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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.

Keywords: Breast cancer; Surveillance; Interval cancer; Growth rate; *BRCA1*; Familial breast cancer; Screening; Sojourn time; MRI; Mammography

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

$$V = 4/3\pi \cdot 1/2a \cdot 1/2b \cdot 1/2c.$$

Tumour volumes were assumed to have exponential growth (*i.e.*, growth with a constant volume doubling time). For patients with 2 real volume measurements, the slope of the straight line connecting the 2 log-transformed data points was calculated. In case of 3 or more real volume measurements, this slope was calculated using least-squares regression. For patients with one last real measurement and one previous undetected tumour, the latter tumour size was set at 0.004 cm^3 corresponding to a diameter of 2 mm (assumed lower detection limit). The resulting slopes for these patients therefore may under estimate the true slope. However, not including these for the estimation of growth rates would probably exclude many of the fast growing tumours [18]. Subsequently, tumour volume doubling times were calculated using the following formula:

$$\mathrm{DT} = \log 2/\beta,$$

where β was the slope of the regression line of the logarithm of the tumour volume *vs.* time. This outcome may over estimate the true doubling time for patients with an undetectable tumour at the previous visit and is treated as a left-censored observation in the statistical analysis [18].

4. Statistical methods

Differences in patient and tumour characteristics between the 2 risk groups were tested with the use of the *t* test in case of continuous variables and of the χ^2 test or Fisher's exact test in case of categorical variables. To determine the correlation between tumour size at mammography/MRI and at histopathological examination, we calculated Pearson's correlation coefficient separately for invasive cancers and ductal carcinoma *in situ* (DCIS). To get an approximate normal distribution of volume doubling times, these times were logarithmically transformed for analysis. Comparison of the transformed DT between risk groups was done using the *t* test. Multiple regression was used to evaluate simultaneously the effects of age, risk group and menopausal status. STATA software (procedure CNREG) was used in these calculations to allow for the presence of left-censored volume doubling times. A two-sided *P* value of less than 0.05 was considered to indicate statistical significance.

5. Results

5.1. Patients and tumour characteristics

Of the total group of 55 tumours, in which growth rate could be assessed, 30 (5 DCIS, 4 of the DCIS in *BRCA1*) were detected in mutation carriers (25 *BRCA1* and 5 *BRCA2*) and 25 (3 DCIS) in non-carrier women with an estimated life time risk of 20–50%. Eighteen patients in the non-carrier group had tested negative for *BRCA1/2*, while no DNA test results were available for 7 patients. Only 1/7 tumours in the non-tested group had characteristics suggestive of a *BRCA1*-associated tumour (both high grade and ER and PR negative), but with a mitotic count of 3. Patient and tumour characteristics of the carrier and non-carrier groups are shown in Table 1. Mean age at diagnosis was significantly lower in carriers than in non-carriers (40 years *vs.* 45 years, respectively, $P = 0.007$); (39 years for *BRCA2* and 47 years for the non-tested). Seven of the carriers were post-menopausal at diagnosis, 6 after BPSO (no *BRCA2*), while 6 non-carriers were naturally post-menopausal (3 non-tested). Age of post-menopausal carriers *vs.* non-carriers was 47.0 *vs.* 52.2 years, $P = 0.11$. Only in *BRCA1* carriers, cancers were detected between follow-up visits ($n = 5$). Median diameters of the invasive tumours at pathology were with 12 *vs.* 11 mm comparable between the 2 groups (mean = 9 (6–15) mm in 4 *BRCA2*). Mean mitotic count was higher in carriers than non-carriers (40 *vs.* 8.5, $P = 0.001$); (23 in *BRCA2* and 7.8 in the 7 non-tested range 1–19). Tumours were more often high grade in carriers *vs.* non-carriers ($P = 0.01$); (2 grade 3 and 2 grade 2 in *BRCA2*). The size of DCIS at pathology in carriers was 6–33 mm at age 32–44 years and in non-carriers 12 mm-'large' at age 31–48 years. Growth rates, for reasons mentioned in the methods section, could not be assessed in 10 carriers (2 *BRCA2*) with mean age 38 years (range 29–57) and 15 non-carriers (8 DNA tested) mean age 45.3 years (33–55). There were no interval cancers in this group. One tumour in these carriers was DCIS, mean diameter of the others at pathology was 11.2 mm (2–28) and mean mitotic count was 50 (15–116). The non-carrier tumours that were not evaluable for growth rates had a mean diameter of 15.4 mm (4–45) mean mitotic count 9 (1–45).

