BRCA1 Mutation and Young Age Predict Fast Breast Cancer Growth in the Dutch, United Kingdom, and Canadian Magnetic Resonance Imaging Screening Trials

Madeleine M.A. Tilanus-Linthorst,[1] Inge-Marie Obdeijn,[2] Wim C.J. Hop,[3] Petrina A. Causer,[5] Martin O. Leach,[7] Ellen Warner,[6] Linda Pointon,[7] Kimberley Hill,[6] Jan G.M. Klijn,[4] Ruth M.L. Warren,[8] and Fiona J. Gilbert[9]

Abstract

Purpose: Magnetic resonance imaging (MRI) screening enables early detection of breast cancers in women with an inherited predisposition. Interval cancers occurred in women with a BRCA1 mutation, possibly due to fast tumor growth. We investigated the effect of a BRCA1 or BRCA2 mutation and age on the growth rate of breast cancers, as this may influence the optimal screening frequency.

Experimental Design: We reviewed the invasive cancers from the United Kingdom, Dutch, and Canadian MRI screening trials for women at hereditary risk, measuring tumor size at diagnosis and on preceding MRI and/or mammography. We could assess tumor volume doubling time (DT) in 100 cancers.

Results: Tumor DT was estimated for 43 women with a BRCA1 mutation, 16 women with a BRCA2 mutation, and 41 women at high risk without an identified mutation. Growth rate slowed continuously with increasing age ($P = 0.004$). Growth was twice as fast in BRCA1 ($P = 0.003$) or BRCA2 ($P = 0.03$) patients as in high-risk patients of the same age. The mean DT for women with BRCA1/2 mutations diagnosed at ages ≤40, 41 to 50, and >50 years was 28, 68, and 81 days, respectively, and 83, 121, and 173 days, respectively, in the high-risk group. Pathologic tumor size decreased with increasing age ($P = 0.001$). Median size was 15 mm for patients ages ≤40 years compared with 9 mm in older patients ($P = 0.003$); tumors were largest in young women with BRCA1 mutations.

Conclusion: Tumors grow quickly in women with BRCA1 mutations and in young women. Age and risk group should be taken into account in screening protocols.

Women with a family history of breast cancer or with a mutation in BRCA1 or BRCA2 are at elevated risk of developing breast cancer. Cancers often occur at a very young age in women with mutations. By age 50 years, the estimated cumulative breast cancer risk is 40% for women with BRCA1 mutations and 16% for BRCA2 (1). In women without a BRCA1 or BRCA2 mutation with increased risk based on family history, the estimated cumulative breast cancer risk by age 50 is 5% to 10%, which is two to four times the population risk (2). Several studies have reported that breast cancers in premenopausal high-risk women can often be detected at a favorable stage by annual screening with magnetic resonance imaging (MRI) and mammography (3–7). The purpose of a screening program is to identify breast cancer at an early stage before metastatic spread. The survival of women diagnosed with breast cancers <1 cm and with negative lymph nodes is excellent. In BRCA mutation carriers and in familial high-risk patients, tumor size at detection is a key predictor of survival (8, 9) and mortality risk may be reduced by early tumor detection (10).

Cancers that are missed by screening may present as interval cancers. All other things being equal, the faster the rate of tumor growth, the greater the likelihood that a cancer will present as an interval versus a screen-detected cancer. In three cohorts of women undergoing annual screening with MRI and mammography, seven of the eight reported interval cancers occurred in BRCA1 mutation carriers (3–5, 11). This raises the possibility that one of the hallmarks of BRCA1-associated breast cancers is inherently fast tumor growth. Tumors were shown to grow more rapidly in the younger compared with the older age groups both in mutation carriers and in women at high risk in a recent

