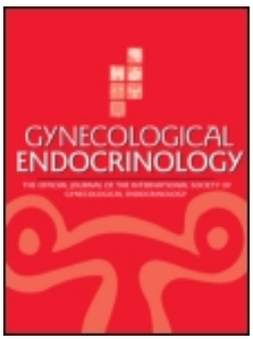

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BREAST CANCER AND FERTILITY

# Attitudes on fertility issues in breast cancer patients: an Italian survey

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**Abstract**

*Background*: Fertility issues should be discussed with young women before the start of any anticancer treatment. The study is aimed to investigate the attitude on fertility among Italian oncologists and breast surgeons dealing with BCa, and to report the consensus achieved on specific statements.

*Methods*: One hundred and sixty-two panelists anonymously expressed an opinion through a web-based platform on 19 statements based on the Delphi method.

*Results*: Ninety-one percent of oncologists considered important to discuss with patients about fertility issues and 83% believed estrogens could stimulate the growth of hidden cancer cells in $ER^+$ tumors. Difficulties in accessing fertility preservation procedures were mainly due to patients' reluctance, but also to lack of coordination with the assisted reproduction specialists. No full consensus was reached on the prognostic role of pregnancy after BCa. Fifty-four percent of oncologists declared that pregnancy does not affect oncologic prognosis. Treatment with GnRHa during chemotherapy was considered the only mean for preserving ovarian function.

*Conclusions*: Fertility preservation in BCa patients is a well-accepted practice among Italian oncologists. A poor knowledge of this specific issue emerged from the survey, even if a certain degree of agreement was observed on most fertility-related issues.

**Keywords**

Breast cancer, fertility preservation, pregnancy after cancer

**History**

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## Introduction

Breast cancer (BCa) is the most common malignant tumor in women, with ~48 000 new cases diagnosed in Italy during 2013 [1]. Survival has been steadily increasing in the last 15 years, with a current 5-year survival of 87%. In 2006, 522 235 women were living in Italy after diagnosis of BCa, representing almost 1% of the whole population [1].

Around 6% of BCa cases occur in women <40 years [2]. These patients face specific issues compared to older women, including an increased risk of recurrence, lower survival and the need of a broader psychosocial support [3]. Issues related to the effects of local and systemic treatments such as the alteration of body image, sexuality complaints and fertility impairment have a higher priority in this young women population [3].

A recently published EUSOMA recommendation states that fertility issues must be discussed before the start of any anticancer treatment and that the optimal technique of fertility preservation, endocrine treatment duration and the effect of subsequent pregnancies on BCa prognosis remain research priorities [4]. Oncologists dealing with BCa may have different attitudes regarding fertility issues in young BCa patients, and few studies have addressed these topics.

The aim of this article is to present results of an online survey conducted through the Delphi technique among Italian oncologists dealing with BCa. Authors developed 19 statements on fertility issues and fertility preservation techniques in young BCa patients and agreement or disagreement on each specific statement is reported.

## Material and methods

### Delphi technique

The essence of Delphi consensus method is to derive quantitative estimates through qualitative assessment of evidence. The technique consists of a series of sequential statements administered to an expert panel to obtain the most reliable consensus. It is an anonymous structured approach, in which information is gathered through a number of rounds. Experts' estimates are aggregated and fed back anonymously to all participants, who then review their initial responses in view of group-wide choices. This practice confers anonymity and allows opinions to be expressed free from peer group pressure. Usually, this technique is used in situations where individual opinions and knowledge are selected, compared and combined in order to address a lack of agreement or a partial knowledge. The Delphi method was applied in accordance with reported literature [5–7].