5.2. Tumour measurements

Calculations were performed using the measurements at Mx for 34 tumours and MRI for 21. The mean time between 2 measurements was 0.9 years (range 0.3–1.8) for the total group and carriers, while for non-carriers it was also 0.9 years but with a different range from 0.4 to 1.3. Fig. 1 and Table 2 gives the number of the used measurements, method and characteristics of the images (*i.e.*, as nucleus shadow or calcifications) of the tumours in the 2 risk groups. The size of the invasive cancers at pathology correlated significantly with the estimated size at diagnostic MRI and Mx, with a correlation coefficient of 0.84 and 0.67, respectively. DCIS at pathology correlated significantly with measurements at Mx ($n = 4$) with a correlation coefficient of 0.99.

Table 1
Patient and tumour characteristics in *BRCA1/2* mutation carriers and non-carriers

	BRCA1/2 carriers ($n = 30$)	Non-carriers ($n = 25$)	P value
Patient characteristic			
Mean age at detection[a] (range)			
Overall	40.1 (27–52)	45.4 (31–59)	0.007
Detected pre-menopausal	38.0 (27–50)	43.1 (31–53)	0.009
Detected post-menopausal	47.0 (37–52)	52.2 (45–59)	0.11
Menopausal status[b]			
Pre-	23 (77%)	19 (76%)	0.95[c]
Post-after BPSO[d]	6 (20%)	0	0.03
Post-natural	1 (3%)	6 (24%)	
Mode of detection[e]			
Interval cancer	5 (17%)	0	0.06
Screen detected	25 (83%)	25 (100%)	
Tumour characteristics			
DCIS[f]	5 (17%)	3 (12%)	0.72
Invasive	25 (83%)	22 (88%)	
Median diameter at pathology mm[g] (range)	12 (3–40)	11 (6–40)	
Median mitotic count[h]	23 (1–319)	4 (1–43)	0.001
Bloom-Richardson grade[i]			
1	10 (0%)	5 (23%)	
2	8 (36%)	10 (45%)	0.01
3	14 (64%)	7 (32%)	

[a] Data was available for 30 carriers and 24 non-carriers.
[b] Menopausal status: number (percentage).
[c] Pre- *vs.* post-menopausal.
[d] BPSO (bilateral prophylactic salping-oophorectomy) *vs.* no BPSO.
[e] Mode of detection: number (percentage).
[f] DCIS ductal carcinoma *in situ*.
[g] Data was available for 30 carriers and 22 non-carriers (missing in 1 invasive and 2 DCIS).
[h] Data was available for 21 invasive tumours in carriers and 16 invasive tumours in non-carriers. Number of mitosis per 2 mm^2 (range) in invasive cancers.
[i] Data available for invasive tumours of 22 carriers and 22 non-carriers.

5.3. Growth rate of invasive cancers in BRCA1/2 mutation carriers vs. non-carriers

Fig. 2 shows the tumour volume doubling times of the invasive and *in situ* cancers in the 2 risk groups according to menopausal status. The geometric mean volume doubling times of the 47 invasive carcinomas and 8 DCIS were 60 and 59 days, respectively. Further analysis was restricted to the invasive tumours only. The geometric mean doubling time for carriers and non-carriers was 45 and 84 days, respectively ($P = 0.048$). It was further found that the doubling time increased with advancing age at diagnosis: 9.8% per year for carriers ($P = 0.01$) and 5.4% per year for non-carriers ($P = 0.064$) and these increases did not significantly differ from each other. When adjusted for the significant age difference between carriers and non-carriers (Table 1), there was no significant difference in geometric mean tumour volume doubling times between the 2 risk-groups (Table 3). Although there was a significant difference between the total group of pre- *vs.* post-menopausal women regarding geometric mean doubling times, 49 days *vs.* 115 days ($P = 0.023$), respectively, (this difference was 35 *vs.* 87 days in carriers and 75 *vs.* 153 days in non-carriers) significance was lost in a similar way after adjustment for age. Table 3 shows results of the multivariable analysis of logarithmically transformed tumour volume doubling times, taking into account carriership, age at diagnosis and menopausal status of the women. Only age was significantly associated with the mean doubling times. The mean of the DT was more than twice higher after a decade. Taking account of age only, the relationship for mean values was $\log_2(\text{doubling time [years]}) = -7.75 + 0.12\ \text{age}$ (standard error for the age-coefficient: 0.03, with $P < 0.001$). The resulting relationship is shown in Fig. 3 and the associated increase of the geometric mean volume doubling time is 9% (95% CI: 4–14%) for each 1-year increase of age. This relationship did not really differ ($P = 0.45$) between MRI and Mx assessed doubling times (Fig. 1). Nor did the multivariate analyses change substantially after exclusion of the 7 cases not tested for *BRCA1* and *BRCA2* (P value for risk-group 0.21, menopausal status 0.7, age 0.03). The tumour characteristics grade and mitotic count differed between the 2 risk-groups. At univariate analysis, mitotic count correlated with DT ($P = 0.03$) while grade did not ($P = 0.3$). When

