proposed six practical stepsfor program development; evaluation of resources and educational materials available for patients and providers (Step 1), conduct of needs assessments in the current system (Step 2), establishment of formal relationships between fertility specialists and cancer care providers (Step 3), initiation of the Onco-fertility programs (Step 4), practice of the fertility preservation program (Step 5), and ongoing program assessment and modification (Step 6) [6]. Step 2 includes not only the assessment of patient volume and available staff but also evaluation of the views of providers, both oncologists and reproductive specialists (RS), and patients.

We and others have examined the perceptions and practice behaviors of oncologists regarding FP [7–9]: the barriers impacting on FP for young women with breast cancer from the view point of oncologists include higher risk of cancer recurrence, lack of RS for consultation/referral, lack of time to discuss fertility issues with patients in the clinic, tumor expression of estrogen receptor, lack of knowledge of available FP options, among others.

Although the issues remain within the responsibilities of the oncologist, lack of communication with a reproductive specialist seems to be a major barrier. Therefore, to better understand the views of RS towards FP of breast cancer patients, we investigated the perception, needs and practice of RS in relation to FP for young women with breast cancer.

Methods

Questionnaire development

A questionnaire was developed by four oncologists (C.S., T.K., N.T and H.B.) and a reproductive specialist (Y.A.). It was validated by an external reproductive specialist via communication by e-mail.

Measure

The questionnaire was originally written in Japanese and consisted of six sections summarized below. Physicians were asked to evaluate their agreement with the statements using a four point grade rating scale (4 = strongly agree, 3 = agree, 2 = disagree, 1 = strongly disagree). The English translation of the full questionnaire is available in the Appendix.

Section A Demographic, medical training, and practice information (ten items).

Section B Perception towards FP of young women with breast cancer (five items using the rating scale). The sum of the inversed score of question 1 and the scores for questions two to five was calculated (the total perception score). We assumed that the higher the total perception score, the more positive the respondents had been in their perception of FP for breast cancer patients.

Section C Interpretation of available evidence regarding fertility issues in breast cancer patients (four items using the rating scale).

Section D Practice behaviors in infertile women without cancer (six items; one item using the rating scale).

Section E Practice behaviors in women with breast cancer (eight items; three items using the rating scale). The respondents were asked whether they could accept fertilized and unfertilized egg preservation at the respondent's affiliating institution.

Section F The requirements for developing a system supporting FP in breast cancer patients from a reproductive specialist's perspective (free text description).

Procedures

The printed questionnaires were sent by mail to all 423 board-certified RS registered in the Japan Society for Reproductive Medicine on 17 February 2012 and collected via mail by 10 March 2012.

Data analyses

Analyses were conducted using IBM SPSS Statistics version 21. Categorical and ordinal data was tested using chi-squared test and Mann–Whitney test, respectively. Pearson's correlation coefficient was calculated to analyze the correlation between perception and attitude score. All p values were two-sided, with a statistical significance set at <0.05. No adjustments for multiple comparisons were considered.

For Section F, grounded-theory approach was utilized to capture the themes and subthemes emerging from the free description about the needs for developing a system to support fertility preservation in breast cancer patients. The coding scheme was developed through discussion with members of the research team (C. S., Y. M., and S. Y.) and the results were peer-reviewed (H. B., T. K., and N. T).

Results

Response rate

Two hundred RS responded to the survey. The response rate was 47 %.

Characteristics of the respondents

Table 1 shows a summary of the demographic backgrounds of responding RS. 87 %were male. Median age of

Table 1 Demographic background of responding RS ($n = 423$)

	n (%)
Age, years, mean (range)	50 (35–71)
Gender	
Male	174 (87)
Female	42 (12)
Spouse/partner	
Yes	190 (95)
No	7 (4)
Experience as a reproductive specialist, years, mean (range)	25 (11–45)
Experience of management of cancer patients	
Yes	192 (96)
No	4 (2)
Affiliation	
Academic hospital	75 (38)
General hospital	42 (21)
Private clinic	77 (39)
Breast Division in the same institution	
Yes	104 (52)
No	92 (46)

respondents was 51 years (range 35–71), 95 % were married and 91 % had offspring. Median duration of practice in reproductive medicine was 25 years (range 4–45 years) and 96 % had experience of oncology practice for a median duration of 14 years (range 1–40 years). About 60 % of the respondents were affiliated to academic or general hospitals, while the remaining 40 % were affiliated to private clinics. 52 % had a breast oncology unit in the same institution. 119 (60 %) of the respondents had had some experience of FP in breast cancer patients within the 2 years prior to the survey.

