Re: Hormone Therapy and the Risk of Breast Cancer in BRCA1 Mutation Carriers

The contribution of Eisen et al. (1) to the risk mitigation associated with hormone therapy (HT) in menopausal BRCA1 mutation carriers is critical because it will help women reach an informed decision about a tough situation, balancing disease risk and quality of life. These data are also valuable for oncologists because they are counterintuitive (2), challenging causation models.

Indeed, the impact of HT on natural history of breast cancer may not be univocal (3). Eisen et al. made the assumption of different impacts at different stages of progression of carcinogenesis. Cellul ar impact of HT is, according to the authors, dependent on cellular state (loss of homozygosity or not, with regard to BRCA1) and on the timing of exposure.

We would like to make an additional hypothesis consistent with the main result: the association between HT exposure and breast cancer may vary according to different subpopulations of BRCA1 mutation carriers, with regard to a wider genetic background. This hypothesis is based on a hypothetical cohort of two equally important subpopulations of BRCA1 mutation carriers: one subpopulation being at increased risk if exposed to hormonal treatments as compared with BRCA1 mutation carriers not exposed to hormonal treatment (relative risk [RR] = 1.5) and the other subpopulation being at decreased risk (RR = 0.5).

It has been estimated that 56% of BRCA1 mutation carriers develop breast cancer before age 50 years (4). If we assume that 85% of BRCA1 mutation carriers who are susceptible to hormonal factors develop breast cancer before menopausal age, it would imply in the above scenario that 27% of nonsusceptible BRCA1 mutation carriers would develop breast cancer before menopause. Thus, most early breast cancers would occur in the susceptible subpopulation. After menopause, the remaining population of BRCA1 mutation carriers who are free of cancer is depleted of women who are most susceptible to hormonal factors. This selection process was initially described in the field of pharmacoepidemiology and referred to as depletion of susceptibles (5). Then, if after menopause, HT is assumed to increase the risk of breast cancer among susceptible BRCA1 mutation carriers but decrease the risk among nonsusceptible carriers with the same magnitude as other hormonal factors before menopause (RR = 1.5 and RR = 0.5, respectively, with 25% of women exposed), then the observed HR for postmenopausal breast cancer would be 0.64, close to the published result.

The issue of genetic background among BRCA1 mutation carriers appears to be critical. First, because it could explain such counterintuitive results. Second, because it could also partly explain the variation observed in the penetrance among BRCA1 mutation carriers in different countries/surveys. Third, because of the remaining high risk of breast cancer observed for some noncarriers in families with a proven BRCA mutation (6).

In the future era of personalized medicine, being able to discriminate among BRCA1 gene carriers who will benefit from HT and those who will not might be the next challenge.

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References


Notes

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