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Breast cancer in adolescents and young women

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Abstract

Breast cancer is very rare in adolescents and very young women. Less than 1% of all breast cancer cases occur before the age of 30 years (Natl Cancer Inst Monogr 16 (1994) 69). Invasive breast cancer occurring in women before the age of 35 years has a more aggressive biological behaviour and is associated with a worse prognosis than in older premenopausal women. Breast cancers in these young women are more frequently poorly differentiated, oestrogen-receptor (ER)-negative, have lymphovascular invasion and high proliferating fractions. Breast-conserving surgery in women <35 years old is associated with a higher risk of local recurrence than in older women. All young women should be considered at moderate-high risk by virtue of their age alone and offered adjuvant therapy. The long-term toxicity of adjuvant therapies is a particular concern when treating these women. The implications of possible fertility impairment and premature menopause require consideration when discussing adjuvant chemotherapy and endocrine therapy. Adolescents and young women are particularly vulnerable to emotional distress and psychosocial problems and should be provided with appropriate support. Young women who are at a potential high-risk of developing breast cancer such as those with germline mutations of *BRCA1*, *BRCA2*, *TP53*, *PTEN* or who have previously received mantle irradiation for Hodgkin's disease need close follow-up and are candidates for screening from a young age.

Keywords: Adolescents; Breast cancer; Management; Psychosocial issues

1. Introduction

Breast cancer in adolescence and early adulthood is a rare condition. The estimated incidence is less than 0.1 per 100 000 women below the age of 20 years, increasing to 1.4 for women 20–24 years, 8.1 for women 25–29 years and 24.8 for women 30–34 years old [1]. Breast cancer in childhood accounts for less than 1% of childhood cancers and less than 0.1% of all breast cancers [2–4]. In the United States, figures from the National Cancer Institute (NCI) Surveillance, Epidemiology and End-Results (SEER) database show that less than 1% of breast cancer patients are younger than 30 years and 2.7% are younger than 35 years [1].

The most common type of breast cancer in childhood is secretory carcinoma, formerly known as juvenile carcinoma, because of its tendency to occur more frequently (although not exclusively) in children [6,7]. This is a morphologically-distinct type of breast carcinoma with a very indolent clinical behaviour. Wide local excision and axillary lymph node dissection are generally all that is required for therapy, as distant metastases are extremely rare. The prognosis is generally favourable, but patients require long-term follow-up due to the risk of late recurrence.

Invasive ductal carcinoma occurring in adolescents and young women has a more aggressive biological behaviour and a worse prognosis than breast cancer arising in older premenopausal women [8]. In previously published studies, tumours in younger women were less well differentiated, had a higher proliferating fraction and had more lymphovascular invasion than those occurring in older patients [9–13]. Review of large databases worldwide shows that women younger than 35 years of age have more advanced disease at diagnosis and a poorer 5- year survival than older premenopausal patients [5,10,14–16]. In several series, age remained independently prognostic when pathological variables were taken into account [13,17–19]. Consensus statements from both the National Institute of Health (NIH)

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and the St Gallen consensus conference have recommended that all women under the age of 35 years receive adjuvant therapy based on the evidence that these patients have biologically more aggressive disease and a poorer survival [20,21].

In addition to these considerations, there are a number of special issues facing these very young women presenting with a diagnosis of breast cancer, including the risk of treatment-induced fertility impairment and premature menopause, and an increased risk of locoregional recurrence with breast-conserving surgery than older premenopausal patients [22–27]. Little is known about the long-term cardiac toxicity of radiation in addition to anthracyclines and taxanes. Moreover, there is evidence that young women are more vulnerable to emotional distress and have a higher risk of psychosocial problems [28–32]. Optimal management of very young women and adolescents requires attention not only to the best treatments for such an inherently biologically aggressive disease, but also consideration of the long-term physical and psychological consequences of such treatments.

2. Diagnosis

Breast cancers in this age group tend to be larger when diagnosed and have a longer history of a palpable mass than tumours diagnosed in older women [33]. The accuracy of physical examination is lower in very young women, as they often have dense or nodular breast tissue that is subject to cyclical hormonal changes. Most discrete breast masses in this age group are fibroadenomas. In a study of 30 women under the age of 30 years with breast cancer, the clinical examination was correctly deemed to be malignant in only 37% of cases [33]. Almost half were thought to have benign disease and 30% were clinically consistent with a fibroadenoma. This reinforces the need for a tissue diagnosis in all young women presenting with a non-cystic breast mass.

