Biology of breast cancer in young women

Breast Cancer RESEARCH

REVIEW

Biology of breast cancer in young women

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Abstract

Breast cancer arising at a young age is relatively uncommon, particularly in the developed world. Several studies have demonstrated that younger patients often experience a more aggressive disease course and have poorer outcome compared to older women. Expression of key biomarkers, including endocrine receptors, HER2 and proliferation markers, appears to be different in younger patients and young women are more likely to harbor a genetic predisposition. Despite these differences, little research to date has focused on the biology of these tumors to refine prognosis, and potentially direct treatment strategies, which remain similar to those offered to older patients. Accumulating evidence suggests the differences in breast stroma in younger patients and changes that occur with pregnancy and breastfeeding likely contribute to the different biology of these tumors. Reproductive behaviors appear to impact the biology of tumors developing later in life. In addition, tumors arising during or shortly following pregnancy appear to exhibit unique biological features. In this review, we discuss our emerging understanding of the biology of breast cancer arising at a young age at both the pathologic and the genomic level. We elucidate the potential role of genomic signatures, the impact of pregnancy and breastfeeding on breast cancer biology, and how even current knowledge might advance the clinical management of young breast cancer patients.

Introduction

Breast cancer is predominantly a disease of aging, with only 5 to 7% of patients diagnosed below the age of 40 years in the developed world [1]. In less developed regions where population-based screening is not routine and populations are much younger on average, such as in Africa and the Middle East, a higher proportion of patients are diagnosed below the age of 40, reaching as high as 20% [2,3]. Whether there are underlying genetic differences or environmental factors that would render women in Africa and the Middle East more prone to develop the disease at a young age is the subject of ongoing research [4].

Nevertheless, young age at diagnosis of breast cancer has emerged world-wide as an independent factor associated with higher risk of relapse and death in several large studies, even when more aggressive therapies are administered [5-9] (Table 1). Expression of key biomarkers, including endocrine receptors, HER2 and proliferation markers, appears to be different in younger patients. Recent studies have attempted to control for tumor molecular subtypes, recognizing that more aggressive subtypes are more common in younger women. Two studies suggested particularly worse outcomes in young patients compared to older women with luminal-B tumors [7,9]. It was hypothesized that younger patients were not offered standard hormonal therapy until a decade ago, and compliance to hormonal therapy is lower in young patients [10]. However, a study of women who were untreated with systemic adjuvant therapy also demonstrated poorer outcomes of young luminal-B patients [9]. These collective findings suggest that tumors arising in younger patients may be more aggressive due to biological differences. In this review we discuss the biological features of breast cancer arising in young women, and the emerging relationship with reproductive behaviors, including pregnancy and breastfeeding, and their potential clinical implications.

Pathological features of tumors arising in young women

Recently, results of the largest prospective observation study evaluating the pathological features and outcome of women who were aged <40 years at diagnosis were reported [11]. This UK-based study included 2,956 patients diagnosed with breast cancer between 2000 and 2008. The median age at diagnosis was 36 years, and the majority had ductal histology (86.5%), and grade III (58.9%) tumors. Node-positive disease and multifocality were observed in 50.2% and 27%, respectively. One third of tumors were estrogen receptor (ER)-negative while

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Table 1 Recent large studies investigating the impact of age on breast cancer prognosis

	Young age, years (*n*)	Control age, years (*n*)	Outcome definition	Impact of young age on outcome[a]		Factors controlled in multivariate model
				Hazard ratio	95% CI	
Gnerlich *et al.* 2009 [5]	<40 (15,548)	≥40 (227,464)	BC-specific survival	1.39	1.34-1.45	T, N, grade, race, marital status, ER, PgR, local therapy
Fredholm *et al.* 2009 [6]	<35 (378)	50-69 (13,486)	BC-specific survival	1.76	1.36-2.28	T, N, grade, ER, multifocality, local and systemic therapy
Cancello *et al.* 2010 [7]	<35 (315)	35-50 (2,650)	BC-related event	1.7	1.33-2.18	T, N, grade, histology, ER, HER2, PgR, ki67 vascular invasion
Han *et al.* 2010 [8]	<35 (1,443)	40-50 (6,354)	Overall survival	30-34 years: 1.43 26–29 years: 1.97	1.18-1.74 1.48-2.62	T, N, ER, systemic therapy
Azim *et al.* 2012 [9]	≤40 (339)	>40 (2,562)	Relapse-free survival	1.34	1.10-1.63	T, N, grade, BC molecular subtype, systemic therapy

[a]In multivariate models. BC, breast cancer; CI, confidence interval; ER, estrogen receptor; *n*, number; N, nodal involvement; PgR, progesterone receptor; T, tumor size.

one quarter were HER2-positive. Very similar results were observed among the first 399 patients evaluated in the Young Women's Breast Cancer Study, which started in 2006 enrolling women aged 40 years or younger at diagnosis [12]. This study further demonstrated high rates of lymphovascular invasion and lymphocytic infiltration, in 34% and 24% of patients, respectively.

Several other retrospective studies have evaluated differences in pathological features according to age [5,13-15]. Gnerlich and colleagues [5] conducted the largest analysis including more than 200,000 patients of whom nearly 15,000 were aged <40 years at breast cancer diagnosis from a Surveillance, Epidemiology, and End Results database. Young patients were more commonly diagnosed with larger tumors ($P < 0.0001$), nodal involvement ($P < 0.0001$), poorly differentiated tumors ($P < 0.0001$), and endocrine receptor-negative tumors ($P < 0.0001$). A population-based study from the California Cancer Registry, which included 5,605 patients aged <40 years at diagnosis, further showed higher expression of HER2 in the younger population [15]. Several other hospital-based studies confirmed the same findings [13,14], underscoring that tumors diagnosed in younger patients have more aggressive pathological features.

Pattern of breast cancer subtypes according to age

In recent years, breast cancer has been increasingly recognized as a heterogeneous disease with at least four subtypes: luminal-A, luminal-B, basal-like and HER2-enriched subtypes [16]. Figure 1 summarizes the two studies that have addressed the pattern of breast cancer molecular subtypes according to age using gene expression profiling. In the largest published study to date, Azim and colleagues [9] evaluated tumors of 3,522 patients, of whom 451 were aged ≤40 years at the time of breast cancer diagnosis. Young patients had a significantly higher proportion of basal-like tumors (34.3%) compared to 27.7%, 20.8% and 17.9% in patients aged 41 to 52, 53 to 64 and ≥65 years, respectively ($P < 0.0001$). A higher proportion of HER2-enriched tumors was also observed in young patients. On the other hand, young women were less likely to have luminal-A tumors (17.2%) compared to 30.7%, 35.1% and 35.4% in the other age groups ($P < 0.0001$).

