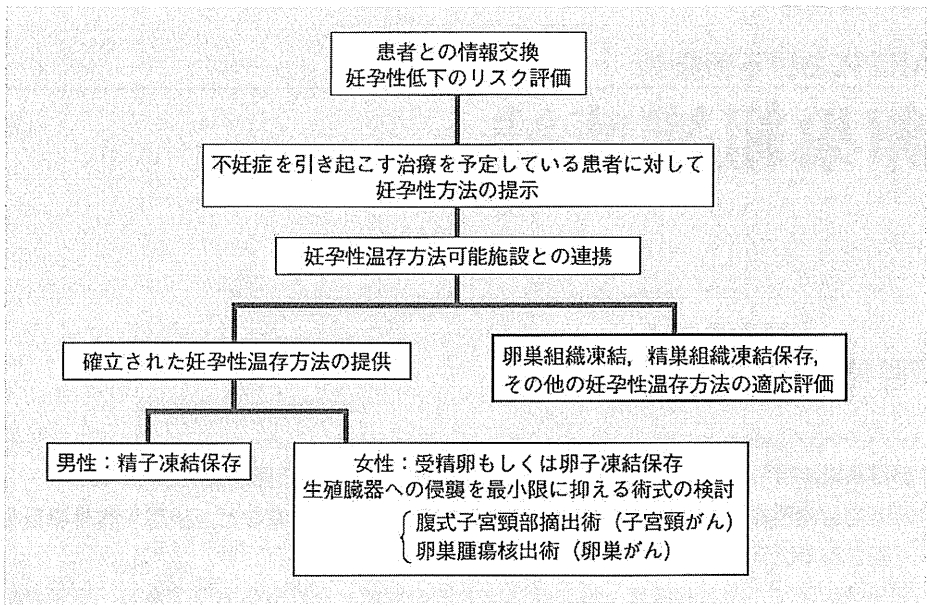

図1　妊孕性温存のアルゴリズム（ASCO 2013）

月経周期に関係なく施行できる，③経腟操作の難しい小児がん患者にも適応できる，④生着卵巣組織からのエストロゲン分泌によるホルモン補充ができるというメリットがあり，妊孕性の温存だけでなく，卵巣欠落症状の改善やエストロゲン低下による心血管系障害の予防や骨密度低下を緩和することができる可能性も有している．

Donnez，Andersen，Pellicer らの3つの研究グループによると，卵巣組織凍結・自家移植はこれまでに60人に施行されており，そのうち73％は化学療法施行前に卵巣が摘出されている．卵巣組織凍結の適応は血液腫瘍疾患が35％，それ以外の悪性腫瘍疾患が45％，Turner 症候群や早発閉経家族歴などの非悪性疾患が20％であった．自家移植後，93％の患者で卵巣機能の回復（卵胞の発育）がみられ，回復が確認できなかった患者の多くは組織学的検査にて残存卵胞が確認できなかったとしている[2]．それ以外にも摘出卵巣組織の処理として，卵巣皮質を薄くしすぎたため不適切だった症例も含まれている．原始卵胞は卵巣皮質表面から約0.8 mm の部位に分布しており，凍結切片を作成する場合は1～1.5 mm の厚さで行われることが勧められる[2]．

表1 にこれまで報告があった24人の出産例について示す．卵巣組織凍結は全例が緩慢凍結法で行われ，同所移植の利点を活かし半数以上は自然妊娠後に出産に至っている．妊娠例の多くは30歳未満であり，卵巣組織凍結時の年齢は結果予測因子となるとしている．17歳で卵巣組織凍結を行った患者は，25歳時に自家移植を行い3年間で3人の児を出産している．また，卵胞が発育し E_2 上昇，FSH 低下に至るまでには3.5～6.5か月（中央値4.5か月）かかり，その時間は化学療法施行前の症例で3.5～4.5か月，施行後の症例で5.5～6.5か月と，化学療法施行前後で差があることから，ホルモン値回復の期間は卵巣摘出時の残存卵胞数に依存すると考えられる[3]．以上より，卵巣摘出時の組織学的検査は重要であり，その結果によって卵巣組織の融解質量や自家移植施行

