2008 was 93.2 per 0.1 million population, which was the highest among all cancers. The age-adjusted incidence was 73.4 per 0.1 million population, which was also the highest. The incidence of breast cancer in women starts to increase in the 30's, reaches a peak between the late 40's and early 50's, and then gradually decreases.

International variation in breast cancer incidence

The annual trend for the age-adjusted incidence of breast cancer worldwide shows that the incidence of breast cancer in East Asian countries is consistently lower than that in Caucasians living in Europe and the US, but there is an apparent increase in East Asia, including in China and Japan. The age-adjusted incidence is similar among Europe countries and has shown a tendency to increase, but with decreases in some countries [2].

Risk factors for breast cancer

Food, nutrition, physical activity, and prevention of cancer: a global perspective

The association between food/nutrition and breast cancer risk has been widely studied, mainly in Western countries. Based on these studies, an expert report entitled, "food, nutrition, physical activity, and the prevention of cancer: a global perspective" was first published in 1997 by the World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) [3]. This first expert report was followed by publication of the second expert report covering results up to the end of 2007. The second expert report evaluated the causality and classified risk factors into five grades: "convincing", "probable", "limited-suggestive", "limited-no conclusion", and "substantial effect on risk unlikely". Factors judged as "convincing" are based on evidence from multiple cohort studies, agreement of results, high-quality studies, presence of a dose–response relationship, and established biological mechanisms. Judgment of "probable" requires evidence from multiple epidemiologic studies that may not be limited to a cohort study, and criteria for a "convincing" judgment, except for the dose–response relationship. For breast cancer, risk factors judged to be "convincing" or "probable", preventive action is recommended. In contrast, when the quality of a study is relatively low, the number of studies is small, or results are inconsistent, risk factors are considered to be "limited-suggestive" or "limited-no conclusion" and preventive action is not recommended. Judgment of a "substantial effect on risk unlikely" requires evidence from multiple cohort studies that should be high quality and indicate a breast cancer risk close to 1 in both minimal and maximal intake groups, with elimination of bias where possible.

Summary of breast cancer risk factors in these guidelines

These guidelines provide a comprehensive evaluation of the causality in accordance with the second expert report. The clinical questions in these guidelines use mostly factors judged to be "limited-suggestive" in the second expert report and factors for which information is required in routine medical practice, such as environmental factors and medical history. Table 1 shows a summary of the results of evaluations used to prepare the guidelines.

"Convincing" factors

Obesity

- A meta-analysis of 14 cohort studies of the association between body mass index (BMI) and breast cancer risk in premenopausal women gave a relative risk (RR) [95 % confidential interval (CI)] of 0.94 (0.92–0.95) with a BMI increase of 2 kg/m^2 [3].
- A meta-analysis of 17 cohort studies in postmenopausal women gave a RR (95 % CI) of 1.03 (1.01–1.04) with a BMI increase of 2 kg/m^2 [3].
- A meta-analysis in 2008 gave a similar result for RR (95 % CI) of 1.12 (1.08–1.16) in postmenopausal women with increased BMI and 0.92 (0.88–0.97) in premenopausal women with increased BMI [4].
- A recent cohort study in Japanese women found an association of low BMI up to 20 years old with an increased risk of breast cancer and showed that a subsequent BMI gain from age 20 was associated with an increased risk of postmenopausal hormone receptor-positive breast cancer [5].

Height in adulthood

- A meta-analysis indicated that the breast cancer risk for each 5 cm increment in height in cohort studies in premenopausal and postmenopausal women was 9 and 11 %, respectively. In light of this finding, the risk factors were judged to be "probable" before menopause and "convincing" after menopause [3].
- A recent large-scale cohort study in the UK found RRs (95 % CI) of 1.17 (1.14–1.20), 1.15 (1.10–1.19), and 1.16 (1.14–1.18) for each 10 cm increment in height in all women, premenopausal women, and postmenopausal women, respectively [6]. A multiethnic cohort study in the US in postmenopausal women gave a RR

Table 1 Summary of evaluation of breast cancer risk factors in these guidelines: judgments are made based on the strength of the evidence