#### *Referee Opinion Leader group*

On the basis of a systematic review of literature about BCa and fertility issues, a national referee group was invited to define the content of the Delphi statements (two rounds) and to supervise

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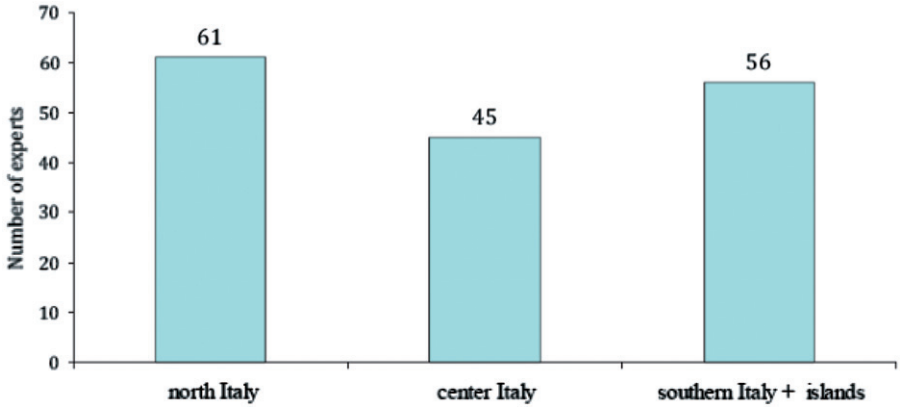


Figure 1. Expert geographic locations (second round expert panel step: $N = 162$).

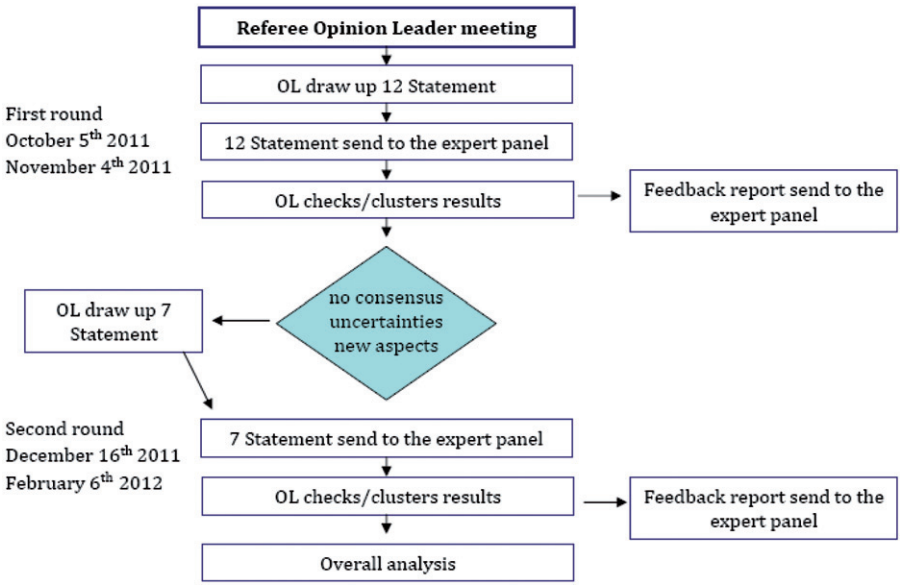


Figure 2. Overview of the Delphi procedures (squares = process steps; rhomboids = decision steps).



and comment the whole process. This group consisted of one gynecologist and two medical oncologists with specific competences in treating young BCa patients and involved in fertility preservation techniques. As members of the referee group, they could not take part into the survey.

### *Expert panel*

Heterogeneity within the expert panel is an important quality criterion. Therefore, oncologists who strictly collaborated with breast surgeons on this specific topic were selected. Furthermore, panelists were representative of all Italian regions, in order to obtain a better picture of the whole national territory (Figure 1). Three hundred and forty and 181 experts for the first and the second round, respectively, were invited to provide their opinion on different issues: reproductive and endocrine aspects of fertility preservation techniques, treatment in fertility preservation, pregnancy and breastfeeding.

