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# Hereditary breast cancer growth rates and its impact on screening policy

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**Abstract**

Imaging is often performed yearly for the surveillance of *BRCA1/2* mutation carriers and women at high familial breast cancer risk. Growth of cancers in carriers may be faster as these tumours are predominantly high grade. Quantitative data on tumour growth rates in these 2 groups are lacking. Here, we have examined 80 high-risk women under surveillance for tumour size at diagnosis and preceding examinations at mammography and/or MRI. Tumour volume doubling time (DT) was assessed in 30 cancers in *BRCA1/2* mutation carriers and 25 non-carriers. Impact of age and menopausal status were also evaluated. Mean DT of all invasive cancers was shorter in carriers (45 days CI: 26–73) than non-carriers (84 days CI: 58–131) ($P = 0.048$). Mean age at diagnosis was lower in carriers (40 years) than non-carriers (45 years) ($P = 0.007$). At multivariable analysis only age ($P = 0.03$), not risk-group ($P = 0.26$) nor menopause ($P = 0.58$) correlated significantly with DT. The mean growth rate slowed down to half in each successive 10 years-older group. In conclusion, age at detection indicated the growth rates of hereditary and familial breast cancers. It is recommended that the screening frequency should be adjusted according to a woman's age and a high-sensitive biannual test may be appropriate before the age of 40 years.
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## 1. Introduction

Early detection is one of the limited options to possibly reduce the risk of mortality from breast cancer for women with a gene mutation (*e.g.*, *BRCA1*, *BRCA2*, *p53*) or with a family history, indicative of an increased

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risk for breast cancer at a relatively young age. For *BRCA1* mutation carriers, the risk of developing breast cancer before 50 years of age is as high as 50% while for *BRCA2* the risk is slightly less [1,2]. Although breast cancer cells may disseminate early during tumour development [3], tumour size and lymph node status remain strong prognostic factors for survival in breast cancer [4–7]. Screening women at hereditary risk with magnetic resonance imaging (MRI) can detect tumours at an early stage [8,9]. In the Dutch MRISC study, 78% of the detected tumours were ductal carcinoma *in situ* (DCIS) or smaller than 2 cm, 79% node-negative [8]. However, a higher percentage of interval cancers have been observed in *BRCA1/2* mutation carriers compared with women with high familial risk without a proven mutation (non-carriers) under the same surveillance scheme [8,10]. One of the likely causes is different growth rates of tumours, as high mitotic count and high grade tumours (63% and 69%, respectively) were more frequently found in cancers from *BRCA1* mutation carriers in comparison to sporadic cancers (32% and 38%, respectively) and *BRCA1/2*-negative hereditary breast cancers (17% and 23%, respectively) [11,12].

To our knowledge no quantitative data have been published on tumour growth rates in these hereditary risk groups based on measurements from imaging. Finding the optimal frequency at which a screening method should be applied can be as important to improve its effectiveness as the ability to detect cancers at an early stage [13]. Screening too frequently increases the medicalisation of healthy women, the risk of false-positive results, cost and radiation risk [14]. However, too low a frequency may result in a delay in diagnosing breast cancer, missing the chance to improve prognosis. In this study, we have investigated the influence of a *BRCA1/2* mutation, age and menopausal status/bilateral preventive salpingo-oophorectomy (BPSO) on tumour growth rate in women at high familial risk. Based on our results, we have tried to define the optimal screening frequency for women in different risk categories.

## 2. Material and methods

We could evaluate the size of 55 tumours at diagnosis and with the same radiologique technique, either mammography (Mx) or MRI, at previous screening(s), for 80 breast cancer patients examined. All tumours were detected in women under surveillance, because of : (a) a proven *BRCA1* or *BRCA2* mutation (carrier group), or (b) an estimated hereditary risk of 20–50% according to modified tables of Claus [8,15], while no *BRCA1* or *2* mutation could be demonstrated or no DNA investigation had been performed (non-carriers). The methods for *BRCA1/2* mutation analyses are described elsewhere [16,17].

From November 1, 1999 to July 1, 2003, 47 breast cancers were detected in women participating in the Dutch surveillance study MRISC in 2 cancer centers and 4 university hospitals. Screening consisted of clinical breast examination every 6 months and annual Mx and MRI. Imaging technique and protocol have been previously described [8]. Tumour growth rate were evaluable in 32 cases. Thirty-three consecutive cancers were detected in the women under surveillance for the same indication outside this study after January 1, 1995 at the ErasmusMC. Surveillance for them was performed with biannual clinical examination and annual mammography. Additional MRI was performed with the same Tesla strength, intravascular contrast and subtractions as in the MRISC in 13 patients. Tumour growth rate was evaluable in 23 cases. In total, growth rates were assessed in 55 patients. In 25 patients, tumour growth rates could not be calculated as the tumour was neither measurable at diagnostic Mx or at MRI.

The diameter at pathology, mitotic count and Bloom-Richardson grading of the tumours; menopausal status and BPSO were taken from medical files.

## 3. Measurements and calculation of tumour growth rate

To estimate the growth rates of tumours, all diagnostic mammograms and MRI, were reevaluated by a radiologist (CB or IO). For all the cancers visible at the diagnostic Mx/MRI, the previous examination(s) were also reassessed. If the tumour could be clearly identified at the diagnostic MRI, 3D measurements at right angles, including the single largest dimension (SLD), were taken from the diagnostic and previous MRI. For all cancers positively identified at the diagnostic Mx, tumour size was measured at both oblique and craniocaudal views at diagnostic and previous Mx. The tumour diameter was measured using the longest axis ($a$ = SLD) and a second maximum diameter was measured perpendicular to the first ($b$). For tumours measurable at both views, the largest, smallest and mean of the 2 sizes were used to calculate tumour volume. In the case of a stellate mass, the centre was measured. For cancers with a measurable tumour at 2 or more subsequent mammograms or MRI and where a previous mammogram/MRI showed no visible tumour (9 Mx, 2 MRI), only the measurable tumour sizes were used for the calculation of individual tumour volume doubling time (DT). To calculate the DT of each cancer, the method (Mx or MRI) with the most measurement points was used. In case of equal number of measurements, the method with the single largest tumour diameter at diagnosis closest to the size at pathology was used. The volume of the tumour was estimated using the formula for obloid spheroids

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