表4　がん種別卵巣転移リスク分類

高リスク	中等度リスク	低リスク
白血病	乳がん stageⅣ	乳がん stage Ⅰ～Ⅱ
神経芽細胞腫	浸潤性小葉癌	浸潤性乳管癌
Burkitt リンパ腫	結腸がん	子宮頸部扁平上皮癌
	子宮頸部腺癌	Hodgkin リンパ腫
	非 Hodgkin リンパ腫	横紋筋肉腫
	Ewing 肉腫	Wilms 腫瘍

乳がんに関して，卵巣への転移率は 13.2～37.8%とする報告[17, 18]があるが，進行症例を多く含んでいる．Sanchez ら[19]，Rosendhal ら[20]によると，初期乳がん患者の凍結融解卵巣皮質組織には組織学的，免疫組織学的検査にてがん細胞を認めなかったとしている．以上より，初期乳がんはがん細胞の卵巣転移リスク（MRD のリスク）は低リスクとなり[15]，本邦においても女性がんの罹患率トップで若年化も進んでいる乳がんは，卵巣組織凍結保存の適応疾患の上位となっている．

おわりに

欧米では，卵巣組織凍結保存はすべての若年女性がん患者へ妊孕性温存方法の選択肢として提供すべき医療行為となっている．「幅広い年齢層に対応できる」「月経周期によらず即座に施行可能である」「より多くの卵子を保存できる」など，本技術は若年女性がん患者に対する妊孕性温存方法の主翼となりうる方法である．しかし，今後の技術的な発展とともに，安全性の確保，ならびにアウトカムの正確な検討が重要な課題であると考えられる．ASCO 2013 指針にもあるように，卵巣組織凍結・移植は，倫理委員会にて施行が検討され認可された施設でのみ施行されるべきである[1]．

● 文献

1) Loren AW, Mangu PB, Beck LN, et al : Fertility preservation for patients with cancer : American Society of Oncology clinical practice guideline update. J Clin Oncol 31 : 2500–2510, 2013
2) Donnez J, Dolmans MM, Pellicer A, et al : Restoration of ovarian activity and pregnancy after transplantation of cryopreserved ovarian tissue : a review of 60 cases of reimplantation. Fertil Steril 99 : 1503–1513, 2013
3) Donnez J, Silber S, Andersen CY, et al : Children born after autotransplantation of cryopreserved ovarian tissue. A review of 13 live birth. Ann Med 43 : 437–450, 2011
4) Van Eyck AS, Bouzin C, Feron O, et al : Both host and graft vessels contribute to vascularization of xenografted human ovarian tissue in a murine model. Fertil Steril 93 : 1676–1685, 2010
5) Amorim CA, David A, Dolmans MM, et al : Impact of freezing and thawing of human ovarian tissue on follicular growth after long-term xenotransplantation. J Assist Reprod Genet 28 : 1157–1165, 2011
6) Keros V, Xella S, Hultenby K, et al : Vitrification versus controlled-rate freezing in cryopreservation of human ovarian tissue. Hum Reprod 24 : 1670–1683, 2009
7) Amorium CA, Dolmans MM, et al : Vitrification and xenografting of human ovarian tissue. Fertil Steril 98 : 1291–1298, 2012
8) Ting AY, Yeoman RR, Lawson MS, et al : In vitro development of secondary follicles from cryopreserved rhesus macaque ovarian tissue after slow-rate freeze or vitrification. Hum Reprod 26 : 2461–2472, 2011
9) Hashimoto S, Suzuki N, Yamanaka M, et al : Effects of vitrification solutions and equilibration times on

the morphology of cynomolgus ovarian tissues. Reprod Biomed Online 21 : 501–509, 2010
10) Suzuki N, Hashimoto S, Igarashi S, et al : Assessment of long-term function of heterotopic transplants of vitrified ovarian tissue in cynomolgus monkeys. Hum Reprod 27 : 2420–2429, 2012
11) Sheikhi M, Hultenby K, Niklasson B, et al : Preservation of human ovarian follicles within tissue frozen by vitrification in xeno-free closed system using only ethylene glycol as a permeating cryoprotectant. Fertil Steril 100 : 170–177, 2013
12) Igarashi S, Suzuki N, Hashimoto S, et al : Heterotopic autotransplantation of ovarian cortex in cynomolgus monkeys. Hum Cell 23 : 26–34, 2010
13) Ting AY, Yeoman RR, Zelinski MB, et al : Morphological and functional preservation of pre-antral follicles after vitrification of macaque ovarian tissue in a closed system. Hum Reprod 28 : 1267–1279, 2013
14) Dolmans MM, Jadoul P, Gilliaux S, et al : A review of 15 years of ovarian tissue bank activities. J Assist Reprod Genet 30 : 305–314, 2013
15) Ajala T, Rafi J, Larsen-Disney P, et al : Fertility preservation for cancer patients ; a review. Obstet Gynecol Int 2010 : 160386, 2010
16) Rosendahl M, Andersen CY, Ralfkiaer E, et al : Evidence of residual disease in cryopreserved ovarian tissue in cancer patients with leukemia. Fertil Steril 94 : 2186–2190, 2010
17) Perrotin F, Marret H, Bouquin R, et al : Incidence, diagnosis and prognosis of ovarian metastasis in breast cancer. Gynecol Obstet Fertil 29 : 308–315, 2001
18) Kyono K, Doshida M, Toya M, et al : Potential indications for ovarian autotransplantation based on the analysis of 5571 autopsy finding of females under the age of 40 in Japan. Fertil Steril 1 : 2429–2430, 2010
19) Sanchez-Serrano M, Novella-Maestre E, Roselló-Sastre E, et al : Malignant cells are not found in ovarian cortex from breast cancer patients undergoing ovarian cortex cryopreservation. Hum Reprod 24 : 2238–2243, 2009
20) Rosendahl M, Timmermans Wielenga V, Nedergaard L, et al : Cryopreservation of ovarian tissue from patients with breast cancer. Fertil Steril 95 : 2158–2161, 2011

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SPECIAL FEATURE

Breast cancer in young women: Issues and perspectives regarding patients' and survivors' care

Issues of concern in risk assessment, genetic counseling, and genetic testing of younger breast cancer patients in Japan

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Abstract About 5–10 % of breast cancer cases are considered to be hereditary, and germ line mutations in the *BRCA1* and *BRCA2* genes have been proven to contribute to the development of hereditary breast and/or ovarian cancer syndrome (HBOC). Breast cancer diagnosed at a young age is an indication of a higher likelihood of HBOC. Risk assessment, genetic counseling, and *BRCA1/BRCA2* mutation testing, especially for younger women with breast cancer, have started to be an integral element of practice due to advances in gene sequencing technologies and accumulating evidence for the clinical implications of *BRCA* mutation status for not only early breast cancer management, but also for the patient's own and their family's next cancer risk, and proactive steps toward a risk-reducing approach. As yet, the cancer genetic service system is immature in Japan. There are several problems to be solved to improve cancer genetic services in clinical practice for breast cancer.

Keywords Hereditary breast cancer · Early onset · Cancer genetic service · Genetic testing

Background

Breast cancer is a common disease among Japanese women, with over 56,000 new cases diagnosed in 2007, and the incidence of breast cancer diagnosis has been increasing in recent years [1]. Ovarian cancer is less common, with approximately 8,600 new cases diagnosed per year [1]. The clinical features of familial breast cancer are early onset, high frequency of multiple or bilateral breast cancer, and multiple malignancies of other organs including ovarian cancer [2, 3]. It has various causative factors including environmental factors, but genetic factors seem to be most common. About 5–10 % of breast cancer cases are considered to be hereditary, and recent studies have confirmed that germ line mutations in the *BRCA1* and *BRCA2* (*BRCA1/2*) genes contribute to the development of hereditary breast and/or ovarian cancer syndrome (HBOC) [2]. HBOC is an autosomal dominant disease, so the mutation of *BRCA1* or *2* is transferred to 50 % of offspring. *BRCA1* mutation carriers have 40–87 % life-time risk of breast cancer and 16–63 % of ovarian cancer, and *BRCA2* mutation carriers have 28–84 and 27 % risks of breast and ovarian cancers, respectively. BRCA mutation carriers' relatives without BRCA mutation have average risks of breast and ovarian cancers. Breast cancer diagnosed at a young age is an indication of a higher likelihood of HBOC or rarer genetic conditions such as Cowden syndrome and Li–Fraumeni syndrome [3–5]. Genetic analysis of *BRCA* is useful when planning a surgical procedure, systemic treatment, cancer prevention, or surveillance of mutation carriers.

