19. Iwasaki M, Otani T, Inoue M, Sasazuki S, Tsugane S (2007) Role and impact of menstrual and reproductive factors on breast cancer risk in Japan. Eur J Cancer Prev 16:116–123
20. Fukao A, Tsubono Y, Komatsu S et al (1995) A cohort study on the relation of lifestyle, personality and biologic markers to cancer in Miyagi, Japan: study design, response rate and profiles of the cohort subjects. J Epidemiol 5:153–157
21. Naganuma T, Kuriyama S, Kakizaki M et al (2008) Coffee consumption and the risk of oral, pharyngeal, and esophageal cancers in Japan: the Miyagi Cohort Study. Am J Epidemiol 168:1425–1432
22. Doll R, Payne P, Waterhouse JAH (1966) Cancer incidence in five continents: a technical report. Vol 3: IARC scientific publications. International Union against Cancer, Genève, pp 118–123
23. Cox DR (1972) Regression models and life-tables (with discussion). J Roy Statist Soc 34:187–220
24. Gao YT, Shu XO, Dai Q 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
25. Pharoah PDP, Day NE, Duffy S, Easton DF, Ponder BAJ (1997) Family history and the risk of breast cancer: a systematic review and meta-analysis. Int J Cancer 71:800–809
26. Tamakoshi K, Yatsuya H, Wakai K 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
27. Health and Welfare Department Miyagi Prefecture (1993) Miyagi Prefecture. Report on special investigation for cancer prevention. Miyagi Cancer Society, Sendai (in Japanese)
28. Adami HO, Bergström R, Lund E, Meirik O (1990) Absence of association between reproductive variables and the risk of breast cancer in young women in Sweden and Norway. Br J Cancer 62:122–126
29. Pathak DR, Speizer FE, Willett WC, Rosner B, Lipnick RJ (1986) Parity and breast cancer risk: possible effect on age at diagnosis. Int J Cancer 37:21–25
30. Rosner B, Colditz GA, Willett WC (1994) Reproductive risk factors in a prospective study of breast cancer: the Nurses' Health Study. Am J Epidemiol 139:819–835
31. Collaborative Group on Hormonal Factors in Breast Cancer (2001) Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58 209 women with breast cancer and 101 986 women without the disease. Lancet 358:1389–1399
32. Pike MC, Krailo MD, Henderson BE, Casagrande JT, Hoel DG (1983) 'Hormonal' risk factors, 'breast tissue age' and the age-incidence of breast cancer. Nature 303:767–770
33. Antoniou AC, Easton DF (2006) Models of genetic susceptibility to breast cancer. Oncogene 25:5898–5905
34. Bernstein L, Ross RK (1993) Endogenous hormones and breast cancer risk. Epidemiol Rev 15:48–65
35. Chubak J, Tworoger SS, Yasui Y, Ulrich CM, Stanczyk FZ, McTiernan A (2004) Associations between reproductive and menstrual factors and postmenopausal sex hormone concentrations. Cancer Epidemiol Biomarkers Prev 13:1296–1301
36. Hankinson SE, Colditz GA, Hunter DJ et al (1995) Reproductive factors and family history of breast cancer in relation to plasma estrogen and prolactin levels in postmenopausal women in the nurses' health study (United States). Cancer Causes Control 6:217–224
37. Dorgan JF, Reichman ME, Judd JT et al (1995) Relationships of age and reproductive characteristics with plasma estrogens and androgens in premenopausal women. Cancer Epidemiol Biomarkers Prev 4:381–386
38. Eliassen AH, Tworoger SS, Hankinson SE (2007) Reproductive factors and family history of breast cancer in relation to plasma prolactin levels in premenopausal and postmenopausal women. Int J Cancer 120:1536–1541
39. 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
40. Nagata C, Matsushita Y, Inaba S, Kawakami N, Shimizu H (1997) Unapproved use of high-dose combined pills in Japan: a community study on prevalence and health characteristics of the users. Prev Med 26:565–569
41. Romieu I, Willett WC, Colditz GA et al (1989) Prospective study of oral contraceptive use and risk of breast cancer in women. J Natl Cancer Inst 81:1313–1321
42. Kahlenborn C, Modugno F, Potter DM, Severs WB (2006) Oral contraceptive use as a risk factor for premenopausal breast cancer: a meta-analysis. Mayo Clin Proc 81:1290–1302
43. Shantakumar S, Terry MB, Paykin A et al (2007) Age and menopausal effects of hormonal birth control and hormone replacement therapy in relation to breast cancer risk. Am J Epidemiol 165:1187–1198
44. Nelson HD, Humphrey LL, Nygren P, Teutsch SM, Allan JD (2002) Postmenopausal hormone replacement therapy: scientific review. JAMA 288:872–881

Epidemiology of Breast Cancer in Japan and the US

JMAJ 52(1): 39–44, 2009

Kumiko SAIKA,[*1] Tomotaka SOBUE[*1]

Abstract

A comparison of breast cancer occurring in American and Japanese women reveals that both the incidence and mortality rates are markedly higher in the US. However, both the age-adjusted incidence and mortality rates have been increasing in Japan. On the other hand, in the US, where the age-adjusted incidence rate tended to increase before the 1990s, the rate has tended to decline after reaching a peak in the late 1990s. The age-adjusted mortality rate has also tended to decline since the 1980s in the US.

Risk factors for breast cancer include early menarche, late menopause, and late first delivery. The higher frequencies of these risk factors in American women than in Japanese women may explain the higher incidence and mortality rates of breast cancer in the US. The recent increase in the incidence and mortality rates of breast cancer in Japan seems to be a reflection of a trend toward late marriage and declining birthrates in this country. The recent decrease in the mortality rate from breast cancer in the US may be attributable to the spread of screening by mammography and improved therapeutic modalities. Major risk factors for breast cancer are difficult to control at the individual level, and effective prevention of the disease is unlikely. Improvement in the screening rate will be necessary for achieving a decrease in the mortality from breast cancer.

Key words Mortality, Incidence, Risk factors

Introduction

Although the incidence and mortality rates of breast cancer among women in Japan are lower than those in western countries, they have been increasing recently. In Japan in 1994, the age-adjusted breast cancer incidence rate ranked first among cancer incidence rates by site of cancer. Understanding the trends in the incidence and mortality rates and established risk factors for breast cancer, and considering Japan's differences from the US, where the incidence and mortality rates have been decreasing, has important implications for the future prevention of breast cancer in Japan.

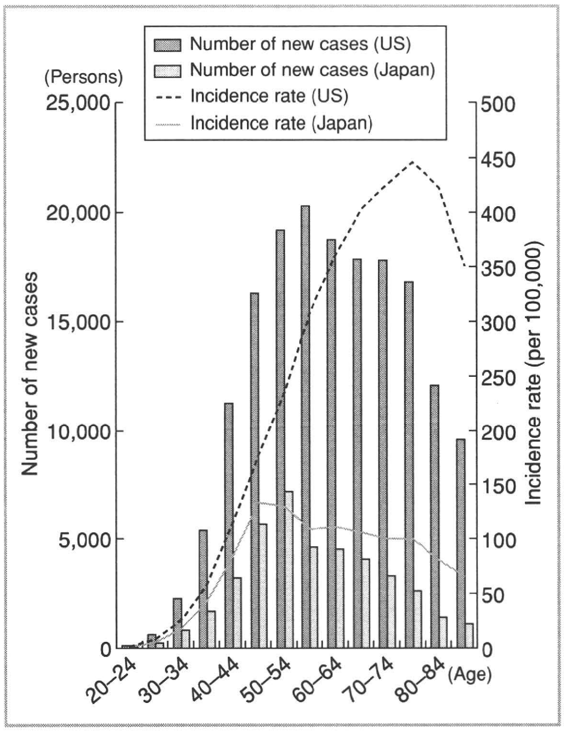
Descriptive Epidemiology

Number of new cases and incidence rate of breast cancer

Information on cancer morbidity in Japan is available from the Research Group for the Population-Based Cancer Registry in Japan, whereas that in the US is available from the Surveillance Epidemiology and End Results (SEER) and the National Program of Cancer Registries (NPCR). However, it should be noted that Japanese data include cases of carcinoma in situ.

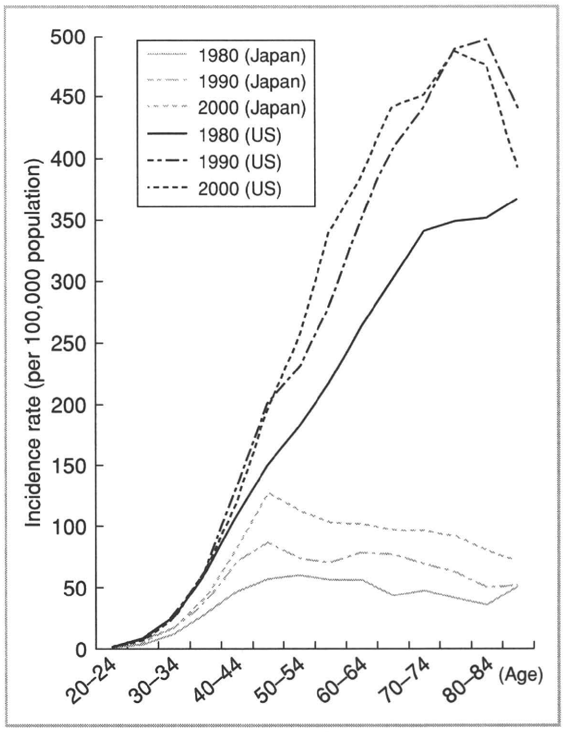
In 2001, there were 40,675 women with breast cancer in Japan (ranking second among cancer cases by site of cancer), accounting for 16.7% of all cases of cancer. In 2002, the number of American women with breast cancer was 168,632

*1 Center for Cancer Control and Information Service, National Cancer Center, Tokyo, Japan (ksaika@ncc.go.jp).
This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol.137, No.4, 2008, pages 657–661).



(Japan: Research Group for the Population-Based Cancer Registry in Japan,* US: US Cancer Statistics**)
* Including carcinoma in situ.
** Excluding Connecticut, Hawaii, Iowa, Kansas, Maryland, Mississippi, New Mexico, South Dakota, Tennessee, Utah, Virginia, and Wyoming.

