistently shown early age at menarche, late age at menopause, nulliparity and late age at first birth as the major risk factors (Paffenbarger *et al.*, 1980; Ewertz and Duffy, 1988; Layde *et al.*, 1989; Albrektsen *et al.*, 1994; Talamini *et al.*, 1996; Chie *et al.*, 2000; Clavel Chapelon, 2002), these findings should be considered in view of the inconclusivity and overall paucity of epidemiological studies comparing risk factors for hormone receptor-defined breast cancer (Habel and Stanford, 1993; Potter *et al.*, 1995; Yoo *et al.*, 1997; Huang *et al.*, 2000; Althuis *et al.*, 2004). Studies in Asian countries, albeit few in number, have produced findings on menstrual and reproductive factors generally consistent with those in Western countries (Hirose *et al.*, 1995; Nagata *et al.*, 1995; Goodman *et al.*, 1997; Gao *et al.*, 2000; Tamakoshi *et al.*, 2005), and the increasing incidence in Japanese women may be explained by the increasing prevalence of Japanese women with these risk factors (Minami *et al.*, 2004). Even more so than in Western populations, however, little is known about differences in risk estimates for well known risk factors by hormone receptor-defined subtypes in Asian populations (Yoo *et al.*, 1997).

The purpose of the present study was to clarify the role and impact of menstrual and reproductive factors in relation to breast cancer and its hormone receptor-defined subtype, overall and separately in premenopausal and postmenopausal women. Specifically, we used data from a large-scale population-based prospective cohort in Japanese women to examine the association of well known risk factors such as age at menarche, age at menopause, use of exogenous female hormones, parity, age at first birth and breast feeding with breast cancer, and further investigated the relationship of these factors with hormone receptor-defined subtype.

Materials and methods

Study cohort

The Japan Public Health Center-based Prospective Study (JPHC Study), which began in 1990 for cohort I and in 1993 for cohort II, included 140 420 study participants (68 722 men and 71 698 women) living in 29 municipalities supervised by 11 public health centers (PHCs). The study population was defined as all registered Japanese inhabitants aged 40–59 years at baseline in cohort I, except for Katsushika PHC in Tokyo, which enrolled participants of a health check-up program; and 40–69 years at baseline in cohort II, except for those from Suita PHC in Osaka Prefecture, which enrolled two populations, namely participants of a health check-up program and residents randomly selected from that area's population registry. Details of the study design have been reported elsewhere (Watanabe *et al.*, 2001). The JPHC study was approved by the Institutional Review Board of the National Cancer Center, Tokyo, Japan.

In the present analysis, participants from Katsushika PHC (2919 men and 4178 women) were not included because incidence data for them were not collected. During follow-up, 95 women were found to be ineligible for participation and were excluded because of non-Japanese nationality ($n = 20$), late report of relocation out of the study area before the start of follow-up ($n = 69$), age ineligibility due to an incorrect date of birth ($n = 5$) and duplicate registration ($n = 1$). The final population-based cohort consisted of 67 426 women, 27 389 in cohort I and 40 037 in cohort II.

Baseline questionnaire survey

A self-administered questionnaire was distributed by hand or mail to the JPHC study participants in 1990 (cohort I) and 1993–1994 (cohort II). The participants were asked about their personal and family medical histories, menstrual and reproductive history, anthropometric factors, smoking history, habitual intake of foods and beverages (including alcohol), physical activity and other lifestyle factors. Among eligible participants, 55 891 women (83%) [22 482 (82%) in cohort I and 33 409 (83%) in cohort II] returned valid responses. Among respondents, those with a history of breast cancer were excluded ($n = 354$).

The questions on menstrual and reproductive history included age at menarche, menopausal status at baseline, age at menopause, use of exogenous female hormones, parity, age at first birth and history of breast feeding. Regarding female hormone use, because both oral contraceptives and hormone replacement therapy were rarely used in Japan at the time of the baseline survey (Liu *et al.*, 2005), participants were simply asked whether they had experience of using exogenous female hormones. For analysis, these menstrual and reproductive

Table 1 Characteristics of study participants at baseline

	All participants	Premenopausal women	Postmenopausal women
Number of participants	55 537	21 953	32 440
Age (years)[a]	52.0 ± 8.0	44.6 ± 3.8	56.9 ± 6.2
Family history of breast cancer (yes) (%)	1.1	1.2	1.0
History of mastopathy (yes) (%)	4.3	5.6	3.4
Age at menarche (years)[a]	14.7 ± 1.9	13.8 ± 1.5	15.3 ± 2.0
Age at natural menopause (years)[a]	-	-	49.3 ± 3.5
Use of exogenous female hormones (current users) (%)	1.1	1.2	1.1
Parity (nulliparous) (%)	6.3	6.2	6.4
Number of births[a]	2.7 ± 1.5	2.5 ± 1.2	2.9 ± 1.7
Age at first birth (years)[a]	24.9 ± 3.5	25.0 ± 3.5	24.8 ± 3.5
Breast feeding (yes) (%)	87.3	84.4	89.3
Height (cm)[a]	151.9 ± 5.6	153.5 ± 5.3	150.9 ± 5.6
Body mass index (kg/m^2)[a]	23.4 ± 3.2	23.1 ± 3.1	23.6 ± 3.2
Smoking status (current smokers) (%)	6.8	8.1	5.8
Alcohol consumption (100 g ethanol or more per week) (%)	4.1	5.6	3.1
Physical exercise (once or more per week) (%)	18.0	16.5	19.1
Miso soup consumption (three or more bowls per day) (%)	16.5	13.8	18.3
Green vegetable intake (everyday) (%)	30.4	26.4	33.3

[a]Values are reported as means with standard deviations.

factors were arbitrarily categorized as shown in Tables 2 and 3.

Follow-up and identification of cancer cases

All registered participants were followed from the start of the study period to 31 December 2002. Data on residential relocation were obtained from residential registries. Among study participants, 3981 (7.1%) moved out of the study area and 27 (0.05%) were lost to follow-up within the study at-risk period. Death certificates coded according to the requirements of the Ministry of Health, Labor and Welfare were collected through local PHCs. Incidence data on breast cancer were collected through two data sources, major local hospitals and population-based cancer registries (usually prefecture-based). Death certificates were used to supplement the information on cancer incidence. Cancer incidence data were collected only for participants living in the study area. Site of origin and histologic type were coded by members of our study group using the International Classification of Diseases for Oncology, third edition (ICD-O-3), code: C500-509. Information on ER and PR status was collected from medical records or pathology reports. Hormone receptor status was determined in a relatively large number of clinical laboratories, primarily using enzyme-linked immunoassay rather than immunohistochemical techniques. Hormone receptor positivity values were determined either as specified by the laboratory that performed the assay, or in accordance with the laboratory's written interpretation thereof, or both. Up to the end of the study period, 441 new breast cancer cases were identified among 55 537 women. Diagnosis was microscopically verified in 97% of cases. During the same period, 56 breast cancer deaths were identified through death certificates (mortality/incidence ratio = 0.13), giving a ratio of 0.9% of cases identified by death certificate only.

Statistical analysis

Person-years of follow-up were calculated from the baseline survey until the date of diagnosis of breast cancer, date of relocation from the study area, date of death or end of the study period (31 December 2002), whichever occurred first.

The crude incidence rate for breast cancer was calculated by dividing the number of breast cancer cases by the number of person-years. The Cox proportional hazards model was used to estimate hazard ratio (HR) and 95% confidence intervals (CIs) of breast cancer by menstrual and reproductive factors using the SAS program (the PHREG procedure) (SAS Institute Inc., Cary, North Carolina, USA). Associations between menstrual and reproductive factors and hormone receptor-defined subtype were investigated by applying the marginal approach of Wei, Lin, and Weissfeld, referred to as the WLW model (Wei *et al.*, 1989), to the Cox proportional hazards model. The following variables were used for adjustment as potential confounders: age, area, history of mastopathy, body mass index, height, miso soup consumption, menopausal status at baseline and age at menopause, age at menarche, number of births and age at first birth (see footnotes in Tables 2–4). Although most variables used for adjustment are well known risk factors for breast cancer, frequent consumption of miso soup, a traditional Japanese dish made using miso, a fermented soybean paste, was associated with a reduced risk of breast cancer in the JPHC study (Yamamoto *et al.*, 2003). Linear trends were tested in the Cox proportional hazards models by treating each exposure category as a continuous variable. All P values reported are two-sided, and significance level was set at $P < 0.05$.

Results

In 564 305 person-years for 55 537 study participants (average follow-up period: 10.2 years), 441 newly arising cases of breast cancer cases were recorded. The baseline characteristics of study participants are shown in Table 1. At baseline, approximately 40% of participants were premenopausal and the rest were postmenopausal.