Authors' Affiliations: Departments of [1]Surgery, [2]Radiology, [3]Epidemiology and Biostatistics, and [4]Medical Oncology, Erasmus University Medical Centre, Rotterdam, the Netherlands; [5]Centre for Research on Women's Health; [6]Sunnybrook and Women's College Health Sciences Centre, Toronto, Ontario, Canada; [7]Department of Medical Imaging, Institute of Cancer Research and Royal Marsden NHS Trust, Sutton, Surrey, United Kingdom; [8]Department of Radiology, Addenbrooke's Hospital, Cambridge, United Kingdom; and [9]Department of Radiology, University of Aberdeen, Scotland, United Kingdom

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Requests for reprints: Madeleine M.A. Tilanus-Linthorst, Department of Surgery, Erasmus University Medical Centre, Groene Hilledijk 301, 3075 EA Rotterdam, the Netherlands. Phone: 31-10-4391-161; Fax: 31-10-4391-412; E-mail: m.tilanus-linthorst@erasmusmc.nl.

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Dutch study (12), but tumors occur more commonly at a young age in women with BRCA1 and, to a lesser extent, BRCA2 mutations. Tumor growth rate and screening frequency can influence the effectiveness of screening and may be important factors when considering a surveillance strategy in a particular age group (13–15).

Breast cancers are more often high grade in women with BRCA1 mutations than in other high-risk women both before age 50 (84% grade 3 versus 17%) and after age 50 (47% versus 23%; ref. 16). This may suggest faster growth of tumors in women with BRCA1 mutation. The pathologic characteristics of BRCA2-related cancers are more similar to those in high-risk and sporadic cases (17, 18). Tumor growth rates may therefore differ between women with BRCA1 versus BRCA2 mutations but could only be assessed in five women with BRCA2 mutations in the previously reported Dutch study (12).

Induced menopause by bilateral preventive salpingo-oophorectomy halves breast cancer risk in women with BRCA1/2 mutations (19). It may be that menopause and bilateral preventive salpingo-oophorectomy slow the growth rate of hereditary breast cancer.

Beside family history and age, high breast density at mammography is one of the longest known and best documented risk factors for breast cancer (20–23). The stroma of the breast, containing collagen and blood vessels, is known to influence tumor growth in human breast cancer cell cultures (24, 25). We speculated that dense breast tissue might influence tumor growth rate.

We investigated the influence of age, hereditary risk group, menopause, and breast density on tumor growth rate in three MRI screening studies in high-risk women with annual imaging, complete registration of DNA testing, and follow-up.

Materials and Methods

Invasive tumors found during screening in patients of the Dutch Erasmus screening group and 6-center MRISC study, the 22-center United Kingdom MARIBS study, and the Canadian single-center study were included in this analysis. All studies had been given institutional ethical approval and all women had given informed consent. The eligibility criteria for each study were previously published (3–5, 12). All three studies included women with BRCA1/2 gene mutations and women at 20% to 40% lifetime risk of developing breast cancer (high risk). Patients were included in this analysis if the MRI and/or mammogram from the diagnostic screen were available for review together with the previous screening examinations. The Dutch images were reviewed by I-M. Obdeijn, the United Kingdom images were reviewed by R.M.L. Warren and F.J. Gilbert, and the Canadian images were reviewed by P.A. Causer.

Patients. (*a*) In the Dutch MRISC study, we could evaluate the size of 22 invasive tumors detected between July 1, 2003 and January 1, 2006, which had been imaged at least 1 year previously with the same radiological technique, either MRI or mammography. These results were added to the previously described results of 26 invasive tumors detected in the MRISC study before July 2003 (3, 12) and the Erasmus University Medical Centre group of 9 invasive tumors detected at high-risk screening with yearly MRI, mammography, and clinical examination and 12 tumors detected at surveillance with annual mammography and clinical examination (12). (*b*) Tumor size could be evaluated in 14 cancers detected within the MARIBS study between August 1997 and May 2004 (4). This study included women ages 35 to 50 years. All patients with BRCA1 or BRCA2 mutations had been tested before the study or were anonymously DNA tested within the study. (*c*) The size of 17 cancers detected between November 1997 and September 2005 in the Canadian high-risk MRI screening study could be evaluated (5). The study included women ages 25 to 60 years with or without a previous history of breast or ovarian cancer. In total, tumor volume doubling time (DT) could be assessed in 100 invasive tumors.

