Journal of Medical & Surgical Pathology

Yang et al., J Med Surg Pathol 2016, 1:2
DOI: 10.4172/2472-4971.1000120

Commentary Open Access

Expression of Oncodrivers HER-3 and C-MET during Breast Tumorigenesis in BRCA Mutation Carriers

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Received date: March 05, 2016; **Accepted date:** April 13, 2016; **Published date:** April 21, 2016

Commentary

BRCA1 and BRCA2 germ line mutations confer a substantial risk of breast cancer, with studies reporting an average cumulative risk of breast cancer by age 70 years as 57-65% in BRCA1-mutation carriers 45-47% in BRCA2-mutation carriers [1,2]. Today, the prevention of breast cancer among mutation carriers has focused on surgical options such as risk-reducing bilateral mastectomy and bilateral salpingo-oophorectomy [3,4] which have significant associated morbidity. In the general population chemoprevention strategies have been developed to target the known phenotypes of spontaneous DCIS in order to prevent the development of invasive breast cancer [5-7]. As such, evaluation of the pre-invasive progression pathways of BRCA-associated tumors is critical in the effort to develop directed prevention therapies for this vulnerable population.

Prior studies have demonstrated the morphological and immunohistochemical differences between BRCA-associated and sporadic invasive breast cancers, specifically with regards to the low expression of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor in BRCA1-associated breast cancers [8]. While much is known about the phenotypic differences between BRCA-associated and sporadic breast invasive cancers, there is a paucity of data about the differences in their pre-invasive progression pathways. Furthermore, because more BRCA-related breast cancers are discovered between screening mammograms and with no prior pathologic findings [9,10] it has previously been thought that the DCIS-associated premalignant pathway that exists in sporadic breast cancers is not present within the BRCA-associated disease spectrum.

In our recent original article "DCIS in BRCA1 and BRCA2 Mutation Carriers: Prevalence, Phenotype, and Expression of Oncodrivers C-MET and HER3" [11], we examined 114 tumor specimens from BRCA mutation carriers who underwent breast surgery at a single academic institution over a 20-year time period. We found that 80.2% of all BRCA-associated invasive breast cancer (IBC) specimens had ductal carcinoma in situ (DCIS) present, and this did not differ by mutation status (p=0.95). We found that the majority of BRCA-associated DCIS was high grade (BRCA1: 68.9%, BRCA2: 53.6%) and the DCIS was either intermixed with the IBC (BRCA1: 42.9%, BRCA2: 56.0%) or just on the periphery of the IBC (BRCA1: 50.0%, BRCA2: 44.0%). In BRCA1 mutation carriers with IBC and concurrent DCIS, the correlation between the DCIS and IBC was highly significant for ER, PR, HER1, HER3, and C-MET ($p<0.01$). In BRCA2 mutation carriers with IBC and concurrent DCIS, the correlation between the DCIS and IBC was highly significant for ER, PR, HER2, and HER3 ($p<0.01$). Most BRCA1-associated DCIS and IBC had 0/3 staining intensity for ER, PR and HER2, while most BRCA2-associated DCIS and IBC had 3/3 staining intensity for ER and PR. BRCA1-associated DCIS had higher expression of HER3 and C-MET (H-Score 99.5 and 101.9, respectively) and lower expression of HER1 (H-Score 6.5). BRCA-2 associated DCIS similarly had higher expression of HER3 and C-MET (H-Score 84.3 and 124.8, respectively) and lower expression of HER1 (H-Score 16.5).

While it has been previously thought that the DCIS-associated premalignant pathway that exists among sporadic breast cancers is not present within the BRCA-associated disease spectrum [12,13] we found that over 80% of all BRCA-associated invasive tumors had concurrent DCIS. Prior studies have found rates of BRCA-associated DCIS among invasive tumors to be as low as 20% to 56% [14,15], while studies of sporadic invasive breast tumors have found rates of concurrent DCIS ranging from 56% to 71% [13,15]. In our study we also found that among patients with IBC and concurrent DCIS, the concordance of biomarker expression between the in situ and the invasive components was remarkably high, the majority of DCIS was found intermixed with the invasive tumor or in close proximity of it, and most of the DCIS was high-grade. Together, these findings provide a strong argument for the existence of a DCIS-associated premalignant pathway among patients with BRCA mutations, with the entrance point for BRCA-associated DCIS at the high-grade stage, unlike the progression pathway of sporadic breast tumors which is thought to begin with low-grade in situ disease [16,17].

There are few studies that have examined expression of oncodrivers aside from estrogen receptor, progesterone receptor, and/or HER2/neu in BRCA-associated DCIS [8,18]. In addition to these known receptors, our study evaluated HER1, HER3, and c-MET in a large cohort of DCIS specimens providing a substantial contribution to the current literature regarding oncodriver expression in hereditary breast cancer. Unlike sporadic breast cancer where HER-2 is very prevalent in DCIS, there was a paucity of HER-2 expression in BRCA1- and BRCA2-carriers but rather both HER3 and c-MET were expressed in the DCIS. Expression of these oncodrivers was maintained in the associated invasive breast cancer. This finding begs the consideration of how to implement strategies to target these oncodriver signaling pathways in BRCA mutation carriers, so to prevent the development of DCIS and invasive tumors.

The findings described above substantiate the existence of a DCIS-associated premalignant pathway in BRCA mutation carriers, and as such, calls attention to in situ carcinoma as an unexploited target for prevention of hereditary invasive breast cancers. Furthermore, the results bring light to two understudied oncodrivers: c-MET and HER-3, both which are present in BRCA-associated DCIS independent of triple negative or estrogen receptor positivity and may serve as targets for the development of prevention strategies moving forward. BRCA mutation carriers are a unique patient population deserving to be the subject of further investigation in the arena of cancer

prevention. Until we develop and implement novel prevention strategies targeted for BRCA mutation carriers, these high-risk patients will unfortunately be left with few efficacious prevention strategies outside of invasive surgical prophylaxis.

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