Other studies have addressed the question using immunohistochemical surrogates with variable definitions [7,12,17,18] (Figure 2). This has resulted in different distributions of subtypes observed in the different studies. Of note, these studies were also hospital-based with potential for selection bias. The California Cancer Registry examined the differences in breast cancer subtypes according to age (<40, 40 to 49 and ≥50 years) but only based on the expression of ER and HER2 [15]. In line with other studies, there was a lower prevalence of ER-positive/HER2-negative tumors in younger patients (49% versus 63.9% versus 71.6%), but a high proportion of triple-negative tumors (22.8% versus 14.3% versus 11.7%), and also HER2 expression irrespective of ER status.

Differences in pathological features and subtypes within premenopausal patients: does actual age matter?

In the previously discussed studies, different age cutoffs were used to define 'young age'. In addition, the term 'young age' has often been used synonymously with 'premenopausal' in evaluations of women with breast cancer, requiring further evaluation of whether differences exist within the premenopausal population according to actual age. In 2002, Colleoni and colleagues [13] published a large analysis including 1,427 premenopausal patients who were aged ≤50 years at the time of breast cancer diagnosis. They compared the expression of ER, progesterone receptor (PgR), and ki67 and other features by young age group (<35, 35 to 40, 40 to 45 and 45 to 50 years). Significant differences were observed according to age, with aggressive

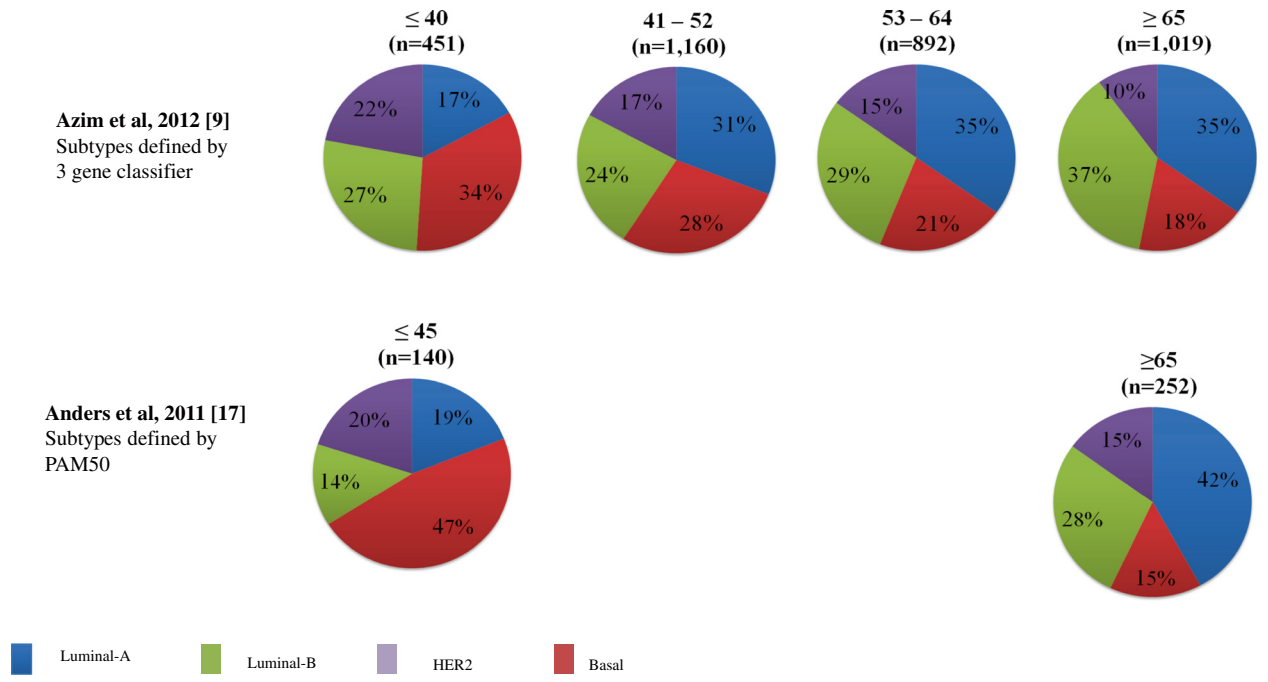

Figure 1 Breast cancer subtypes. Subtypes determined by gene expression profiling.

features more frequently observed in tumors arising in younger patients. Similar results were also reported by the Korean Breast Cancer Society registry, which included 9,885 premenopausal breast cancer patients aged ≤50 years at diagnosis [8].

In comparing groups of very young women, however, Collins and colleagues [12] did not find significant differences in histological features or the expression of ER, PgR and HER2 between patients aged ≤30 (n = 47), 31 to 35 (n = 111) and 36 to 40 (n = 241) years at breast cancer diagnosis in a prospective study, except for a trend of higher tumor necrosis in the youngest group (32% versus 14% and 21%, $P = 0.06$). A retrospective analysis of 500 patients who were aged <35 years at the time of diagnosis reported the same findings, albeit a modest higher prevalence of ER-negative (31% versus 23%), and highly proliferative tumors (ki67 > 30%; 59% versus 49%) among patients aged <30 and 30 to 34 years, respectively [19]. Collectively, these findings suggest that the younger the patient, the more aggressive the tumor features within the premenopausal population. Yet, it appears that differences are more subtle in women below 35 or 40 years.

Molecular profiling of breast cancer in young women

Gene expression differences

In 2008, Anders and colleagues [20] published one of the first attempts to describe the biology of breast cancer in young women using gene expression profiling. In this analysis, which included 200 patients in the young group (≤45 years) and 211 patients in the control group (≥65 years), a higher probability of phosphatidylinositide 3-kinase (PI3K; $P = 0.006$) and Myc ($P = 0.03$) pathway deregulation was observed in tumors arising in younger patients. However, this analysis was not adjusted for potential differences in breast cancer molecular subtypes as well as other known prognostic factors. Subsequently, a similar analysis was performed by the same group with appropriate adjustment for molecular subtypes among other features [17], using two publicly available datasets; the first including 48 patients aged ≤45 years and 144 patients ≥65 years, and the second including 92 patients ≤45 years and 108 patients ≥65 years. As expected, younger patients in their datasets had more basal-like tumors but, after adjustment for subtype differences, no distinct molecular aberrations were found that were related to age.