Fig. 1 The number of breast cancer new cases and incidence rates by age group in Japan (2001) and the US (2002)



(Japan: Research Group for the Population-Based Cancer Registry in Japan, US: SEER database)

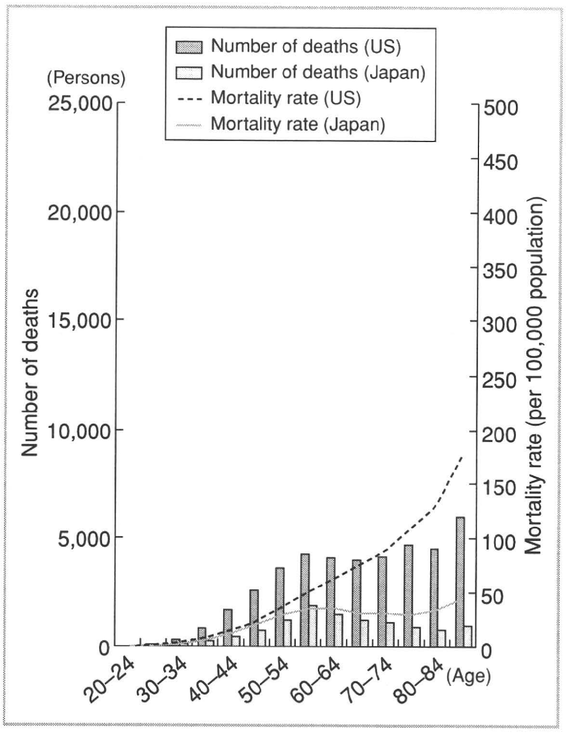
Fig. 2 Breast cancer incidence rates by age group

(ranking first among cancer cases by site of cancer), accounting for 30.4% of all cases of cancer.

The age-adjusted incidence rate has been increasing in Japan since 1975, with the 1985 model population being used as the reference population. The incidence rate of breast cancer was third highest (21.7 per 100,000 population) among various cancers in 1975, following stomach cancer and uterine cancer. After reaching a peak (101.4 per 100,000 population) in 1999, the incidence rate has been declining, showing a figure of 89.8 per 100,000 population in 2004.

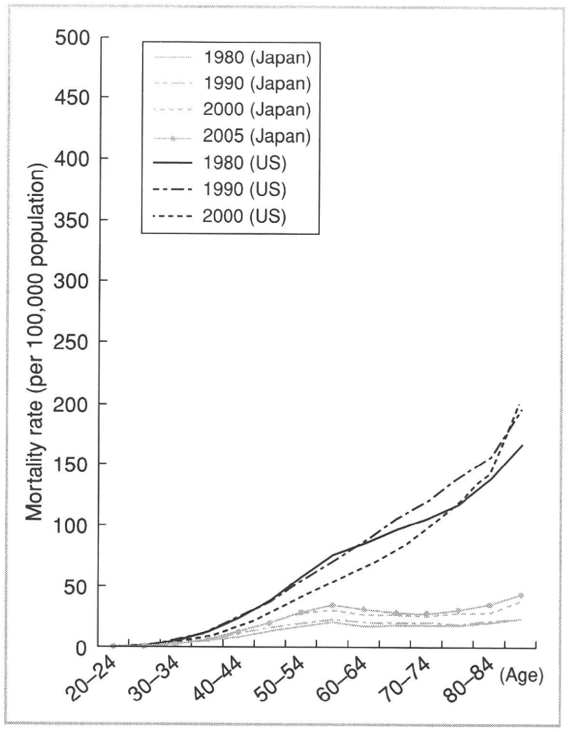
Figure 1 shows the number of new cases and incidence rates by age group in Japan (2001) and the US (2002). In both countries, the number of new cases began to increase after the age of 20 years, reaching a peak at the age of 50–59 and declining thereafter. Breast cancer was most frequent in women 50–54 years of age in Japan, whereas the corresponding age was 55–59 years in the US. The incidence rate began to increase after 20 years of age in both Japan and the US, continuing to increase similarly until 45–49 years. However, the incidence rate reached a peak (133.7 per 100,000 population) at the age of 45–49 years in Japan, whereas there was a continuous increase (446.8 per 100,000 population) until 75–79 years in the US.

Figure 2 shows the trend in the incidence rates of breast cancer by age group at 10-year intervals. In Japan, the peak incidence rate was found in women aged 50–54 (59.8 per 100,000) in 1980, and in those aged 45–49 (86.4 and 126.4 per 100,000 in 1990 and 2000, respectively). The peak has been even more dramatic in recent years. In addition, regardless of age group, the incidence rate has been higher in recent years. In the US, the incidence rate was higher in women of more advanced age in 1980. The peak incidence rate was found in women aged 80–84 (497.7 per 100,000) in 1990, and in those aged 75–79 (487.4 per 100,000) in 2000. Although there was a marked increase in the incidence rate of breast



(Japan: Vital statistics of Japan, Ministry of Health, Labor and Welfare; US: WHO database)

Fig. 3 The number of breast cancer deaths and mortality rates by age group in Japan (2006) and the US (2004)



(Japan: Vital statistics of Japan, Ministry of Health, Labor and Welfare; US: WHO database)

Fig. 4 Breast cancer mortality rates by age group

cancer from 1980 to 1990, no substantial changes were noted from 1990 to 2000.

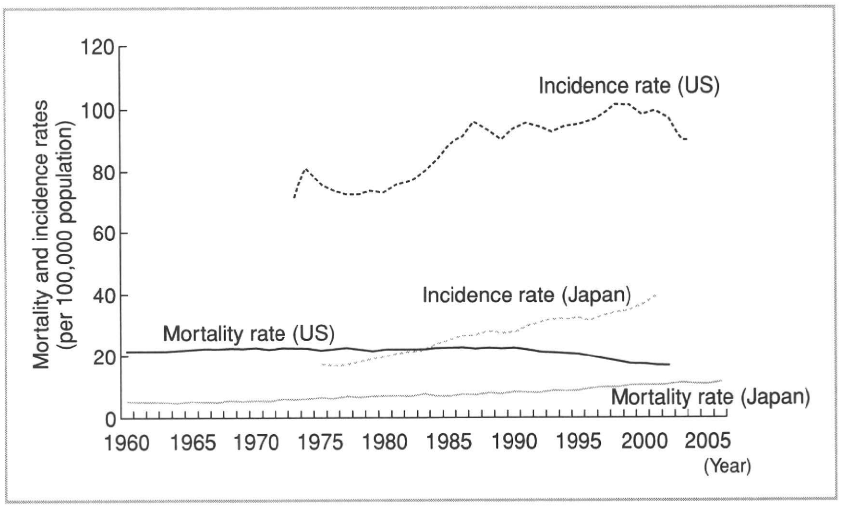
Trends in the number of deaths and the mortality

Data on cancer mortality in Japan were obtained from the Vital Statistics by the Ministry of Health, Labor and Welfare, and data on cancer mortality in the US were obtained from the Vital Statistics of the United States.

In 2006, the number of breast cancer deaths in Japan was 11,174 (ranking fourth by site of cancer), accounting for 8.5% of all cancer deaths. The number of cancer deaths in the US in 2004 was 40,954 (ranking second by site of cancer), accounting for 15.3% of all cancer deaths, about two-fold higher than in Japan. The age-adjusted breast cancer mortality rate in Japan has tended to increase since 1960; although the mortality rate ranked fifth (5.1 per 100,000) in 1960, following stomach cancer, uterine cancer, liver cancer, and colorectal cancer. In 2006, it ranked third (11.7 per 100,000) together with lung cancer, following colorectal cancer and stomach cancer. In the US, the breast cancer mortality rate was ranked first (21–22 per 100,000) from 1960 to 1986, but it has dropped to second place since 1987, having been replaced by lung cancer, which had increased rapidly.

Figure 3 shows the number of deaths and mortality rates of breast cancer in Japan (in 2006) and the US (in 2004) by age group. The number of deaths began to increase in individuals after 30 years of age both in Japan and the US. Deaths were most frequent in women aged 55–59 (1,897 individuals) in Japan. In contrast, in the US, a peak was found in those aged 55–59 (4,282 individuals), but breast cancer deaths were most frequent (5,986 individuals) in those aged 85 years old or older. The mortality rate tended to be higher with advancing age in both Japan and the US, although there was a peak at age 60–64 in Japan. Differences in the mortality rate between Japan and the US were noteworthy in women after 50 years of age.

Figure 4 presents breast cancer mortality rate



[Incidence rates (Japan: Research Group for the Population-Based Cancer Registry in Japan*; US: SEER database), Mortality rates (Japan: Vital statistics of Japan, Ministry of Health, Labor and Welfare; US: WHO database)]
*Including carcinoma in situ.

Fig. 5 Trends in the age-adjusted breast cancer mortality and incidence rates (age adjusted for world population)

by age group at 10-year intervals. In Japan, the mortality rates have been higher in more recent years in all age groups. On the other hand, in the US, although there were no marked changes in the mortality rates in women aged 75 years or older, the mortality rates tended to be lower in 2000 than in 1990 in all of the age groups from 20–74 years.

The proportions of particular age groups to overall breast cancer deaths were influenced by the increased population of elderly individuals both in Japan and the US. Women in their 50s and those aged 75 years or older accounted for higher proportions among all patients who died of breast cancer in Japan, whereas the group 75 years or older accounted for a higher proportion in the US. The percentage of Japanese women in the 50s remained at 25–30% during the period from 1960 to 2006. Those aged 75 years or more accounted for 12% in 1960, but increased to 24% in 2006. In the US, the proportion of women aged 75 years or older was 18.8% in 1960, and increased to 37.2% in 2004.

Comparison of incidence and mortality rates

Figure 5 shows the trends in the age-adjusted breast cancer incidence and mortality rates in Japan and the US (the reference population is world population). Although both breast cancer incidence and mortality rates among Japanese women have been tending to increase, the incidence/mortality ratio increased from 3.4 in 1975 to 4.2 in 2001. In the US, although the mortality rate declined after 1990, and the incidence rate has decreased since 2000, the incidence/mortality ratio increased from 2.9 in 1973 to 4.8 in 2004.

Survival rate

According to data on survival from population-based cancer registries in Japan, the 5-year relative survival rate for women with breast cancer diagnosed from 1993 to 1996 was 83.1%.[1] On the other hand, according to the SEER database in the US, the 5-year relative survival rate for patients diagnosed from 1993 to 1995 was 86.6%.

