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ARTICLE

Knowledge, attitudes and practice of physicians towards fertility and pregnancy-related issues in young *BRCA*-mutated breast cancer patients

BIOGRAPHY

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KEY MESSAGE

This survey exploring physicians' perspectives towards fertility and pregnancy-related issues in young *BRCA*-mutated breast cancer patients showed that several misconceptions on these topics persist even among professionals directly involved in breast cancer care. Focused research efforts in *BRCA*-mutated patients and education to improve physicians' adherence to guidelines are needed.

ABSTRACT

Research question: This study explored the knowledge, attitudes and practice of physicians towards fertility and pregnancy-related issues in young *BRCA*-mutated breast cancer patients.

Design: Physicians attending two international breast cancer conferences completed a 26-item questionnaire exploring fertility preservation, pregnancy during (BCP) or after breast cancer. A statistical comparison was carried out of the responses exploring the same issues in young breast cancer patients overall or specifically in those with *BRCA* mutations.

Results: The survey was completed by 273 physicians. Ovarian tissue cryopreservation (33% versus 40%; $P = 0.009$) and gonadotrophin-releasing hormone analogues during chemotherapy (74% versus 81%; $P = 0.001$) were less commonly suggested in *BRCA*-mutated patients than in the overall breast cancer population. 42% of respondents agreed or were neutral on the statement that ovarian stimulation should not be considered safe in *BRCA*-mutated breast cancer patients. 45% and 30% agreed or were neutral on the statement that pregnancy in breast cancer survivors may increase the risk of recurrence in *BRCA*-mutated patients or in the overall breast cancer population, respectively ($P < 0.001$). 15% and 3% disagreed that transplanting the cryopreserved ovarian tissue can be considered safe in *BRCA*-mutated patients or in the overall breast cancer population, respectively ($P < 0.001$). 33.3% were against the addition of platinum agents as neoadjuvant chemotherapy in *BRCA*-mutated patients with BCP.

Conclusions: Several misconceptions on fertility preservation and pregnancy-related issues in breast cancer patients persist even among physicians directly involved in breast cancer care. Focused research efforts to address these issues in *BRCA*-mutated breast cancer patients and education to improve physicians' knowledge and adherence to available guidelines are urgently needed.

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KEYWORDS

BRCA mutations
breast cancer
fertility preservation
physicians
pregnancy
survey

INTRODUCTION

More than 10% of all breast malignancies arising in women diagnosed at ≤40 years of age are expected to be hereditary tumours related to germline deleterious mutations in the breast cancer susceptibility genes *BRCA1* or *BRCA2* (*Copson et al., 2018; Rosenberg et al., 2016*). Carrying a germline deleterious *BRCA* mutation significantly impacts on the management of cancer prevention, diagnosis and treatment (*Paluch-Shimon et al., 2016*). Moreover, there is a biologic rationale supported by preclinical evidence that these mutations can also negatively impact on female reproductive potential (*Lambertini et al., 2017b*). In addition, considering the significant lifetime risk of ovarian cancer (*Kuchenbaecker et al., 2017*), *BRCA* carriers are candidates for prophylactic gynaecological surgery at a young age (*Paluch-Shimon et al., 2016*). Hence, fertility and pregnancy-related issues can be particularly overwhelming in young *BRCA*-mutated breast cancer patients (*Lambertini et al., 2017b*).

In recent years, thanks to the availability of a growing amount of data on these topics, specific guidelines on fertility preservation (*Oktay et al., 2018; Peccatori et al., 2013*), pregnancy following anticancer treatments (*Peccatori et al., 2013*), and management of breast cancer diagnosed during pregnancy (BCP) (*Loibl et al., 2015; Peccatori et al., 2013*) have been developed to help physicians dealing with these important topics. However, limited evidence exists to support the current available recommendations during the counselling of young *BRCA*-mutated breast cancer patients facing fertility- and pregnancy-related issues (*Paluch-Shimon et al., 2016*). Several surveys exploring the reproductive decision-making and attitudes of *BRCA* carriers towards fertility preservation and childbearing habits have raised awareness of the importance to implement the counselling of these women after test disclosure (*Chan et al., 2017; Gietel-Habets et al., 2017; Woodson et al., 2014*). Nevertheless, there is a lack of data on physicians' perspectives and behaviour around these topics in the specific cohort of *BRCA*-mutated breast cancer patients.

We have recently reported the results of a survey conducted among different specialists involved in breast cancer care who participated in two international breast cancer conferences exploring physicians' knowledge, attitudes and practice towards fertility- and pregnancy-related issues in young breast cancer patients (*Lambertini et al., 2018a*). Although the overall picture was positive and encouraging, we observed that adherence to guidelines around these topics remains suboptimal (*Lambertini et al., 2018a*). In the present analysis, we report the questions that explored physicians' knowledge, attitudes and practice towards fertility- and pregnancy-related issues in the specific subgroup of young *BRCA*-mutated breast cancer patients. We postulated a poorer performance of responding physicians in this area than previously observed in the overall breast cancer population (*Lambertini et al., 2018a*), considering the more limited available data to properly counsel *BRCA*-mutated patients in this setting.

MATERIALS AND METHODS

Details of this survey were previously reported (*Lambertini et al., 2018a*). Briefly, this was a 26-item questionnaire investigating fertility- and pregnancy-related issues among physicians who attended the 2016 3rd ESO-ESMO Breast Cancer in Young Women International Conference (BCY3) (*Paluch-Shimon et al., 2017*) and the 15th St Gallen International Breast Cancer Conference 2017 (BCC 2017) (*Curigliano et al., 2017*). Different specialists as well as non-medical personnel and advocates involved in breast cancer care participated in these conferences.

A specific questionnaire was prepared on the basis of prior surveys on these topics (*Adams et al., 2013; Forman et al., 2010; Quinn et al., 2009*) that was then adapted to the BCY3/BCC 2017 context by a team of physicians specifically experienced in this field to also include some unaddressed questions. The survey explored demographic, medical training and background information of responding physicians, as well as their knowledge, attitudes and practice towards fertility preservation, pregnancy after breast cancer and BCP (**Supplementary Appendix**). Ethical approval of this study was not required.

The survey was distributed electronically by email to all BCY3 and BCC 2017 participants but only physicians were allowed to complete it; for those who attended both the BCY3 and BCC 2017 conferences, only one access was allowed.

Study objectives

The objective of the survey was to describe physicians' knowledge, attitudes and practice towards fertility preservation, pregnancy after breast cancer and BCP in young breast cancer patients (*Lambertini et al., 2018a*).

The present analysis focuses on the questions exploring fertility- and pregnancy-related issues in the specific subgroup of *BRCA*-mutated breast cancer patients.

Statistical analysis

Details on sample size calculation were previously reported (*Lambertini et al., 2018a*). The present analysis provides descriptive statistics on physicians' knowledge, attitudes and practice towards fertility preservation, pregnancy after breast cancer and BCP in young *BRCA*-mutated breast cancer patients.

A four-point Likert scale (from 'not at all knowledgeable' to 'very knowledgeable') or a five-point Likert scale (from 'strongly disagree' to 'strongly agree') were used to assess physicians' knowledge, attitudes and practice around these topics. The answers 'strongly agree' and 'agree' as well as 'strongly disagree' and 'disagree' were grouped together when a five-point Likert scale was used to assess physicians' knowledge, attitudes and practice.