### *The Delphi process*

A multi-round process was created by a web platform and was started on October 2011 with the first list of 12 statements. Each statement was formatted allowing to express a different level of consensus (1 = strong disagreement, 2 = moderate disagreement, 3 = agreement with high reservation, 4 = agreement with minor reservation and 5 = strong agreement). A disagreement consensus was declared when $\geq$66% of answers where $1+2$, while an agreement consensus was declared when $\geq$66% of answer where $3+4+5$.

In accordance with the Delphi methodology, after a first list of statements, a second list was generated in order to better clarify some aspects of the questionnaire. A total of 181 participants completed a first statements-list. The second round of statements was sent only to those specialists who actively participated in the first step and was put into the web-based platform on December 2011. The overall Delphi process is represented in Figure 2. The complete statement list is reported in Tables 1–3.

## Results

After proposing the questionnaire to a panel of experts in two rounds, the percentage of adhesion of the first phase was 53%, while the second phase showed 90% adhesion. Approximately 91% of responders considered important to discuss fertility issues and 93% of them stated that they approached this topic even when the patient did not introduce it. More than 60% of panelists referred patients to a team of fertility experts for a targeted counseling (Statement 1).

When answering questions about the most used fertility preservation techniques, 86% of panelists favored the concomitant administration of GnRHa and chemotherapy and 78% of them believed that analogs do not interact with chemotherapy (Statement 2 and 2a).

Table 1. Endocrine and reproductive aspects and procedures to preserve fertility.

| Statement | Options |
|---|---|
| 1. The diagnosis of BCa in young women has become more frequent. In my opinion, is it important to discuss about endocrine and reproductive aspects of adjuvant therapies? | • No<br>• Yes, I discuss these aspects, even if patient don't ask me about<br>• Yes, I discuss these aspects, only when patient ask me about<br>• I invite my patients to contact an expert team |
| 2. In clinical practice, what are the feasible therapeutic options to preserve fertility in young women with BCa? | • Cryopreservation of ovarian tissue<br>• Ovarian stimulation and oocyte cryopreservation<br>• Ovarian stimulation and embryo cryopreservation<br>• GnRHa in association with chemotherapy<br>• Association of ovarian stimulation and oocyte/embryo cryopreservation with GnRHa adjuvant therapy |
| 2a. About the use of medically assisted reproduction program (oocyte, embryo and ovarian tissue cryopreservation) to preserve the fertility in young women affected by BCa: | • In my hospital there is a network/collaboration with a specialized center for medically assisted reproduction<br>• I agree to propose the ovarian stimulation<br>• I'm confident about the real possibility to obtain a pregnancy |
| 3. When could the ovarian stimulation with gonadotropin be performed to retrieve mature oocytes? | • In all patients with $ER^+$ BCa<br>• Only in patients with $ER^-$ BCa<br>• Only choosing ovarian stimulation protocols that avoid an estrogenic peak<br>• Never, because the ovarian stimulation delays the start of chemotherapy<br>• It is not relevant because its use is limited |
| 3a. In my clinical practice, I consider feasible the ovarian stimulation to retrieve mature oocytes in patients with $ER^+$ BCa because | • The ovarian stimulation doesn't influence the prognosis<br>• Protocols that limit the estrogenic peak are currently available<br>• A delay in starting chemotherapy is not relevant |
| 3b. In my clinical practice, I consider feasible the ovarian stimulation to retrieve oocytes in patients with $ER^-$ BCa because | • The ovarian stimulation doesn't influence the prognosis<br>• Protocols that limit the estrogenic peak are currently available<br>• A delay in starting chemotherapy is not relevant |
| 4. In the fertility preservation procedures in patients with BCa, I'm worried about the following disadvantages: | • Estrogen can promote cellular growth of hidden $ER^+$ cancer cells<br>• It is possible a negative interaction between chemotherapy and GnRHa treatment<br>• I don't consider important this observation for the final prognosis<br>• The cost of medically assisted reproduction program<br>• The experimental nature of medically assisted reproduction procedures |
| 5. Which are the factors preventing the access to fertility preservation procedures? | • Few information about these procedures<br>• Lack of coordination between the oncologic center and the medically assisted reproduction center<br>• Complexity for patients to talk about this problem with the oncologist<br>• Disturbance factors such as age, instruction, social status, etc.<br>• Resistance of the oncologist to any type of therapy, that can Induce hormonal stimulation |
| 5a. Which are the factors preventing the access to ovarian stimulation? | • Lack of knowledge about this problem in patients<br>• Worry of patients about the hormonal stimulation required by medically assisted reproduction protocols<br>• Lack of knowledge about this problem among oncologists |