Judgment	Decreases risk	Increases risk
Convincing	Parity	Obesity
	Younger age at first delivery	Height in adult
	Lactation	Radiation exposure
		Benign breast disease (proliferative lesion with atypia)
		Family history of breast cancer
		Hormone replacement therapy (combined estrogen–progestogen therapy)
Probable	Obesity (premenopausal)	Alcoholic drinks
	Physical activity (postmenopausal)	Tobacco smoking
		Greater birth weight
		Younger age at menarche
		Older age at menopause
		Diabetes mellitus
Limited-suggestive	Dairy foods	Environmental tobacco smoke
	Soy foods	Oral contraceptive
	Benign ovarian cysts	Night shift work
Limited-no conclusion	Fats; Green tea; Folic acid; Vitamin A; Vitamin C; Vitamin E; Vitamin D; Multivitamin supplement; Statin; Physical activity (premenopausal); Electromagnetic fields; Fertility treatment; Hormone replacement therapy (estrogen therapy); Stress; Stressful life events; Personality factors	
Substantial effect on risk unlikely	None identified	

(95 % CI) of 1.14 (1.07–1.21) for each 10 cm increment in height [7], and a large-scale cohort study in Korean women gave a RR (95 % CI) of 1.18 (1.11–1.25) for each 5 cm increment in height [8].

Reproductive factors

- A review in 1993 showed that breast cancer risk was higher in nulliparous women (RR 1.2–1.7) than in multiparous women. The risk decreased in grand multiparous women and RR was approximately 0.5 in women with five and more pregnancies compared with nulliparous women. A younger age at first birth lowers the risk of breast cancer, while women who have their first baby after age 30 have a higher breast cancer risk compared with nulliparous women [9].
- A population-based cohort study in Japan gave a hazard ratio (HR) (95 % CI) of 2.23 (1.3–3.84) for nulliparous women compared to multiparous women, indicating a significant association of nulliparity with an increased risk of breast cancer. There was a significant decrease in risk with increasing parity number among parous women [10]. Other cohort studies have shown similar results [11, 12].

Lactation

- A 2002 review of 47 epidemiologic studies indicated that breast cancer risk significantly decreased by 4.3 % for every 12 months of breastfeeding, and decreased by 7.0 % for each birth [13].
- A meta-analysis showed a 2 % decreased risk per 5 months of total breastfeeding [3].

Radiation

Atomic bomb survivors Cohort studies in atomic bomb survivors in Hiroshima and Nagasaki showed that the incidence of breast cancer increased after ≥10 years of exposure and that the risk was higher with a younger age at exposure; in particular, under 10 years old [14, 15]. The radiation dose to mammary glands in atomic bomb survivors was about 0–6 Gy (0–6.08 Sv, mean 0.276 Sv) and a strong linear pattern was found with increased radiation dose, which indicated an increased incidence of breast cancer.

Medical exposure There is no legal limit of medical exposure because diagnosis and treatment of diseases outweigh the disadvantages associated with radiation exposure. Breast cancer risk due to medical radiation exposure includes frequent radiographs after pneumothorax for tuberculosis, mastitis, benign breast disorders, thymic hypertrophy during infancy, and radiotherapy for cutaneous angioma [16, 17]. The cumulative incidence of breast cancer by age 40–45 of women undergoing radiotherapy for the treatment of thoracic malignancies during childhood

or adolescence ranges from 13 to 20 % and the risk for breast cancer increased linearly with chest radiation dose [18]. A current issue is to establish follow-up surveillance in this high-risk population.

Low-dose exposure An epidemiological study in atomic bomb survivors in Hiroshima and Nagasaki revealed that a dose of ≥100 mSv was linearly associated with cancer incidence. However, the dose–response curve at doses <100 mSv has not been determined. There are no reports on the association between low-dose exposure and breast cancer risk, and thus we cannot draw a conclusion on this relationship.