表1 卵巣組織凍結・自家移植後の妊娠出産報告

参考文献	卵巣組織凍結方法	移植部位	妊娠方法別の出産人数	
			自然妊娠	IVF
Donnez, et al	緩慢凍結法	腹膜孔	1	
	緩慢凍結法	腹膜孔		2
	緩慢凍結法	卵巣髄質	3	
Meirow, et al	緩慢凍結法	卵巣皮質直下		1
Demeestere, et al	緩慢凍結法	卵巣・腹膜孔	2	
Andersen, et al	緩慢凍結法	卵巣皮質	1	1
	緩慢凍結法	卵巣髄質	1	1
Silber, et al	緩慢凍結法	卵巣髄質	2	
Piver, et al	緩慢凍結法	卵巣・腹膜孔	1	
Roux, et al	緩慢凍結法	不明	1	
Sanchez, et al	緩慢凍結法	腹膜孔		2（双胎）
Revel et al	緩慢凍結法	腹膜孔		1
	緩慢凍結法	腹膜孔		1
Dittrich, et al	緩慢凍結法	腹膜孔	1	
Revelli, et al	緩慢凍結法	卵巣髄質	1	
Garcia, et al	緩慢凍結法	腹膜孔		1

表2 移植部位による相違点

	同所性	異所性
長所	もともとの環境に近い 卵胞発育環境として適している 妊娠例の報告がある	移植卵巣容積の制限がない 手技が比較的容易である モニタリング，卵子採取が容易である
短所	移植卵巣容積の制限がある 侵襲的手技を要する	IVFを要する 卵胞発育環境として不適な可能性がある

の是非について検討する必要があると考えられる．

移植部位の検討

卵巣組織片の移植部位として，①残存卵巣を切開したのち組織片を挿入後に縫合・固定する同所性移植法，あるいは②腹膜，腹壁，卵管間膜などへ卵巣組織片を移植する異所性移植法が挙げられ，それぞれの特徴を**表2**に示す．なお，移植された卵巣組織片の再酸素化には通常4〜5日を要し，移植部位の血管新生と血管網の存在が重要であると考えられている[4]．

一般的に残存卵巣が存在する場合は同所性移植が選択される．一方，異所性移植の利点として，①骨盤腔の癒着に影響を受けず侵襲的な処置を避けられる，②卵子獲得が容易である，③費用が抑えられるなどが挙げられる．しかし，皮下などは，温度，組織圧力，内分泌環境そして血液供給の点から，最適な異所性移植部位であるとは考えられていない．しかし，卵巣門近傍の腹膜孔など血流豊富な部位を選択することで，適した環境に近づけることはできるため，症例ごとに適切と思われる移植部位の検討が必要である．

卵巣組織凍結方法の検討

前述のごとく，これまでの生児獲得の報告はすべて緩慢凍結法によるものである．しかしながら，緩慢凍結法は細胞外に形成される氷晶による細胞膜，細胞小器官への物理的障害が予想されることから，融解後の卵胞発育過程における卵母細胞の発育と顆粒膜細胞の成熟のバランスが損なわれていると考えられている．一方，ガラス化法は氷晶形成が比較的少ない卵巣組織の凍結保存方法と考えられており[5]，至適凍結方法の検討として緩慢凍結法とガラス化法を比較した報告が散見される．