Risk assessment, including genetic counseling and testing for the cancer predisposition genes *BRCA1/2,* has become an integral element of comprehensive patient evaluation and cancer risk management in the United States (US), and Europe. Per the current NCCN recommendations, women diagnosed with breast cancer under age 50 should be referred to cancer genetic counseling for further risk evaluation [3]. Of the over 56,000 newly diagnosed breast cancer female patients occurring annually in Japan, 27 % are women under 50, and 7 % are women

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under 40 [1]. If a woman meets the criteria other than age as described in the guidelines or has a mutation detection rate that exceeds a predefined threshold by risk estimation models such as Claus table, BRCAPRO, Myriad or Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA), it is recommended that she will be informed and offered genetic counseling and information about possible germ line mutation in *BRCA1* and *BRCA2* [6].

Significance of genetic information

Cancer genetic services, including risk assessment, counseling and germ line mutation testing for *BRCA1* and *BRCA2* genes, provide several possible meanings to cancer patients and their family. According to the recent cancer genetic counseling recommendations published by the National Society of Genetic Counselors (NSGC), genetic counseling is defined as the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease [7]. This process integrates: (a) interpretation of family and medical histories to assess the chance of disease occurrence or recurrence; (b) education about inheritance, testing, management, prevention, resources and research; (c) counseling to promote informed choices and adaptation to the risk or condition [7]. Genetic consultation is recommended broadly for breast cancer patients and unaffected women with known risk factors for hereditary breast cancer [8]. The cancer genetic service includes four essential components: collecting information about personal and 3–4 generation family history; cancer genetic risk assessment using the personal and family history, and information from a physical examination; the offer of genetic testing when appropriate conditions apply; an informed consent process, and disclosure of test results, including personalized interpretation of results, cancer risk reassessment, and identification of at-risk family members regardless of whether the test is positive, negative, or inconclusive. Attention to psychosocial issues is also critical for effective genetic counseling [3, 7, 9, 10]. The skills of qualified cancer genetics professionals are necessary to guide patients through complex essential components and to encourage women at high risk to adopt appropriate screening and preventive strategies.

Genetic counseling and testing offered shortly after a breast cancer diagnosis to consider one's treatment choices is called "TFGT" (treatment-focused genetic testing) [11]. TFGT has started to enter clinical practice worldwide, especially in cancer specialized hospitals in the US, and is likely to be a part of common practice in primary breast cancer management, especially for younger women. But the optimal way to deliver information about TFGT to younger women newly diagnosed with breast cancer, and its cost effectiveness has not been broadly investigated, particularly not in Japan.

Women newly diagnosed with breast cancer with a *BRCA* mutation need to choose whether to undergo breast conserving treatment (BCT), unilateral mastectomy, or prophylactic bilateral mastectomies to prevent future breast cancer development [12]. The incidence of local recurrence or secondary ipsilateral primary cancer developing in the treated breast increases in *BRCA* mutation carriers with longer follow-up [12], and it may depend on age. *BRCA1/2* mutation carriers with breast cancer have similar survival whether treated with mastectomy or BCT. However, women undergoing BCT have an elevated risk of a second in-breast event compared to carriers treated with mastectomy: at 10 years (10.5 versus 3.5 %) and at 20 years (30.2 versus 5.5 %). The events were significantly reduced in the presence of chemotherapy, and contralateral breast cancer events were very common in both groups [13]. Compared with non-mutation carriers, *BRCA1/2* mutation carriers have a substantially increased lifetime risk of contralateral breast cancer that is age dependent and can be up to 68 %, if the age of the first cancer is <40 [14, 15]. While there is no evidence that prophylactic mastectomy improves breast cancer survival for *BRCA* mutation carriers [16], the risk of and potential emotional impact of a subsequent breast cancer and the need for further treatment are important issues to consider [12]. Moreover, timely *BRCA* mutation testing extends to selection of specific systemic chemotherapy, once the optimal systemic therapy for *BRCA* mutation carriers is established, including the role of poly (ADP-ribose) polymerase (PARP) inhibitors and platinum-based chemotherapy [17, 18].

The gene expression profiles of sporadic and *BRCA1*-associated tumors are distinct [19] and the pathological profile of *BRCA1*-associated tumors, phenotypically a subset of basal-like tumors, is also distinguishable from other tumor subtypes [20, 21]. Around 80 % of *BRCA1*-related breast cancers are triple-negative breast cancers (TNBCs), which lack the ER, the PR, and amplification of HER2, and women with TNBCs are candidates for *BRCA1* testing. An analysis in Canada demonstrated that it is cost-effective to perform genetic testing in women with TNBCs diagnosed before age 50 [22]. *BRCA1* breast cancers also tend to be high-grade, frequently have p53 mutations, and often stain for the epithelial "basal" cytokeratins 5/6 and 14. In contrast, there are no consistent pathologic features of *BRCA2*-associated breast cancers; like nonhereditary cancers, they are most often ER-positive [23].

In Japan, *BRCA1* and *BRCA2* mutation testing is not covered by national insurance and is very expensive. Also, getting the result of the testing has to date taken around

4 weeks from blood sampling. Soon, further advances in sequencing technology will reduce the cost and the time taken to get the results of genetic analysis [24], and give the opportunity for genetic testing to more women who might benefit from this information at the time of primary cancer treatment. A woman's *BRCA* mutation status can feasibly be used to inform her surgical decisions and choice of systemic therapy agent.

On the other hand, genetic counseling and testing is not time dependent for patients who have undergone breast cancer treatment or for cancer-free individuals considered at high risk of HBOC or familial breast cancer from family history, and focuses more on their own and their family members' future cancer risk, informed life decisions (e.g., reproduction), and proactive steps toward risk-reducing approaches including surgery and cancer surveillance will be discussed [3].

For a woman with a *BRCA1* mutation, the cumulative lifetime risk of breast cancer and ovarian cancer can exceed 80 and 40 %, respectively. [25] In *BRCA* mutation carriers, contra-lateral prophylactic mastectomy is known to decrease their risk of subsequent breast cancer by up to 95 % [26–28]. The prevention role of premenopausal risk-reducing bilateral salpingo-oophorectomy (RRSO) for secondary breast cancer is less well established. Although breast cancer risk reduction of between 39 % (*BRCA1*) and 72 % (*BRCA2*) [29] among mutation carriers who have RRSO before the age of 50 years has been reported, another study did not find a similar reduction in women who had prior breast cancer [28]. Identifying individuals at risk of developing cancer in future can have dramatic effects on early detection and cancer outcomes, which is one reason why genetic counseling and risk assessment are becoming more important. As awareness of genetic testing has increased substantially in the US, the number of "previvors" who opt for prophylactic mastectomies has increased [30]. At the same time, cultural attitudes regarding prophylactic surgery also come into play, as evidenced by the greater popularity of preventative mastectomies in North America than in Europe [31]. Up to now, prophylactic surgery for breast or ovary is not covered by national insurance in Japan and it is not yet a common procedure in clinics.

Perception of genetic services

In the US, the concept of genetic counseling developed early, and in a 1990s study, nearly half of the individuals who reported having at least one relative with breast cancer agreed to participate in genetic counseling when offered that opportunity. The individuals who chose to participate were younger, more highly educated, more anxious about developing breast cancer, and tended to perceive themselves as having a higher risk for breast cancer [32, 33]. In reality, the use of genetic testing for HBOC among high-risk individuals has been lower than expected even in the US, varying between 26 and 80 % [34, 35], and a significant number of those who get tested do not seek their results [36].

