Breast cancer in young women: climbing for progress in care and knowledge

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Approximately a third of newly diagnosed invasive breast cancers occur in women aged under 50 years and it is likely that the incidence of the disease in younger women will further increase as a result of demographic and lifestyle changes and progress in screening. Breast cancer in young women is different from that in older patients. Young women with breast cancer represent a distinct population for which tailored diagnostic, therapeutic and supportive interventions are required. This review highlights the complex diagnostic and therapeutic processes that women and care providers are faced with. Topics addressed include the need for more sensitive and specific diagnostic tools that are capable of detecting cancer in dense breasts, the development of individualized surgical and medical treatments in the early and advanced disease setting aimed at improving outcome and reducing long-term side effects, and adequate psychosocial interventions.

Epidemiology

Female breast cancer (BC) incidence in developed countries increased overall by 0.4%/year from 1987 to 2002, a slower rate than from 1980 to 1987 (3.7%/year), while disease-related death rates decreased, beginning in the early 1990s [1].

BC rarely occurs in young women: only 2.5% and 6.5% of the patients are aged under 35 years and 40 years of age at diagnosis, respectively [2]. Table 1 shows the annual incidence by age and Table 2 the temporal trends in age-adjusted incidence and death rates from 1973 to 1999 in the USA. No reliable data are available in emerging countries.

Risk factors

High breast density confers a two- to sixfold risk increase in BC both in premenopausal and postmenopausal women [3].

Germline mutations (e.g., *BRCA1* or *BRCA2*) account for 5–10% of BC overall and for 25% of cases in those aged under 30 years of age [4]. Another 15–20% of BCs are associated with gene polymorphisms and some rare genetic disorders: these include Cowden disease (phosphatase and tensin homolog [*PTEN*] gene mutation associated with hamartomas, breast and thyroid cancer at young age), and Li-Fraumeni syndrome (*p53* gene mutation, with predisposition to soft-tissue and bone sarcomas, brain, adrenocortical and BC). The contribution of other genes (i.e., *CHK2*) to BC predisposition requires further confirmation.

Young women who received radiotherapy during childhood and adolescence, for example, Hodgkin's disease survivors treated with mantle fields and chemotherapy, also have an increased BC risk [5].

The association between lifestyle and BC is controversial: in most case–control and prospective cohort studies, an inverse relationship has been found between weight and BC among premenopausal women [6], whereas the apparent positive correlation between alcohol intake and BC risk is independent from menopausal status.

The epidemiological association between physical activity and BC risk-reduction is stronger for postmenopausal than for premenopausal women [7].

Elevated blood concentrations of androgens, as opposed to progesterone levels, have been associated with increased BC risk in premenopausal women [8], whereas no clear evidence is available from recent data that dietary phytoestrogens may influence breast carcinogenesis.

Insulin-like growth factor I (IGF-I) may directly stimulate breast cell proliferation and the growth of transformed cells. High IGF-I levels have been shown to increase premenopausal but not postmenopausal BC risk [9]. The potential role of IGF-I as a preventive and therapeutic target needs to be further investigated [10].

Preventive strategies

Tamoxifen (TAM) is the only preventive drug approved by the US FDA based on a meta-analysis of four randomized trials showing a significant 38% overall reduction in relative risk (RR) of developing BC (odds ratio: 0.62; 95% confidence interval [CI]: 0.42– 0.89) [11]; however, no data as yet demonstrate an overall health benefit or increased survival. Risk/benefit models suggest that premenopausal women are less likely to develop treatment-related complications such as

Keywords: breast cancer, chemotherapy, endocrine therapy, fertility, genetic predisposition, menopausal symptoms, pregnancy, premenopausal women

future medicine

thromboembolic events and uterine cancer. TAM chemoprevention should be discussed as part of an informed decision-making process balancing individually calculated risks and benefits.

Retinoids induce a long-term 38% reduction of contralateral BC in premenopausal women. Fenretinide administration for 1 year in premenopausal women was associated with plasma IGF-I reduction and IGFBP-3 increase and low-dose TAM is known to reduce circulating IGF-I levels. The combination of low-dose TAM and fenretinide proved to be safe, but not synergistic in lowering IGF-I levels in premenopausal women [12]. Further investigation in high-risk young female groups is warranted.

Breast cancer in adolescents

BC among teenagers is very rare, is predominantly secretory carcinoma and has an excellent prognosis after local therapy alone. Only anecdotal information exists on lobular and duct carcinoma at this age.

Diagnosis

Breast density in women aged under 50 years impairs the diagnostic sensitivity of mammography [13], reducing the benefit of radiological screening in younger women, which is nevertheless associated with a significant 15–20% mortality reduction. Recently, a significantly higher accuracy of digital mammography has been reported among pre- and perimenopausal women with heterogeneously/extremely dense breasts on film mammography (Figure 1) [14], which must be weighed against an approximately 1.5- to 4-times cost increase. High-frequency breast ultrasound, together with mammography, significantly improves the positive predictive value of either technique.

Table 1. Breast cancer incidence by age.

Age (years)	Yearly incidence/ 100,000 women
Under 20	0.1
20–24	1.4
25–29	8.1
30–34	24.8
35–39	58.4
40–44	116.1
45–49	198.5

Adapted from [2].

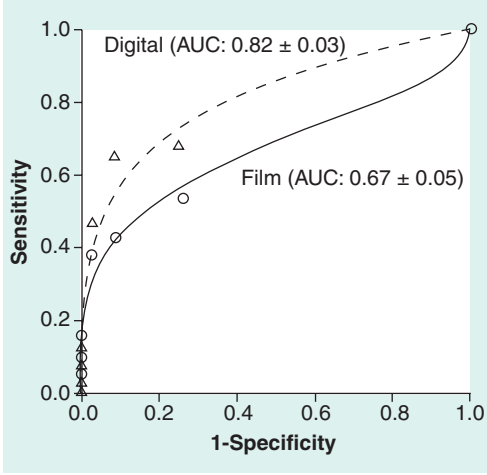
Breast magnetic resonance imaging (MRI) is of clinical value in patients with BC to assess for multifocal/multicentric disease, chest wall involvement, chemotherapy response, occult BC and in case of inconclusive conventional imaging findings. MRI is still investigational for screening of asymptomatic women with normal conventional imaging. Apart from cost, the most important limit is the low positive predictive value and specificity, together with its low sensitivity for ductal carcinoma *in situ* (DCIS). Small series of premenopausal women support breast MRI in supplementing conventional mammography for early detection of BC but additional data are awaited [15].

Table 2. Temporal trends in age-adjusted incidence and death rates.