Hovattaらのグループ[6]は，ヒト卵巣組織を緩慢凍結法あるいはガラス化法〔プロパンジオール，エチレングリコール（EG)〕で凍結したのち，1～15週間後に融解し，卵子，顆粒膜細胞，間質細胞の形態学的変化を光学顕微鏡，電子顕微鏡を用いて形態学的に評価している．その結果，卵胞に関しては差が認められなかった一方，間質の形態についてはガラス化法で有意に良好であったと報告している．Amoriumら[7]は，ヒト卵巣組織を緩慢凍結法ならびに2種類のガラス化法〔EG＋ジメチルスルホキシド（DMSO)，EG＋DMSO＋ポリビニルピロリドン（PVP）＋スクロース〕により凍結後，ヌードマウスに異種移植し，1週間後にTUNEL法にてヒト前胞状卵胞のアポトーシスを評価している．その結果，卵胞の形態はすべての群で高い確率（約60％）で保たれており差が認められなかったが，TUNEL法による解析の結果，卵胞のアポトーシスはガラス化法で有意に低い傾向が認められた（特にEG＋DMSO＋PVP＋スクロース)．また，サル卵巣組織を緩慢凍結法とガラス化法により凍結・融解後に組織学的評価を行った結果，原始卵胞と1次卵胞においては差が認められなかったものの，2次卵胞，間質細胞はガラス化法のほうが組織学的に良好に保存されたとする報告もある[8]．

ガラス化法の成功率は，凍結保護剤の種類，濃度，曝露時間と，凍結時の冷却の速度ならびに融解時の加温の速度，組織の大きさにより左右されると考えられる．EGは最も一般的に使用されている浸透性の凍結保護剤であり，細胞毒性が低く，浸透も早いとされている．また，非浸透性凍結保護剤であるPVPと糖類（スクロース）などの高分子物質は細胞を効果的に脱水させ，凍結保護剤の曝露時間を減少させ，卵母細胞の生存能力を支えるために不可欠と考えられている．われわれは，ガラス化法の凍結保護剤としてEG＋DMSO，EG＋PVPの2種類混合，ならびに浸漬時間を5，10，20分間としたときの比較を，光学顕微鏡，電子顕微鏡により形態学的に評価した．EG＋DMSOに5分間浸漬した際，正常形態卵胞の比率がほかの群と比べ有意に低く，また前胞状卵胞の正常構造ミトコンドリアの比率も同様に有意に低くなったことから[9]，EG＋

表3 卵巣組織凍結・ガラス化法溶液の組成内容

Hashimoto ら[12] (2010年)	35% EG+5% PVP+0.5M スクロース 平衡時間：5分
Keros ら[6] (2009年)	0.38M EG+0.35M DMSO+0.38M PrOH+PVP 0.75M EG+0.7M DMSO+0.75M PrOH+PVP 1.5M EG+1.4M DMSO+1.5M PrOH+PVP 平衡時間：5分あるいは10分
Amorium ら[7] (2012年)	26% EG+10% DMSO+2.5% PVP+1M スクロース 平衡時間：11分
Ting ら[13] (2013年)	26% EG+25%グリセロール+0.2% PVP+0.2% PVA+0.4% PG 平衡時間：5分

EG：エチレングリコール，PVP：ポリビニルピロリドン，PrOH：プロパンジオール，PVA：ポリビニルアセテート，PG：ポリグリセロール

PVPを用いてカニクイザルを用いた前臨床試験を行い[10]，2010年1月以降臨床応用を開始している．

一方，Sheikhi ら[11]はヒト卵巣組織を，EGのみ，またはEG+プロパンジオール+DMSOの3種類混合の凍結保護剤を用いてガラス化法にて凍結，融解，培養ののち，光学顕微鏡，電子顕微鏡により形態学的に評価し，アポトーシスについては活性化カスパーゼ3の免疫染色にて新鮮組織と凍結組織で比較検討している．形態学的評価では卵子，顆粒膜細胞，間質細胞はどちらの凍結保護剤でも同等に良好であり，原始卵胞，1次卵胞，間質細胞では両群ともにアポトーシスが確認されなかった．生存卵胞数は新鮮組織に比べ凍結組織群は低下したが，生存率は有意に低下せず，凍結方法による差もなかった．

これまでに報告されている主な卵巣組織凍結・ガラス化法の凍結保護剤ならびに浸漬時間を**表3**に示す[12, 13]．現在，至適なプロトコールは決まっておらず，凍結保護剤の組み合わせ，組織片の大きさなど至適凍結方法の確立が必要である．