Table 2 Hazard ratio (HR) and 95% confidence intervals (CIs) of breast cancer according to menstrual and reproductive factors

	Number of cases	Person-years	Incidence rate per 100 000	Age and area-adjusted			Multivariable-adjusted		
				HR[a]	95% CI	*P* for trend	HR[b]	95% CI	*P* for trend
Age at menarche (years)									
<14	134	145749	91.9	1.00		0.01	1.00[c]		0.03
14	111	129722	85.6	0.92	0.71, 1.18		0.91	0.70, 1.18	
15	87	116264	74.8	0.79	0.60, 1.05		0.79	0.59, 1.06	
≥16	96	155064	61.9	0.69	0.51, 0.93		0.73	0.53, 1.00	
Per 1-year increase				0.92	0.87, 0.98		0.93	0.87, 0.99	
Menopausal status									
Premenopause	201	224247	89.6	1.00			1.00[d]		
Postmenopause by natural	187	268409	69.7	0.83	0.61, 1.13		0.79	0.57, 1.09	
Postmenopause by others	44	60155	73.1	0.85	0.59, 1.24		0.80	0.54, 1.17	
Use of exogenous female hormones									
Never	359	452689	79.3	1.00			1.00		
Past	51	62959	81.0	0.91	0.67, 1.23		0.86	0.63, 1.18	
Current	8	6225	128.5	1.45	0.72, 2.93		1.35	0.63, 2.85	
Parity									
Parous	380	496406	76.6	1.00			1.00[e]		
Nulliparous	43	31178	137.9	1.84	1.34, 2.52		1.92	1.38, 2.65	
Number of births									
1	46	39362	116.9	1.00		<0.0001	1.00[f]		0.0001
2	166	183272	90.6	0.79	0.57, 1.09		0.87	0.61, 1.23	
3	102	151462	67.3	0.57	0.40, 0.81		0.64	0.44, 0.93	
4	47	65564	71.7	0.58	0.38, 0.88		0.70	0.44, 1.09	
5+	19	56746	33.5	0.28	0.16, 0.48		0.37	0.21, 0.68	
Per one birth				0.77	0.70, 0.85		0.81	0.73, 0.90	
Age at first birth (years)									
<22	42	72845	57.7	1.00		0.0002	1.00[g]		0.03
22–25	169	239476	70.6	1.23	0.87, 1.74		1.11	0.78, 1.58	
26–29	113	134665	83.9	1.48	1.03, 2.13		1.27	0.88, 1.85	
30+	49	42427	115.5	2.03	1.33, 3.07		1.63	1.05, 2.52	
Per 1-year increase				1.05	1.02, 1.08		1.03	1.004, 1.06	
Breast feeding									
No	61	62833	97.1	1.00			1.00[h]		
Yes	312	429629	72.6	0.80	0.61, 1.06		0.86	0.65, 1.15	

[a]Adjusted for age (continuous) and area [10 public health centers (PHCs)].

[b]Adjusted for age (continuous), area (10 PHCs), history of mastopathy, body mass index (−20, 21–23, 24–26, 27–29, 30+), height (−147, 148–151, 152–155, 156–160+), miso soup consumption (not daily, one bowl per day, two bowls per day, three or more bowls per day), menopausal status at baseline [premenopausal women, age at menopause for postmenopausal women (−47, 48–50, 51–53, 54+)], age at menarche (−13, 14, 15, 16+), number of births (0, 1, 2, 3, 4, 5+) and age at first birth (−21, 22–25, 26–29, 30+, nulliparous).

[c]Adjustments as in footnote b except age at menarche (−13, 14, 15, 16+).

[d]Adjustments as in footnote b except menopausal status at baseline [premenopausal women, age at menopause for postmenopausal women (−41, 48–50, 51–53, 54+)].

[e]Adjustments as in footnote b except number of births (0, 1, 2, 3, 4, 5+) and age at first birth (−21, 22–25, 26–29, 30+, nulliparous).

[f]Adjustments as in footnote b except number of births (0, 1, 2, 3, 4, 5+) and age at first birth (−21, 22–25, 26–29, 30+, nulliparous) and additionally adjusted for age at first birth (−21, 22–25, 26–29, 30+).

[g]Adjustments as in footnote b except number of births (0, 1, 2, 3, 4, 5+) and age at first birth (−21, 22–25, 26–29, 30+, nulliparous) and additionally adjusted for number of births (1, 2, 3, 4, 5+).

[h]Adjustments as in footnote b except number of births (0, 1, 2, 3, 4, 5+) and age at first birth (−21, 22–25, 26–29, 30+, nulliparous) and additionally adjusted for number of births (1, 2, 3, 4, 5+) and age at first birth (−21, 22–25, 26–29, 30+).

The HRs and 95% CIs of breast cancer according to menstrual and reproductive factors are shown in Table 2. The risk of breast cancer significantly decreased with increasing age at menarche. No significant difference in risk was seen between premenopausal and postmenopausal women. Relative to parous women, the multivariable-adjusted HR for nulliparous women was 1.92 (95% CI 1.38–2.65). Among parous women, risk decreased significantly with increasing number of births, even after adjustment for age at first birth. In addition, risk significantly increased with increasing age at first birth even after adjustment for the number of births. No significant association was observed between risk and breast feeding or the use of exogenous female hormones.

We next stratified participants into premenopausal and postmenopausal (natural and others) women using self-reported menopausal status at baseline. The effect of menstrual and reproductive factors on breast cancer risk was assessed in separate menopausal strata (Table 3). A significantly inverse association between age at menarche and risk of breast cancer was seen for premenopausal women but not for postmenopausal women. Late age at natural menopause was significantly associated with an increased risk of breast cancer. Duration of menstruation

Table 3 Hazard ratio (HR) and 95% confidence intervals (CIs) of breast cancer according to menstrual and reproductive factors by menopausal status at baseline

	Premenopausal women				Postmenopausal women			
		Multivariable-adjusted				Multivariable-adjusted		
	Number of cases	HR[a]	95% CI	*P* for trend	Number of cases	HR[a]	95% CI	*P* for trend
Age at menarche (years)								
<14	95	1.00[b]		0.002	39	1.00[b]		0.70
14	63	0.85	0.61, 1.19		48	1.06	0.68, 1.66	
15	34	0.68	0.45, 1.03		52	1.02	0.65, 1.58	
≥ 16	8	0.24	0.10, 0.56		87	1.07	0.70, 1.64	
Per 1-year increase		0.84	0.75, 0.94			0.98	0.91, 1.07	
Age at natural menopause (years)								
<48	–	–	–	–	34	1.00[c]		0.006
48–50	–	–	–		73	1.10	0.71, 1.70	
51–53	–	–	–		57	1.36	0.86, 2.13	
54+	–	–	–		21	1.98	1.12, 3.52	
Per 1-year increase	–	–	–			1.07	1.02, 1.13	
Use of exogenous female hormones								
Never	162	1.00			194	1.00		
Past	29	1.07	0.71, 1.62		22	0.67	0.41, 1.08	
Current	6	2.07	0.85, 5.07		2	0.73	0.18, 3.00	
Parity								
Parous	178	1.00[d]			198	1.00[d]		
Nulliparous	17	1.66	1.01, 2.74		26	2.16	1.40, 3.31	
Number of births								
1	20	1.00[e]		0.02	26	1.00[e]		0.004
2	82	0.72	0.44, 1.19		83	1.01	0.62, 1.66	
3	46	0.48	0.27, 0.83		54	0.81	0.48, 1.36	
4	24	0.73	0.39, 1.39		22	0.65	0.34, 1.24	
5+	6	0.37	0.14, 0.99		13	0.42	0.19, 0.89	
Per one birth		0.82	0.69, 0.97			0.81	0.71, 0.94	
Age at first birth (years)								
<22	17	1.00[f]		0.57	25	1.00[f]		0.01
22–25	94	1.33	0.79, 2.26		73	0.92	0.57, 1.48	
26–29	51	1.26	0.72, 2.22		62	1.28	0.78, 2.11	
30+	16	1.13	0.55, 2.30		33	2.10	1.20, 3.70	
Per 1-year increase		1.01	0.97, 1.06			1.05	1.01, 1.09	
Breast feeding								
No	34	1.00[g]			27	1.00[g]		
Yes	142	0.80	0.55, 1.17		166	0.94	0.60, 1.47	

[a]Adjusted for age (continuous), area (10 public health centers), history of mastopathy, body mass index (–20, 21–23, 24–26, 27–29, 30+), height (–147, 148–151, 152–155, 156–159, 160+), miso soup consumption (not daily, one bowl per day, two bowls per day, three or more bowls per day), age at menarche (–13, 14, 15, 16+), number of births (0, 1, 2, 3, 4, 5+), age at first birth (–21, 22–25, 26–29, 30+, nulliparous) and age at menopause (–47, 48–50, 51–53, 54+) for postmenopausal women.

[b]Adjustments as in footnote a except age at menarche (–13, 14, 15, 16+).

[c]Adjustments as in footnote a except age at natural menopause (–47, 48–50, 51–53, 54+).

[d]Adjustments as in footnote a except number of births (0, 1, 2, 3, 4, 5+) and age at first birth (–21, 22–25, 26–29, 30+, nulliparous).

[e]Adjustments as in footnote a except number of births (0, 1, 2, 3, 4, 5+) and age at first birth (–21, 22–25, 26–29, 30+, nulliparous) and additionally adjusted for age at first birth (–21, 22–25, 26–29, 30+).

[f]Adjustments as in footnote a except number of births (0, 1, 2, 3, 4, 5+) and age at first birth (–21, 22–25, 26–29, 30+, nulliparous) and additionally adjusted for number of births (1, 2, 3, 4, 5+).

[g]Adjustments as in footnote a except number of births (0, 1, 2, 3, 4, 5+) and age at first birth (–21, 22–25, 26–29, 30+, nulliparous) and additionally adjusted for number of births (1, 2, 3, 4, 5+) and age at first birth (–21, 22–25, 26–29, 30+).

was defined as the period between age at menarche and age at natural menopause for women who reached natural menopause. Breast cancer risk significantly increased with increasing duration of menstruation, with multivariable-adjusted HR in the highest quartile of duration (more than 37 years) of 1.93 (95% CI 1.18–3.18) compared with the lowest quartile (less than 32 years) (data not shown). Nulliparous women had a higher risk than parous women, and risk among parous women significantly decreased with increasing number of births for both premenopausal and postmenopausal women. Late age at first birth was significantly associated with an elevated risk for postmenopausal but not premenopausal women. Use of exogenous female hormones and breast feeding did not relate to risk in either premenopausal or postmenopausal women.