	Year	APC	Year	APC	Year	APC	Year	APC
Incidence								
All ages	1973–1980	-0.6	1980–1987	3.7*	1987–1999	0.5*		
Under 50 years	1973–1980	-1.5	1980–1986	2.9*	1986–1999	-0.3		
50 years and over	1973–1980	-0.3	1980–1987	4.1*	1987–1999	0.7*		
Death								
All ages	1973–1979	-0.3	1979–1989	0.6*	1989–1995	-1.4*	1995–1999	-3.2*
Under 50 years	1973–1980	-1.5*	1980–1989	0.1	1989–1997	-2.7*	1997–1999	-7.4*
50 and over	1973–1991	0.5*	1991–1999	-2.1*				

**The APC is significantly different from zero ($p < 0.05$).*
APC: Annual percent change (based on rates age-adjusted to the 2000 US standard population).
Data from [2].

Figure 1. Diagnostic accuracy of digital and film mammography in premenopausal or perimenopausal women.



Perimenopausal women had last menstrual period at least 1 month but less than 12 months before mammography (95% CI: 0.05–0.24; p = 0.002). AUC: Area under curve. Reproduced with permission from [14].

To date, no specific data are available with positron-emission tomography (PET) and combined PET/computerised tomography (CT) in young patients [16].

Histopathology

BC at a young age has a more aggressive biological behavior: specifically, tumors show a higher grade and proliferating fraction, and more vascular invasion. Comparison of younger (<35 years) and older (≤50 years) premenopausal women in a single referral institution (1427 consecutive patients) indicated a greater proportion of endocrine unresponsive disease (i.e., tumors with no steroid hormone receptor expression) (38.8 vs 21.6%; $p < 0.001$), and a higher proportion of Ki-67 expression in more than 20% of the cells (71.4 vs 56%; $p < 0.001$) in the younger cohort. However, pathological tumor size, nodal status, number of positive axillary nodes and proportion of tumors with *HER2/neu* overexpression had a similar distribution among younger and older patients, thus not supporting previous data indicating more advanced disease at diagnosis in this patients' subset [17]. In addition, recent data do not support the inverse correlation reported in postmenopausal patients with ER-positive disease between *HER-2/neu* and progesterone receptor expression [18].

A recent analysis from 11 National Cancer Institute's (NCI) surveillance, epidemiology, and end results (SEER) registries showed age-specific incidence rates for different BC histological types [19]. Incidence for infiltrating duct, tubular, and lobular carcinomas increased rapidly until the age of 50 years then rose more slowly, medullary and inflammatory subtypes increased rapidly until 50 years then reached a plateau and papillary and mucinous carcinomas increased steadily at all ages. This observation suggests a greater impact of menopause on medullary and inflammatory carcinomas than on duct, tubular and lobular subtypes, and no effect on papillary or mucinous tumors. If confirmed by further studies with systematic histological slide review, standardized data for ER expression and menopausal status, this observation could reflect age-specific risk factors on different BC histopathologic types, with a potential impact on risk assessment, prevention and treatment.

Prognosis

A worse prognosis for young patients has been reported from the NCI-SEER database, the Finnish Cancer Registry, the SouthWest Oncology Group (SWOG) database, and a Danish study on young patients who did not receive adjuvant therapy [20].

Retrospective data suggest a possible angiogenic triggering of distant dormant micrometastases induced by surgery in premenopausal node-positive patients: tumor cells would synchronize into a temporal, highly chemosensitive state which, if confirmed by additional data, could explain the benefit of adjuvant chemotherapy and tumor aggressiveness in younger patients [21].

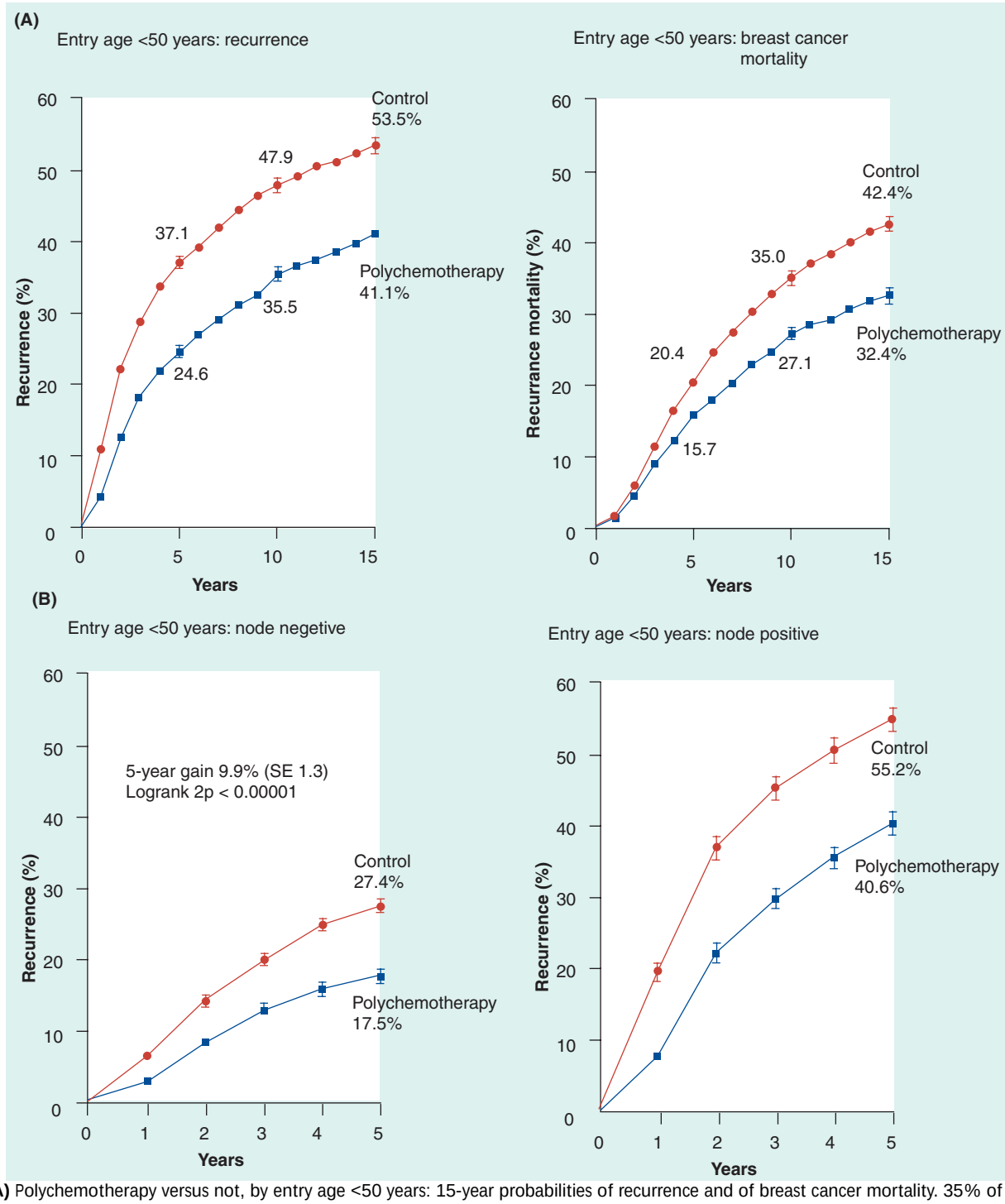
Local therapy

Young patients have a significantly higher risk for local/regional relapse [22]. The irradiation boost to the tumor bed significantly reduces the local recurrence rate (LRR) in women aged 40 years or younger, and breast-conserving therapy as compared with radical mastectomy apparently does not adversely affect overall survival despite a higher 5-year recurrence rate [23].

