Teaching Lecture

E10. Issues around hereditary breast cancer and local treatment

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Women with inherited germline *BRCA1* (familial breast/ovarian cancer gene 1) or *BRCA2* (*BRCA1/2*) mutations have approximately a 55–85% cumulative risk of developing breast cancer by the age of 70. Knowledge of expected outcomes for *BRCA1*/2 mutation carriers following various breast cancer treatments is needed for decision-making [1,2]. The treatment goals for a woman with a *BRCA*-associated breast cancer should be to prevent recurrence of the initial cancer and to prevent second primary breast and ovarian cancers. Risk-reduction interventions for *BRCA*-related breast cancer are relevant not only for clinical decisions in breast cancer patients but also for healthy subjects who are potential candidates for undergoing similar interventions. The literature on the impact of different surgical options and adjuvant systemic approaches aimed towards risk reduction for recurrences of ipsilateral and contralateral breast cancer will be reviewed.

Breast-conserving therapy (BCT), defined as surgical excision and radiotherapy (RT), has been shown in multiple trials to result in comparable rates of tumour control and survival as mastectomy in women with sporadic early-stage disease. There are only limited data comparing outcomes following BCT versus mastectomy exclusively in women with known *BRCA1/2* mutations. Estimates of local recurrence and contralateral new breast cancers following BCT compared with mastectomy could aid in surgical decision-making in a *BRCA1/2* mutation carrier newly diagnosed with breast cancer.

Pierce et al. [3] compared the clinical outcomes in women with *BRCA1/2* mutations treated with BCT to outcomes in similarly staged *BRCA1/2* mutation carriers treated with mastectomy. This study included 655 patients with *BRCA1/2* mutations, and had a median follow-up of 8.2 years for BCT and 8.9 years for mastectomy.

BRCA1/2 mutation carriers with breast cancer have similar survival rates whether treated with mastectomy or BCT. However, women undergoing BCT have an elevated risk of a second in-breast event that is significantly reduced with chemotherapy. Contralateral breast cancer events are very common. From this study we can conclude that breast-conserving surgery is associated with a higher probability of local recurrence, but is counterbalanced by effectiveness of chemotherapy in reducing this risk.

Consistent support for the hypothesis that anti-oestrogens are effective in reducing contralateral breast cancer risks is available from the literature. On the other hand, data on chemoprevention approaches for healthy subjects are too preliminary to draw any conclusions from. Studies including conventional and newer hormonal drugs are needed to demonstrate the benefit of chemoprevention approaches. These may also deepen our knowledge on possible differences in the likelihood of clinical benefit to be expected among *BRCA1/2*-altered tumours.

Assessment of long-term risks of ipsilateral [4] and both ipsilateral and contralateral [5] breast cancer have been studied. These studies led to the conclusion that patients with germline mutations have high risks for second primary tumours, although local recurrence rates were not statistically different. The rate of contralateral breast cancer is significantly higher in mutation carriers, which is why prophylactic surgery of the contralateral breast is a treatment option that needs to be discussed with the patient. Kirova et al. [6,7] investigated, after long-term follow-up, whether mutation status influenced the rate of ipsilateral and contralateral breast cancers after BCT. *BRCA1* and *BRCA2* genes were screened for germline mutations in 131 patients with a family history of breast and/or ovarian cancer who had undergone BCT and radiotherapy. Patients were matched to 261 controls with sporadic breast cancer according to age at diagnosis and year of treatment. Controls were followed up for at least as long as the interval between diagnosis and genetic screening in familial cases. Rates of ipsilateral and contralateral cancer between groups were compared by the log-rank test. The *BRCA1/2* mutations occurred in 20.6% of tested patients. Overall median follow-up was 161 months. In this study there was no significant difference in ipsilateral tumours between mutation carriers, non-carriers and controls ($P = 0.13$). On multivariate analysis, age was the most significant predictor for ipsilateral recurrence ($P < 10^{-3}$). The rate of contralateral cancer was significantly higher in familial cases: 40.7% (mutation carriers), 20% (non-carriers), and 11% (controls) ($P < 10^{-4}$) (Fig. 1). After 13.4 years of follow-up, the rate of ipsilateral tumours was statistically not significantly higher in mutation carriers than in non-carriers or controls. The conclusion was that as tumours in *BRCA1/2* mutation carriers might be more sensitive to radiation, BCT is a possible treatment option.