微少残存病変（minimal residual disease：MRD）

がん治療による完全寛解後の光学顕微鏡で認識できない病変をMRDと呼称し，移植後にがん再発を起こす卵巣組織内のがん細胞混入に関心が集まっており，卵巣組織凍結保存時の疾患の適応は慎重に決定すべきである．近年Dolmans ら[14]は，がん細胞の卵巣転移リスク（MRDのリスク）を疾患ごとに**表4**のごとくまとめている．

白血病では組織所見ならびに免疫組織化学染色でがん細胞が確認されなかった患者の75%で染色体異常がPCR法にて検出されたと報告されており[15]，デンマークの報告[16]では，完全寛解している白血病患者の凍結卵巣組織片に，PCR法によって50%で特異的分子マーカーが陽性であったことから，白血病は卵巣組織凍結の適応外と考えるべき疾患である．白血病においては，完全寛解とは白血病細胞の根絶を意味せず，体内に10億個以下の残存白血病細胞をもっている可能性がある．

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]．

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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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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

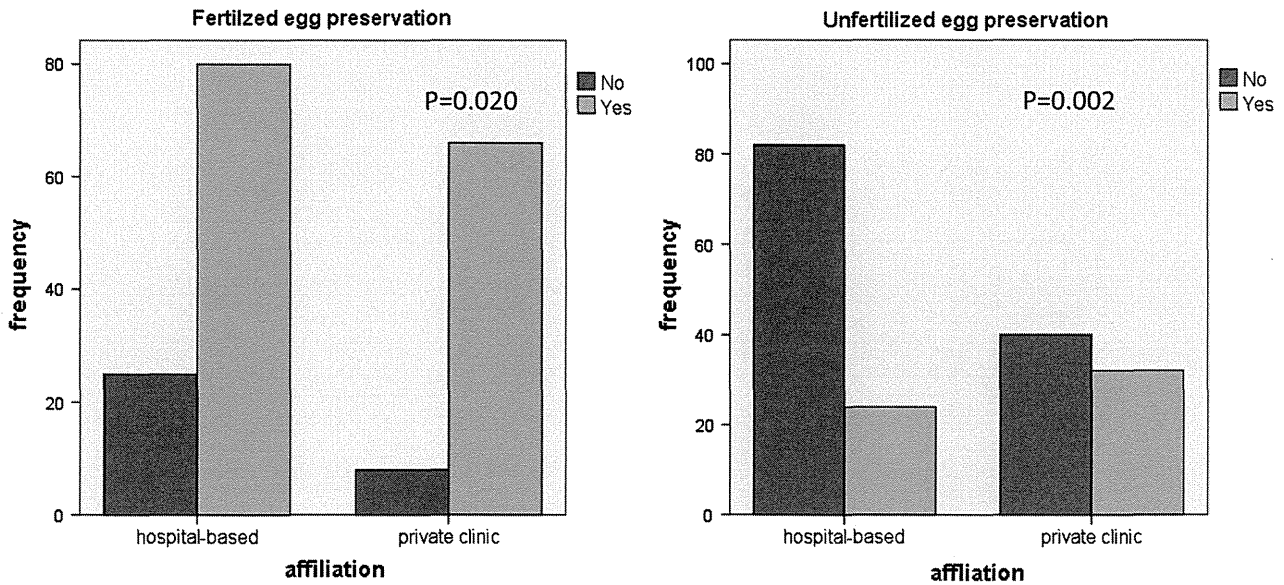
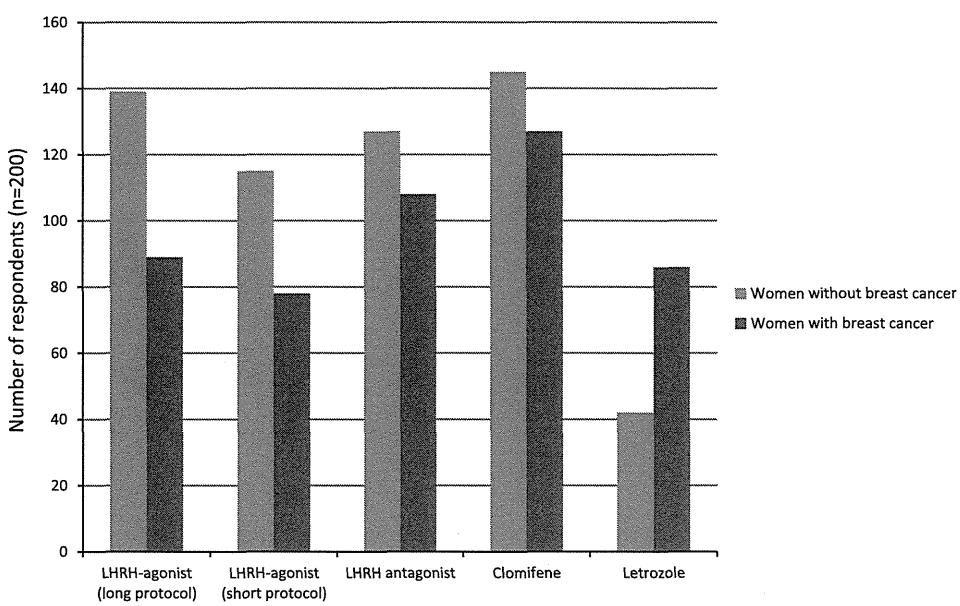


