The association of estrogen receptor (ER) negativity in breast cancer with BRCA1 germline mutation carrier status is so engrained in the literature that there is a tendency to regard all patients with ER-positive tumors as sporadic or nonfamilial. In a recent paper published in Breast Cancer Research, Tung and colleagues report the clinical and histological features of ER-positive breast cancers in BRCA1 mutation carriers [1].

The study cohort comprised 172 women with BRCA1-associated breast cancer, of which 36% were ER-positive. Pathological analysis was only possible, however, in 117 of these patients (68 ER-negative and 49 ER-positive). The ER-positive patients were also compared with 138 matched, population-based, nonfamilial controls. The study produced three fundamental conclusions. First, there was an association between the ER status of tumors in BRCA1 carriers and age of diagnosis – age >50 years was a predictor of ER-positive tumors (as was menopausal status, which is associated with age). Second, the ER-positive and ER-negative tumors in BRCA1 carriers were different in type, grade, mitotic activity, necrosis and type of margins (pushing versus invasive). Finally, the ER-positive tumors in BRCA1 carriers were different to sporadic/control ER-positive cancers, showed a trend towards higher grade and mitotic activity, and were predominantly ductal carcinoma – no special type. This last conclusion is the most significant, suggesting that ER-positive, BRCA1-associated tumors are not simply incidental. Although the data are not conclusive, they are intriguing.

There are some inevitable limitations to the study. The number of patients analyzed is small, the pathological data in parts are incomplete, and the data on ER status are a mixture of biochemical and immunohistochemistry analyses. The pathologists were blinded to ER status but do not appear to have been blinded to BRCA1 status. Many of the limitations are unavoidable due to the nature of the population studied and the type of analysis attempted. However, they do limit the eventual conclusions that can be drawn.

There is a clear and strong association between older age (and hence menopausal status) and the development of ER-positive breast cancers in BRCA1 mutation carriers. Although these data are consistent with those of Vaziri and colleagues [2] and Foulkes and colleagues [3], the latter study demonstrated that at every age interval, the likelihood of developing an ER-negative breast cancer for BRCA1 mutation carriers is much greater than in controls. There is also clear evidence in the literature that in the general population there is an increase in ER-positive cancers with increasing age [4,5]. Collectively, this would be consistent with the hypothesis that a high proportion of ER-positive cancer in BRCA1 mutations carriers is incidental. The pathology data from the study, however, argue against this. The ER-positive breast cancers in BRCA1 mutation carriers are not only different to the ER-negative cancers, they are also different to sporadic ER-positive breast cancers in the general population matched for age and year of diagnosis. This suggests a biological effect, although the exact mechanism remains elusive.

There are compelling data that estrogen plays a key role in the development of BRCA1-dependent breast cancers. Premenopausal oophorectomy in BRCA1 mutation carriers substantially reduces the risk of subsequent carcinoma [6], as does treatment with Tamoxifen [7]. Furthermore, BRCA1 function is linked to ER expression...
and knockdown of BRCA1 leads to loss of ER expression [8]. It is therefore confusing that some BRCA1 mutation carriers develop tumors that are ER-positive. It is not clear whether these tumors arise as a result of BRCA1 haploinsufficiency – additional methylation, expression and loss of heterozygosity studies are needed to address this question. The Consortium of Investigators of Modifiers of BRCA1/2 is currently collecting data to stratify BRCA1-associated tumors by ER status in order to determine whether polymorphisms that alter the risk of ER-positive, but not ER-negative, unselected breast cancer also modify risk of ER-positive, but not of ER-negative, BRCA1-related breast cancer (GChenevix-Trench, personal communication).

The authors postulate that ER-positive and ER-negative cancers in BRCA1 mutation carriers may arise from different cell populations (early progenitor cells versus stem cells). Although it is tempting to speculate on the cell of origin, especially as it has recently been suggested that BRCA1/basal breast cancers may arise from luminal progenitors [9], it is worth noting that we know little about cell plasticity in normal development or tumorigenesis. It is equally plausible that a combination of age-related metabolic changes, locally within the breast and systemically, environmental exposures together with the predisposition of the cells to genomic instability as a result of BRCA1 DNA repair dysfunction could result in the same cell populations producing different tumor subtypes.

An important unanswered question is whether preventive strategies in BRCA1 mutation carriers will change the age distribution and hence the subtypes of cancers seen in diagnostic practice, and how this will impact management.

Abbreviations
ER, estrogen receptor.

Competing interests
The authors declare that they have no competing interests.

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