More recently, Azim and colleagues [9] conducted a pooled gene expression analysis on two datasets including 1,188 and 2,334 patients. The aim was to evaluate the association between patients' age and nearly 50 genes that were identified based on literature search to be related to early-onset breast cancer. The analysis was adjusted for differences in breast cancer molecular subtype, histological grade, tumor size, and nodal status. Results on the first dataset (n = 1,188, ≤40 years = 191) showed

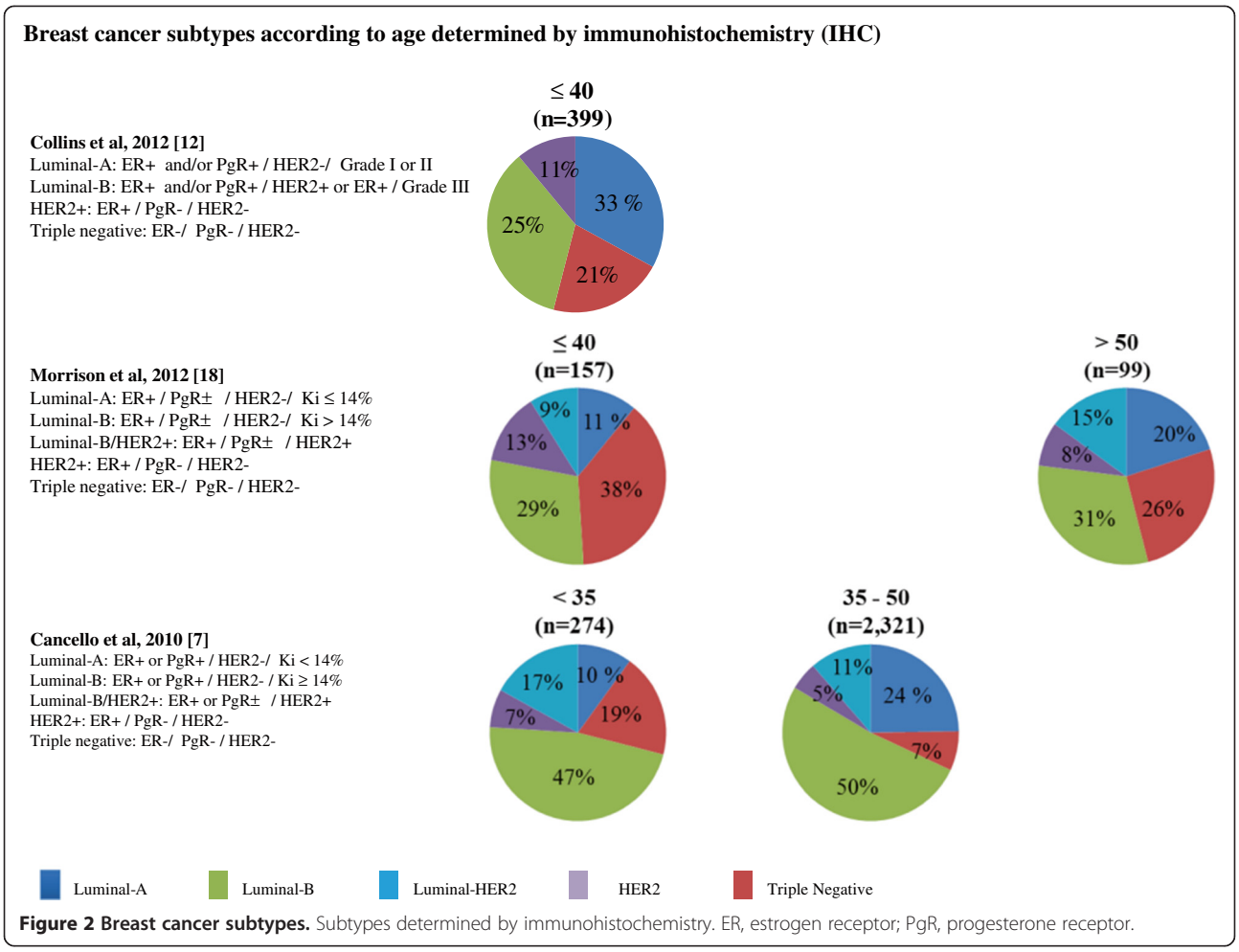

Figure 2 Breast cancer subtypes. Subtypes determined by immunohistochemistry. ER, estrogen receptor; PgR, progesterone receptor.

that, independent of subtype, grade and stage, younger patients have higher expression of *RANK-ligand* ($P < 0.0001$), *c-kit* ($P < 0.001$), in addition to mammary stem cell ($P < 0.0001$) and luminal progenitors and *BRCA1* mutation signatures ($P = 0.007$). In addition, there was more disruption of the mitogen-activated protein kinase and PI3K pathways ($P < 0.0001$) and lower expression of *BRCA1* ($P = 0.003$) and several apoptosis-related genes, particularly *FAS* ($P = 0.03$). The very same findings were reproduced in an independent dataset that included 2,334 patients, of whom 260 were aged ≤40 years. At a glance these results appear in direct conflict with those of Anders and colleagues [17]. However, the Anders analysis included four times fewer patients and utilized an unbiased approach in searching for genes associated with age, which requires a relatively high number of patients, especially with adjustment for several confounders and multiple comparisons.

The results by Azim and colleagues suggest interesting insights into the biology of early onset breast cancer. The high *BRCA1* mutation signature expression is consistent with the known relatively high prevalence of *BRCA1* mutations in younger patients [21,22]. Patients with *BRCA1* mutations are commonly diagnosed with basal-like tumors [23]; earlier work suggested that luminal progenitors appear to be the cell of origin of these tumors and are regulated by c-kit [24]. The high expression of the *BRCA1* mutation signature, luminal progenitors and c-kit in younger patients all may suggest why young women tend to develop basal-like tumors at higher frequencies. The high expression of RANKL (Receptor activator of nuclear factor kappa-B ligand) is also intriguing given RANKL is known to stimulate osteoclastogenesis and targeting RANKL has been shown to reduce risk of osteoporosis and related skeletal events secondary to bone metastases [25]. RANKL has also emerged as a PgR-regulated gene that is involved in the expansion of mammary stem cells, increasing their proliferation and protecting them from undergoing apoptosis [25]. In young women, the normal breast is enriched with an immature mammary cell population (that is, stem cells and progenitors), which increases during pregnancy and breastfeeding, an effect

that has been shown to be mainly regulated by RANKL [26]. In preclinical breast cancer models, RANKL inhibition arrested progestin-induced cancer and reduced the mammary stem cell component [27]. Thus, RANKL appears to be a potentially relevant breast cancer target beyond its established role in managing bone metastases.

Prognostic genomic signatures in young breast cancer patients

Currently several genomic tests are available to improve prognostication and aid decision making in the adjuvant setting [16]. This includes Oncotype Dx®, Mammaprint®, Endopredict, PAM50, Breast Cancer Index and many others [28]. They add prognostic information to classic prognostic variables in patients with ER-positive tumors and appear to distinguish reliably between patients at low and high risk of recurrence [28]. They are increasingly integrated in standard clinical practice, yet there have been concerns about whether they carry the same prognostic value in young women given these signatures were mainly developed using populations of postmenopausal women.

