Breast Cancer RESEARCH

EDITORIAL

Have the roles of two functional polymorphisms in breast cancer, R72P in *P53* and MDM2-309 in *MDM2*, become clearer?

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See related research by Schmidt *et al.*, http://breast-cancer-research.com/content/11/6/R89

Abstract

Genetic differences between individuals have been predicted to account for disparate outcomes in patients diagnosed with cancer. The search for genetic determinants has been ongoing for a considerable amount of time and it is only now that insights have been gained into which polymorphisms are most likely to be important in determining not only disease likelihood but also outcome. The quest to be able to accurately predict patient outcomes in breast cancer may now be a step closer as increased sample size is leading to more robust statistical analysis and a better understanding of molecular mechanisms of disease are forthcoming.

Predicting disease outcome after the diagnosis of breast cancer, which is important for the choice of treatment of women diagnosed with this malignancy, remains a major challenge. Over the past decade there has been an increasing awareness of the power of genetic prediction, which is now beginning to provide some information that may be useful in the assessment of disease outcome. As an example, several reports in the literature indicate that genetic signatures are potentially useful approaches for prognostication. A major impediment to rapid progress in the identification of genetic determinants of outcome has been, and continues to be, our limited ability to assess gene-gene and gene-environment interactions. Nevertheless, inroads into understanding gene-gene interactions are being made due, in part, to a better appreciation of molecular pathway analysis. Particularly attractive targets of study have been genetic polymorphisms in genes associated with the repair of DNA damage and those involved in cell cycle control since an inability to tightly regulate either of these two processes is likely to result in a less than optimal outcome.

In the report by Schimdt and colleagues [1] the gene-gene interaction between the cell cycle checkpoint control gene *P53* and its negative regulator *MDM2* has been examined in a large group of women diagnosed with breast cancer to determine whether two single nucleotide polymorphisms (SNPs), R72P in *P53* (rs1042522) and *MDM2*-309 (rs2279744), could be associated with disease outcome. This is not the first study to examine the relationship between the tumour suppressor gene *P53* and MDM2, but it is one of the first to investigate the relationship between polymorphisms in these genes and disease outcome as opposed to breast cancer risk. The importance of the two SNPs lies in their functional consequence. R72 is reported to have a 15-fold greater capacity to induce apoptosis than P72 [2] and the *MDM2* polymorphism has been shown to be associated with deficiencies in the P53 response pathway [3].

Studies examining the relationship between R72P and *MDM2*-309 and cancer risk have been somewhat inconsistent, but many larger studies examining common malignancies (including breast cancer) are converging towards the notion that neither SNP appears to be associated with the risk of developing disease [4-8]. These results are in contrast, however, to investigations into cancers developing in patients diagnosed with germline *P53* mutations, where both R72P and *MDM2*-309 SNPs do appear to be associated with differences in the age at which disease is diagnosed [3,9,10]. This is perhaps not surprising as loss of *P53* will underlie subsequent events associated with tumour development in this setting.

The pooled analysis presented by Schmidt and colleagues [1] of four studies, three hospital- and one

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population-based, including 3,749 breast cancer patients, provided sufficient power to detect whether or not there were any associations between the combined polymorphisms and disease outcome. The results revealed that there is an association between the two SNPs and breast cancer outcome, suggesting that they could be used as potential markers to stratify patients into different risk groups. Nevertheless, even with this large number of patients only 26 were homozygous for both variants, thereby making it impossible to quantify statistically the strongest effect. This emphasizes the necessity of acquiring large numbers of patients for genetic studies since smaller ones run the risk of having insufficient power to detect these types of effect. The magnitude of the effect, however, remains relatively small (with an 11% difference) and emphasises the point that these two markers account for only some of the differences between patients with good or poor survival.

Previously, Schmidt and colleagues [8] had demonstrated for breast cancer that neither R72P nor *MDM2*-309 was associated with the risk of developing disease, which was supported by several other larger studies [4-7]. Placing this in context, the results of Schmidt and colleagues [1] are significant as they indicate that R72P and *MDM2*-309 act as affect modifiers as opposed to being causal. If R72P and *MDM2*-309 are indeed affect modifiers, then further studies in different populations should yield similar results as the effects of the two SNPs would be predicted to be similar in diverse groups of patients. In support of this, the results are consistent with a report by Do and colleagues [11], who identified that both polymorphisms also act as disease modifiers in lymphoblastic leukaemia.

Since the advent of gene expression array technology, it is now well recognised that there are multiple subgroups of breast cancer that can be characterised not only by their histopathology but also by gene expression profiling and that these differences are correlated with disease survival [12-14]. In relation to R72P and *MDM2*-309, it would be predicted that these two SNPs, acting as disease modifiers, are likely to remain associated with survival even in different subgroups of patients as they would still remain affect-modifiers and continue to contribute to disease progression irrespective of the molecular profile of the tumour.

Finally, this study and those that have preceded it raise important points in relation to the choice of disease in which to examine polymorphisms in two key regulators of cell cycle checkpoint control. If one of the primary molecular alterations involves P53, then it is to be expected that differences in the remaining wild-type *P53* allele (or its downstream partners) will be influenced by intrinsic functional polymorphisms, which are likely to correlate with the age at disease diagnosis. If P53 is not involved in a disease's initiation but in its progression, then it is more prone to be associated with differences in prognosis. The report by Schmidt and colleagues [1] has significantly contributed to our understanding of risk recurrence in patients diagnosed with breast cancer. It is to be expected that with larger, more definitive studies, more precise information about the role of R72P and *MDM2*-309 in disease outcome will be forthcoming.

Abbreviations

SNP = single nucleotide polymorphisms.

Competing interests

The author declares that he has no competing interests.

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