Type of breast cancer provides clues to genetic susceptibility

Breast cancer is a common disease affecting 1 in 11 women in the UK but like many common cancers incidence increases with increasing age. Only 1 in 1,700 women younger than 30 and 1 in 228 women between 30 and 40 develop breast cancer. Young age at diagnosis for breast cancer raises the question of an inherited susceptibility. Genetic testing for BRCA gene variants that increase cancer risk was brought to public attention when Angelina Jolie wrote about her own experience of managing her high cancer risk due to a BRCA1 gene variant inherited from her mother. Carriers of a faulty BRCA1 gene have a high lifetime risk of developing both breast and ovarian cancer. She described undergoing risk reducing mastectomy and reconstruction and later removal of her ovaries and fallopian tubes.

Genetic testing of a cancer affected individual is often the key to finding a high risk genetic variant. Amongst all breast cancers around 15% are the known as triple negative (known as triple negative breast cancer, TNBC, because the cancer cells do not have hormonal receptors or the HER2 receptor). Increasingly women who develop this type of breast cancer are offered a BRCA test because BRCA gene carriers often develop this type of breast cancer. BRCA gene carriers rarely develop the type of breast cancer that is strongly expressing HER2 receptors (HER2+). HER2+ breast cancer is important to identify because it can be treated with a targeted drug called Herceptin which greatly improves the previously poor outcome for this type of cancer.

As part of a large cohort study of very young (? 41 years at diagnosis), we collected genetic testing data for women who had developed a HER2 amplified breast cancer. We looked at the outcome of testing for inherited breast cancer susceptibility genes (CSGs) using different genetic testing strategies. We considered either BRCA1 and BRCA2 testing, testing for a gene called TP53 where very young breast cancer is part of the pattern of susceptibility, and testing for 17 CSGs including BRCA1, BRCA2 and TP53.

Out of nearly 400 patients identified with HER2 amplified breast cancer diagnosed age ?40 years, approximately a quarter met typical criteria family history for offering BRCA testing (?10% probability of finding a faulty gene). BRCA testing in this group yielded 11% who had a clear BRCA mutation (6 BRCA2, 5 BRCA1), in addition surprisingly we found 12% who had a TP53 mutation (surprising because of the rarity of this genetic fault amongst breast cancer patients in general). Where there was no significant family history only 1% of the patients had BRCA mutations and 1% had TP53 mutations. For the remaining genes tested, rare alterations in the sequence that may increase risk were found in some 5% of all cases tested but patients with these variants were not more likely to have a family history. Translating this genetic information into a future cancer risk prediction and rational guidance for a carrier can be difficult.

Although some young patients who have had a breast cancer diagnosis may want genetic testing

in order to decide whether to opt for bilateral risk reducing mastectomy, the test may identify difficult to interpret information. The more genes that are sequenced, and the lower the prior chance that someone carries a high risk gene i.e. the less strong the family history, the greater this risk and misunderstanding or over-interpretation of the significance of a variant may lead to inappropriate action. Physicians need to help their patients weigh up the risks and benefits of genetic testing in the context of their probability of carrying a high risk susceptibility gene and of their cancer treatment and prognosis.

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