The accuracy of mammography is inferior in young women, who have denser breast tissue [34]. Ashley and colleagues found that only 55% of mammograms in young women with breast cancer demonstrated clearly malignant findings, with 23% being reported as clearly benign [33]. Ultrasound showed malignant features in only 58% and was read as clearly benign in 30%. Fine-needle aspiration (FNA) cytology has the greatest accuracy with 78% definitely malignant and 15% suspicious, giving an overall proportion of 93%. When the classical triple test of examination, radiology and FNA were combined, 95% of all cancers could be recognised preoperatively.

Mammography has a role once the diagnosis has been made in excluding extensive microcalcifications associated with widespread ductal carcinoma *in situ* (DCIS) [35]; the presence of these might influence a choice of mastectomy over breast-conserving surgery. The role of magnetic resonance imaging (MRI) in the management of very young women remains to be defined. MRI has lower specificity in young women and benign fibroadenomas in this age group share more features in common with malignancy than fibroadenomas in older women [36]. With the ready availability of minimally invasive diagnostic procedures, there is no reason to delay the cytological diagnosis of a persistent palpable breast mass in any young woman.

3. Prognosis of breast cancer in very young women

A number of studies have compared the stage and pathological characteristics of breast tumours occurring in very young women with those occurring in older premenopausal women. Colleoni and colleagues [37] looked at 1837 premenopausal women treated at the European Institute of Oncology between April 1997 and August 2000. Of these, 185 were aged less than 35 years at the time of diagnosis. When compared to older premenopausal women, young women were more likely to have tumours that were oestrogen receptor (ER)-negative (38.8 versus. 21.6% $P<0.001$), progesterone receptor (PgR)-negative (49.1 versus. 35.3% $P=0.001$), and grade 3 (61.9% versus 37.4% $P<0.001$). Young women were also more likely to have lymphovascular invasion and Ki-67 staining in $\geqslant 20\%$ of cells. No difference was found in the proportion of tumours which overexpressed HER2/neu. Other studies have confirmed these findings [9,19]. In multivariate analyses, age younger than 35 years remained a significant predictor for time to recurrence Relative Risk (RR) = 1.7), time to distant failure (RR = 1.6) and overall mortality (RR = 1.5) [19].

In De La Rochefordiere's analysis of 1703 patients treated at the Institut Curie between 1981 and 1985, young age predicted for poorer survival [18]. The relationship between the hazard of recurrence and age was a continuous one, best fitted to a log-linear function and indicating a 4% decrease in the risk of recurrence and 2% decrease in the risk of death for every year of age. In multivariate analysis for both survival and disease-free interval, young age was independently prognostic when tumour size, nodal status, grade, hormone receptor status, locoregional treatment and adjuvant systemic therapy were taken into account.

Dubsky and colleagues [38] retrospectively analysed the outcome of 885 premenopausal patients and showed that age <35 years was a powerful independent prognostic factor in multivariate analyses for recurrence-free (RR = 2.5 $P<0.0001$) and overall survival (RR = 2.2 $P<0.0039$). In their analyses, young age was seen as the second most powerful risk factor after lymph node status. Kothari and colleagues have published the only reported series of breast cancers in women aged less

than 25 years [35]. The survival of the 15 women aged under 25 years was not significantly different from that of women aged 26–35 years, but the survival of all women aged ⩽35 years was significantly worse than that of women aged 36–65 years ($P = 0.0003$).

In a Danish population study looking at 10 356 premenopausal women with breast cancer, the negative prognostic effect of young age was seen almost exclusively in women <35 years diagnosed with low-risk disease who did not receive adjuvant therapy [16]. Young women (<35 years) with node-negative disease who did not receive adjuvant treatment had a significantly increased risk of dying (RR 2.18; 95% Confidence Interval (CI) 1.64–2.89) when compared with women aged 45–49 years who did not receive adjuvant therapy. No such effect of age was seen in patients who received adjuvant cytotoxic treatment. Xiong and colleagues also found particularly poor outcomes for women <30 years with stage I disease who did not receive adjuvant treatment [39]. These young women had a 5-year recurrence-free and overall survival of 46 and 87%, respectively, compared with 97% 5-year survival seen in older patients with stage I disease in the National Cancer Database.