Benign breast disease

- In a series of papers, Page and Dupont et al. defined cysts, fibrosis, apocrine change, and simple fibroadenoma as a "non-proliferative lesion"; florid hyperplasia, columnar cell hyperplasia, complex fibroadenoma, sclerosing adenosis, radial scar, and papilloma as a "proliferative lesion without atypia"; atypical ductal hyperplasia, and atypical lobular hyperplasia as a "proliferative lesion with atypia". The RRs for proliferative lesions without and with atypia were 1.3–2.0 and 4–6, respectively, and the risk of breast cancer was mild and moderate or severe, respectively [19–24].
- A meta-analysis gave a RR (95 % CI) for breast cancer of 3.7 (3.2–4.3) in patients with atypical ductal hyperplasia [25].

Family history

In a meta-analysis of 52 case–control studies and 22 cohort studies, the RRs (95 % CI) for the association with the type of relative affected, age at which the relative developed breast cancer, and the number of relatives affected were as follows [26]:

- Any relative with breast cancer: 1.9 (1.7–2.0)
- A first-degree relative (parent, sisters, daughters): 2.1 (2.0–2.2)
- Mother 2.0 (1.8–2.1)
- Sister 2.3 (2.1–2.3)
- Daughter 1.8 (1.6–2.0)
- Mother and sister 3.6 (2.5–5.0)
- A second-degree relative (relatives shared 25 % of gene, such as grandmother, granddaughter, aunt, and niece): 1.5 (1.4–1.6)

These findings indicate that breast cancer risk is increased in women with family members with breast cancer, particularly when there are multiple onsets of breast cancer in closer blood relatives.

Hormone replacement therapy

Combined estrogen–progesterone therapy (EPT)

- The Women's Health Initiative (WHI) was a randomized control trial performed in conjugated equine estrogen (CEE) + medroxyprogesterone acetate (MPA) (E + P) and placebo groups. Significantly, higher HRs (95 % CI) of 1.25 (1.07–1.46) for invasive breast cancer risk and of 1.96 (1.0–4.1) for deaths attributed to breast cancer were found in the E + P group [27]. However, EPT within 5 years did not increase the risk.
- A meta-analysis also showed that breast cancer risk is increased by EPT [28–30]
- The association of estrogen–progesterone combinations with breast cancer risk varies significantly according to the type of progesterone [31].

Estrogen therapy (ET)

The WHI study gave significantly lower HRs (95 % CI) of 0.77 (0.62–0.95) and 0.37 (0.13–0.91) for breast cancer risk and mortality, respectively, in postmenopausal women with hysterectomy who received CEE [32]. These findings suggested that ET for about 5 years might be effective for reducing the breast cancer incidence and mortality in women with hysterectomy.

Studies in Japanese women

A case–control study and a cohort study in Japanese women showed no increase in breast cancer incidence in those who received HRT [33, 34].

"Probable" factors

Alcohol

- The second expert report concluded that "alcoholic drinks are a cause of breast cancer at all ages" and that "a dose–response relationship is apparent" and "no threshold is identified" [3].
- In contrast, a review of epidemiologic studies in Japanese women found that only 1 of 3 cohort studies identified an increased risk of breast cancer caused by alcohol consumption. In addition, the risk of breast cancer increased in only 2 of 8 case–control studies. Thus, data on the association between alcohol intake and breast cancer risk in the Japanese population remain insufficient [35].
- One of 2 cohort studies published after this review reported a significant association between alcohol intake and the risk of breast cancer [36, 37]. Thus,

there is little evidence for an association between alcohol intake and increased risk of breast cancer in the Japanese population, but data from Western countries consistently show that alcohol intake increases the risk of breast cancer.
- The biological mechanism underlying the association of breast cancer with alcohol consumption is unknown and epidemiological results vary with sample size, race, and type of alcoholic drink, indicating that this area requires further study.

Tobacco smoking

- In 2009, the Ontario Tobacco Research Unit examined 11 cohort studies of the association of breast cancer with duration or pack-years of smoking and concluded that there was a causal relationship based on the finding of an increased risk in 8 of these studies. The International Agency for Research on Cancer monographs on evaluation of carcinogenic risks in humans also upgraded the judgment from "no evidence for carcinogenicity in humans" to "probably carcinogenic in humans" in 2009.
- A review of epidemiologic studies in the Japanese population found a significant increased risk of smoking in 1 of 3 cohort studies, with a RR of 1.7 for smokers compared to non-smokers. An increased risk of smoking was also found in 4 of 8 case–control studies. Based on these results, tobacco smoking was concluded to possibly increase the risk of breast cancer in the Japanese population [38].