Information on ER and PR status was available for 221 (50%) and 206 (47%) cases, respectively. Of these, 136 (62%) and 105 (51%) cases were ER+ or PR+ breast cancer, respectively. Association of menstrual and reproductive factors with hormone receptor-defined breast cancer is shown in Table 4. Risks associated with age at menarche and age at natural menopause did not significantly differ by ER-defined breast cancer. The risk of PR– breast cancer decreased with increasing age at

Table 4 Hazard ratio (HR) and 95% confidence intervals (CIs) of breast cancer according to menstrual and reproductive factors by estrogen and progesterone receptor (ER/PR) status

	ER-positive		ER-negative			PR-positive		PR-negative		
	HR	95% CI	HR	95% CI	*P* value[a]	HR	95% CI	HR	95% CI	*P* value[b]
All study participants[c]										
Age at menarche (per 1-year increase)[d]	0.96	0.87, 1.05	0.91	0.79, 1.05	0.57	1.00	0.90, 1.11	0.87	0.76, 0.99	0.10
Parity (parous vs. nulliparous)[e]	2.50	1.45, 4.31	1.41	0.61, 3.23	0.26	2.01	1.04, 3.88	2.15	1.12, 4.14	0.89
Number of births (per one birth)[f]	0.85	0.73, 1.01	0.80	0.65, 0.99	0.65	0.84	0.69, 1.02	0.86	0.72, 1.02	0.84
Age at first birth (per 1-year increase)[g]	1.00	0.95, 1.05	1.01	0.96, 1.06	0.80	0.99	0.93, 1.05	1.03	0.98, 1.08	0.26
Premenopausal women[h]										
Age at menarche (per 1-year increase)[d]	0.82	0.71, 0.95	0.86	0.73, 1.03	0.67	0.88	0.76, 1.02	0.77	0.65, 0.92	0.29
Parity (parous vs. nulliparous)[e]	2.04	0.87, 4.81	0.89	0.22, 3.65	0.32	1.11	0.34, 3.66	2.44	0.97, 6.15	0.31
Number of births (per one birth)[f]	0.91	0.71, 1.17	0.72	0.54, 0.97	0.24	0.92	0.69, 1.22	0.76	0.60, 0.95	0.29
Age at first birth (per 1-year increase)[g]	0.92	0.86, 0.98	0.93	0.86, 1.00	0.88	0.92	0.85, 0.99	0.93	0.87, 1.00	0.81
Postmenopausal women[h]										
Age at menarche (per 1-year increase)[d]	1.04	0.93, 1.18	0.95	0.78, 1.15	0.40	1.10	0.97, 1.25	0.92	0.78, 1.09	0.09
Age at natural menopause (per 1-year increase)[i]	1.05	0.95, 1.16	1.03	0.95, 1.13	0.80	0.99	0.90, 1.10	1.12	1.02. 1.23	0.08
Parity (parous vs. nulliparous)[e]	2.80	1.37, 5.70	1.96	0.69, 5.55	0.58	2.97	1.33, 6.64	1.88	0.74, 4.75	0.46
Number of births (per one birth)[f]	0.82	0.66, 1.03	0.94	0.70, 1.26	0.49	0.78	0.58, 1.04	0.95	0.76, 1.20	0.27
Age at first birth (per 1-year increase)[g]	1.05	0.98, 1.13	1.10	1.03, 1.17	0.38	1.05	0.96, 1.14	1.10	1.04, 1.16	0.37

[a]*P* value for the null hypothesis that estimate from ER-positive equals estimate from ER-negative.
[b]*P* value for the null hypothesis that estimate from PR-positive equals estimate from PR-negative.
[c]Adjusted for age (continuous), area (10 public health centers), history of mastopathy, body mass index (BMI) (−20, 21–23, 24–26, 27–29, 30+), height (−147, 148–151, 152–155, 156–159, 160+), miso soup consumption (not daily, one bowl per day, two bowls per day, three or more bowls per day), menopausal status at baseline [premenopausal women, age at menopause for postmenopausal women (−47, 48–50, 51–53, 54+)], age at menarche (−13, 14, 15, 16+), number of births (0, 1, 2, 3, 4, 5+) and age at first birth (−21, 22–25, 26–29, 30+, nulliparous).
[d]Adjustments as in footnote c or footnote h except age at menarche (−13, 14, 15, 16+).
[e]Adjustments as in footnote c or footnote h except number of births (0, 1, 2, 3, 4, 5+) and age at first birth (−21, 22–25, 26–29, 30+, nulliparous).
[f]Adjustments as in footnote c or footnote h except number of births (0, 1, 2, 3, 4, 5+) and age at first birth (−21, 22–25, 26–29, 30+, nulliparous) and additionally adjusted for age at first birth (−21, 22–25, 26–29, 30+).
[g]Adjustments as in footnote c or footnote h except number of births (0, 1, 2, 3, 4, 5+) and age at first birth (−21, 22–25, 26–29, 30+, nulliparous) and additionally adjusted for number of births (1, 2, 3, 4, 5+).
[h]Adjusted for age (continuous), area (10 PHCs), history of mastopathy, BMI (−20, 21–23, 24–26, 27–29, 30+), height (−147, 148–151, 152-155, 156-159, 160+), miso soup consumption (not daily, one bowl per day, two bowls per day, three or more bowls per day), age at menarche (−13, 14, 15, 16+), number of births (0, 1, 2, 3, 4, 5+), age at first birth (−21, 22–25, 26–29, 30+, nulliparous) and age at menopause (−47, 48–50, 51–53, 54+) for postmenopausal women.
[i]Adjustments as in footnote c except menopausal status at baseline [premenopausal women, age at menopause for postmenopausal women (−47, 48–50, 51–53, 54+)].

menarche and a difference in HRs between PR+ and PR− breast cancer was suggested for all participants and postmenopausal women (*P* for difference in HRs = 0.10 and 0.09, respectively). Age at natural menopause was significantly associated with an increased risk of PR− breast cancer (HR = 1.12, 95% CI 1.02–1.23) but no association was observed for PR+ breast cancer (HR = 0.99, 95% CI 0.90–1.10) (*P* for difference in HRs = 0.08). Risks associated with parity, number of births and age at first birth did not significantly differ by hormone receptor-defined breast cancer.

Discussion

Our findings suggest that menstrual and reproductive factors play an important role in the development of breast cancer among not only Western populations but also low-risk populations as well. As previously shown elsewhere (Paffenbarger *et al.*, 1980; Ewertz and Duffy, 1988; Layde *et al.*, 1989; Kelsey *et al.*, 1993; Albrektsen *et al.*, 1994; Hirose *et al.*, 1995; Nagata *et al.*, 1995; Talamini *et al.*, 1996; Goodman *et al.*, 1997; Chie *et al.*, 2000; Gao *et al.*, 2000; Clavel Chapelon, 2002; Tamakoshi *et al.*, 2005), the present study confirmed that early age at menarche for premenopausal women, late age at natural menopause, nulliparity for all women and late age at first birth for postmenopausal women were significantly associated with an increased risk of breast cancer. High parity showed an overall strong protective effect independent of age at first birth.

Although previous studies in Asian countries have generally shown that early age at menarche, late age at menopause, nulliparity and late age at first birth are the major risk factors for breast cancer (Hirose *et al.*, 1995; Nagata *et al.*, 1995; Goodman *et al.*, 1997; Gao *et al.*, 2000; Tamakoshi *et al.*, 2005), two previous cohort studies in Japan failed to observe a significant association for age at menarche (Tamakoshi *et al.*, 2005), age at menopause (Goodman *et al.*, 1997; Tamakoshi *et al.*, 2005) or age at first birth (Tamakoshi *et al.*, 2005). The present study did find significant associations for these four risk factors, however, probably owing to several methodological improvements. First, compared with these two cohort studies ($n = 161$ and 151, respectively) (Goodman *et al.*, 1997; Tamakoshi *et al.*, 2005), we included a relatively large number of cases ($n = 441$). Second, our prospective design potentially avoided selection bias and recall bias. Finally, we included a large population-based sample with a high response rate (more than 80%) and low rate of loss to follow-up.

Ovarian hormones, primarily estrogen, are believed to play a role in the etiology of breast cancer (Pike *et al.*, 1993; Clemons and Goss, 2001). The earlier the age at menarche, the earlier a woman is exposed to increased ovarian hormone levels, and menarche at a young age is associated with an earlier onset of ovulatory cycles (Apter and Vihko, 1983). In addition, women with an early age at menarche have higher estrogen levels for several years thereafter (MacMahon *et al.*, 1982). Meanwhile, later age at menopause necessarily prolongs exposure to ovarian hormones. In the present study, early age at menarche was significantly associated with an increased risk of breast cancer for premenopausal women only, while an association with late age at natural menopause was seen for postmenopausal women. This result suggests that early exposure to the hormonal milieu might be important for premenopausal women, whereas later or longer exposure might be more important than early exposure for postmenopausal women.

It is noteworthy that the present study observed a decrease in risk of breast cancer with increasing age at menarche among premenopausal women whose age at menarche was relatively later than that in Western countries. Mean age at menarche varies between countries, and this might partly account for the difference in incidence rates of breast cancer. In addition, age at menarche has decreased in both Western countries and Japan, mainly because of improved nutrition and secular increases in adolescent height and weight (Minami *et al.*, 2004; Onland Moret *et al.*, 2005). For example, Clavel Chapelon (2002) reported that mean age at menarche was 13.3 and 12.7 years for French women born in 1930 and 1950, respectively. Respective menarche ages for the corresponding age groups in our study were 15.9 and 13.5 years.

With regard to mechanism, pregnancy induces differentiation of the mammary cells, and differentiated cells are less susceptible to carcinogenic transformation (Russo and Russo, 1994). The period of protection covers a larger fraction of the woman's remaining lifetime; further, fewer cells are likely to have been initiated when the first pregnancy occurs at an early age. Thus, the beneficial effect of early age at first birth on breast cancer risk might be the same regardless of menopausal status. Only postmenopausal women with late age at first birth, however, were significantly associated with an elevated risk of breast cancer in the present study. The reason for the lack of association between age at first birth and breast cancer risk in premenopausal women is unclear.

Given that the action of estrogen and progesterone on breast cell proliferation appears to be mediated by ER and PR (Pike *et al.*, 1993; Clemons and Goss, 2001), risk factors most closely associated with ER + and/or PR + breast cancer may involve mechanisms related to estrogen and progesterone exposure (Habel and Stanford, 1993; Potter *et al.*, 1995; Yoo *et al.*, 1997; Huang *et al.*, 2000; Althuis *et al.*, 2004). In contrast, the etiology of ER − and/or PR − breast cancer may be independent of hormonal exposure (Yoo *et al.*, 1997; Huang *et al.*, 2000). Several previous studies in Western countries showed that early age at menarche, nulliparity and late age at first birth were more associated with ER + and/or ER + PR + than with ER − and/or ER − PR − breast cancer risk (Potter *et al.*, 1995; Huang *et al.*, 2000; Althuis *et al.*, 2004). In a Japanese case–control study, a difference in risk factor profiles was observed for PR status such that age at menarche was negatively associated with PR + breast cancer but positively associated with PR − breast cancer (Yoo *et al.*, 1997). The present study, however, suggested that age at menarche and age at natural menopause were more closely associated with the risk of PR − breast cancer than with the risk of PR + breast cancer, although risks associated with reproductive factors such as parity, number of births and age at first birth did not differ by hormone receptor status. Given the small number of cases in each hormone receptor-defined subtype, this finding might have been due to chance. If not, however, its interpretation is complex because age at menarche and age at menopause might act through hormone-related mechanisms rather than nonhormone-related mechanisms, as mentioned above.

