Commentary

Are *BRCA1*- and *BRCA2*-related breast cancers associated with increased mortality?

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Abstract

There has been contradictory evidence as to whether *BRCA1* associated breast cancers have a poorer prognosis than non-*BRCA1* cancers. In this issue of *Breast Cancer Research* Robson and colleagues provide further evidence for poorer survival in *BRCA1* carriers and show that it could be attributed to failure to treat small node-negative grade 3 breast cancers with chemotherapy. There still remains little evidence for a survival difference for *BRCA2* related breast cancers. Although the high contralateral breast cancer risk is confirmed by this study there is no real evidence for an increase in ipsilateral recurrence or new primary breast cancers in mutation carriers up to the 10-year point.

Keywords: BRCA1, BRCA2, breast cancer, ipsilateral, survival

Introduction

In an article published in this issue of *Breast Cancer Research*, Robson and colleagues present important findings that show a decrease in long-term survival in breast cancer patients who carry *BRCA1* mutations. The study also looked at ipsilateral recurrence and new primary breast cancers, and found no difference between those with *BRCA1* mutations and those without [1]. A number of researchers have focused their research on the mortality associated with inherited mutations in *BRCA1* and *BRCA2*. Apart from mere interest in the epidemiological aspects of breast malignancy, knowledge of the associated mortality is important to the families of patients with breast cancer, and to clinicians and scientists involved with improving the outcomes of breast cancer. We are entering the era of tailored therapies with targeted drugs such as Herceptin (trastuzumab), and a vital starting point in assessing the impact of interventions such as new drug therapy and screening is the mortality associated with standard care. Women making decisions about preventive options such as risk reducing surgery need to have reliable information on their chances of surviving breast cancer should it occur. Indeed, decisions about the type of surgery for an incident breast cancer will also depend on any difference in ipsilateral recurrence and new primary breast cancers between those opting for breast conserving treatment and those having mastectomy. These issues have been substantially addressed in the article by Robson and colleagues [1].

Methodological problems with *BRCA1/2* mortality studies

The purest study to assess mortality in *BRCA1/2* carriers would be a prospective study of all incident breast cancer in an outbred population. In order for this to occur every woman would have had to give consent for testing of fresh biological tissue (usually blood) for genetic alterations. Many women do not wish to know their genetic status even if they have breast cancer and to counsel women adequately for the potential outcome of genetic testing at the very time they are weighing up different options regarding their treatment is distinctly problematic. Although an argument could be made that knowledge of *BRCA1/2* status could alter treatment including management of the contralateral breast, the outcomes of the present study by Robson and colleagues [1] show that such a strategy may be misplaced. Indeed any change in treatment would confound the main aims of any prospective study.

ER = Oestrogen receptor.

An alternative strategy would be to test samples anonymously, by coding them and blinding any clinician involved in treatment of the patient to the results. This approach has some ethical problems, as many women would wish to know their mutation status. There is also likely to be a substantial refusal rate even to anonymous testing. This could lead to a significant bias if for instance those with a strong family history of breast cancers with poor outcomes were more likely to decline testing. Even in a large prospective study with very high ascertainment there are still the problems of accrual of follow-up time and the genetic testing process itself. The cost of testing a large enough cohort with a highly sensitive technique such as full sequencing is likely to be prohibitive. As only 2-3% of breast cancers in outbred populations are due to mutations in *BRCA1* or *BRCA2* [2], as many as 2,800 women would have to be accrued to arrive at a study with similar power to the one by Robson and colleagues [1]. Such a study would be likely to cost in excess of $3 million for the genetic testing aspect alone (over $7.7 million at full Myriad Genetic testing rates).

Flaws of previous mortality studies

The first studies to report on mortality associated with *BRCA1* actually suggested a survival advantage [3,4]. Although these studies were the best that could be achieved at that stage, these reports should be discounted as there was a substantial bias in the necessity of having a (and more likely several) living affected individual(s) in a family in order to identify linkage to chromosome 17q in the first instance. The next phase of reports were of studies based on mutation analysis. These studies were still subject to bias as individuals were either ascertained through existing proven *BRCA1* families (the necessity again for a living affected individual) [5,6,7] or some time after diagnosis in Jewish families [8]. Interestingly the latter article [8] shares some authors with the present study [1] and it is likely that there is some overlap of patients. Nonetheless the potential bias in the older study will have been corrected by the methodologies of testing tumour material in the present study. Whilst there were trends to worse prognosis in *BRCA1* carriers in these studies they were not significant after correction for other factors.