More than 80% of panelists were not in favor of ovarian stimulation and embryo cryopreservation procedures. No clear position was observed on cryopreservation of ovarian tissue (Statement 2). Conflicting opinions were expressed on the ovarian stimulation with gonadotropins to obtain mature oocytes: 37% of oncologists feared a delay in starting chemotherapy and 80% believed that stimulation could be detrimental in both $ER^+$ and $ER^-$ patients. Sixty-five percent of oncologist believed that high estrogen levels during stimulation could impair the prognosis of $ER^+$ patients and 83% feared that estrogens could stimulate the growth of hidden ER+ cancer cells. Thirty-three percent of panelists showed the same reluctance also in $ER^-$ patients. Sixty percent of panelists believed that ovarian stimulation should be performed only with modified protocols that limit circulating estrogen levels (Statement 3, 3a and 3b).

More than 80% of panel members were confident that a successful pregnancy could be obtained after BCa treatment with the support of fertility preservation techniques, but ~50% of them deemed these techniques still experimental (Statement 4). A strong patients' related drawback was pointed out: 65% of oncologists claimed that women were reluctant to talk with their physician about fertility and desire for motherhood. Eighty-seven percent of the panelists thought that scanty information was given to patients. According to 74% of panelists, this was due to patient's young age, low level of education or marital status. Oncologists' attitude and knowledge are far from optimal as well: 93% of them acknowledged having poor insight into the subject; 64% were reluctant to prescribe any treatment involving hormonal stimulation and 90% underscored a lack of coordination between cancer centers and centers for medically assisted reproduction (Statement 5 and 5a).

A general consensus was obtained among panelists about most issues relating to the choice of adjuvant systemic therapy in women who desire to preserve their fertility (Statement 6).

As for chemotherapy, 66% of panelists did not contemplate to choose a different regimen, just to reduce ovarian toxicity. In particular, 68% of panelists did not omit alkylating agents and 83% would not consider shorter regimens. A definite consensus

Table 2. The fertility preservation treatment.