Genetic inheritance may be viewed as unchangeable fate and lack of primary prevention techniques negates the value of genetic testing [37]. Women with a family history of breast cancer perceive a higher risk of getting breast cancer [38]. It has been demonstrated that genetic testing may not lead to an increase in psychological distress in breast cancer patients, while a recent breast cancer diagnosis adds to general and cancer-specific distress prior to genetic counseling and after DNA test disclosure [39]. McAllister et al. [40] describe how professional interventions designed to adjust the modifying conditions and to help manage the emotional distress are important. In Japan, Ando et al. [41] have described patients' expressions of concern about their genetic risk of breast cancer prior to a definitive diagnosis of cancer, and in general, family history of breast cancer did not increase psychological distress. Patients with a family history of breast cancer experienced anxiety/worry, risk-reducing behavior, acceptance, objective fact, and denial; whereas patients without a family history of breast cancer experienced anxiety/worry, risk-reducing behavior, surprise/shock, acceptance, objective fact, denial, optimistic thought, regret, and realistic thought [41].

Studies regarding the effects of cancer related genetics on behavior are limited. In an Ontario study, in a high risk population, women believing in annual screening mammograms were associated with better screening adherence than women who believed they should return less often [42]. A randomized trial of the effects of a personalized risk assessment and genetic counseling intervention on knowledge, risk perception, and decision making in a group of healthy women who had a first-degree relative with breast cancer has been reported [43]. Although the counseling intervention did affect both knowledge and risk perception, overall, intervention was not a motivator to undergo any form of preventive systemic therapy.

Genetic information offered to young women soon after breast cancer diagnosis might provide psychological distress at a very susceptible time in their life [44]. There is limited prospectively collected data available on psychosocial implications, which focus on younger women. Several studies have described the behavioral and psychological impact of TFGT, pre-treatment genetic counseling and *BRCA1/2* testing for surgical decision-making among breast cancer patients at high-risk [45–48]. In a US study, 194 patients newly diagnosed with breast

cancer who had at least a 10 % probability of carrying a *BRCA1/2* mutation were offered free genetic testing before initiating definitive treatment, and the impact on surgical decision-making was evaluated. In the study, 28 % of the participants were below age 40, and 86 % of the patients chose to receive *BRCA1/2* test results while 14 % declined. Definitive treatment was defined as mastectomy or BCT, including commencement of radiation treatment [45]. Forty-eight percent of women who were found to carry a *BRCA1* or *BRCA2* mutation opted for bilateral mastectomy (BM), compared to 24 % of patients in whom no mutation was detected and 4 % of test decliners, regardless of age. Other predictors of BM included physician recommendations for *BRCA1/2* testing and BM. Compared to women who chose BCT or unilateral mastectomy, those who chose BM did not report diminished quality of life or increased distress [47].

A Dutch prospective study assessed the psychological impact of TFGT in women diagnosed with breast cancer who were about to begin adjuvant radiotherapy [48]. Patients' distress levels did not increase after genetic counseling and testing. These results demonstrate that *BRCA1/2* test results significantly affect patients' surgical decision-making. In-depth semi-structured interviews with 26 younger women (aged 50 years or less) diagnosed with breast cancer have been reported [11, 49]. All of the participants viewed TFGT as highly acceptable and wanted to receive information about it early, either at diagnosis or shortly thereafter, to inform their treatment options and to assist family members. The availability of genetic counseling and testing could serve as a valuable support to patient decision-making for newly diagnosed breast cancer patients at high risk of carrying a mutation. A randomized controlled trial is currently in progress in Europe to assess the impact of rapid genetic testing and counseling of women newly diagnosed with breast cancer on surgical decision making and psychosocial outcomes [50].

In recent years, knowledge of medical genetics has rapidly spread; over the past few years direct-to-consumer (DTC) personal genome testing has become commercially available, and data shows public interest has increased [51]. It has been demonstrated that predictive genomic risk information obtained from DTC testing modestly influences risk perception and worry [52].

Motivators and barriers to receiving genetic services

Several studies have been published on motivators, facilitators, and/or barriers to patients attending familial/high risk cancer clinics, genetic counseling, and risk assessment, using various populations and recruitment methods [53–58].

A study using questionnaires from 833 women with a family history of breast cancer in the United Kingdom has been reported. Among the reasons identified for attending a familial breast cancer clinic, personal risk was ranked highest, followed by risk to family members, to gain reassurance, and interest in genetic testing [55]. A multicenter study in England surveyed 162 men and women, both affected and unaffected with cancer, who were referred to regional cancer genetics centers. They found clear differences in personal motivation for referral follow-through between those with and those without cancer and found the main motivator for attending a clinic in those with a personal history of cancer was altruistic concern for their family members and children [56]. In a study of 39 adult family members in Australia with a family history of HBOC due to a genetic mutation in *BRCA* genes [53], the top facilitators for cancer genetic referrals were the desire for *BRCA* testing and having a strong family history of breast and/or ovarian cancer. The top barriers were lack of awareness of the *BRCA* mutation in their family and appropriateness of referral. In a US study, which recruited 69 adult women of all ages at risk for HBOC who had received genetic counseling and risk assessment, the top facilitators for receiving genetic counseling and risk assessment were having a family history of breast and/or ovarian cancer and having a personal history of cancer [54].

In young populations, one study looked at the facilitators and barriers to referral for and receipt of genetic counseling and risk assessment in young breast cancer survivors in the US. It was reported that among 289 women diagnosed with breast cancer when under 50 years old, 122 of them (42.2 %) received cancer genetic counseling. The top motivator for receiving services was to benefit their family's future, followed by knowing their own future risk of cancer, and the top reasons for not attending were "no one recommended it" and "medical insurance coverage issues" [59]. There are now an increasing number of young breast cancer patients and survivors, and lack of time due to social or family responsibilities is one of the personal barriers. This population has a unique and complex set of roles such as patient, mother, worker, and caregiver. Also, it is noted that poor communication between relatives from a family with a genetic heritage of breast cancer also contributes to poor uptake of genetic testing [60].

One may speculate that ethnic and racial identity may influence perceived benefits and barriers related to genetic testing. Our understanding about attitudes towards genetic testing of *BRCA* in non-Caucasian populations is largely based on studies done on minority populations in the US, particularly amongst the African-American and Hispanic populations. Pal et al. [57] worked with the Florida state cancer registry to recruit 82 young black breast cancer

survivors for genetic counseling and *BRCA1/2* genetic testing to demonstrate that young black women are interested in participating in genetic studies. In these populations, disparities in uptake of cancer genetic services may be attributable to differences in exposure to genetic information and referral by health care providers, but are not explained by differences in risk factors for carrying a BRCA1/2 mutation, socioeconomic factors, risk perception, attitudes, or cost [61, 62].

There have been a few reports on the acceptance of genetic services in Asian populations. Among 164 Singaporean female breast cancer survivors of all ages, the majority were receptive to cancer genetics counseling and perceived potential benefits. And the top facilitator identified was "the information may help my family understand their cancer risk" [63]. A higher education level and use of English were associated with greater acceptance, while concerns about not understanding the information, cost issues, and fear of bad news, were important barriers. In Malaysia, only 78 % of *BRCA* mutation carrying patients informed their families of their risks and 11 % of relatives asked for the genetic service when offered free counseling and testing [64].

Another important barrier to genetic counseling and risk assessment could be social issues. One might worry that a genetic test may count against oneself. In 2008 in the US, the Genetic Information Non-Discrimination Act (GINA) was passed as a federal law and is currently enforced by various federal agencies [65]. GINA provides protection against discrimination in health coverage and employment on the basis of genetic information. In Japan, such legal protection is strongly recommended to overcome this barrier.

