Breast Cancer: Targets and Therapy

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LETTER

Triple-Negative Breast Cancer on the Rise or…? [Letter]

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Dear editor

The recent review by Agelidis et al in the Journal[1] discusses triple-negative breast cancer (TNBC) epidemiology and therapy, two timely subjects. We are concerned about their statement regarding a rising incidence of TNBC. Among the two papers cited in relation to this statement, one[2] confirms an increasing incidence of breast cancer (BC) in general among young women. The other[3] reveals a contemporary trend for an increased incidence of estrogen receptor-positive (ER+) BC, particularly among young women, in the USA, contrasting with a non-significant trend for a *reduced* incidence of TNBC across all age groups. While trends in TNBC incidence may vary somewhat between studies, partly related to ethnicity,[4,5] a consistent finding is that the increase in BC incidence mainly relates to ER+ disease among young as well as postmenopausal women, with limited or no increase in TNBC incidence for several decades.[6–8] Taken together, these epidemiological findings strongly indicate different aetiologies for most TNBC and ER+ BCs.

While TNBC tumors present a certain heterogeneity in biological characteristics such as gene expression profiles, the majority reveal a basal-like gene expression profile and genomic signatures related to defects in homologous recombination repair (HRR), a characteristic of most BCs arising in women harboring pathogenic *BRCA1* variants.[9,10] Although a number of patients diagnosed with TNBC harbor germline pathogenic *BRCA1* variants, and some pathogenic variants in *BRCA2*, the contribution from such germline variants and variants in other genes,[11] as well as somatic mutations in *BRCA1/2* or other genes involved in HRR,[10,12] only explains a minor fraction of TNBCs carrying HRR defects (HRDs). However, recent evidence has shown 25–30% of TNBCs to harbor *BRCA1* epimutations, ie, promoter hypermethylation,[13,14] in most cases arising as clonal expansions from constitutional (prenatal, normal tissue) *BRCA1* epimutations.[14–17] While constitutional epimutations in other tumor-suppressor genes, eg, *MLH1*, have been recorded,[18] these cases are rare. The fact that around 20% of all TNBC are associated with *BRCA1* constitutional epimutations, and that these tumors reveal a genomic biology mirroring tumors arising in *BRCA1* germline mutation carriers,[13] establishes *BRCA1* constitutional epimutations as a major underlying cause of TNBC. These findings raise the question of whether epimutations affecting other genes involved in HRR also cause TNBC. While some cases carrying constitutional epimutations in *RAD51C* have been described,[19] the potential importance of this finding remains to be learned.

The different incidence trend between TNBC and ER+ BC may signal different biological mechanisms of carcinogenesis, a pivotal finding in understanding contemporary trends. Apart from BCs related to germline mutations, TNBC represents the only subtype for which a distinct underlying molecular cause, i.e. prenatal *BRCA1* constitutional epimutations, has been identified. Whether these epimutations themselves are caused by internal cellular processes or external environmental factors remains to be learned. Similarly, the potential role of early epimutations in other genes remains to be explored. Addressing these questions may significantly expand our understanding of TNBC risk, biology, and, not least, therapy.

Disclosure

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