| Statement | Options |
|---|---|
| 6. When I choose the systemic adjuvant treatment in women with BCa and wishing a pregnancy, do I module the treatment and choose medications in order to preserve also the fertility? | • Never<br>• I choose a treatment with reduced ovarian toxicity<br>• I reduce the duration of tamoxifen therapy<br>• I don't use tamoxifen also in patients with $ER^+$ BCa |
| 6a. In my clinical practice, do I module the systemic adjuvant therapy in order to preserve the fertility in women with BCa? | • I choose a chemotherapeutic treatment without alkylating agents<br>• I reduce the duration of chemotherapy<br>• I use a standard chemotherapeutic protocol in association with GnRHa treatment in patients with $ER^+$ BCa<br>• I use a standard chemotherapeutic protocol in association with GnRHa treatment in patients with $ER^-$ BCa |
| 7. Recent meta-analysis studies indicate that the combination of chemotherapy with GnRHa treatment also in patients with $ER^-$ BCa reduces the risk of permanent amenorrhea in comparison to chemotherapy alone | • I never consider this option<br>• I don't think this could be efficient<br>• I usually use this option in young patients (also ER) candidated for chemotherapy<br>• Literature data are not conclusive<br>• I'm not informed and I would like to update |
| 7a. The results from the Cochrane Reviews and the PROMISE study support the notion that the concomitant use of GnRHa treatment and chemotherapy is efficient to reduce the risk of permanent amenorrhea in young patients | • Up to date, data from literature are not conclusive<br>• I will consider this option for young women candidate to chemotherapy<br>• I already use this option to preserve the ovarian function |
| 8. Could a young woman be affected by precocious menopause after adjuvant therapy for BCa? | • I think that this consequence is ineluctable and of little relevance<br>• I show her non-hormonal alternatives for menopausal symptoms<br>• I think that this could be positive, especially for hormone sensitive carcinomas |
| 9. My attitude toward the combination of GnRHa with tamoxifen treatment in patients with $ER^+$ BCa is | • I choose a treatment with reduced ovarian toxicity<br>• I don't propose the combination<br>• I propose the combination for 2 years<br>• I propose the combination for 2 years, eventually prolonged for 5 years<br>• I propose the combination for 5 years<br>• I prescribe the tamoxifen treatment for 5 years and GnRHa until menopause |
| 9a. I choose to prolong the GnRHa treatment for 5 years in combination with tamoxifen | • In young women (35–40 years old)<br>• In women with high risk of recurrence<br>• In women near to physiologic menopause<br>• In absence of pathologies related with precocious menopause (osteoporosis, vaginal dryness) |

Table 3. Pregnancy and breastfeeding.

| Statement | Options |
|---|---|
| 10. May a pregnancy in women previously affected by BCa increase the risk of recurrence? | • Yes, because the elevated circulating estrogen levels during pregnancy may induce cellular growth in hidden cancer cells<br>• Yes, but only if pregnancy occurs within 2 years after surgical intervention<br>• No, it doesn't influence the prognosis<br>• No, the pregnancy is not dangerous for the mother, but it presents an increased incidence of malformation and abortion as a consequence of pharmacologic treatments previously used |
| 11. In young women affected by mutated BRCA BCa and wishing pregnancy | • I discourage any ovarian stimulation procedure to retrieve oocytes<br>• I discourage the cryopreservation of ovarian tissue for the high risk of ovarian carcinoma in this population<br>• I don't see any counter indication<br>• I discourage the pregnancy because of the risk to transmit the mutated gene to babies |
| 12. To a patient previously affected by BCa that wishes to breastfeed | • I discourage to breastfeed because it is contraindicated after chemotherapy<br>• I explain that it is possible the unilateral breast-feeding<br>• I explain that it is not necessary because bottle-feeding is equivalent to breast-feeding<br>• I support as I can this desire |

was obtained also for endocrine therapy: 94% of panelists did not omit tamoxifen and 76% did not shorten tamoxifen duration (Statement 6 and 6a).

Eighty-six percent and 72% of panelists considered the administration of GnRHa during chemotherapy as the only medical strategy available for preserving ovarian function independently of the expression of hormone receptors (Statement 6a).

No definite consensus, however, was obtained on the concomitant administration of GnRHa and chemotherapy in their common clinical practice, although 65% of panelists declared to use it regularly. On the other hand, according to 43% of panelists, scientific evidence about this is not convincing (Statement 7). When panelists were made aware of the PROMISE study [8] and the Cochrane Review [9] results, 90% of them admitted that scientific data were solid enough and the proportion of panelists declaring to regularly use GnRHa in clinical practice rose up to 79%, while 92% would consider to use it (Statement 7a).

As for the safety and feasibility of pregnancy after BCa, conflicting opinions emerged from panelists, without achieving a consensus. Only 54% of oncologists believed that pregnancy does not affect the prognosis of BCa patients, while 49% of them supports that an increase in estrogen levels during pregnancy could stimulate the growth of hidden tumor cells (Statement 10). However, 40% of them expressed that the increased risk of relapse occurs only when pregnancy comes in the first 2 years after diagnosis. Most panelists (60%) disagreed with the statement that a higher percentage of fetal malformations is present in pregnancies occurring after BCa (Statement 10). Many panelists (56 and 57%, respectively) agreed on avoiding hormonal stimulation or cryopreservation of ovarian tissue in BRCA positive BCa patients.