As our data on hormone receptor status were limited, care should be taken in interpreting the results in Table 4. First, the small number of cases in each analysis limited the statistical power. Second, despite the generally high agreement between the enzyme-linked immunoassay and immunohistochemical techniques, differences in classification and interlaboratory variation may account for discrepancies among findings. In addition, such misclassification, if present, may have attenuated the true risk. These limitations might account for this study's lack of differences in risk by receptor-defined subtype.

In conclusion, in this prospective cohort study in Japanese women, we confirmed that early age at menarche for premenopausal women, late age at natural menopause, nulliparity and low parity for all women, and late age at first birth for postmenopausal women played an important role in the development of breast cancer. Further studies are required to clarify the role of hormone receptor status in breast cancer etiology.

Acknowledgements

We wish to thank all staff members in each study area and in the central offices for their cooperation and technical assistance. We also wish to thank the Iwate, Aomori, Ibaraki, Niigata, Osaka, Kochi, Nagasaki and Okinawa Cancer Registries for their provision of incidence data. We also thank Drs S. Yamamoto and S. Tanaka of the

Statistics and Control Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan for statistical advice.

References

Albrektsen G, Heuch I, Tretli S, Kvale G (1994). Breast cancer incidence before age 55 in relation to parity and age at first and last births: a prospective study of one million Norwegian women. *Epidemiology* **5**:604–611.

Althuis MD, Fergenbaum JH, Garcia Closas M, Brinton LA, Madigan MP, Sherman ME (2004). Etiology of hormone receptor-defined breast cancer: a systematic review of the literature. *Cancer Epidemiol Biomarkers Prev* **13**:1558–1568.

Apter D, Vihko R (1983). Early menarche, a risk factor for breast cancer, indicates early onset of ovulatory cycles. *J Clin Endocrinol Metab* **57**:82–86.

Chie WC, Hsieh C, Newcomb PA, Longnecker MP, Mittendorf R, Greenberg ER, *et al.* (2000). Age at any full-term pregnancy and breast cancer risk. *Am J Epidemiol* **151**:715–722.

Clavel Chapelon F (2002). Differential effects of reproductive factors on the risk of pre- and postmenopausal breast cancer. Results from a large cohort of French women. *Br J Cancer* **86**:723–727.

Clemons M, Goss P (2001). Estrogen and the risk of breast cancer. *N Engl J Med* **344**:276–285.

Ewertz M, Duffy SW (1988). Risk of breast cancer in relation to reproductive factors in Denmark. *Br J Cancer* **58**:99–104.

Gao YT, Shu XO, Dai Q, Potter JD, Brinton LA, Wen W, *et al.* (2000). Association of menstrual and reproductive factors with breast cancer risk: results from the Shanghai Breast Cancer Study. *Int J Cancer* **87**:295–300.

Goodman MT, Cologne JB, Moriwaki H, Vaeth M, Mabuchi K (1997). Risk factors for primary breast cancer in Japan: 8-year follow-up of atomic bomb survivors. *Prev Med* **26**:144–153.

Habel LA, Stanford JL (1993). Hormone receptors and breast cancer. *Epidemiol Rev* **15**:209–219.

Hirose K, Tajima K, Hamajima N, Inoue M, Takezaki T, Kuroishi T, *et al.* (1995). A large-scale, hospital-based case–control study of risk factors of breast cancer according to menopausal status. *Jpn J Cancer Res* **86**:146–154.

Huang WY, Newman B, Millikan RC, Schell MJ, Hulka BS, Moorman PG (2000). Hormone-related factors and risk of breast cancer in relation to estrogen receptor and progesterone receptor status. *Am J Epidemiol* **151**:703–714.

Kelsey JL, Gammon MD, John EM (1993). Reproductive factors and breast cancer. *Epidemiol Rev* **15**:36–47.

Layde PM, Webster LA, Baughman AL, Wingo PA, Rubin GL, Ory HW (1989). The independent associations of parity, age at first full term pregnancy, and duration of breastfeeding with the risk of breast cancer. Cancer and Steroid Hormone Study Group. *J Clin Epidemiol* **42**:963–973.

Liu Y, Inoue M, Sobue T, Tsugane S (2005). Reproductive factors, hormone use and the risk of lung cancer among middle-aged never-smoking Japanese women: a large-scale population-based cohort study. *Int J Cancer* **117**: 662–666.

MacMahon B, Trichopoulos D, Brown J, Andersen AP, Cole P, deWaard F, *et al.* (1982). Age at menarche, urine estrogens and breast cancer risk. *Int J Cancer* **30**:427–431.

Minami Y, Tsubono Y, Nishino Y, Ohuchi N, Shibuya D, Hisamichi S (2004). The increase of female breast cancer incidence in Japan: emergence of birth cohort effect. *Int J Cancer* **108**:901–906.

Nagata C, Hu YH, Shimizu H (1995). 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* **86**:910–915.

Onland Moret NC, Peeters PH, van Gils CH, Clavel Chapelon F, Key T, Tjonneland A, *et al.* (2005). Age at menarche in relation to adult height: the EPIC study. *Am J Epidemiol* **162**:623–632.

Paffenbarger RS Jr, Kampert JB, Chang HG (1980). Characteristics that predict risk of breast cancer before and after the menopause. *Am J Epidemiol* **112**:258–268.

Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB (2002). *Cancer incidence in five continents.* Vol. VIII. IARC Scientific Publications No. 155. Lyon: IARC Press.

Pike MC, Spicer DV, Dahmoush L, Press MF (1993). Estrogens, progestogens, normal breast cell proliferation, and breast cancer risk. *Epidemiol Rev* **15**: 17–35.

Potter JD, Cerhan JR, Sellers TA, McGovern PG, Drinkard C, Kushi LR, *et al.* (1995). Progesterone and estrogen receptors and mammary neoplasia in the Iowa Women's Health Study: how many kinds of breast cancer are there? *Cancer Epidemiol Biomarkers Prev* **4**:319–326.

Russo J, Russo IH (1994). Toward a physiological approach to breast cancer prevention. *Cancer Epidemiol Biomarkers Prev* **3**:353–364.

Talamini R, Franceschi S, La Vecchia C, Negri E, Borsa L, Montella M, *et al.* (1996). The role of reproductive and menstrual factors in cancer of the breast before and after menopause. *Eur J Cancer* **32A**:303–310.

Tamakoshi K, Yatsuya H, Wakai K, Suzuki S, Nishio K, Lin Y, *et al.* (2005). Impact of menstrual and reproductive factors on breast cancer risk in Japan: results of the JACC study. *Cancer Sci* **96**:57–62.

The Research Group for Population-based Cancer Registration in Japan (2003). Cancer incidence and incidence rates in Japan in 1998: estimates based on data from 12 population-based cancer registries. *Jpn J Clin Oncol* **33**: 241–245.

Watanabe S, Tsugane S, Sobue T, Konishi M, Baba S (2001). Study design and organization of the JPHC study. *J Epidemiol* **11**:S3–S7.

Wei LJ, Lin DY, Weissfeld L (1989). Regression analysis of multivariate incomplete failure time data by modeling marginal distribution. *J Am Stat Assoc* **84**:1065–1073.

Yamamoto S, Sobue T, Kobayashi M, Sasaki S, Tsugane S (2003). Soy, isoflavones, and breast cancer risk in Japan. *J Natl Cancer Inst* **95**:906–913.

Yasui Y, Potter JD (1999). The shape of age–incidence curves of female breast cancer by hormone-receptor status. *Cancer Causes Control* **10**: 431–437.

Yoo KY, Tajima K, Miura S, Takeuchi T, Hirose K, Risch H, *et al.* (1997). Breast cancer risk factors according to combined estrogen and progesterone receptor status: a case–control analysis. *Am J Epidemiol* **146**:307–314.

American Journal of Epidemiology

Vol. 165, No. 9
DOI: 10.1093/aje/kwk112
Advance Access publication March 6, 2007

Original Contribution

Patterns of Alcohol Drinking and All-Cause Mortality: Results from a Large-Scale Population-based Cohort Study in Japan

Tomomi Marugame[1], Seiichiro Yamamoto[1], Itsuro Yoshimi[2], Tomotaka Sobue[1], Manami Inoue[3], and Shoichiro Tsugane[3] for the Japan Public Health Center-based Prospective Study Group

[1] Cancer Information Services and Surveillance Division, Center for Cancer Control and Information Services, National Cancer Center, Tokyo, Japan.
[2] Tobacco Control Information Section, Center for Information Research & Library, National Institute of Public Health, Saitama, Japan.
[3] Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan.

Received for publication May 24, 2006; accepted for publication October 20, 2006.

To evaluate the hypothesis that, in terms of all-cause death, drinking alcohol 1–4 days per week is less harmful than daily (5–7 days/week) drinking of the same quantity of alcohol, a prospective cohort study using a self-administered questionnaire was conducted in Japan between 1990 and 2003 of 88,746 subjects (41,702 men and 47,044 women) aged 40–69 years at baseline. Among male regular drinkers consuming alcohol more than 1 day per week, light drinkers (<300 g/week) showed no increase in all-cause mortality irrespective of frequency of alcohol intake. Heavy drinkers (≥300 g/week), however, showed an increased risk of all-cause mortality among those who consumed alcohol 5–7 days per week, while no obvious increase was observed among those who consumed alcohol less than 4 days per week. Hazard ratios for drinkers who consumed alcohol 5–7 days per week were 1.29 (95% confidence interval: 1.12, 1.50) for 300–449 g per week and 1.55 (95% confidence interval: 1.32, 1.81) for ≥450 g per week when compared with those for occasional drinkers who consumed alcohol 1–3 days per month. These findings support the Japanese social belief that "liver holidays," abstaining from alcohol for more than 2 days per week, are important for heavy drinkers.

alcohol drinking; cohort studies; drinking behavior; Japan; mortality

Abbreviations: CI, confidence interval; HR, hazard ratio; ICD-10, *International Statistical Classification of Diseases and Related Health Problems*, Tenth Edition.