No consistent data are available on late cardiac effects of radiotherapy plus anthracyclines and/or taxanes as well as other radiotherapy-related complications in young patients with very long life expectancy.

Further prospective studies are warranted in young patients to assess the relationship between endocrine therapies, radiotherapy efficacy and late local complications.

Figure 2. Polychemotherapy alone versus nil in patients 50 years old or younger.

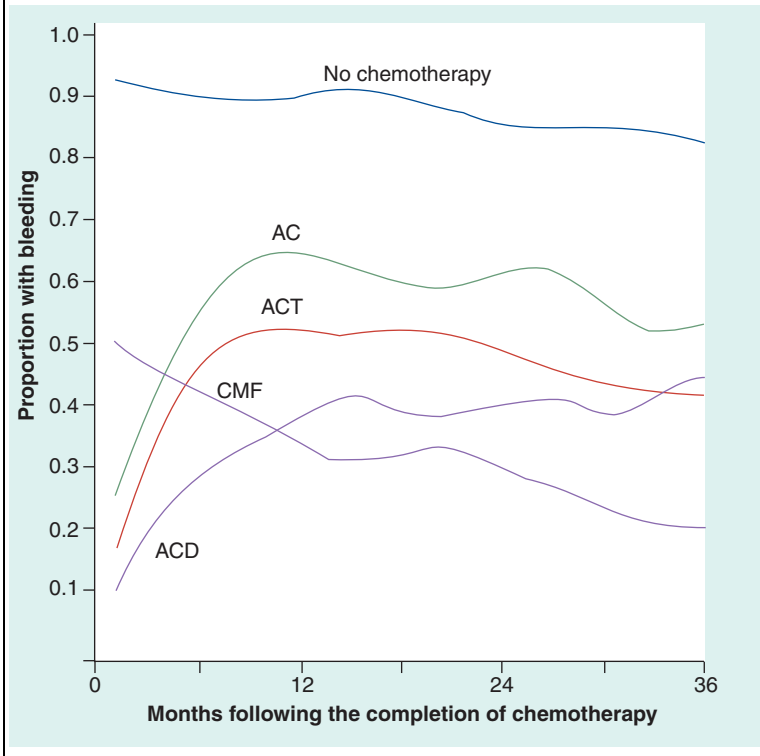


(A) Polychemotherapy versus not, by entry age <50 years: 15-year probabilities of recurrence and of breast cancer mortality. 35% of patients node-positive. **(B)** Polychemotherapy versus not, by nodal status and entry age: 5-year probabilities of recurrence. Reproduced from [42] with permission from Elsevier.

Hereditary breast cancer

Individualized preventive and therapeutic strategies are recommended to women with identified mutations. Tailored information by a multidisciplinary team (family doctors, oncologists, gynecologists, surgeons, geneticists and psychologists) is essential to provide qualified support during and after the complex decision process [24].

Figure 3. Bleeding after chemotherapy by type of regime.



AC: Doxorubicin and cyclophosphamide; ACT: Doxorubicin, cyclophosphamide, paclitaxel; CMF: Cyclophosphamide, methotrexate, fluorouacil; ACD: Doxorubicin, cyclophosphamide, docetaxel. Reprinted with permission from the American Society of Clinical Oncology [47].

Systematic surveillance with breast MRI allows an earlier diagnosis of hereditary BC compared with mammography alone or in combination with high-frequency breast ultrasound [25].

Bilateral prophylactic mastectomy

Bilateral prophylactic mastectomy reduces the risk of BC by more than 90%, but is a major surgical procedure with commonly associated concomitant reconstruction [26].

Five years of TAM reduces BC incidence by as much as 49%, but increases the risk of endometrial cancer and venous thromboembolism by twofold or more [4]. Lowering the dose or adding aspirin are proposed strategies to improve the cost:benefit ratio. Pharmacological ovarian function suppression (OFS) by luteinizing hormone-releasing analogs (LH-RH-a) in mutation carriers is under evaluation, together with different interventions to prevent bone loss (e.g., raloxifene, hormone replacement therapy [HRT] or bisphosphonates) and assessment of bone surrogate markers, quality of life and lipid profile [27].

Bilateral prophylactic salpingo-oophorectomy

Bilateral prophylactic salpingo-oophorectomy (BSO) not only reduces BC risk by approximately 40%, but also improves OS and cancer-specific survival [28]. The benefit is not appreciably diminished by short-term HRT (used to lessen menopause-related symptoms), in terms of both breast cancer risk and life expectancy [26]. Questions arise regarding HRT formulation, length of treatment and possible total hysterectomy to allow subsequent unopposed estrogen administration.

Histopathology

Many breast cancer 1 (BRCA1) carcinomas show the basal-cell phenotype – a high-grade, highly proliferating ER- and HER2/neu-negative BC subtype – while BRCA2 carcinomas are of higher grade than sporadic age-matched controls, but tend to be ER+ [29].

The best local therapy in mutation carriers is controversial; breast-conserving therapy is associated with late side effects, recurrence rates and OS comparable to sporadic disease controls, despite the supposed increased radiotherapy sensitivity and the risk of contralateral disease [30].

Systemic treatment

Preclinical information strongly indicates that *BRCA1* mutated cells are hypersensitive to platinum-compounds and relatively resistant to doxorubicin and taxanes.

Breast cancer during pregnancy

With the recent trend for women to delay childbearing, the incidence of pregnancy-associated BC (within 12 months postpartum), reported as an average of 1/1000 births, is increasing [31].

The optimal management of gestational BC is provided by an interdisciplinary and dedicated team (gynecologists/obstetricians, oncologists, surgeons, neonatologists, psychologists and nursing staff) as effective maternal treatments have to be balanced with fetal wellbeing. The decision-making process includes consideration of the biological characteristics and stage of the disease, the date of pregnancy, the mother/parents opinion concerning abortion, the need for preterm delivery and treatment-associated morbidity.