The initial work by the Dutch group on MammaPrint® including 295 patients, only 63 (21%) of whom were younger than 40 years, revealed 52/63 young patients (82%) were classified as high risk [29]. The same was observed in earlier studies with Oncotype Dx®, where only 59 out of 668 patients were aged less than 40 years, yet the majority had a high risk score (33/59 young patients; 56%) [30]. This was somewhat higher than the proportions in the high risk group in patients aged 40 to 50 (29%), 50 to 60 (25%) and >60 years (21%). The other signatures were also largely developed using populations of older patients and hence it is hard to extrapolate from these studies the value of genomic signatures in the young population.

A pooled gene expression analysis recently addressed the prognostic value of three signatures according to age: GENE70 (the microarray version of MammaPrint®), the genomic grade index and GENE76 [9]. In an analysis including 755 patients with ER-positive disease, of whom 87 were aged ≤40 years, each of the genomic signatures was significantly associated with disease-free survival and added significant prognostic information to the clinical risk classifier, Adjuvant Online. The prognostic value was the same across all age groups, suggesting that genomic signatures can add prognostic information in younger as well as older women with breast cancer.

Pattern of mutations in young breast cancer patients

Several recent studies have reported on the landscape of somatic mutations in breast cancer using next generation sequencing [31-33]. Point mutations have been observed in *TP53* and *PIK3CA* genes, accounting for nearly 25% of cases. However, very little is known regarding the pattern of somatic mutations in younger women. Stephens and colleagues [33] conducted whole genome sequencing of 100 breast tumors but found no correlation between total number of somatic base substitution and age at diagnosis in both ER-positive ($P = 0.33$) and ER-negative ($P = 0.14$) tumors.

Recently, the pattern of hot spot somatic mutations using Sequenom was evaluated in 167 young breast cancer patients (mean age of 36 years), of whom 54 were diagnosed during pregnancy [34]. A total of 84 mutations in 19 genes were evaluated, including 29 different mutations of *PIK3CA* (94% of known mutations), and 7 and 6 mutations for *ERBB2* and *TP53*, respectively. No differences were observed between the pregnant and non-pregnant groups. While this study lacked a control group, the prevalence of mutations particularly in *PIK3CA* appeared to be in line with their known prevalence in older women: approximately 23%. Only 5% of patients had a *TP53* mutation, although it should be noted that only 12% of known *P53* mutations were explored in this study. No *ERBB2* mutations were observed at all.

Regarding germline mutations, *BRCA1/2* mutations are the most common, accounting for up to 40% of familial breast cancer [35]. In a large analysis including 3,345 patients who were aged ≤50 years at the time of breast cancer diagnosis, 7% of patients had a *BRCA1* mutation [21]. However, *BRCA1* carriers were significantly younger (mean age 41.9 versus 44.1, $P < 0.001$), and had more ER-negative (84.1% versus 38.1%, $P < 0.001$) and HER2-negative (93% versus 79%, $P < 0.001$) tumors.

Data on other familial breast cancer syndromes in young women are very scarce. CHEK2*1100delC is another germline mutation that has been described to occur more commonly in younger patients. A recent study from Denmark evaluating 25,571 patients found that 1.8% were CHEK2*1100delC heterozygous [36]. These patients were younger and were more likely to be premenopausal and have ER-positive disease (all $P < 0.001$).

The fact that women with familial breast cancer syndromes appear to develop the disease more frequently at an earlier age adds further complexity to the biological make-up of breast cancer in young women. Further research to elucidate the triggers for the development of disease in this high risk young population in particular is clearly warranted.

Impact of pregnancy/breastfeeding on breast cancer biology

Reproductive behavior and biology of subsequent breast cancer

Decades ago it was shown that pregnancy increases breast cancer risk in the short term but has a long-term

protective effect [37]. More recently, several large studies have evaluated the relationship between different reproductive behaviors and not only the risk but also the phenotype of subsequent breast cancer [38-42] (Table 2). Recent studies suggest a protective effect of parity on the development of ER-positive tumors at the expense of a relatively higher proportion of patients diagnosed with triple-negative disease particularly in the absence of breastfeeding. On the other hand, breastfeeding appears to be protective against triple-negative breast cancer [38,40,42]. This is also true for *BRCA1* carriers, in whom breastfeeding for 1 or 2 years was shown to be associated with a 32% and 49% reduction in breast cancer risk, respectively [43]. Breastfeeding was protective for both early- and late-onset cancers in this high risk population.

The biological explanation of the effect of pregnancy and breastfeeding on breast cancer risk is poorly understood. Russo and colleagues [44] compared gene expression profiles of microdissected epithelial cells from normal breast tissue of 41 parous and 8 nulliparous post-menopausal breast cancer patients with those of 18 parous and 7 nulliparous post-menopausal women without breast cancer. They found that parous non-cancer patients had unique gene expression patterns including differential expression of apoptosis-related genes and others related to cell cycle and cell signaling. This suggested that pregnancy may induce a signature that protects from developing breast cancer. However, this study was based on few study subjects, and lacked long-term follow-up to confirm that the parous non-cancer group did not develop subsequent breast cancer. Asztalos and colleagues [45] studied gene expression patterns in human breast after pregnancy to try to elucidate the bidirectional effect of pregnancy on cancer risk. They grouped 52 young women (median age 29 years) as nulliparous, recently pregnant (that is, 0 to 2 years since last pregnancy) and distantly pregnant (that is, 5 to 10 years since last pregnancy) and evaluated a panel of 64 genes related to immune, angiogenesis, extracellular remodeling and hormone signaling. The parous groups had lower expression of ERα, PgR, and HER2 but higher expression of ERβ and inflammation-associated genes. No considerable differences were observed between the recently and distantly pregnant groups. A more recent preclinical study was able to show that parity downregulates Wnt/Notch signaling and suppresses progenitor cells, suggesting that this could be a potential mechanism explaining the long-term protective effect of pregnancy [46].

Pregnancy-associated breast cancer

Several studies and a recent meta-analysis have shown that patients diagnosed with breast cancer during or shortly after pregnancy have poor prognosis, particularly those diagnosed shortly after pregnancy [47]. Clearly, delays in diagnosis in this unique population has some effect, although it is also plausible that the hormonal milieu and the massive increase of female sex hormones during pregnancy can modulate the breast microenvironment, and consequently stimulate aggressive tumor growth. An alternative hypothesis is that the processes of breast involution that occurs following delivery, similar to wound healing where angiogenesis, inflammation and extracellular matrix alterations are activated, results in more aggressive breast cancer biology [48].

