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Breast Cancer (EA Comen, Section Editor)

Diagnosis and Treatment of Breast Cancer in Young Women

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Opinion statement

Despite the increase of breast cancer incidence with age, approximately 7 to 10% ofwomen diagnosed with breast cancer are younger than the age 40. This subgroup ofpatients has different risk factors, tumour biology, clinical outcomes, and specific psy- chosocial issues, such as fertility preservation, family planning, and job reintegration. However, age alone should not be the main consideration when choosing the aggressive- ness of the treatment, as other factors must be considered, including the biologic aggressiveness of the tumour, potential long-term toxicities, and the preferences of the patient. Fertility preservation techniques should be discussed with the patient before starting any cancer treatment. Despite the significant percentage of breast cancer patients younger than age 40, fewclinical studies have specifically investigated disease characteristics and outcomes of this population, and most therapies routinely administered to these younger women were tested in older patients. Moreover, young women who have breast cancer are at a greater risk of sexual and psychological distress, and clinicians should address these issues in order to properly support patients during the long diagnostic and therapeutic journey. Consequently, it is essential to follow diagnostic and treatment guidelines specificallyaddressed to young women. Additional specific procedures should be followed to treat pregnant patients with breast cancer.

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Introduction

Breast cancer (BC) is the most common cancer in women [1]. Although the incidence of BC is age-dependent, a constant increase in BC diagnoses in women younger than 40 years has been recently reported in several countries [2, 3], with approximately 11% of new cases diagnosed in women who are 45 years of age or younger [4]. The definition of "young women" (YW) in the field of breast oncology is not standardized, but most of the literature refers to women aged ≤ 40 years.

Despite the extensive literature on BC, little is known about BC in YW who face specific issues related to body image, sexuality, fertility preservation, pregnancy desire, lactation, impact on current and future relationships, child care, career opportunities, and long-term toxicity potentially affecting survivorship. In this review, we will analyse these issues and also briefly address the topic of BC associated with pregnancy (PABC).

Tumour biology

Some retrospective studies have shown a worse 5-year survival in YW with BC compared with older, premenopausal patients [5]. This is partly related to diagnostic delays [6] and a higher rate of local recurrences [7]. Also, BC in younger patients more frequently has a high histological grade and low or absent expression of oestrogen receptors (ER) and/or progesterone receptors (PR) [8, 9], suggesting that BC in YW may be a distinct histological entity. Data on genomic differences between BC in YW and older women are controversial. Several studies [10–12] showed age-related differences in the expression of key genes involved in proliferation, invasion, metastases development, and angiogenesis. Conversely, in other large data sets, microarray analysis showed no differences between YW and older counterparts when correcting for significant clinical and histopathological features, including grade, nodal status, ER status, and intrinsic BC subtype [13].

Genetics

Younger age alone is associated with a higher risk of harbouring germline BC-predisposing gene mutations. The most frequently involved genes in YW with BC are *BRCA1/2* and, more rarely, *TP53*.

In patients with BC who are younger than 35 years of age, the probability to detect a *BRCA1/2* mutation is significantly higher than in the general population (9.4% versus 0.2%) [14]. A BC diagnosis in a young woman, independent of her family history, must raise suspicion of a familial BC syndrome; therefore, genetic counselling/testing for *BRCA1/2* mutations must be discussed.

The presence of *BRCA* mutations, and specifically of *BRCA1* mutations, is also associated with "triple negative" BC (TNBC) (characterized by the absence of ER, PR, and human epidermal growth factor-2 receptor-HER2 expression). The probability of 30- to 34-year-old women with a TNBC to be a *BRCA1* mutation carrier is 26.5% whereas the probability in a woman of the same age with another BC subtype is 5% [15].

The knowledge of *BRCA1/2* mutational status is important for treatment planning (including, for example, bilateral prophylactic mastectomy) and for primary prevention of other forms of cancer. In fact, *BRCA1/2* carriers have an

increased risk of ovarian cancer (40–50% lifetime risk for *BRCA1* and 10–20% for *BRCA2* mutation carriers [16]), as well as pancreatic, stomach, and colon cancers [17]. Finally, the presence of a *BRCA1/2* mutation indicates the use of breast MRI for diagnosis and follow-up, as discussed below.