The main analysis was conducted by pooling the answers obtained from both the BCY3 and BCC 2017 conferences. An exploratory statistical comparison of the answers obtained individually in the two events was also performed considering the potentially different professional profile of physicians who participated in the two conferences (**Supplementary Appendix**). As previously reported (*Lambertini et al., 2018a*), the scoring system applied in the ESMO guidelines on cancer, pregnancy and fertility (*Peccatori et al., 2013*) was also used to report levels of evidence and grades

of recommendation in the present manuscript (Supplementary TABLE 1).

When the same question explored a specific issue in both breast cancer patients overall and specifically in those with *BRCA* mutations, a formal statistical comparison was conducted to investigate potential differences in the knowledge, attitudes and practice towards these issues in the two populations of breast cancer patients.

The Wilcoxon–Mann–Whitney test was applied to assess differences in participants' age and years of clinical practice, while the chi-squared test was used for exploring differences between the two conferences in categorical variables and answers. The McNemar test for paired proportions was applied for the comparison between the responses in *BRCA*-mutated patients or in the overall breast cancer population.

All tests were two-sided and *P*-values <0.05 were considered statistically significant. SPSS for Windows Version 24.0 was used for all statistical analyses.

RESULTS

At the BCY3 conference, 124 (45.1%) out of 275 participants accessed the survey, of whom 19 were not physicians, leaving 105 completed questionnaires to be included. At the BCC 2017 conference, 210 (7.0%) out of approximately 3000 participants accessed the survey, of whom 20 were not physicians and 22 had previously filled in the BCY3 survey, leaving 168 completed questionnaires to be included. Therefore, all the analyses were conducted with a sample size of 273 responding physicians.

As shown in TABLE 1, the respondents had a median age of 46 years (interquartile range 38–55); more physicians who attended the BCC 2017 conference were older than 50 years as compared with those participating in the BCY3 conference (42.3% versus 23.8%; $P = 0.001$). A total of 57.1% of responding physicians were female, with a higher proportion among physicians attending the BCY3 conference (67.6% versus 50.6%; $P = 0.006$). The majority of respondents came from Western Europe (56.4%), with a higher proportion from America among those who attended the BCC 2017 conference (17.3% versus 6.7%; $P = 0.004$). Most of the responding physicians were medical oncologists (53.8%) working in a dedicated breast unit (81.7%) and in an academic setting (86.1%).

Fertility issues

A similar proportion of responding physicians reported to always or usually suggest the use of embryo cryopreservation (42.9% versus 39.2%; FIGURE 1A) and/or oocyte cryopreservation (62.3% versus 63.3%; FIGURE 1B) as a strategy for fertility preservation in *BRCA*-mutated patients or in the overall breast cancer population, respectively.

On the contrary, significant differences were reported for the other two strategies. Specifically, 32.9% and 40.0% ($P = 0.009$; FIGURE 1C) of respondents reported to always or usually suggest ovarian tissue cryopreservation in *BRCA*-mutated patients or in the overall breast cancer population, respectively. Temporary ovarian suppression with gonadotrophin-releasing hormone analogues (GnRHa) during chemotherapy was the most commonly suggested strategy overall, but with a significantly lower number of responding physicians that reported to always or usually suggest its use in patients with *BRCA*-mutated breast cancer (74.0% versus 81.0%; $P = 0.001$; FIGURE 1D).

No significant difference between the BCY3 and the BCC 2017 participants was observed in the attitudes towards the different strategies (Supplementary TABLE 2).

Overall, 42 (15.4%) respondents suggested that ovarian stimulation for embryo/oocyte cryopreservation should not be considered safe in the specific subgroup of *BRCA*-mutated breast cancer patients, while 73 (26.7%) were neutral and 158 (57.9%) disagreed with this statement; there was no significant difference between the BCY3 and the BCC 2017 participants (Supplementary TABLE 2).

Pregnancy-related issues

Eighty-three (30.4%) and 124 (45.4%) respondents agreed or were neutral on the statement that a pregnancy in breast cancer survivors may increase the risk of recurrence overall and in *BRCA*-mutated breast cancer patients, respectively ($P < 0.001$; FIGURE 2A).

A total of 25 (9.2%) responding physicians were in favour and 69 (25.3%) were neutral towards the statement that a pregnancy in *BRCA*-mutated breast cancer survivors should be discouraged due to the risk of transmitting the mutated gene to the baby. Fourteen (5.1%) and 85 (31.1%) respondents disagreed or were neutral on the statement that information about preimplantation genetic testing (PGT) should be given to these women.

TABLE 2 reports the knowledge, attitudes and practice of physicians towards different aspects of managing breast cancer patients overall or specifically those with *BRCA* mutations having pregnancy desire. No significant differences were observed in terms of number of respondents who agreed about the safety of breastfeeding as well as use of assisted reproductive technology including ovarian stimulation and egg donation in young *BRCA*-mutated survivors or in the overall breast cancer population. On the contrary, a different attitude was observed towards the safety of proceeding to auto-transplantation of the cryopreserved ovarian tissue harvested at the time of cancer diagnosis, with 41 (15.0%) respondents that disagreed about the safety of this approach in *BRCA*-mutated breast cancer survivors as compared with 8 (2.9%) in the overall breast cancer population ($P < 0.001$; FIGURE 2B).

Regarding the management of BCP, 214 (78.4%) responding physicians were in favour of the use of chemotherapy in the second and third trimesters of pregnancy. The only question specifically focused to *BRCA*-mutated patients with BCP investigated the attitude of physicians towards the addition of a platinum agent as neoadjuvant chemotherapy in these women. The majority of respondents (114, 41.8%) were neutral towards this statement, 68 (24.9%) were in favour of its use while 91 (33.3%) were against the addition of these agents.

No significant difference between the BCY3 and the BCC 2017 participants was observed in the attitudes towards pregnancy-related issues in *BRCA*-mutated breast cancer patients (Supplementary TABLE 3).

DISCUSSION

To our knowledge, this is the first survey among physicians with specific interest in breast cancer care to

TABLE 1 DEMOGRAPHIC, MEDICAL TRAINING AND BACKGROUND INFORMATION OF THE RESPONDING PHYSICIANS, OVERALL AND SEPARATELY AT THE BCY3 AND BCC 2017 CONFERENCES

