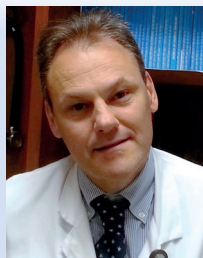


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The biology of breast cancer in young women is unique – a debate

Breast cancer in young women frequently presents with an aggressive phenotype, leading to a poorer prognosis than in older women. The critical issue centres on whether the drivers of this 'poor-prognosis' phenotype in young women represent a distinct biology or reflect an over-representation of molecular and cellular processes that underpin aggressive disease in all women with this common malignancy. Addressing whether or not the biology of breast cancer in young women is truly unique is an important ques-

tion, as it increases our understanding of the disease process, while informing the provision of appropriate optimal quality care for the young breast cancer patient. Here, Marco Colleoni, from the European Institute of Oncology in Milan, Italy, and Carey Anders, of the Lineberger Comprehensive Cancer, in North Carolina, USA, offer alternative viewpoints, which they originally presented in a live debate conducted during the European School of Oncology's conference on Breast Cancer in Young Women (BCY1, November 2012, Dublin, Ireland).



IN FAVOUR Marco Colleoni

Breast cancer at a young age has been reported to pursue a more aggressive clinical course and to be associated with a poorer prognosis compared with disease in older women¹.

Factors influencing poor prognosis in this patient group include higher tumour grade at diagnosis, high tumour proliferation, pronounced vessel-invasive disease, increased expression of HER2 (ErbB2) and reduced expression of both oestrogen (ER) and progesterone receptor (PR)².

Both immunohistochemical (IHC) and molecular classifications have been employed to address whether cancer biology defines a unique disease in young women with breast cancer³⁻⁶. Previous research has identified four subtypes: luminal A (less-aggressive subtype), and luminal B, HER2-enriched, and triple negative (more-aggressive subtypes), which have prognostic relevance^{6,7}. Evaluation of these four subtypes in a cohort of 2970 young patients, which included a subset of 'very young women' (<35 years) with breast cancer, indicated that there were significantly more patients with triple-negative subtypes and significantly fewer luminal A subtypes in the 'very young' cohort when compared with the 'less young' women⁸. Other studies have also identified luminal subtypes in older patients⁹, with triple-negative subtypes over-represented in women younger than 40 years of age¹⁰. The finding that 'very young' patients with tumours classified as luminal B, HER2-enriched and triple-negative subtypes were at increased risk of relapse, when compared with older patients with the same subtype⁸, suggests that younger patients with breast cancer may exhibit a unique biology.

Further evidence for a unique biology in breast cancer in young women comes from molecular ➤



AGAINST Carey Anders

There is no question that breast cancer arising in young women is unique in many aspects. Challenges faced by young women diagnosed with breast cancer are often quite different from

those experienced by older women. These unique challenges may include disruption of career in its early phase, child-bearing and ongoing family responsibilities, impact of therapy on sexuality and body image, and the psychosocial toll of facing a life-threatening illness at a young age. Historically, multiple studies have shown that younger women tend to experience worse breast cancer outcomes as compared to their older counterparts¹⁻³; however, the reason for this observation is not entirely understood.

Immunohistochemical (IHC) and gene expression profile studies have also shown that the more-aggressive subtypes of breast cancer (i.e. basal-like and HER2-enriched) are over-represented among younger women as compared with older women^{4,5}. Analysis of 784 early-stage breast cancers, which included women aged ≤45 years ($n=200$) and women aged ≥65 years ($n=211$) identified distinct clinical-pathological features (low IHC oestrogen receptor [ER] expression, high IHC HER2 expression, larger tumours and higher tumour grade) in younger women⁶. Gene expression analysis indicated a significantly lower expression of ER and progesterone receptor mRNA and a significantly higher expression level of HER2 and epidermal growth factor receptor (EGFR) mRNA in younger women.

A more detailed view of the biology of young women's breast tumours, obtained by analysing microarray data from several large, publicly available data sets in a non-subtype-dependent manner, indicated that breast tumours arising in younger women were enriched for 367 biologically relevant gene sets ➤

studies. Young women with breast cancer have a significantly increased prevalence of the more-aggressive subtypes, in particular the 'basal-like' tumours^{9,10}. Meta-analysis of prognostic signatures and gene classifiers from 20 data sets, representing over 3500 patients aged ≤ 40 years, indicated that distinct molecular processes, including those related to immature mammary epithelial cells and growth factor signalling, are over-represented in breast cancer arising at a young age¹¹. Particular genes/processes that were enriched included RANKL, c-Kit, BRCA1-mutated phenotype, mammary stem cells, luminal progenitor cells (immature mammary epithelial cell phenotype), mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)-related pathways (growth factor signalling phenotype). A prognostic effect of stromal-related gene signatures was also observed, suggesting a role for the microenvironment in mediating breast cancer growth and proliferation in young women, leading to a more-aggressive phenotype.

Thus, both IHC-defined subtype and molecular classification data indicate that breast cancer that develops at a young age is different biologically from that arising in older premenopausal and postmenopausal women.

when compared with older women⁶, suggesting, with the IHC data, a unique biology for breast cancer in younger women. Independent analysis of a second pooled data set, which included women aged ≤ 45 years and women aged ≥ 65 years confirmed the increased incidence of the more-aggressive basal-like and HER2-enriched subtypes in younger women⁷. However, when correcting for significant clinical-pathological and histopathological features, including grade, nodal status, ER status and intrinsic breast cancer subtype, adjusted models yielded negligible gene differences between breast tumours arising from defined age groups of ≤ 45 versus ≥ 65 years^{6,7}. As is standard in the field, this finding was replicated in an independent data set as part of this analysis, further confirming these results.

Based on these results, age alone does not appear to offer an additional layer of biological complexity above that of breast cancer subtype and grade. These data support the argument that the biology of young women's breast tumours may not be unique, but rather an over-representation of aggressive, biologically driven subtypes is accounting for the disparities observed in outcome by age.

While the information generated by gene expression profiling is compelling, many unanswered questions remain, including: (1) why are younger women more prone to aggressive subtypes of breast cancer? (2) what is the role of the microenvironment? (3) how does breast density and/or other factors (e.g. breastfeeding, parity) contribute to these findings? and (4) will disparities in outcome persist in the era of modern targeted therapies? – all areas deserving of further research.

Overall conclusion

The question as to whether younger patients with breast cancer exhibit a unique biology is a controversial one. All of the data presented both in favour of and against this hypothesis indicate an increased incidence of more-aggressive molecular subtypes in young women with breast cancer. It may be that factors such as the cut-off age for younger patients need to be considered – perhaps a different biology underpinned by basal-like or HER2-enriched molecular subtypes is impli-

cated in very young patients (i.e. younger than 35 years of age). A precise consideration of the role of the stromal microenvironment may also be relevant and should be pursued. In any case, it is clear that our increased understanding of breast cancer tumour biology in younger women is starting to inform a new scientific rationale (e.g. targeting of genes like RANKL or growth factor pathways like PI3K), that may be of particular benefit to this poor-prognosis cohort of patients. ■

Details of the references cited in this article can be found at www.cancerworld.org