Although consensus was not achieved, 56% of panelists stated that pregnancy in BRCA patients could be harmful, but 62% did not believe that pregnancy should be avoided for the risk of inherited mutated gene (Statement 11).

A full consensus was reached on statements related to breastfeeding after BCa. Most panelists (91%) believed that, when a woman desires to breastfeed her baby, she should be encouraged to do so and supported, and 70% of them regularly informed their patients that unilateral breastfeeding is possible. Only 16% of oncologists discouraged maternal breastfeeding and 46% believed that breastfeeding is not necessary due to the equivalence with bottle feeding (Statement 12).

## Discussion

We have used the Delphi method to investigate the attitudes on fertility issues among Italian oncologists and breast surgeons and to report the consensus achieved on specific statements. This method is anonymous and doesn't allow any discussion or possible direct contact between panellists and referees who analyze and comment on the survey results without interfering with responses and attitudes. The first and second rounds of the survey have a different number of participants because the second list of question was sent only to panellists who participated in the first round.

From our interviews to a representative panel of Italian oncologists expert in BCa treatment, it was clear that they consistently declare their interest in fertility preservation in BCa patients. There was a strong consensus in considering relevant the discussion with patients on fertility preservation issues and in dealing with this topic even when women were not mentioning it.

Inconsistent opinions emerged about specific fertility preservation strategies. Currently, fertility preservation techniques rely on cryopreservation of embryos, cryopreservation of mature oocytes, cryopreservation of ovarian tissue and the concomitant administration of GnRHa and chemotherapy [10]. The first three techniques are part of a medically assisted reproduction programs and require patient's referral to a specialized center. Each of these techniques shows advantages and disadvantages that must be evaluated considering each single case, but all of them must be started before oncologic treatments.

Embryo cryopreservation is a well-established technique but in Italy this procedure is forbidden by the law [11]. Oocyte cryopreservation requires ovarian stimulation, mature oocyte retrieval and subsequent freezing or vitrification. Thawing and intracytoplasmic sperm injection (ICSI) with embryo transfer can be performed years after the procedure. The reluctance to accept ovarian stimulation and oocyte cryopreservation derives from the fear that this procedure might delay the beginning of adjuvant therapy and that the high estrogen levels during the stimulation could promote the growth of hidden cancer cells. The delay is not a major issue because ovarian stimulation takes ~2 weeks and several studies show no difference in terms of survival or recurrence, if chemotherapy is started within 12 weeks after surgery [12]. A further controversy concerning ovarian stimulation is the use of gonadotrophins in $ER^+$ and in $ER^-$ patients.

Panelists agreed that ovarian stimulation does not influence the prognosis in ER- patients, while 65% of panelists believe that it could worsen the prognosis of $ER^+$ patients since estrogens may promote the growth of occult $ER^+$ cancer cells. The levels of serum estradiol (E2) during ovarian stimulation can be 20 times higher than in a natural menstrual cycle. Some authors believe that there is no real risk in having a short-term increase in hormones levels, if chemotherapy is administered shortly after [13]. Recently, ovarian stimulation protocols with aromatase inhibitors have been proposed to avoid high estradiol levels and the recurrence rate of BCa does not seem to be increased [14,15]. Due to the short-term follow-up and the small number of patients, a final statement on the safety of this approach cannot be issued yet. Azim et al. [16] suggest that the use of letrozole and gonadotrophins for controlled ovarian stimulation was unlikely to result in a significant increase in recurrence of BCa. Further research, including longer term follow-ups, is needed to confirm these findings; in the meantime, the use of letrozole-FSH protocol in women with BCa who wish to preserve their fertility by oocyte or embryo cryopreservation is certainly an option [16]. In fact, ovarian stimulation protocols that determine a limited increase in estrogen levels are accepted by the vast majority of panelists.