Birth weight

- In a systematic review of 57 articles, a meta-analysis of 22 studies (12 case–control and 10 cohort studies) indicated a RR (95 % CI) of 1.15 (1.09–1.21) for birth weight [39].
- An increased risk of breast cancer is more likely with increased birth weight, with this tendency being stronger in premenopausal women. Greater birth weight almost certainly carries an increased risk of developing breast cancer before menopause.

Menstrual factors

Age at menarche

- A meta-analysis concluded that a younger age at menarche was a breast cancer risk factor based on the finding that breast cancer risk is increased by 5 % for each year younger at menarche [40].
- A meta-analysis of case–control studies in the Japanese population confirmed that an early age at menarche was significantly associated with a risk of breast cancer, with RRs (95 % CI) of 0.96 (0.83–1.12) and 0.68 (0.59–0.77) in women with onset of menstruation at age 14–15 and after age 16, respectively, compared to before age 14 [41]. One of 3 cohort studies in the Japanese population reported that an early age at menarche was also significantly associated with an increased risk of breast cancer in premenopausal women [12].

Age at menopause

- A 1993 review showed that late menopause increased the risk of breast cancer by approximately 17 % for a 5-year older age at menopause [9]. A meta-analysis in Western countries also showed that late menopause increased the breast cancer risk by 2.9 % for every year older at menopause [40].
- Cohort studies in the Japanese population have produced conflicting results, with late menopause found to increase the risk of breast cancer or showing no association with breast cancer [10–12]. A meta-analysis of case–control studies in Japan indicated no increased risk of breast cancer [41].
- Conclusions in Japanese women are inconsistent, but the results of a meta-analysis of large-scale cohort studies show that late menopause is a highly probable risk factor for breast cancer.

Physical activity

- A meta-analysis of case–control studies gave a RR (95 % CI) of 0.90 (0.88–0.93) for women who did leisure-time physical activity of 7 metabolic equivalent (MET) hours/week in the menopause status-unspecified group [3].
- A meta-analysis of case–control studies gave a RR (95 % CI) of 1.00 (0.97–1.04) in premenopausal women who did leisure-time physical activity of 7 MET-hours/week, indicating no significant association between physical activity and breast cancer risk [3].
- A meta-analysis of cohort studies gave a RR (95 % CI) of 0.97 (0.95–0.99) in postmenopausal women who did leisure-time physical activity of 7 MET-hours/week, showing a significantly decreased risk [3].
- Seven cohort studies in postmenopausal women (2 conducted in Japan) reported after the Expert Report were published also showed that physical activity significantly decreased the risk of breast cancer [42, 43].

Diabetes mellitus

Obesity and physical activity are established risk factors for breast cancer, in particular for postmenopausal women. Obesity and physical activity are also associated with diabetes mellitus, which may induce hyperinsulinemia and/or hyperglycemia and increase the risk of cancer.

- Four meta-analyses have shown that a history of diabetes was significantly associated with an increased risk of breast cancer.
- A meta-analysis of 15 cohort studies and 5 case–control studies reported in 2007 gave a RR (95 % CI) of 1.20 (1.12–1.28) for subjects with a history of diabetes compared to those without this history [44]. Of these 20 studies, 3 were cohort studies in the Japanese population, and one of these 3 studies indicated a significantly increased risk of breast cancer.
- A meta-analysis of 22 cohort studies, 15 case–control studies, and 3 cross-sectional studies conducted in 2012 gave a RR (95 % CI) of 1.27 (1.16–1.39) in subjects with a history of diabetes compared to those without this history, similar to the results in 2007 [45].