	Responding physicians (*n* = 273)	BCY3 (*n* = 105)	BCC 2017 (*n* = 168)	*P*-value (BCY3 vs BCC 2017)
Age, median (interquartile)	46 (38–55)	43 (38–50)	49 (38–57)	0.01
Age category				
<40	79 (28.9)	32 (30.5)	47 (28.0)	0.001
40–50	93 (34.1)	48 (45.7)	45 (26.8)	
>50	96 (35.2)	25 (23.8)	71 (42.3)	
Missing	5 (1.8)	0 (0.0)	5 (3.0)	
Gender				
Female	156 (57.1)	71 (67.6)	85 (50.6)	0.006
Male	117 (42.9)	34 (32.4)	83 (49.4)	
Country of practice				
Western Europe	154 (56.4)	64 (61.0)	90 (53.6)	0.004
Eastern Europe	29 (10.6)	18 (17.1)	11 (6.5)	
America	36 (13.2)	7 (6.7)	29 (17.3)	
Asia	35 (12.8)	13 (12.4)	22 (13.1)	
Africa	10 (3.7)	3 (2.9)	7 (4.2)	
Oceania	5 (1.8)	0 (0.0)	5 (3.0)	
Missing	4 (1.5)	0 (0.0)	4 (2.4)	
Religion				
Catholic	114 (41.8)	41 (39.0)	73 (43.5)	NS
Protestant	34 (12.4)	9 (8.6)	25 (14.9)	
Muslim	18 (6.6)	9 (8.6)	9 (5.4)	
Jewish	12 (4.4)	4 (3.8)	8 (4.8)	
Hindu	6 (2.2)	4 (3.8)	2 (1.2)	
Atheist/none	61 (22.3)	25 (23.8)	36 (21.4)	
Prefer not to answer	28 (10.3)	13 (12.4)	15 (8.9)	
Children				
Yes	213 (78.0)	82 (78.1)	131 (78.0)	NS
No	60 (22.0)	23 (21.9)	37 (22.0)	
Specialty				
Medical oncology	147 (53.8)	51 (48.6)	96 (57.1)	NS
Surgery	82 (30.0)	32 (30.5)	50 (29.8)	
Gynaecology	26 (9.5)	11 (10.5)	15 (8.9)	
Family physician	2 (0.7)	1 (0.9)	1 (0.6)	
Fertility specialist	1 (0.4)	1 (0.9)	0 (0.0)	
Other (radiologists, radiation oncologists)	15 (5.5)	9 (8.6)	6 (3.6)	
Practice environment				
Public	14 (5.1)	6 (5.7)	8 (4.8)	NS
Private	24 (8.8)	4 (3.8)	20 (11.9)	
Academic	235 (86.1)	95 (90.5)	140 (83.4)	
Years of clinical practice, median (interquartile)	18 (10–26)	17 (11–24)	20 (10–29)	NS
Work in breast cancer unit				
Yes	223 (81.7)	91 (86.7)	132 (78.6)	NS
No	50 (18.3)	14 (13.3)	36 (21.4)	
New young breast cancer patients				
(≤40 years) every year	47 (17.2)	18 (17.1)	29 (17.3)	NS
<10	173 (63.4)	66 (62.9)	107 (63.7)	
10–50	53 (19.4)	21 (20.0)	32 (19.0)	
>50				
Patients with breast cancer treated during				
pregnancy every year	51 (18.7)	21 (20.0)	30 (17.9)	NS
0	188 (68.9)	69 (65.7)	119 (70.8)	
1–5	32 (11.7)	13 (12.4)	19 (11.3)	
6–10	2 (0.7)	2 (1.9)	0 (0.0)	
>10				

Values presented as number (%), unless otherwise stated.

NS = not statistically significant.

explore their knowledge, attitudes and practice towards fertility preservation and pregnancy-related issues in the subgroup of young *BRCA*-mutated breast cancer patients. Overall, our survey showed some peculiarities in physicians' perspectives and behaviour around these topics in *BRCA*-mutated breast cancer patients. These results may reflect both the persistence of several misconceptions on this regard even among physicians directly involved in breast cancer care,

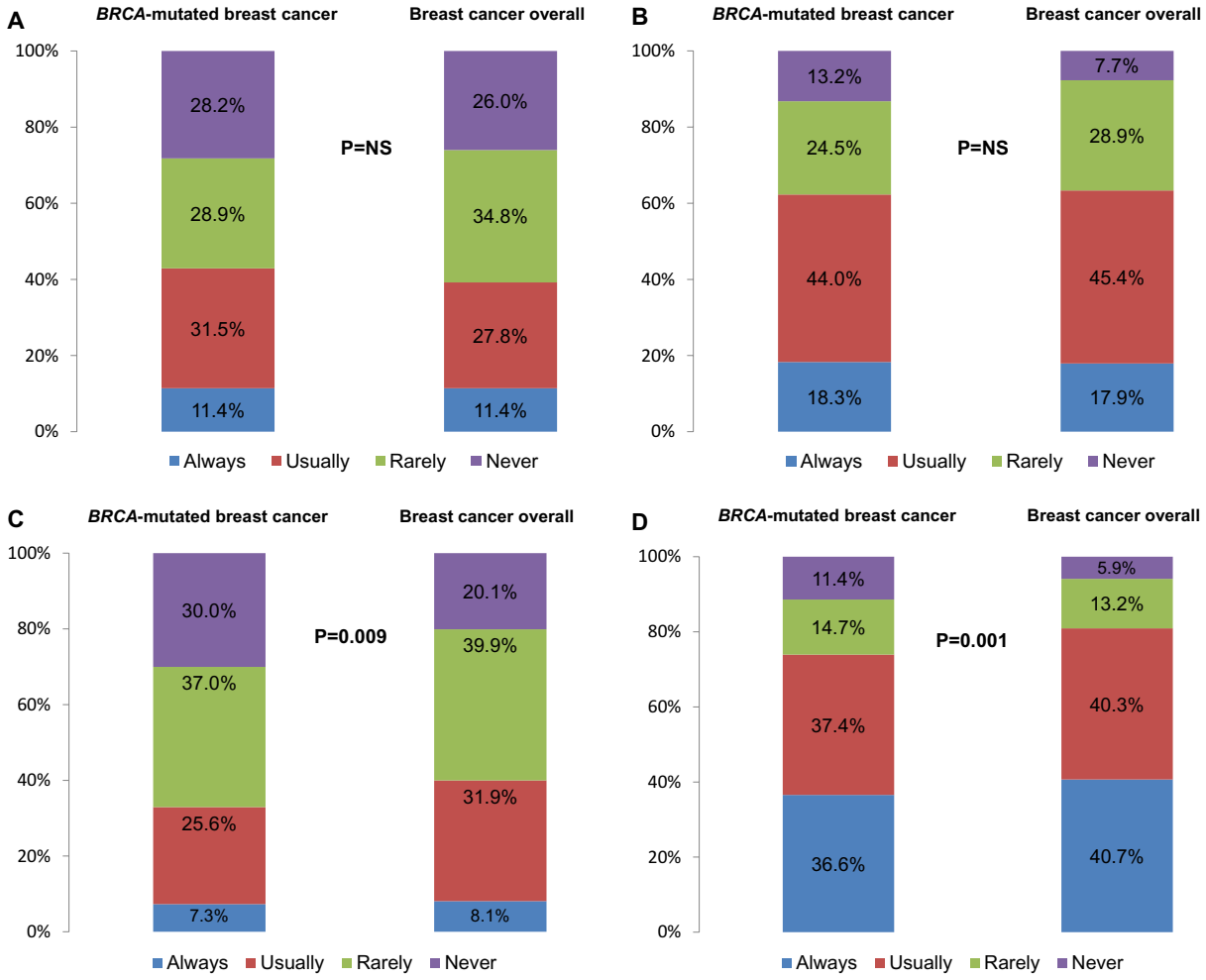

FIGURE 1 Physicians' prescription of the different strategies for fertility preservation in *BRCA*-mutated patients and in the overall breast cancer population: (A) embryo cryopreservation; (B) oocyte cryopreservation; (C) ovarian tissue cryopreservation; (D) temporary ovarian suppression with GnRHa during chemotherapy. GnRHa = gonadotrophin-releasing hormone analogues.

and the limited evidence available on many of these issues to specifically counsel *BRCA*-mutated patients.

According to current guidelines, all women with a new cancer diagnosis during their reproductive years who are concerned about the gonadotoxicity of the proposed anticancer treatments should be offered the available strategies for ovarian function and/or fertility preservation (*Oktay et al., 2018; Paluch-Shimon et al., 2017; Peccatori et al., 2013*). However, notably, the adherence to these guidelines remains suboptimal (*Lambertini et al., 2018a*) and no specific recommendations exist for counselling *BRCA*-mutated breast cancer patients (*Lambertini et al., 2017b*).

