Letters to the Editor

Histopathological data

Sir

We read with interest the recent paper by Pichon MF et al (1996). We first noted that the following histopathological data had been used in this study: tumour classification, tumour grading, maximum tumour diameter and axillary lymph node status. These data were derived from the records of the pathological examination of 2257 tumorectomies or mastectomies. We then noticed that the histology slides had apparently not been reviewed by a panel of pathologists. Surely, this has become an indispensable way of ensuring a minimum of quality control in any multicentre study of this type. Being further aware that the authors of this paper did not include a single pathologist, we were dismayed by the complete lack of any reference to the several pathologists who had obviously contributed to this monumental series.

We wish to strongly urge editors and referees of international oncology journals, when reviewing multicentre studies primarily based on histopathological data, to ensure that such papers are adequately reviewed by a panel of pathologists and that the identity and affiliation of contributing or panelist pathologists are clearly indicated.

REFERENCE

Pichon MF, Broet P, Magdelenat H, Delarue JC, Spyrotos F, Basuyau JP, Saez S, Rallet A, Courriere P, Millon R and Asselain B (1996) Prognostic value of steroid receptors after long-term follow-up of 2257 operable breast cancers. Br J Cancer 73: 1545–1551

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Histopathological data – reply

Sir

The aim of our study, using the data of medical records obtained under the conditions of current medical practice, was to evaluate the relationship between the results of quantitative measurements of hormone receptors in primary tumours and the occurrence of events during the monitoring of breast cancers. In French Cancer Centres, the diagnosis, treatment and monitoring of breast cancers is carried out by multidisciplinary teams made up of specialists who all contribute to the elaboration of the medical records common to the Institution.

This paper did not purport to focus on histological correlations, which merely represent four out of nine criteria studied.

Consequently, we saw no case for a specific post-review of histopathological data, as the main criteria of this study, oestriadiol and progesterone receptors, were permanently subject to quality control. This is common standard practice for all laboratories engaged in steroid receptor assays.

Furthermore, no recent similar studies include post-verification of histological data (Spyrotos et al, 1992; Pujol et al, 1994; Romain et al, 1995, 1996).

In so far as no further work is required from any other speciality outside the present team, there is no justification for certain specialists rather than others in the list of authors. In addition, the majority of this series of patients’ records has already been the object of previous publications to which pathologists were associated (more than 25 papers in all).

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On behalf of
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BRCA1 polymorphisms

Sir

Determining the clinical significance of germline alterations in BRCA1 has serious implications for predicative assessment of breast and ovarian cancer risk. While the majority of alterations in BRCA1 are frameshift or nonsense mutations that are likely to damage gene function severely, determining the status of intronic sequence variants or of rare sequence variants that result in missense alterations is more difficult and conflicting interpretations of such variants have been published. We report here on two such variants which we believe can now be classified as non-pathological rare sequence variants.

Perhaps the most controversial of these variants is a 12-nucleotide duplication 48 base pairs downstream of the 3’ boundary of exon 20. Although this is in a region unlikely to affect RNA splicing, it was tentatively classified as a mutation by
Takahashi et al (1995) because it was found in a woman diagnosed with both breast and ovarian cancer and who also had five maternal relatives with breast cancer. Subsequently, the variant was reported by Langston et al (1996a) in a woman diagnosed with breast and cervical cancer, and in two independent cases of prostate cancer (Langston et al, 1996b). In none of these studies was the alteration observed in 174, 237 and 145 non-cancer controls respectively. The classification of this variant as a ‘definite’ variant by Langston et al (1996a) attracted criticism (Mathew et al, 1996), as in the absence of a functional test the evidence for its pathological nature is at best circumstantial.

In the course of our analysis for BRCA1 mutations in 300 cases of early-onset breast cancer or sporadic ovarian cancer we detected this variant in four apparently unrelated individuals, three diagnosed with breast cancer aged 23, 29 and 38 and one with bilateral mucinous cystadenomata of the ovaries aged 70. None of these women had a family history of BRCA1-related cancers apart from one breast cancer patient whose mother died of breast cancer aged 40. In the two other isolated breast cancer cases, in which the parents were available for analysis, the insertion was inherited from the mother in one case and from the father in the other.

Consistent with a tumour-suppressor role of BRCA1, previous analyses of tumours with loss of heterozygosity at the BRCA1 locus have revealed that in every case it is the wild-type allele that is lost (Merajver et al, 1995). However, analysis of tumours from our cases revealed that all three breast cancers showed loss of heterozygosity, and in each case it was the 12 bp insertion allele that was lost (Figure 1), suggesting that the intron 20 insertion is in fact a rare non-pathological sequence variant.

The second variant we investigated was the missense mutation designated R1347G caused by an A→G substitution at nucleotide 4158 first detected in Utah kindred K2039 by Shattuck-Eidens et al (1995). This variant was not detected in 232 controls, but the individual carrying this alteration also had a frameshift mutation, casting doubt on its pathological significance.

We have detected the R1347G in nine apparently unrelated cases of early-onset breast cancer. In two of these cases we also detected frameshift mutations caused by a 1 bp deletion at nucleotide 2594 in one and a 4 bp deletion at nucleotide 3875 in the other. In the former case, DNA was available from the mother, who was found to be carrying the 1 bp deletion at 2594 but not the R1347G variant. In contrast to the strong family history of breast and ovarian cancer on the maternal side (one ovarian cancer, three breast cancers, one colon cancer and one stomach cancer among 18 first- and second-degree relatives) there were no reported cancers among nine first- and second-degree relatives on the paternal side, including the father and two aunts, who were over the age of 70.

Among the other carriers of the R1347G variant four had no family history of cancer. The remaining three cases had family histories consistent with inherited BRCA1 or BRCA2 mutations but the analysis of these genes is incomplete. We conclude that R1347G is a non-pathological sequence variant that may have its origins in the south of England.

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