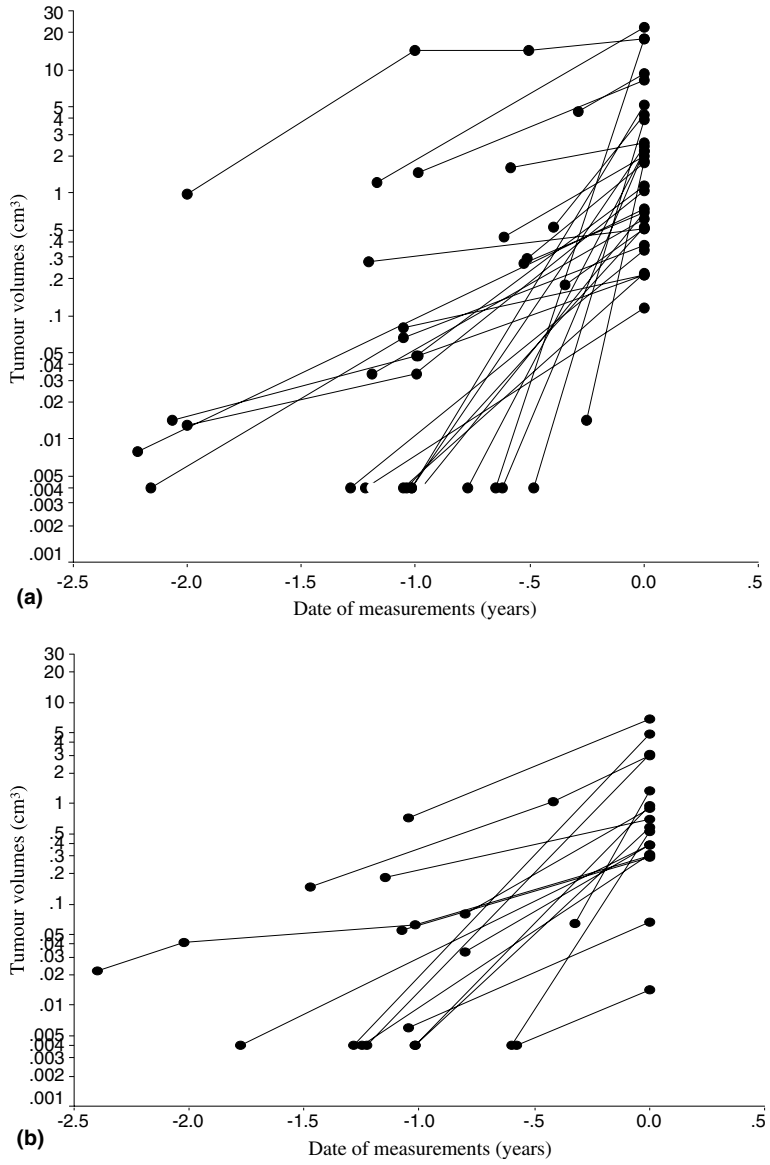

Fig. 1. Measurements at Mx (a) and MRI (b) used for the calculations of doubling times. Data points with volume = 0.004 cm^3 denote tumours undetectable in mammograms or MRI prior to the diagnostic ones. 0.0 is time of diagnosis.

mitotic count and grade were entered into the multivariable model the results remained essentially unchanged with P value for age, grade and mitotic count $P = 0.015$, $P = 0.8$ and $P = 0.4$, respectively.