Embryo and oocyte cryopreservation are the first strategies to be offered to patients interested in fertility preservation, including *BRCA* carriers (*Oktay et al., 2018; Paluch-Shimon et al., 2017; Peccatori et al., 2013*). No difference in the proportion of physicians suggesting the use of these options in *BRCA*-mutated patients or in the overall breast cancer population was observed but the rates of those who always or usually propose these strategies remained quite low (39–43% for embryo cryopreservation and 62–63% for oocyte cryopreservation). Besides lack of knowledge on embryo and oocyte cryopreservation strategies, these findings may also reflect the still limited efficacy (*Cobo et al., 2018; Massarotti et al., 2017; Oktay et al., 2015*) and safety (*Kim et al., 2016; Lambertini and Fontanella, 2018; Rodriguez-Wallberg et al., 2018*) data available on these strategies in cancer patients and particularly in *BRCA* carriers (*Lambertini et al., 2017b*). Importantly, embryo and oocyte cryopreservation would allow access to PGT. Of note, two of the three studies that have investigated specifically the performance of embryo and oocyte cryopreservation in young breast cancer patients carrying a *BRCA* mutation showed a possible lower response to ovarian response in these women as compared with those without mutations (*Lambertini et al., 2018; Shapira et al., 2015; Turan et al., 2018*). However, the numbers remain too limited to draw conclusions on the need for personalized ovarian stimulation protocols in *BRCA*-mutated patients. From a safety perspective, we observed that 42.1% of the respondents agreed or were neutral on the statement that ovarian stimulation for embryo/oocyte cryopreservation should not be considered safe in the specific subgroup of *BRCA*-mutated breast cancer patients. Nevertheless, the available but limited data on this regard

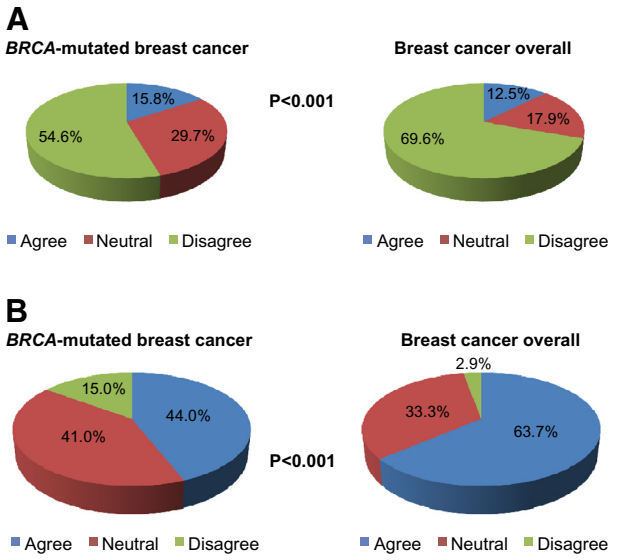

FIGURE 2 Physicians' attitudes towards the statements that (A) a pregnancy in breast cancer survivors may increase the risk of recurrence and (B) that auto-transplantation of cryopreserved ovarian tissue harvested at the time of cancer diagnosis can be considered safe in *BRCA*-mutated patients and in the overall breast cancer population.

do not support these concerns. Among the 47 *BRCA*-mutated breast cancer patients included in the study by Kim and colleagues, no significant difference in relapse-free survival was observed between women who underwent ovarian stimulation and those who did not pursue any fertility-preserving procedure (*Kim et al., 2016*).

A different attitude of physicians was observed towards the use of ovarian tissue cryopreservation and temporary ovarian suppression with GnRHa during chemotherapy, with a significant lower percentage of respondents that replied to always or usually suggest their use in *BRCA*-mutated patients as compared with the overall breast cancer population. These findings may reflect the specific considerations that should be made around these two options in the subgroup of *BRCA*-mutated patients. Despite being still considered an experimental strategy in most of the countries (*Oktay et al., 2018; Paluch-Shimon et al., 2017; Peccatori et al., 2013*), ovarian tissue cryopreservation should now be regarded an option for selected patients including some young women with breast cancer (*Lambertini et al., 2016*), considering the recent availability of a growing amount of data on its efficacy (*Pacheco and Oktay, 2017*). However, only two live births have been described after ovarian tissue transplantation in *BRCA*-mutated breast cancer patients (*Jensen et al., 2017; Lambertini et al., 2018*). Based on recent data reporting the efficacy and safety of this strategy in preserving ovarian function and potential fertility (*Lambertini et al., 2015, 2018c*), temporary ovarian suppression with GnRHa during chemotherapy is now considered an option to be discussed with young breast cancer patients (*Lambertini et al., 2017a; Oktay et al., 2018; Paluch-Shimon et al., 2017*). However, there are no specific data on its performance in *BRCA*-mutated patients. Besides the limited or lack of evidence on these options for *BRCA*-mutated patients, it should be highlighted that both ovarian tissue cryopreservation and temporary ovarian suppression with GnRHa during chemotherapy are not optimal strategies in this setting, particularly among women who are diagnosed close to the recommended age of prophylactic gynaecological surgery (*Lambertini et al., 2017b*). In our survey, a significantly higher number of respondents (up to 15%) considered not safe proceeding to auto-transplantation of the cryopreserved ovarian tissue harvested at the time of cancer diagnosis in *BRCA* carriers as compared with the overall breast cancer population. Importantly, to reduce these concerns when the transplantation procedure is performed in *BRCA*-mutated patients, the ovarian fragments should be transplanted directly into the remaining gonads so that all ovarian tissue can be removed after completing the reproductive plans (*Lambertini et al., 2018*).

Despite a significant proportion of young breast cancer survivors wishing to complete their family plans (*Letourneau et al., 2012; Pagani et al., 2017; Ruddy et al., 2014*), their chances of conceiving remain significantly lower compared with those of the general non-oncologic population (*Anderson et al., 2018; Peccatori et al., 2013*). This can be also partly explained by the safety concerns shared by both patients and their treating physicians on the potential negative prognostic effect of having a pregnancy following breast cancer (*Biglia et al., 2015; Lambertini et al., 2018a; Senkus et al., 2014*). Our survey showed that these concerns are significantly greater towards *BRCA*-mutated breast cancer patients, with up to 45.5% of respondents that agreed or were neutral on the statement that a pregnancy in this setting may increase the risk of recurrence compared with 30.4% when considering breast cancer patients overall. Recently, a growing amount of data have supported the safety of having a pregnancy in breast cancer survivors after adequate treatment and follow-up (*Hartman and Eslick, 2016; Iqbal et al., 2017; Lambertini et al., 2018b, 2019*). However, the evidence about this in the *BRCA*-mutated population relies only on a small retrospective cohort study showing no difference in breast cancer specific mortality among *BRCA*-mutated patients with or without a pregnancy after prior history of breast cancer (*Valentini et al., 2013*). In addition, while limited data are available in the breast cancer population on the safety and feasibility of breastfeeding (*Lambertini et al., 2018b*) and on the use of assisted reproductive technology procedures in breast cancer survivors (*Goldrat et al., 2015*), no specific evidence on this topic exists for *BRCA* carriers. This probably explains the neutral answers of approximately 25–30% of the responding physicians on the statements that investigated these issues in breast cancer patients with a *BRCA* mutation. Additional research efforts, including the ongoing POSITIVE trial (IBCSG 48-14 NCT02308085) (*Pagani et al., 2015*) are needed to provide more definitive answers on the several unanswered issues in this field. Finally, in *BRCA*-mutated breast cancer survivors interested in conceiving, we observed that a high percentage of respondents (36.2%) disagreed or were neutral on the statement that information about PGT should be given to these women. Although the reasons for these findings

TABLE 2 KNOWLEDGE, ATTITUDES AND PRACTICE TOWARDS FERTILITY AND PREGNANCY-RELATED ISSUES IN YOUNG BREAST CANCER PATIENTS OVERALL OR SPECIFICALLY IN THOSE WITH A *BRCA* MUTATION

