Pergamon

European Journal of Cancer Vol. 30A, No. 12, pp. 1738–1739, 1994

0959–8049/94 $7.00+0.00

0959-8049(94)00455-2

Comments and Critique

BRCA1, BRCA2, BRCA3 . . . A Myriad of Breast Cancer Genes

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The publication of three papers in *Science* made September and October bonanza months for those interested in breast cancer [1–3]. Under pressure from numerous rumours and public interest, *Science*'s editors chose to come clean and circulated drafts of the papers over 2 weeks prior to publication. The resulting press coverage produced items, long in preparation (since this announcement had been expected at any time since December 1990), discussing the time until a test for those predisposed to breast cancer would be available, the dilemmas of those with a positive test and the rights and wrongs of patenting genes.

The long awaited paper, describing the cloning of a gene for a hereditary breast cancer called *BRCA1* appeared in the 7 October issue [1]. The name *BRCA1* was given to a gene located on human chromosome 17, the location of which was identified in 1990 by Dr Mary-Claire King and colleagues after an intensive mapping study [4]. In rare families, susceptibility to breast cancer is inherited as an autosomal dominant so that on average half of the offspring of a parent with the mutation will inherit the same mutation and the females will be at high risk of breast cancer. Subsequent confirmation of this result and examination by the Cancer Family Study Group Breast Cancer Linkage Consortium showed that the effects of *BRCA1* were not limited to breast cancer but instead extended to increased risk of cancer at a variety of other sites, the most noticeable of which was the ovary [5]. An estimate based on the families contributed to the linkage consortium estimated that the lifetime risk of breast cancer was 73% by age 50 years and 87% by age 70 years and of ovarian cancer was 29% by age 50 years and 44% by age 70 years. Males do not escape *BRCA1* entirely free of risk since they have a 3.3-fold increased risk of prostate cancer while males and females have an estimated 4.1-fold increased risk of bowel cancer (but by comparison with the risks for breast or ovarian cancer, these risks for other cancers are modest) [6]. Further analysis of tumours taken from *BRCA1*-linked families showed loss of the wild-type chromosome (i.e. the chromosome not carrying the *BRCA1* mutation) in the tumours, a signature of a tumour suppressor gene [7, 8].

BRCA1 was cloned by a collaboration between scientists from the University of Utah, Myriad Genetics Inc. (both based in Salt Lake City, U.S.A. and led by Mark Skolnick) and the National Institute of Environmental Health Sciences (led by Roger Wiseman) [1]. The gene is large consisting of 24 coding exons distributed over 100 kb of genomic DNA with a 7.8 kb product visualised on Northern blots and shown to be expressed in both the breast and the ovary. The authors found a zinc-finger domain, similar to another familial tumour suppressor gene, WT1, but besides this there was little clue to function. Five distinct mutations were identified in the germline in separate families, while in three families, a mutation had not been recognised at the time of the publication.

Since the spectrum of mutations is not yet known, it is impossible to comment on the ease with which a test for *BRCA1* mutations will be produced or even the utility of this test. Some mutations in *BRCA1* clearly are associated with extremely high risks of cancer (as given above) but this does not mean that all mutations will have the same risk. Epidemiological work will be required to correlate site and type of mutation with cancer risk; such work may take several years to collate if mutations can be spread throughout the gene. Until then, testing is only of use in those few high risk families already attending genetics clinics; in these families the high risk of cancer is proven. It has been estimated that between 1 in 2000 and 1 in 500 live-births carry high risk mutations in *BRCA1* [9]. If there are lower risk mutations, then the carrier frequency could well be much higher. Until this is known, the utility and appropriateness of population-testing will remain a matter of speculation.

The second *BRCA1*-related paper in this series described the finding of mutations in "sporadic" breast and ovarian tumours [2]. These tumours (32 breast and 12 ovarian) were chosen to come from early-onset cases and had to show loss of heterozygosity in the region of *BRCA1*; such tumours would be the most likely candidates for a *BRCA1* mutation since inactivation of both copies of the tumour suppressor gene *BRCA1* should be required. In fact, only four mutations were detected and, even more surprisingly, all mutations were germline. No somatic mutations (i.e. mutations detected in the tumours which were not present in the germline) were detected. Two of the four mutations occurred in women from families which were consistent with the results expected from the linkage consortium (extremely early onset, bilateral disease, family history of breast and ovarian cancer) while the other two women had no notable

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family history. Clearly, more detailed studies, which are epidemiologically-based are required to examine this in more detail but these findings already suggest that somatic *BRCA1* mutations may not be that important and that mutations in other genes may circumvent the necessity of *BRCA1* mutations during tumorigenesis.

One of the clearest conclusions from the linkage consortium analysis was that there was at least one more gene for breast cancer [5]. While almost all of the families with predisposition to breast cancer and ovarian cancer were due to *BRCA1*, this gene did not explain those families in which a male also had breast cancer, or a number of large families with breast cancer the only cancer in obvious excess. A number of groups (led by scientists from the Institute of Cancer Research, Sutton, England and the University of Utah, U.S.A.) embarked on a genome-wide search for *BRCA2* taking those families clearly not attributable to *BRCA1*. Chronologically, the first of the three papers to be published reported the mapping of *BRCA2*, in this case to 13q12-q13 and in the proximity of the retinoblastoma gene (*RB1*) (although this clearly is not *BRCA2* since recombination events exclude it) [3]. The evidence for this location is impressive with a LOD score of 11.65 and a clear definition of a region encompassing *BRCA2* of 5 cM. Examination of sporadic breast tumours shows loss of heterozygosity to be common around *BRCA2* which suggests again that *BRCA2* is a tumour suppressor gene (or, possibly close to another tumour suppressor gene). Interpretation of these results is again complicated (as was the interpretation of such studies for *BRCA1*) by the presence of a known tumour suppressor gene in the region (*RB1*).

Unlike *BRCA1*, a mutation in *BRCA2* does not appear to confer such a dramatically increased risk of ovarian cancer [3]. It does, however, seem to produce an increased risk of breast cancer in men. Crude calculations suggest that *BRCA1* and *BRCA2* explain approximately equal proportions of breast cancer families (perhaps 40% each) and that therefore at least one more gene (*BRCA3*?) is required to explain dominantly inherited susceptibility to breast cancer. Watch this space . . .

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European Journal of Cancer Vol. 30A, No. 12, pp. 1739–1741, 1994

0959–8049/94 $7.00+0.00

0959-8049(94)00373-4

Second-line Chemotherapy in Epithelial Ovarian Carcinoma: Platinum Again? Taxanes? How to Choose?

J.P. Guastalla

ALTHOUGH ADVANCED stage ovarian cancers are sensitive to chemotherapy, the prognosis remains poor. Thus despite an 80% clinical response rate for platinum-based first-line chemotherapy, with an almost 50% complete clinical response and a 10–30% pathological complete response (PCR), the overall survival rate is only of the order of 20% at 5 years [1]. Although patients in PCR have the best prognosis, 50% relapse after 5 years. Patients in partial response have a 10% survival rate at 5 years, and all patients who are stable or progress , die within 3 years [2]. It is, therefore, appropriate to consider second-line chemotherapy in the majority of cases of ovarian cancers.

Second-line chemotherapy has not improved survival, but its aim is palliative and improvement of the quality of life of patients is the priority [3]. Bolis and coworkers, in a paper in this issue of the *European Journal of Cancer* (pp. 1764), confirm, as has been reported by other authors [4,5], that in a large number of cases the disease remains sensitive to second-line platinum-based

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Received 5 Sep. 1994; accepted 7 Sep. 1994