Pergamon

European Journal of Cancer, Vol. 34, No. 7, pp. 966–967, 1998

Printed in Great Britain
0959-8049/98 $19.00+0.00

PII: S0959-8049(98)00060-4

Point of View

The *BRCA* Paradox in Breast and Ovarian Cancer

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INTRODUCTION

THE CONTRIBUTION of genetics and molecular biology to the art of medicine is radically changing our way of understanding human diseases. Initially evolved in the fields of non-neoplastic diseases, these specialities have now entered the complex area of cancer, generating the suggestion that virtually all types of human cancer can occur in genetically susceptible individuals.

It is generally accepted that a cancer results from the accumulation of genetic changes in a target cell. The mutation of several genes eventually leads to the onset of a cancerous phenotype; the inheritance of these mutated genes in the germline will cause cancer susceptibility in the next generation.

More than 50 different genes appear to confer cancer susceptibility to heterozygous carriers, raising the issue of genetic testing for those at high risk of having inherited the mutation. Guidelines are being endorsed by several medical organisations to regulate the increasing demand for the availability of genetic testing. Three categories of indication for genetic testing have been developed, whether the medical benefit derived from the identification of a carrier status is established, presumed or not apparent [1].

THE KNUDSON HYPOTHESIS

The dominant transmission of a trait implicates its acquisition in 50% of the offspring. More that 25 years ago, the observation that the penetrance for cancer mutation in the germline is incomplete prompted Alfred G. Knudson to suggest that something else had to take place at the genotypic level for the development of cancer [2]. He hypothesised that cancer results from the occurrence of a second mutation in a somatic target cell, so that the only difference between hereditary and non-hereditary tumours is the timing of the first mutation (prezygotic or postzygotic). The second mutation can either affect the remaining normal allele of the same gene (recessive trait) or one copy of a different gene (dominant trait). The first direct evidence substantiating the recessive model or two-hit hypothesis was derived from the assay of esterase D activity, a biochemical marker whose gene is closely linked to the retinoblastoma gene (*RB1*). Indeed, esterase D activity is decreased to 50% in the normal cells of individuals with a *RB1* germline deletion, whereas in tumour cells it is completely absent. The complete loss of esterase D expression results from the mutation of both copies of the same chromosomal site where esterase D and *RB1* genes are located [3].

The development of new technologies led to the cloning of *RB1* and other genes, such as the Wilms' tumour gene (*WT1*), for which it was possible to confirm at the molecular level the recessive hypothesis. These genes were then defined as tumour suppressor genes or anti-oncogenes [4].

THE TWO-HIT HYPOTHESIS FOR HEREDITARY BREAST AND OVARIAN CANCER

The discovery of the *BRCA1* and *BRCA2* cancer susceptibility genes initially raised great expectations, as they were thought to explain most cases of familial breast cancer. Furthermore, it was hoped that the understanding of hereditary breast tumours could shed light on the pathogenesis of sporadic cases.

Studies conducted on families with multiple individuals affected by breast and ovarian cancer suggested that *BRCA1* and *BRCA2* could act as tumour suppressor genes and that the two-hit model could explain the onset of cancer among carriers of germline mutations. It was thus hypothesised that, as genetic susceptibility to breast and ovarian cancer results from the inactivation of one allele in the germline followed by the loss of the other allele in somatic breast tissue, the mutations are recessive at the cellular level, although inheritance of breast and ovarian cancers in high risk families follows an autosomal dominant pattern.

This model has been substantiated experimentally by detecting a consistent loss of the wild-type allele in breast cancer cells obtained from *BRCA1*- and *BRCA2*-related tumours [5, 6].

THE PARADOX

Breast and ovarian cancers represent an exception to the two-hit hypothesis, as they do not show the predicted relationship between the hereditary and non-hereditary forms of the tumours. Unlike other tumour suppressor genes, no definite disease-causing *BRCA1* or *BRCA2* mutations have so far been detected in sporadic breast and ovarian cancers. Actually, *BRCA1* and *BRCA2* somatic mutations have only been found in specimens of breast and ovarian cancer tissue from individuals carrying a mutated germline allele.

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Received 17 Nov. 1997; accepted 26 Jan. 1998.