As described above, genetic information involves complex medical and psychological issues and has important ethical, social, economic and legal implications for individuals and their families. The acceptance of genetic testing and genetic counseling and its psychosocial impact are modulated by religious, cultural, social, educational and other factors, but studies of these factors in the client interaction in cancer genetic counseling in Japan have not been deeply analyzed.

The role of a healthcare provider

The role of a healthcare provider has been shown to be a strong facilitator for receiving genetic counseling and risk assessment [53, 59, 63]. In one study in the US, three-quarters of the young breast cancer survivors who were encouraged by the physician to have genetic counseling and risk assessment followed through with this recommendation [59]. On the other hand, the most frequently reported barrier to receiving genetic counseling and risk assessment in young breast cancer survivors was that "no one had ever recommended" genetic counseling and risk assessment. Lack of provider recognition of high risk family history has been identified as an important concern.

Considering the influential role of healthcare providers in motivating patients to receive genetic counseling and risk assessment, there is a need for provider education regarding appropriate indications for cancer genetic referrals. Some studies have demonstrated that referring providers are not able to consistently recognize appropriate referral indications for hereditary breast and ovarian cancer risk assessment and genetic counseling. A recent study of primary physicians in the US showed that while 87 % were aware of *BRCA* genetic testing, only 19 % correctly identified the low and high risk clinical scenarios they were given [9]. A survey of 3,200 physicians in the US found that for high risk women, only 41 % of physicians self-reported recognizing high risk women and adhering to referral recommendations for genetic counseling or testing [10]. One study indicated that family history information was most often completed only on new patients and not routinely updated. The lack of identification of patients at highest risk seems to be directly correlated with insufficient data collection, risk assessment, and documentation by medical staff [66]. Provider understanding and awareness should be improved through promotion of current evidence-based practice guidelines on hereditary breast and ovarian cancer.

In Japan, we conducted a cross-sectional survey in 2010 of Japanese breast cancer specialists ($n = 843$) to self-evaluate their attitude and behavior regarding cancer genetic issues for young breast cancer patients (under 40 years of age) [67]. The survey included questions regarding attitude toward young breast cancer patients, cancer genetic-related practice, potential barriers for the referral of patients to cancer genetic specialists and the responding physicians' socio-demographic background; 52 % of the breast cancer specialists responded to the survey. One quarter of the responding doctors' facilities provide cancer genetic services. Although 36.3 % of the respondents were aware of the potential risk of HBOC and its clinical implications in young breast cancer patients, a total of 13.5 % of the respondents recommended young breast cancer patients to visit cancer genetic specialists. Younger physicians as well as physicians working in a facility with a multi-disciplinary team and cancer genetic services had positive attitudes and behavior regarding referral to cancer genetic specialists. Lack of collaborating cancer genetic specialists and time constraints in the clinic were identified as major barriers to discussion of genetic risk with young breast cancer patients.

Current status of HBOC-related cancer genetic services in Japan

In Japan, the prevalence of *BRCA* mutation for high risk subjects is comparable or even higher than that of non-Ashkenazi populations [68]. In Caucasians, it is reported that up to 27 % of women under the age of 50 diagnosed with TNBC and 36 % of women diagnosed at or under age 40, unselected for family history, are *BRCA1* mutation carriers [69].

Although Japanese breast cancer patients, their families, and physicians have become more aware of hereditary breast cancer, cancer genetic service systems in Japan for familial breast cancer, including HBOC, are far behind compared to those in the US and Europe. In Japanese clinical practice, genetic testing of *BRCA* mutations is limited to research settings or highly specialized centers and only a few dozen hospitals provide a genetic service for *BRCA1* and *BRCA2* mutations. As a result, HBOC-related clinical and translational research is not broadly investigated in Japan, and one of the reasons for this is because the *BRCA1/2* sequence has been patented by a US company, Myriad Genetics, Inc, and genetic testing of *BRCA1/2* germ line mutation is provided by one company (FALCO biosystems) that has a patent license agreement with Myriad Genetics Inc. in our country. The other problem is the insufficiency of human resources for hereditary breast cancer practice. In 2012, there were 140 certified genetic counselors in Japan, but only a few of those were specialists in oncology, and cancer genetics professionals are still seriously lacking. Additionally, genetic testing for *BRCA*, prophylactic procedures such as prophylactic bilateral mastectomy coupled with immediate reconstruction, RRSO, and/or prophylactic systemic treatment are not covered by Japanese national health insurance, so that the issue of the cost lies with the patient or the subject.

In 2011, "Guidelines for Genetic Tests and Diagnoses in Medical Practice" was issued by The Japanese Association of Medical Sciences in Japan. It recommends as follows: for genetic testing for multifactorial disease/genetic predisposition diagnosis, it is necessary to clarify the scientific grounds for the analytical and clinical validity and clinical utility of the tests when they are implemented in clinics. As for HBOC, a Japanese study has confirmed the primary validity of the *BRCA* assay [70]. Recently, nationwide HBOC information in a clinical setting has started to be collected through a Japanese HBOC consortium, and at the same time, the Japanese Ministry has been asked to decide how to fit the assay to the health care system.

Conclusion

The urgent need for development of cancer genetic services with cancer genetics specialists for familial breast cancer should be discussed by health care providers, breast cancer patients, family, high-risk individuals, the Ministry of Health, legislators, and the public in Japan. We also encourage the education of health care providers regarding the potential meaning of genetic counseling and risk assessment for appropriate patients such as young breast cancer patients. Actions and policies to improve use and access to risk assessment, genetic counseling, and genetic testing need to be explored.

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References

1. Center for Cancer Control and Information Services NCC, Japan. Cancer statistics in Japan. http://ganjoho.ncc.go.jp/public/statistics/index.html (cited 1 Jan 2013).
2. Fackenthal JD, Olopade OI. Breast cancer risk associated with BRCA1 and BRCA2 in diverse populations. Nat Rev Cancer. 2007;12:937–48.
3. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Genetic/familial high-risk assessment: breast and ovarian; 2012, http://www.nccn.org/index.asp.
4. Ruddy KJ, Gelber S, Shin J, Garber JE, Rosenberg R, Przypysny M, et al. Genetic testing in young women with breast cancer: results from a web-based survey. Ann Oncol. 2009;21:741–7.
5. US Preventive Services Task Force. Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: recommendation statement. Ann Intern Med. 2005;143:355–61.
6. Antoniou AC, Hardy R, Walker L, Evans DG, Shenton A, Eeles R, et al. Predicting the likelihood of carrying a BRCA1 or BRCA2 mutation: validation of BOADICEA, BRCAPRO, IBIS, Myriad and the Manchester scoring system using data from UK genetics clinics. J Med Genet. 2008;45:425–31.
7. Riley BD, Culver JO, Skrzynia C, Senter LA, Peters JA, Costalas JW, et al. Essential elements of genetic cancer risk assessment, counseling, and testing: updated recommendations of the National Society of Genetic Counselors. J Genet Couns. 2012;21:151–61.
8. Berliner JL, Fay AM, Cummings SA, Burnett B, Tillmanns T. NSGC practice guideline: risk assessment and genetic counseling for hereditary breast and ovarian cancer. J Genet Couns. 2013;22:155–63.
9. Bellcross CA, Kolor K, Goddard KAB, Coates RJ, Reyes M, Khoury MJ. Awareness and utilization of BRCA1/2 testing among U.S. primary care physicians. Am J Prev Med. 2011;40:61–6.
10. Trivers KF, Baldwin LM, Miller JW, Matthews B, Andrilla CH, Lishner DM, et al. Reported referral for genetic counseling or BRCA 1/2 testing among United States physicians: a vignette-based study. Cancer. 2011;117:5334–43.
11. Zilliacus E, Meiser B, Gleeson M, Watts K, Tucker K, Lobb EA, et al. Are we being overly cautious? A qualitative inquiry into the experiences and perceptions of treatment-focused germline BRCA genetic testing amongst women recently diagnosed with breast cancer. Support Care Cancer. 2012;20:2949–58. doi: 10.1007/s00520-012-1427-6.