Perception of fertility preservation for breast cancer patients

99 % responded that RS should be engaged in FP of breast cancer patients. 83 % responded that they would accept young breast cancer (YBC) patients by themselves. However, 70 % of the RS responded that they were anxious about treating breast cancer patients. 46 % responded that cancer treatment is more important than childbirth, even when a patient is recurrence free 5 years after primary treatment, and 39 % responded that fertility after breast cancer is difficult because of the risk of death for the mother. The total perception score was significantly higher in RS affiliated to a private clinic than in those affiliated to a hospital (Mann–Whitney $U = 5{,}303.0$, $p = 0.026$).

63 % were concerned about hereditary breast cancer. Interestingly, male respondents, respondents with a partner or offspring, and those affiliated to a private clinic were more concerned about hereditary breast cancer than female respondents, respondents without a partner or offspring, and those affiliated to a hospital, respectively.

Attitude to fertility preservation of breast cancer patients

Overall, 78 % of the RS responded that they would accept breast cancer patients in their daily practice. A higher perception score was correlated with a higher willingness to accept breast cancer patients as clients (Section E, Question 2) (Pearson's coefficient -0.297, $p < 0.001$) and less anxiety about or barriers to FP of breast cancer patients (Section E, Question 7) (Pearson's coefficient 0.222, $p = 0.002$).

76 % answered that they could accept married patients who wished to have fertilized egg preservation. On the other hand, only 29 % of respondents answered that they could accept single patients who wished to have unfertilized egg preservation. Respondents affiliated to a private clinic were more likely to accept both fertilized and unfertilized egg preservation than those affiliated to an academic or general hospital (Fig. 1).

Choice of ovulation induction method in breast cancer patients

58 % responded that ovulation induction methods should be modified in YBC patients. The choice of ovulation induction method varied in both non-cancer women and YBC patients; however, the frequency of the use of letrozole was significantly higher in the management of breast cancer patients than in the practice for non-cancer women (Fig. 2).

Barriers to supporting fertility preservation in young breast cancer patients

Concerns about a greater or unknown risk of cancer recurrence (66 %), insufficient knowledge about breast cancer (47 %), and lack of patient's spouse/partner (24 %) were identified as major barriers in supporting FP for YBC patients (Fig. 3). Significantly more RS affiliated to institutions without breast oncology units noted difficulty in direct communication with oncologists than those affiliated to institutions with breast oncology units ($p < 0.05$).

The needs for developing a system to support fertility preservation

Seventy-five RS filled out the free description section about the needs for development of an FP program for breast

