

Editorial

Identification of women with an increased risk of developing radiation-induced breast cancer

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See related research article by Broeks *et al.*, <http://breast-cancer-research.com/content/9/2/R26>

Abstract

In the previous issue of *Breast Cancer Research*, Broeks and collaborators present the results of a study suggesting that germline mutations in *BRCA1*, *BRCA2*, *ATM* or *CHEK2* may double the risk of radiation-induced contralateral breast cancer following radiotherapy for a first breast cancer. The association appeared to be strongest among women who were below the age of 40 at the time of their first breast cancer and among women who developed their second cancer 5 years or more after the first. While there were a number of methodological issues that might limit the conclusions drawn from this paper, this is one of several recent studies suggesting that carriers of pathogenic alleles in DNA repair and damage recognition genes may have an increased risk of breast cancer following exposure to ionising radiation, even at low doses. This finding has important implications for the protection of breast cancer patients and their close relatives. If confirmed, mutation carriers may wish to consider alternatives to X-ray for diagnostic purposes. The need for tailored cancer treatment strategies in carriers should also be evaluated carefully.

Breast cancer (BC) is the most common cancer and one of the leading causes of death among women worldwide, with nearly 1,000,000 new cases per year [1]. Known risk factors include genetic susceptibility and exposure to ionising radiation [2]. The risks are highest among women exposed in childhood and adolescence and are among the highest known radiation-related risks for any cancer type [3].

Associations have been reported between inherited BC and pathogenic alleles in ten different genes involved in pathways critical for genomic integrity [4]. *BRCA1* and *BRCA2* mutations confer very high risks of breast and ovarian cancer. *p53* and *PTEN* mutations lead to very high BC risks associated with rare cancer syndromes. Mutations in *CHEK2*, *ATM*, *NBS1*, *RAD50*, *BRIP1*, and *PALB2* are associated with at least a doubling of BC risk. Because many of these genes are specifically implicated in the response to ionising radiation,

women who carry pathogenic alleles in these genes might be more sensitive to radiation-induced BC than non-carriers, as suggested by recent studies [5,6]

In the previous issue of *Breast Cancer Research*, Broeks and collaborators [7] present results suggesting that pathogenic alleles in four specific DNA repair and damage recognition genes increase the risk of radiation-induced contralateral BC following radiotherapy for a first BC.

The study used a case-only design and included 247 cases of contralateral BC diagnosed at two of the main cancer treatment institutions in the Netherlands among women who had a first BC before age 50 in the period 1966 to 2000. Overall, 21% of cases carried a pathogenic allele in *BRCA1*, *BRCA2*, *CHEK2* or *ATM*. The percentages were 24.3% among women who received radiation therapy for their first cancer (169) and 12.8% among those who did not (78). The odds ratio (OR) of developing contralateral BC following radiation therapy was 2.18 (95% confidence interval (CI) 1.03-4.62) in women carrying a pathogenic allele compared to women without. The association appeared to be strongest among women aged less than 40 at the time of their first BC (OR 2.77, 95%CI 0.74-10.39) and among women who developed their second cancer 5 years or more after the first (OR 2.51, 95%CI 1.03-6.10). The OR appeared to be lowest for mutations in *BRCA1* and highest for mutations in *CHEK2*, although these results were based on small numbers of cases and are not statistically significantly different.

In interpreting the results of this study, a number of methodological issues must be kept in mind. Firstly, because of the techniques used for the screening of *BRCA1* and *BRCA2*, a number of sequence variants will have been missed, disproportionately missense substitutions and particularly in

BC = breast cancer; CI = confidence interval; OR = odds ratio.

BRCA2. Secondly, a full screen was not carried out for *CHEK2*. Whilst 1100delC appears to be the major pathogenic allele in some European populations (for example, the UK), in others (for example, Poland) *CHEK2* harbours additional pathogenic alleles with appreciable frequencies. We do not know where in this spectrum the population of the Netherlands falls because the number of Dutch subjects who have been completely mutation screened is quite small [8]. The proportion of carriers of deleterious mutations is, therefore, likely to be underestimated in this study. The impact of this is unclear; if these other mutations do not confer an increased risk of radiation-induced BC, one could expect a reduction in the OR. If, on the other hand, the effect is greater than for those studied, the OR may be underestimated.

Of the four genes screened, the analysis of *ATM* was the most complete. Perhaps in order to make the *ATM* data more compatible with the limited sensitivity of the mutation screening for the other genes, the authors excluded from their risk calculations the *ATM* missense substitutions detected in this cohort. In a simultaneously published paper on the same study subjects, *ATM* missense substitution carriers appear to have a shorter latency of contralateral BC following radiation therapy than non-carriers [9], thus lending support to the hypothesis that rare missense sequence variants in *ATM* may also influence the risk of radiation-induced BC.

Another issue in the interpretation of these findings is the possibility that the choice of treatment protocols might be biased by clinico-pathological factors related to carrier status (even when it is unknown). For example, patients with estrogen receptor negative basal tumours may have received a more aggressive therapy because of their poorer prognosis, and it is known that *BRCA1* carriers present with a disproportionate frequency of estrogen receptor negative basal tumours [10]. The authors report, however, that adjustment of the analyses for stage, size of tumour and lymph node involvement had little effect on the results (resulting ORs not shown).

It has been known for almost a decade that, after a first diagnosis of BC, *BRCA1* and *BRCA2* mutation carriers have a very high risk of developing a second breast tumour [11-13]. Because of the success rates of treatment, increasing numbers of women are surviving their first tumour. Five-year survival rates are about 75% in Europe [14]. The risk of developing a therapy-related tumour is, therefore, of increasing concern, both from the public health and patient management perspectives.

The GENE-RAD-RISK project, a large European study, is currently underway to evaluate whether carriers of pathogenic alleles in DNA repair and damage recognition genes may confer an increased risk of breast cancer following medical irradiation [15]. If, as suggested in this paper, the treatment is

exacerbating the already disproportionate risk of second primary BC in mutation carriers, treatment protocols designed to minimize the risk of a second cancer need to be investigated in careful clinical studies.

Conclusions

While results of this and other recent studies still need to be confirmed, there is increasing evidence that carriers of pathogenic alleles in DNA repair and damage recognition genes may have an increased risk of BC following exposure to ionising radiation, even at low doses. This finding has important implications for the protection of patients and their close relatives.

If confirmed, mutation carriers may wish to consider alternatives to X-ray for diagnostic purposes, such as magnetic resonance imaging (MRI). The need for tailored cancer treatment strategies in carriers should also be evaluated carefully.

Competing interests

EC and JH declare that they have no competing interests. SVT is a previous employee of, and owns stock in, Myriad Genetics, Inc.

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