Risk Factors

Reproductive factors

Estrogen plays an important role in the development of breast cancer. Many of the established risk factors for breast cancer are known to influence endogenous estrogen levels. It is apparent that prolonged exposure to estrogen increases the risk of breast cancer, as in cases of early menarche, late menopause, late first delivery, low parity, and absence of breast-feeding.[2,3]

Exogenous hormones

Although it is apparent that postmenopausal hormone replacement therapy increases the risk of breast cancer, most previous studies have focused on estrogen-progestin combined therapy. No consistent results have been obtained from reports on estrogen-only therapy. High postmenopausal blood estrogen levels and high premenopausal blood IGF-I levels are also established risk factors.[2]

In regard to oral contraceptives, it has been reported that the rate of oral contraceptive use and the risk of developing breast cancer are higher among Japanese and other Asian immigrants in the US than among women in their home countries.[4] However, a relation between the use of oral contraceptives and the increased risk of breast cancer has not been established.

Nutritional factors and physical activity

While attention has been given to fat, fiber, fruits and vegetables, and soy isoflavones as possible prophylactic factors for breast cancer, only alcohol is a clearly established risk factor for premenopausal breast cancer. For postmenopausal breast cancer, fat as well as alcohol are regarded as established risk factors.[4]

Physical activity may be associated with a reduction in the risk of postmenopausal breast cancer.[4]

Anthropometric factors

Being tall and postmenopausal obesity are established risk factors. However, it has been reported that obesity is associated with a reduced risk in premenopausal women.[4]

Genetic and familial susceptibility

A family history of breast cancer in a first-degree relative is an established risk factor, and BRCA1 and BRCA2 are known to be the responsible genes. However, BRCA abnormality may not be the only cause of familial breast cancer; it is possible that environmental factors in the family are involved.

Prevention

It is difficult to modify such risk factors as reproductive factors, genetic and familial susceptibility of breast cancer, for the purpose of preventing breast cancer. However, it is possible to cut down on alcohol consumption or to exercise regularly. Early detection of breast cancer by mammographic screening also helps reduce deaths from breast cancer.

Differences between Japan and the US as Related to Risk Factors

Both the incidence and mortality rates of breast cancer are considerably lower in Japan than in the US. This may be explained by the higher proportion of obese people in the US than in Japan and differences between people in the two countries in eating habits, physical features, age at menarche, and reproductive history.

The age-adjusted incidence rates in the US had been increasing until 2000, partly because mammographic screening became widespread in the 1980s. It is reported that the percentage of women aged 40 years of age or over who received screening within the previous 2 years was 29.1% in 1987, but increased to 70.1% in 2000.[5] Improved therapeutic efficacy may be involved in the decrease in the mortality rate in the US after 1990, because there was improvement in survival rates in addition to the benefit of early detection by screening and early treatment after screening. In recent years, tamoxifen has been widely used since its efficacy as an agent for postoperative chemotherapy was demonstrated. The decrease in the age-adjusted incidence rates after 2000 in the US may be partially attributable to a decrease in women who were receiving postoperative hormone replacement therapy, a risk factor for breast cancer.[6]

In contrast to the decrease in the incidence and mortality rates in the US, both the incidence and mortality rates have been increasing in Japan. This may be explained by an increased population of women at risk of breast cancer due to an overall tendency to late marriage and declining birthrates as well as changes in the lifestyle and physical features of the Japanese people. A clinical breast physical examination had been carried out in women aged 30 years or more as a part of the cancer screening based on the Health and Medical Services Laws for the aged since 1987. Mammography began to be used for women aged 50 years or more in 2000, and for those aged 40 or more in 2005. The screening rate, however, was 12.4% for breast cancer screenings conducted by municipal governments in 2002, with the mammographic screening rate as low as 2.1%,[7] showing hardly any influence on the incidence rate or mortality rate. The breast cancer screening rate increased to 17.6% in 2005,[8] and it is expected that, if the screening rate continues to increase, it may lead to a reduction in the breast cancer mortality rate.

Breast Cancer in Men

The crude mortality rate of breast cancer in men was 0.2 (per 100,000 population) in Japan in 2006, and 0.3 (per 100,000 population) in the US in 2004. The mortality rates were 85- to 90-fold higher in women than in men in both Japan and the US. Risk factors of breast cancer in men are also unclear.

Conclusion

The increase in the breast cancer incidence and mortality rates in Japan may be attributable to changes in eating habits and physical features, the tendency to marry late, and decreased birthrates. On the other hand, the recent decrease in the breast cancer mortality rate in the US may be due to early detection of the disease by mammographic screening, implementation of early treatment, and the efficacy of tamoxifen therapy. To decrease the breast cancer incidence rate, it is important to modify lifestyle, e.g., to decrease alcohol consumption and to practice adequate exercise. To increase the screening rate is important in decreasing the mortality rate.

References

1. Tsukuma H, Ajiki W, Oshima A, et al. Survival of cancer patients diagnosed in 1993–1996: collaborative study of population-based cancer registries in Japan. Jpn J Clin Oncol. 2006;36: 602–607.
2. Graham AC, Heather JB, Rulla MT. Breast cancer. In: David S, Joseph FF ed. Cancer Epidemiology and Prevention, 3rd ed. New York: Oxford University Press Inc.; 2006:995–1012.
3. Iwasaki M, Otani T, Inoue M, et al. Role and impact of menstrual and reproductive factors on breast cancer risk in Japan. Eur J Cancer Prev. 2007;16:116–123.
4. World Cancer Research Fund/American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington DC: AICR; 2007: 289–295.
5. Swan J, Breen N, Burhansstipanov L, et al. Cancer screening and risk factor rates among American Indians. Am J Public Health. 2006;96:340–350.
6. Espey DK, Wu XC, Swan J, et al. Annual report to the nation on the status of cancer, 1975–2004, featuring cancer in American Indians and Alaska Natives. Cancer. 2007;110:2119–2152.
7. Statistics and Information Dept., Minister's Secretariat, Ministry of Health, Labor and Welfare. Report of the 2002 Regional Health and Health for the Elderly Projects. (in Japanese)
8. Statistics and Information Dept., Minister's Secretariat, Ministry of Health, Labor and Welfare. Report of the 2005 Regional Health and Health for the Elderly Projects. (in Japanese)

Breast Cancer (2009) 16:18–22
DOI 10.1007/s12282-008-0082-8

Ultrasound screening of breast cancer

Eriko Tohno · Ei Ueno · Hiroshi Watanabe

Received: 4 August 2008 / Accepted: 30 September 2008 / Published online: 14 November 2008

Abstract Ultrasound (US) screening of breast cancer was surveyed with the results of breast screening combined with mammography (MMG), US and clinical breast examination (CBE) at Ibaraki Health Service Association. Breast cancer is common among women in their late 40s in Japan, who tend to have small and dense breasts. Our results showed that US works as well as MMG in detecting breast cancers in women in their 40s, and both modalities are compensatory. There are many reports that the combination of MMG and US is a suitable method for breast screening in Japan. A large-scale randomized control trial is now ongoing to investigate whether breast screening by both MMG and US is useful to decrease breast cancer mortality.

Keywords Breast · Screening · Ultrasound

Introduction

In Japan, breast screening was initiated around 1965 [1]. It has been conducted by the Japan Cancer Society since 1975. Breast screening has garnered widespread popularity since 1987 when the Second Health Enterprise for the aged was launched by the government. Women aged 35 years or older underwent breast cancer screening, which involved inspection and palpation, and was conducted mainly by surgeons or gynecologists. In 1998, reports on the effectiveness of cancer screening revealed that breast screening by palpation and inspection was not useful. Thereafter, mammography (MMG) screening, whose effectiveness has been proven by many randomized trials held in the United States and European countries, was officially introduced and practiced all over Japan.

Japan has been leading the world in developments in the field of ultrasound (US) in medicine. The application of US for the diagnosis of breast diseases was reported by Kikuchi et al. in 1957 [2]. Ultrasonography is an excellent diagnostic method for breast diseases in the clinical setting. It can detect masses at the site of concern, and, in many cases, determine whether a mass is benign or malignant. When differentiation between benign and malignant masses is difficult, fine-needle aspiration cytology (FNAC) or core-needle biopsy (CNB) can be performed under US guidance. Takahashi et al. [3] reported that in clinical cases, the sensitivity of breast cancer detection by MMG was 92.9%, while Koike et al. [4] reported it was 64.6%. There are reports that US is better in detection of breast cancer if the patient is young or the masses are small [5–7].

US breast screening combined with MMG has been attempted mainly in private medical institutes, and this screening combination has been reported to be complementary.

In 1998, the cost of breast screening was borne by local governments, such as those of cities and towns; each prefecture prepared guidelines on how breast screening should be performed. In Ibaraki Prefecture, we, the members of the breast section meeting of the committee for administration and guiding for adult diseases, adopted a combination of modalities that can supposedly detect the maximum number of breast cancers. Table 1 shows the

E. Tohno (✉) · E. Ueno
Graduate School of Comprehensive Human Sciences,
University of Tsukuba, 1-1-1 Tennodai,
Tsukuba, Ibaraki 305-8575, Japan
e-mail: etohno@sakura.cc.tsukuba.ac.jp

H. Watanabe
Ibaraki Health Service Association,
489-5, Kasahara, Mito 310-8501, Japan

Table 1 Guidelines for breast screening in Ibaraki Prefecture, April 2001

Age	Modalities and intervals
30–39	CBE (once/1 year) + US (once/1 year)
40–56	CBE (once/1 year) + US (once/1 year) + MMG (once/2 years)
57–65	MMG (once/2 years)

CBE clinical breast examination, *US* ultrasound, *MMG* mammography

guidelines prepared for the Ibaraki Prefecture, which were published in 2001. These guidelines were not based on the reduction in mortality due to breast cancer, and all local governments were not able to strictly follow them. Nevertheless, US breast screening was implemented on an experimental basis. Here, I show some of the results of breast screening by using combined MMG and US in Ibaraki Prefecture.