12. Tung N. Management of women with BRCA mutations: a 41-year-old woman with a BRCA mutation and a recent history of breast cancer. JAMA. 2011;305:2211–20.
13. Pierce LJ, Phillips K-A, Griffith KA, Buys S, Gaffney DK, Moran MS, et al. Local therapy in BRCA1 and BRCA2 mutation carriers with operable breast cancer: comparison of breast conservation and mastectomy. Breast Cancer Res Treat. 2010;121:389–98.
14. Evans DGR, Moran A, Hartley R, Dawson J, Bulman B, Knox F, et al. Long-term outcomes of breast cancer in women aged 30 years or younger, based on family history, pathology and BRCA1/BRCA2/TP53 status. Br J Cancer. 2010;102:1091–8.
15. Metcalfe K, Gershman S, Lynch HT, Ghadirian P, Tung N, Kim-Sing C, et al. Predictors of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. Br J Cancer. 2011;104:1384–92.
16. Heemskerk-Gerritsen B. Is risk-reducing mastectomy in BRCA1/2 mutation carriers with a history of unilateral breast cancer beneficial with respect to distant disease-free survival and overall survival [abstract]? Eur J Cancer. 2010;8:s206.
17. Tutt A, Robson M, Garber JE, Domchek SM, Audeh MW, Weitzel JN, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. Lancet. 2010;376:235–44.
18. Chionh F, Mitchell G, Lindeman GJ, Friedlander M, Scott CL. The role of poly adenosine disphosphate ribose polymerase inhibitors in breast and ovarian cancer: current status and future directions. Asia Pac J Clin Oncol. 2011;7:197–211.
19. Hedenfalk I, Duggan D, Chen Y, Radmacher M, Bittner M, Simon R, et al. Gene-expression profiles in hereditary breast cancer. N Engl J Med. 2001;344:539–48.
20. Armes JE, Trute L, White D, Southey MC, Hammet F, Tesoriero A, et al. Distinct molecular pathogeneses of early-onset breast cancers in BRCA1 and BRCA2 mutation carriers: a population-based study. Cancer Res. 1999;59:2011–7.
21. Livasy CA, Karaca G, Nanda R, Tretiakova MS, Olopade OI, Moore DT, et al. Phenotypic evaluation of the basal-like subtype of invasive breast carcinoma. Mod Pathol. 2006;19:264–71.
22. Kwon JS, Gutierrez-Barrera AM, Young D, Sun CC, Daniels MS, Lu KH, et al. Expanding the criteria for *BRCA* mutation testing in breast cancer survivors. J Clin Oncol. 2010;28:4214–20.
23. Mavaddat N, Barrowdale D, Andrulis IL, Domchek SM, Eccles D, Nevanlinna H, et al. Pathology of breast and ovarian cancers among BRCA1 and BRCA2 mutation carriers: results from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). Cancer Epidemiol Biomarkers Prev. 2012;21:134–47.
24. Klee E, Hoppman-Chaney N, Ferber M. Expanding DNA diagnostic panel testing: is more better? Expert Rev. Mol Diagn. 2011;11:703–9.
25. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol. 2007;25:1329–33.
26. McDonnell SK, Schaid DJ, Myers JL, Grant CS, Donohue JH, Woods JE, et al. Efficacy of contralateral prophylactic mastectomy in women with a personal and family history of breast cancer. J Clin Oncol. 2001;19:3938–43.
27. Herrinton LJ, Barlow WE, Yu O, Geiger AM, Elmore JG, Barton MB, et al. Efficacy of prophylactic mastectomy in women with unilateral breast cancer: a cancer research network project. J Clin Oncol. 2005;23:4275–86.
28. Domchek SM, Friebel TM, Singer CF, Evans DG, Lynch HT, Isaacs C, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA. 2010;304:967–75.
29. Kauff ND, Domchek SM, Friebel TM, Robson ME, Lee J, Garber JE, et al. Risk-reducing oophorectomy for the prevention of BRCA1- and BRCA2-associated breast and gynecologic cancer: a multicenter, prospective study. J Clin Oncol. 2008;26:1331–7.
30. Tuttle TM, Habermann EB, Grund EH, Morris TJ, Virnig BA. Increasing use of contralateral prophylactic mastectomy for breast cancer patients: a trend toward more aggressive surgical treatment. J Clin Oncol. 2007;25:5203–9.
31. Metcalfe KA, Lubinski J, Ghadirian P, Lynch H, Kim-Sing C, Friedman E, Hereditary Breast Cancer Clinical Study Group, et al. Predictors of contralateral prophylactic mastectomy in women with a BRCA1 or BRCA2 mutation: the Hereditary Breast Cancer Clinical Study Group. J Clin Oncol. 2008;26:1093–7.
32. Weitzel JN, Blazer KR, Macdonald DJ, Culver JO, Offit K. Genetics, genomics, and cancer risk assessment: state of the art and future directions in the era of personalized medicine. CA Cancer J Clin. 2011. doi:10.3322/caac.20128.
33. Bowen D, McTiernan A, Burke W, Powers D, Pruski J, Durfy S, et al. Participation in breast cancer risk counseling among women with a family history. Cancer Epidemiol Biomarkers Prev. 1999;8:581–5.
34. Lerman C, Croyle RT, Tercyak KP, Hamann H. Genetic testing: psychological aspects and implications. J Consult Clin Psychol. 2002;70:784–97.
35. Ropka ME, Wenzel J, Phillips EK, Siadaty M, Philbrick JT. Uptake rates for breast cancer genetic testing: a systematic review. Cancer Epidemiol Biomark Prev. 2006;15:840–55.
36. Pasacreta JV. Psychosocial issues associated with genetic testing for breast and ovarian cancer risk: an integrative review. Cancer Invest. 2003;21:588–623.
37. Ryan EL, Skinner CS. Risk beliefs and interest in counseling: focus-group interviews among first-degree relatives of breast cancer patients. J Cancer Educ. 1999;14:99–103.
38. Gil F, Méndez I, Sirgo A, Llort G, Blanco I, Cortés-Funes H. Perception of breast cancer risk and surveillance behaviours of women with family history of breast cancer: a brief report on a Spanish cohort. Psychooncology. 2003;12:821–7.
39. Schlich-Bakker KJ, ten Kroode HF, Ausems MG. A literature review of the psychological impact of genetic testing on breast cancer patients. Patient Educ Couns. 2006;62:13–20.
40. McAllister M, Davies L, Payne K, Nicholls S, Donnai D, MacLeod R. The emotional effects of genetic diseases: implications for clinical genetics. Am J Med Genet A. 2007;143A:2651–61.
41. Ando N, Iwamitsu Y, Kuranami M, Okazaki S, Yamamoto K, Watanabe M, et al. Concerns about inherited risk of breast cancer prior to diagnosis in Japanese patients with breast complaints. Fam Cancer. 2011;10:681–9.
42. Ritvo P, Edwards SA, Glendon G, Mirea L, Knight JA, Andrulis IL, et al. Beliefs about optimal age and screening frequency predict breast screening adherence in a prospective study of female relatives from the Ontario site of the Breast Cancer Family Registry. BMC Public Health. 2012;12:518.
43. Matloff ET, Moyer A, Shannon KM, Niendorf KB, Col NF. Healthy women with a family history of breast cancer: impact of a tailored genetic counseling intervention on risk perception, knowledge, and menopausal therapy decision making. J Womens Health (Larchmt). 2006;15(7):843–56.
44. Ardern-Jones A, Kenen R, Eeles R. Too much too soon? Patients' and health professionals' views concerning the impact of genetic testing at the time of breast cancer diagnosis in women under the age of 40. Eur J Cancer Care. 2005;14:272–81.
45. Schwartz MD, Lerman C, Brogan B, Peshkin BN, Hughes Halbert C, DeMarco T, et al. Impact of BRCA1/2 counseling and testing on newly diagnosed breast cancer patients. J Clin Oncol. 2004;22:1823–9.
46. Schwartz MD, Lerman C, Brogan B, Peshkin BN, Isaacs C, DeMarco T, et al. Utilization of BRCA1/BRCA2 mutation testing in newly diagnosed breast cancer patients. Cancer Epidemiol Biomarkers Prev. 2005;14:1003–7.