Attempts to correct for these selection biases have been made in a cohort study of incident familial breast cancers [9] and in prospectively ascertained breast cancers in screened women in family history clinics [10]. These studies convincingly showed for the first time a worse prognosis in *BRCA1* carriers in terms of survival. However, matching to other familial breast cancer cases may be problematic as non *BRCA1/2* familial breast cancer may even have a better prognosis than sporadic breast cancer. A further case control study of early stage breast cancer failed to reveal a worse prognosis [11].

Results of increased mortality for *BRCA2* are also conflicting, but less clear than for *BRCA1*. They are based on smaller numbers (total of only 70 patients), and have the same methodological flaws [5,10,12,13].

The study by Robson and colleagues

The study reported in this issue of *Breast Cancer Research* [1] circumvents most of the methodological problems of the previous studies and expands on a previous report by some of the same authors [14]. Although retrospective a very high proportion (496/584) of incident cases have been tested for the three common Jewish *BRCA1/2* mutations. As these mutations account for >90% of involvement of *BRCA1/2* in the Jewish population [15] such testing is equivalent to full gene sequencing in an outbred population. As the testing was based on tumour tissue, follow up was from diagnosis and there is little likelihood of selection bias.

The study has strengthened the evidence for worse prognosis in *BRCA1* carriers, but shows that this survival disadvantage largely disappears if patients receive chemotherapy. The results do, nonetheless, depend on only 17 *BRCA1* carriers of uncertain age who were not treated with chemotherapy. A further breakdown on age rather than just using under/over 50 years threshold would have been helpful. While data on grade and oestrogen receptor (ER) status were not testable, it is likely that the worse prognosis is associated with the known poor prognostic factors in *BRCA1* carriers: high-grade ER negativity and postive p53 staining. Interestingly the authors have also recently reported on the increased presence of glomeruloid microvascular proliferation being associated with *BRCA1* mutation carriers and poor prognosis [16]. If these results are borne out, it may well be that previous failure to treat small node negative *BRCA1* patients with chemotherapy accounts for much of the survival disadvantage. Current treatment protocols are likely to address this with nearly all small grade 3 node negative tumours now receiving chemotherapy, but this might even be extended to grade 2 tumours. Not surprisingly, there was little evidence in this study for any efficacy for tamoxifen in a largely ER-negative group of tumours.

Unfortunately, the present study adds little to the limited information on *BRCA2* with only 13 heterozygote carriers identified (this excludes the compound heterozygote carrying a *BRCA1* mutation). On current evidence in some 83 *BRCA2* mutation carriers prognosis does appear very similar to sporadic breast cancer and may well reflect the very similar tumour characteristics [17].

Ipsilateral and contralateral recurrence and new primary breast cancer

After a median follow up of nearly 10 years the current study has not shown an increase in ipsilateral risk in

BRCA1 carriers, but has confirmed the known substantial contralateral risk. This is at variance with other studies, which show an increase in ipsilateral risk at longer follow up [18]. While the authors correctly point out that when considering treatment options at initial diagnosis it should be the patient's absolute risk of a further ipsilateral tumour that determines decision-making, the authors' own findings of increased survival in the more recent patients managed aggressively with chemotherapy mean that more women will be surviving to develop ipsilateral disease. It should not be forgotten that in most long-term follow-up studies of radiotherapy at other sites, the incidence of true new primary disease in the radiation field does not really occur until 10–15 years after therapy. It is nonetheless reassuring that the ipsilateral rates in *BRCA1* are still substantially less than the contralateral rates. This means that the radiotherapy must be eliminating some of the new primary risk by destroying pre-existing tumours, and perhaps preventing cancers by eliminating a large proportion of breast epithelial cells. The final proof in this situation will only be from studies with in excess of 20 years follow up.

Conclusion

Robson and colleagues have provided further evidence to help in the management of breast cancer in *BRCA1* mutation carriers. Whilst the population studied is limited to the two common *BRCA1* mutations in the Jewish population, it is likely to extrapolate to other mutation carriers. It would appear that *BRCA1* mutation carriers have substantially better survival when treated with chemotherapy, and even small node-negative tumours should be treated. Further evidence is needed to determine whether the type of chemotherapy is important. Greater numbers are required for firm evidence on prognosis related to *BRCA2* breast cancers. While there is encouraging news for *BRCA1/2* carriers opting for breast conserving surgery, longer follow up is required before a woman can reliably be told her ipsilateral risk is no different than average.

Competing interests

None declared.

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