A diagnosis of BC in very young women (< 35 years) falls within the diagnostic criteria of Li Fraumeni syndrome (LFS), an autosomal dominant genetic syndrome characterized by the onset of other cancers such as brain neoplasms, sarcomas, and adrenocortical carcinoma [18–20]. This syndrome has been correlated to a germline mutation in the *TP53* gene [21], which rarely appears as a de novo mutation. *TP53* genetic testing is not performed routinely, but only in cases of personal or family history suggestive of LFS, according to established diagnostic criteria [22, 23]. Pathogenic gene variants in other genes, discovered by multi-gene next-generation sequencing, although less common, can also lead to inherited BC. Among them, *PALB2* and *PTEN* confer a high BC risk, whereas in *CHEK2*, *ATM*, and *NF1* mutation carriers, the risk is two-to-four times higher than in the general population [24]. Specialized pre- and post-test genetic counselling is mandatory because there is still limited evidence regarding medical management for mutation carriers of these moderate- and low-penetrance genes.

Diagnosis

Radiological BC screening programs are generally not accessible to YW, due to both the rarity of the disease and the low mammographic sensitivity in young, dense breasts [25]. For this reason, the first-choice imaging tool is breast ultrasonography, which is associated with higher sensitivity and the absence of risks related to ionizing radiation exposure [26]. More recently, breast MRI has been recommended by the American Cancer Society as a diagnostic tool in high-risk women, such as women who have a genetic predisposition or previous thoracic irradiation for childhood malignancies [27]. MRI is characterized by high sensitivity in women who have dense breasts but also by low specificity, with consequent increased risk of unnecessary biopsies and false positives [28]. Therefore, outside of selected cases (e.g. women who have known *BRCA1/2* mutations or after preoperative chemotherapy), MRI should be considered a second-level investigation and cannot yet replace breast ultrasound.

Treatment

A multidisciplinary approach, including fertility and genetic counselling, oncoplastic surgery, breast nurses, and psychosocial individualized support, is crucial to plan personalized treatments and avoid over- or undertreatment. Evidence-based international guidelines to optimize the treatment of YW with BC have been specifically developed [29••].

Loco-regional treatments

Although surgical decisions (e.g. breast-conserving surgery versus mastectomy) should be made according to the same criteria as for older counterparts (mainly tumour stage and anticipated cosmetic outcomes), YW with BC have higher

local recurrence rates after breast-conserving surgery [30, 31], especially in the presence of an extensive intraductal component. Retrospective data [32] show that in very YW with negative margins and without an extensive intraductal component, the rate of local recurrence is similar to that in older patients.

With regard to radiotherapy, standard-fractionated whole breast irradiation (SF-WBI) has been the standard of care for several decades. Currently, hypofractionation schedules (HF-WBI) are widely used because they provide the same efficacy of SF-WBI but have less acute toxicity [33•]. Although YW were less represented in the key trials on HF-WBI (21–30%) [33•] and no long-term toxicity data are yet available, young age is no longer considered an exclusion criterion for HF-WBI [34•].

Partial breast irradiation is not indicated for YW due to a lack of evidence in this age group. Finally, YW who have invasive BC seem to receive the greatest benefit from the boost to the tumour bed [35].

Surgery as primary prevention

Young age is an important risk factor for contralateral BC in women who have already been treated for BC [36, 37]. In this context, primary prevention can be crucial.

Primary surgical prevention generally concerns women who have *BRCA1/2* mutations, and it is achieved by prophylactic bilateral mastectomy (PBM), which reduces the risk of BC up to 95% [38, 39]. Young women choose PBM more frequently than older patients [40], and the rate of women undergoing PBM is continually increasing in the USA, with a doubling between 1998 and 2003 [41]. Bedrosian and colleagues [42] reported an increase in survival with bilateral mastectomy at the time of diagnosis in women younger than 50 years of age who had early *TNBC*, but there are no additional data to support this strategy. Moreover, PBM is not without risks, and patients should be aware of the risks, benefits, and uncertainties of this procedure.

Systemic treatments

The indication and regimens of chemotherapy and HER2-targeted therapies in YW are the same as their older counterparts. Both age groups are guided by the stage and biological features of the tumour and patient's preferences, but young age alone does not justify more aggressive treatments [29••].