Aebi and colleagues [8] retrospectively reviewed the outcome of 3700 premenopausal women in International Breast Cancer Study Group (IBCSG) trials I, II, V and VI. 314 patients were younger than 35 years at the time of diagnosis. The distribution of tumour size and number of involved nodes was similar in the younger and older premenopausal women. The proportion of ER+ tumours was lower in the younger age group (51% versus 63%). Younger women had significantly worse disease-free and overall survival than older premenopausal women (10 year disease-free survival (DFS) 35% versus 47%; Hazard Ratio (HR) 1.41 (1.22–1.63); $P < 0.001$; 10- year Overall Survival (OS) 49% versus 62%; HR 1.51 (1.28–1.78) $P < 0.001$). Contrary to the pattern seen in older women, young women with ER+ve tumours had a poorer prognosis than young women with ER− tumours (10- year DFS 25% versus 47%; HR 1.49; (1.09–2.04), $P = 0.014$; 10 year OS 39% versus 56%; HR 1.32 (0.93–1.89), $P = 0.12$). This was postulated to be due to the insufficient endocrine effect of chemotherapy in these very young women and the absence of any adjuvant endocrine therapy in these studies. Data from IBCSG, South Western Oncology Group (SWOG), and National Surgical Adjuvant Breast and Bowel Project (NSABP) studies of premenopausal women has consistently revealed a worse outcome for younger women with ER+ tumours treated with adjuvant chemotherapy alone [37,40].

In our own series of 1161 patients receiving adjuvant chemotherapy for early breast cancer at the Royal Marsden Hospital between 1990 and 2001, 104 were under 35 years of age, and these had significantly poorer DFS than older women (5-year DFS 48% versus. 74% for older women; $P = 0.0003$) (Table 1) (author's own data). The effect of age on DFS was confined to the subset of women with ER+ disease (5-year DFS 54% versus 79%; $P = 0.02$) (Table 1 and Fig. 1). This occurred despite 82% of the patients aged <35 years with ER+ve tumours receiving adjuvant endocrine therapy. Age continued to independently predict DFS when prognostic and treatment-related variables were taken into account (RR 1.6; 95% CI 1.1–2.6) (Table 2). Young women with ER+ve tumours had a particularly high risk of relapse despite adjuvant chemotherapy and endocrine therapy (RR 3.1; 95% CI 1.6–5.8).

4. Management

The principles of managing invasive breast carcinoma in very young women are the same as that for older women, but there are a number of special issues which require consideration. Consensus panels of the NIH and the St Gallen conference have recommended adjuvant

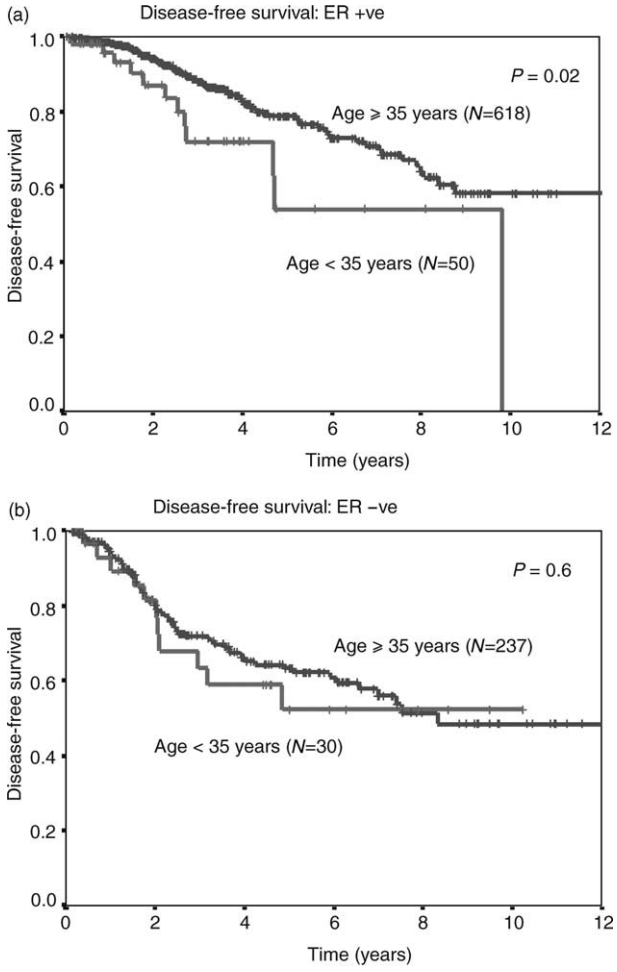

Fig. 1. Disease-free survival (DFS) of patients treated with adjuvant chemotherapy by age and oestrogen-receptor (ER) status.