The usual diagnostic modalities are not always applicable or effective during pregnancy: mammography has a high false-negative rate, and ultrasound findings are somewhat different from nonpregnant women as a consequence of the increased breast density. Atypical

Figure 4. Relapse-free survival by 12-month amenorrhea status (receptor positive patients only.)

Reproduced from [36].

cytomorphologic features are often seen in fine-needle aspirates, making core-needle biopsy a more appropriate procedure.

Overall, the prognosis of pregnancy-associated BC is worse because a large proportion of patients are diagnosed with advanced disease: when matched for age and disease stage, the prognosis is similar to nonpregnant women.

Treatment modalities

Typical anesthetics readily reach the fetus but are not known to be teratogenic [32].

Modified radical mastectomy is the traditional surgical option in pregnant patients with early disease, but breast-conserving therapy and sentinel node biopsy have been shown to be feasible and safe [33].

Breast or chest wall radiotherapy should be avoided because the fetal dose, regardless of the trimester, can cause permanent complications.

Systemic treatment

Little information is available concerning the effects of chemotherapy during pregnancy. Several drugs are available (mainly anthracyclines, cyclophosphamide and fluorouracil combinations) starting from the second trimester, upon completed organogenesis [34]. In the second/third trimester, chemotherapy can be associated with intrauterine growth retardation and prematurity, although the risk seems low with standard doses.

Tamoxifen

TAM, a known teratogenic drug, is generally contraindicated [32].

Fertility & pregnancy after breast cancer

The median age of first pregnancy has gradually increased from 26.2 years in 1972 to 29.1 in 2000. Many young patients with BC are therefore childless and have a strong desire to become mothers.

Fertility

Fertility after BC treatment should be discussed prior to planning of adjuvant therapies [35]. Rates of permanent amenorrhea after chemotherapy depend on the agents used and woman's age at the time of treatment [36]. The administration of LHRH-a before and during chemotherapy has been suggested to protect ovarian function [37]. A Phase III trial of LHRH-a administration during chemotherapy in early stage, endocrine-unresponsive premenopausal BC is currently being conducted by the SWOG.

Other methods to retain fertility are under evaluation: transplantation of cryopreserved ovarian tissue [38], *in vitro* fertilization and embryo cryopreservation after ovarian stimulation with follicle-stimulating hormone (FSH) and TAM or letrozole are promising but both their safety and efficacy are still unknown [39].

Pregnancy after breast cancer

Pregnancy after BC does not seem to increase the risk of recurrence, and it may even be protective [40]. The reluctance to consider pregnancy, even for women with node-negative disease, is therefore unjustified.

Recent data are apparently reassuring concerning the safety of subsequent pregnancies for *BRCA1* and *BRCA2* carriers [41]. The relationship between pretreatment with TAM and neonatal malformations is also an issue of concern.

Adjuvant systemic therapy

Trial results of adjuvant treatments for premenopausal women largely reflect outcomes for patients in their 40s. Thus, findings from studies that consider the average results for 'premenopausal' women may not be directly applicable to younger patients.

The available consensus guidelines for the systemic adjuvant therapy of premenopausal BC patients give different recommendations due to somewhat conflicting and complex data [42–45]. Risk assessment based mainly on nodal status, vascular invasion, tumor size and proliferation

Table 3. Relative risk of relapse* and corresponding 5-year disease-free survival for premenopausal women in chemotherapy-alone groups in trials conducted by IBCSG, NSABP, ECOG and SWOG.

Group	Total patients	ER-positive		ER-negative		Interaction p-value
		< 35	*>35‡*	*< 35*	*>35‡*	
IBCSG	2233	1.84 (72/96)	1.00 (737/1353)	1.13 (50/88)	1.02 (370/696)	0.009
NSABP	5849	1.72 (254/402)	1.00 (1210/2716)	1.27 (214/441)	1.12 (1045/2290)	0.0001
ECOG	1112	1.54 (42/71)	1.00 (274/602)	1.40 (40/73)	1.26 (195/366)	0.17
SWOG	670	2.67 (11/29)	1.00 (48/293)	0.81 (7/55)	1.13 (52/293)	0.012

Cohorts defined by age and estrogen receptor status are compared with the reference population of older women with ER-positive tumors (number of events/number of patients are shown in parentheses).

**Includes breast cancer relapses, second primary breast tumors and deaths without relapse for IBCSG (also includes nonbreast second primaries) ECOG and SWOG; includes only breast cancer relapses (other events are censored) for NSABP.*

‡Premenopausal ≥35 years old for IBCSG, ECOG and SWOG; 35–49 years old for NSABP.

ECOG: Eastern Cooperative Oncology Group; ER: Estrogen receptor; IBCSG: International Breast Cancer Study Group; NSABP: National Surgical Adjuvant Breast and Bowel Project; SWOG: Southwest Oncology Group.

Reproduced from [51].

markers is no longer the major determinant in the 2005 St. Gallen algorithm for clinical decision-making. Endocrine responsiveness has become the primary factor determining treatment choice [44].

Most data on adjuvant treatment efficacy were obtained during an era when details on endocrine responsiveness (determined by ligand-binding measurement of receptor content) were either incomplete or imprecise.

Adjuvant chemotherapy

Adjuvant chemotherapy is extensively used across the board in premenopausal patients due to its overwhelming beneficial effects on outcome. In the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis, on average, anthracycline-based regimens produce BC death rate ratios of approximately 0·62 and 0·80 (i.e., proportional mortality reductions of 38 and 20%), in women under 50 years and in those aged 50–69 years, respectively [42]. These reductions are independent of ER status (Figure 2).

Endocrine-responsive tumors

Among patients with endocrine-responsive tumors, the favorable impact of chemotherapy is probably due to a complex mixture of cytotoxic and endocrine effects. The majority of premenopausal BC patients are 40 years of age or over and more than 80% of them will develop amenorrhea following six cycles of classical cyclophosphamide, methotrexate and fluorouracil (CMF) chemotherapy. By contrast, less than 50% of women aged under 40 years develop amenorrhea with CMF. Short, anthracycline-based regimens result in less frequent premature menopause compared with classic CMF (34 versus 69%) [46].

Women receiving CMF are more likely to bleed during chemotherapy than women receiving doxorubicin and cyclophosphamide (AC)-containing regimens; however, after a year these women are less likely to resume menses than those who received the AC regimens (Figure 3) [47]. The incidence of chemotherapy-induced amenorrhea is also apparently higher in women treated in the follicular phase rather than in other menstrual cycle phases (67.6 versus 45.5%) [48].

The addition of taxanes does not seem to increase the rate of permanent amenorrhea as compared with anthracycline-only regimens [47,49].

The prognosis of women who develop amenorrhea, even temporarily, after chemotherapy tends to be better than that of those who continue to menstruate (Figure 4) [36,46].