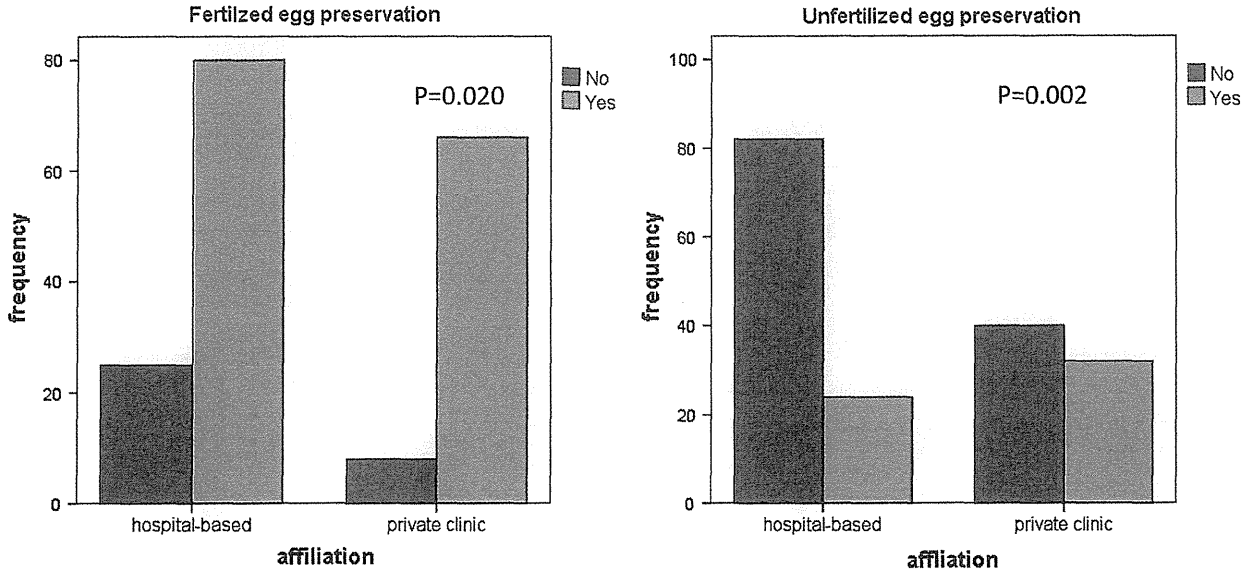
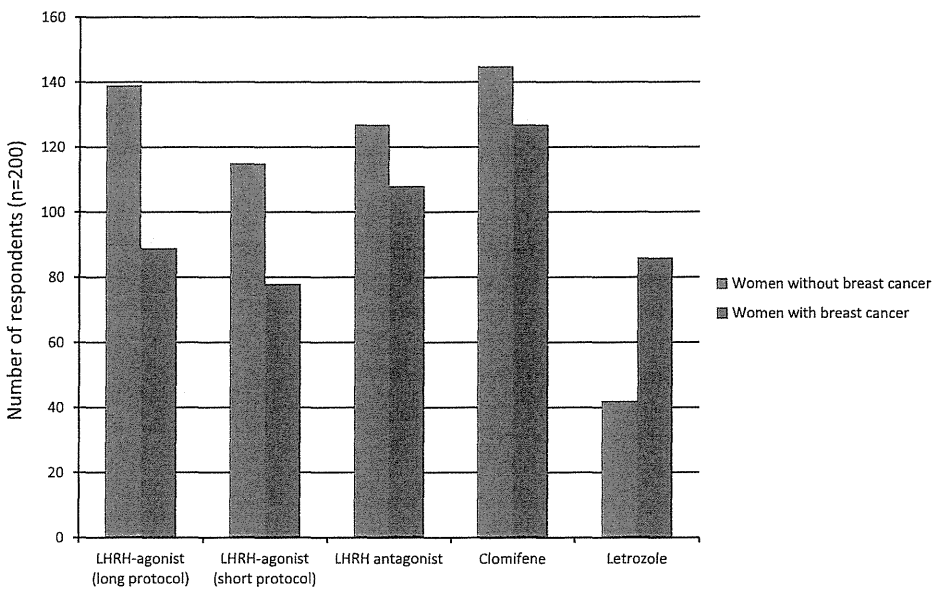


Fig. 1 Acceptance of fertilized and unfertilized egg preservation of YBC patients according to affiliated institution of the respondents

Fig. 2 Ovulation induction methods used for women with and without breast cancer. RS were asked to *circle* "Yes, I use it." and "No, I don't use it." for each ovulation stimulation method in women with and without breast cancer, respectively. The denominator is 200



cancer patients. The captured themes and subthemes regarding the needs of RS are summarized in Table 2.

Discussion

To our knowledge, this is the first exploration of perspectives of RS towards FP for breast cancer patients. RS were aware of the needs of YBC patients and the majority had positive attitudes towards FP, but at the same time the majority was anxious about treating breast cancer patients. There are several limitations of this study. This survey involved Japanese RS who might have different views about cancer, reproduction, and life compared with those from a different culture. Indeed, egg donation is not allowed and adoption is not common in Japan. Also, the practice behavior deduced from this survey might not reflect their real-world practice because the data was generated from the respondents' replies only. However, we think that this study has important implications for program development for FP for breast cancer patients.

The major barriers from the RS' perspective were concerns about cancer recurrence, insufficient knowledge about breast cancer, and lack of a patient's spouse/partner. The risk of recurrence and death due to breast cancer is an anxiety shared between breast oncologists and RS. Direct