Fig. 1 Acceptance of fertilized and unfertilized egg preservation of YBC patients according to affiliated institution of the respondents

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

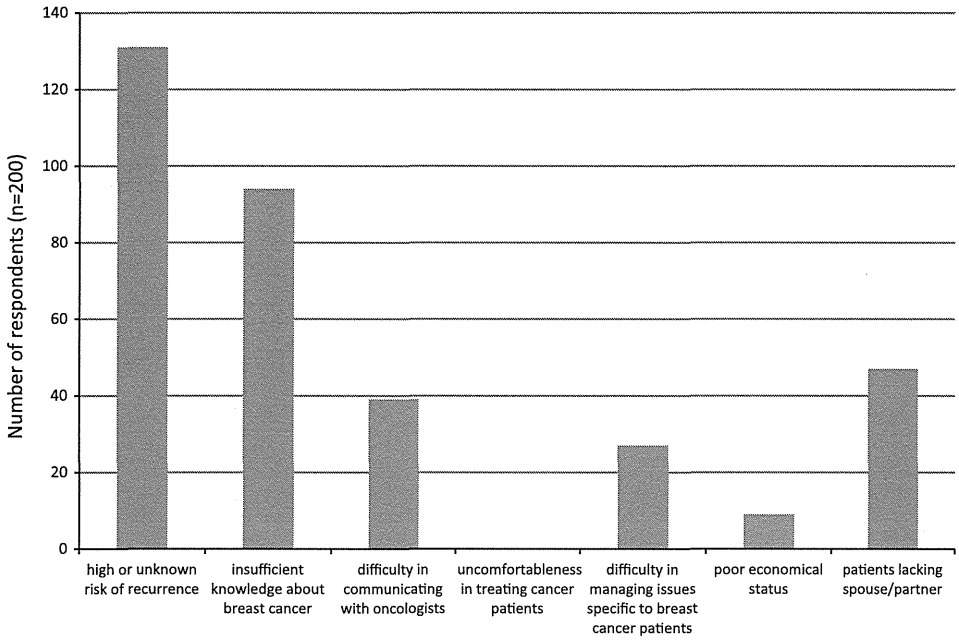


Fig. 3 Barriers to supporting FP in YBC patients. RS were asked to *circle* the barrier that matched their feelings from eight choices. Multiple selections were allowed. The eighth choice was "others" with a space for free text entries provided. The denominator is 200

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.