mutations predispose to ovarian cancer, an apparent association may be inferred with any additional phenotype studied in relatives of mutation-positive ovarian cancer cases if the exact relationships between family members (both affected and unaffected) and mutation segregation with each of the phenotypes is not taken into account. These factors need to be considered in risk calculations; failure to do so will inevitably lead to overestimation of the risk of the second phenotype. Our results are also consistent with the data presented in other follow-up studies[3–12]. Analysis of large series of ovarian cancer cases from the general population would now be of value to better estimate the frequency of and risk conferred by *RAD51C* and *RAD51D* mutations and to inform clinical implementation of these genes.

The identification of *RAD51C* as a cancer predisposition gene was an important discovery[1,2]. However, we note that Meindl *et al.* did not present any risk analyses to quantify the extent of associations between *RAD51C* mutations and risk of breast and/or ovarian cancer, and we believe that their data warranted a more cautious interpretation. As we enter an era in which mutational data will become readily obtainable, appropriate genetic and epidemiological experiments are required for the clinical promise of genetic research to be realized.

Note: Supplementary information is available on the Nature Genetics website.

AUTHOR CONTRIBUTIONS
N.R., C.L. and C.T. designed the experiment. M.W.-P., C.T., K.S., D.E., D.G.E., BCSC (UK), M.G. and N.R. coordinated recruitment of cases and samples. C.L., R.M.M.X., E. Ramsay, D.H., A.R. and S.S. performed sequencing of *RAD51C*. C.T., E. Ruark and A.C.A. performed statistical analyses. N.R. oversaw all aspects of the study.

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COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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Meindl *et al.* reply:

Loveday *et al.*[1] claim, as do Pelttari *et al.*[2], that *RAD51C* is a predisposing gene for ovarian cancer. However, their screening results do not falsify or disprove our assertion that *RAD51C* is a predisposing gene for breast cancer and ovarian cancer[3]. Indeed, we found that *RAD51C* mutations segregated with breast cancer in two out of the seven families with breast cancer and ovarian cancer we analyzed[3]. Furthermore, Vuorela *et al.*[4] found an in-frame deletion in one individual with breast cancer from a family with four cases of breast cancer and four cases of ovarian cancer. However, they were unable to establish segregation in this pedigree.

The skepticism of Loveday *et al.* toward a pathogenic role for missense mutations is unwarranted. In general, these authors refuse to accept the causality of missense mutations in *RAD51C* in breast cancer. In fact, most of the variants discussed here are predicted to affect amino-acid residues conserved in at least three of the five RAD51 paralogs, and the effects of the variants have been characterized by functional approaches. It is, of course, easier to classify a truncating mutation as pathogenic. We note that Clague *et al.*[5] recently reported a missense variant in *RAD51C*, which seems to compromise the interaction between the RAD51C protein and its interacting partners RAD51B and XRCC3.

The statistical arguments presented[1] might be valid only for a subgroup of families or populations. Here we agree with Rahman and colleagues that *RAD51C*, as well as *RAD51D*, have to be validated in larger cohorts to generate reasonable clinical proposals or conclusions. Rahman *et al.*, as in our study[3], found the p.Gly264Ser alteration in RAD51C (encoded by a c.790G>A mutation) overrepresented in families with breast cancer and ovarian cancer compared to controls. However, there was also a statistically significant overrepresentation of this variant in individuals with ovarian cancer from Australia[6]. Although screening of samples of larger size is required, these observations are consistent with population-specific effects.

AUTHOR CONTRIBUTIONS
A.M. wrote the paper and designed the concept. K.E., S.E., A.B., D.E. and N.D. provided experimental or clinical data. R.K.S. designed the concept and collected clinical data. D.S. supervised the experiments.

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