In germline mutation carriers, the mutation of the remaining normal *BRCA1* allele leads to a loss of heterozygosity (LOH) in chromosome 17q21, where *BRCA1* is localised. Interestingly, up to 80% of sporadic breast and ovarian cancers also have allelic deletions leading to LOH in 17q21. Nevertheless, either other genes are involved or alternative mechanisms of inactivation abrogate *BRCA1* function, as these sporadic cancers do not contain mutations in the *BRCA1* sequence. For *BRCA2*, 30–40% of sporadic breast cancers and 50–60% sporadic ovarian cancers show LOH in 13q12-13, the region where *BRCA2* is localised. Again, no definite disease-causing mutations of *BRCA2* have been observed in sporadic cancers.

Why are *BRCA1* and *BRCA2* mutations virtually absent in sporadic breast cancers, although LOH in the same chromosomal regions where they are localised is so common? This is even more extraordinary considering that, if the average lifetime risk of breast cancer in women who inherit a copy of a mutated *BRCA1* gene is almost 90% (and just slightly less for *BRCA2*), there is almost a 90% chance of a second somatic mutation occurring in *BRCA1*.

THE NEW HYPOTHESIS

We believe that the paradox that we have just detailed has been surprisingly disregarded by most experts by accepting the Knudson model of cancer susceptibility for hereditary breast and ovarian cancer. The recent advancements of basic and clinical research may provide a clue to clarifying these issues.

Several experimental data suggest that *BRCA1* and *BRCA2* may act synergistically with the DNA repair protein Rad51 to modulate cell proliferation and to preserve genomic stability by repairing DNA breaks. Their possible role in the genesis of hereditary cancers has been illustrated in the very elegant theory of gatekeeper and caretaker genes presented by Kinzler and Vogelstein [7]. Gatekeeper genes directly regulate the growth of tumours and their inactivation leads to a very specific tissue distribution of cancer. For example, inherited mutations of the retinoblastoma, von Hippel Lindau, neurofibromatosis type I and adenomatous polyposis coli genes lead to the onset of tumours of the retina, kidney, Schwann cells and colon, respectively. The cancer predisposition acquired with the mutation of these genes is consistent with the two-hit hypothesis.

Conversely, the inactivation of a caretaker gene indirectly promotes cancer by causing genomic instability which in turn may result in accelerated mutation of other genes, such as the gatekeeper genes. Caretaker genes are represented by those responsible for xeroderma pigmentosum, non-polyposis colorectal cancers and ataxia-teleangectasia. It is likely that *BRCA1* and *BRCA2* also belong to this group of genes.

Does this explain the paradox? For gatekeeper genes, in sporadic cases two mutations are necessary at the somatic level for a cancer to develop, whereas individuals who inherit one inactivated copy of the gene need only one additional somatic mutation, so their cancer is exponentially higher. In contrast, for caretaker genes, three somatic mutations (mutation of the caretaker allele inherited from the unaffected parent, followed by mutation of both alleles of gatekeeper gene) are required to initiate cancer in hereditary cases. This explains why cancer risk in *BRCA1* and *BRCA2* carriers is at most 15-fold higher than in the general population and why caretaker genes are never involved in sporadic cancer, which would require the very unlikely occurrence of four somatic mutations.

The latest estimates of both the cancer risk and the percentage of cancer cases attributable to the mutation of *BRCA1* and *BRCA2* genes are in line with the hypothesis that they may function as caretaker genes. Actually, cancer risk among *BRCA1* and *BRCA2* carriers appears to be much lower than initially calculated. Among carriers belonging to a population not selected on the basis of family history, breast cancer risk might be lower than 50% and ovarian cancer risk lower than 15% by the age of 70 years [8]. Furthermore, *BRCA1* may account for much less than 45% of hereditary breast cancer cases, as until recently believed and *BRCA2* mutations could be responsible of as little as 20% of cases attributable to *BRCA1* [9]. This is expected if one considers *BRCA1* and *BRCA2* to be genes *predisposing* to cancer and not *causing* cancer. That is to say that their mutation may be a non-obligate, non-self-sufficient event of a multistep pathway leading to breast cancer development.

In conclusion, unfortunately *BRCA1* and *BRCA2* are far from explaining the pathogenesis of all breast and ovarian cancers. It seems that the loss of many other genes can produce the same affect determined by *BRCA* loss (i.e. genomic instability) and that even if breast cancer is the final result in heredity and sporadic tumours, the *primum movens* can be totally different. At the other extreme, *BRCA* genes can no more be regarded as specific determinants of breast and ovarian cancers, as already predicted by the observation that *BRCA* carriers are susceptible to the development of tumours at several anatomical sites.

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