47. Tercyak KP, Peshkin BN, Brogan BM, DeMarco T, Pennanen MF, Willey SC, et al. Quality of life after contralateral prophylactic mastectomy in newly diagnosed high-risk breast cancer patients who underwent BRCA1/2 gene testing. J Clin Oncol. 2007;25:285–91.
48. Schlich-Bakker KJ, Wárlám-Rodenhuis CC, van Echtelt J, van den Bout J, Ausems MG, ten Kroode HF. Short-term psychological distress in patients actively approached for genetic counselling after diagnosis of breast cancer. Eur J Cancer. 2006;42:2722–8.
49. Meiser B, Gleeson M, Watts K, Peate M, Zilliacus E, Barlow-Stewart K, et al. Getting to the point: what women newly diagnosed with breast cancer want to know about treatment-focused genetic testing. Oncol Nurs Forum. 2012;39:E101–11.
50. Wevers MR, Ausems MG, Verhoef S, Bleiker EM, Hahn DE, Hogervorst FB, et al. Behavioral and psychosocial effects of rapid genetic counseling and testing in newly diagnosed breast cancer patients: design of a multicenter randomized clinical trial. BMC Cancer. 2011;11:6.
51. McGuire AL, Diaz CM, Wang T, Hilsenbeck SG. Social networkers' attitudes toward direct-to-consumer personal genome testing. Am J Bioeth. 2009;9(6–7):3–10. doi:10.1080/15265160902928209.
52. James KM, Cowl CT, Tilburt JC, Sinicrope PS, Robinson ME, Frimannsdottir KR, et al. Impact of direct-to-consumer predictive genomic testing on risk perception and worry among patients receiving routine care in a preventive health clinic. Mayo Clin Proc. 2011;86:933–40.
53. Wakefield CE, Ratnayake P, Meiser B, Suthers G, Price MA, Duffy J, et al. "For all my family's sake, I should go and find out": an Australian report on genetic counseling and testing uptake in individuals at high risk of breast and/or ovarian cancer. Genet Test Mol Biomarkers. 2011;15:379–85.
54. Morgan D, Sylvester H, Lucas FL, Miesfeldt S. Cancer prevention and screening practices among women at risk for hereditary breast and ovarian cancer after genetic counseling in the community setting. Fam Cancer. 2009;8:277–87.
55. Brain K, Gray J, Norman P, Parsons E, Clarke A, Rogers C, et al. Why do women attend familial breast cancer clinics? J Med Genet. 2000;37:197–202.
56. Fraser L, Bramald S, Chapman C, Chu C, Cornelius V, Douglas F, et al. What motivates interest in attending a familial cancer genetics clinic? Fam Cancer. 2003;2:159–68.
57. Pal T, Rocchio E, Garcia A, Rivers D, Vadaparampil S. Recruitment of black women for a study of inherited breast cancer using a cancer registry-based approach. Genet Test Mol Biomarkers. 2011;15:69–77.
58. Rolnick SJ, Rahm AK, Jackson JM, Nekhlyudov L, Goddard KA, Field T, et al. Barriers in identification and referral to genetic counseling for familial cancer risk: the perspective of genetic service providers. J Genet Couns. 2011;20:314–22.
59. Anderson B, McLosky J, Wasilevich E, Lyon-Callo S, Duquette D, Copeland G. Barriers and facilitators for utilization of genetic counseling and risk assessment services in young female breast cancer survivors. J Cancer Epidemiol. 2012;2012:298745. doi:10.1155/2012/298745.
60. Katapodi MC, Northouse L, Pierce P, Milliron KJ, Liu G, Merajver SD. Differences between women who pursued genetic testing for hereditary breast and ovarian cancer and their at-risk relatives who did not. Oncol Nurs Forum. 2011;38:572–81.
61. Armstrong K, Micco E, Carney A, Stopfer J, Putt M. Racial differences in the use of BRCA1/2 testing among women with a family history of breast or ovarian cancer. JAMA. 2005;293:1729–36.
62. Susswein LR, Skrzynia C, Lange LA, Booker JK, Graham ML 3rd, Evans JP. Increased uptake of BRCA1/2 genetic testing among African American women with a recent diagnosis of breast cancer. J Clin Oncol. 2008;26:32–6.
63. Chin TM, Tan SH, Lim SE, Iau P, Yong WP, Wong SW, et al. Acceptance, motivators, and barriers in attending breast cancer genetic counseling in Asians. Cancer Detect Prev. 2005;29:412–8.
64. Yoon SY, Thong MK, Taib NA, Yip CH, Teo SH. Genetic counseling for patients and families with hereditary breast and ovarian cancer in a developing Asian country: an observational descriptive study. Fam Cancer. 2011;10:199–205.
65. Genetic Information Non-Discrimination Act of 2008. H.R. 493, 110th Cong; 2007–2008.
66. Sweet KM, Bradley TL, Westman JA. Identification and referral of families at high risk for cancer susceptibility. J Clin Oncol. 2002;20(2):528–37.
67. Bando H, Shimizu C, Yamamoto S, Mizota Y, Katou T. Current situation survey on provision of information about hereditary breast cancer by Japanese physician to young breast cancer patients [abstract] J Japan Soc. Clin Oncol. 2011;452:MS1–6.
68. Sugano K, Nakamura S, Ando J, Takayama S, Kamata H, Sekiguchi I, et al. Cross-sectional analysis of germline BRCA1 and BRCA2 mutations in Japanese patients suspected to have hereditary breast/ovarian cancer. Cancer Sci. 2008;99:1967–76.
69. Fostira F, Tsitlaidou M, Papadimitriou C, Pertesi M, Timotheadou E, Stavropoulou AV, et al. Prevalence of BRCA1 mutations among 403 women with triple-negative breast cancer: implications for genetic screening selection criteria: a Hellenic Cooperative Oncology Group Study. Breast Cancer Res Treat. 2012;134:353–62.
70. "Guidelines for Genetic Tests and Diagnoses in Medical Practice" The Japanese Association of Medical Sciences. http://jams.med.or.jp/.

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ORIGINAL ARTICLE

Perception and needs of reproductive specialists with regard to fertility preservation of young breast cancer patients

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Abstract
Background Treatment-related infertility is one of the important quality-of-life issues in young breast cancer (YBC) patients. Although existing guidelines recommend supporting fertility preservation (FP) of YBC, the perceptions of reproductive specialists (RS) has not been evaluated. We investigated the perceptions and needs of RS with regard to FP of YBC patients.
Methods A cross-sectional survey was sent to 423 certified RS registered to the Japan Society for Reproductive Medicine to self-evaluate their perceptions and needs regarding FP in YBC patients.
Results Two hundred RS (47 %) responded to the survey. 99 % responded that RS should be engaged in FP of YBC patients. 88 % responded that they would like to treat YBC patients, while 46 % responded that cancer treatment is more important than childbirth, even when the patient is recurrence-free 5 years after primary treatment. Respondents affiliated to private clinics were more likely to accept both fertilized and unfertilized egg preservation than those affiliated with academic or general hospitals. 70 % responded that they were anxious about treating breast cancer patients: concerns regarding a greater or unknown risk of recurrence (66 %), insufficient knowledge about breast cancer (47 %), and lack of a patient's spouse/partner (24 %) were identified as major barriers in supporting FP for YBC patients.
Conclusions RS recognize the need for FP in YBC patients and are willing to participate in their care. Affiliation of RS was related to a positive attitude to egg preservation. Various concerns regarding FP among RS indicate the need for evidence that supports the safety of FP, inter-disciplinary communication, and practice guidelines.