"Limited-suggestive" factors

Dairy foods

A meta-analysis of 18 prospective cohort studies reported in 2011 gave a RR (95 % CI) of 0.85 (0.76–0.95) for the highest intake of total dairy food compared with the lowest, indicating a significantly decreased breast cancer risk with dairy product consumption [46]. For milk consumption, the RR was 0.91 (0.8-1.02) for highest intake compared with lowest intake. It has been suggested that increased consumption of total dairy food may be associated with a reduced risk of breast cancer, but some reports have warned that high-fat dairy intake may increase the risk.

Soy foods

A prospective cohort study in the Japanese population showed that consumption of miso soup and isoflavones was inversely associated with the risk of breast cancer. [47]. A study of isoflavone levels in this cohort indicated that plasma genistein was inversely associated with the risk of breast cancer and proved this association [48]. However, the results of other studies in the Japanese population, systematic reviews, and meta-analyses are inconsistent [49, 50].

Benign ovarian cysts

A few reports have suggested an inverse association between benign ovarian cyst and breast cancer risk [51–53]. The mechanism is unknown, but there is an evidence of decreased breast cancer risk associated with oophorectomy for ovarian cysts [54, 55].

Environmental tobacco smoke

The California Environmental Protection Agency reviewed the association between exposure to environmental tobacco smoke and breast cancer in 2007. This meta-analysis gave a RR (95 % CI) of 1.68 (1.31–2.15) for passive smoking compared to non-passive smoking in premenopausal women who were non-smokers. This result indicates a causal relationship between passive smoking and breast cancer risk in premenopausal women [56]. A meta-analysis of 25 publications up to 2008 gave RRs (95 % CI) for passive smoking compared to non-passive smoking of 0.99 (0.93–1.05) in cohort studies and 1.21 (1.11–1.32) in case–control studies [57]. Recall bias in the case–control studies was suggested to have caused the variation in the results with study design [57].

Oral contraceptives

A meta-analysis gave a RR of 1.1–1.2, indicating a slight but significant increase in breast cancer risk [58–60]. Oral contraceptives are usually based on a combination of estrogen and progesterone analogs and have been developed to avoid estrogen-related adverse events without losing the contraception effect. The contents and types of estrogen and progesterone analogs, the ratio of these hormones during the estrous cycle, and the duration of the hormone preparation have changed with age. Thus, it is unclear whether previous results can be applied to current oral contraceptives.

Night shift work

The International Agency for Research on Cancer published a monograph on breast cancer and night shift work in 2010, and classified night shifts into Group 2A (probably carcinogenic to humans). A 2005 meta-analysis of the association between night shift work and breast cancer gave a RR (95 % CI) of 1.48 (1.36–1.61) for night shift female workers, and night shift work was a significant risk factor [61]. However, this meta-analysis included a lot of studies that did not aim to evaluate the association between night shift work and onset of breast cancer. Recent cohort studies have disagreed about the association between night shift work and breast cancer risk [62, 63].

"Limited-no conclusion" factors

A systematic review of the literature indicated unclear causal relationships of breast cancer risk with intake of fat, green tea, folic acid, antioxidants vitamins such as vitamin A, C, and E, multivitamin supplements, and vitamin D; oral administration of statins; infertility treatment; physical activity in premenopausal women; exposure to electromagnetic waves; and psychosocial factors such as life events, stress, and personality traits.

Risk assessment and chemoprevention

Gail model

Gail et al. [64] analyzed breast cancer risk factors by extracting matched pairs of 2,852 white women who developed breast cancer in the Breast Cancer Detection Demonstration Project (BCDDP), which was performed using mammography for breast cancer screening from 1973 to 1980. The results indicated that age at menarche, age at first birth, the number of first-degree relatives with breast cancer, and previous mammary gland biopsies were associated with onset of breast cancer. The Gail model 1 was developed based on age-specific BCDDP data to allow the calculation of future breast cancer probabilities. However, this model was based on data for women undergoing annual mammography for breast cancer, and thus may overestimate the risk of breast cancer in young women who do not receive regular breast cancer screening. Therefore, a modified model, the Gail model 2, was developed using the breast cancer incidence obtained from NCI SEER (Surveillance, Epidemiology, and End Results) data to calculate the risk of invasive breast cancer [65]. The Gail model is based on epidemiologic data in women living in the US, and Asian-Americans including Japanese were considered from 2011. However, the Japanese participants are residents in the US and data for the Japanese population in Japan are not included. Therefore, the Gail model should not be used in Japanese women.