Very young women (younger than 35 years) with endocrine-responsive tumors who received adjuvant CMF without endocrine therapies within several trials conducted by the International Breast Cancer Study Group (IBCSG) had a statistically significant higher risk of relapse than older premenopausal patients. By contrast, outcome was similar in younger and older premenopausal patients with endocrine-unresponsive disease [50].

A joint retrospective analysis of 9864 patients treated within trials of chemotherapy alone from four cooperative groups across the world (IBCSG,

National Surgical Adjuvant Breast and Bowel Project [NSABP], Eastern Cooperative Oncology Group [ECOG] and SWOG) in the same patients' population confirmed this observation. Table 3 summarizes the results: in each trial the relative risk of an event, stratified by study and treatment group, was substantially higher for younger patients compared with older patients. This phenomenon was not observed for patients with ER-negative tumors. The disease-free survival (IBCSG and SWOG) and relapse-free interval (NSABP) curves were similar (Figure 5), suggesting that the endocrine effects of chemotherapy alone are insufficient for the younger age group [51].

Adjuvant chemotherapy in patients with endocrine-unresponsive disease

Overview analyzes for the ER-poor cohort in trials not confounded by TAM show that the benefits of adjuvant chemotherapy are substantial and unrelated to age in such patients (Table 4) [42].

Current relevant questions include the timing of chemotherapy after surgery, type, schedule and duration of treatment, chemotherapy dose escalation and dose density [44].

Several potential markers for response or resistance (e.g., HER2/neu, p53 and p95) [52,53] or gene profiling [54] might help to refine the selection of chemotherapy for patients whose tumors are exclusively affected by cytotoxics.

Chemoendocrine therapy

Nearly all the evidence on chemoendocrine therapy (either concurrent or sequential) refers to postmenopausal women [42].

The recently published landmark results of IBCSG trial 13–93 (adjuvant TAM after anthracycline-containing chemotherapy versus chemotherapy alone) in 1246 node-positive premenopausal patients showed a significantly improved outcome in endocrine-responsive disease by the addition of TAM and confirm similar observations in previous smaller trials (Figure 6) [55].

Adjuvant endocrine therapies

Approximately 60% of premenopausal patients with BC have endocrine-responsive disease. The ovary is the major site of estrogen production, but a smaller amount is also converted from androstenedione and testosterone by the aromatase in extragonadal tissues (mainly fat and breast) [56].

Currently available therapies either decrease estrogen production (OFS and aromatase inhibitors [AIs]), modulate ER activity (TAM and other selective ER modulators [SERMs]), or downregulate ER (SERDs) (fulvestrant).

Ovarian function suppression

Permanent ovarian ablation can be achieved by bilateral salpingo-oopherectomy (BSO) or radiotherapy, reversible pharmacological ovarian suppression by LHRH-a administration.

Almost 8000 women aged under 50 years with ER+ or ER-unknown disease have been randomized into trials of ovarian ablation by surgery or radiotherapy (63% ER-untested) or of OS by some years of LHRH-a treatment (26% ER-untested). The EBCTCG meta-analysis of these trials has unequivocally established that overall there is a significant positive effect of OFS on BC recurrence and mortality that is not age-dependent (<40 years versus 40–49 years at entry) (Figure 7) [42]. The effect is not as impressive as in earlier meta-analyzes, when OFS was not generally tested against effective chemotherapies [57]. The benefit from OFS appears in fact smaller in trials including chemotherapy, presumably due to the endocrine effects of chemotherapy.

There is no convincing comparison among the different forms of OFS. Besides the indirect antitumor effect obtained through the downregulation of pituitary LHRH receptors and the consequent interruption of ovarian steroid production, emerging data suggest that LHRH-a may also exert a direct antitumor effect.

Acceptance of OFS is a significant problem for younger patients; issues include menopausal symptoms/signs, psychological distress, and adjustment in personal and family plans. Symptoms of treatment-induced early menopause may be more debilitating than those of natural menopause due to more rapid decline in estrogen levels.

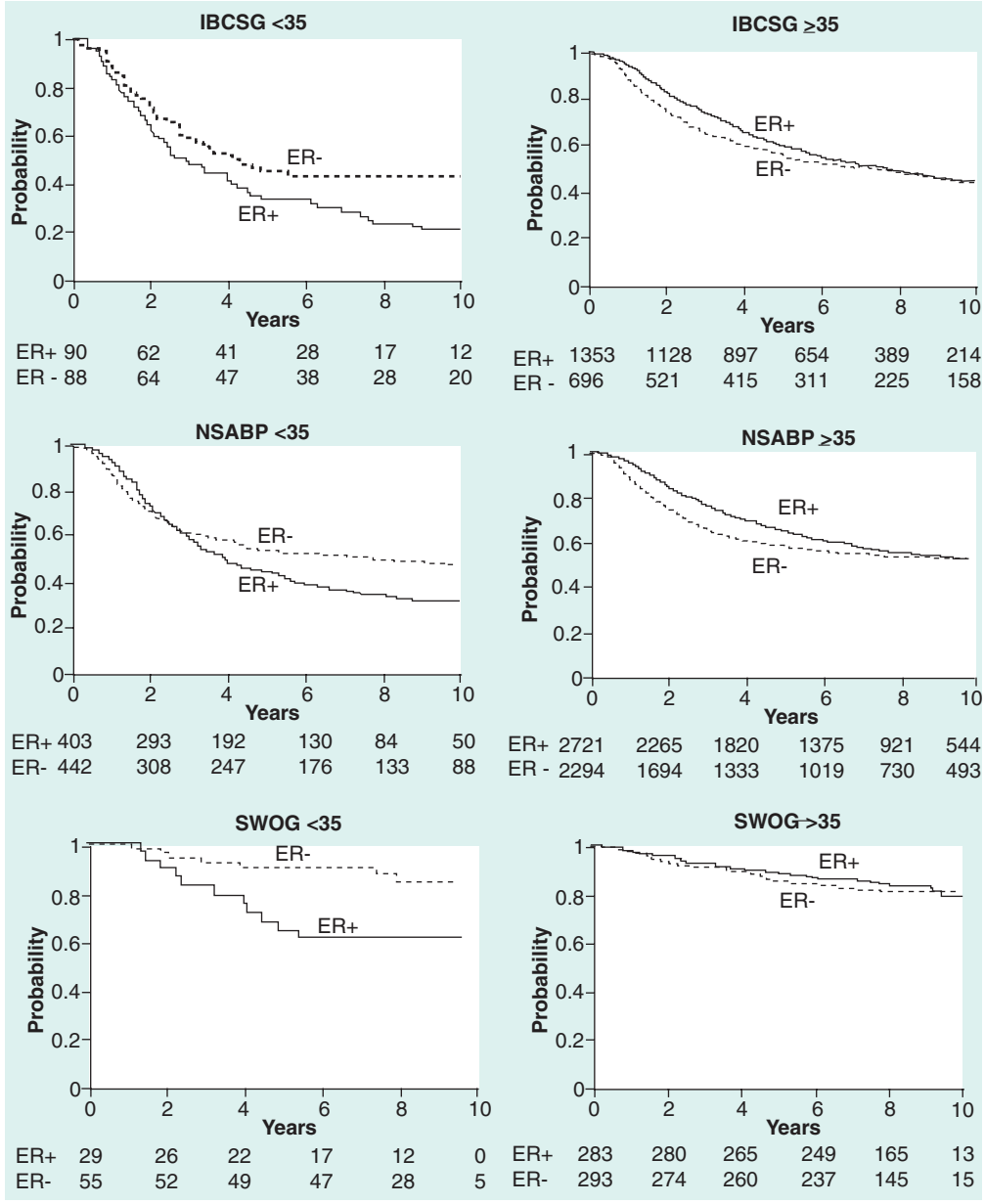
A survey in 102 women aged 40 years or younger at BC diagnosis suggested that modest gains in survival are sufficient to make adjuvant endocrine therapies worthwhile. About half of participants thought treatment was acceptable for a survival absolute gain of 2%, and for a gain in life expectancy of 3 months. Women who suffered more severe side-effects required larger gains to make endocrine therapies worthwhile [58].