Table 1
Disease-free survival (DFS) of women who received adjuvant chemotherapy at the Royal Marsden Hospital, 1990–2001

	Age <35 years		Age ⩾35 years		*P* value
	N	% 5-year	*N*	% 5-year	
All patients	104	48	1057	74	0.0003
ER-positive	50	54	618	79	0.02
ER-negative	30	52	237	63	0.6

ER, oestrogen receptor.

therapy for all patients aged under 35 years based on the evidence that they have a poorer prognosis [20,21]. The use of adjuvant therapies in young women raises issues of the long-term side-effects such as the induction of an early menopause, fertility impairment, and the effects on bone mineral density and cognition.

4.1. Surgery

Breast-conserving surgery is obviously desirable in young women. The two principle considerations when deciding between breast-conserving surgery and mastectomy are the cosmetic result and the risk of local recurrence. The most important risk factors for local recurrence after breast-conserving surgery are young age (<35 years) [25–27,41–48], infiltrating tumour with an extensive intraductal component [25,48–51], vascular invasion [47,52] and microscopic involvement of excision margins [44,53–56]. In an analysis of two large trials of mastectomy versus conservative surgery and radiotherapy, Voogd and colleagues found that patients aged <35 years at the time of surgery had a 9 times higher risk of local recurrence (95% CI 3.74–22.81) after conservative surgery than patients older than 60 years [27]. However, young patients who were treated with mastectomy did not have an increased risk of local recurrence compared with older patients. Similarly, Arriagada and colleagues found that conservatively-treated women aged less than 40 years had a 5-fold greater risk of local recurrence compared with older patients, but the effect of young age on the risk of local recurrence was not seen with mastectomy [26].

Young women should be aware of the increase in the risk of local recurrence associated with conservative surgery in this age group, but this should not preclude breast conservation. None of the studies above have demonstrated that conservative surgery in these young women has a negative impact on survival.

4.2. Adjuvant therapies

Current choice of adjuvant therapy for premenopausal patients includes cytotoxic chemotherapy, ovarian ablation (by surgery, irradiation or chemical ovarian suppression), anti-oestrogen therapy or any combination of these. Adjuvant chemotherapy for early breast cancer in patients under 50 years old reduces the relative risk of recurrence by 35% and death by 27% [57]. Overview data showed that 5 years of adjuvant tamoxifen reduced the relative risk of recurrence by 54% (standard deviation (SD) 13) in women with ER + ve disease randomised prior to age 40 years [58]. By virtue of age alone, patients under the age of 35 years are regarded as having average/high risk of recurrence warranting recommendation of adjuvant therapies [20,21]. For patients with ER-negative tumours, adjuvant chemotherapy alone is appropriate. Patients with ER-positive tumours would be candidates for either chemotherapy and endocrine therapy or endocrine therapy alone.

4.3. Adjuvant chemotherapy

In the Danish population study and the MD Anderson study, women under 30 years of age with early-stage disease not given adjuvant chemotherapy had a particularly poor relapse-free survival [16,39]. Anthracycline-containing regimens are more effective than cyclophosphamide, methotrexate, 5-fluorouracil (CMF). In the overview analysis, the use of anthracycline-containing chemotherapy when compared with CMF resulted in a 2.7% absolute survival benefit at 5 years of follow-up [57]. A Canadian study comparing cyclophosphamide, epirubicin and 5-fluorouracil (CEF) with classical CMF showed an improvement in outcome with the anthracycline-containing combination [59]. Women receiving CEF had a significantly improved relapse-free survival (RFS) and OS (5-year RFS 63% versus 53%; $P = 0.009$; 5-year actuarial survival 77% versus 70%; $P = 0.03$). Optimal chemotherapy for young women remains controversial, particularly with the recent publication of

Table 2
Multivariate analysis of disease-free and overall survival

	Relative risk (RR) of relapse for young patients (95% CI)	*P* values	Relative risk (RR) of death for young patients (95% CI)	*P* values
All patients	1.6 (1.1–2.6)	0.03	1.1 (0.5–2.2)	0.9
ER-positive	3.1 (1.6–5.8)	0.001	1.3 (0.4–4.3)	0.7
ER-negative	1.1 (0.6–2.2)	0.7	1.0 (0.5–2.2)	0.6

95% CI, 95% Confidence Interval; ER, oestrogen receptor.

several studies examining the use of taxanes and dose-dense therapy in the adjuvant setting.