Materials and methods

Ibaraki Health Service Association conducts approximately 85% of the public breast screening in Ibaraki Prefecture. Most of the screening is performed using mobile units carried on buses. The MMG units used are MAMMOMAT1000 and MAMMOMAT300 (Siemens-Asahi Medical Technology Ltd.), Senographe 800T (GE Hearthcare) and MGU-200B (Toshiba Medical Systems Co.). The combinations of the screen/film used are MIN-R2190/MIN-R2000 and MIN-R2000/MIN-R2000 (Kodak Co.). The films were processed by CEPROS M2 (Fuji Film Medical Co., Ltd.). Both the radiographers and interpreting doctors are qualified by the Central Committee on Quality Control of Mammographic Screening. A total of 5 radiographers and 13 doctors are engaged in MMG screening. Each film was read by two doctors (double reading).

The US equipment consists of Toshiba SSA340A equipped with 7.5-MHz annular array mechanical transducers. US examination was performed by nine sonographers who had attended a 2-day course on breast US held by the educational committee of the Japanese Association of Breast and Thyroid Sonology (JABTS). The sonographers screen both breasts and save pictures of both normal areas and of masses, cysts or any abnormal areas they detect. The findings in each case are interpreted by a doctor among eight doctors who are skilled in breast US and have also attended the above-mentioned course. Clinical breast examination (CBE) is performed by doctors who attended at least one of the seminars on breast screening.

Results

Between April 2004 and March 2006, 41,653 women underwent MMG, 48,294 underwent US examination, and 21,389 underwent CBE. Table 2 shows the age distribution of the participants, recall rates and rates of breast cancer detection by using each modality according to age. The rate of early cancer (stage I) detection was 72% by US examination, 66% by MMG and 42% by CBE. The recall rates of US examination, MMG and CBE were 4, 4.3 and 1.8%,

Table 2 Number of participants (a), recall rate (b) and detection rate (c) of breast cancer according to the modality and age (from April 2004 to March 2006)

Age	US	MMG	CBE
(a) Numbers of participants			
>29	295	0	49
30–34	5,340	21	948
35–39	7,199	69	3,504
40–44	7,050	5,821	2,963
45–49	6,872	5,401	2,786
50–54	8,151	7,154	3,608
55–59	5,470	10,273	3,423
60–64	430	8,600	1,617
65–69	352	6,288	1,426
70<	304	4,667	1,065
All	41,653	48,294	21,389
(b) Recall rate (%)			
>29	1.7	–	4.1
30–34	3.7	9.5	2.7
35–39	4.0	5.8	2.2
40–44	3.6	5.3	2.2
45–49	5.7	5.4	2.4
50–54	4.1	5.2	1.5
55–59	3.0	4.1	1.1
60–64	6.3	3.8	1.4
65–69	1.4	3.2	0.8
70<	3.0	3.0	1.8
All	4.0	4.3	1.8
(c) Detection rate (%)			
>29	0	0	0
30–34	0.04	0	0
35–39	0.07	0	0
40–44	0.13	0.1	0.03
45–49	0.22	0.22	0.14
50–54	0.16	0.15	0.03
55–59	0.27	0.23	0.15
60–64	0.47	0.22	0
65–69	0.28	0.22	0
70<	0.66	0.30	0
All	0.15	0.21	0.06

respectively. While the recall rates of US examination did not differ with age, those of MMG tended to be high among young women. The detection rate of breast cancer was the highest in the case of MMG, but no difference existed in the detection rates by MMG and US in the case of women in their 40s and 50s. The detection rate of cancer is low among women in their 30s, and this decreases the overall detection rate of breast cancer by using US examination.

Figure 1 shows the number of cancers detected according to the modality in patients who underwent more than one examination. Only 1 of 18 cancers was detected by CBE alone. Cancer detection by MMG and US is complementary, and approximately one-third of cancers would have been missed if only one of these tests had been performed.

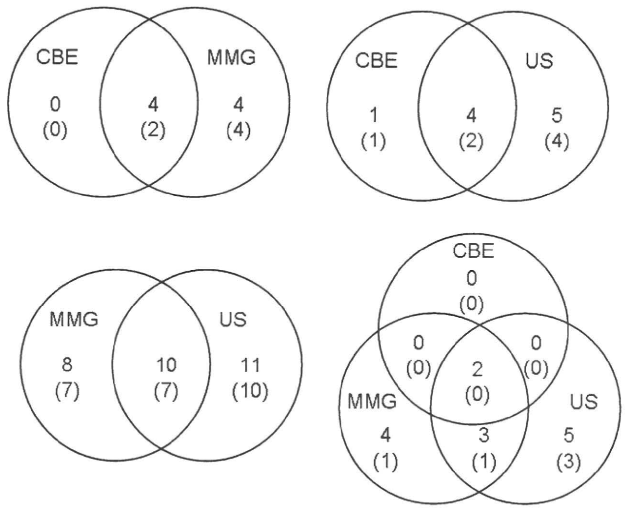


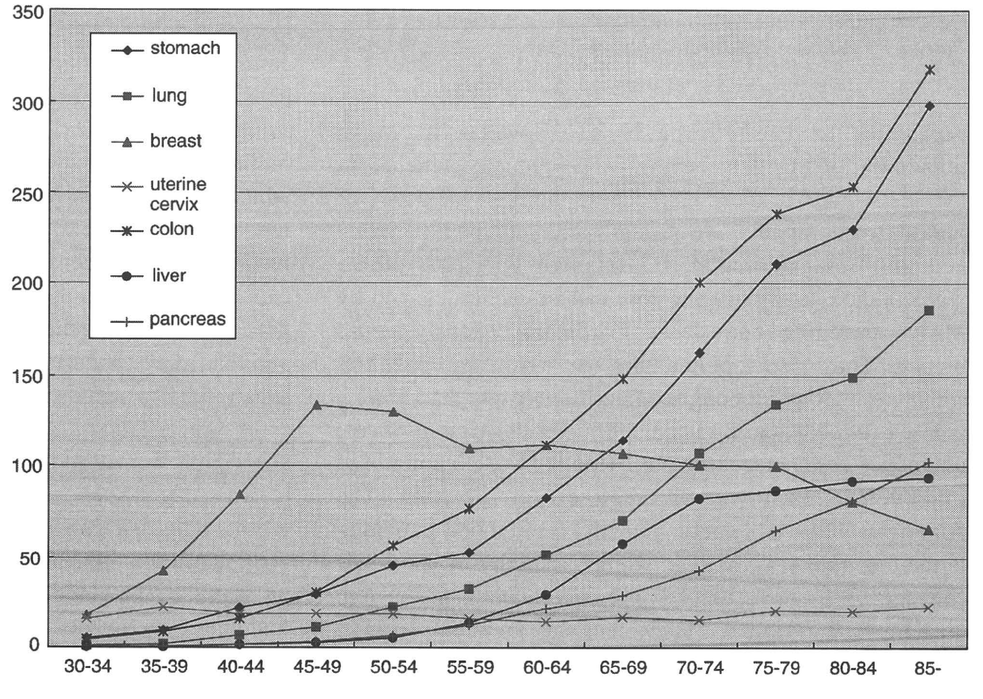
Fig. 1 Number of cancers detected according to the modality in participants who underwent more than one examination. *Number in parentheses* indicates numbers of early cancers

Discussion

Breast cancer has become the most common cancer among Japanese women since 1994 and is the leading cause of mortality among women aged between 35 and 64 years [8]. Effective breast screening has become an important health issue. Figure 2 shows the incidence rate of cancers by age and site in Japan. The incidence of breast cancer is the highest between the late 40s and early 50s. This differs not only from the incidence of other major cancers in Japan but also from the incidence of breast cancer in other countries, where breast cancer incidence increases with age.

MMG screening is an established method for breast cancer detection, and its effectiveness has been proven in randomized trials held in the United States and European countries. Although this has not been proven in Japan, no alternative modality is available, and hence, MMG screening was recommended by the Japanese government and has been rapidly gaining popularity throughout Japan. MMG is less sensitive in dense breasts. In Japan, MMG screening was initially targeted toward women in their 50s. This was because it was considered that in the case of women in their 40s, some cancers might not be detected

Fig. 2 Cancer incidence rate by age and site in Japan (2001) [8]



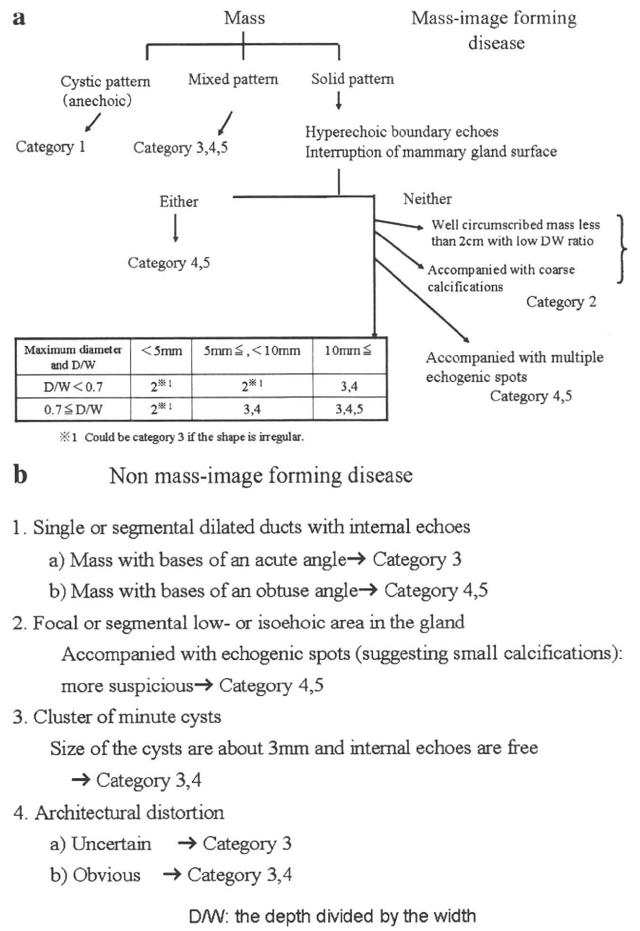


Fig. 3 Criteria of mass-image forming diseases and non-mass-image forming diseases for recall in breast US screening (translated from [18]). *Category 1* indicates normal, including normal variations. *Category 2* indicates benign disease, which does not require further examination. *Category 3* indicates probably benign disease, which requires further examination. *Category 4* indicates suspicious lesion. *Category 5* indicates typical breast cancer

because of the density of the breasts. However, the target population of MMG screening was eventually widened to include women in their 40s because the high incidence of breast cancer in this age group warranted medical intervention. Hasegawa et al. [9] reported that 70% of the women aged 40–49 years whose cancers were detected by MMG screening had dense or heterogeneously dense breasts. They also reported that the sensitivity of MMG screening is lower among women in their 40s than among women in their 50s: 83 versus 90%. In the United States, magnetic resonance imaging (MRI) was reported to improve the sensitivity of breast cancer detection. The American Cancer Society recently revised its screening guidelines for breast MRI in women at high risk for breast cancer [10]. In Japan, the risk of breast cancer is not as high as that in the United States, and the potential benefits of breast MRI do not justify its cost and the risks of MRI-enhancement agents. US, on the other hand, is harmless and suitable for small and dense breasts, which are common among Japanese women. This may explain why US is better for diagnosing breast cancer in the clinical setting. US is beneficial to detect and diagnose small (<1 cm) invasive cancers [5, 11], while MMG is suited to detect ductal carcinoma in situ (DCIS) by calcifications [7]. The detection of small invasive cancers may decrease the mortality from breast cancer. Furthermore, US equipment is considerably cheaper than an MRI unit and is already commonly used in Japan. Due to this, breast US is already used for screening breast cancer in many private medical institutes. Takebe et al. [12] reported that the detection rate of breast cancer by whole breast screening was 0.26%, which is as good as MMG screening. In fact, it has been reported that US is equivalent to [13] (consistent with our results) or even better than MMG for the detection of breast cancer in women in their 40s [14]. Moreover, some reports have also indicated that US and MMG are complementary and that more cancers can be detected by combining these tests [15]. Our results are in agreement with these reports.