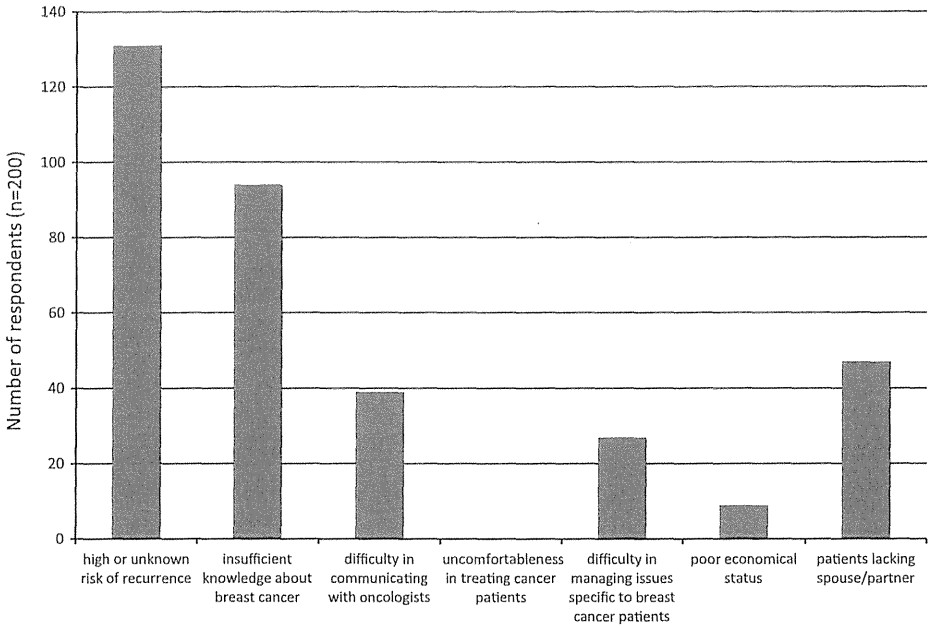


Fig. 3 Barriers to supporting FP in YBC patients. RS were asked to *circle* the barrier that matched their feelings from eight choices. Multiple selections were allowed. The eighth choice was "others" with a space for free text entries provided. The denominator is 200

communication about cancer prognosis and treatment outcome evaluation by both oncological and reproductive experts is most important in individual patient care planning. Facilitation of communication is especially important in the setting where the consulting RS and oncologists are not affiliated to the same institution.

The barriers and needs raised by RS were compatible with those of oncologists identified in our previous survey of Breast Care Specialists of the Japanese Society of Breast Cancer [7]. Although published retrospective studies suggest that pregnancy after breast cancer does not seem to impact on the risk of recurrence, even in estrogen-receptor-positive breast cancer patients [10, 11], there are no convincing data that support the safety of pregnancy using assisted reproductive technologies. The safety of ovarian stimulation which could induce temporarily high estradiol levels is of concern in patients with hormone-receptor-positive breast cancer. In a small prospective study evaluating ovarian stimulation using letrozole and gonadotropins in breast cancer patients, a technique which already seems to be utilized more frequently in Japan, there did not seem to be compromised long-term outcome of breast cancer, but longer follow-up and further research is needed [12]. Moreover, the newer assisted reproductive technology, such as unfertilized egg preservation and ovarian tissue preservation, has not been established and the efficacy of such technologies, especially when applied to cancer patients, should be measured not by the success rate of fertilization but by the success rate of live birth and the morbidity of mothers and children.

The delay, interruption, or omission of effective systemic cancer treatment is also of concern. A challenging clinical trial is proposed by the Breast International Group and the North American Breast Cancer Group [13].The proposed trial is directed to young women with endocrine-responsive, early breast cancer and a desire for pregnancy, who are disease free after 2 years of adjuvant endocrine therapy. It includes an observational phase which investigates the feasibility and impact of a temporary treatment interruption to allow conception. The subsequent experimental phase will investigate the optimal duration of endocrine treatment after delivery or the last failed attempt to become pregnant. Patient and offspring outcomes will be assessed [13].Without convincing data, for the time being, patients, oncologists and RS should make realistic decisions based on the limited evidence.

Acceptance of unfertilized egg preservation for unmarried patients was low in general and biased to RS working in private clinics. The ethics committee of the American Society for Reproductive Medicine and others have raised ethical issues related to FP of cancer patients [14–17]. In the opinion of The Japan Society of Obstetrics and Gynecology, unfertilized egg preservation of unmarried patients can be justified in the context of a clinical trial but such a study platform has not yet been developed for breast cancer patients.

