

Author's response to reviews

Title: High penetrances of BRCA1 and BRCA2 mutations confirmed in a prospective series.

Authors:

Pål Møller (moller.pal@gmail.com)
Lovise Mæhle (Lovise.Olaug.Mahle@radiumhospitalet.no)
Lars F Engebretsen (lars.engebretsen@helse-bergen.no)
Trond Ludvigsen (Trond.Ludvigsen@stolav.no)
Christoffer Jonsrud (Christoffer.Jonsrud@unn.no)
Jaran Apold (jaran.apold@helse-bergen.no)
Anita Vabø (Anita.Vabo@radiumhospitalet.no)
Neal Clark (nealclark@hotmail.com)

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Response to referee # 1:

1. In his first comment, this referee commented that 'the addition of the annual rates would exceed a lifetime risk of 100%'. It was explained in our coverletter to first revision that this is so, and that the difference between cumulative risk by age and annual incidence rate by age are conceptually different was discussed in Discussion, section 4. The referee returns to this point and state that 'I agree with their arguments but they need to make it explicit.' We have calculated annual incidence rate according to standard references (Hill – ref 21), and cannot see that we should discuss this methodology further in a study were we apply the method – we have not written a methodological discussion on annual incidence rate, we use the method. The concept of adding the annual incidence rate year by year, has to us no meaning. An example: if you have annual incident rate of 50% for those healthy at the beginning of each year in three consecutive year, three times 50 is 150, while the cumulative rate of affected would be 50% + 25% + 12.5% = 87.5%. The summing up of three times 50 has to us no meaning, and we cannot see how to discuss this further.

2. The referee indicates that we should 'explicitly state that all women had their first examination as a known unaffected'. As described in methods, this was not so but as described in results, section 3, we took away all others and the annual incidence rates in those having no cancer before or at first examination, was our goal to describe and are what we discuss. To make this explicit, we have included an additional line at the end of the introduction, stating that: 'The main goal was to describe annual incidence rate in those who had had no cancer before inclusion and who had no cancer demonstrated at first (prevalence) round.'