Younger women also have unmet needs for information on fertility and menopause [59]: further prospective research should clarify the association between improvement in information and psychological adjustment.

Tamoxifen & other selective estrogen receptor modulators

Since the 1990s TAM has also gained acceptance as adjuvant therapy for premenopausal women. The EBCTCG meta-analysis of all

Figure 5. Kaplan–Meier plots of disease-free survival (IBCSG and SWOG) and relapse-free survival (NSABP) for ER-positive versus ER-negative cohorts separately for younger (<35 years old) and older (≥35 years old) premenopausal women enrolled in chemotherapy-alone treatment groups.



ER: Estrogen receptor; ISCSG: Internation Breast Cancer Study Group; NSABP: National Surgical Adjuvant Breast and Bowel Project; SWOG: Southwest Oncology Group. Reproduced from [51].

randomized trials of adjuvant TAM versus no therapy revealed that 2–5 years of treatment have similar efficacy in all age groups, including patients aged under 40 years (Figure 8) [42].

TAM is associated with a variety of side effects: investigations of bone mineral density in patients after prolonged TAM have reported a possible decrease of density in premenopausal as compared with post-menopausal women [60].

No data on other SERMs (e.g., raloxifene, toremifene and idoxifen) or SERDs, (e.g., fuwlvestrant), are yet available in premenopausal women.

Table 4. Polychemotherapy alone versus nil by age in ER-poor patients.

	Events/woman-years		Polychemotheraphy events		Ratio of annual event rates
Category	*Allocated polychemotherapy*	*Adjusted control*	*Logrank O-E*	*Variance of O-E*	*Polychemotherapy: Control*
Entry age <50 years: recurrence/woman -years	272/6904 (3.9%/year)	358/5326 (6.7%/year)	-67.1	135.6	0.61 (SE 0.07)
Entry age <50 years: breast cancer mortality/women	195/876 (22.3%)	248/797 (31.1%)	-37.7	99.3	0.68 (SE 0.08)
Entry age 50–69 years: recurrence/women -years	282/5641 (50%/year)	363/4859 (7.5%/year)	-51.5	131.0	0.67 (SE 00.7)
Entry age 50–69 years: breast cancer mortality/women	222/721 (30.8%)	292/753 (38.8%)	-33.4	108.4	0.74 (SE 0.08)

ER: Estrogen receptor; O-E: Observed=expected; SE: Standard error. Reprinted from [42] with permission from Elsevier.

Ovarian function suppression plus tamoxifen

In premenopausal women TAM increases estradiol levels, thus reducing the occupancy of ERs by TAM [56]. This effect is prevented by LHRH-a, which might explain the observed superiority of the combination in advanced disease.

Several adjuvant studies have shown that the combination of OFS plus TAM is safe and at least as effective as chemotherapy for endocrine-responsive premenopausal patients [61]. Definitive evidence of superiority compared with TAM alone, especially after chemotherapy, is missing.

There is some evidence that *HER2/neu* overexpression not only has no detrimental effect on treatment outcome, as is the case with TAM alone, but might even be favorable on response to adjuvant ovarian ablation and TAM in endocrine-responsive disease [62].

Aromatase inhibitors

The combination of LHRH-a and AIs is an effective second-line therapy in premenopausal patients progressing under LHRH-a and TAM [63]: the combination is currently being tested as adjuvant treatment in several trials (Table 5).

Future research in endocrine therapy

Additional questions need to be answered: specifically, the optimal duration of LHRH-a administration, the value of sequential chemotherapy and OFS, particularly in women without chemotherapy-related amenorrhea and the utility of combined OFS and TAM/AIs. The rarity of the disease makes the global collaboration between cooperative groups essential to conduct tailored and powered clinical trials (Table 4).

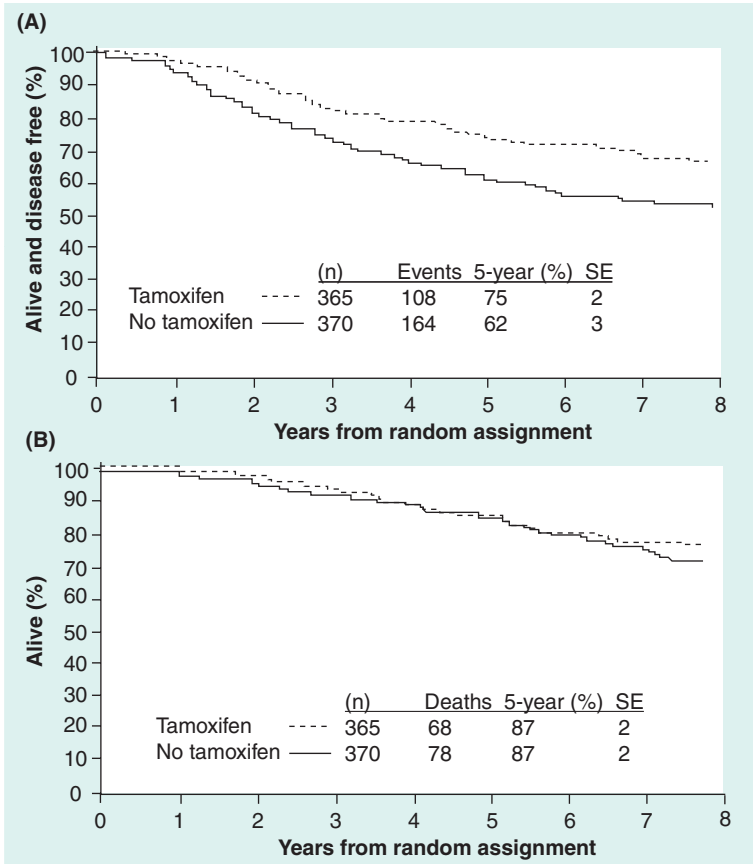
Gene expression profiling could also possibly identify patients' subsets deriving different benefit from endocrine therapies [54]. Polymorphisms in TAM metabolizing genes are known to affect plasma concentrations of TAM metabolites [64]: the possible impact on clinical outcome needs to be investigated.