In addition to traditional clinical–pathological criteria, multi-gene prognostic tests (e.g. Oncotype DX, MammaPrint, Endopredict) sometimes can be used in patients who have hormone receptor-positive (HR+), HER2-negative early BC. In the TailorX trial, which tested Oncotype DX [43•], an improvement in disease-free survival (DFS) was reported by adding chemotherapy to endocrine therapy (ET) in women 50 years of age or younger who had an intermediate recurrence risk score (16–25). This result should be taken with caution because it is derived by an unplanned subgroup analysis in a population of premenopausal women who were mostly treated with tamoxifen alone. Until a few years ago, aromatase inhibitors (AIs) were not used in premenopausal patients to avoid the loop stimulation of ovarian function through the increase of the hypothalamic secretion of gonadotropin-releasing hormones (GnRH) [44]. Over time, the scenario of ET in YW with BC changed, and now several options are available [45, 46].

The results of the Tamoxifen and Exemestane Trial (TEXT) [47] and Suppression of Ovarian Function Trial (SOFT) [48] (Fig. 1) have widened the therapeutic possibilities for YW who have HR+ early BC. In the updated analysis of the two trials, after a median follow-up of 8 and 9 years, exemestane plus ovarian function suppression (OFS) showed a sustained improvement of DFS (86.8% versus 82.8%, absolute benefit of 4%) and of distant recurrence–free interval (91.8% versus 89.7%, absolute benefit of 2.1%), more evident in younger patients (≤ 35 years). The most recent SOFT analysis confirmed, in higher risk patients, the DFS improvement by adding OFS to oral endocrine therapy (78.9% with tamoxifen alone, 83.2% with tamoxifen plus OFS, and 85.9% with exemestane plus OFS), and an overall survival (OS) benefit starts to emerge (91.5% with tamoxifen alone, 93.3% with tamoxifen plus OFS, 92.1% with exemestane plus OFS) [49•]. For women who have a low risk of relapse, tamoxifen alone remains the standard of care.

In TEXT/SOFT, the greatest benefit from adding OFS was shown in the small subgroup of patients with HR+, HER2+ BC (n = 700, 12%), regardless of HER2-targeted therapy. Data on the most efficacious oral ET in these women are unclear and heterogeneous [50•].

On this basis, the most recent guidelines recommend considering OFS plus AIs, rather than tamoxifen, in patients at higher risk of relapse (e.g. ≥ 4 positive nodes, age ≤ 35 years, grade 3, and premenopausal oestrogen levels after adjuvant chemotherapy) [29••, 51•, 52•]. The absolute treatment effects in preventing recurrence may be quantified according to the individual risk of recurrence and may help physicians and patients estimate the individual risk-based benefit of escalating ET.

An exploratory analysis of TEXT and SOFT investigated the best timing for initiating OFS when chemotherapy is given [53•]. After a median follow-up of 5 years, data suggest neither a detrimental nor a beneficial effect of concurrent versus sequential OFS with chemotherapy in terms of BC-free interval. Therefore, the concomitant administration of GnRHa with chemotherapy can be a reasonable option that also allows preservation of fertility (see below).

The SOFT-Estrogen substudy (SOFT-EST) evaluated the risk of ineffective OFS by measuring estradiol (E2) levels in 116 premenopausal patients (8% < 35 years) who were receiving exemestane (n = 86) or tamoxifen (n = 30) in association with OFS. In up to 20% of cases, high E2 levels (> 2.72 pg/mL) were measured at all time points, suggesting an incomplete OFS, and 4% of patients had vaginal bleeding. The very low number of recurrences (five in the exemestane plus OFS group, none with suboptimal OFS) does not allow for an

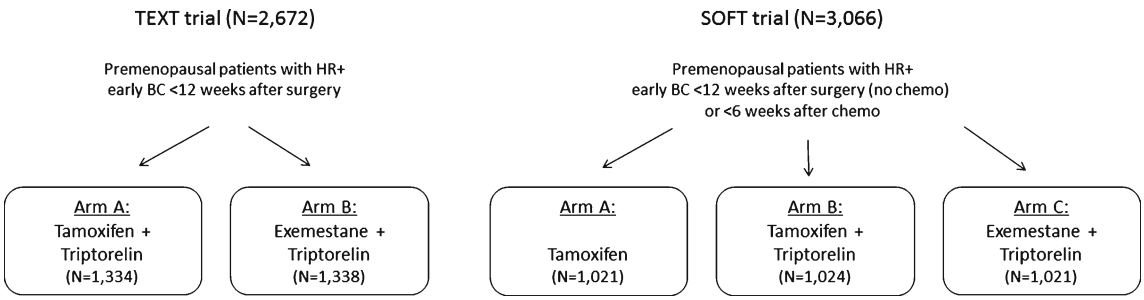

Fig. 1. Summary of the TEXT and SOFT trials. N, number of patients, HR+, expression of hormonal receptor

