CCBIO Opinion

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Challenges in breast cancer prevention

More than 80% of breast cancers in Norway, Western Europe, and the U.S. are diagnosed in women aged over 50. Although aging is generally associated with loss of function in tissues, age-related cancers may be paradoxical examples of gains of function; e.g. uncontrolled growth and the appearance of novel functions like invasion and metastasis. A long-held paradigm is that accrual of somatic mutations accounts for increased cancer incidence with age. Some cancers indeed show an exponential increase in incidence with age consistent with the accumulated mutation hypothesis, whereas the incidence of breast cancers in the U.S. decreases sometime after age 70. In addition, women from different countries, e.g. Japan versus the U.S., exhibit completely different distributions for the age of first diagnosis, whereas accumulation of somatic mutations should be due to entropic forces that are experienced by all life on Earth[1]. Moreover, when normalized for incidence, most cancers are diagnosed after age 50, even chronic myeloid leukemias that can be driven by a single oncogene.

There is undeniably a genetic component to all cancers, however mutations alone are insufficient to explain the age-related increases of breast cancer incidence. A hypothesis that can encompass all of the observations that relate to aging and cancer is that increased cancer incidence results from gradual loss of function at the level of tissue structure and organization that corrupt tumor suppressive activity of normal tissue architecture, cause epigenetic changes that alters gene expression, thereby altering normal stem and somatic cell functions. These alterations lead to tissue-level phenotypes that make breast epithelia susceptible to cancer initiation. The hypothesis that accumulation of somatic mutations with age drives the age-related increase in breast cancer incidence, if correct, has a somewhat nihilistic conclusion; that cancers will be impossible to avoid. Alternatively, if microenvironment-driven epigenetic changes are key to explaining the tissue-level changes that make older women more susceptible to breast cancer, there is hope that primary prevention is possible[2]. Whereas genomes are nearly intractable to change, there is translational promise for altering the course of deleterious age-related tissue-level and epigenetic changes with therapeutic prevention, nutrition, and exercise[3]. Breast cancer prevention has fallen short so far, and there are practical and philosophical challenges ahead.

The standard of care for primary breast cancer prevention is screening by mammography, physical exam, and risk estimates based on Gail Scores. In high-risk scenarios (e.g. germline genetic risk or very strong family histories), prophylactic surgical modalities may be employed. Results from some exercise interventions suggest that more than four hours of weekly exercise may reduce risk, early pregnancy and breast feeding may also reduce overall risk, but these are not considered prevention modalities in a prescriptive sense. Indeed, therapeutic options for breast cancer prevention are limited. Selective estrogen receptor modulators (SERMs) and aromatase inhibitors are effective preventions because SERMs can reduce risk of recurrence by at least 30%. However, they are not for routine use in no-to-low risk patients, and compliance is bad due to side effects like deep vein thrombosis and bone loss.

Prevention clinical trials present philosophical and practical challenges that are less problematic in other types of disease intervention trials. Endpoints based on efficacy are impractical due to

the length of follow-up that is needed, and any molecule used as a putative prevention must be exquisitely safe because there is a strong case that doing nothing is likely to be as effective. A compromise to studying completely average-risk populations is to perform the intervention in high-risk populations who are more likely to progress to disease in a shorter time. In these populations, efficacy could be judged in a reasonable time, and a stronger argument can be made that these individuals are likely to benefit from an intervention. A compromise to efficacy is to examine endpoints that determine if an intervention exerts a biological activity indicative of a desired change in the breast within a shorter window of time: e.g. epithelial-cell proliferation, breast density, estrogen concentrations in tissue, and Masood scores.

There are a handful of trials in the U.S. testing chemical therapeutic interventions in high-risk populations that did not explicitly target hormone receptors or aromatases. Celecoxib treatment for six months was associated with a decreasing trend of breast density but no differences in Ki67+ cells (NCT00291694). Omega-3 treatment for six months in pre-menopausal women was associated with modest decreases in Ki67+ cells and Masood scores (NCT01252290). Vitamin D had no biological impact in breast tissues (NCT01224678). Genistein treatment in pre-menopause high risk women for six months did not affect proliferation, but lowered estrogen concentration compared to placebo (NCT00290758). Sulforaphane from broccoli extract had no effect after two weeks of treatment (NCT00982319). Therapeutic intervention-based prevention trials that are still recruiting, but have not reported outcomes, include: hydroxytyrosol in olive oil (NCT02068092), rapamycin (NCT02642094), omega-3 FA (NCT02295059), denosumab (NCT04067726), and metformin (NCT01905046). Whereas SERM use is associated with early biological impacts such as reduced Ki67+ cells and decreased breast density, most other interventions have shown minimal biological effect by the commonly applied outcome measures. We interpret this as either most of these non-SERM agents having minimal biological impact in breast, or that the wrong endpoints are being assessed.

Breast cancer prevention has been led by epidemiology, which is heavily influenced by what we can measure, or can think to measure. The associations that have been revealed between age, hormone receptors, and incidence are incontrovertible. However, the lack of success in translating those findings into durable cancer prevention strategies suggests that we must go deeper into the underlying biology of aging to understand and manipulate our susceptibility to breast cancer, as well as to identify the most telling biomarkers for prevention studies. ••

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