Author's response to reviews

Title: TP53 mutations in ovarian carcinomas from sporadic cases and carriers of two distinct BRCA1 founder mutations; relation to age at diagnosis and survival

Authors:

Pedro Kringen (pedrok@broadpark.no)
Yun Wang (yun.wang@medisin.uio.no)
Vanessa Dumeaux (vanessa.dumeaux@medisin.uio.no)
Jahn M Nesland (j.m.nesland@medisin.uio.no)
Gunnar Kristensen (gunnar.kristensen@klinmed.uio.no)
Anne-Lise Borresen-Dale (a.l.borresen-dale@medisin.uio.no)
Anne Dorum (anne.dorum@dnr.uio.no)

Version: 2 Date: 3 April 2005

Author's response to reviews: see over
Dear Editor

Please find the revised version of our manuscript entitled “TP53 mutations in ovarian carcinomas from sporadic cases and carriers of two distinct BRCA1 founder mutations; relation to age at diagnosis and survival” by Pedro Kringen, Yun Wang, Vanessa Dumeaux, Jahn M. Nesland, Gunnar Kristensen, Anne-Lise Børresen-Dale and Anne Dørum.

The referees’ comments were helpful and constructive and we have carefully taken their suggestions into account.

The following is a point-by-point listing of our responses to the comments.

Reviewer: David Goldgar

Major Compulsory Revisions

1) We mean that the uncertainty about which tumors have TP53 mutations is low. The numbers of patients that only have a silent mutation is 1 (familial case number 28) and two patients with IVSs. Further, the bands in cases with aberrant TTGE bands and no sequence did not show resemblance to common polymorphism or known IVSs’ (page 9). Thus we conclude that there is a very high probability that these aberrant bands represent nonsense or missense mutations.

2) For clinicians age at diagnosis is of importance. We think that even though the relationship between age at onset and survival in figure 1 are similar when adjusted for TP53 mutations this will be of interest for clinicians (abstract and page 1). The missing label in Figure 1 is corrected.

3) Sporadic and hereditary tumors have been closer “matched”. Histology-serous tumor were already matched, we removed 6 oldest age of onset sporadic cases, thereby reducing age of onset and matching FIGO stage 4, a worse prognostic factor, and as you pointed out; problematic in comparison age of onset and survival (table 1 and page 7). The changes did not alter the results significantly. We removed the word “matched” in the material.

Minor Compulsory Revisions

1) Table 1 corrected.

2) More details of cases included (page 7).
Reviewer: Richard Buller

Major Compulsory Revisions
1) The inter relationship of TP53 mutations in sporadic and hereditary BRCA1 related ovarian cancer and survival differences in the literature is discussed more thoroughly (page 12, 13 and 14).

Minor Essential Revisions
1) See our answer to Goldgars comments (nr 1) which deals with methodological concerns regarding the TP53 mutations.

2) All aberrant bands from TTGE were isolated and sequenced repeatedly. This is commented under table 2 along comments regarding the high sensitivity of TTGE which may result in loosing some of the mutations when sequencing. We also stressed that the aberrant bands were isolated and re-sequenced in the text on page 8.

3) The missing label is added in Table 3. Table 3 was referred to in page 11 in the original manuscript and now also on page 16.

Statistical review
All statistics rerun. The basis for the statistics is clearly stated in the manuscript.

Yours sincerely

Anne Dørum MD PhD