The Cancer and Leukemia Group B (CALGB) 9344 trial randomised 3121 patients with node-positive early breast cancer to either four cycles of doxorubicin, cyclophosphamide (AC) or four cycles of AC followed by four cycles of paclitaxel [60]. Patients who received paclitaxel in addition to AC had a 17% reduction in the risk of recurrence ($P=0.0023$) and an 18% reduction in the risk of death ($P=0.0064$). Recent presentation of the results of NSABP-B28 also show a 17% reduction in the risk of recurrence ($P=0.008$) with the addition of four cycles of paclitaxel, although there is as yet no significant overall survival benefit [61]. The Breast Cancer International Research Group (BCIRG) 001 trial compared six cycles of docetaxel, doxorubicin, and cyclophosphamide (TAC) to 5-fluorouracil, doxorubicin and cyclophosphamide (FAC) [62]. At a median follow-up of 33 months, there was a significant improvement in DFS (32% risk reduction; $P=0.0011$) and OS (54% risk reduction; $P=0.006$) for patients with 1–3 positive nodes treated on the TAC arm.

The recently published results of CALGB 9741 show a survival advantage for a dose-dense regimen of AC followed by paclitaxel given every 2 weeks with growth factor support [63]. 2005 women were randomised to one of four regimens: (1) sequential Ax4-Tx4-Cx4, 3-weekly (2) sequential Ax4-Tx4-Cx4, 2-weekly (3) concurrent ACx4-Tx4, 3-weekly or (4) concurrent ACx4-Tx4, 2-weekly. At a median follow-up of 36 months, there was a 26% reduction in the risk of relapse ($P=0.010$) and a 31% reduction in the risk of death ($P=0.013$) associated with the dose-dense arms, but no significant differences between the sequential or concurrent schedules. Caution is required in the interpretation of the results of these studies as they are immature and have yet to be confirmed. At the current time, anthracycline-containing combinations remain the 'standard of care' for adjuvant chemotherapy.

4.4. Adjuvant endocrine therapy

For young women with ER− tumours, cytotoxic chemotherapy is the only useful adjuvant therapy. The situation for young women with ER+ve tumours is more complex. Do they require chemotherapy, endocrine therapy or a combination of both? As previously described, a retrospective review of four IBCSG trials showed that women aged less than 35 years with ER+ve tumours actually had a worse outcome than young women with ER− tumours [8]. In this study, none of the patients received adjuvant endocrine therapy. Suppression of ovarian function creates significant problems for very young women, including menopausal symptoms, psychological distress and the need to adjust personal and family plans.

Amenorrhoea may be an important constituent in the action of chemotherapy in premenopausal patients. Premenopausal women undergoing an amenorrhoeic process induced by chemotherapy have a better prognosis than those retaining their menstrual cycle [64–67]. RFS and OS appears to be improved by the induction of amenorrhoea, but the optimal duration of amenorrhoea is unknown. The likelihood of becoming amenorrhoeic following adjuvant chemotherapy is dependent on age [68]. Younger women are less likely to become amenorrhoeic and may therefore be less likely to realise the benefits of the endocrine effect of adjuvant chemotherapy [68].