To conclude, we believe that guidelines, networks and a national registry system to facilitate the practice and communication between oncologists and RS based on existing evidence, local healthcare system, and regulations

Table 2 Requirements of RS for a FP program for YBC patients

Themes	Subthemes
Consensus building and development of guidelines	1. Guidelines
	2. Standardization of treatment protocols
	3. Clear indications (age, stage, estrogen-receptor status, marital status)
	4. Maximum permissible estradiol level induced by ovulation stimulation
Development of database and production of evidence	1. National registry system
	2. Influence of assisted reproductive technology on breast cancer prognosis
	3. Outcome data of assisted reproductive technology (pregnancy/live birth success rates, morbidity of the offspring)
Network building	1. Intra-institutional network
	2. Inter-institutional consultation system
	3. Communication and collaboration
System	1. Centralization of functions (information, storage of preserved eggs/embryos)
	2. Sustainability of the system (quality assured long-term storage)
	3. Certification of core facilities
	4. Share of responsibility
	5. Procedure of informed consent
Practical support	1. Financial support for patients
	2. Assisting personnel (multidisciplinary team)
	3. Practical support for physicians (real-time consultation system, treatment/prognosis information)
Education	1. Patients, partners and families
	2. Mutual education opportunities for oncologists and RS
	3. Public awareness

are urgent needs. In such guidelines, we think that the following items should be included: (1) information to be provided to the patients; (2) the influence of pregnancy and assisted reproductive technology on breast cancer; (3) the indications for, safety, and success rate of various assisted reproductive technologies in breast cancer patients; (4) the timing of assisted reproductive technology intervention; (5) available resources and supporting tools; and (6) potential ethical and legal issues. We, together with the Japanese Society for FP which was launched in 2012, are now developing a guideline for FP for Japanese breast cancer patients supported by a grant from the Ministry of Health, Labor and Welfare.

Acknowledgments We thank Ms. Masayo Kawamura for her support in data collection and Dr. Richard Theriault of University of Texas, M. D. Anderson Cancer Center for his generous help in editing and reviewing this manuscript. This study was supported by a Health Labor Sciences Research Grant of the Ministry of Health, Labor and Welfare (H21-021) and Third Term Comprehensive 10-year Strategy for Cancer Control (H24-Sanjigan-Ippan-010). The results of this study were partly presented at the 35th Annual San Antonio Breast Cancer Symposium.

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

Appendix

This is an English translation of the survey (the original version is in Japanese).

Section A: demographic, medical training, and practice information

1. How old are you?
2. What is your gender?
3. Do you have a partner/spouse?
4. Do you have any children?
5. What kind of institution are you affiliated to?
6. How large is your institution?
7. Do you have a breast oncology unit in your institution?
8. How many years have you served as a clinician?
9. How many years have you specialised in reproductive medicine?
10. Have you ever specialised in cancer management?
11. Do you have any cancer patients among your family or close friends?

Section B: attitude to fertility preservation of young women with breast cancer

1. I think that RS should be engaged in FP of breast cancer patients.
2. I think that it is difficult for cancer patients to pursue FP because of the risk of dying from cancer.
3. I am concerned about hereditary breast cancer when treating breast cancer patients.
4. I think that patients are concerned about hereditary transmission of cancer to their offspring.
5. I think that cancer treatment is more important even if the patient has been disease free for 5 years since the initial diagnosis.

Section C: interpretation of available evidence regarding fertility issues in breast cancer patients

1. I think that pregnancy after cancer increases the risk of recurrence and progression of breast cancer.
2. I think that cancer chemotherapy increases risk of miscarriage or teratism during subsequent pregnancy.
3. I think that luteinizing-hormone releasing-hormone agonists are useful for ovarian protection during chemotherapy.
4. I think that ovulation stimulation using letrozole will have an influence on breast cancer.

Section D: practice behavior with infertile women without cancer

1. I talk about the potential risk of development of cancer to my patients.
2. How many patients a week do you take care of in a typical week?
3. How many egg retrievals do you perform in a typical week?
4. How many fertilized egg preservations do you perform in a typical week?
5. How many unfertilized egg preservations do you perform in a typical week?
6. What kind of ovulation methods would you use for ovulation induction? Circle "Yes, I use it." or "No, I don't use it." for each ovulation stimulation method listed.

Section E: practice behavior with women with breast cancer

1. Have you had any clinical experience of treating breast cancer patients? If yes, how many patients have you treated in the past 2 years (2010–2011).
2. I would like to accept breast cancer patients as my clients.
3. What kind of ovulation methods would you use for ovulation induction in breast cancer patients? Circle "Yes, I use it." or "No, I don't use it." for each ovulation stimulation method listed.
4. I think that the method of ovulation induction should be modified in breast cancer patients.
5. Can you accept married breast cancer patients for fertilized egg preservation in your affiliating institution?
6. Can you accept unmarried breast cancer patients for unfertilized egg preservation in your affiliating institution?
7. I feel anxiety or barriers to treating FP of breast cancer patients.
8. Please circle the items that give you cause for anxiety or barriers. Multiple selections are allowed.