How to best manage menopausal symptoms remains controversial: decisions must be taken after individual evaluation of the risk/benefit profile of each potential intervention (e.g., hormone replacement therapy, bisphosphonates).

Targeted therapies

The role of HER in BC cell growth is well characterized. The recently published positive results of four multi-institutional trials of trastuzumab (anti-*HER2/neu* monoclonal antibody) in

Figure 6. Sequential chemoendocrine therapy in premenopausal women with endocrine-responsive node-positive disease (IBCSG trial 13–93).



(A) Disease free survival; **(B)** Overall survival. IBCSG: International Breast Cancer Study Group; SE: Standard error. Adapted from [55].

addition to adjuvant chemotherapy for patients with *HER2/neu* overexpression/amplification were significant regardless of patients' age [65].

New drugs targeting other HER family members (e.g., HER1), their potential crosstalk with the endocrine pathway and antiangiogenic agents will be systematically assessed as adjuvant or palliative therapies in BC.

Treatment of young women with advanced disease

Young women with advanced BC are usually treated considering the general incurability of the disease, employing OFS together with other treatment options if the disease is endocrine-responsive. The sequential use of endocrine therapies followed on progression by chemotherapy might be a reasonable approach, although this has not been specifically tested in the very young population.

In the future, assessment of circulating tumor cells could provide an early and reliable indication of treatment response/resistance [66].

Interpersonal & family relations & professional decisions

Younger women might be particularly vulnerable to the emotional distress and disease-related uncertainty forcing patients to face complex decisions and treatments before attaining many personal accomplishments [67]. Psychological support is associated with a better quality of life, but trial results are not generally age group-specific [68].

Conclusions

A significant proportion of the youngest patients with BC have an adverse prognosis due, in part, to a more aggressive disease presentation, thus urging better diagnostic tools and targeted local interventions.

The belief that an increased relapse risk justifies the systematic use of cytotoxics and the demonstration of significant chemotherapy efficacy for premenopausal women (most of whom are >34 years) contributed to a lack of progress in evaluating endocrine therapies for this subset of BC patients.

There is an urgent need for tailored treatment investigations in this younger population, for whom chemotherapy is prescribed across the board. endocrine therapies must be investigated in endocrine-responsive disease in which current approaches are still suboptimal. We must improve our understanding regarding how best to use endocrine approaches, including timing of surgery according to the menstrual cycle phase, OFS and the use of SERMs/SERDs and AIs.

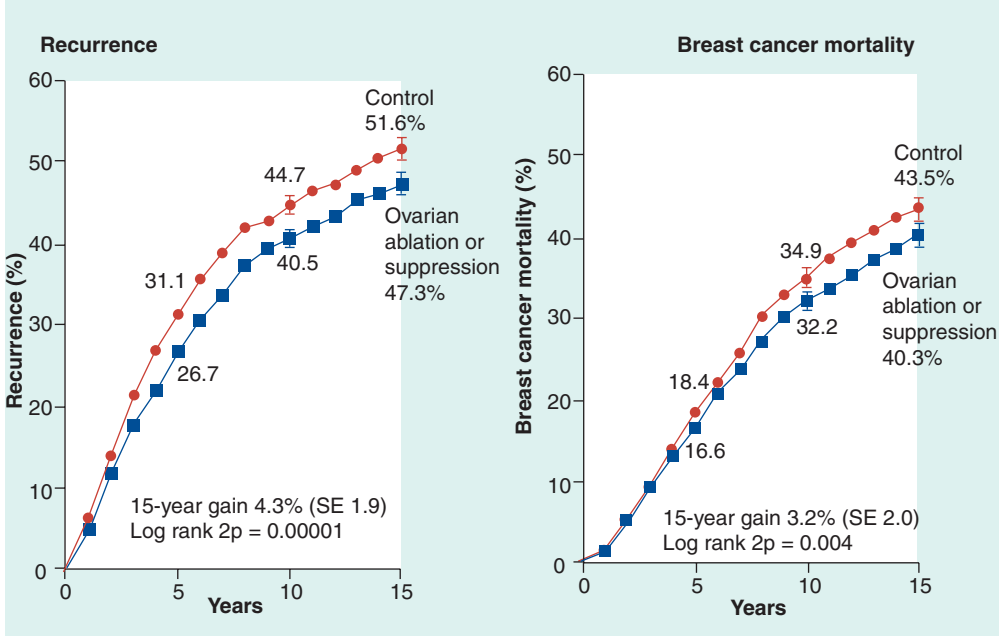
Chemotherapy-related questions in younger patients, such as the timing, duration and intensity of treatment, might be better answered in patients with endocrine-unresponsive tumors, for whom the endocrine effects of chemotherapy do not confound observations.

Questions of endocrine therapies (SERMs, SERDs, AIs or OFS or the combination of both) and of chemo–endocrine combinations should also consider patients' desire to become pregnant and the presence of *BRCA1/2* mutations.

Accrual of younger women to past and current clinical trials is insufficient to allow significant progress on treatment of these patients. Prospectively designed global collaborations to specifically investigate diagnostic/therapeutic approaches are ongoing and will hopefully improve the outcome results in this complex patient population.