A U- or J-shaped association between alcohol intake and all-cause mortality has been observed in several population studies (1, 2), including Japanese prospective studies (3, 4). These studies, however, focused primarily on the association between mortality and average quantity of alcohol consumed. Recently, attention has been focused on the relation between health outcome and more complex and multidimensional drinking patterns (5). Specifically, average quantity of alcohol consumed, frequency of alcohol intake, and the combination of these factors in a pattern of drinking have been investigated.

In Japan, it is widely believed that persistent heavy drinking can damage the liver; therefore, 2 or more days per week in which a person abstains from heavy drinking, a so-called liver holiday, is considered important for general health and for maintaining the metabolic function of the liver. Unfortunately, limited epidemiologic evidence supports this socially accepted idea. Therefore, in the present study, we

Reprint requests to Dr. Tomomi Marugame, Statistics and Cancer Control Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan (e-mail: tmarugam@gan2.res.ncc.go.jp).

tested the "liver holiday" hypothesis, which proposes that 1–4 days per week of drinking has less of an effect than daily drinking on all-cause mortality if the same quantity of alcohol is consumed.

MATERIALS AND METHODS

Study population

The Japan Public Health Center-based Prospective Study (5) was launched in 1990 for cohort I and in 1993 for cohort II. Cohort I was composed of five prefectural public health center areas and cohort II of six public health center areas. The study protocol was approved by the institutional review board of the National Cancer Center, Japan. In the present analysis, two public health center areas were excluded because different definitions of the study population were applied.

The study population was defined as all registered Japanese inhabitants of the nine public health center areas aged 40–69 years at the beginning of each baseline survey. Initially, 116,893 subjects were identified as eligible for participation in the present study. A total of 218 subjects were excluded: 51 were of non-Japanese nationality, 164 were late in reporting their emigration before the start of the follow-up period, and three were ineligible because of an incorrect birth date. Following these exclusions, a population-based cohort of 116,675 subjects (55,580 men and 59,095 women) was established.

Baseline survey

A baseline self-administered questionnaire survey assessing various lifestyle factors was conducted in 1990 for cohort I and in 1993–1994 for cohort II, with a response rate of 81 percent. Because our aim was to examine the effect of alcohol intake on all-cause mortality among healthy subjects, we excluded those with a present or past history of self-reported serious illness (cancer, cerebrovascular disease, myocardial infarction, or chronic liver disease). After we further excluded subjects who did not answer the questionnaire and subjects for whom no information on current alcohol drinking status was available, data from 88,746 subjects (41,702 men and 47,044 women) were included in the present analysis.

Information on alcohol intake was obtained regarding frequency and quantity by using a validated questionnaire at the baseline survey (6). The average frequency of alcohol intake was reported according to six categories for cohort I: less than 1 day per month, 1–3 days per month, 1–2 days per week, 3–4 days per week, 5–6 days per week, and every day. Subjects consuming alcohol less than 1 day per month were defined as nondrinkers. Subjects consuming alcoholic beverages at least once a week were also asked about the types of drinks consumed and the average quantity consumed. Subjects in cohort II were also asked to indicate their alcohol drinking status as never, past, or current drinker. Past and current drinkers provided information on the average frequency of intake, the types of drinks consumed, and the average quantity consumed per day. The average frequency of intake was reported based on four categories: 1–3 days per month, 1–2 days per week, 3–4 days per week, and almost every day. Participants in cohort II were also asked to indicate the number of days per month that they drink alcohol at social events.

Because the response categories for frequency of alcohol intake differed slightly between the questionnaires for cohorts I and II, we reclassified the drinkers into the following categories: occasional drinkers (1–3 days/month) and three categories of regular drinkers (1–2 days/week, 3–4 days/week, and 5–7 days/week). For cohort I, subjects drinking less than 1 day per month were defined as nondrinkers. For cohort II, subjects who answered that they were never or past drinkers were analyzed separately.

To calculate total quantity of alcohol consumed per week, we assigned a score to each category or frequency as follows: 1.5 for 1–2 days per week, 3.5 for 3–4 days per week, 5.5 for 5–6 days per week, and 7 for every day in the cohort I questionnaire; and 1.5 for 1–2 days per week, 3.5 for 3–4 days per week, and 6 for almost every day in the cohort II questionnaire. The quantity of ethanol in each type of alcoholic beverage was calculated as follows: 180 ml of sake (rice wine) was regarded as 23 g of ethanol, 180 ml of shochu or awamori (white spirits) as 36 g, 633 ml of beer as 23 g, 30 ml of whiskey or brandy as 10 g, and 60 ml of wine as 6 g. Finally, weekly ethanol intake was estimated by multiplying the quantity by the score. For regular drinkers only, we categorized weekly alcohol intake into four categories (1–149 g/week, 150–299 g/week, 300–449 g/week, and $\geq$450 g/week).

Regarding validity, Spearman's correlation coefficients comparing questionnaires and 28-day dietary records with respect to weekly ethanol intake and frequency of alcohol intake were 0.77 and 0.54 for men and 0.55 and 0.27 for women, respectively. Compared with that for 28-day dietary records, mean daily intake of alcohol (g/day) calculated from questionnaires was nearly the same for men (23.4 g for dietary records and 22.3 g for questionnaires) but was underestimated for women (1.6 g for dietary records and 0.8 g for questionnaires) (6).

Follow-up survey

Subjects were followed from the baseline survey until December 31, 2003. Residence status, including survival, was confirmed annually through the residential registry maintained for each municipality. Of all study subjects, 6.3 percent moved away and 0.06 percent was lost to follow-up during the study period. Information on the cause of each death was supplemented by checking against death certificate files with permission.

Analysis

The numbers of person-years in the follow-up period were calculated from the baseline survey until the date of death or the end of the study period, whichever occurred first. For persons who were lost to follow-up, the last confirmed date was used as the date of censoring.

Hazard ratios and their 95 percent confidence intervals for the pattern of alcohol drinking on all-cause death were calculated by using Cox proportional hazards models with adjustment for potential confounding factors, such as age at baseline (continuous), smoking status (never, past, and current), body mass index (weight (kg)/height $(m)^2$), green vegetable intake (≤3–4 times/week, every day), and leisure-time physical activity (≤1–3 times/month, ≥1–2 times/week). These variables are either known or suspected risk factors for all-cause death according to previous studies (3, 7). In the Cox model, different baseline hazards were allowed for the study areas (nine Japan Public Health Center-based Prospective Study areas) using the strata statement in the PHREG procedure of SAS version 8 software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

During the 1,058,796.4 person-years of follow-up (average, 11.9 years), 5,970 deaths (3,916 men and 2,054 women) from all causes were included in the analysis. Regarding all causes of death, 1,628 men (42 percent) and 912 women (44 percent) died from cancer of all sites (*International Statistical Classification of Diseases and Related Health Problems*, Tenth Edition (ICD-10) codes C00–C96), 498 men (13 percent) and 235 women (11 percent) from heart disease (ICD-10 codes I01–I02, I05–I09, I20–I25, I27, and I30–I52), 391 men (10 percent) and 255 women (12 percent) from cerebrovascular disease (ICD-10 codes I60–I69), 515 men (13 percent) and 196 women (10 percent) from injuries and external causes (ICD-10 codes S01–S77 and T00–T91), and 98 men (3 percent) and 27 women (1 percent) from liver disease (ICD-10 codes K70–K76).

At baseline, 68 percent of men and 11 percent of women were regular drinkers. Increased quantity of alcohol consumed was positively associated with smoking and negatively associated with physical activity (table 1). Female heavy drinkers tended to be young. Those who drank 5–7 days per week were more frequently identified in the highest category of alcohol intake.

When compared with occasional drinkers who consumed alcohol 1–3 days per month, both men and women nondrinking participants in cohort I showed a significantly increased risk of all-cause mortality (hazard ratio (HR) = 1.28, 95 percent confidence interval (CI): 1.06, 1.55 and HR = 1.42, 95 percent CI: 1.11, 1.82, respectively). For never and past drinkers, the analysis was conducted among participants in cohort II only. An increased risk of all-cause mortality was observed; the respective hazard ratios for never and past drinkers compared with occasional drinkers were 1.30 (95 percent CI: 1.07, 1.57) and 2.14 (95 percent CI: 1.70, 2.69) for men and 1.10 (95 percent CI: 0.85, 1.44) and 1.68 (95 percent CI: 0.98, 2.90) for women.

When subjects were divided according to the quantity of alcohol consumed per week (table 2), a statistically significant increase for men and a nonsignificant increase for women in the risk of all-cause mortality were observed as the quantity of alcohol increased.

The adjusted hazard ratios of all-cause death according to frequency of alcohol intake are presented in table 3. Among regular drinkers, no elevation in risk of all-cause mortality was observed for men and women, irrespective of the frequency of drinking.

To assess the joint effects of quantity and frequency of alcohol intake, we examined the risk for the categories stratified by the combination of quantity and frequency of alcohol intake (figure 1 and table 4). Because the number of female regular drinkers in our study population was small, the analysis was restricted to men. Men consuming ≥450 g of alcohol 5–7 days per week showed the highest crude mortality rate of all-cause death (figure 1). Compared with occasional drinkers, men who drank <150 g of alcohol per week had a nonsignificant decrease in all-cause mortality irrespective of drinking frequency (table 4). A consistent risk was observed among men consuming <300 g of alcohol per week, regardless of drinking frequency. For men consuming 300–449 g and ≥450 g of alcohol per week, the risk of all-cause mortality was significantly increased among those whose frequency of intake was 5–7 days per week, although this trend was not statistically significant. The highest hazard ratio was observed for men consuming ≥450 g of alcohol 5–7 days per week.

