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Review

Accuracy of screening women at familial risk of breast cancer without a known gene mutation: Individual patient data meta-analysis

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Abstract ***Introduction:*** Women with a strong family history of breast cancer (BC) and without a known gene mutation have an increased risk of developing BC. We aimed to investigate the accuracy of screening using annual mammography with or without magnetic resonance imaging (MRI) for these women outside the general population screening program.
Methods: An individual patient data (IPD) meta-analysis was conducted using IPD from six prospective screening trials that had included women at increased risk for BC: only women with a strong familial risk for BC and without a known gene mutation were included in this analysis. A generalised linear mixed model was applied to estimate and compare screening accuracy (sensitivity, specificity and predictive values) for annual mammography with or without MRI.
Results: There were 2226 women (median age: 41 years, interquartile range 35–47) with 7478 woman-years of follow-up, with a BC rate of 12 (95% confidence interval 9.3–14) in 1000 woman-years. Mammography screening had a sensitivity of 55% (standard error of mean [SE] 7.0) and a specificity of 94% (SE 1.3). Screening with MRI alone had a sensitivity of 89% (SE 4.6) and a specificity of 83% (SE 2.8). Adding MRI to mammography increased sensitivity to 98% (SE 1.8, $P < 0.01$ compared to mammography alone) but lowered specificity to 79% (SE 2.7, $P < 0.01$ compared with mammography alone).
Conclusion: In this population of women with strong familial BC risk but without a known gene mutation, in whom BC incidence was high both before and after age 50, adding MRI to mammography substantially increased screening sensitivity but also decreased its specificity.

1. Introduction

About 15–20% of breast cancer (BC) cases are associated with a family history of BC [1]. Women without a known mutation in a hereditary BC gene, but with a family history of breast with/without ovarian cancer, are at a higher risk of developing BC, the extent of the increased risk depends on the number of affected relatives and the age at cancer diagnosis in the relative(s) [2,3]. These women at familial risk, who have a cumulative lifetime risk of developing BC over 15–20%, are usually offered a BC screening regimen outside of the general population screening program, starting at an earlier age and including more frequent (annual) mammography [4,5].

Results of many prospective trials evaluating the accuracy of adding annual MRI to mammography for screening these women have been published [6–15]. Although these studies emphasised the significantly greater sensitivity of annual magnetic resonance imaging (MRI) and mammography in combination for screening this high-risk population, several issues remain unclear. First, inclusion criteria were heterogeneous and all the studies also included women with known gene mutations. Furthermore, the definition of familial risk for BC varied across countries and centres depending on referral criteria and risk assessment tools. Also, few studies reported results separately for women at familial risk without a known gene mutation [8,11,12] and none of the studies reported results stratified by age for this population.

In this meta-analysis, pooling individual patient data (IPD) from prospective trials, we aimed to assess the accuracy of screening women at familial risk of BC without a known gene mutation, adding MRI to mammography and stratifying outcomes by age.

2. Methods

2.1. Study design

An IPD meta-analysis was conducted, including individual data from 6 of 12 prospective trials, in which women at high risk of BC due to an inherited *BRCA* gene mutation or a strong family history of BC were screened with annual mammography and MRI, and the accuracy of each screening modality was reported separately [16,17]. All studies were performed in developed countries. More details about the study inclusion criteria, data acquisition and assembly and quality assessment were reported in our previous publication which focused on *BRCA1/2* gene mutation carriers [17]. In the present study, we focus only on women with a strong family history of BC (defined as a cumulative lifetime BC risk of at least 15%) and without a known gene mutation. Specific inclusion criteria for the original studies contributing to this IPD meta-analysis, outlining family history criteria and whether women with a personal history of BC were included are summarised in Supplementary appendix 1.

2.2. Study population

Women aged 25 or older, who had a strong family history of BC and no known gene mutation and had