Keywords Fertility preservation · Breast cancer · Reproductive specialist · Needs

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Introduction

The potential for infertility caused by cancer treatment is one of the important quality-of-life issues in young women with breast cancer [1, 2]. There are several existing guidelines for fertility preservation (FP) and all of the guidelines recommend that fertility issues should be addressed for all patients of reproductive age [3–5]. To help develop a patient-directed FP program for breast cancer patients, the International Society of FP has

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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

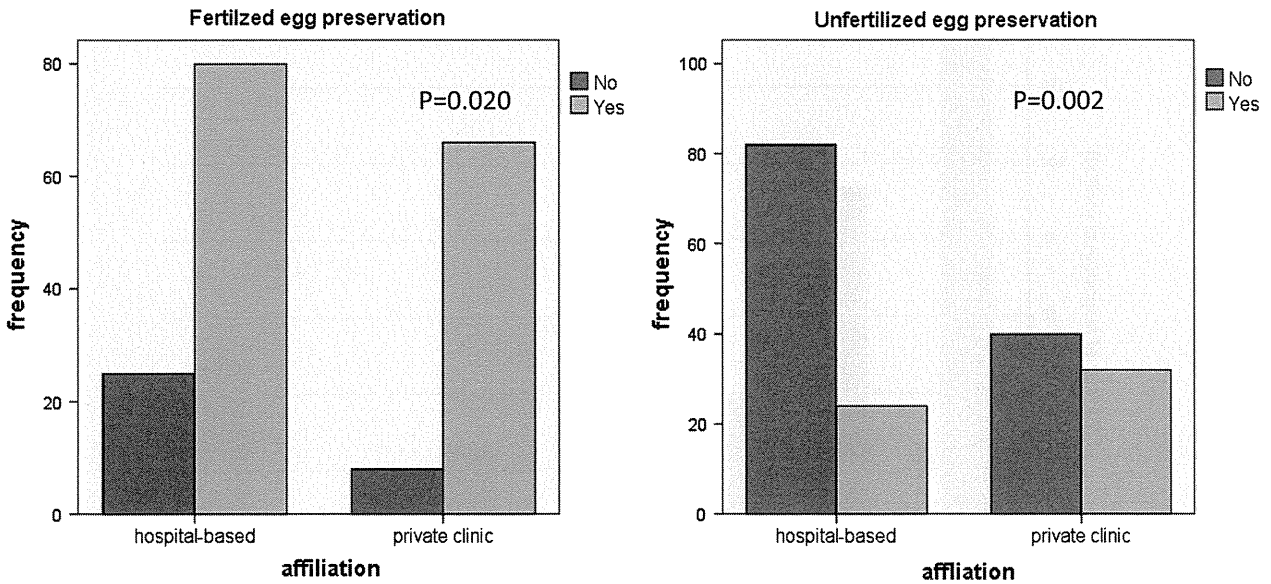
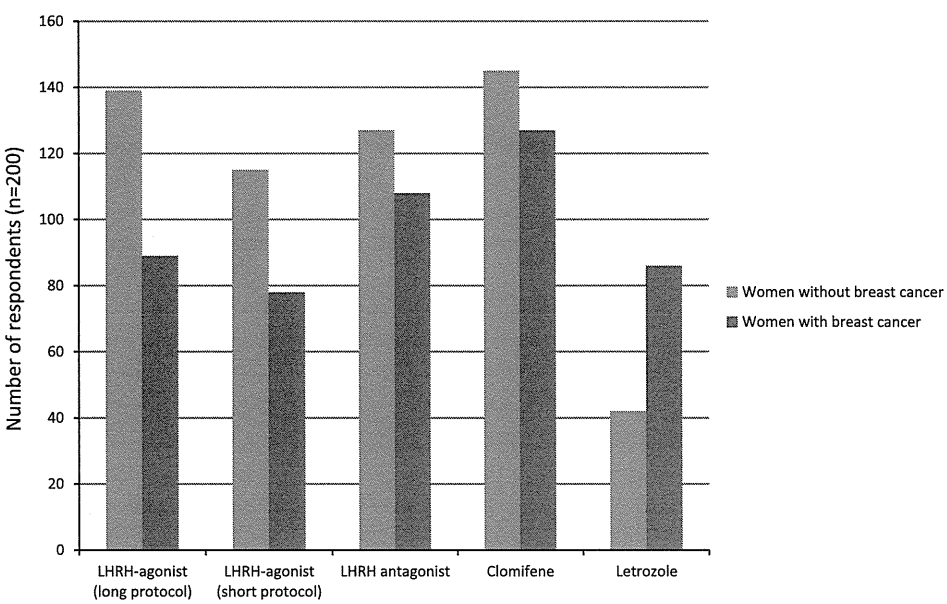


Fig. 1 Acceptance of fertilized and unfertilized egg preservation of YBC patients according to affiliated institution of the respondents

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

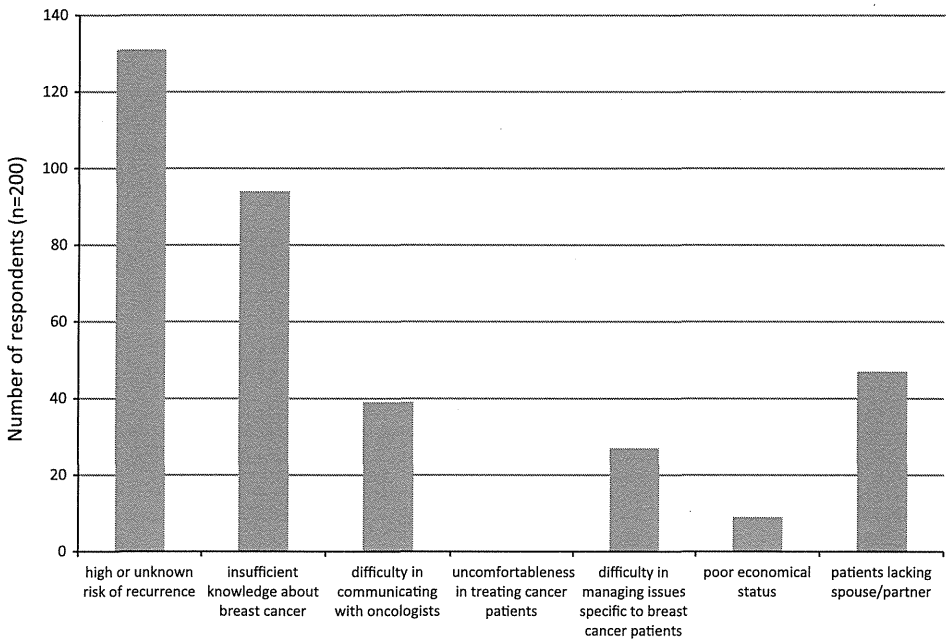


Fig. 3 Barriers to supporting FP in YBC patients. RS were asked to *circle* the barrier that matched their feelings from eight choices. Multiple selections were allowed. The eighth choice was "others" with a space for free text entries provided. The denominator is 200

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.

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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.