To test the "liver holiday" hypothesis, the effect of frequency of drinking among men who drank the same quantity of alcohol was investigated for heavy drinkers. When 1–2 days per week was used as a reference category, men consuming alcohol 3–4 days per week showed no increase in the risk of all-cause mortality (HR = 1.16, 95 percent CI: 0.41, 3.28), whereas men consuming alcohol 5–7 days per week showed a nonsignificant 50 percent increased risk (HR = 1.48, 95 percent CI: 0.55, 3.97) for those consuming 300–449 g of alcohol per week. For men consuming ≥450 g of alcohol per week, those drinking alcohol 3–4 days per week also showed no increase in the risk of all-cause mortality (HR = 0.99, 95 percent CI: 0.24, 4.23), whereas men who consumed alcohol 5–7 days per week showed a nonsignificant 80 percent increased risk (HR = 1.77, 95 percent CI: 0.66, 4.75).

Finally, we further divided men who consumed ≥450 g per week into three categories: 450–599 g, 600–749 g, and ≥750 g of alcohol per week. In this analysis, because heavy drinkers who drank 1–2 days per week were very few, we recategorized frequency of drinking as 1–4 days per week (men with "liver holidays") and 5–7 days per week (men without "liver holidays"). When occasional drinkers were used as a reference, the respective hazard ratios for 1–4 days per week and 5–7 days per week were 0.89 (95 percent CI: 0.48, 1.68) and 1.15 (95 percent CI: 0.92, 1.44) among men who consumed 450–599 g of alcohol per week, 1.21 (95 percent CI: 0.57, 2.55) and 1.71 (95 percent CI: 1.41, 2.08) among men who consumed 600–749 g of alcohol per week, and 1.72 (95 percent CI: 0.64, 4.62) and 1.55 (95 percent CI: 1.12, 2.17) among men who consumed ≥750 g of alcohol per week.

DISCUSSION

In the present study, quantity of alcohol consumed was clearly associated with an increased risk of all-cause

TABLE 1. Baseline characteristics of study subjects according to weekly quantity of alcohol consumed, Japan Public Health Center-based Prospective Study, 1990–2003

	Nondrinkers	Occasional drinkers (1–3 days/month)	Regular drinkers (g/week)*			
			<150	150–299	300–449	≥450
Men						
No.	8,542	3,956	9,545	9,055	5,451	3,516
Age in years (SD†)	53.4 (8.2)	50.5 (7.3)	51.3 (7.8)	51.9 (7.7)	51.7 (7.3)	50.8 (7.4)
Weekly frequency of alcohol intake (%)						
1–2 days/week			31.6	4.9	1.5	1.2
3–4 days/week			22.9	18.2	9.9	11.2
5–7 days/week			45.5	77.0	88.6	87.7
Smoking status (%)						
Current cigarette smoker	48.4	47.0	46.0	57.3	62.7	60.9
Former cigarette smoker	22.2	19.9	25.2	23.4	22.0	21.8
Body mass index‡ (SD)	23.4 (3.4)	24.0 (3.1)	23.4 (2.8)	23.5 (2.8)	23.5 (2.9)	23.9 (3.1)
Green vegetable intake (%)						
Almost every day	24.0	24.1	24.4	24.3	24.0	22.5
Leisure-time physical activity (%)						
≥1–2 times/week	16.1	19.1	21.1	18.4	18.1	17.0
Women						
No.	37,145	4,617	3,671	551	209	200
Age in years (SD†)	53.3 (8.0)	49.2 (6.8)	50.0 (7.2)	49.8 (7.4)	49.1 (6.8)	48.8 (6.2)
Weekly frequency of alcohol intake (%)						
1–2 days/week			47.7	4.0	2.4	1.5
3–4 days/week			27.7	34.9	20.6	10.0
5–7 days/week			24.7	61.2	77.0	88.5
Smoking status (%)						
Current cigarette smoker	3.9	7.7	11.9	35.4	40.9	48.5
Former cigarette smoker	0.9	2.2	2.2	5.6	5.8	3.5
Body mass index (SD)	23.6 (3.4)	23.5 (3.0)	23.1 (2.9)	23.3 (3.8)	23.2 (3.4)	23.8 (3.3)
Green vegetable intake (%)						
Almost every day	31.4	28.2	31.8	25.1	26.3	27.5
Leisure-time physical activity (%)						
≥1–2 times/week	16.2	18.2	20.4	18.5	15.8	12.0

* 884 men and 358 women were excluded because of missing data regarding alcohol quantity.
† SD, standard deviation.
‡ Weight (kg)/height $(m)^2$.

mortality among regular drinkers, while frequency of alcohol intake did not appear to be related to all-cause mortality when these factors were investigated separately. When they were examined in combination, pattern of drinking emerged as an important factor in the mortality of male regular drinkers, with the highest hazard ratios observed among those consuming ≥450 g of alcohol 5–7 days per week. Interestingly, the increased risk of all-cause mortality associated with frequency of alcohol intake was seen among heavy drinkers only (≥300 g alcohol/week). These results support the hypothesis that "liver holidays" reduce the harmful effects of heavy drinking on mortality.

Regarding only the quantity of alcohol consumed, we previously identified a similar pattern among men, but not women, in our study on total cancer risk (the leading cause of death in Japan) (8) and stroke (the third leading cause of death in Japan), especially hemorrhagic stroke (9). In addition, the increased risk of all-cause mortality among heavy drinkers, which is associated with quantity of alcohol consumed, has been consistently observed in our previous

TABLE 2. Hazard ratios and 95% confidence intervals for all-cause deaths according to quantity of alcohol consumed, Japan Public Health Center-based Prospective Study, 1990–2003

	Occasional drinkers (1–3 days/month)	Regular drinkers (g/week)*				
		<150	150–299	300–449	≥450	*p* for trend†
Men						
No.	3,956	9,545	9,055	5,451	3,516	
No. of deaths	280	674	753	574	388	
Adjusted HR‡,§	1.00	0.91	0.98	1.27	1.51	<0.0001
95% CI‡	Reference	0.79, 1.05	0.85, 1.12	1.10, 1.47	1.30, 1.77	
Women						
No.	4,617	3,761	551	209	200	
No. of deaths	134	100	24	11	12	
Adjusted HR§	1.00	0.88	1.26	1.55	1.83	0.002
95% CI	Reference	0.67, 1.95	0.81, 1.95	0.84, 2.88	0.98, 3.41	

* 884 men and 358 women were excluded because of missing data regarding alcohol quantity.

† Calculated among regular drinkers.

‡ HR, hazard ratio; CI, confidence interval.

§ Adjusted for age at baseline (continuous), study area (nine public health center areas), smoking status, body mass index (weight (kg)/height (m)^2), green vegetable intake (≤3–4 times/week and almost every day), and leisure-time physical activity (≤1–3 times/month, ≥1–2 times/week).

analysis of the 7-year follow-up data from cohort I (3), other Japanese prospective cohort studies (4, 10), and studies conducted in other countries (11–13). Although the present finding supported the J-shaped association between quantity of alcohol consumed and all-cause mortality, a smaller reduction in hazard ratios was observed in our study population compared with other populations in Western countries (13, 14). This finding might be due to differences in causes of death between Japanese and Caucasian populations, for whom the leading cause is cardiovascular death, which mostly influences the lowering effects on all-cause mortality among light-to-moderate drinkers (13).

The level of alcohol intake among men in the present study was relatively high compared with that in the other studies conducted in Western countries (13, 15) but was similar to that in other Japanese studies (16). Because the

TABLE 3. Hazard ratios and 95% confidence intervals for all-cause deaths according to frequency of alcohol intake, Japan Public Health Center-based Prospective Study, 1990–2003

	Occasional drinkers (1–3 days/month)	Regular drinkers (no. of days/week)			
		1–2	3–4	5–7	*p* for trend*
Men					
No.	3,956	3,888	4,939	19,624	
No. of deaths	280	246	356	1,866	
Adjusted HR†,‡	1.00	0.93	1.02	1.12	0.007
95% CI†	Reference	0.79, 1.11	0.87, 1.19	0.99, 1.28	
Women					
No.	4,617	2,034	1,373	1,672	
No. of deaths	134	65	40	60	
Adjusted HR‡	1.00	1.08	0.96	1.02	0.82
95% CI‡	Reference	0.80, 1.46	0.67, 1.36	0.75, 1.40	

* Calculated among regular drinkers.

† HR, hazard ratio; CI, confidence interval.

‡ Adjusted for age at baseline (continuous), study area (nine public health center areas), smoking status, body mass index (weight (kg)/height (m)^2), green vegetable intake (≤3–4 times/week and almost every day), and leisure-time physical activity (≤1–3 times/month, ≥1–2 times/week).

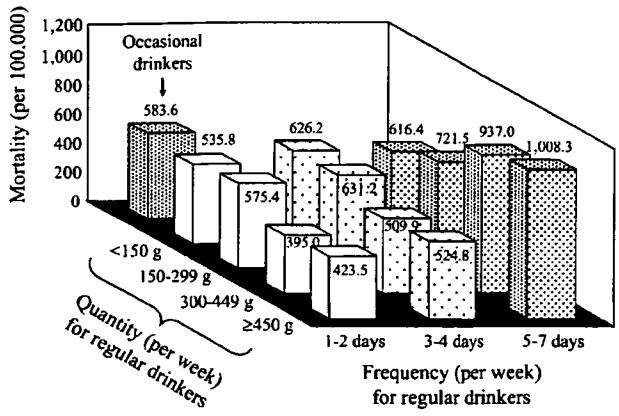

FIGURE 1. Crude mortality rates of all-cause deaths according to quantity and frequency of alcohol intake among men, Japan Public Health Center-based Prospective Study, 1990–2003.

present study comprised a population-based cohort with high response rates to the baseline questionnaire, the level of alcohol intake in our study was regarded as representative of the Japanese population. In fact, the prevalences of male drinkers in our study are almost the same as those for persons aged 40–69 years from the National Health and Nutrition Survey (17); the prevalences of occasional and regular drinkers were 76 percent for the present study and 72–75 percent for the National Health and Nutrition Survey, and the prevalences of drinkers consuming alcohol 5–7 days per week were 47 percent for the present study and 41–45 percent for the National Health and Nutrition Survey. As for drinking pattern, the prevalence of daily drinking (5–7 days/week) and heavy alcohol intake (>300 g) was high in the present study (21 percent of drinkers) as well as in the National Health and Nutrition Survey (31 percent of drinkers). This fact shows that the "liver holiday" belief is not necessarily put into practice, although it is well known in Japanese society.