Section F: the needs for developing a system to support FP in breast cancer patients from a reproductive specialist's perspective

1. We are planning to develop a program to support YBC patients who wish for future fertility. Please describe, using your expertise, your opinion on what kind of information or system is necessary to build such a program.

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Breast Cancer (2015) 22:16–27
DOI 10.1007/s12282-014-0555-x

The Japanese Breast Cancer Society clinical practice guideline for epidemiology and prevention of breast cancer

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Received: 28 May 2014 / Accepted: 14 July 2014 / Published online: 2 August 2014

Descriptive epidemiology of breast cancer in Japan

Mortality

The vital statistics of the Ministry of Health, Labour and Welfare show that the crude and age-adjusted death rates of patients with breast cancer increased consistently from the 1960s to 2011, but decreased in 2012. The number of deaths due to breast cancer in women was 12,529 in 2012. The crude death rate was 19.4 per 0.1 million population and ranked fifth highest, behind colon/rectum, lung, stomach, and pancreatic cancers in descending order. The age-adjusted death rate was 11.5 per 0.1 million population, which was second only to colon/rectum cancer and was followed by lung and stomach cancers. The age-specific death rate increased in a linear fashion under the age of 50 and slightly decreased until 80 years old. The age-adjusted death rate from breast cancer in Western countries is substantially greater than that in Japan, but has shown a tendency to decrease after reaching a peak around 1990, and thus the gap with Japan has been reduced [1].

Incidence

The crude and age-adjusted incidences of breast cancer in women have tended to increase since 1975. The crude incidence of breast cancer including carcinoma in situ in

This article is an English digested edition of the Nyugan Shinryo guideline 2013 nen ban, published by Kanehara & Co., LTD.

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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 $\geq$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.

Acknowledgments This work was sponsored by Japan Breast Cancer Society. We thank the clinical practice guideline committee and clinical practice guideline assessment committee for support for this work.

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

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13. がん領域における今後十年の先制医療の動向

山本精一郎，溝田友里

がんは，1981年に脳血管疾患を抜き，わが国の死因別死亡数のトップとなった．その後も死亡数は増え続け，2013年には，死亡者の約3割ががんで亡くなっている．がんの先制医療としては，予防・早期発見が大きな柱になるが，現在，利用可能な予防法としては，禁煙や身体活動量の増加，ウイルス肝炎などがんのリスクとなる感染症の治療などであり，早期発見としては，胃，肺，大腸，乳，子宮頸がんに対するがん検診である．現在，個人のがんリスク診断の方法やそれに基づく予防法，早期発見法が開発されているところであり，これらを用いた効果的な先制医療が望まれる．

はじめに—がんの疫学

がんは，1981年に脳血管疾患を抜き，わが国の死因別死亡数のトップとなった．その後も死亡数は増え続け，2013年には，死亡者の約3割，364,872人（男性216,975人，女性147,897人）ががんで亡くなっている．'10年のがん罹患数は約80万人である（地域がん登録による罹患全国推計値）．'10年のデータに基づくと，がんの生涯罹患リスクは男性60％，女性45％，'13年のデータに基づくと生涯死亡リスクは男性26％，女性16％と推定される[1]．

がんと一口にいっても，その中身はさまざまである．臓器別に見ると，'13年の死亡数では，男性では肺，胃，大腸，肝臓，膵臓の順に多く，女性では大腸，肺，胃，膵臓，乳房が多い．年齢調整死亡率で見ると，男女とも，胃，大腸，肝臓が（男性では肺がんも）減少傾向を示しており，死亡数の増加には高齢化の影響が大きく寄与していることがわかる．しかし，年齢調整罹患率でみると，女性の乳がんは大きな増加傾向，男女とも大腸，肺，膵がんは減少しているとはいえず，罹患対策も必要である（図）[1]．

がんの生存率については，これまで特定の病院の限られた対象に対する成績や，学会に登録された症例の成績など，代表的とはいえない数字しか利用できなかったが，近年，がん登録などの整備が進み，ある程度代表的といえる数値が利用できるようになった．地域がん登録によるがん生存率データによると，'03年～'05年にがんと診断された症例では，5年相対生存率は全がんで男性55.4％，女性62.9％である[2]．これらは，年を追うごとに改善されてきているが，いまだ十分な数字とはいえない．

[キーワード]
がん，予防，早期発見，がん検診，リスク診断

Prevention and Early Detection of Cancer in the Next Decade

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