Schedin and colleagues [49,50] have developed a preclinical model investigating the impact of post-partum mammary involution on breast cancer initiation and progression. In this model, tumors developing in an involuting breast were larger, greater in number and had a higher proliferation index compared to those developing in a nulliparous breast. They reported that this phenomenon was related to high deposition of collagen and expression of Cox-2 in both the tumor and the involuting breast. Furthermore, inhibition of Cox-2 by a Cox-2 inhibitor resulted in reductions in the size of the tumors arising in the involuting breast. This study provided a proof-of-concept that pregnancy alters the breast microenvironment, which could subsequently impact tumor development and tumor biology.

In patients diagnosed during pregnancy, several analyses of clinical data have not revealed different expression of key biomarkers like ER and HER2 compared

Table 2 Recent large studies investigating the impact of pregnancy and breastfeeding on the risk of developing breast cancer according to biology

	Population	Number	Impact of parity on breast cancer risk according to subtype	Impact of breastfeeding on breast cancer risk according to subtype
Shinde *et al.* 2010 [38]	MD Anderson	2,473	Increase TNBC risk	Reduce TNBC risk
Palmer *et al.* 2011 [39]	African American	457	Reduce ER + BC risk	Reduce TNBC risk
Redondo *et al.* 2012 [40]	Spanish	501		Reduce TNBC risk
Chung *et al.* 2013 [41]	Korean	6,952	Reduce ER + BC risk	
Li *et al.* 2013 [42]	American	1,962 (<45 years)	Reduce ER + BC risk	Reduce TNBC risk

BC, breast cancer; ER+, estrogen receptor-positive; TNBC, triple-negative breast cancer.

with non-pregnant age-matched breast cancer patients [51-53]. A recent gene set enrichment analysis that included 54 pregnant and 113 age- and stage-matched non-pregnant breast cancer patients revealed that tumors diagnosed during pregnancy were associated with activated signaling pathways like the serotonin receptor pathway and G-protein-coupled receptor pathway [34]. There was also high expression of relevant cancer targets related to PD1/PDL1, SRC, insulin growth factor and Wnt/β-catenin. The expression of these genes in normal breast increased steadily over the course of pregnancy in a mouse model, underscoring the potential role of the breast microenvironment during pregnancy on the tumor phenotype. While it is difficult to validate these experiments clinically given the rarity of the disease and complexities of enrolling pregnant women into clinical trials, these collective findings underline that changes that occur during pregnancy and in the post-partum period likely impact the biology of breast cancer development in young women. These changes are most likely induced by the hormonal and inflammatory changes in these periods, and the resulting perturbation of the breast microenvironment. However, current data do not confirm that such effects play a key role in driving carcinogenesis and tumor biology.

Future directions

There is clear evidence that breast cancer arising at a young age is more aggressive and has potentially unique biological features and that events occurring during the childbearing period, including pregnancy and breastfeeding, impact on not only breast cancer risk but also breast cancer phenotype and biology. Nevertheless, to date, management strategies are often the same irrespective of age and hence there is a need to adapt a biology-driven approach to refine treatment for younger breast cancer patients [54].

These patients have a relatively high risk of relapse and hence it would be vital to integrate novel genomic tools to refine the treatment-decision process. Genomic tests could guide not only those patients who derive little benefit from adjuvant chemotherapy but also those who might be more suitable for extended adjuvant therapy, a strategy that has proven effective in recent studies [55,56]. Three genomic signatures, PAM50, Endopredict and Breast Cancer Index, were shown to reliably determine risk of recurrence beyond 5 years [57-59]. Considering that nearly 40 to 50% of young ER-positive patients relapse after 5 years [11], they could serve as a tool to identify those that would derive higher benefit from extended adjuvant therapy. This approach needs to be validated in clinical trials.

Based on the results obtained from the large gene expression analysis showing high expression of RANKL in younger patients, a preoperative window trial is currently ongoing to evaluate the impact of denosumab, a RANKL inhibitor, on the biology of breast cancer in young women (D-BEYOND; NCT01864798). This study could potentially define a role for denosumab in future management of young patients.

Another ongoing study in patients with pregnancy-associated breast cancer is investigating the role of Cox-2 inhibition (NCT01881048). Patients in the post-partum period will receive one week of celecoxib to evaluate its effect on the proliferation marker ki67 prior to surgical intervention.

Poly ADP ribose polymerase inhibitors are emerging as very promising drugs in managing patients with *BRCA1* or *BRCA2* mutations [60]. A study in the adjuvant setting is currently evaluating the value of 1 year of adjuvant olaparib in *BRCA1* mutated patients (NCT02032823) and a relatively large number of young patients will likely enroll.

In light of the emerging evidence that young women with luminal-B tumors have particularly disparate outcomes, and in consideration of the high deregulation of the PI3K pathway in tumors arising in young patients [9,20] and its vital role in endocrine resistance [61], targeting the PI3K pathway is an approach that is worth investigating further in young breast cancer patients. Targeting premature mammary cell subpopulations that appear to be abundant in younger patients is also worth exploring with agents such as Notch inhibitors, a novel class targeting stem cells-like features [62].

Finally, better characterization of somatic mutations occurring in tumors arising in young women using next generation sequencing could further identify key driver mutations that can be targeted in this challenging disease. These strategies and others underscore that a lot of work is still required to elucidate the biology and consequently improve the outcomes of young women with breast cancer.

Abbreviations

ER: Estrogen receptor; RANKL: Receptor activator of nuclear factor kappa-B ligand; PgR: Progesterone receptor; PI3K: Phosphatidylinositide 3-kinase.

Competing interests

HAA received honoraria for consultancy/advisory board roles from Glaxo-Smith Kline, Novartis, Nanostring and Celgene, and received research support from Amgen. AHP declares that she has no competing interests.

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References

1. Brinton LA, Sherman ME, Carreon JD, Anderson WF: **Recent trends in breast cancer among younger women in the United States.** *J Natl Cancer Inst* 2008, **100**:1643–1648.
2. Akarolo-Anthony SN, Ogundiran TO, Adebamowo CA: **Emerging breast cancer epidemic: evidence from Africa.** *Breast Cancer Res* 2010, **12**:S8.