5.4. DCIS

Four *in situ* cancers were only visible at diagnosis not on previous imaging: 3 in carriers (6, 7 and 33 mm) and 1 non-carrier (>40 mm) (Fig. 2).

6. Discussion

The growth rates of hereditary breast cancer are important to estimate the optimal test frequency for screening, be it by breast imaging (Mx or MRI) or new emerging screening tools, *e.g.*, serum-proteomic-pattern markers [9,13,19].

Tumour volume doubling time was 45 *vs.* 84 days, twice as short in invasive cancers of *BRCA1/2* mutation carriers compared to non-carriers and twice as short in pre- *vs.* post-menopausal women. However, mean age at detection differed significantly between the 2 risk groups and carriers were more often post-menopausal at a relatively young age after BPSO. Age at diagnosis and not risk-group or menopausal status, was the only significant indicator of tumour growth rate from multivariate analysis. The on average higher tumour growth rates in carriers *vs.* non-carriers and pre- *vs.* post-menopausal women contributed apparently to earlier ages at detection. Tumours were more often high grade and

Table 2
Characteristics, number and modality of the measurements of tumours in carriers and non-carriers

Risk group	Carriers (n = 30)	Non-carriers (n = 25)	Total (n = 55)
Rad. characteristic[a]			
Calcifications	3 (3)	4 (1)	7 (4)
Nucleus shadow	27 (2)	21 (2)	48 (4)
			55 (8)
Number of measurements			
Mx[b] ⩾ 2[c]	9 (2)	12 (1)	21 (3)
MRI ⩾ 2	7	6 (1)	13 (1)
Mx 1 + n.o.t.[d]	7 (2)	6	13 (2)
MRI 1 + n.o.t.	7 (1)	1 (1)	8 (2)
Total	30 (5)	25 (3)	55 (8)

Between brackets number *in situ* cancers.
[a] Rad.: radiological.
[b] Mx: mammogram.
[c] ⩾2: measurable tumour on at least 2 consecutive images.
[d] n.o.t.: on previous imaging "no observable tumour".

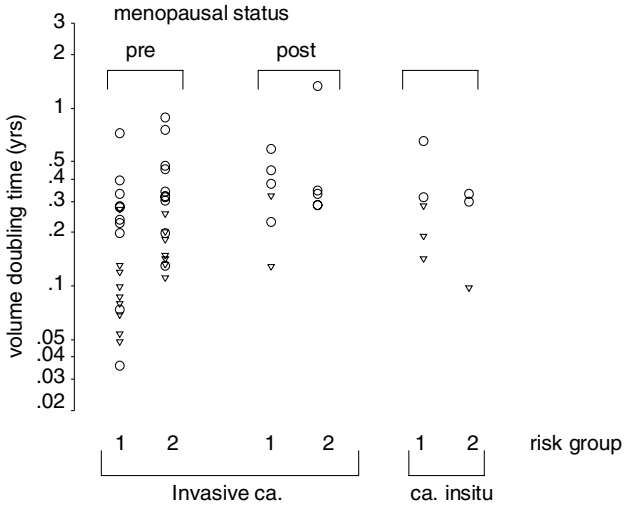

Fig. 2. Tumour volume doubling times (DT) for invasive and *in situ* cancers according to risk group and menopausal status. 1, DT of cancers in *BRCA1/2* mutation carriers; 2, DT of cancers in women at non-*BRCA1/2* hereditary risk. ○, calculated with ⩾2 measurements; △, left censored.

the average mitotic count was higher in our younger carrier group as expected. When these indicators of growth rate were entered into the multivariate model, still only

Table 3
Multivariate impact of carriership, menopausal status and age at detection on tumour doubling times (DT)

Factor	Multivariate ratio of geometric mean doubling time	95% CI	P value from multivariate analysis
Carrier status[a]	0.7[a]	0.4–1.3	0.26
Menopausal status[b]	1.3[b]	0.6–2.8	0.58
Age[c]	1.9[c]	1.1–3.4	0.03

[a] Carriers *vs.* non-carriers.
[b] Post-menopausal *vs.* pre-menopausal.
[c] Per 10 years older age.