	Responding physicians (*n* = 273)		*P*-value[a]
	***BRCA*-mutated breast cancer**	**Breast cancer overall**	
Breastfeeding is safe and can be encouraged			
Agree	191 (70.0)	209 (76.6)	NS
Neutral	68 (24.9)	49 (17.9)	
Disagree	14 (5.1)	15 (5.5)	
Despite the limited available data, breastfeeding in breast cancer survivors showed to be feasible without compromising patients' outcomes (*Lambertini M et al., 2018b*). Level of Evidence[b]: IV, C. No specific data in *BRCA*-mutated breast cancer survivors are available on this regard.			
Assisted reproductive technologies can be safely performed in breast cancer survivors			
Agree	164 (60.1)	163 (59.7)	NS
Neutral	86 (31.5)	80 (29.3)	
Disagree	23 (8.4)	30 (11.0)	
Despite the limited available data, the use of assisted reproductive techniques in breast cancer survivors showed to be feasible without compromising patients' outcomes (*Goldrat et al., 2015*). Level of Evidence[b]: V, C. No specific data in *BRCA*-mutated breast cancer survivors are available on this regard.			
Controlled ovarian stimulation can be safely performed also in breast cancer survivors			
Agree	150 (54.9)	157 (57.5)	NS
Neutral	89 (32.6)	80 (29.3)	
Disagree	34 (12.5)	36 (13.2)	
Despite the limited available data, the use of controlled ovarian stimulation in breast cancer survivors showed to be feasible without compromising patients' outcomes (*Goldrat et al., 2015*). Level of Evidence[b]: V, C. No specific data in *BRCA*-mutated breast cancer survivors are available on this regard.			
Egg donation can be safely performed also in breast cancer survivors			
Agree	133 (48.7)	141 (51.6)	NS
Neutral	113 (41.4)	104 (38.1)	
Disagree	27 (9.9)	28 (10.3)	
Despite the limited available data, the use of egg donation in breast cancer survivors showed to be feasible without compromising patients' outcomes (*Goldrat et al., 2015*). Level of Evidence[b]: V, C. No specific data in *BRCA*-mutated breast cancer survivors are available on this regard.			

Values presented as number (%).

NS = not statistically significant.

[a] McNemar test (agree or neutral versus disagree).

[b] Defined as in the ESMO guidelines (Peccatori *et al*., Ann Oncol 2015; Supplementary Table 1).

were not assessed in our survey, recent data suggest that lack of physicians' awareness and knowledge about PGT may represent an important barrier to discuss this option and refer interested patients (*Gietel-Habets et al., 2018*).

Regarding the management of patients with BCP, in recent years several studies have provided evidence on the feasibility and safety of administering chemotherapy during the second and third trimesters of pregnancy (*Amant et al., 2015; Loibl et al., 2012*). In this period, the use of both anthracycline-based chemotherapy and taxanes is allowed by current guidelines (*Loibl et al., 2015; Peccatori et al., 2013*). The use of platinum agents in *BRCA*-mutated breast cancer patients is now considered standard of care in the metastatic setting (*Cardoso et al., 2018*) but remains controversial in the early setting (*Curigliano et al., 2017; Paluch-Shimon et al., 2017*). In fact, while the addition of a platinum agent to anthracycline- and taxane-based chemotherapy was shown to significantly improve the rate of pathological complete response in patients with triple-negative breast cancer, no clear benefit was observed for the cohort of *BRCA* carriers (*Poggio et al., 2018*). Although platinum-based chemotherapy is not contraindicated in pregnant patients (*Loibl et al., 2015; Peccatori et al., 2013*), evidence deriving mainly from the treatment of women with malignancies other than breast cancer suggests an increased risk of small for gestational age with in utero exposure to these agents (*de Haan et al., 2018*). These data, together with the unclear benefit of using platinum-based chemotherapy in the neoadjuvant setting, may explain the high proportion of responding physicians that were neutral (41.8%) or disagreed (33.3%) on the need to include these agents in *BRCA*-mutated patients with BCP.

A few limitations should be considered in the interpretation of our findings, including the low response rate during the BCC 2017 congress. In addition, the target of our survey (i.e. physicians

with specific interest in breast cancer care and thus expected to have higher than average knowledge on these issues and willingness to discuss them) should be highlighted to better interpret the results. Most of the respondents were medical oncologists working in Western Europe, in dedicated breast units and in an academic setting. We did not collect information on the knowledge, attitudes and practice towards these issues of nursing staff, patients or caregivers. However, this was indeed the main intent of our study, focused to a selected population of physicians. This allowed an even better interpretation of the challenges and the needs for further education required for managing fertility and pregnancy-related issues in young breast cancer patients.

In conclusion, results from the BCY3/BCC 2017 survey on fertility preservation and pregnancy-related issues in the specific subgroup of young *BRCA*-mutated breast cancer patients highlight the presence of several misconceptions on these topics that persist even among physicians directly involved in breast cancer care. These findings also underscore the lack of evidence on many of these issues to properly counsel young *BRCA*-mutated breast cancer patients. Education to improve physicians' knowledge and adherence to available guidelines as well as focused research efforts to address the several existing grey zones in the field are urgently needed to improve the oncofertility counselling of young *BRCA*-mutated breast cancer patients.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.rbmo.2018.11.031.

REFERENCES

Adams, E., Hill, E., Watson, E. **Fertility preservation in cancer survivors: a national survey of oncologists' current knowledge, practice and attitudes.** Br. J. Cancer 2013; 108: 1602–1615. https://doi.org/10.1038/bjc.2013.139

Amant, F., Vandenbroucke, T., Verheecke, M., Fumagalli, M., Halaska, M.J., Boere, I., Han, S., Gziri, M.M., Peccatori, F., Rob, L., Lok, C., Witteveen, P., Voigt, J.-U., Naulaers, G., Vallaeys, L., Van den Heuvel, F., Lagae, L., Mertens, L., Claes, L., Van Calsteren, K. **International Network on Cancer, Infertility, and Pregnancy (INCIP). Pediatric Outcome after Maternal Cancer Diagnosed during Pregnancy.** N. Engl. J. Med. 2015; 373: 1824–1834. https://doi.org/10.1056/NEJMoa1508913

Anderson, R.A., Brewster, D.H., Wood, R., Nowell, S., Fischbacher, C., Kelsey, T.W., Wallace, W.H.B. **The impact of cancer on subsequent chance of pregnancy: a population-based analysis.** Hum. Reprod. 2018; 33: 1281–1290. https://doi.org/10.1093/humrep/dey216

Biglia, N., Torrisi, R., D'Alonzo, M., Codacci Pisanelli, G., Rota, S., Peccatori, F.A. **Attitudes on fertility issues in breast cancer patients: an Italian survey.** Gynecol. Endocrinol. 2015; 31: 458–464. https://doi.org/10.3109/09513590.2014.1003293

Cardoso, F., Senkus, E., Costa, A., Papadopoulos, E., Aapro, M., André, F., Harbeck, N., Aguilar Lopez, B., Barrios, C.H., Bergh, J., Biganzoli, L., Boers-Doets, C.B., Cardoso, M.J., Carey, L.A., Cortés, J., Curigliano, G., Diéras, V., El Saghir, N.S., Eniu, A., Fallowfield, L., Francis, P.A., Gelmon, K., Johnston, S.R.D., Kaufman, B., Koppikar, S., Krop, I.E., Mayer, M., Nakigudde, G., Offersen, B.V., Ohno, S., Pagani, O., Paluch-Shimon, S., Penault-Llorca, F., Prat, A., Rugo, H.S., Sledge, G.W., Spence, D., Thomssen, C., Vorobiof, D.A., Xu, B., Norton, L., Winer, E.P. **4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)†.** Ann. Oncol. 2018; 29: 1634–1657. https://doi.org/10.1093/annonc/mdy192