3. El Saghir NS, Khalil MK, Eid T, El Kinge AR, Charafeddine M, Geara F, Seoud M, Shamseddine AI: **Trends in epidemiology and management of breast cancer in developing Arab countries: a literature and registry analysis.** *Int J Surg* 2007, **5:**225–233.
4. Chouchane L, Boussen H, Sastry KS: **Breast cancer in Arab populations: molecular characteristics and disease management implications.** *Lancet Oncol* 2013, **14:**e417–e424.
5. Gnerlich JL, Deshpande AD, Jeffe DB, Sweet A, White N, Margenthaler JA: **Elevated breast cancer mortality in women younger than age 40 years compared with older women is attributed to poorer survival in early-stage disease.** *J Am Coll Surg* 2009, **208:**341–347.
6. Fredholm H, Eaker S, Frisell J, Holmberg L, Fredriksson I, Lindman H: **Breast cancer in young women: poor survival despite intensive treatment.** *PLoS One* 2009, **4:**e7695.
7. Cancello G, Maisonneuve P, Rotmensz N, Viale G, Mastropasqua MG, Pruneri G, Veronesi P, Torrisi R, Montagna E, Luini A, Intra M, Gentilini O, Ghisini R, Goldhirsch A, Colleoni M: **Prognosis and adjuvant treatment effects in selected breast cancer subtypes of very young women (<35 years) with operable breast cancer.** *Ann Oncol* 2010, **21:**1974–1981.
8. Han W, Kang SY: **Relationship between age at diagnosis and outcome of premenopausal breast cancer: age less than 35 years is a reasonable cut-off for defining young age-onset breast cancer.** *Breast Cancer Res Treat* 2010, **119:**193–200.
9. Azim HA Jr, Michiels S, Bedard PL, Singhal SK, Criscitiello C, Ignatiadis M, Haibe-Kains B, Piccart MJ, Sotiriou C, Loi S: **Elucidating prognosis and biology of breast cancer arising in young women using gene expression profiling.** *Clin Cancer Res* 2012, **18:**1341–1351.
10. Murphy CC, Bartholomew LK, Carpentier MY, Bluethmann SM, Vernon SW: **Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: a systematic review.** *Breast Cancer Res Treat* 2012, **134:**459–478.
11. Copson E, Eccles B, Maishman T, Gerty S, Stanton L, Cutress RI, Altman DG, Durcan L, Simmonds P, Lawrence G, Jones L, Bliss J, Eccles D, POSH Study Steering Group: **Prospective observational study of breast cancer treatment outcomes for UK women aged 18–40 years at diagnosis: the POSH study.** *J Natl Cancer Inst* 2013, **105:**978–988.
12. Collins LC, Marotti JD, Gelber S, Cole K, Ruddy K, Kereakoglow S, Brachtel EF, Schapira L, Come SE, Winer EP, Partridge AH: **Pathologic features and molecular phenotype by patient age in a large cohort of young women with breast cancer.** *Breast Cancer Res Treat* 2012, **131:**1061–1066.
13. Colleoni M, Rotmensz N, Robertson C, Orlando L, Viale G, Renne G, Luini A, Veronesi P, Intra M, Orecchia R, Catalano G, Galimberti V, Nolé F, Martinelli G, Goldhirsch A: **Very young women (<35 years) with operable breast cancer: features of disease at presentation.** *Ann Oncol* 2002, **13:**273–279.
14. El Saghir NS, Seoud M, Khalil MK, Charafeddine M, Salem ZK, Geara FB, Shamseddine AI: **Effects of young age at presentation on survival in breast cancer.** *BMC Cancer* 2006, **6:**194.
15. Keegan TH, DeRouen MC, Press DJ, Kurian AW, Clarke CA: **Occurrence of breast cancer subtypes in adolescent and young adult women.** *Breast Cancer Res* 2012, **14:**R55.
16. Sotiriou C, Pusztai L: **Gene-expression signatures in breast cancer.** *N Engl J Med* 2009, **360:**790–800.
17. Anders CK, Fan C, Parker JS, Carey LA, Blackwell KL, Klauber-Demore N, Perou CM: **Breast carcinomas arising at a young age: unique biology or a surrogate for aggressive intrinsic subtypes?** *J Clin Oncol* 2011, **29:**e18–e20.
18. Morrison DH, Rahardja D, King E, Peng Y, Sarode VR: **Tumour biomarker expression relative to age and molecular subtypes of invasive breast cancer.** *Br J Cancer* 2012, **107:**382–387.
19. Cancello G, Maisonneuve P, Mazza M, Montagna E, Rotmensz N, Viale G, Pruneri G, Veronesi P, Luini A, Gentilini O, Goldhirsch A, Colleoni M: **Pathological features and survival outcomes of very young patients with early breast cancer: how much is 'very young'?** *Breast* 2013, **22:**1046–1051.
20. Anders CK, Acharya CR, Hsu DS, Broadwater G, Garman K, Foekens JA, Zhang Y, Wang Y, Marcom K, Marks JR, Mukherjee S, Nevins JR, Blackwell KL, Potti A: **Age-specific differences in oncogenic pathway deregulation seen in human breast tumors.** *PLoS One* 2008, **3:**e1373.
21. Huzarski T, Byrski T, Gronwald J, Górski B, Domagala P, Cybulski C, Oszurek O, Szwiec M, Gugala K, Stawicka M, Morawiec Z, Mierzwa T, Janiszewska H, Kilar E, Marczyk E, Kozak-Klonowska B, Siolek M, Surdyka D, Wisniowski R, Posmyk M, Sun P, Lubinski J, Narod SA: **Ten-year survival in patients with BRCA1-negative and BRCA1-positive breast cancer.** *J Clin Oncol* 2013, **31:**3191–3196.