In a recent report published in the United States, it was stated that the addition of a US scan to MMG screening increases the detection of breast cancer among women who are at high risk and have heterogeneously dense breasts [16]. The important difference between the US screening programs in the United States and Japan is that the actual scanning is performed by a physician in the United States, while it is performed by sonographers in Japan. Screening

Table 3 Program of US seminar (for doctors)

Lecture
Clinical aspects of breast diseases (20 min)
Pathology of breast diseases (40)
Basic aspects of ultrasound and ultrasound tissue characterization (40)
Examination methods (30)
Breast ultrasound lexicon (1) (30)
Breast ultrasound lexicon (2) (30)
Criteria for recall in screening (30)
Small group activities (50 min)
Mass-forming diseases 1
Mass-forming diseases 2
Non-mass-forming diseases
Hands on 1
Hands on 2 (interventional technique)
Ultrasound images of various diseases
Training to find lesions
Test (100 cases, 100 min.)
Movies (50 cases)
Static images (50 cases)

by sonographers reduces the cost, but failure to detect cancer by real-time scanning performed by a sonographer is a worrisome issue. In such cases, whether the sonographer or the interpreting doctor is accountable is a matter of debate. I personally do not consider this to be a major shortcoming of the US screening program because some cancers may go undetected even when doctors perform the US scans. The major problem associated with US is its low specificity. We reported that the rate of positive findings on US screening is 24%, which decreases to 10% if simple cysts are excluded [17]. To reduce the recall rate and standardize US screening, the JABTS formulated criteria for recall in breast US screening [18] (Fig. 3). To popularize these criteria, the educational committee of the JABTS has established a 2-day training seminar for both sonographers and interpreting doctors. Table 3 shows the program of the seminar for doctors. In the seminar for sonographers, the clinical aspects of breast diseases are explained for a longer duration (30 min), and a test on basic knowledge of breast diseases and breast US is added. The group session of Hands on 2 (interventional technique) is not included in the seminar for sonographers. We previously reported that such a course will increase the rate of detection of breast lesions and improve the examiner's ability to diagnose these lesions [19].

Finally and most importantly, the usefulness of breast screening is reflected in the potential reduction in death due to breast cancer. Thus far, evidence proving that breast US screening reduces mortality from breast cancer is lacking. A large-scale research project funded by the Ministry of Health, Labor and Welfare was undertaken in 2006 to gather evidence linking breast US screening and decreased breast cancer mortality. This research project is headed by Dr. Ohuchi, Tohoku University, and will last until March 2011. The basic protocol of the research is a randomized control trial (RCT) with invitations to 60,000 women to undergo either MMG alone or MMG combined with US screening at 2-year intervals. Whether or not breast US screening is adopted in the future largely depends on the results of this research. Considerable effort will be required to successfully carry out this massive undertaking.

References

1. Izuo M. Memorial address of the 10th annual meeting. The History of breast cancer screening in Japan. J Jpn Assoc Breast Cancer Screen. 2001;10:3–16.
2. Kikuchi K, Tanaka K, Wagai T. Early cancer diagnosis through ultrasonics. J Acoust Soc Am. 1957;29:824–33.
3. Takahashi K, Nishimura S, Tada K, Makita M, Tada T, Yoshimoto M, et al. Palpable breast cancers that are undetectable by mammography: The importance of palpation in breast cancer screening. J Jpn Assoc Breast Cancer Screen. 2003;12:163–8.
4. Koike Y, Terai N. A comparative study of diagnostic accuracy rate and unimaged rate of mammography for breast cancer. J Jpn Surg Assoc. 2001;62:2102–9.
5. Yanagida Y, Koida T, Kimura M, Tamaki Y, Horikoshi H, Higuchi K, et al. Diangosis of invasive breast cancer whose size is 1 cm or less (in Japanese, no English abstract). Nyugan no Rinsho. 2003;18:484–5.
6. Tunoda H, Tohno E, Ueno E, Aiyoshi Y, Yashiro T, Hara H, et al. Examination of effectiveness of breast cancer detection by modalities and age groups. J Jpn Assoc Breast Cancer Screen. 1998;7:281–5.
7. Osako T, Takahashi K, Iwase T, Iijima K, Miyagi Y, Nishimura S, et al. Diagnostic ultrasonography and mammography for invasive and noninvasive breast cancer in women aged 30 to 39 years. Breast Cancer. 2007;14:229–33.
8. Cancer Statistics in Japan 2007, http://ganjoho.ncc.go.jp/public/statistics/backnumber/2007_jp.html.
9. Hasegawa S, Ohnuki K, Nagakubo J, Kitami A, Oyama K, Koizumi R, et al. Breast cancer imaging by mammography: effects of age and breast composition. J Jpn Assoc Breast Cancer Screen. 2003;12:101–7.
10. Saslow D, Boetes C, Burke W, Harms S, Leach MO, Lehman CD, et al. For the American Cancer Society breast cancer advisory group, "American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography". CA Cancer J Clin. 2007;57:75–89.
11. Hamada I, Nasu S, Yoshimura R, Yoshimoto M, Koga S, Watanabe R. Results of breast cancer screening with mammography and ultrasonography in a health check-up organization. Ningen Doq. 2006;21:32–6.
12. Takebe K, Nakamura K, Misao T. Usefulness of whole-breast scanning by physicians in mass breast-cancer screening of young women. J Jpn Assoc Breast Cancer Screen. 2000;9:155–60.
13. Hirokaga T, Namba K, Watanabe R, Furusawa H, Matsunaga T, Namba S. Effectiveness of evaluation of breast cancer screening using ultrasound combined with mammography. J Jpn Assoc Cancer Detect Diagn. 2004;11:131–5.
14. Yamasaki M, Nasu S, Koga S, Mori H. Detection rate of breast cancer by mammography and ultrasonography screening in women aged between 40 and 49. J Jpn Assoc Breast Cancer Screen. 2002;11:265–9.
15. Maruyama M, Ooba S, Uchida K, Kamiya K, Aritomi H. Breast cancer screening by both mammography and ultrasound is recommended for women aged 40–49 y in Japan. J Jpn Assoc Breast Cancer Screen. 2000;9:161–5.
16. Czyzewski A. Ultrasound should be added to breast cancer screening for at-risk women. JAMA. 2008;299:2151–63.
17. Tohno E, Ide S, Shibata K, Kujiraoka Y, Koseki E. Occurrence of focal detection abnormalities in breast cancer screening by ultrasound. J Jpn Assoc Breast Cancer Screen. 2000;9:231–6.
18. Japan Association of Breast and Thyroid Sonology ed. Guideline for breast ultrasound—management and diagnosis, 2nd ed. Nankodo Co. Ltd., Tokyo 2008. p. 103–13.
19. Tohno E, Sawai K, Shimamoto K, Ueno E, Endou T, Tsunoda-Shimizu H, et al. Establishment of Seminars to improve the diagnostic accuracy and effectiveness of breast ultrasound. J Med Ultrasonics. 2006;33:239–44.

Breast Cancer Res Treat
DOI 10.1007/s10549-011-1381-x

EPIDEMIOLOGY

Alcohol consumption and breast cancer risk in Japanese women: The Miyagi Cohort Study

Masaaki Kawai · Yuko Minami · Masako Kakizaki · Yoichiro Kakugawa · Yoshikazu Nishino · Akira Fukao · Ichiro Tsuji · Noriaki Ohuchi

Received: 27 January 2011 / Accepted: 29 January 2011

Abstract Alcohol consumption is known to be a risk factor for breast cancer in Western countries, but few epidemiologic data have been available in Japan. This population-based prospective cohort study evaluated the associations of alcohol consumption with breast cancer risk in a Japanese population. A total of 19,227 women aged 40–64 years were followed from 1990 to 2003. During 246,703 person-years of follow-up, 241 breast cancer cases were identified. Hazard ratios (HRs) were estimated by the Cox proportional-hazard regression model. After adjustment for potential risk factors of breast cancer and nutritional factors, the HR and 95% confidence interval (CI) for current drinkers was 1.00 (0.74–1.34) compared with never drinkers. According to the amount of alcohol intake per day, a higher amount ($\geq$15.0 g/day) had no significant relation to breast cancer risk (HR = 0.87, 95% CI: 0.40–1.91; *P* for trend = 0.85). Age upon starting to drink, and the frequency of drinking, were not associated with breast cancer risk. In analysis stratified according to exogenous female hormone use, a higher alcohol intake ($\geq$15.0 g/day) was associated with an increased risk of breast cancer among hormone users (HR = 1.67, 95% CI: 0.17–16.73); however, this was not statistically significant. Stratification according to folate intake with energy adjustment (<219, $\geq$219 μg/day) found that breast cancer risk tended to increase with increasing alcohol consumption among women with a low intake of folate (*P* for trend = 0.09). Our findings suggest that alcohol consumption has no overall effect on breast cancer risk among Japanese women, whereas nutritional factors such as folate intake may modify the alcohol-breast cancer risk relationship.