Ovarian tissue cryopreservation is still an experimental technique but in recent years has achieved interesting results. Ovarian tissue sampling can be carried out at any time of menstrual cycle, without delay in starting therapies, and it may be performed laparoscopically. At an appropriate time, when the patient decides to attempt pregnancy, the orthotopical transplantation has the greatest chances of success [17]. This technique does not require hormonal stimulation and allows the storage of a very large number of follicles.

In our survey, the lack of confidence in the cryopreservation of ovarian tissue derives from the experimental nature of the technique and the small number of pregnancies reported in literature. To date, >30 children have been born worldwide after ovarian tissue cryopreservation [1] and the first live birth in Italy has been reported in February 2012 [18].

Finally, other difficulties emerged from our survey about fertility preservation in Italy. Patients are reluctant to talk about their fertility and desire for motherhood with their doctor. Moreover, they are poorly informed and fear that hormonal stimulation may be harmful to their health. Physicians admit a lack of knowledge on these issues as well. More than 50% of panelists were against any hormonal stimulation and 90% of them underscored a lack of coordination between cancer centers and centers for medically assisted reproduction.

Should the desire of fertility preservation affect the choice of adjuvant systemic therapy? According to panelists participating in this survey, no change in indications both for chemotherapy and endocrine therapy should be taken into account in young patients who plan future pregnancies. In particular, oncologists would not omit alkylating agents and would not shorten the duration of chemotherapy to decrease the risk of ovarian impairment. Also, a sharp consensus was obtained on the modulation of endocrine therapy.

Endocrine therapies do not directly affect ovarian reserve except for the aging of ovaries during treatment. Virtually no oncologist would omit tamoxifen and about three out of four would not shorten the duration of treatment. Indeed, the recently updated results of the ABCSG12 study showed a 5-year disease-free interval of 90% in women receiving the combination of GnRHa + tamoxifen for 3 years [19].

GnRHa have been consistently considered the only medical tool to preserve fertility during the administration of adjuvant chemotherapy. A high proportion of oncologists would prescribe concurrent GnRHa and chemotherapy in both $ER^+$ and $ER^-$ tumors. On the other hand, mixed opinions were expressed by panelists on the soundness of available scientific evidence on the role of GnRHa in the preservation of ovarian reserve. After the first interview 65% of panelists declared they routinely co-prescribe GnRHa and chemotherapy. Nonetheless, about half of them declared that the scientific evidence was not convincing and a similar proportion expressed the need for further information. These opinions reflect the ongoing uncertainty about this issue. Despite the increasing amount of published data, an international consensus on the gonadoprotective role of GnRHa has not been reached and ovarian suppression with GnRHa during chemotherapy as a method to preserve fertility remains a highly controversial topic. The very recently updated clinical practice guidelines for fertility preservation in cancer patients released by ASCO in 2013 conclude that, given the current status of knowledge on this issue, GnRHa is not an effective method for fertility preservation and encourage the inclusion of patients in clinical studies [20]. ESMO recommendations on cancer, pregnancy and fertility draw similar conclusions [21]. The large differences among studies in the definition of amenorrhea and the lack of standardized and reliable markers of residual ovarian reserve contribute to keep this debate open. A recent Cochrain review including only randomized clinical trials showed a positive effect of GnRHa administration on the likelihood of resuming menses [relative risk (RR) 1.90; 95% confidence interval (CI) 1.30–2.79] and concluded that GnRHa should be given before or during chemotherapy in reproductive age women, although no significant difference in pregnancy rates was observed [9]. In the largest published randomized study (PROMISE) which included ~300 patients, ~9% of patients in the GnRHa arm resumed menses or showed FSH levels in the premenopausal range after 1 year versus 26% in the arm treated with chemotherapy alone [8]. On the other hand, the ZORO study failed to show any protective effect of the concurrent administration of goserelin on the rate of amenorrhea at 6 months, anyhow the sample size was much smaller than in the other studies [22]. These studies were provided to the panelists before the second round, as a result, the proportion of panelists who acknowledged that scientific evidence was sound enough rose from 43 to 90%, with >90% declaring that they would consider prescribing GnRH analogs in their clinical practice.