22. Young SR, Pilarski RT, Donenberg T, Shapiro C, Hammond LS, Miller J, Brooks KA, Cohen S, Tenenholz B, Desai D, Zandvakili I, Royer R, Li S, Narod SA: **The prevalence of BRCA1 mutations among young women with triple-negative breast cancer.** *BMC Cancer* 2009, **9:**86.
23. Criscitiello C, Azim HA Jr, Schouten PC, Linn SC, Sotiriou C: **Understanding the biology of triple-negative breast cancer.** *Ann Oncol* 2012, **23:**vi13–vi18.
24. Lim E, Vaillant F, Wu D, Forrest NC, Pal B, Hart AH, Asselin-Labat ML, Gyorki DE, Ward T, Partanen A, Feleppa F, Huschtscha LI, Thorne HJ, ConFab K, Fox SB, Yan M, French JD, Brown MA, Smyth GK, Visvader JE, Lindeman GJ: **Aberrant luminal progenitors as the candidate target population for basal tumor development in BRCA1 mutation carriers.** *Nat Med* 2009, **15:**907–913.
25. Azim H, Azim HA Jr: **Targeting RANKL in breast cancer: bone metastasis and beyond.** *Expert Rev Anticancer Ther* 2013, **13:**195–201.
26. Asselin-Labat ML, Vaillant F, Sheridan JM, Pal B, Wu D, Simpson ER, Yasuda H, Smyth GK, Martin TJ, Lindeman GJ, Visvader JE: **Control of mammary stem cell function by steroid hormone signalling.** *Nature* 2010, **465:**798–802.
27. Gonzalez-Suarez E, Jacob AP, Jones J, Miller R, Roudier-Meyer MP, Erwert R, Pinkas J, Branstetter D, Dougall WC: **RANK ligand mediates progestin-induced mammary epithelial proliferation and carcinogenesis.** *Nature* 2010, **468:**103–107.
28. Azim HA Jr, Michiels S, Zagouri F, Delaloge S, Filipits M, Namer M, Neven P, Symmans WF, Thompson A, André F, Loi S, Swanton C: **Utility of prognostic genomic tests in breast cancer practice: The IMPAKT, Working Group Consensus Statement.** *Ann Oncol* 2012, **2013:**647–654.
29. van de Vijver MJ, He YD, van't Veer LJ, Dai H, Hart AA, Voskuil DW, Schreiber GJ, Peterse JL, Roberts C, Marton MJ, Parrish M, Atsma D, Witteveen A, Glas A, Delahaye L, van der Velde T, Bartelink H, Rodenhuis S, Rutgers ET, Friend SH, Bernards R: **A gene-expression signature as a predictor of survival in breast cancer.** *N Engl J Med* 2002, **347:**1999–2009.
30. Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, Baehner FL, Walker MG, Watson D, Park T, Hiller W, Fisher ER, Wickerham DL, Bryant J, Wolmark N: **A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer.** *N Engl J Med* 2004, **351:**2817–2826.
31. Nik-Zainal S, Alexandrov LB, Wedge DC, Van Loo P, Greenman CD, Raine K, Jones D, Hinton J, Marshall J, Stebbings LA, Menzies A, Martin S, Leung K, Chen L, Leroy C, Ramakrishna M, Rance R, Lau KW, Mudie LJ, Varela I, McBride DJ, Bignell GR, Cooke SL, Shlien A, Gamble J, Whitmore I, Maddison M, Tarpey PS, Davies HR, Papaemmanuil E, *et al*: **Mutational processes molding the genomes of 21 breast cancers.** *Cell* 2012, **149:**979–993.
32. Shah SP, Roth A, Goya R, Oloumi A, Ha G, Zhao Y, Turashvili G, Ding J, Tse K, Haffari G, Bashashati A, Prentice LM, Khattra J, Burleigh A, Yap D, Bernard V, McPherson A, Shumansky K, Crisan A, Giuliany R, Heravi-Moussavi A, Rosner J, Lai D, Birol I, Varhol R, Tam A, Dhalla N, Zeng T, Ma K, Chan SK, *et al*: **The clonal and mutational evolution spectrum of primary triple-negative breast cancers.** *Nature* 2012, **486:**395–399.
33. Stephens PJ, Tarpey PS, Davies H, Van Loo P, Greenman C, Wedge DC, Nik-Zainal S, Martin S, Varela I, Bignell GR, Yates LR, Papaemmanuil E, Beare D, Butler A, Cheverton A, Gamble J, Hinton J, Jia M, Jayakumar A, Jones D, Latimer C, Lau KW, McLaren S, McBride DJ, Menzies A, Mudie L, Raine K, Rad R, Chapman MS, Teague J, *et al*: **The landscape of cancer genes and mutational processes in breast cancer.** *Nature* 2012, **486:**400–404.
34. Azim HA Jr, Brohee S, Peccatori FA, Desmedt C, Loi S, Lambrechts D, Dell'Orto P, Majjaj S, Jose V, Rotmensz N, Ignatiadis M, Pruneri G, Piccart M, Viale G, Sotiriou C: **Biology of breast cancer during pregnancy using genomic profiling.** *Endocr Relat Cancer* 2014, **21:**545–554.
35. Shuen AY, Foulkes WD: **Inherited mutations in breast cancer genes - risk and response.** *J Mamm Gland Biol Neoplasia* 2011, **16:**3–15.
36. Weischer M, Nordestgaard BG, Pharoah P, Bolla MK, Nevanlinna H, Van't Veer LJ, Garcia-Closas M, Hopper JL, Hall P, Andrulis IL, Devilee P, Fasching PA, Anton-Culver H, Lambrechts D, Hooning M, Cox A, Giles GG, Burwinkel B, Lindblom A, Couch FJ, Mannermaa A, Grenaker Alnæs G, John EM, Dörk T, Flyger H, Dunning AM, Wang Q, Muranen TA, van Hien R, Figueroa J, *et al*: **CHEK2*1100delC heterozygosity in women with breast cancer associated with early death, breast cancer-specific death, and increased risk of a second breast cancer.** *J Clin Oncol* 2012, **30:**4308–4316.