Keywords Breast cancer · Cohort study · Alcohol · Folate

Abbreviations

CI	Confidence interval
FFQ	Food frequency questionnaire
HRT	Hormone replacement therapy
HR	Hazard ratio
ALDH	Asldehyde dehydrogenase

M. Kawai · N. Ohuchi
Department of Surgical Oncology, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi 980-8574, Japan

Y. Minami (✉)
Division of Community Health, Tohoku University Graduate School of Medicine, 2-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi 980-8575, Japan
e-mail: adym@med.tohoku.ac.jp

M. Kakizaki · I. Tsuji
Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, 2-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi 980-8575, Japan

Y. Kakugawa
Department of Breast Oncology, Miyagi Cancer Center Hospital, 47-1 Nodayama, Medeshima-Shiode, Natori, Miyagi 981-1293, Japan

Y. Nishino
Division of Epidemiology, Miyagi Cancer Center Research Institute, 47-1 Nodayama, Medeshima-Shiode, Natori, Miyagi 981-1293, Japan

A. Fukao
Department of Public Health, Yamagata University School of Medicine, 2-2-2 Iida-nishi, Yamagata 990-9585, Japan

Published online: 12 February 2011

Introduction

There is a variation in the incidence of breast cancer among countries [1]. Although Japan has a lower risk of breast cancer than Western countries, breast cancer ranks first in terms of the age-standardized rates of cancers among women as a whole, and its incidence continues to increase [1]. From the viewpoint of breast cancer risk, changes in exposure to reproductive and anthropometric risk factors among Japanese women [2, 3] may be responsible for this increase [4].

Among various risk factors for breast cancer, alcohol consumption has been considered important in Western countries. A meta-analysis including 53 studies showed that alcohol consumption was related to breast cancer risk [5]. In another meta-analysis including 98 studies, the combined odds ratio for drinkers versus non-drinkers was 1.22 (95% confidence interval (CI) 1.09–1.37) [6]. In addition, epidemiologic studies in Western countries have also demonstrated that the risk attributable to alcohol consumption might be modified by nutrient intake or exogenous female hormone use [7–9]. For example, breast cancer risk appeared to be increased among alcohol drinkers with a low intake of folate [8, 10].

On the other hand, in Japan, the association of alcohol consumption with breast cancer risk has been unclear. Two earlier cohort studies demonstrated no significant relationship between alcohol consumption and breast cancer risk [11, 12], whereas more recent cohort studies showed that higher alcohol consumption was associated with an increased risk of breast cancer [13, 14]. The available epidemiologic data regarding the association between alcohol drinking and breast cancer risk in Japan appear to be insufficient [15]. Japanese women may have different lifestyles from women in Western countries; for example, the proportion of exogenous female hormone users in Japan is lower than in Western countries [3] and the Japanese diet is rather unique [16]. Therefore, the risk associated with alcohol consumption confirmed in Western countries may not necessarily be applicable to Japanese women.

In the population-based cohort study, we evaluated the association of alcohol consumption with breast cancer risk among Japanese women, taking into account modifiable risk factors such as nutrient intake.

Materials and methods

Study cohort

This study was based on the Miyagi Cohort Study, whose study design has been described in detail elsewhere [17]. Briefly, 25,279 men and 26,642 women aged 40–64 years living in 14 municipalities, which were randomly selected from 62 municipalities in Miyagi Prefecture, Northeastern Japan, were entered into a cohort on June 1, 1990. A self-administered questionnaire on various health habits was delivered between June and August, 1990. Usable questionnaires were collected from 22,836 men and 24,769 women, and the response rates were 90.3 and 93.0%, respectively. All the residents in the study area were entered into the cohort, and the response rates of questionnaires were very high; thus, the subjects were thought to be sufficiently representative of this area.

In this study, 705 individuals who were diagnosed as having cancer before the baseline survey and 4,837 for whom information about alcohol drinking habits was lacking were excluded. Consequently, 19,227 women were entered into the analytic cohort. The study protocol was approved by the institutional review board of Tohoku University School of Medicine. This study was conducted in accordance with the principles of the Declaration of Helsinki. We considered the return of self-administered questionnaires signed by the subjects to imply their consent to participate in the study.

Questionnaire at the baseline survey

The questionnaire covered personal history including age, height, weight, education level, occupation, family history of breast cancer in mother or sisters, general lifestyle factors including cigarette smoking, walking status, and dietary history, menstrual and reproductive histories, and exogenous female hormone use. Dietary history including alcohol intake was assessed using a food frequency questionnaire (FFQ). Based on the average frequency of intake of 40 food items and 9 food groups during the year prior to the baseline survey, the estimated intakes of nutrient and food per day were computed using the Japanese Standard Tables of Food Composition, fourth and fifth editions. The FFQ has been validated for these composition tables [18]. For the assessment of alcohol consumption, the questionnaire asked firstly if subjects were never, past, or current drinkers. Never drinkers were defined as women who had never or hardly ever drunk alcohol. Past drinkers were defined as those who had quit drinking before the baseline survey. Past or current drinkers were asked to state the age at which they had started drinking, frequency of drinking [almost every day (more than five times a week), three to four times a week, one to two times a week, and less than once a week (occasional)], the types of alcohol beverages consumed [Japanese *sake*, Japanese spirits (*shochu*), beer, whisky, wine and others], and the volume drunk on each occasion. The amount of alcohol consumed per day was calculated as: (total amount of alcohol drunk on each occasion) × (frequency of drinking)/7. The Spearman correlation coefficient for comparison of the amount of alcohol consumed estimated from the FFQ with the amount estimated from 12 daily diet records kept over a 1-year period was 0.60 for women [19].

Ascertainment of cases and follow-up

The subjects were followed from the start of the study until December 31, 2003. The end point of our analysis was incidence of breast cancer defined as the topography code C50.0–C50.9 according to the International Classification of Disease for Oncology, Second Edition (ICD-O-2). The incidence of breast cancer was confirmed by the Miyagi Prefecture Cancer Registry, which is one of the oldest and most accurate population-based cancer registries in Japan [20, 21]. The relevant cases were abstracted from the medical records of the hospitals by a medical doctor or trained medical records reviewer, except for the cases reported to the registry from an institution. The percentage registered by death certificates only (DCO) for breast cancer was 2.5% for women during 1991–2003.

A follow-up Committee was established consisting of the Miyagi Cancer Society, the Divisions of Community Health of all 14 municipalities, the Department of Health and Welfare, Miyagi Prefectural Government, and the Division of Epidemiology, Tohoku University School of Medicine. The Committee periodically reviewed the Residential Registration Record of each municipality. This checkup identified subjects who had either died or emigrated during the observation period. Follow-up of subjects who had moved from the study municipalities was discontinued because the Committee could not review the Residential Registration Record from outside the study area. During the study period, 1,182 women (6.1%) were lost to follow-up.

Statistical analysis

The person-years of follow-up were counted for each of the subjects from the start of the study until the date of diagnosis of breast cancer, the date of emigration from the study area, the date of death, or the end of follow-up, whichever occurred first. The mean follow-up period was 12.8 years. The exposure variables analyzed in this study were alcohol drinking status (never/past/current), frequency of alcohol drinking (never/occasional/1–2 times per week/3–4 times per week/5–7 times per week), age upon starting to drink (never/$<$25 year/$\geq$25 to $<$35 year/$\geq$35 year), amount of alcohol consumed per occasion (never/$<$11.5 g/$\geq$11.5 to $<$23.0 g/$\geq$23 g), and amount of alcohol consumed per day (never/$<$5.0 g/$\geq$5.0 to $<$15.0 g/$\geq$15.0 g). All these exposures were determined at the baseline.

The Cox proportional-hazard regression model was used to estimate hazard ratios (HRs) and 95% CIs for the incidence of breast cancer according to category of exposure variable and to adjust for confounding variables [22]. Never drinkers served as a reference group. Linear trends were tested in the Cox model by treating each exposure category as a continuous variable. We considered the following variables to be potential confounders: age, education level, occupation, cigarette smoking, walking status, body mass index, use of exogenous female hormones, menstrual and reproductive factors, and family history of breast cancer in mother or sisters, which are all known, or possible, risk factors for breast cancer. In addition, intakes of fat and folate, which have been suspected to confound the effect of alcohol consumption on breast cancer risk [7, 14, 23], were controlled for. In the analysis, the intakes of these nutrients were adjusted for energy intake, and were categorized by quintile based on the distribution among the population. Missing values for confounders were treated as an additional variable category, and were included in the model.

Separate analyses were conducted after dividing the subjects into premenopausal and postmenopausal status. Stratification according to some selected potential factors, such as exogenous female hormone use (ever, never) and intake of fat and folate (higher or lower than the median intake per day), was also conducted to evaluate their modification effects on the study variables.

The results were regarded as significant if the two-sided P values were $<$0.05. All statistical analyses were performed using SAS software (version 9.2; SAS Institute, Cary, NC).

Results

The characteristics of the study subjects at the baseline are presented in Table 1. During 246,703 person-years of follow-up from 19,227 subjects, 241 breast cancer cases were documented. At the baseline, 13,461(70.0%), 772(4.0%) and 4,994(26.0%) of the subjects were never, past and current drinkers, respectively. Current drinkers were slightly younger and had a longer period of education. Past or current drinkers tended to smoke. There was no large difference in nutrient intake between never and current drinkers. Heavy drinkers ($\geq$15.0 g/day) tended to have specific characteristics; they tended to be less educated, and about 40% were current smokers. Furthermore, even though they consumed a higher amount of energy, mean intakes of fat and folate were lower than those in other categories.

The HRs and 95% CIs for current alcohol drinking status among women overall are presented in Table 2.