Controversies and different opinions were expressed by panelists on the safety of pregnancy after BCa without reaching consensus. Many of them (54 and 49%) do not feel confident in suggesting pregnancy in BCa patients as they believe that it could promote hidden cancer cells growth and impair prognosis. Many studies have shown that pregnancy does not affect prognosis, both in $ER^+$ and $ER^-$ patients, some even suggest a protective effect of pregnancy [23]. In 2010, a large meta-analysis was published by Azim et al. [24], with data from 14 studies for a total number of 1244 cases and 18 145 controls. Authors showed a better overall survival in women who got pregnant following BCa diagnosis compared to those who did not get pregnant [hazard ratio (HR) 0.59; 95% CI 0.50–0.70] [24]. Authors hypothesized that these results could be weakened by a selection bias, known as the ''healthy mother effect'' phenomenon, but also the sensitivity analysis, performed including only those studies that had BCa controls known to be relapse-free, showed a trend toward improved survival in women who got pregnant (HR 0.85; 95% CI 0.53–1.35) [24]. Consistent results were described by Kranick et al. [25] in the same period.

Recently, this evidence has been confirmed by Azim et al. [26] in another large multicenter study, evaluating the prognostic impact of pregnancy in a subgroup of women with a previous $ER^+$ BCa. A total of 1207 patients were included in the study, 333 women who became pregnant after BCa and 874 controls, who did not became pregnant [27]. No difference in overall event rate was observed between cases and controls (HR 0.84; 95% CI 0.66–1.06; $p = 0.14$). Of note, no difference was observed in either $ER^+$ or $ER^-$ cohorts. Better overall survival rates were reported in the pregnant patients group ($p = 0.03$), independent of ER status ($p = 0.11$). Moreover, in this study breastfeeding and time to pregnancy seemed to have no effect on risk of relapse in women who achieved a term pregnancy [26]. Studies that analyzed the effect of pregnancy in BRCA positive BCa patients came to the same conclusions: pregnancy seems to have a favorable effect on prognosis in BRCA positive population as well [27,28]. Italian oncologists agreed on the importance of breastfeeding in BCa patients who underwent surgery, and on the need to counsel patients about it. Advantages of breastfeeding on babies' health are undisputed but many studies have shown also the positive role of breastfeeding on BCa patients outcome [29,30]. After surgery and radiotherapy the treated breast is usually hypotrophic, produces less or no milk and therefore, it is not possible to breastfeed from it. Unilateral breastfeeding should be encouraged and supported in BCa patients because it is frequently enough for baby's growth. Great importance should be given to breastfeeding counseling and to supporting patients, since misinformation is the main cause for avoiding breastfeeding [31].

## Conclusions

Recently published clinical practice guidelines update by ASCO, reviews >200 new publications from 2006 to 2012 reporting studies results on fertility intervention in cancer patients [20]. This large number of publications underscores the extreme relevance gained by this topic and supports the guidelines recommendation to offer to all young patients a fertility counseling before starting any antineoplastic treatment.

Our survey, administered to a large panel of experts dealing with BCa, confirms that Italian health care providers are aware of this issue but points out they have a limited knowledge on several aspects of it and underscores the practical difficulties oncologists meet when considering referring a patient to a fertility center. Young patients must not be undertreated when expressing a desire of pregnancy, physicians should share with them the updated evidence on the feasibility and safety of pregnancy after cancer and the available options for fertility preservation in order to take a thoroughly informed decision.

## Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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