Chan, J.L., Johnson, L.N.C., Sammel, M.D., DiGiovanni, L., Voong, C., Domchek, S.M., Gracia, C.R. **Reproductive Decision-Making in Women with BRCA1/2 Mutations.** J. Genet. Couns. 2017; 26: 594–603. https://doi.org/10.1007/s10897-016-0035-x

Cobo, A., García-Velasco, J., Domingo, J., Pellicer, A., Remohí, J. **Elective and Onco-fertility preservation: factors related to IVF outcomes.** Hum Reprod. 2018; 33: 2222–2231. https://doi.org/10.1093/humrep/dey321

Copson, E.R., Maishman, T.C., Tapper, W.J., Cutress, R.I., Greville-Heygate, S., Altman, D.G., Eccles, B., Gerty, S., Durcan, L.T., Jones, L., Evans, D.G., Thompson, A.M., Pharoah, P., Easton, D.F., Dunning, A.M., Hanby, A., Lakhani, S., Eeles, R., Gilbert, F.J., Hamed, H., Hodgson, S., Simmonds, P., Stanton, L., Eccles, D.M. **Germline BRCA mutation and outcome in young-onset breast cancer (POSH): a prospective cohort study.** Lancet. Oncol. 2018; 19: 169–180. https://doi.org/10.1016/S1470-2045(17)30891-4

Curigliano, G., Burstein, H.J., P Winer, E., Gnant, M., Dubsky, P., Loibl, S., Colleoni, M., Regan, M.M., Piccart-Gebhart, M., Senn, H.-J., Thürlimann, B. **St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2017.**, André, F., Baselga, J., Bergh, J., Bonnefoi, H., Y Brucker, S., Cardoso, F., Carey, L., Ciruelos, E., Cuzick, J., Denkert, C., Di Leo, A., Ejlertsen, B., Francis, P., Galimberti, V., Garber, J., Gulluoglu, B., Goodwin, P., Harbeck, N., Hayes, D.F., Huang, C.-S., Huober, J., Hussein, K., Jassem, J., Jiang, Z., Karlsson, P., Morrow, M., Orecchia, R., Osborne, K.C., Pagani, O., Partridge, A.H., Pritchard, K., Ro, J., Rutgers, E.J.T., Sedlmayer, F., Semiglazov, V., Shao, Z., Smith, I., Toi, M., Tutt, A., Viale, G., Watanabe, T., Whelan, T.J., Xu, B. **De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017.** Ann. Oncol. 2017; 28: 1700–1712. https://doi.org/10.1093/annonc/mdx308

de Haan, J., Verheecke, M., Van Calsteren, K., Van Calster, B., Shmakov, R.G., Mhallem Gziri, M., Halaska, M.J., Fruscio, R., Lok, C.A.R., Boere, I.A., Zola, P., Ottevanger, P.B., de Groot, C.J.M., Peccatori, F.A., Dahl Steffensen, K., Cardonick, E.H., Polushkina, E., Rob, L., Ceppi, L., Sukhikh, G.T., Han, S.N., Amant, F. **International Network on Cancer and Infertility Pregnancy (INCIP). Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients.** Lancet Oncol. 2018; 19: 337–346. https://doi.org/10.1016/S1470-2045(18)30059-7

Forman, E.J., Anders, C.K., Behera, M.A. **A nationwide survey of oncologists regarding treatment-related infertility and fertility preservation in female cancer patients.** Fertil. Steril. 2010; 94: 1652–1656. https://doi.org/10.1016/j.fertnstert.2009.10.008

Gietel-Habets, J.J.G., de Die-Smulders, C.E.M., Derks-Smeets, I.a.P., Tibben, A., Tjan-Heijnen, V.C.G., van Golde, R., Gomez-Garcia, E., Kets, C.M., van Osch, L.a.D.M. **Awareness and attitude regarding reproductive options of persons carrying a BRCA mutation and their partners.** Hum. Reprod. 2017; 32: 588–597. https://doi.org/10.1093/humrep/dew352

Gietel-Habets, J.J.G., de Die-Smulders, C.E.M., Tjan-Heijnen, V.C.G., Derks-Smeets, I.a.P., van Golde, R., Gomez-Garcia, E., van Osch, L.a.D.M. **Professionals' knowledge, attitude and referral behaviour of preimplantation genetic diagnosis for hereditary breast and ovarian cancer.** Reprod. Biomed. Online. 2018; 36: 137–144. https://doi.org/10.1016/j.rbmo.2017.11.005

Goldrat, O., Kroman, N., Peccatori, F.A., Cordoba, O., Pistilli, B., Lidegaard, O., Demeestere, I., Azim, H.A. **Pregnancy following breast cancer using assisted reproduction and its effect on long-term outcome.** Eur. J. Cancer. 2015; 51: 1490–1496. https://doi.org/10.1016/j.ejca.2015.05.007

Hartman, E.K., Eslick, G.D. **The prognosis of women diagnosed with breast cancer before, during and after pregnancy: a meta-analysis.** Breast. Cancer. Res. Treat. 2016; 160: 347–360. https://doi.org/10.1007/s10549-016-3989-3

Iqbal, J., Amir, E., Rochon, P.A., Giannakeas, V., Sun, P., Narod, S.A. **Association of the Timing of Pregnancy with Survival in Women With Breast Cancer.** JAMA. Oncol.

2017; 3: 659–665. https://doi.org/10.1001/jamaoncol.2017.0248

Jensen, A.K., Macklon, K.T., Fedder, J., Ernst, E., Humaidan, P., Andersen, C.Y. **86 successful births and 9 ongoing pregnancies worldwide in women transplanted with frozen-thawed ovarian tissue: focus on birth and perinatal outcome in 40 of these children.** J. Assist. Reprod. Genet. 2017; 34: 325–336. https://doi.org/10.1007/s10815–016–0843–9

Kim, J., Turan, V., Oktay, K. **Long-Term Safety of Letrozole and Gonadotrophin Stimulation for Fertility Preservation in Women with Breast Cancer.** J. Clin. Endocrinol. Metab. 2016; 101: 1364–1371. https://doi.org/10.1210/jc.2015–3878

Kuchenbaecker, K.B., Hopper, J.L., Barnes, D.R., Phillips, K.-A., Mooij, T.M., Roos-Blom, M.-J., Jervis, S., van Leeuwen, F.E., Milne, R.L., Andrieu, N., Goldgar, D.E., Terry, M.B., Rookus, M.A., Easton, D.F., Antoniou, A.C. **BRCA1 and BRCA2 Cohort Consortium, null.**, McGuffog, L., Evans, D.G., Barrowdale, D., Frost, D., Adlard, J., Ong, K.-R., Izatt, L., Tischkowitz, M., Eeles, R., Davidson, R., Hodgson, S., Ellis, S., Nogues, C., Lasset, C., Stoppa-Lyonnet, D., Fricker, J.-P., Faivre, L., Berthet, P., Hooning, M.J., van der Kolk, L.E., Kets, C.M., Adank, M.A., John, E.M., Chung, W.K., Andrulis, I.L., Southey, M., Daly, M.B., Buys, S.S., Osorio, A., Engel, C., Kast, K., Schmutzler, R.K., Caldes, T., Jakubowska, A., Simard, J., Friedlander, M.L., McLachlan, S.-A., Machackova, E., Foretova, L., Tan, Y.Y., Singer, C.F., Olah, E., Gerdes, A.-M., Arver, B., Olsson, H. **Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers.** JAMA 2017; 317: 2402–2416. https://doi.org/10.1001/jama.2017.7112