Table 1 Characteristics of study population according to drinking habit at baseline

	Never drinkers	Past drinkers	Total	Current drinkers			
				Alcohol amount consumed per day			
				<5.0 g	≥5.0 to <15.0 g	≥15.0 g	Missing
Number of subjects (*n*)	13461	772	4994	2915	945	568	566
Age group (%)							
40–44	21.4	23.7	33.1	38.0	28.5	31.9	17.0
45–49	15.5	17.9	21.1	21.5	21.0	22.2	18.7
50–54	18.7	18.0	17.9	17.0	18.9	18.5	20.0
55–59	21.9	22.0	15.5	13.6	17.1	15.1	23.0
60–64	22.5	18.4	12.3	9.8	14.5	12.3	21.4
Age (mean, years)	52.4 ± 7.4	51.7 ± 7.4	49.5 ± 7.2	48.6 ± 7.0	50.3 ± 7.2	49.6 ± 7.0	52.6 ± 7.2
Body mass index (%)							
<20	9.5	11.3	9.1	8.6	10.7	10.2	7.4
≥20 to <23	32.4	30.1	34.7	35.0	36.1	35.4	30.4
≥23 to <25	24.2	22.7	24.4	25.7	22.2	22.9	23.1
≥25	30.0	30.4	27.7	28.0	26.3	27.5	29.0
Missing	3.9	5.6	4.1	2.7	4.7	4.0	10.1
Smoking (%)							
Current smoker	3.9	25.6	15.8	10.7	18.3	40.1	13.1
Past smoker	0.9	10.1	2.9	2.5	3.4	5.1	2.1
Never smoker	86.4	49.7	63.8	73.2	62.6	43.1	37.8
Missing	8.9	14.5	17.5	13.5	15.7	11.6	47.0
Occuption (%)							
Housewife/no occupation	15.6	13.9	13.9	14.4	15.3	13.7	9.2
Others	68.8	65.0	70.4	72.8	71.0	72.4	55.7
Missing	15.6	21.1	15.7	12.9	13.7	13.9	35.2
Walking status (%)							
Longer than 1 h per day	42.1	38.5	39.7	39.9	40.4	37.9	39.2
Less than 1 h per day	51.0	53.9	52.8	55.2	53.3	54.8	37.3
Missing	6.8	7.6	7.5	4.9	6.2	7.4	23.5
Family history of breast cancer in mother or sisters (%)							
No	98.4	97.8	98.3	98.3	98.0	98.2	98.8
Yes	1.6	2.2	1.7	1.7	2.0	1.8	1.2
Educational level (%)							
Junior high school or less	37.2	39.1	32.9	31.1	32.3	36.6	39.8
High school	44.4	41.2	46.5	49.2	45.5	44.5	36.4
College/university or higher	12.4	10.0	13.9	15.0	15.6	11.6	8.1
Missing	6.1	9.7	6.6	4.7	6.7	7.2	15.7
Age at menarche (years) (%)							
≤13	22.3	25.5	27.8	31.3	27.0	26.1	12.7
14	21.7	20.7	23.6	25.6	22.6	21.8	16.4
15	20.2	16.3	18.6	19.0	18.4	19.5	16.3
≥16	23.9	23.3	19.4	17.3	21.8	22.0	24.0
Missing	11.8	14.1	10.6	6.8	10.2	10.6	30.6

Table 1 continued

	Never drinkers	Past drinkers	Total	Current drinkers			
				Alcohol amount consumed per day			
				<5.0 g	≥5.0 to <15.0 g	≥15.0 g	Missing
Parity number (%)							
0	2.4	4.5	2.9	2.8	3.4	4.0	1.4
1	6.8	10.6	7.3	7.0	8.5	8.5	6.4
2	39.6	34.5	40.2	42.1	40.0	40.3	30.2
3	32.5	26.2	31.3	32.9	29.9	28.0	28.6
4	9.8	10.8	9.1	8.7	8.8	8.8	11.7
5≤	3.4	5.3	3.2	2.7	3.6	3.2	4.8
Missing	5.5	8.2	6.1	3.8	5.8	7.2	17.0
Use of exogenous female hormones and/or OC (%)							
Never	75.9	69.6	71.8	74.3	72.5	70.6	58.7
Ever	10.2	14.0	14.8	15.4	15.1	15.8	9.7
Missing	13.9	16.5	13.5	10.3	12.4	13.6	31.6
Nutrient intake							
Energy (Kcal)	1325.9 ± 348.8	1268.1 ± 385.0	1312.1 ± 371.3	1334.9 ± 349.0	1289.9 ± 380.0	1372.8 ± 382.9	1170.9 ± 418.2
Fat intake (mean, g/day)	25.1 ± 9.1	24.3 ± 10.1	25.1 ± 9.5	26.1 ± 8.9	25.6 ± 9.5	21.3 ± 8.6	22.8 ± 11.8
Folate intake (mean, μg/day)	229.8 ± 89.0	221.9 ± 99.3	225.3 ± 91.8	229.9 ± 87.5	233.5 ± 92.0	210.9 ± 86.3	202.4 ± 11.5

Table 2 Hazard ratio (HR) and 95% confidence interval (CIs) of breast cancer incidence according to history of alcohol drinking

	Number of subjects	Cases	Person-years	Age-adjusted model		Multivariate-adjusted model 1[a]		Multivariate-adjusted model 2[b]	
				HR	95% CI	HR	95% CI	HR	95% CI
Never	13,461	171	173,506	1.00	(reference)	1.00	(reference)	1.00	(reference)
Past	772	4	9,601	0.42	0.16–1.13	0.39	0.14–1.08	0.39	0.14–1.07
Current	4,994	66	63,596	1.01	0.76–1.34	1.00	0.74–1.35	1.00	0.74–1.34

[a] Adjusted for age (continuous variable), body mass index (<20, ≥20 to <23, ≥23 to <25, ≥25), smoking (current, past, never), occupation (housewife/no occupation, others), walking (less than 1 h per day, longer than 1 h per day), educational level (junior high school or less, high school, college/university or higher), age at menarche (≤13, 14, 15, >16), parity number (0, 1, 2, 3, 4, ≥5), family history of breast cancer (present, absent), age at menopause (premenopausal, <48, 48–50, >50 years, missing for age at menopause, missing for menopausal status) and use of exogenous female hormones and/or OC (never, ever)

[b] Additionally adjusted for energy-adjusted intakes of fat (quintiles) and folate (quintiles) and energy intake

After adjustment for age, the HR and 95% CI for past drinkers was less than unity, 0.42 (0.16–1.13), but not statistically significant. The HR and 95% CI for current drinkers was 1.01 (0.76-1.34). After adjustment for potential risk factors for breast cancer in multivariate-adjusted model 1, the HRs and 95% CIs for past and current drinkers were 0.39 (0.14–1.08) and 1.00 (0.74–1.35), respectively. Further adjustment for intakes of fat and folate in multivariate adjusted model 2 showed quite similar results. In terms of menopausal status, the HRs and 95% CIs for breast cancer risk among current drinkers compared with never drinkers was 1.05 (0.70–1.56) for premenopausal women and 1.06 (0.66–1.71) for postmenopausal women (data not shown).

Table 3 shows the associations with breast cancer incidence according to frequency of drinking, age upon starting to drink, and amount of alcohol drunk per occasion and per day. After adjustment for potential risk factors for breast cancer in multivariate-adjusted model 1, women who were current frequent drinkers at 5–7 times per week appeared to have a decreased risk (HR = 0.66, 95% CI: 0.29–1.53). However, the trend test showed non-significance (P for trend = 0.94). The multivariate-adjusted model 2 taking into account nutritional factors also showed no association (P for trend = 0.89). Early exposure to alcohol drinking at age under 25 had no significant relationship to breast cancer risk (HR in multivariate-adjusted model 2 = 0.91, 95% CI: 0.57–1.44). A higher amount of alcohol consumed

Table 3 Hazard ratio (HR) and 95% confidence interval (CIs) of breast cancer incidence according to frequency, first age, and amount of alcohol drinking

	Number of subjects	Cases	Person-years	Age-adjusted model			Multivariate-adjusted model 1[a]			Multivariate-adjusted model 2[b]		
				HR	95% CI	*P* for trend	HR	95% CI	*P* for trend	HR	95% CI	*P* for trend
Alcohol drinking frequency[c]												
Never	13,461	171	173,506	1.00	(reference)	0.95	1.00	(reference)	0.94	1.00	(reference)	0.89
Current	2,031	26	26,142	0.95	0.63–1.44		0.94	0.62–1.44		0.94	0.61–1.43	
Occasional												
1–2 per week	1,205	19	15,353	1.21	0.75–1.95		1.23	0.76–1.99		1.22	0.76–1.98	
3–4 per week	779	12	9,807	1.21	0.67–2.17		1.18	0.65–2.14		1.17	0.64–2.12	
5–7 per week	666	6	8,265	0.72	0.32–1.62		0.66	0.29–1.53		0.65	0.28–1.49	
		234										
Alcohol drinking—age upon starting to drink[c]												
Never	13,461	171	173,506	1.00	(reference)	0.81	1.00	(reference)	0.94	1.00	(reference)	0.93
Current												
<25	1,824	23	23,074	0.92	0.59–1.45		0.92	0.58–1.46		0.91	0.57–1.44	
25–35	1,366	19	17,340	1.06	0.66–1.71		1.05	0.65–1.70		1.05	0.64–1.70	
>35	1,174	13	15,059	0.90	0.51–1.58		0.96	0.54–1.70		0.96	0.54–1.70	
Alcohol drinking—amount per occasion[c]												
Never	13,461	171	173,506	1.00	(reference)	0.77	1.00	(reference)	0.93	1.00	(reference)	0.98
Current												
<11.5 g	2,685	40	34,457	1.13	0.80–1.60		1.14	0.80–1.62		1.14	0.80–1.62	
≥11.5 to <23.0 g	1,298	17	16,512	1.00	0.61–1.65		0.98	0.59–1.63		0.97	0.58–1.62	
≥23.0 g	604	8	7,454	1.04	0.51–2.11		0.95	0.46–1.99		0.93	0.44–1.94	
Alcohol drinking—amount per day[c]												
Never	13,461	171	173,506	1.00	(reference)	0.64	1.00	(reference)	0.80	1.00	(reference)	0.85
Current												
<5.0 g	2,915	40	37,494	1.03	0.73–1.46		1.03	0.72–1.47		1.02	0.72–1.46	
≥5.0 to <15.0 g	945	15	11,917	1.24	0.73–2.11		1.21	0.71–2.07		1.21	0.71–2.08	
≥15.0 g	568	7	6,972	0.98	0.46–2.10		0.90	0.41–1.98		0.87	0.40–1.91	

[a] Adjusted for age (continuous variable), body mass index (<20, 20≤ <23, 23≤ <25, 25≤), smoking (current, past, never), occupation (housewife/no occupation, others), walking (less than 1 h per day, longer than 1 h per day), educational level (junior high school or less, high school, college/university or higher), age at menarche (≤13, 14, 15, 16<), parity number (0, 1, 2, 3, 4, 5≤), family history of breast cancer (present, absent), age at menopause (premenopausal, <48, 48-50, >50 years, missing for age at menopause, missing for menopausal status) and use of exogenous female hormones and/or OC (never, ever)

[b] Additionally adjusted for energy-adjusted intakes of fat (quintiles) and folate (quintiles) and energy intake

[c] Women of past drinkers were excluded from the analysis

per occasion (≥23 g/occasion) also had no statistically significant relationship to breast cancer risk (HR in multivariate-adjusted model 2 = 0.93, 95% CI: 0.44–1.94). Regarding the risk for the amount of alcohol consumed per day, women who consumed ≥5.0 to <15.0 g/day tended to have an increased risk (HR in multivariate-adjusted model 2 = 1.21, 95% CI: 0.71–2.08); however, no such increased risk was observed among women who consumed ≥15.0 g/day (HR in multivariate-adjusted model 2 = 0.87, 95% CI: 0.40–1.91). The trend test showed no linear relationship between the amount of alcohol consumed per day and breast cancer risk (*P* for trend = 0.85).