accurate estimation of the clinical impact of suboptimal oestrogen suppression [54, 55]. Nevertheless, monitoring E2 levels under AIs is of crucial importance, and, in the case of incomplete OFS, a switch to tamoxifen should be considered.

In the recent EBCTCG meta-analysis [56•] (62,923 women with HR+ early BC disease-free after 5 years of ET, 15% of whom < 44 years at diagnosis), recurrence occurred until 20 years from diagnosis. The risk was mostly related to tumour size and nodal involvement (from 13% with T1-N0 disease to 41% with T2 disease and nodal involvement). These observations reinforce the debated question regarding the optimal duration of ET, especially in patients who have a potentially long life expectancy.

In YW, the duration of treatment must also be balanced against long-term toxicity and interference with family planning. Data evaluating the efficacy and toxicity of extended ET in premenopausal patients are scarce [57]. In particular, the ATLAS Trial, a large trial assessing the efficacy of extended adjuvant tamoxifen up to 10 years, randomized 1058 premenopausal patients (16% of all patients), 630 of whom had HR+ BC. After a median follow-up of 7.6 years, the extended arm had an overall 3% reduction of BC recurrence (18% vs 21%, relative risk [RR] 0.84, 95% CI 0.76–0.94), regardless of age [58]. Similarly, the aTTom Trial, conducted in approximately 7000 pre- and postmenopausal women with HR+ early BC, clearly demonstrated that 10 years of tamoxifen improved relapse-free survival (RFS) and OS in comparison with 5 years of tamoxifen [59]. Therefore, extending the length of time a patient takes tamoxifen is a valid option for premenopausal women who are at high risk of late relapse. Finally, there are no specific data to establish the optimal duration of pharmacological OFS. Based on the limited data available, OFS should be given for at least 2 to 3 years [60] but not exceeding 5 years [61, 62]. In combination with AIs, GnRHa should be given for 5 years.

Tamoxifen has been used for several years as a cost-effective pharmacoprevention in women who are at a higher BC risk or who have already been diagnosed with ductal or lobular carcinoma in situ (DCIS and LCIS respectively). The NSABP B-24 Trial showed a significant benefit with tamoxifen after lumpectomy and radiotherapy in patients who had DCIS (HR of subsequent BC at 10 years 0.49, $p < 0.001$) [63]. Similarly, the NSABP-P1 Trial, after a median follow-up of 69 months, demonstrated a reduction of the risk of invasive BC by 49% with tamoxifen versus placebo (cumulative incidence 22% versus 43.4%, $p < 0.00001$) in 13,388 women at increased risk of BC [64]. Women who were 49 years of age or younger achieved the lowest benefit (44%) compared with women aged 50–59 years (51%) or older (55%). However, even the rate of endometrial cancer, an uncommon adverse effect of tamoxifen, was lower in women who were younger than 50 years of age. Despite these clear advantages in terms of prevention of second primary BC, the question remains whether we should expose healthy women to the side effects of tamoxifen. A recent randomized trial from De Censi and colleagues [65] showed that low-dose tamoxifen (5 mg daily) for 3 years effectively reduces the risk of primary BC and of DCIS/LCIS recurrence in women who have intraepithelial neoplasia, without serious adverse events or menopausal symptoms. Because the study was randomized against placebo and not the standard 20-mg dose, interpretation of the results is limited. Moreover, treatment adherence, directly correlated with clinical outcomes [66], was only 64.8% in the tamoxifen arm

and 60.7% in the placebo arm.

