Towards a dietary prevention of hereditary breast cancer

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Abstract

Inheritance of a deleterious mutation in BRCA1 or BRCA2 confers a high lifetime risk of developing breast cancer. Variation in penetrance between individuals suggests that factors other than the gene mutation itself may influence the risk of cancer in susceptible women. Several risk factors have been identified which implicate estrogen-induced growth stimulation as a probable contributor to breast cancer pre-disposition. The protein products of both of these genes appear to help preserve genomic integrity via their participation in the DNA damage response and repair pathways. To date, the evidence for a cancer-protective role of dietary nutrients, for the most part those with antioxidant properties, has been based on women without any known genetic pre-disposition and it is important to identify and evaluate dietary factors which may modify the risk of cancer in BRCA carriers. Here we propose that diet modification may modulate the risk of hereditary breast cancer by decreasing DNA damage (possibly linked to estrogen exposure) or by enhancing DNA repair. The prevention of hereditary breast cancer through diet is an attractive complement to current management strategies and deserves exploration.

BRCA mutation carriers of today

It has been estimated that between five and ten% of breast cancers are hereditary [1, 2]. Approximately 30–40% of familial cases can be attributed to a germline mutation in one of the two breast cancer susceptibility genes, BRCA1 and BRCA2 [3]. Deleterious BRCA1 or BRCA2 mutations are associated with a very high lifetime risk of breast cancer, currently estimated at 80% by age 70 [3, 4]. Both mutations also confer increased lifetime risks of ovarian cancer and pre-dispose men and women to a range of other malignancies [5–7].

Lifetime risks of breast cancer as low as 38% and as high as 87% have been reported in women carrying a deleterious BRCA1 or BRCA2 mutation [3, 8–12]. The variability in risks between women in different studies has prompted the search for factors other than the gene itself which might influence the risk of cancer in susceptible women. In 1993 we reported in a large American family of BRCA1 mutation carriers that the incidence of breast cancer was five times greater among women born after 1930 than for those before 1930, suggesting an important role for external factors in BRCA-associated carcinogenesis [13]. In the past decade, both genetic and non-genetic factors have been suggested to influence breast cancer risk in BRCA1 and BRCA2 mutation carriers (reviewed in [14–16]). Genetic risk factors include both the type and position of the mutation [17–19], and the presence of specific alleles of modifying genes [20–23]. Non-genetic or environmental factors include hormonal factors, particularly those related to estrogen exposure (reviewed in [14]). Oophorectomy (removal of the ovaries) and breastfeeding are protective [24–27]. A positive relationship between early oral contraceptive use and breast cancer risk has been suggested by one study [28] and confirmatory studies are underway. These
observations suggest that sex hormones play an important role in BRCA-carcinogenesis. The cloning of both breast cancer susceptibility genes, along with the introduction of predictive genetic testing, has allowed for the identification of high-risk women. Options currently available for these women include primary prevention and specialized surveillance programs aimed at early detection. Prophylactic bilateral mastectomy appears to be the most effective choice for high-risk women, conferring a decrease of 90% or greater in the incidence of breast cancer [29]; however, the proportion of women who elect to undergo this invasive surgery is low and varies between countries (reviewed in [30]). Currently, non-surgical chemopreventive options available for BRCA carriers are based on interrupting the estrogen-signaling pathway (reviewed in [14, 15]), although the effectiveness of estrogen blockade still remains to be elucidated especially because the majority of BRCA1 tumours are estrogen-receptor negative.

The heterogeneity in penetrance associated with a BRCA mutation suggests that the potential exists to modify risk in carriers. More importantly, the lack of effective chemoprevention suggests a need to pursue novel alternatives, such as dietary or lifestyle strategies. Prospective trials with breast cancer as an endpoint to evaluate chemoprotective agents are generally not feasible in the high-risk population. Thus, there is a need to identify biomarkers of cancer susceptibility that can be used as intermediate endpoints. In turn, the identification of molecular or genetic changes which are valid biomarkers of breast cancer risk in carriers will allow for the evaluation of dietary or lifestyle interventions.

The BRCA gene products, DNA repair capacity, and biomarkers of breast cancer susceptibility

The BRCA1 gene has multiple functions, and is involved in DNA transcription, cell cycle checkpoint control, DNA damage repair, protein ubiquitination, regulation of apoptosis and chromatin remodeling [31–33]. In addition to double-strand DNA break repair by homologous recombination, other repair functions attributed to BRCA1 include transcription-coupled repair and global genomic repair, both of which are sub-pathways of nucleotide-excision repair [32, 34–36]. Both BRCA1 and BRCA2 have been shown to interact with Rad51, a protein believed to participate in homologous recombination [37–40]. Although not as diverse, the molecular functions of BRCA2 are better understood than that of BRCA1. In addition to regulating Rad51 [41], BRCA2 has recently been implicated in stabilizing DNA structures at stalled replication forks [42]. Collectively, the data suggests that BRCA1 and BRCA2 participate in a common DNA damage repair pathway associated with homologous recombination-mediated and double-strand DNA repair [43, 44].

Various chromosomal instability disorders have been identified (including xeroderma pigmentosum, ataxia telangiectasia, Bloom syndrome, Fanconi anemia and Nijmegen breakage syndrome) which pre-dispose an individual to cancer due to the inheritance of a defective gene critical for the repair of DNA lesions (reviewed in [45–47]). Individuals with mutations in genes involved in DNA repair demonstrate hypersensitivity to DNA-damaging agents, an increased tendency to accumulate mutations, chromosomal instability, and a high risk of developing cancer [46, 48]. These individuals are identified through cytogenetic tests that quantify chromosome breaks [49] or that assess the ability to repair radiation-induced DNA damage [50, 51].

The functional roles of BRCA1 and BRCA2 proteins suggest that the inheritance of a mutated gene may be associated with faulty DNA repair, chromosomal instability and consequently pre-disposition to breast and ovarian cancer. An impaired cellular response to DNA damage appears to be a plausible mechanism by which BRCA carriers are at an increased risk of breast cancer [52]. Hence, the evaluation of an individual’s capacity to repair DNA may serve as a biomarker of breast cancer risk in carriers. Although there are numerous techniques to assess DNA repair capacity, there is presently no gold standard for humans [53, 54]. Various cytogenetic endpoints, including counting chromosomal aberrations, micronuclei and sister chromatic exchanges, have been utilized as biomarkers of cancer susceptibility [55]. The epidemiological evidence is strongest for the association between an elevated frequency of chromosomal aberrations and an increased risk of cancer [56]. However, each of these endpoints has limitations including the need to use proliferating cells and the large volume of blood required. The techniques are often laborious and time-consuming [57]. Other markers of DNA repair capacity include an assessment of DNA damage in the form of DNA adducts or strand breaks [53, 58].

When there is an imbalance between the rate of oxidant production and the antioxidant defense mechanisms, oxidative stress occurs. The deleterious effects of oxidative stress have been implicated in aging and other chronic conditions, including cardiovascular disease, immune-system decline and cancer [59–63]. Of particular importance for carcinogenesis is oxidative damage to DNA. Carcinogenesis is a multi-step process and damage to DNA is believed to be a critical step in this process. Given the role of DNA mutation in