Regarding the pattern of drinking, inconsistent results were found in the other epidemiologic studies conducted in the Western countries, in which the level of alcohol intake among men was relatively lower than that in the present study. In a Danish study, men in the highest intake of alcohol–less frequent drinker category, compared with frequent drinkers, showed a higher risk of all-cause mortality (15). Of the five categories of alcohol intake, the highest was 21 drinks (252 g of alcohol) per week, which corresponds approximately to the second category in the present study, for which no increased risk associated with frequency of alcohol intake was found. In the United States, in a study of male health professionals in which the effects of drinking patterns on coronary heart disease were investigated, similar risks were found within the same categories of drinking frequency, regardless of the quantity of alcohol consumed per day (13). Similarly, the highest category of alcohol intake was more than 30 g of alcohol per day, corresponding to 150–210 g of alcohol per week if the person drinks on 5–7 days per week, which is also low compared with the present study.

TABLE 4. Hazard ratios and 95% confidence intervals for all-cause deaths according to quantity and frequency of alcohol intake among men,* Japan Public Health Center-based Prospective Study, 1990–2003

Quantity (g/week)	Frequency (no. of days/week)			
	1–2	3–4	5–7	*p* for trend
<150				
No.	3,018	2,181	4,346	
No. of deaths	195	160	319	
Adjusted HR†,‡	0.94	0.96	0.87	0.31
95% CI†	0.78, 1.13	0.79, 1.17	0.74, 1.03	
150–299				
No.	441	1,644	6,970	
No. of deaths	31	123	599	
Adjusted HR‡	1.10	1.03	0.96	0.21
95% CI	0.75, 1.60	0.83, 1.28	0.83, 1.11	
300–449				
No.	81	538	4,832	
No. of deaths	4	33	537	
Adjusted HR‡	0.87	1.01	1.29	0.12
95% CI	0.33, 2.34	0.71, 1.46	1.12, 1.50	
≥450 g				
No.	41	392	3,083	
No. of deaths	2	24	362	
Adjusted HR‡	1.17	1.17	1.55	0.20
95% CI	0.29, 4.71	0.77, 1.78	1.32, 1.81	

* Occasional drinkers (1–3 days/month) were considered the reference group.

† HR, hazard ratio; CI, confidence interval.

‡ Adjusted for age at baseline (continuous), study area (nine public health center areas), smoking status, body mass index (weight (kg)/height (m)^2), green vegetable intake (≤3–4 times/week and almost every day), and leisure-time physical activity (≤1–3 times/month, ≥1–2 times/week).

Note that the harmless effect of a "liver holiday" might not be applicable to excessively heavy drinkers. In our study, although the finding was not statistically significant, men who consumed ≥750 g of alcohol per week showed an increased risk of all-cause mortality regardless of their frequency of alcohol intake (with or without a "liver holiday"). Other epidemiologic studies have consistently indicated the hazardous effects of drinking large quantities of alcohol in 1 day among men in Russia (18) and men and women in the United States (14).

Physiologic evidence remains unclear. The observed association between patterns of drinking and all-cause mortality among male drinkers might be explained largely by death from cancer, which was responsible for 42 percent of all-cause deaths among men in the present study. Mortality from cancer at all sites according to quantity and frequency

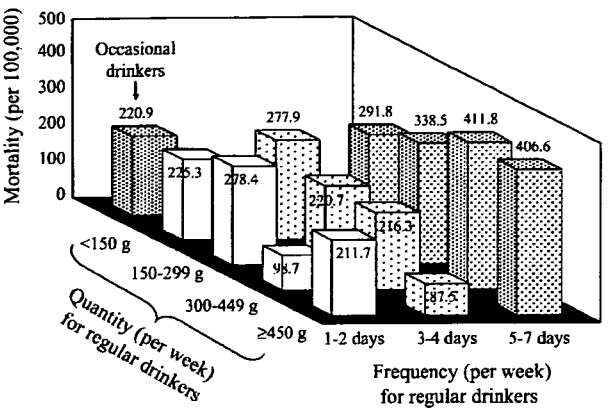

FIGURE 2. Crude mortality rates of cancer deaths according to quantity and frequency of alcohol intake among men, Japan Public Health Center-based Prospective Study, 1990–2003.

of drinking was similar to all-cause mortality (figure 2). Approximately half of the Japanese persons were found to have a deficient phenotype for aldehyde dehydrogenase-2, a key enzyme in the conversion of acetaldehyde to acetate (19, 20), resulting in higher levels of acetaldehyde exposure, which is considered carcinogenic (21). Compared with heavy drinkers adopting the "liver holiday," heavy daily drinkers might be exposed more persistently to the acetaldehyde. On the other hand, in view of the heart disease, because there was some evidence that heavy intake of alcohol on a single occasion was associated with a higher rate of progression of carotid atherosclerosis (22), there seemed to be no effect of a "liver holiday." The small number of deaths from heart disease as well as from other specific diseases, however, did not enable further analysis.

It has been suggested that social integration is a predictor of mortality (23). In Japan, social drinking is an important social event, especially among middle-aged men, and the individual pattern of drinking might reflect their opportunity for social drinking. Indeed, among men in cohort II who were asked the number of days of social drinking, the prevalence of social drinkers tended to be higher among men who had "liver holidays" compared with men who drank on 5–7 days per week. Furthermore, we observed that men who drank at least 1 day per month as a social event had a lower risk of all-cause mortality compared with nonsocial drinkers. However, we did not confirm that the harmless effect of a "liver holiday" could be explained by the lower mortality of the men with more opportunity for social drinking because nonsocial drinkers were quite few (7 percent) among male drinkers in cohort II.

A possible alternative explanation for the different effect on all-cause mortality according to drinking pattern might be the discrepancies in sociological or psychological backgrounds. Our questionnaire was designed primarily to assess lifestyle factors; thus, relevant questions regarding sociological and psychological factors were limited. However, the limited number of questions associated with personality did reveal some distinctive characteristics of male frequent heavy drinkers. Male frequent (5–7 day/week) heavy (≥300 g of alcohol/week) drinkers tended to indicate that they are impatient, irritable, positive, and have a competitive spirit but are not punctual. Regarding the question about stress, male frequent heavy drinkers do not appear to experience a great deal of stress (data not shown).

A potential limitation of our study is the residual confounding; even in the same category of quantity of alcohol consumed, persons in the more frequent weekly intake category might have consumed a higher quantity of alcohol. Further adjustment by including individual quantities of alcohol consumed as continuous variables in the multivariate model did not change the hazard ratios substantially. When we subdivided the ≥450 g weekly intake level into three categories (450–599 g, 600–749 g, and ≥750 g of alcohol/week), the consistent tendency of the harmless effect of a "liver holiday" was observed, except in the ≥750 g category.

Measurement error regarding self-reported alcohol intake should be discussed. Misclassification due to modified alcohol-drinking behavior during the study period is possible. However, it probably caused the results to be attenuated. Furthermore, with the same level of intake, less frequent drinking might be a marker of healthy lifestyle factors, such as nonsmoking, more exercise, and eating more vegetables. Although we controlled for these lifestyle variables in the statistical model, we cannot exclude the possible residual confounding effects of other lifestyle and risk factors.

Our data supported the "liver holiday" hypothesis, which proposes that drinking on 1–4 days per week is better than daily drinking for male heavy drinkers. Regarding the public health implications of this study, we recommend that persons, especially male heavy drinkers, abstain from consuming alcohol for more than 2 days per week.

ACKNOWLEDGMENTS

This work was supported by Grants-in-Aid for Cancer Research and for the Third Term Comprehensive 10-Year-Strategy for Cancer Control from the Ministry of Health, Labour, and Welfare of Japan.

The authors thank all staff members in each study area for their efforts to conduct the baseline and follow-up surveys. They are also indebted to the Ibaraki, Niigata, Osaka, Kochi, Nagasaki, and Okinawa cancer registries for providing their incidence data.

Members of the Japan Public Health Center-based Prospective Study Group—S. Tsugane, M. Inoue, T. Sobue, and T. Hanaoka, National Cancer Center, Tokyo; J. Ogata, S. Baba, T. Mannami, and A. Okayama, National Cardiovascular Center, Suita; K. Miyakawa, F. Saito, A. Koizumi, Y. Sano, and I. Hashimoto, 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, and Y. Miyakawa, 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, and F. Shoji, Katsushika Public Health Center, Tokyo; A. Murata, K. Minato, K. Motegi, and T. Fujieda, Ibaraki Prefectural Mito Public Health Center, Mito; K. Matsui, T. Abe, and M. Katagiri, Niigata Prefectural Kashiwazaki Public Health Center, Kashiwazaki; M. Suzuki, Niigata Prefectural Nagaoka Public Health Center, Nagaoka; M. Doi, A. Terao, and Y. Ishikawa, Kochi Prefectural Chuo-Higashi Public Health Center, Tosayamada; H. Sueta, H. Doi, M. Urata, N. Okamoto, and F. Ide, Nagasaki Prefectural Kamigoto Public Health Center, Arikawa; H. Sakiyama, N. Onga, and H. Takaesu, Okinawa Prefectural Miyako Public Health Center, Hirara; F. Horii, I. Asano, H. Yamaguchi, K. Aoki, S. Maruyama, and M. Ichii, 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 and K. Okada, Ehime University, Matsuyama; H. Iso, Osaka University, Osaka; K. Tsubono, Tohoku University, Sendai; K. Yamagishi and Y. Honda, Tsukuba University, Tsukuba; H. Sugimura, Hamamatsu University, Hamamatsu; M. Kabuto, National Institute for Environmental Studies, Tsukuba; S. Tominaga, Aichi Cancer Center, Nagoya; M. Iida and W. Ajiki, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka; S. Sato, Osaka Medical Center for Health Science and Promotion, Osaka; N. Yasuda, Kochi Medical School, Nankoku; S. Kono, Kyushu University, Fukuoka; K. Suzuki, Research Institute for Brain and Blood Vessels Akita, Akita; Y. Takashima, Kyorin University, Mitaka; E. Maruyama, Kobe University, Kobe; the late M. Yamaguchi, S. Watanabe, Y. Matsumura, and S. Sasaki, National Institute of Health and Nutrition, Tokyo; and T. Kadowaki, Tokyo University, Tokyo.