Chemoprevention

Randomized control trials (RCTs) of chemoprevention using endocrine agents have produced findings on efficacy and safety. These RCTs have been performed in women with high breast cancer risk; i.e., women with a 5-year risk of invasive breast cancer of $\geq$1.66 % in the Gail model and those with a history of lobular carcinoma in situ. In Japan, breast cancer risk assessment has yet to be established and thus the value of preventive effects for inhibition of development of breast cancer is unknown.

- A meta-analysis of RCTs of the preventive effects of Tamoxifen (TAM) showed a 38 % reduction in breast cancer incidence [66]. Regarding adverse events, TAM administration for 5–8 years increased the risks of endometrial cancer and thrombosis by 2.4 and 1.9 times, respectively.
- Four RCTs of Raloxifene (MORE, CORE, STAR, and RUTH trials) [67] showed a reduction in invasive breast cancer incidence of 44–66 % compared to placebo, and a RCT for comparison with TAM gave similar results. In adverse events, Raloxifene increased the risks of cerebral stroke and venous thrombosis by 1.49 and 1.44 times, respectively [67].
- Preventive data for the aromatase inhibitor, Exemestane, were obtained in the National Cancer Institute of Canada MAP.3 trial, which was a double blind RCT in postmenopausal women with a high breast cancer risk who were randomly assigned to Exemestane and placebo groups [68]. The risk of invasive breast cancer was significantly decreased by Exemestane, with a HR (95 % CI) of 0.35 (0.18–0.7).

Hereditary breast and ovarian cancer syndrome

Among women with breast cancer, 5–10 % cases appear due to hereditary factor, mainly germline mutations of *BRCA1* or *BRCA2*, causing typical hereditary breast and ovarian cancer syndrome (HBOC). The average cumulative risks (95 % CI) in carriers of these mutations at age 70 years old are 65 % (44–78 %) and 45 % (31–56 %), respectively, for breast cancer; and 39 % (18–54 %) and 11 % (2.4–19 %), respectively, for ovarian cancer [69]. Therefore, evaluation of the risk of hereditary breast cancer and early medical intervention should be performed in these high-risk patients to improve the prognosis.

Counseling and genetic testing

There are no established criteria for evaluation of the genetic basis of breast cancer based on clinical findings and family history. The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines recommend a 2-step evaluation method [70]. The first step is to screen by present illness and family history of relatives on both sides of the family in general practice settings and to tentatively advise patients on the possibility of hereditary breast cancer if an item agrees with criteria for further genetic risk evaluation. In the next step, these patients are then examined by cancer genetics professionals. If a patient is likely to have hereditary breast cancer, genetic testing and screening are recommended for patients and family members.

Breast MRI screening for BRCA mutation carriers

- Onset of HBOC can occur at a relatively young age and thus follow-up surveillance should be started as early as possible. Currently, there is no established age at which screening is initiated in *BRCA* mutation carriers, but it is recommended that screening starts at 25–30 years old. The desirable age to initiate screening is 5 years younger than the age at which the youngest relative was diagnosed with breast cancer.
- Given the young age at the start of screening, radiation exposure cannot be ignored. A retrospective cohort study in *BRCA* mutation carriers showed no significant association of exposure to diagnostic radiation and breast cancer risk from 30 to 39 years old, but any exposure to diagnostic radiation before age 30 was associated with an increased risk of breast cancer [71]. Given this finding, caution is required in performing mammography using ionizing radiation. Furthermore, the sensitivity and specificity of mammography are generally lower in a dense breast, which is more common in younger women.
- Breast MRI screening in high-risk groups has been widely studied in Western countries. In a multicenter study in 3,818 patients in 52 medical institutions, the sensitivity of breast MRI of 77–100 % was significantly higher than those of mammography (16–40 %) and breast ultrasound (16–40 %) [72].
- A cohort study of breast cancer detection in high-risk women found a significantly higher cancer rate of 14.9/1,000 with breast MRI, compared to rates of 5.4/1,000, 6.0/1,000, and 7.7/1,000 using mammography, breast ultrasound, and a combination of mammography and breast ultrasound, respectively [73]. Based on diagnostic accuracy and safety, breast MRI may be most effective for screening in *BRCA* mutation carriers.

