E3. Management of women at increased risk

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The early detection strategies available for the general population are inadequate for women with hereditary risk of developing breast and/or ovarian cancer. Population mammographic breast screening generally starts at the age of 50, an age at which half of the *BRCA1* mutation carriers will already have developed breast cancer. Earlier detection and preventive measures that may reduce morbidity and mortality in *BRCA* mutation carriers include prophylactic surgery, preventative drugs and intensified surveillance and should be offered to women at risk in tertiary care centres.

Prospective cohort studies show that bilateral prophylactic salpingo-oophorectomy (BPSO) reduces the risk of ovarian cancer in *BRCA* mutation carriers by >90%.[1] The remaining risk of breast cancer is also significantly reduced to 50% and remains in the same range after low hormonal add-back.[2] It has recently been demonstrated that BPSO reduces overall mortality by 70%.[3] BPSO is hence recommended around the age of 40 and well accepted.

Retrospective cohort studies demonstrate that breast cancer risk in *BRCA* mutation carriers is greatly reduced by bilateral prophylactic mastectomy (BPM).[4] To achieve the best preventive effect, bilateral mastectomy should include removal of the pectoralis fascia, the mamillar areola complex, and the lobus axillaris. Simultaneous reconstruction should routinely be offered. Interestingly, the acceptance for BPM varies greatly among countries and seems to depend on both cultural influences and the availability of screening programmes.

No reliable data yet exist on the efficacy of antihormonal drugs for the reduction of hereditary breast cancer. Retrospective genetic analysis of the affected women in the NSABP P1 study indicated that tamoxifen has a protective effect in women with a *BRCA2* mutation that frequently develop hormone receptor positive breast cancer.[5] This is supported by the reduction in contralateral secondary carcinomas under tamoxifen treatment.[6] However, *in vitro* data suggest that in the absence of *BRCA1,* breast cancer development can be promoted by an agonistic activity of tamoxifen.[7] Currently, women at risk are offered participation in the Europe-wide IBIS II study in which an aromatase inhibitor is employed.

Imaging surveillance is important for those women who do not opt for mastectomy. Also, even with a reduced risk after mastectomy (or subcutaneous mastectomy) imaging surveillance may remain necessary depending on the amount of residual breast tissue.

As shown by several prospective studies (including > 9000 examinations and > 190 carcinomas),[8] no imaging modality is perfect. MRI has proven to significantly further increase sensitivity compared to conventional imaging. Considering that at least part of the just MR-detected malignancies concern DCIS only, a randomised study regarding true survival benefits may remain of interest. Reported sensitivities of mammography and ultrasound (as far as both methods are used) range around 50% (36–66%), while sensitivity of MRI ranges around 86% (77–91%) in the larger studies. Thus, overall, MRI appears to be the most senisitve method. While some surveillance programmes promise to detect cancers at earlier stages, this is not yet generally proven[9,10]. Overall, an effect on survival may be suspected, but remains to be checked. While sensitivity of multimodality imaging is superior to conventional imaging, false positive calls increase. Biopsy rates on eventually false positive findings have been reported in up to 12.5% of the examined women (on average around 3–7%). The rate of short term follow-up is not indicated for most studies, but may range around more than 10%. Since false positive biopsies and short-term follow-up are undesirable side effects for screening of healthy women, close monitoring and further improvement appears mandatory. Also, it appears important to appropriately inform women about the potentials and limitations of imaging surveillance.

To date, based on the existing data and based on the disappointing sensitivity of conventional imaging alone, surveillance including MRI Is recommended for women at high risk (NICE guideluide, German programme for familial breast cancer). The ACS recommends MR screening for moderate risk as well. Close monitoring of the results will remain necessary.

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For women who opted for (subcutaneous) mastectomy without silicon implant (no reconstructive surgery or just a flap), mammography (flap) and ultrasound may be sufficient. In case of diagnostic problems concerning recurrence versus scarring, MRI may be an option.

Conflict of interest statement

None declared.

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