Breast density was assessed visually at diagnostic mammography using a semiquantitative four-point scale (<25% of dense breast tissue = 1; 25-50% = 2; 50-75% = 3; and >75% = 4) in the Dutch and Canadian patients. The MARIBS study used a three-point scale: fatty, mixed, or dense. These were reclassified as 1, 2.5, and 4. Women were regarded as postmenopausal if menstruation had spontaneously ceased more than 12 months earlier.

Measurements and calculation of tumor growth rates. The MRI and mammography methods have been described (3–5).

The method of taking the measurements and the DT and growth rate (1/DT) calculations has been described (12, 26). In short, if the tumor could be clearly identified at the diagnostic MRI and previous MRI was available, three mutually perpendicular measurements, including the single largest diameter (SLD = a) of the tumor, were made. For all cancers positively identified at diagnostic mammography with a previous mammogram available, the largest diameter (a = SLD) was measured together with a second maximum diameter perpendicular to the first (b) on both the oblique and craniocaudal views. For tumors measurable in both views, the largest, the smallest, and the mean of the other two sizes (c) were used to calculate tumor volume. The volume of the tumor was estimated using the following formula for obloid spheroids: $V = 4/3\pi \times 1/2a \times 1/2b \times 1/2c$.

Tumors were assumed to have exponential growth (i.e., growth with a constant volume DT) as this is usually assumed to be the best approximation for the range of tumor sizes in our study (4-42 mm; refs. 27, 28).

For cancers with a measurable tumor at two or more previous MRI and/or mammography evaluations, and where a previous image showed no visible tumor, only the measurable sizes were used for the calculation of individual DTs (Fig. 1).

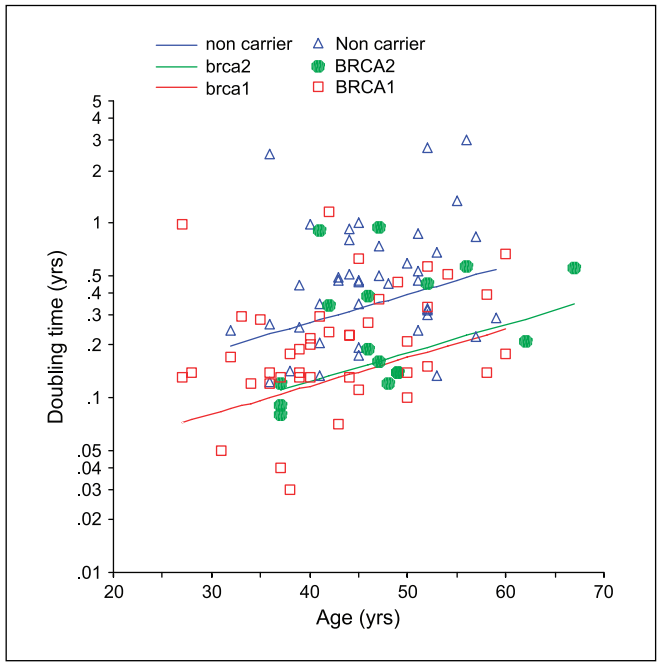

Fig. 1. Correlation between DTs of the 100 invasive tumors and age in the three risk groups. Each red square indicates the measurements for a BRCA1 mutation carrier, each green dot indicates the measurements of a BRCA2 carrier, and each blue triangle indicates the measurements of a noncarrier. The corresponding lines connect the geometric mean values for the risk group.

The group with no visible tumor at the previous examination was included so that the potentially fastest growing tumors were counted for the estimation of growth rate.