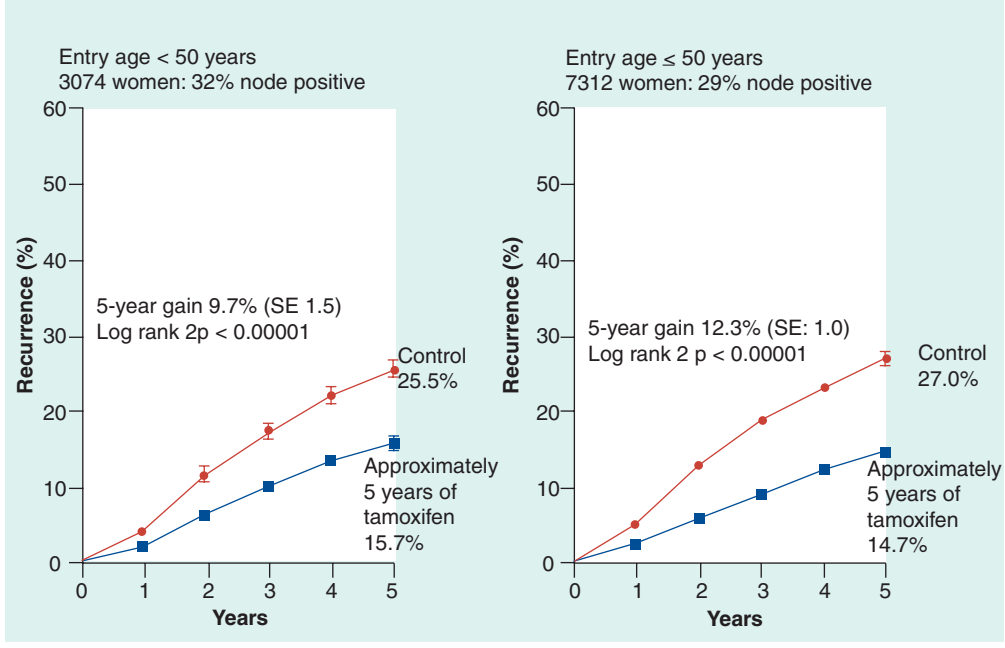
'Breast cancer knows no boundaries, it's an equal-opportunity disease and does not discriminate on the basis of age or race.' A survey of the American Young Survival Coalition underscores the perception of 'age discrimination or bias' related to the rarity of the disease at young

Figure 7. Ovarian ablation or suppression versus not in ER-positive (or ER-unknown) disease: 15-year probabilities of recurrence and of breast cancer mortality.



A total of 7601 women, all with entry age <50 years: 47% ER-unknown, 61% node-positive. ER: Estrogen receptor; SE: Standard error. Reprinted from [42] with permission Elsevier.

Figure 8. About 5 years of tamoxifen versus not in premenopausal women with ER-positive (or ER-unknown) disease.



ER: Estrogen receptor; SE: Standard error. Adapted from [42].

Table 5. Ongoing clinical trials testing endocrine therapies and endocrine effects of chemotherapy for premenopausal patients with endocrine responsive breast cancer.

Study	Design
ABCSG	Tamoxifen + LHRH-a ± bisphosphonate
	Anastrozole + LHRH-a ± bisphosphonate
IBCSG/BIG SOFT	Tamoxifen × 5 years
	OFS + tamoxifen × 5 years
	OFS + exemestane × 5 years
IBCSG/BIG TEXT	LHRH-a (± CT) + tamoxifen × 5 years
	LHRH-a (± CT) + exemestane × 5 years
IBCSG/BIG PERCHE	OFS + tamoxifen/exemestane × 5 years
	OFS + CT + tamoxifen/exemestane × 5 years

ABCSG: Austrian Breast and Colorectal Cancer Study Group; BIG: Breast International Group; CT: Computed tomography; IBCSG: International Breast Cancer Study Group; LHRH-a: Luetinising hormone releasing hormone a; OFS: Ovarian function suppression with oophorectomy or ovarian radiation or LHRH analog; PERCHE: Premenopausal Endocrine Responsive Chemotherapy trial; SOFT: Suppression of Ovarian Function Trial; TEXT: Tamoxifen and Exemestane Trial.

age, the need for easily available and cost-effective diagnostic tools and for rigorous and global disease approach by healthcare providers [69].

Future perspective

Upfront and multidisciplinary global planning within experienced breast units should become the standard of care in young women with breast cancer.

Widespread genetic profiling by novel microarray techniques will hopefully lead to better subtype classifications with predictive and prognostic relevance, allowing individualization of care.

Well designed and conducted international trials should address the several unresolved questions of optimal treatment combinations and duration (chemotherapy and endocrine treatments), integration of novel target therapies (growth factors' inhibitors, antiangiogenic agents, vaccines), innovative local therapies, and focused diagnostic interventions.

Quality of life and psychosocial assessment, in particular addressing menopause-related side effects, fertility issues and cosmetic long-term results, should be systematically investigated.

Advocacy groups should be involved in educating young women and care providers to improve early detection, treatment opportunities and outcome results in this selected patient population.

Executive summary

Risk factors and prevention

- Breast density and genetic predisposition are recognized breast cancer risk factors in premenopausal women.
- Weight, diet, physical activity, sex steroids and growth factors play a different and complex role in breast carcinogenesis in younger as compared with older women.
- Tamoxifen is approved as chemoprevention in high-risk premenopausal women in the USA only. Prophylactic surgery is available to women with known genetic predisposition. The long-term risk:benefit ratio of these interventions has to be individually and thoroughly addressed.

Diagnosis

- Breast density complicates breast cancer screening and early diagnosis in premenopausal women. Mammography (film and/or digital), high-frequency breast ultrasound and magnetic resonance, performed by dedicated and experienced radiologists, can improve early detection. The best combination of the different techniques is still controversial. No data on positron emission tomography/computerized tomography in young women are available yet.

Tumor characteristics and prognosis

- Breast cancer at a young age is associated with more aggressive biological behavior, a significantly higher risk for local/regional relapse and a worse prognosis. Specific surgical and radiation therapy approaches need to be implemented with particular attention to long-term toxicity and cosmetic results.

Adjuvant systemic therapy

- Endocrine responsiveness (i.e., steroid hormone-receptor expression) is the primary factor determining treatment choice.

Executive summary

Adjuvant chemotherapy

- Among patients with endocrine-responsive tumors the favorable impact of chemotherapy is probably due to a complex mixture of cytotoxic and endocrine effects.
- In patients with endocrine-nonresponsive disease current relevant questions include the timing of chemotherapy after surgery, type, schedule and duration of the cytotoxic regimens, as well as dose escalation and dose density.

Adjuvant endocrine therapies

- Currently available therapies either decrease estrogen production (ovarian function suppression) or modulate estrogen receptor activity (tamoxifen).
- Several questions still need to be answered: specifically, the optimal duration of pharmacological ovarian function suppression, the value of sequential chemotherapy and ovarian function suppression, particularly in those women without chemotherapy-related amenorrhea, and the utility of combined endocrine therapies (e.g., ovarian function suppression and tamoxifen or aromatase inhibitors).
- Better tools to manage early menopause signs/symptoms (e.g., bone density, serum lipid levels and sexual disturbances) need to be implemented and monitored.

Hereditary breast cancer, breast cancer during pregnancy and pregnancy after breast cancer

- Individualized, multidisciplinary approaches are needed to best address the complex physical and psychosocial aspects of familial breast cancer predisposition, fertility after breast cancer treatment and tumors occurring during pregnancy.

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