Lambertini, M., Ceppi, M., Poggio, F., Peccatori, F.A., Azim, H.A., Ugolini, D., Pronzato, P., Loibl, S., Moore, H.C.F., Partridge, A.H., Bruzzi, P., Del Mastro, L. **Ovarian suppression using luteinizing hormone-releasing hormone agonists during chemotherapy to preserve ovarian function and fertility of breast cancer patients: a meta-analysis of randomized studies.** Ann. Oncol. 2015; 26: 2408–2419. https://doi.org/10.1093/annonc/mdv374

Lambertini, M., Cinquini, M., Moschetti, I., Peccatori, F.A., Anserini, P., Valenzano Menada, M., Tomirotti, M., Del Mastro, L. **Temporary ovarian suppression during chemotherapy to preserve ovarian function and fertility in breast cancer patients: A GRADE approach for evidence evaluation and recommendations by the Italian Association of Medical Oncology.** Eur. J. Cancer. 2017; 71: 25–33. https://doi.org/10.1016/j.ejca.2016.10.034

Lambertini, M., Del Mastro, L., Pescio, M.C., Andersen, C.Y., Azim, H.A., Peccatori, F.A., Costa, M., Revelli, A., Salvagno, F., Gennari, A., Ubaldi, F.M., La Sala, G.B., De Stefano, C., Wallace, W.H., Partridge, A.H., Anserini, P. **Cancer and fertility preservation: international recommendations from an expert meeting.** BMC. Med. 2016; 14: 1. https://doi.org/10.1186/s12916–015–0545–7

Lambertini, Matteo, Di Maio, M., Pagani, O., Curigliano, G., Poggio, F., Del Mastro, L., Paluch-Shimon, S., Loibl, S., Partridge, A.H., Demeestere, I., Azim, H.A., Peccatori, F.A. **The BCY3/BCC 2017 survey on physicians' knowledge, attitudes and practice towards fertility and pregnancy-related issues in young breast cancer patients.** Breast 2018; 42: 41–49. https://doi.org/10.1016/j.breast.2018.08.099

Lambertini, M., Fontanella, C. **How reliable are the available safety data on hormonal stimulation for fertility preservation in young women with newly diagnosed early breast cancer?** Breast. Cancer. Res. Treat. 2018; 168: 773–774. https://doi.org/10.1007/s10549–017–4654–1

Lambertini, M., Goldrat, O., Ferreira, A.R., Dechene, J., Azim, H.A., Desir, J., Delbaere, A., t'Kint de Roodenbeke, M.-D., de Azambuja, E., Ignatiadis, M., Demeestere, I. **Reproductive potential and performance of fertility preservation strategies in BRCA-mutated breast cancer patients.** Ann. Oncol. 2018; 29: 237–243 https://doi.org/10.1093/annonc/mdx639

Lambertini, M., Goldrat, O., Toss, A., Azim, H.A., Peccatori, F.A., Ignatiadis, M., Del Mastro, L., Demeestere, I. **Fertility and pregnancy issues in BRCA-mutated breast cancer patients.** Cancer. Treat. Rev. 2017; 59: 61–70. https://doi.org/10.1016/j.ctrv.2017.07.001

Lambertini, Matteo, Kroman, N., Ameye, L., Cordoba, O., Pinto, A., Benedetti, G., Jensen, M.-B., Gelber, S., Del Grande, M., Ignatiadis, M., de Azambuja, E., Paesmans, M., Peccatori, F.A., Azim, H.A. **Long-term Safety of Pregnancy Following Breast Cancer According to oestrogen Receptor Status.** J. Natl. Cancer. Inst. 2018; 110: 426–429. https://doi.org/10.1093/jnci/djx206

Lambertini, M., Martel, S., Campbell, C., Guillaume, S., Hilbers, F.S., Schuehly, U., Korde, L., Azim, H.A.Jr., Di Cosimo, S., Tenglin, R.C., Huober, J., Baselga, J., Moreno-Aspitia, A., Piccart-Gebhart, M., Gelber, R.D., de Azambuja, E., Ignatiadis, M. **Pregnancies during and after trastuzumab and/or lapatinib in patients with human epidermal growth factor receptor 2-positive early breast cancer: analysis from the NeoALTTO (BIG 1–06) and ALTTO (BIG 2–06) trials.** Cancer 2019; 125: 307–316. https://doi.org/10.1002/cncr.31784

Lambertini, Matteo, Moore, H.C.F., Leonard, R.C.F., Loibl, S., Munster, P., Bruzzone, M., Boni, L., Unger, J.M., Anderson, R.A., Mehta, K., Minton, S., Poggio, F., Albain, K.S., Adamson, D.J.A., Gerber, B., Cripps, A., Bertelli, G., Seiler, S., Ceppi, M., Partridge, A.H., Del Mastro, L. **Gonadotrophin-Releasing Hormone Agonists During Chemotherapy for Preservation of Ovarian Function and Fertility in Premenopausal Patients With Early Breast Cancer: A Systematic Review and Meta-Analysis of Individual Patient-Level Data.** J. Clin. Oncol. 2018; 36: 1981–1990. https://doi.org/10.1200/JCO.2018.78.0858

Letourneau, J.M., Ebbel, E.E., Katz, P.P., Katz, A., Ai, W.Z., Chien, A.J., Melisko, M.E., Cedars, M.I., Rosen, M.P. **Pretreatment fertility counselling and fertility preservation improve quality of life in reproductive age women with cancer.** Cancer 2012; 118: 1710–1717. https://doi.org/10.1002/cncr.26459

Loibl, S., Han, S.N., von Minckwitz, G., Bontenbal, M., Ring, A., Giermek, J., Fehm, T., Van Calsteren, K., Linn, S.C., Schlehe, B., Gziri, M.M., Westenend, P.J., Müller, V., Heyns, L., Rack, B., Van Calster, B., Harbeck, N., Lenhard, M., Halaska, M.J., Kaufmann, M., Nekljudova, V., Amant, F. **Treatment of breast cancer during pregnancy: an observational study.** Lancet. Oncol. 2012; 13: 887–896. https://doi.org/10.1016/S1470–2045(12)70261–9

Loibl, S., Schmidt, A., Gentilini, O., Kaufman, B., Kuhl, C., Denkert, C., von Minckwitz, G., Parokonnaya, A., Stensheim, H., Thomssen, C., van Calsteren, K., Poortmans, P., Berveiller, P., Markert, U.R., Amant, F. **Breast Cancer Diagnosed During Pregnancy: Adapting Recent Advances in Breast Cancer Care for Pregnant Patients.** JAMA. Oncol. 2015; 1: 1145–1153. https://doi.org/10.1001/jamaoncol.2015.2413

Massarotti, C., Scaruffi, P., Lambertini, M., Remorgida, V., Del Mastro, L., Anserini, P. **State of the art on oocyte cryopreservation in female cancer patients: A critical review of the literature.** Cancer. Treat. Rev. 2017; 57: 50–57. https://doi.org/10.1016/j.ctrv.2017.04.009

Oktay, K., Harvey, B.E., Partridge, A.H., Quinn, G.P., Reinecke, J., Taylor, H.S., Wallace, W.H., Wang, E.T., Loren, A.W. **Fertility Preservation in Patients with Cancer: ASCO Clinical Practice Guideline Update.** J. Clin. Oncol. 2018; 36: 1994–2001. https://doi.org/10.1200/JCO.2018.78.1914