There are now several published studies comparing adjuvant CMF chemotherapy with endocrine therapy in premenopausal women. Boccardo and colleagues compared six cycles of oral CMF with the combination of tamoxifen and ovarian suppression in patients with ER+ve early breast cancer [69]. There were no differences in DFS or OS between the two groups. 68% of patients randomised to CMF became amenorrhoeic as a result of their chemotherapy and there was a significant difference in OS in favour of the patients who became amenorrhoeic during chemotherapy ($P=0.05$). More recently, Jakesz and colleagues have published the results of a study comparing 3 years of goserelin plus 5 years of tamoxifen to six cycles of intravenous (i.v.) CMF [70]. At a median follow-up of 5 years, the group who received adjuvant endocrine therapy had a significant improvement in RFS (81% versus 76%; $P=0.037$), but there were no differences in OS. Only 7% of patients in this trial were aged less than 35 years. Jonat and colleagues compared 2 years of goserelin with six cycles of either oral or i.v. CMF in 1640 patients with node-positive early breast cancer unselected for ER status [71]. In patients with ER+ve disease, 2 years of goserelin was equivalent to CMF chemotherapy for DFS (HR 1.01; 95% CI 0.84–1.2) and OS (HR 0.99; 95% CI 0.76–1.28), whereas in ER− or unknown patients, CMF chemotherapy was superior to goserelin. It could be argued that all three of these trials have used a chemotherapy arm which would now be considered sub-optimal. The proportion of very young women (<35 years) in these trials is small and this is reflected in the high proportion of women becoming amenorrhoeic from the chemotherapy. These results are not directly transferable to very young women who have less chance of becoming amenorrhoeic from adjuvant chemotherapy.

In the 1998 Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview, there were only 177 premenopausal women with ER+ve disease who were randomised to adjuvant chemotherapy or a combination of chemotherapy and tamoxifen [57]. More recently Davidson and colleagues have reported on a trial comparing cyclophosphamide, doxorubicin, 5-fluorouracil (CAF), with CAF plus goserelin or CAF followed by

tamoxifen and goserelin [72]. The addition of goserelin to CAF failed to improve DFS, whereas tamoxifen added to CAF plus goserelin significantly improved the outcome compared to CAF plus goserelin (5- year RFS 78% versus 67%) [72]. Further trials will be required to define the benefit of the addition of optimal endocrine therapy, as defined by ovarian ablation and tamoxifen, to optimal adjuvant chemotherapy in very young women.

4.5. Fertility issues

Very young women are more likely to have concerns related to the effect of chemotherapy and endocrine therapy on their fertility. Chemotherapy is cytotoxic to the ovaries and a proportion of premenopausal women having chemotherapy for early breast cancer will develop menstrual abnormalities and premature menopause. The histological effect of cytotoxic chemotherapy is a progressive, permanent, dose-related depletion of primordial follicles with ovarian fibrosis and atrophy [73,74]. Increasing age is significantly correlated with increasing ovarian failure rate [68,73–76]. The risk of ovarian failure is also related to the chemotherapeutic agent and the cumulative dose. Alkylating agents (e.g. cyclophosphamide) appear to be the most gonadotoxic, but there is limited information about the newer agents such as the taxanes [73,75]. Young women require higher cumulative doses of chemotherapy to develop gonadal failure [73].

Most of the data pertaining to the likelihood of becoming amenorrhoeic with adjuvant chemotherapy for early breast cancer comes from women having CMF and these results may not be directly comparable to anthracycline-based chemotherapy regimens. In the MD Andersen series [77], no patient under 30 years of age treated with a doxorubicin-containing regimen stopped menstruating compared with 33% of patients aged 30–39 years and 96% of those aged 40–49 years. In young women, chemotherapy-related amenorrhoea may be reversible in 22–56% [73]. For patients with ER + ve tumours, it is not clear that there is any advantage to permanent menopause over reversible hormonal manipulations. Indeed, Jonat and colleagues showed that 90% of patients treated with goserelin for 2 years who were aged less than 40 years at randomisation had a return of menstrual function and this did not adversely affect their outcome [71].

Current options for women embarking on adjuvant chemotherapy in which preservation of fertility is desirable are limited. Women have the option of undergoing a cycle of ovarian hyperstimulation and egg harvest, but there are theoretical concerns about the safety of ovarian hyperstimulation in the breast cancer setting. The possibility of ovarian cryopreservation awaits clinical progress in *in-vitro* maturation of thawed primordial follicles, their *in vitro* fertilisation and embryo transfer. There has been some interest in attempting to minimise the gonadotoxic effect of chemotherapy by the co-treatment with a gonadotropin-releasing hormone (GnRH) agonist analogue to induce a temporary prepubertal hormonal milieu. Fox and colleagues reported on 13 breast cancer patients aged between 26 and 39 years who were given leuprolide during their adjuvant chemotherapy [78]. All patients resumed spontaneous menstruation within one year of completion of therapy. Recchia and colleagues have published a report on 64 patients who received goserelin 3.6 mg monthly in combination with their adjuvant chemotherapy [79]. With a median follow-up of 55 months, 86% of patients had resumed normal menses and one patient had a successful pregnancy.