In the previous study, tumor size at "no visible tumor" was set to be <0.004 cm^3 corresponding to a diameter of <2 mm. Taking into account the smallest measurements at MRI and mammography and the extrapolated tumor size from the tumors with two or more real measurements and no visible tumor at a previous image, we set the tumor size for no visible tumor at MRI as <2 mm and at mammography as <4 mm (assumed lower detection limit).

The slope of the straight line connecting the two log-transformed volume measurements was calculated using least-squares regression for three or more real volume measurements.

Tumor volume DTs were calculated using the following formula: DT = $1/\beta$, where β is the slope of the regression line of the logarithm (base 2) of the tumor volume versus time. The assumed lower detection limit may result in an underestimation of the true slope, and consequently, the tumor DT may be overestimated (i.e., a left-censored observation of the DT).

Statistical methods. Differences in patient and tumor characteristics between the three risk groups were tested with the use of the Kruskal-Wallis test in case for continuous variables and with the χ^2 test for categorical variables. To determine the correlation between tumor size at mammography/MRI and at histopathologic examination, we calculated Pearson's correlation coefficient (r). To provide an approximate normal distribution of volume DTs, these were logarithmically transformed for all analyses. Therefore, all reported mean DTs represent geometric means. Comparison of the transformed DT between risk groups was done using ANOVA. Multiple regression was used to evaluate simultaneously the effects of age, risk group, and breast density. STATA software (CNREG) was used in these calculations to allow for the presence of left-censored volume DTs in 40 cases. A two-sided P value of <0.05 was considered to indicate statistical significance.

Results

Patients and tumor characteristics. Tumor size could be assessed at diagnosis and on previous imaging in 100 patients with invasive tumors: 43 who had a BRCA1 mutation, 16 who had a BRCA2 mutation, and 41 high-risk women. The characteristics of the patients in the three centers are given in Table 1. Patients were on average significantly younger in the United Kingdom and Dutch groups than in the Canadian group (P = 0.009 and 0.004, respectively; average age: 42, 44, and 50 years, respectively). Median tumor size was 8 mm in the Canadian study compared with 12 mm in the Dutch study (P = 0.02) and 13 mm in the United Kingdom study (P = 0.03).

Ten cancers in the Dutch study were detected between screens [3 in the MRISC study before July 2003 and 2 in the Erasmus screening group (12)] and 1 in the Canadian study. The tumor was visible in retrospect in five interval cases (four on the MRI and one on the mammogram). Five of the interval cancers were in patients ages ≤40 years (range, 31-58 years). Only one of the interval cancers was diagnosed within 6 months of the previous imaging.

Patient and tumor characteristics in the three hereditary risk groups are given in Table 2. The average age was significantly lower for patients with BRCA1 mutations than for BRCA2 and high-risk patients. Forty-six percent of the BRCA1 patients were ages ≤40 years. The median tumor size was larger in the women who were ages ≤40 years than in the older women (P = 0.003) and was largest in the women with BRCA1 mutations who were ages ≤40 years. The median size of the tumors differed between BRCA1-related, BRCA2-related, and high-risk cases (13 versus 8 versus 11 mm, respectively; P < 0.001). Invasive tumor size decreased continuously with increasing age (P = 0.001) at univariate analysis. There was no significant difference in mammographic breast density between the groups. Significantly more cancers were detected in the interval between screens in the BRCA1 group (9 of 43) than in the BRCA2 (0 of 16; P = 0.045) or the high-risk group (2 of 41; P = 0.049). The median tumor size at pathology was 18 mm in interval cancers versus 13 mm in screen-detected cancers (P = 0.1).

Tumor measurements and DTs of the 100 invasive tumors. Calculations of tumor volume DTs were done using two or more real measurements at MRI or mammography for 60 tumors (uncensored group) and one real measurement at diagnosis with a previous examination showing no visible tumor for 40 (censored group) as shown in Table 3. There was no significant difference between the uncensored and censored group with regard to tumor size at pathology, median size (12 versus 10 mm, respectively; P = 0.7), and grade distribution (P = 0.7). The difference in age tended toward significance (mean age, 46 versus 43 years, respectively; P = 0.06).