Oktay, K., Turan, V., Bedoschi, G., Pacheco, F.S., Moy, F. **Fertility Preservation Success Subsequent to Concurrent Aromatase Inhibitor Treatment and Ovarian Stimulation in Women with Breast Cancer.** J. Clin. Oncol. 2015; 33: 2424–2429. https://doi.org/10.1200/JCO.2014.59.3723

Pacheco, F., Oktay, K. **Current Success and Efficiency of Autologous Ovarian Transplantation: A Meta-Analysis.** Reprod. Sci. 2017; 24: 1111–1120. https://doi.org/10.1177/1933719117702251

Pagani, O, Bagnardi, V, Ruggeri, M, Bianco, N, Gallerani, E, Buser, K, Giordano, M, Gianni, L, Rabaglio, M, Freschi, A, Cretella, E, Clerico, M, Amadori, D, Simoncini, E, Ciccarese, M, Rauch, D, Rosti, G, Glaus, A, Berardi, R, Franzetti Pellanda, A, Ruddy, KJ, Gelber, S, Partridge, AH, Colleoni, M **HOHO Study (IBCSG 43–09): how European and US young women cope with breast cancer and fertility concerns.** Cancer. Res. 2017; 77

Pagani, O., Ruggeri, M., Manunta, S., Saunders, C., Peccatori, F., Cardoso, F., Kaufman, B., Paluch-Shimon, S., Gewefel, H., Gallerani, E., Abulkhair, O.M., Pistilli, B., Warner, E., Saloustros, E., Perey, L., Zaman, K., Rabaglio, M., Gelber, S., Gelber, R.D., Goldhirsch, A., Korde, L., Azim, H.A., Partridge, A.H. **Pregnancy after breast cancer: Are young patients willing to participate in clinical studies?** Breast 2015; 24: 201–207. https://doi.org/10.1016/j.breast.2015.01.005

Paluch-Shimon, S., Cardoso, F., Sessa, C., Balmana, J., Cardoso, M.J., Gilbert, F., Senkus, E. **ESMO Guidelines Committee. Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening.** Ann. Oncol. 2016; 27: v103–v110. https://doi.org/10.1093/annonc/mdw327

Paluch-Shimon, S., Pagani, O., Partridge, A.H., Abulkhair, O., Cardoso, M.-J., Dent, R.A., Gelmon, K., Gentilini, O., Harbeck, N., Margulies, A., Meirow, D., Pruneri, G., Senkus, E., Spanic, T., Sutliff, M., Travado, L., Peccatori, F., Cardoso, F. **ESO-ESMO 3rd international consensus guidelines for breast**

cancer in young women (BCY3). Breast 2017; 35: 203–217. https://doi.org/10.1016/j.breast.2017.07.017

Peccatori, F.A., Azim, H.A.Jr., Orecchia, R., Hoekstra, H.J., Pavlidis, N., Kesic, V., Pentheroudakis, G. **ESMO Guidelines Working Group. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.** Ann. Oncol. 2013; 24: vi160–vi170. https://doi.org/10.1093/annonc/mdt199

Poggio, F., Bruzzone, M., Ceppi, M., Pondé, N.F., La Valle, G., Del Mastro, L., de Azambuja, E., Lambertini, M. **Platinum-based neoadjuvant chemotherapy in triple-negative breast cancer: a systematic review and meta-analysis.** Ann. Oncol. 2018; 29: 1497–1508. https://doi.org/10.1093/annonc/mdy127

Quinn, G.P., Vadaparampil, S.T., Lee, J.-H., Jacobsen, P.B., Bepler, G., Lancaster, J., Keefe, D.L., Albrecht, T.L. **Physician referral for fertility preservation in oncology patients: a national study of practice behaviours.** J. Clin. Oncol. 2009; 27: 5952–5957. https://doi.org/10.1200/JCO.2009.23.0250

Rodriguez-Wallberg, K.A., Eloranta, S., Krawiec, K., Lissmats, A., Bergh, J., Liljegren, A. **Safety of fertility preservation in breast cancer patients in a register-based matched cohort study.** Breast. Cancer. Res. Treat. 2018; 167: 761–769. https://doi.org/10.1007/s10549–017–4555–3

Rosenberg, S.M., Ruddy, K.J., Tamimi, R.M., Gelber, S., Schapira, L., Come, S., Borges, V.F., Larsen, B., Garber, J.E., Partridge, A.H. **BRCA1 and BRCA2 Mutation Testing in Young Women with Breast Cancer.** JAMA. Oncol. 2016; 2: 730–736. https://doi.org/10.1001/jamaoncol.2015.5941

Ruddy, K.J., Gelber, S.I., Tamimi, R.M., Ginsburg, E.S., Schapira, L., Come, S.E., Borges, V.F., Meyer, M.E., Partridge, A.H. **Prospective study of fertility concerns and preservation strategies in young women with breast cancer.** J. Clin. Oncol. 2014; 32: 1151–1156. https://doi.org/10.1200/JCO.2013.52.8877

Senkus, E., Gomez, H., Dirix, L., Jerusalem, G., Murray, E., Van Tienhoven, G., Westenberg, A.H., Bottomley, A., Rapion, J., Bogaerts, J., Di Leo, A., Nešković-Konstantinović, Z. **Attitudes of young patients with breast cancer toward fertility loss related to adjuvant systemic therapies. EORTC study 10002 BIG 3–98.** Psychooncology 2014; 23: 173–182. https://doi.org/10.1002/pon.3384

Shapira, M., Raanani, H., Feldman, B., Srebnik, N., Dereck-Haim, S., Manela, D., Brenghausen, M., Geva-Lerner, L., Friedman, E., Levi-Lahad, E., Goldberg, D., Perri, T., Eldar-Geva, T., Meirow, D. **BRCA mutation carriers show normal ovarian response in *in vitro* fertilization cycles.** Fertil. Steril 2015; 104: 1162–1167. https://doi.org/10.1016/j.fertnstert.2015.07.1162

Turan, V., Bedoschi, G., Emirdar, V., Moy, F., Oktay, K. **Ovarian Stimulation in Patients with Cancer: Impact of Letrozole and BRCA Mutations on Fertility Preservation Cycle Outcomes.** Reprod. Sci. 2018; 25: 26–32. https://doi.org/10.1177/1933719117728800

Valentini, A., Lubinski, J., Byrski, T., Ghadirian, P., Moller, P., Lynch, H.T., Ainsworth, P., Neuhausen, S.L., Weitzel, J., Singer, C.F., Olopade, O.I., Saal, H., Lyonnet, D.S., Foulkes, W.D., Kim-Sing, C., Manoukian, S., Zakalik, D., Armel, S., Senter, L., Eng, C., Grunfeld, E., Chiarelli, A.M., Poll, A., Sun, P., Narod, S.A. **Hereditary Breast Cancer Clinical Study Group. The impact of pregnancy on breast cancer survival in women who carry a BRCA1 or BRCA2 mutation.** Breast. Cancer. Res. Treat. 2013; 142: 177–185. https://doi.org/10.1007/s10549–013–2729–1

Woodson, A.H., Muse, K.I., Lin, H., Jackson, M., Mattair, D.N., Schover, L., Woodard, T., McKenzie, L., Theriault, R.L., Hortobágyi, G.N., Arun, B., Peterson, S.K., Profato, J., Litton, J.K. **Breast cancer, BRCA mutations, and attitudes regarding pregnancy and preimplantation genetic diagnosis.** The Oncologist 2014; 19: 797–804. https://doi.org/10.1634/theoncologist.2014–0057

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