BC treatment can cause a number of side effects, both temporary and prolonged. Some of these have a specific impact on YW (e.g. menopausal symptoms, increased risk of osteoporosis, cognitive impairment, and psychological and sexual effects). Bisphosphonates have been recently added in several guidelines as part of the adjuvant treatment plan to prevent bone loss caused by iatrogenic menopause [29••, 51•]. The treatment of cognitive impairment, sleep disorders, and psychological and sexual distress, as well as encouragement to improve lifestyle, should all be part of a comprehensive multidisciplinary treatment plan that includes physiotherapists, nutritionists, and psychologists possibly dedicated to this particular population, with the purpose of improving quality of life (QoL) and treatment compliance. In fact, treatment compliance/adherence (especially to ET) influences clinical outcomes [66] and it is lower in YW in comparison with older patients (HR 1.51, 95% CI 1.23–1.85) [67].

As in the adjuvant setting, even in advanced disease, young age is not a reason to choose more aggressive treatments. In this setting, the main objectives, aside from increasing progression-free survival (PFS), are the maintenance or improvement of QoL. In the case of oligometastatic disease, multimodal treatments (surgery, radiotherapy, systemic therapies) can achieve cure in a subset of patients. Evidence-based international guidelines to treat advanced BC are available and should be followed [68].

Pregnancy after BC and fertility preservation

Fertility can be impaired by chemotherapy, targeted therapies, and ET through various mechanisms [69]; fertility preservation is a crucial topic in YW with BC. Patients and physicians have long been concerned that pregnancy could increase the risk of BC recurrence, especially in HR+ disease, but all data show that no difference in DFS or OS between patients who became pregnant after BC and those who did not, regardless of ER status [70–72]. Despite the evidence, in a recent survey conducted by Lambertini and colleagues on 273 physicians, 30.4% agreed with the statement that pregnancy after BC may increase the risk of recurrence. Moreover, up to 37% did not know international guidelines on fertility preservation, and up to 47% never consulted guidelines on pregnancy after BC [73]. The prospective global POSITIVE Study (IBCSG 48-14/BIG 8-13, NCT02308085) will assess the safety and feasibility of interrupting ET to allow pregnancy after BC. International guidelines recommend discussing the risk of infertility before starting anticancer therapies and to offer the available strategies for fertility preservation [62, 74, 75].

Fertility preservation techniques include GnRHa during chemotherapy and oocyte, embryo, or ovarian tissue cryopreservation [76]. The efficacy of GnRHa as fertility preservation has been recently summarized in a large meta-analysis of individual data [77]. Temporary OFS with GnRHa during chemotherapy was associated with a significant reduction of chemotherapy-induced amenorrhea (adjusted OR 0.38; 95% CI 0.26–0.57) and with a higher chance of pregnancy after BC treatment (incidence rate ratio 1.83; 95% CI 1.06–3.15), without a detrimental impact on long-term outcomes. The 15th and 16th St. Gallen Consensus Conferences strongly support temporary OFS with GnRHa during chemotherapy as a fertility preservation strategy [34, 51].

Embryo and oocyte cryopreservation require controlled ovarian stimulation. Embryo cryopreservation is the most effective technique, but it requires in vitro fertilization and a male partner or sperm donor. For patients who do not have a male partner or who do not want sperm donors, oocyte or ovarian tissue cryopreservation is an effective alternative. Of note, the most used ovarian stimulation protocol uses letrozole plus FSH [78]. During ovarian stimulation, there is a minimal and transient elevation in E2 levels, but accumulating data suggest that this is not an added risk for BC relapse [78, 79]. Ovarian tissue cryopreservation and transplantation, unlike oocyte cryopreservation, can preserve many primordial follicles, but the graft can be exposed to ischemia and potential follicular depletion during the revascularization stage. Therefore, this technique must still be considered experimental [80].

Despite the growing evidence on this topic, there are still too many limitations (organizational and economic) to access fertility preservation techniques [81, 82].

Pregnancy-associated breast cancer

Pregnancy-associated breast cancer (PABC) includes three different clinical entities: BC diagnosed during pregnancy, during the first year following delivery, or at any time during lactation. In general, the incidence of PABC is between 1:3000 and 1:10,000 pregnancies and represents approximately 3% of all BCs [83]. The prevalence of PABC could increase in the coming years, especially in Western countries where there is a greater tendency to postpone the first pregnancy to an age range in which the incidence of BC is more frequent.