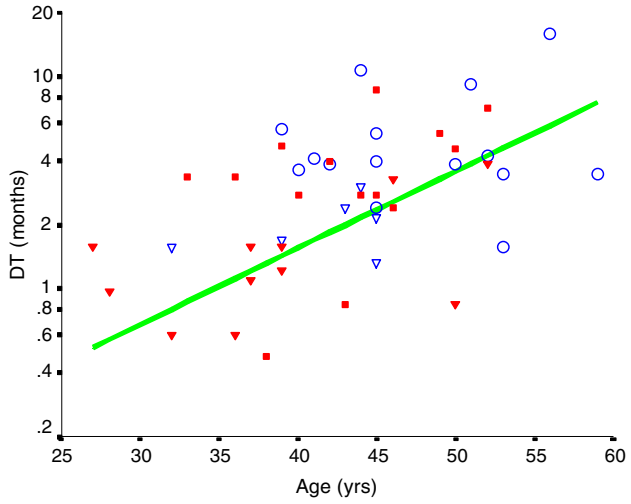

Fig. 3. Tumour doubling time (DT) in months according to age at diagnosis. Solid symbols, *BRCA1/2*-carrier; open symbols, non-carrier. Triangles represent left-censored DTs. The increase in geometric mean volume doubling time equals 9% (95% CI: 4–14%) for each 1-year increase of age. $\log_2$(doubling time [years]) = −7.75 + 0.12 age.

age correlated independently with the estimated tumour doubling times (P = 0.015). Tumour growth rates gradually slowed down (9% yearly) with increasing age at diagnosis, without a clear cut-off between the risk-groups or at menopause.

Our study was performed in women with a well-defined hereditary risk, within surveillance schemes with complete follow-up. The relatively low number of interval cancers (in 5 *BRCA1* carriers only) may be due to the rather short screening intervals. We assessed the growth rates in only 4 invasive breast cancers in *BRCA2* mutation carriers, who did not differ significantly with regard to age, tumour size, grade or mitotic count from the *BRCA1* mutation carriers. The DT pattern for *BRCA1* mutation carriers and non-carriers of the same age were similar.

In 7 patients, no test for deleterious *BRCA1/2* mutations was performed or completed. But after exclusion of those 7 cases, results from the analyses were essentially the same. In the 2 risk groups, patient and tumour characteristics did not differ between those with and without DT assessment. Therefore, DT measurements in both risk groups may be representative for that group. Measurements at Mx or MRI were used for DT calculations and both methods correlated well with size at pathology. Neither the mean doubling time nor the results at multivariable analyses differed significantly between assessments with either method.

The radiologist knew from the diagnostic imaging, where and how the cancer was depicted, therefore we estimated tumour size at the previous image with "no observable tumour" on retrospect, to have a max size of 2 mm. This seemed realistic as 5 tumours with MRI and 8 Mx cases were <4 mm despite high breast density. By extrapolating growth curves of tumours measurable

at $\geqslant$2 Mx/MRI but where tumour was not detected at the previous image (9 Mx, 2 MRI), occult-tumour-size was at Mx twice <2 mm and 7 times <4 mm and at MRI twice <2 mm. Importantly, when we calculated DTs with the assumption that occult-tumour-size at Mx was <4 mm), results of the multivariable analysis did not change.

Growth may not be continuous and possibly speed up or slow down under influence of host factors or size. However, we performed calculations on the assumption that tumours will follow exponential growth, as this is usually assumed to be the best approximation for the range of tumour sizes in our study (3–40 mm) [20,21]. Our findings in 12 of the 15 cases with more than 2 measurements were consistent with exponential growth, while in 1 there seemed to be a period without growth (Fig. 1).

Although tumours in *BRCA1* mutation carriers are more frequently oestrogen- and progesteron receptor negative, a clear influence on the occurrence of (contralateral) cancers has been described for hormonal factors like menopause and BPSO, and less consistently for breastfeeding, use of oral contraceptives, pregnancy, parity and tamoxifen [22]. All these hormonal influences may, like other host factors, have an impact on tumour growth rate. These factors may affect tumour growth to varying degrees between carriers of *BRCA1/2* mutations and non-carriers. Within the size and scope of our study we could only account for the strongest proven hormonal influence of menopause/BPSO. Extended and different studies are needed to clarify these complex issues.