Table 4 shows the results of analyses stratified according to exogenous female hormone use and fat and folate intake. Among users of female hormone, higher alcohol intake (≥15.0 g/day) was associated with an increased risk of breast cancer, but not to a statistically significant degree. Analysis according to folate intake indicated that the association between alcohol intake and breast cancer risk differed between women with low and high intakes of folate. Among women with low folate intake, HRs tended to increase with increasing alcohol consumption (*P* for trend = 0.09); however, no such trend was observed among women with high folate intake. The interaction term

Table 4 Hazard ratio (HR) and 95% confidence interval (CIs) of breast cancer incidence according to history of alcohol drinking within strata of potential risk factors

	Use of exogenous hormones[a]						Fat intake[b]						Folate intake[c]					
	Ever			Never			<24.5 g/day[d]			≥24.5 g/day			<219 μg/day[d]			≥219 μg/day		
	Cases	HR	95% CI	Cases	HR	95% CI	Cases	HR	95% CI	Cases	HR	95% CI	Cases	HR	95% CI	Cases	HR	95% CI
Alcohol drinking																		
Never	17	1.00	(reference)	131	1.00	(reference)	86	1.00	(reference)	85	1.00	(reference)	81	1.00	(reference)	90	1.00	(reference)
Past	1	1.09	0.12–9.57	2	0.27	0.07–1.11	3	0.58	0.18–1.89	1	0.20	0.03–1.48	3	0.57	0.18–1.83	1	0.22	0.03–1.60
Current	5	0.66	0.22–1.97	55	1.10	0.79–1.54	33	1.06	0.69–1.62	33	0.96	0.63–1.47	40	1.29	0.86–1.93	26	0.77	0.49–1.22
Alcohol drinking—amount per day[e]																		
Never	17	1.00	(reference)	131	1.00	(reference)	86	1.00	(reference)	85	1.00	(reference)	81	1.00	(reference)	90	1.00	(reference)
Current																		
<5.0 g/day	2	0.39	0.08–1.88	32	1.05	0.70–1.56	21	1.20	0.74–1.97	19	0.88	0.53–1.47	22	1.27	0.78–2.08	18	0.85	0.50–1.43
≥5.0 to <15.0 g/day	2	1.54	0.32–7.45	13	1.37	0.77–2.45	6	1.12	0.48–2.60	9	1.32	0.65–2.68	9	1.68	0.83–3.40	6	0.88	0.38–2.04
≥15.0 g/day	1	1.67	0.17–16.73	6	0.98	0.42–2.32	4	0.86	0.30–2.46	3	1.09	0.33–3.56	6	1.58	0.65–3.86	1	0.28	0.04–2.03
P for trend	0.86			0.55			0.45			0.76			0.09			0.21		
	Interaction *P* = 0.42						Interaction *P* = 0.55						Interaction *P* = 0.09					

[a] Adjusted for age (continuous variable), body mass index (<20, ≥20 to <23, ≥23 to <25, ≥25), smoking (current, past, never), occupation (housewife/no occupation, others), walking (less than 1 h per day, longer than 1 h per day), educational level (junior high school or less, high school, college/university or higher), age at menarche (≤13, 14, 15, >16), parity number (0, 1, 2, 3, 4, ≥5), family history of breast cancer (present, absent), age at menopause (premenopausal, <48, 48–50, >50 years, missing for age at menopause, missing for menopausal status), energy-adjusted intakes of fat (quintiles) and folate (quintiles) and energy intake

[b] Adjusted for age (continuous variable), body mass index (<20, ≥20 to <23, ≥23 to <25, ≥25), smoking (current, past, never), occupation (housewife/no occupation, others), walking (less than 1 h per day, longer than 1 h per day), educational level (junior high school or less, high school, college/university or higher), age at menarche (≤13, 14, 15, >16), parity number (0, 1, 2, 3, 4, ≥5), family history of breast cancer (present, absent), age at menopause (premenopausal, <48, 48–50, >50 years, missing for age at menopause, missing for menopausal status), use of exogenous female hormones (never, ever), and energy-adjusted intakes of folate (quintiles)

[c] Adjusted for age (continuous variable), body mass index (<20, ≥20 to <23, ≥23 to <25, ≥25), smoking (current, past, never), occupation (housewife/no occupation, others), walking (less than 1 h per day, longer than 1 h per day), educational level (junior high school or less, high school, college/university or higher), age at menarche (≤13, 14, 15, >16), parity number (0, 1, 2, 3, 4, ≥5), family history of breast cancer (present, absent), age at menopause (premenopausal, <48, 48–50, >50 years, missing for age at menopause, missing for menopausal status), use of exogenous female hormones (never, ever), and energy-adjusted intakes of fat (quintiles)

[d] Median value of energy-adjusted intake per day

[e] Women of past drinkers were excluded from the analysis

(folate intake * amount of alcohol consumed per day) was marginally significant ($P = 0.09$). Regarding to fat intake, breast cancer risk for alcohol intake did not differ between women with low and high intake ($P = 0.55$).

Discussion

This population-based prospective cohort study in Japan revealed that breast cancer risk was not associated with alcohol drinking history, age upon starting to drink, frequency of drinking, or the amount of alcohol consumed per occasion or per day. Analysis according to menopausal status also yielded similar results. Our result is important because few studies in Asian countries have evaluated the relationship between alcohol drinking and breast cancer risk in a prospective setting [5, 6].

Alcohol consumption has been considered a convincing risk factor for breast cancer in Western countries. In Japan, two cohort studies have demonstrated positive associations between current alcohol consumption of more than 15 g/day [13] or 150 g/week (21.4 g/day) [14] and breast cancer risk. However, our study did not support such a significant association for alcohol consumption. Although women with a current alcohol intake of ≥5.0 to <15.0 g/day tended to have an increased risk of breast cancer, the risk was lower for women who consumed ≥15 g/day. We interpreted the inconsistency between our study and others as follows. First, Japanese women probably have lifestyle factors that differ from those of women in Western countries. For example, the higher prevalence of hormone replacement therapy (HRT) in Western countries may contribute to the significant relationship. In previous studies, the significant risk elevation resulting from alcohol consumption was limited to women receiving HRT [7]. Our study also observed an increased risk among exogenous female hormone users, although this was non-significant (Table 4). However, the prevalence of hormone use in our cohort was much lower than that in Western countries [2]. Therefore, alcohol intake might have no overall relationship with breast cancer risk. Second, differences in distributions of exposure and confounding variables among study areas may affect the risk. Our study was conducted in a confined area, whereas the major population-based cohort studies in Japan have covered multiple areas [14]. The associations with alcohol consumption might therefore have been confounded by some area-related factors. For example, heavy drinkers (≥15.0 g alcohol/day) in our cohort included high proportions of current smokers and individuals with a shorter period of education (Table 1), unlike subjects in other studies. This inconsistency may reflect the background characteristics of heavy drinkers in different study areas [24].

The presence of unmeasured mechanisms could also have explained our results. One such mechanism is gene polymorphism. Acetaldehyde is a metabolite of ethanol that causes genetic damage [23], and is metabolized by aldehyde dehydrogenases (ALDHs). The inactive form of ALDH resulting from gene polymorphism is rare in Caucasians, but frequent in Japanese [25, 26], and this is thought to cause accumulation of acetaldehyde, and thus increase the incidence of cancer. However, previous studies have shown that this polymorphism is not related to breast cancer risk in Japanese [27]. The polymorphisms of ALDH among Japanese may not have much influence on the alcohol–breast cancer risk relationship in a practical situation.

Several studies have suggested that the association of alcohol consumption with breast cancer risk might be modified by dietary factors [8, 10]. In our study, the amount of alcohol consumed per day was positively associated with breast cancer risk among women with low folate intake, although statistical analysis demonstrated marginal significance. This finding suggests that alcohol drinkers with low folate intake may have a higher risk of breast cancer, even though overall breast cancer risk for alcohol drinkers is close to unity. Alcohol acts as antagonist for folate; therefore, low folate intake is thought to increase breast cancer risk among alcohol drinkers through impaired DNA repair [28].

Analysis based on history of alcohol drinking showed that past drinkers tended to have a lower risk of breast cancer. No association was observed for age upon starting to drink or frequency of drinking. Previous cohort studies have revealed that age upon starting to drink [13, 29] and frequency of drinking [13] were not related to breast cancer risk, although the risk for past drinkers was unity. To elucidate the associations between drinking patterns and breast cancer risk, further studies are required.

The strengths of this study included its prospective design and the high quality of the follow-up survey. Participants were recruited from the general population, and breast cancer cases were identified by the Miyagi Prefecture Cancer Registry, which is one of the most accurate of its kind in Japan. Furthermore, the rate of loss to follow-up was low. Therefore, several types of bias, i.e., selection and information bias, were avoided. Another strength was that we controlled for nutrient intake, such as that of fat and folate. Only one previous study in Japan has controlled for these factors [14]. With regard to limitations, we must consider the effects of missing data. Subjects for whom details of alcohol drinking status were unknown were excluded. HR and 95% CI for these subjects was 0.73 (0.53–1.03) compared to never drinkers. This exclusion was unlikely to have distorted the results.

In summary, this prospective cohort study has demonstrated no associations of alcohol drinking status,