4.6. Breast cancer and pregnancy

Cancer complicates between 0.02 and 0.1% of all pregnancies [80]. A high index of suspicion is required to diagnose breast cancer during pregnancy due to the anatomical and physiological changes occurring in the breast during this period. Previous studies have found an average delay of 5 months between first symptoms and the diagnosis [81]. Pregnant women have a 2.5-fold higher risk of being diagnosed with metastatic disease and a decreased chance of diagnosis with stage I disease [82]. Delay in diagnosis may contribute, at least partially, to the more advanced stage of presentation. The pathology of pregnancy-associated breast cancer is identical to that occurring in non-pregnant women [83,84]. Some studies have shown higher incidence of ER− tumours, but this probably reflects the young age of the patient cohort [84].

Treatment of pregnancy-associated breast cancer should adhere to the same principles as for non-pregnant women. Early termination of pregnancy has not been shown to improve outcome [85]. Modified radical mastectomy is the standard surgical treatment as radiotherapy during pregnancy would deliver high doses of radiation to the developing foetus. Breast conservation is an alternative if radiotherapy is likely to be scheduled after the delivery of the foetus. Recommendations for adjuvant chemotherapy should be based on the stage, age and pathological findings as for non-pregnant women. Chemotherapy should be delayed until the second trimester as exposure of the foetus to cytotoxics during organogenesis increases the risk of foetal loss and teratogenesis. Administration of chemotherapy in the second and third trimesters does not appear to carry an increased risk of teratogenesis [86].

Reported series show that matched for age and stage, pregnant women have similar actuarial survival and RFS to their non-pregnant counterparts [82,87,88]. Pregnancy after treatment for early-stage breast cancer does not appear to have an adverse effect on recurrence or survival [89].

5. Psychosocial issues

A diagnosis of breast cancer is obviously a stressful life-event for a woman at any age, but younger women are likely to face unique concerns and studies have shown them to be particularly vulnerable [90]. Young women more frequently have concerns about the impact of the diagnosis on their partner and may have practical issues related to the care of young children during their treatment. Research suggests that peer support and self-help groups decrease feelings of social isolation, depression and anxiety [91–93]. The development of specific support groups to deal with the unique issues related to breast cancer in adolescents and very young women is difficult due to the rarity of this condition. Young age of onset of disease has been identified as a risk factor predicting adverse psychological outcomes [28–32]. Very young women are especially vulnerable to psychological distress related to body image and sexuality. Loss of fertility may also be the source of psychological distress in young patients. Between 10 and 50% of women experience sexual problems following the diagnosis and treatment of breast cancer [94]. Adjuvant chemotherapy and endocrine therapy may affect sexual response and the induction of premature menopause may produce atrophic vaginitis. Physicians should be aware that these young patients have an increased risk of psychological problems and refer patients early for counselling.

6. Management of young women that are potentially at a high risk

A further consideration is the management of young women who are at an increased risk of developing breast cancer at a young age. These include women who have germline mutations in *BRCA1*, *BRCA2*, *TP53* (Li–Fraumeni syndrome) or *PTEN* (Cowden's syndrome). Factors which define women at potentially high risk of developing breast cancer are summarised in Table 3 [95]. For women with a mutated *BRCA1* gene, clinical disease may develop in approximately 50% by age 50 years and 80% by age 70 years. The risk of ovarian cancer is thought to be up to 20% by age 50 years [96].

Li–Fraumeni syndrome is a rare, dominantly-inherited condition caused by germline mutation in the *TP53* gene on chromosome 17 [97]. Affected patients have a 50% risk of cancer by age 35 years and a 90% lifetime risk. The syndrome is characterised by paediatric bone or soft-tissue sarcoma, early onset breast cancer, other cancers including those affecting the brain, lung and adrenals, and leukaemia. Cowden's syndrome is caused by a rare mutation in the *PTEN* gene on chromosome 10 [98]. Affected patients have an increased risk of developing breast or thyroid carcinoma at a young age and often have multiple hamartomas.