Spratt and colleagues calculated in sporadic breast cancer patients, a wide ranging DT from 10 to 7051 days with an age range 18–88 years. With age sorted into categories, they did not find a clear relationship between growth rates and age [23]. However, they assessed less fast growing tumours by not including cancers that were only visible at diagnosis. Kusama and colleagues [24] on the other hand, found significantly less tumours with short doubling times in patients age 60 years and over than in younger patients. Peer and colleagues [18], calculated a median DT of 80 days (95% CI 44–147) for breast cancers in women less than 50 years of age who were not selected for risk, which was twice as fast as in women aged 50–70 years. These results are quite similar to the pre- and post-menopausal growth rates we calculated from non-carriers (mean 75 and 153 days, respectively), reflecting most likely the comparable ages at detection. The data available from sporadic breast cancers in the literature substantially support our current analyses.

Breast screening women aims to detect cancers at an earlier stage at which the future development of metastases is less likely, in order to possibly improve survival. Tumour size at diagnosis and the number of positive axillary nodes are strong prognostic factors for survival in sporadic and hereditary breast cancers [4–7,25], even though other evidence suggests that the proclivity to metastasise is acquired early in tumour genesis [3]. The percentage of patients with metastases seems to increase faster with size in high grade breast cancers than in low grade [26]. Tabar *et al*. [27], however, found good cumulative 12 year disease specific survival rates of over 90% of all high grade tumours $\leqslant$1 cm.

If we try to assess the optimal screening interval, taking the impact of tumour stage into account, we should consider, that a tumour with a diameter of 2 mm, missed at imaging, needs 4 doubling times to reach 5 mm, where it becomes easier to detect but is most likely still node-negative. In that period, a tumour with the same growth rate missed at 4 mm may reach 1 cm. With regard to stage at detection a 4 times DT screening interval seems acceptable. In our study this would result in screening intervals of 3–7 months from age 30 till 40 years; 7–16 months from 40 till 50 years. and 16–32 months from 50 till 60 years (Fig. 3), reflecting the gradual decrease in growth rate for tumours detected at increasing age. In practice, and because of the range of DTs at a given age, this might translate into a biannual screening-test before age 40 years, annual between 40 and 50 years and once every 2 years at age 50–60 years. It has been suggested by different models that in selected groups of women, biannual imaging might be necessary to improve survival [13,19,28,29].

At such frequency, a test with high sensitivity for invasive cancer seems the method of choice. In *BRCA1/2* mutation carriers, MRI seems preferable over mammography because the tumour characteristics cause frequent false-negative mammography results [30]. In MRI screening studies, sensitivity for invasive cancers proved better for MRI than mammography, but separate estimates for *BRCA1/2* carriers are not yet available [8,9]. The number of *BRCA1/2* mutation carriers under surveillance is relatively small and their expected tumour incidence is high (2% yearly between age 25 and 50 years) [1,2]. Cost-effectiveness analyses have now been performed while impact on survival has yet to be shown.

In the large group of women at hereditary risk without a known *BRCA1/2* mutation in the family, screening is usually started at an older age than in *BRCA1/2* mutation carriers. Imaging annually between ages 40 and 50 years and once every 2 years between 50 and 60 years may be appropriate. This is in agreement with studies that have estimated the sojourn time (*i.e*., the length of time the disease is in the preclinical detectable phase) in women aged 40–49 to be 1 year [31,32].

With 4 DCIS out of 30 cancers detected in *BRCA1* carriers (and 1 in *BRCA2*) we cannot confirm that the *in situ* stage is skipped in *BRCA1* cancers. With screening DCIS can be detected. We could recognise DCIS 4 times only at diagnosis, not the previous year. We do not know for how long DCIS may grow before invasion starts–the event we aim to prevent. But DCIS could reach a considerable size (33 and >40 mm, respectively) in carriers and non-carriers.

In conclusion, age at detection is the main indicator for growth rates of hereditary and familial breast cancers. If screening may prove indicated from a certain age on, the woman's age and not the risk group should determine the screening interval. A high sensitivity biannual test may be appropriate before age 40 years.

Conflict of interest statement

None declared.

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