37. Albrektsen G, Heuch I, Tretli S, Kvale G: **Breast cancer incidence before age 55 in relation to parity and age at first and last births: a prospective study of one million Norwegian women.** *Epidemiology* 1994, **5:**604–611.
38. Shinde SS, Forman MR, Kuerer HM, Yan K, Peintinger F, Hunt KK, Hortobagyi GN, Pusztai L, Symmans WF: **Higher parity and shorter breastfeeding duration: association with triple-negative phenotype of breast cancer.** *Cancer* 2010, **116:**4933–4943.
39. Palmer JR, Boggs DA, Wise LA, Ambrosone CB, Adams-Campbell LL, Rosenberg L: **Parity and lactation in relation to estrogen receptor negative breast cancer in African American women.** *Cancer Epidemiol Biomarkers Prev* 2011, **20:**1883–1891.
40. Redondo CM, Gago-Domínguez M, Ponte SM, Castelo ME, Jiang X, García AA, Fernández MP, Tomé MA, Fraga M, Gude F, Martínez ME, Garzón VM, Carracedo Á, Castelao JE: **Breast feeding, parity and breast cancer subtypes in a Spanish cohort.** *PLoS One* 2012, **7:**e40543.
41. Chung S, Park SK, Sung H, Song N, Han W, Noh DY, Ahn SH, Yoo KY, Choi JY, Kang D: **Association between chronological change of reproductive factors and breast cancer risk defined by hormone receptor status: results from the Seoul Breast Cancer Study.** *Breast Cancer Res Treat* 2013, **140:**557–565.
42. Li CI, Beaber EF, Tang MT, Porter PL, Daling JR, Malone KE: **Reproductive factors and risk of estrogen receptor positive, triple-negative, and HER2-neu overexpressing breast cancer among women 20–44 years of age.** *Breast Cancer Res Treat* 2013, **137:**579–587.
43. Kotsopoulos J, Lubinski J, Salmena L, Lynch HT, Kim-Sing C, Foulkes WD, Ghadirian P, Neuhausen SL, Demsky R, Tung N, Ainsworth P, Senter L, Eisen A, Eng C, Singer C, Ginsburg O, Blum J, Huzarski T, Poll A, Sun P, Narod SA, Hereditary Breast Cancer Clinical Study Group: **Breastfeeding and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers.** *Breast Cancer Res* 2012, **14:**R42.
44. Russo J, Balogh GA, Russo IH: **Full-term pregnancy induces a specific genomic signature in the human breast.** *Cancer Epidemiol Biomarkers Prev* 2008, **17:**51–66.
45. Asztalos S, Gann PH, Hayes MK, Nonn L, Beam CA, Dai Y, Wiley EL, Tonetti DA: **Gene expression patterns in the human breast after pregnancy.** *Cancer Prev Res* 2010, **3:**301–311.
46. Meier-Abt F, Milani E, Roloff T, Brinkhaus H, Duss S, Meyer DS, Klebba I, Balwierz PJ, van Nimwegen E, Bentires-Alj M: **Parity induces differentiation and reduces Wnt/Notch signaling ratio and proliferation potential of basal stem/progenitor cells isolated from mouse mammary epithelium.** *Breast Cancer Res* 2013, **15:**R36.
47. Azim HA Jr, Santoro L, Russell-Edu W, Pentheroudakis G, Pavlidis N, Peccatori FA: **Prognosis of pregnancy-associated breast cancer: a meta-analysis of 30 studies.** *Cancer Treatment Rev* 2012, **38:**834–842.
48. Schedin P: **Pregnancy-associated breast cancer and metastasis.** *Nat Rev Cancer* 2006, **6:**281–291.
49. Lyons TR, O'Brien J, Borges VF, Conklin MW, Keely PJ, Eliceiri KW, Marusyk A, Tan AC, Schedin P: **Postpartum mammary gland involution drives progression of ductal carcinoma in situ through collagen and COX-2.** *Nat Med* 2011, **17:**1109–1115.
50. O'Brien J, Lyons T, Monks J, Lucia MS, Wilson RS, Hines L, Man YG, Borges V, Schedin P: **Alternatively activated macrophages and collagen remodeling characterize the postpartum involuting mammary gland across species.** *Am J Pathol* 2010, **176:**1241–1255.
51. Azim HA Jr, Botteri E, Renne G, Dell'orto P, Rotmensz N, Gentilini O, Sangalli C, Pruneri G, Di Nubila B, Locatelli M, Sotiriou C, Piccart M, Goldhirsch A, Viale G, Peccatori FA: **The biological features and prognosis of breast cancer diagnosed during pregnancy: a case–control study.** *Acta Oncol* 2012, **51:**653–661.
52. Litton JK, Warneke CL, Hahn KM, Palla SL, Kuerer HM, Perkins GH, Mittendorf EA, Barnett C, Gonzalez-Angulo AM, Hortobágyi GN, Theriault RL: **Case control study of women treated with chemotherapy for breast cancer during pregnancy as compared with nonpregnant patients with breast cancer.** *Oncologist* 2013, **18:**369–376.
53. Amant F, von Minckwitz G, Han SN, Bontenbal M, Ring AE, Giermek J, Wildiers H, Fehm T, Linn SC, Schlehe B, Neven P, Westenend PJ, Müller V, Van Calsteren K, Rack B, Nekljudova V, Harbeck N, Untch M, Witteveen PO, Schwedler K, Thomssen C, Van Calster B, Loibl S: **Prognosis of women with primary breast cancer diagnosed during pregnancy: results from an international collaborative study.** *J Clin Oncol* 2013, **31:**2532–2539.
54. Freedman RA, Partridge AH: **Management of breast cancer in very young women.** *Breast* 2013, **22:**S176–S179.
55. Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V, Abraham M, Medeiros Alencar VH, Badran A, Bonfill X, Bradbury J, Clarke M, Collins R, Davis SR, Delmestri A, Forbes JF, Haddad P, Hou MF, Inbar M, Khaled H, Kielanowska J, Kwan WH, Mathew BS, Mittra I, Müller B, Nicolucci A, Peralta O, Pernas F, Petruzelka L, Pienkowski T, *et al*: **Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial.** *Lancet* 2013, **381:**805–816.
56. Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Livingston RB, Davidson NE, Perez EA, Chavarri-Guerra Y, Cameron DA, Pritchard KI, Whelan T, Shepherd LE, Tu D: **Impact of premenopausal status at breast cancer diagnosis in women entered on the placebo-controlled NCIC CTG MA17 trial of extended adjuvant letrozole.** *Ann Oncol* 2013, **24:**355–361.
57. Dubsky P, Brase JC, Jakesz R, Rudas M, Singer CF, Greil R, Dietze O, Luisser I, Klug E, Sedivy R, Bachner M, Mayr D, Schmidt M, Gehrmann MC, Petry C, Weber KE, Fisch K, Kronenwett R, Gnant M, Filipits M, Austrian Breast and Colorectal Cancer Study Group (ABCSG): **The EndoPredict score provides prognostic information on late distant metastases in ER+/HER2- breast cancer patients.** *Br J Cancer* 2013, **109:**2959–2964.
58. Sestak I, Dowsett M, Zabaglo L, Lopez-Knowles E, Ferree S, Cowens JW, Cuzick J: **Factors predicting late recurrence for estrogen receptor-positive breast cancer.** *J Natl Cancer Inst* 2013, **105:**1504–1511.
59. Sgroi DC, Sestak I, Cuzick J, Zhang Y, Schnabel CA, Schroeder B, Erlander MG, Dunbier A, Sidhu K, Lopez-Knowles E, Goss PE, Dowsett M: **Prediction of late distant recurrence in patients with oestrogen-receptor-positive breast cancer: a prospective comparison of the breast-cancer index (BCI) assay, 21-gene recurrence score, and IHC4 in the TransATAC study population.** *Lancet Oncol* 2013, **14:**1067–1076.
60. Balmana J, Domchek SM, Tutt A, Garber JE: **Stumbling blocks on the path to personalized medicine in breast cancer: the case of PARP inhibitors for BRCA1/2-associated cancers.** *Cancer Discov* 2011, **1:**29–34.
61. Zardavas D, Fumagalli D, Loi S: **Phosphatidylinositol 3-kinase/AKT/mammalian target of rapamycin pathway inhibition: a breakthrough in the management of luminal (ER+/HER2-) breast cancers?** *Curr Opin Oncol* 2012, **24:**623–634.
62. Suman S, Das TP, Damodaran C: **Silencing NOTCH signaling causes growth arrest in both breast cancer stem cells and breast cancer cells.** *Br J Cancer* 2013, **109:**2587–2596.

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