Risk-reducing mastectomy

- No RCTs of risk-reducing mastectomy (RRM) have been performed in *BRCA* mutation carriers because of ethical reasons. Therefore, the efficacy of RRM is assumed based on a comparison of breast cancer risk between *BRCA* mutation carriers who underwent RRM of both breasts through their own choice and those who did not receive RRM. Based on this comparison, RRM definitely reduces breast cancer risk and the risk reduction rate may be around 90 % [74–76].
- RRM has not been shown to reduce overall and breast cancer-related mortality. The majority of *BRCA1* mutation carriers develop triple negative breast cancer, which is likely to be highly malignant. Thus, some mutation carriers may have benefits by RRM. This speculation requires verification in a future study.

Chemoprevention

A retrospective analysis of the Breast Cancer Prevention Trial (P-1 trial) by the NSABP is the only evaluation of the efficacy of adjuvant endocrine therapy in *BRCA* mutation carriers. The results showed that TAM did not significantly reduce the breast cancer risk. There is no evidence showing the efficacy of TAM in *BRCA* mutation carriers [77].

Risk-reducing salpingo-oophorectomy

- Risk-reducing salpingo-oophorectomy (RRSO) has been associated with a significant reduction in the risk of ovarian or fallopian tube cancer in *BRCA* mutation carriers, and a meta-analysis showed a definite risk reduction with a HR of 0.21 [78].
- This meta-analysis also indicated that RRSO is associated with a significant reduction in the risk of breast cancer, with a HR (95 % CI) of 0.49 (0.37–0.65) [78].
- RRSO may also reduce all-cause mortality. In a cohort study in *BRCA* mutation carriers performed by the Prevention and Observation of Surgical Endpoints consortium, the all-cause mortalities in women who did and did not undergo RRSO were 3 and 10 %, respectively, and the breast cancer-specific and ovarian cancer-specific mortality also decreased in RRSO cases [79].

Ovarian cancer screening

RRSO is recommended for *BRCA* mutation carriers in Western countries, but this procedure is not widely used in Japan and these patients are usually followed up. Transvaginal ultrasound and CA125 measurements are potential candidates for screening for ovarian cancer, but neither has been shown to reduce mortality in silent ovarian cancer. Therefore, the benefits of these procedures are uncertain.

- Neither transvaginal ultrasound nor CA125 measurement facilitated early detection of ovarian cancer or decreased mortality in *BRCA* mutation carriers [80]. However, despite the unknown efficacy, many guidelines indicate that internal examination, transvaginal ultrasound, and CA125 measurements should be used in *BRCA* mutation carriers.
- NCCN recommends screening for women with *BRCA* mutations, starting at age 30–35 or 5–10 years before the age of earliest diagnosis in a family member, using a combination of serum CA 125 and transvaginal

ultrasound every 6–12 months. The benefit of screening for ovarian cancer in *BRCA* mutation carriers has not been established, but internal examination, transvaginal ultrasound, and CA125 measurements are currently being studied with the expectation of future use.

Lifestyle after breast cancer

Various lifestyles are associated with a risk for breast cancer. However, it is unclear how lifestyle after diagnosis of breast cancer influences prognoses such as recurrence and death. These guidelines verified the association of prognosis with obesity, intake of fat, alcohol, isoflavones, and dairy products; physical activity; and smoking after diagnosis of breast cancer, as shown in Table 2.

