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ORIGINAL ARTICLE

Management of women at high risk for breast cancer: New imaging beyond mammography

C.K. Kuhl[a,*], W. Kuhn[b], H. Schild[a]

[a]*Department of Radiology, University of Bonn, Sigmund-Freud-Strasse 25, 53105 Bonn, Germany*
[b]*Department of Gynaecology and Gynaecologic Oncology, University of Bonn, Sigmund-Freud-Strasse 25, 53105 Bonn, Germany*

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Summary The management of women with an increased lifetime risk of breast cancer is a difficult task. This is especially true for women with a documented mutation in a breast cancer susceptibility gene (BRCA), and also for those who tested negative for a mutation, but have a family history that is suggestive of familial breast cancer. Primary prevention by prophylactic mastectomy has been shown to reduce breast cancer incidence in these women, but this intervention is still not considered a "first-line" option in the majority of guidelines. Instead, secondary prevention (intensified surveillance) is recommended. However, due to the early onset of familial breast cancer, screening must start at a substantially younger age than in women at average risk. This, together with the fact that familial breast cancers may differ from sporadic cancers in many aspects, will have a significant impact on the design and on the success rates of surveillance protocols. This article describes the different management options that exist for women at increased genetic risk and provides a survey of the current evidence regarding mammographic and non-mammographic imaging techniques. The conclusion is that mammographic screening, with or without concomitant ultrasound and clinical breast examination, is probably not sufficient to ensure an early diagnosis of familial breast cancer. If MRI is integrated in surveillance programs, early diagnosis seems to be possible. Still, the efficacy of screening even with MRI is unclear in terms of morbidity and mortality, and this lack of evidence must be communicated to women at high genetic risk.

Introduction

Groups at high risk of breast cancer

Based on current data, the average lifetime risk of breast cancer amounts to about 10% in women in the western world.[1] A substantially increased

*Corresponding author. Tel.:+49 228 287 9875; fax: +49 228 287 9877.
E-mail address: kuhl@uni-bonn.de (C.K. Kuhl).

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lifetime risk may be associated with a variety of conditions: a prior tissue diagnosis of breast cancer or of a lesion with borderline biologic behaviour (atypical ductal hyperplasia, lobular carcinoma in situ); a history of mediastinal irradiation for, e.g. Hodgkin's disease; and a familial clustering of breast and/or ovarian cancer, with early onset. Cancers arising in this latter group are usually referred to as "familial" or "hereditary" breast cancers. The distinction between "familial" and "hereditary" breast cancer can be difficult in individual cases. In general, "familial cancer" is a descriptive term that indicates an increased incidence of breast cancer on the same side of a family. "Hereditary breast cancer" suggests that a specific germline mutation in a breast cancer susceptibility gene is passed on in the family and has been identified by mutational analysis, or is suspected based on pedigree analysis revealing a specific (autosomal-dominant) inheritance pattern.[2]

Familial or hereditary breast cancers

Hereditary breast cancer accounts for approximately 10% of all cases of breast cancer per year. The breast and ovarian cancer susceptibility genes identified thus far, BRCA1 and BRCA2, account for about 50% of the actually hereditary breast cancer cases; the remaining half of hereditary cancers seem to be caused by other, as yet unidentified genes. The majority of this second half will probably be due to a third BRCA gene, the existence of which has been documented by pedigree analysis, but which has to date not been identified.[3–6]

Women with a documented pathogenic BRCA mutation face a substantially increased lifetime risk of both breast and ovarian cancer. The lifetime risk of breast cancer accumulates to 65–87% for carriers of the BRCA1 and BRCA2 mutation, respectively.[7,8] In BRCA1 mutation carriers, the risk increases from the age of 25 onwards continuously to peak in the age group between 45 and 49 years (with annual incidence rates of $>4\%$), and decays thereafter. In BRCA2 mutation carriers, the annual incidence seems to increase steadily, but remains lower than that observed for BRCA1 carriers in all age groups. For both BRCA1 and BRCA2, the average age at first diagnosis of breast cancer is lower than that observed in women with sporadic breast cancer. Women with familial breast cancer tend to develop the disease significantly younger, i.e. at a pre-menopausal age; according to recent data, about 50% already had breast cancer by the age of 50. Also, and again in contrast to women with sporadic breast cancer, women with BRCA mutations face a high risk of developing a second primary breast cancer, which has been estimated to be as high as 60%.

In addition, breast cancers arising in mutation carriers often exhibit adverse histopathologic features that are indicative of aggressive biologic behaviour; with respect to sporadic breast cancers, they exhibit high proliferative rates, are more likely to show a high nuclear grading, a medullar or an atypical-medullar differentiation, and are more often receptor negative.[9–12]

Preventive measures in women with familial or hereditary breast cancer

There are several options available for the management of (or rather the care of) women with suspected or proven hereditary breast cancer.[13–16] Primary prevention aims at reducing the incidence of familial breast cancer in women at high risk. It can be achieved by prophylactic mastectomy and/or by other risk-reducing strategies, e.g. by chemoprevention with tamoxifen, or by oophorectomy. Preventive oophorectomy is established as the most important preventive means of reducing the risk of ovarian cancer—which is, at least in part, also due to the fact that there are no efficient imaging strategies available that would allow a reliably early diagnosis of ovarian cancer. Furthermore, oophorectomy serves two purposes because it should also help reduce the risk of subsequent breast cancer. Unlike preventive oophorectomy, preventive mastectomy is usually not propagated as "first-line choice" for the management of women with familial breast cancer. The perceived mutilating effects of mastectomy, together with the difficulty of predicting the outcome in individual cases, make the decision on surgical prevention very difficult for most women. Still, it is important to note that preventive mastectomy has been demonstrated to be efficient in that it will significantly reduce the incidence of breast cancer.[17–20]

Secondary prevention, i.e. intensified surveillance, aims at the earliest possible diagnosis of familial breast cancer at a prognostically favourable stage. The underlying assumption is that the same correlation exists between stage at diagnosis and outcome (morbidity, mortality) as has been demonstrated for sporadic breast cancer. This, however, has not been proved so far, and there is evidence to suggest that the correlation between