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Frequency of *CHEK2* mutations in a population based, case–control study of breast cancer in young women

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Abstract

Introduction The cell-cycle checkpoint kinase (CHEK)2 protein truncating mutation 1100delC has been associated with increased risk for breast or prostate cancer. Multiple studies have found an elevated frequency of the 1100delC variant in specific stratifications of breast cancer patients with a family history of the disease, including *BRCA1*/*BRCA2* negative families and families with a history of bilateral disease or male breast cancer. However, the 1100delC mutation has only been investigated in a few population-based studies and none from North America.

Methods We report here on the frequency of three *CHEK2* variants that alter protein function – 1100delC, R145W, and I175T – in 506 cases and 459 controls from a population based, case–control study of breast cancer conducted in young women from western Washington.

Results There was a suggestive enrichment in the 1100delC variant in the cases (1.2%) as compared with the controls (0.4%), but this was based on small numbers of carriers and the differences were not statistically significant. The 1100delC variant was more frequent in cases with a first-degree family history of breast cancer (4.3%; $P = 0.02$) and slightly enriched in cases with a family history of ovarian cancer (4.4%; $P = 0.09$).

Conclusion The *CHEK2* variants are rare in the western Washington population and, based on accumulated evidence across studies, are unlikely to be major breast cancer susceptibility genes. Thus, screening for the 1100delC variant may have limited usefulness in breast cancer prevention programs in the USA.

Keywords: breast cancer, case–control study, CHEK2, population based

Introduction

Cell-cycle checkpoint kinase (CHEK)2 has been shown to play a role in cell cycle regulation, apoptosis, and DNA repair, at least in part through phosphorylation of p53 and BRCA1 in response to DNA damage [1,2]. Several studies have reported associations of germline mutations in *CHEK2,* especially the 1100delC mutation, with increased susceptibility to breast and prostate cancer [3-8]. Although *CHEK2* germline variants other than 1100delC have been associated with prostate cancer risk, these have not yet been shown to be enriched in breast cancer cases [3,4,9,10].

The association between the *CHEK2* 1100delC variant and risk for breast cancer was initially reported by the *CHEK2* Breast Cancer Consortium [5]. They found that the frequency of the variant was greater among breast cancer patients with a positive family history of breast cancer who do not carry germline mutations in the *BRCA1* or *BRCA2* genes, and in families with male breast cancer, as compared with healthy control individuals from the UK, The Netherlands, and North America [5]. Additionally, they noted that the frequency of the 1100delC variant did not differ significantly between breast cancer patients and matched control individuals from a population-based series of young women from the UK (age < 45 years) and of older women from The Netherlands (age ≥ 55 years) [5].

bp = base pairs; CHEK = cell-cycle checkpoint kinase; PCR = polymerase chain reaction.