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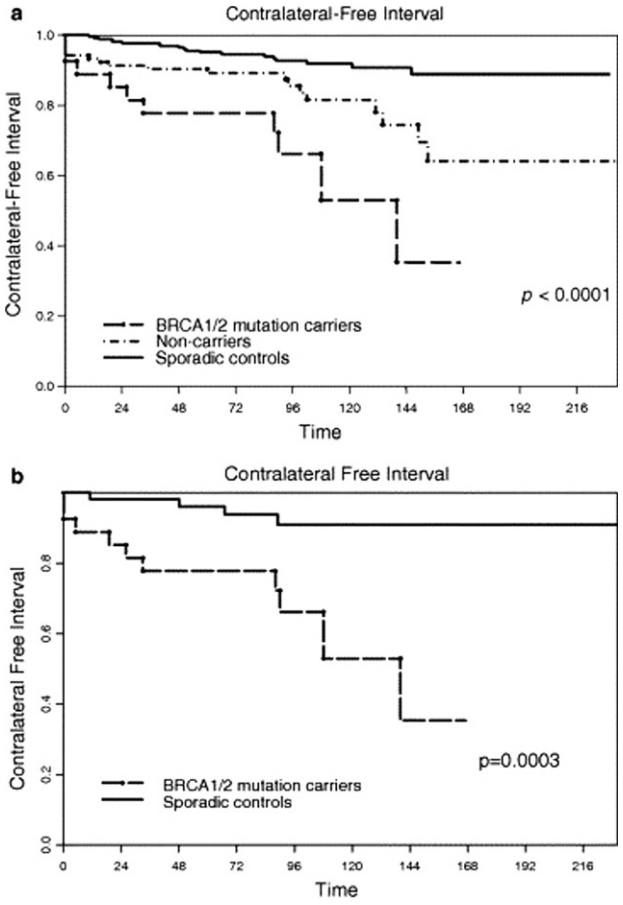

Contralateral breast cancer. (a) *BRCA1/2* mutation carriers versus non-carriers versus controls. (b) Contralateral breast cancer: *BRCA1/2* mutation carriers versus their controls. (Kirova et al.)

In our institute Kaas et al. [8] examined the outcome of prophylactic mastectomy in a hospital-based series of *BRCA1/2* gene mutation carriers with and without a history of breast cancer; 254 *BRCA1/2* gene mutation carriers that had prophylactic mastectomy were studied. One hundred forty-seven asymptomatic carriers underwent bilateral mastectomy, and 107 symptomatic women had contralateral mastectomy after a mean cancer-free interval of 3.6 years. In one asymptomatic *BRCA2* carrier (0.7%) an occult small invasive breast cancer was diagnosed, while in six asymptomatic carriers (4.0% *BRCA1* and 4.3% *BRCA2*) and in five symptomatic carriers (2.5% *BRCA1* and 10.7% *BRCA2*) ductal carcinoma in situ (DCIS) was detected at prophylactic mastectomy. No breast cancer occurred in the asymptomatic group after a postprophylactic follow-up period of 778 women-years. In the symptomatic carriers one invasive breast cancer was detected after 580 follow-up years. From age-, cohort-, and gene-specific reference data we calculated that 15 invasive first cancers in the asymptomatic carriers were prevented during follow-up.

The prophylactic procedure is highly effective in preventing invasive breast cancer in *BRCA1/2* mutation carriers. Since the remaining risk is less than 0.2%/woman-year, continued surveillance of the asymptomatic carriers is not warranted.

Conflict of interest statement

None declared

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