Table 2 Summary of evaluation for associations between lifestyle factors after breast cancer diagnosis and prognosis (recurrence or breast cancer-specific mortality)

Judgment	Decreases risk	Increases risk
Convincing	None identified	Obesity at diagnosis
Probable	Physical activity after diagnosis	Obesity after diagnosis
Limited-suggestive	Isoflavones	Tobacco smoking
Limited-no conclusion	Fats; Alcohols; Dairy foods	
Substantial effect on risk unlikely	None identified	

Judgments are made based on the strength of the evidence

Obesity and breast cancer prognosis

- Many large-scale cohort studies have evaluated the association of obesity at diagnosis of breast cancer with the risk of recurrence and death from breast cancer, including 3 meta-analyses. A recent meta-analysis showed that the risk for breast cancer mortality was 1.33 (95 % CI: 1.19–1.50) in obese patients [81].
- Regarding the association between obesity and medication, an exploratory RCT indicated that inhibition of recurrence by Anastrozole as postoperative endocrine therapy was lower in obese women with hormone receptor-positive breast cancer than in non-obese patients [82, 83].
- Only a few studies have investigated the effects of weight gain or obesity after diagnosis of breast cancer on the risk of recurrence and death from breast cancer. Three studies found an association between obesity after diagnosis of breast cancer and risk of recurrence, including 2 large-scale cohort studies and 1 exploratory RCT.
- The cohort study showed that the risk of breast cancer death increased by 1.64 (95 % CI: 1.07–2.51) when BMI increased by $\geq$2.0 kg/m^2 for 1 year after diagnosis [84]. The exploratory RCT showed that breast cancer mortality was 1.6 times greater in treated premenopausal patients with a median weight gain of $\geq$5.9 kg [85].
- There are few studies on the association between obesity after diagnosis of breast cancer and prognosis, but it is almost certain that obesity after diagnosis increases breast cancer mortality.

Physical activity and breast cancer prognosis

- In a meta-analysis reported in 2010, subjects were divided into groups with low physical activity (L-PA), intermediate physical activity (I-PA), intermediate to high physical activity (IH-PA), and high physical activity (H-PA), respectively [86]. Analysis of 4 studies of physical activity after diagnosis of breast cancer indicated that breast cancer mortality was significantly lower in the I-PA, IH-PA and H-PA groups compared with the L-PA group, with a HR (95 % CI) of 0.66 (0.57–0.77) in the I-PA, IH-PA and H-PA groups compared to the L-PA group. All-cause mortality and the risk of breast cancer recurrence showed similar tendencies, with HRs (95 % CI) of 0.59 (0.53–0.65) and 0.76 (0.66–0.87), respectively, in the I-PA, IH-PA and H-PA groups compared to the L-PA group, indicating a definite decrease in risk.
- The tendency for physical activity to improve the prognosis of breast cancer found in cohort studies has not been verified in a RCT. However, an association between physical activity after diagnosis of breast cancer and all-cause mortality risk reduction has been identified [87].

Tobacco smoking and breast cancer prognosis

- A study of smoking status after diagnosis of breast cancer gave RRs (95 % CI) of 1.48 (1.27–1.74), 1.02 (0.83–1.24), and 1.07 (0.88–1.29) for all-cause mortality, breast cancer mortality, and breast cancer recurrence, respectively, in smokers compared to non-smokers [88].
- There have been 10 studies of the association between smoking and prognosis of breast cancer, with evaluation before or after diagnosis, or unknown. Nine of these studies examined breast cancer mortality, and 5 of the 9 found a significantly increased risk in smokers. In 9 studies that investigated the association with all-cause mortality, 6 reported a significantly increased risk.

- Since several studies have shown an association with mortality (all-cause mortality and breast cancer mortality), the mortality risk of breast cancer patients may be increased by smoking.

Isoflavones and breast cancer prognosis

- The number of high-quality studies on the effects of isoflavones in breast cancer patients is limited. There have been 4 studies in Chinese patients and 2 in American patients.
- A meta-analysis of 4 of these studies showed a significant association with recurrence reduction [89]. A combined analysis of 2 datasets in US women and 1 dataset in Chinese women indicated a significant association with mortality and a significantly reduced risk of recurrence [90].

The relationship between intake of fat, alcohol, and dairy products after diagnosis of breast cancer and prognosis was judged to be "limited-no conclusion" based on the lack of an established association between these factors and prognosis, and the absence of high-quality studies.

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Conflict of interest The authors declare that they have no conflict of interest.

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