Generally, PABC has a more aggressive biological behaviour, with a higher frequency of luminal B–like, HER2-positive, and triple-negative subtypes in comparison with non-pregnant women [84]. Overall, pregnancy termination does not seem to improve maternal outcome. The decision to continue or end the pregnancy is personal, and health professionals should inform the patient and family about the different treatment options and related risks to allow for a balanced informed decision.

The imaging procedures for PABC diagnosis/staging include breast ultrasound (86% accuracy) [75] or MRI without gadolinium. Mammography seems to be safe because irradiation to the foetus is negligible, but its sensitivity is low because of the high breast density [85]. Surgery indications and techniques follow the standard practice and can be safely carried out during gestation [75]. Sentinel lymph node biopsy seems safe using technetium-99, whereas blue dye is discouraged [75]. Radiotherapy should be postponed after delivery [75].

The indication for chemotherapy is based on the same criteria applied in non-pregnant patients, but drug pharmacokinetics during pregnancy can be modified by several factors, such as a reduction in plasma albumin, an increase in the water compartment, liver oxidation and renal clearance, and changes in gastrointestinal motility [86]. Moreover, almost all molecules with a molecular weight of more than 600 kD cross the placental barrier and reach the foetal circulation.

Therefore, cytotoxic treatments should not be administered during the first trimester because of the high risk of congenital malformations. After the first trimester, the organogenesis is complete, and the use of cytotoxic drugs is

associated with a < 3% risk of congenital malformations [86, 87]. The European guidelines [75] consider chemotherapy feasible during the second and third trimesters of pregnancy. Anthracycline-based regimens such as AC/EC or FAC/FEC are the most studied during pregnancy and remain the first choice according to the current ESMO guidelines [75] because of the low risk of short- and long-term foetal cardiotoxicity, teratogenic risk [88], or neurocognitive impairment [89].

Data on the use of taxanes during pregnancy are scarce and remain controversial. Some preclinical studies showed that taxanes cross the placenta and are toxic for embryo organogenesis, increasing the risk of intrauterine death and decreasing foetal weight [90]. Docetaxel is mainly metabolized by the cytochrome CYP3A4, which has the highest activity during the third trimester of pregnancy [91], resulting in a suboptimal exposure using the standard schedules. Conversely, a systematic review of 16 articles showed that taxanes during pregnancy are generally safe, with healthy newborns being delivered in 90% of cases after a median follow-up of 16 months [92]. In light of these considerations, current European guidelines suggest postponing taxanes whenever possible until after delivery in sequential schedules after anthracyclines, but they allow for their use in cases of contraindications to anthracyclines [75]. Cyclophosphamide can cause congenital malformations, with a relative risk ranging from 4 to 13% in late pregnancy [93], but it is rarely used as a single agent; therefore, it is difficult to estimate its specific contribution. Concerning other cytotoxic agents, methotrexate can induce abortion and accumulates in the amniotic fluid; therefore, it is absolutely contraindicated. Vinorelbine appears to be sufficiently safe, but it remains the third choice after anthracyclines and taxanes [94].

Any ET is contraindicated at all stages of pregnancy. In particular, tamoxifen is associated with birth defects such as oculo-auriculo-vertebral dysplasia [95], mandible aplasia, cleft palate, glossoptosis (associated in the so-called Pierre-Robin sequence) [96], and ambiguous genitalia [97].

The few data available on the effects of HER2-targeted therapies during pregnancy derive from sporadic case reports almost exclusively with trastuzumab. Its molecular target is also highly expressed in embryonic tissues (especially in kidneys) [98]. The transplacental crossing of trastuzumab increases in parallel with placenta maturation; therefore, the harmful foetal effects (mainly oligo-anhydramnsios and nephrotoxicity) are predominant in the last months of pregnancy [99]. One case report described accidental exposure to lapatinib, another HER2-target therapy, for 11 weeks without complications [100]. The administration of these agents should be avoided, and, in the case of accidental pregnancy, the drug should be stopped during treatment.

Conclusions

The management of YW with BC requires a multidisciplinary approach dedicated to addressing the specific issues of this particular patient population, such as fertility preservation, family planning, job reintegration, and sexual and psychological distress. The inclusion of young patients in clinical trials and the prospective trials designed specifically to focus on YW with BC is urgently needed.

Compliance with Ethical Standards

Conflict of Interest
Lorenzo Rossi, Calogero Mazzara, and Olivia Pagani declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors..

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- • Of importance
- •• Of major importance

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