References

1. Thewes B, Meiser B, Taylor A et al (2005) Fertility- and menopause-related information needs of younger women with a diagnosis of early breast cancer. J Clin Oncol 23:5155–5165
2. Peate M, Meiser B, Hickey M et al (2009) The fertility-related concerns, needs and preferences of younger women with breast cancer: a systematic review. Breast Cancer Res Treat 116: 215–223
3. Lee SJ, Schover LR, Partridge AH et al (2006) American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol 24:2917–2931
4. ISFP Practice Committee, Kim SS, Donnez J et al (2012) Recommendations for fertility preservation in patients with lymphoma, leukemia, and breast cancer. J Assist Reprod Genet 29: 465–468
5. Von Wolff MV, Montag M, Dittrich R et al (2011) Fertility preservation in women–a practical guide to preservation techniques and therapeutic strategies in breast cancer, Hodgkin's lymphoma and borderline ovarian tumours by the fertility preservation network FertiPROTEKT. Arch Gynecol Obstet 284: 427–435
6. Klemp JR, Kim SS, on behalf of ISFP Practice Committee (2012) Fertility preservation in young women with breast cancer. J Assist Reprod Genet 29:469–472
7. Shimizu C, Bando H, Kato T, Mizota Y, Yamamoto S, Fujiwara Y (2013) Physician's knowledge, attitude and behavior regarding fertility issues for young breast cancer patients: a national survey for breast care specialists. Breast Cancer 20:230–240
8. Quinn GP, Vadaparampil ST, Lee JH et al (2009) Physician referral for fertility preservation in oncology patients: a national study of practice behaviors. J Clin Oncol 27:5952–5957
9. King JW, Davies MC, Roche N et al (2012) Fertility preservation in women undergoing treatment of breast cancer in the UK. Oncologist 17:910–916
10. Valachis A, Tsali L, Pesce LL et al (2011) Safety of pregnancy after primary breast carcinoma in young women: a meta-analysis to overcome bias of healthy mother effect studies. Obstet Gyn Survey 65:786–793
11. Azim HA, Kroman N, Paesmans M et al (2013) Prognostic impact of pregnancy after breast cancer according to estrogen receptor status. J Clin Oncol 31:73–79

12. Azim AA, Costantini-Ferrando M, Oktay K (2008) Safety of fertility preservation by ovarian stimulation with letrozole and gonadotropins in patients with breast cancer: a prospective controlled study. J Clin Oncol 26(16):2630-5
13. Pagani O, Partridge A, Korde L et al (2011) Pregnancy after breast cancer: if you wish, ma'am. Breast Cancer Res Treat 129:309–317
14. The Ethics Committee of the American Society for Reproduction Medicine (2005) Fertility preservation and reproduction in cancer patients. Fertil Steril 83:1622–1628
15. Sha DK, Goldman E, Fisseha S (2011) Medical, ethical and legal consideration in fertility preservation. Int J Gynaecol Obstet 115:11–15
16. Rodriguez S, Campo-Engelstein L, Emanuel L (2013) Fertile future? Potential social implications of oncofertility. J Clin Oncol 31:665–667
17. Gracia CR, Jeruss JS (2013) Lives in the balance: women with cancer and the right to fertility care. J Clin Oncol 31:668–669

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EPIDEMIOLOGY

Impact of recent parity on histopathological tumor features and breast cancer outcome in premenopausal Japanese women

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Abstract Although previous studies have reported that onset at young age is associated with poor prognosis in breast cancer, the correlation between reproductive factors, breast cancer characteristics, and prognosis remains unclear. Five hundred and twenty-six premenopausal young women diagnosed with primary invasive breast cancer between January 2000 and December 2007 were included in this study. Patients were classified into four groups according to their reproductive history: women who gave birth within the previous 2 years (group A), women who gave birth between 3 and 5 years previously (group B), women who gave birth more than 5 years previously (group C), and nulliparous women (group N). The correlation between the time since last childbirth to diagnosis, histopathological tumor features, and breast cancer prognosis was evaluated. Breast cancer patients who had given birth more recently had more advanced stage tumors; larger sized tumors; a higher rate of axillary lymph node metastases; a higher histological tumor grade; and increased progesterone receptor (PgR)−, HER2+, and triple negative tumors than patients who had given birth less recently or not at all. Group A patients had significantly shorter survival times than patients in both groups C and N (log rank test; $p < 0.001$). After adjusting for tumor characteristics, the hazard ratio for death in group A was 2.19 compared with group N ($p = 0.036$), and the adjusted hazard ratio restricted to patients in group A with hormone-receptor-positive, and HER2− tumors was 3.07 ($p = 0.011$). Young breast cancer patients who had given birth more recently had tumors with more aggressive features and worse prognoses compared with patients who had given birth less recently or were nulliparous.

Keywords Reproductive history · Subtype · Prognosis · Breast cancer in young women

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Introduction

Many studies have reported that young breast cancer patients have a poor prognosis [1–4]; however, the value of age as a prognostic factor remains a matter of debate [5]. Epidemiological studies have suggested that endogenous host environments, such as reproductive history, body-mass index, and BRCA germline mutation, may correlate with breast cancer features and prognosis [6–14]. In addition, molecular subtypes are known to be associated with survival [15–17], although the correlation between host environments, including reproductive factors and molecular subtype, remains unclear. Our objective was to explore the impact of host-related factors on the histopathological tumor features and prognosis in breast cancer patients.

Patients and methods

Patients

All premenopausal women of 20–44 years of age diagnosed with primary invasive breast cancer between January 2000 and December 2007 at the National Cancer Center Hospital in Tokyo (526 patients) were included in the present study. Clinical and pathological information was retrieved from medical charts. The follow-up period was completed in December 2011, and the median duration of follow-up was 6.3 years (range: 0.1–11.7 years), during which time 90 patients died. This study protocol was approved by the institutional review board at the National Cancer Center Hospital in Tokyo.

Data collection

Data was collected from various sources, including clinical pathology reports and the patients themselves. A questionnaire was routinely used to assess baseline characteristics at the initial visit for all patients. It included host-related factors, such as body-mass index, smoking history, drinking habits, and family history of breast and/or ovarian cancer in first or second-degree relatives (FH), and menstrual and reproductive factors, such as age at menarche, number of pregnancies, number of children, age at first and last delivery, and duration of breastfeeding. Patients were classified into four groups according to their reproductive history: women who gave birth within the previous 2 years (group A), women who gave birth between 3 and 5 years previously (group B), women who gave birth more than 5 years previously (group C), and nulliparous women (group N). Tumor characteristics, including histopathology; estrogen receptor (ER), progesterone receptor (PgR), and human EGFR-related 2 (HER2) statuses; and histological grade were abstracted from the relevant diagnostic pathology reports. Clinical stage was determined according to the TNM clinical classification from the American Joint Committee on Cancer/The International Union Against Cancer (AJCC/UICC) 6th edition.

Breast cancer subtypes were categorized according to expression of ER, PgR, and HER2 determined by immunohistochemistry. Hormone-receptor positivity was defined as positive staining in more than 1 % of the tumor cell nuclei. HER2 positivity was defined as an immunohistochemistry score of 3+ (intense staining of the cell membrane in more than 30 % of the cancer cells) or an IHC score of 2+ and positive fluorescence in situ hybridization (FISH) HER2 amplification signals. Subtypes were defined as follows: HR+HER2−, ER− or PgR+, and HER2−; HR+HER2+, ER− or PgR+, and HER2+; HR−HER2−, ER, PgR−, and HER2− (triple negative); and HR−HER2+, ER− and PgR−, and HER2+ (HER2-enriched).

Statistical analyses

All statistical analyses were performed using SAS Ver. 9.2 statistical software (SAS Statistic Inc., Cary, NC). All the tests were two-sided, and p values of <0.05 were considered significant. For comparison of patient groups, the Chi squared test was used for discrete data, and the Wilcoxon rank sum test was used for continuous data. Overall survival (OS) was calculated from the first day of breast cancer diagnosis until death from any cause. Survival curves were derived from the Kaplan–Meier product limit estimate method, with the log-rank statistic being used to test for differences between groups. Hazard ratios and 95 % confidence intervals (CI) for death were estimated using Cox proportional hazards survival models, with and without adjusting for one or more of the following factors: age at diagnosis, AJCC stage, hormone receptor and HER2 statuses, and histological tumor grade. To determine any trends between age at diagnosis and time from last childbirth to diagnosis, linear regression was used for continuous data, whereas correlation and ANOVA statistics were used for discrete data.

Results

Patient and tumor characteristics

Clinical characteristics at diagnosis according to each group are presented in Table 1. The median age at diagnosis for all patients was 39 years (range: 22–44 years). No difference in the FH of breast cancer was observed between nulliparous and parous women. Among the 526 women included in this study, 37 women (7 %) were classified into