Conflict of interest: none declared.

REFERENCES

1. Doll R, Peto R, Hall E, et al. Mortality in relation to consumption of alcohol: 13 years' observations on male British doctors. BMJ 1994;309:911–18.
2. Fuchs CS, Stampfer MJ, Colditz GA, et al. Alcohol consumption and mortality among women. N Engl J Med 1995; 332:1245–50.
3. 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.
4. Lin Y, Kikuchi S, Tamakoshi A, et al. Alcohol consumption and mortality among middle-aged and elderly Japanese men and women. Ann Epidemiol 2005;15:590–7.
5. 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.
6. Tsubono Y, Kobayashi M, Sasaki S, et al. Validity and reproducibility of a self-administered food frequency questionnaire used in the baseline survey of the JPHC Study Cohort I. J Epidemiol 2003;13:S125–33.
7. Tsugane S, Sasaki S, Tsubono Y. Under- and overweight impact on mortality among middle-aged Japanese men and women: a 10-y follow-up of JPHC study cohort I. Int J Obes Relat Metab Disord 2002;26:529–37.
8. 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.
9. Iso H, Baba S, Mannami T, et al. Alcohol consumption and risk of stroke among middle-aged men: the JPHC Study Cohort I. Stroke 2004;35:1124–9.
10. Nakaya N, Kurashima K, Yamaguchi J, et al. Alcohol consumption and mortality in Japan: the Miyagi Cohort Study. J Epidemiol 2004;14(suppl 1):S18–25.
11. Yuan JM, Ross RK, Gao YT, et al. Follow up study of moderate alcohol intake and mortality among middle aged men in Shanghai, China. BMJ 1997;314:18–23.
12. Hart CL, Smith GD, Hole DJ, et al. Alcohol consumption and mortality from all causes, coronary heart disease, and stroke: results from a prospective cohort study of Scottish men with 21 years of follow up. BMJ 1999;318: 1725–9.
13. Thun MJ, Peto R, Lopez AD, et al. Alcohol consumption and mortality among middle-aged and elderly U.S. adults. N Engl J Med 1997;337:1705–14.
14. Rehm J, Greenfield TK, Rogers JD. Average volume of alcohol consumption, patterns of drinking, and all-cause mortality: results from the US National Alcohol Survey. Am J Epidemiol 2001;153:64–71.
15. Tolstrup JS, Jensen MK, Tjonneland A, et al. Drinking pattern and mortality in middle-aged men and women. Addiction 2004;99:323–30.
16. Nishino Y, Wakai K, Kondo T, et al. Alcohol consumption and lung cancer mortality in Japanese men: results from Japan collaborative cohort (JACC) study. J Epidemiol 2006;16: 49–56.
17. The National Health and Nutrition Survey in Japan, 2003. Ministry of Health, Labour and Welfare, Japan. Tokyo, Japan: Daiichi Shuppan, 2006.
18. Malyutina S, Bobak M, Kurilovitch S, et al. Relation between heavy and binge drinking and all cause and cardiovascular mortality in Novosibirsk, Russia: a prospective cohort study. Lancet 2002;360:1448–54.
19. Shibuya A, Yoshida A. Genotypes of alcohol-metabolizing enzymes in Japanese with alcohol liver diseases: a strong association of the usual Caucasian-type aldehyde dehydrogenase gene (ALDH1(2)) with the disease. Am J Hum Genet 1988; 43:744–8.
20. Agarwal DP, Harada S, Goedde HW. Racial differences in biological sensitivity to ethanol: the role of alcohol dehydrogenase and aldehyde dehydrogenase isozymes. Alcohol Clin Exp Res 1981;5:12–16.
21. Alcohol drinking. IARC monographs on the evaluation of carcinogenic risks to humans. Vol 44. Lyon, France: International Agency for Research on Cancer, 1988.
22. Kauhanen J, Kaplan GA, Goldberg DE, et al. Pattern of alcohol drinking and progression of atherosclerosis. Arterioscler Thromb Vasc Biol 1999;19:3001–6.
23. Berkman LF, Melchior M, Chastang JF, et al. Social integration and mortality: a prospective study of French employees of Electricity of France–Gas of France: the GAZEL Cohort. Am J Epidemiol 2004;159:167–74.

Early- and Late-Onset Breast Cancer Types Among Women in the United States and Japan

Rayna K. Matsuno,[1,5] William F. Anderson,[1] Seiichiro Yamamoto,[2] Hideaki Tsukuma,[3] Ruth M. Pfeiffer,[1] Ken Kobayashi,[4] Susan S. Devesa,[1] and Paul H. Levine[5]

[1]Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Rockville, Maryland; [2]Statistics and Cancer Control Division, Research Center for Cancer Prevention and Screening, National Cancer Center; [3]Department of Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan; [4]Oncology Early Clinical Development, Novartis Pharma KK, Tokyo, Japan; and [5]Department of Epidemiology and Biostatistics, George Washington University, Washington, District of Columbia

Abstract

Background: **Although differences in breast cancer incidence among Occidental and Asian populations are often attributed to variations in environmental exposures and/or lifestyle, fewer studies have systematically examined the effect of age-related variations.**

Methods: **To further explore age-related geographic breast cancer variations, we compared age-specific incidence patterns among cases of female invasive breast cancer from the Surveillance, Epidemiology, and End Results (SEER) program and the Osaka Cancer Registry (1978-1997).**

Results: **In SEER, there were 236,130 Whites, 21,137 Blacks, and 3,304 Japanese-Americans in Hawaii with invasive breast cancer. In Osaka, there were 25,350 cases. Incidence rates per 100,000 woman-years ranged from 87.6 among Whites to 21.8 in Osaka. Age-specific incidence rates increased rapidly until age 50 years for all race/ethnicity groups, and then continued to increase more slowly for Whites, Blacks, and Japanese-Americans in Hawaii but plateaud for Osaka. Age-specific incidence rates in SEER reflected bimodal (early-onset and late-onset) breast cancer populations, whereas Osaka had only an early-onset age distribution. These age-specific differences in incidence among SEER and Osaka persisted after adjustment for calendar-period and birth-cohort effects using age-period-cohort models.**

Conclusions: **Results confirm striking age-specific differences among Occidental and native Japanese breast cancer populations, probably due to complex age-related biological and/or environmental variations among Occidental and Asian breast cancer populations.** (Cancer Epidemiol Biomarkers Prev 2007;16(7):1437–42)

Introduction

Breast cancer incidence rates are generally higher in Occidental than in Asian populations (1-4), possibly due to a combination of environmental, lifestyle, and/or biological factors. For example, presumptive environmental and/or lifestyle factors shift breast cancer incidence among migrant Asian women from the baseline rate in their native country to the rate in their adopted country (5-8). Biological effects seem to alter the shape of the age-specific incidence rate curve among Occidental and native Asian women (1, 3, 4, 9-15). Among Occidental women, age-specific incidence rates increase rapidly until menopause, and then continue to increase more slowly. Among native Asian women, rates increase rapidly until menopause, and then plateau or decrease. These age-related biological effects have generated interest and debate for decades.

In 1980, Moolgavkar et al. fit a two-stage breast cancer model to six high-risk and low-risk populations, including Connecticut and Osaka (14). The model viewed breast cancer as the end result of two discrete and irreversible events, without distinction for premenopausal (early-onset) and postmenopausal (late-onset) breast cancer types. In this model, among native Asian women, the late-onset drop in incidence was due to a birth-cohort artifact (1, 9) in which the progressive increase in risk from one generation to the next gives the appearance of a decreasing age-specific incidence rate curve. In 1981, Pike and colleagues developed the concept of breast tissue "aging," modified by the timing of certain reproductive risk factors such as the age at menarche, first full-term pregnancy, and menopause (15). Still others have suggested that the different age-specific incidence rate patterns among different breast cancer populations result from the mixing of distinct breast cancer types according to age at onset (16-19). Rates that increase rapidly until age 50 years, and then flatten, reflect mostly early-onset breast cancer populations, whereas rates that increase continuously with aging result from mixed early-onset and late-onset breast cancer types.

To further explore geographic age-related variations among Occidental, migrant Asian, and native Asian breast cancer populations, we examined age-specific incidence patterns (rates and age distributions) using data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program and the Osaka Cancer Registry (OCR). To account for calendar-period and/or birth-cohort effects, we used age-period-cohort models to simultaneously adjust for age, calendar-period, and birth-cohort effects.

Materials and Methods

Subjects. Female breast cancer case data for Whites, Blacks, and Japanese-Americans in Hawaii (JAHI) were obtained from the SEER 9-Registry database (November 2004 submission; ref. 20). The SEER 9-Registry database includes data from San Francisco-Oakland, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta, covering ~10% of the U.S. population. Case data for native Japanese women were obtained from the OCR (21). The OCR is a population-based registry in Osaka Prefecture, the second most populous prefecture in Japan, covering ~8 million people or ~7% of

Received 2/5/07; revised 4/16/07; accepted 4/20/07.

Grant support: Intramural Research Program of the NIH/National Cancer Institute.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Requests for reprints: Rayna K. Matsuno, Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, 6120 Executive Boulevard, Room 8105, Rockville, MD 20852-7244. Phone: 301-451-6889; Fax: 301-402-0081. E-mail: matsunora@mail.nih.gov

doi:10.1158/1055-9965.EPI-07-0108