It is important for these women at a potential high risk to maintain breast awareness from a young age [99]. Patients should have a regular clinical breast examination every 6–12 months. Annual mammographic screening has been proposed from age 40 or 5 years earlier than the age of diagnosis of the youngest breast cancer case in the family [100,101], although the value of this remains unproven in this young age group. The use of MRI screening in the surveillance of high-risk women is the subject of ongoing clinical trials. Recently several trials on the use of MRI screening in women with a family history have been reported [102–104]. MRI appears to be more sensitive but less specific than mammography in women with a family history of breast cancer. These young women should be offered consultation with a familial cancer service for advice and counselling should they wish to clarify their genetic risk.

Girls and young women who have received mantle (mediastinal and/or axillary lymph node) radiotherapy for Hodgkin's disease are at subsequent increased risk

Table 3
Characteristics of women with a potential high risk of breast cancer

- Breast or ovarian cancer diagnosed in three or more first- or second-degree relatives on the same side of the family

OR

- Two or more first- or second-degree relatives on one side of the family diagnosed with breast or ovarian cancer, PLUS one or more of the following features (on the same side of the family)
  - Bilaterality
  - Onset of breast cancer before the age of 40 years
  - Onset of ovarian cancer before the age of 50 years
  - Breast and ovarian cancer in one individual
  - Jewish ancestry
  - Breast cancer in a male relative

OR

- One first- or second-degree relative diagnosed with breast cancer at age 45 years or younger, plus another first- or second-degree relative on the same side of the family with bone or soft-tissue sarcoma at age 45 years or younger

OR

- Demonstrated germline mutation in a high-risk breast cancer-associated gene such as *BRCA1*, *BRCA2* or *TP53* by genetic testing

Ref. [95].

of breast cancer [105,106]. The increase in the relative risk of developing breast cancer is most pronounced in women who are treated during puberty (10–16 years). Bhatia and colleagues followed a cohort of 1380 children treated for Hodgkin's disease to determine the incidence of second neoplasms [103]. They found a ratio of observed to expected breast cancer cases as high as 75-fold in a cohort of women previously receiving mantle radiotherapy for Hodgkin's disease [103]. This study reported an actuarial cumulative probability of breast cancer of 35% at age 40 years. The increased risk of breast cancer is detectable at 10 years after treatment with additional increases seen after 15 years or more of follow-up. In Diller's study, mammographic screening began 8 years after radiation and was recommended every other year until age 30 years and then annually [102]. The long-term risk of developing breast cancer falls with increasing age at the time of radiation exposure demonstrating that the predisposition to the development of breast cancer is related to the exposure of mammary tissue to radiation during the pubertal growth phase [103].

7. Conclusions

Breast cancer is a rare condition in adolescents and young adults. Invasive breast cancer occurring at a young age has more aggressive biological behaviour and is associated with a worse prognosis. Even when traditional prognostic factors of size and nodal status are controlled for, young women appear to have worse DFS and OS than older premenopausal women. Women developing breast cancer prior to the age of 35 years should be offered adjuvant therapy based on the poor prognosis in this age group: this would involve chemotherapy or endocrine therapy or both, depending on the ER status of the cancer and prognostic risk factors as described above. The general principles of managing adolescents and very young women with breast cancer are no different to those applying to older women, but there are a number of special considerations in these patients. Young women having breast-conserving surgery have a higher risk of local recurrence [23–27]. Although this does not appear to impact negatively on mortality, young women should be aware of this when considering their surgical options.

Very young patients are more likely to be concerned about the possibility of fertility impairment and premature menopause as a consequence of adjuvant chemotherapy. The risk of ovarian failure following adjuvant therapies for early breast cancer is related primarily to age. Although young women have a small risk of becoming permanently amenorrhoeic, the consequences of this can be devastating and the options should be discussed prior to commencement of adjuvant chemotherapy. Early data investigating the role of GnRH analogues during chemotherapy as a method of preserving ovarian function are encouraging, but we await more definitive data.

There are specific subsets of young women who have a potential high-risk of developing breast cancer at a young age based on a genetic predisposition or having previously received mantle irradiation. Prevention and early detection are vitally important in these women. At the moment, definitive data on effective screening and prevention of breast cancer in very young women are lacking, but there are a number of ongoing trials which should provide some evidence on which to base future recommendations.

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