Tumor size at pathology correlated well with the measured size at diagnostic MRI (r = 0.7) and moderately well with size at mammography (r = 0.6; ref. 28). Including the patients who received neoadjuvant chemotherapy, the mean time between last imaging and pathology size measurement was 2 months (72 days).

The mean DT for the total cohort was 71 days and 46, 52, and 129 days for the BRCA1, BRCA2, and high-risk cases, respectively. The mean DT was 28 days for all patients ages ≤40 years and 103 days for the older group. The mean DT was 37 days for all interval cancers versus 74 days for the screen-detected cancers (P = 0.25).

Growth rates of the 100 cancers by age, risk group, and breast density. At univariate analysis, tumor volume DT correlated significantly with age (P = 0.003). With each 10-year increase in age, the mean DT increased by a factor of 1.6 (95% confidence interval, 1.2-2.1). This factor applies to all three risk groups (difference between risk groups: P = 0.71).

Menopause did not correlate significantly with DT either in univariate analysis (P = 0.1) or after adjustment for age (P = 0.5). Adjusted for age, no significant correlation was found between DT and Bloom-Richardson grade.

A significantly shorter average DT was seen in BRCA1-related cancers (P = 0.003) and in BRCA2-related cancers (P = 0.03) compared with high-risk patients adjusted for age and center (Table 4). The average DTs of BRCA1/2-related cancers were half that of the high-risk cases of the same age (Fig. 1).

DT did not correlate significantly with breast density at mammography (P = 0.3) at univariate analysis. A trend was seen for slower growth at higher density adjusting for age and risk group (P = 0.07).

Results per age cohort. Growth rate (P = 0.003) and tumor size (P = 0.001) decreased with age without a natural cutoff point. When comparing the absolute DT and tumor sizes of the BRCA1, BRCA2, and high-risk patients by age cohort, growth rate and tumor size decreased significantly with increasing age in the total group and in mutation carriers. In the group ages ≤40 years at diagnosis, the mean DT for BRCA1, BRCA2, and high-risk patients was 28, 26, and 83 days, respectively; for ages 41 to 50 years, the mean DT was 69, 65, and 121 days; and for

Table 1. Patient characteristics in the United Kingdom, Canadian, and Dutch studies

	United Kingdom	Canadian	Dutch	Total
Total no.	14	17	69	100
BRCA1	5	8	30	43
BRCA2	4	7	5	16
High risk	5	2	34	41
	United Kingdom	**Canadian**	**Dutch**	***P***
Mean age, y (range)				
BRCA1	40 (34-45)	50 (38-60)	41 (27-60)	0.06
BRCA2	47 (41-52)	54 (46-67)	40 (37-46)	0.01
High risk	43 (36-47)	44 (39-48)	47 (32-59)	0.4
Total	42 (31-52)	50 (38-67)	44 (27-61)	0.02
Mean density at mammography	2.8	2.3	2.4	0.4
Median size at pathology, mm (range)	13 (6-31)	8 (4-20)	12 (4-42)	0.045

patients ages >50 years, DT was 77, 112, and 173 days. As the results for the BRCA1- and BRCA2-related tumors were so similar and there were so few tumors in the BRCA2 group ages ≤40 years (n = 3) and >50 years (n = 4), their DT results are combined with those of the BRCA1 group in Table 5.

Mammographic density did not differ significantly between patients ages ≤40 years and those ages 41 to 50 years (P = 0.4), but density was significantly lower in the women ages >50 years (P = 0.04). Multiple regression showed that pathologic tumor size at diagnosis decreased significantly in older cohorts (P < 0.001) but did not correlate with density (P = 0.3).

Subgroup analyses. Testing for effect modification, the effect of age on DT did not differ between the three centers (P = 0.92). In addition, the independent influence of a BRCA1/2 mutation on DT (adjusted for age) was consistent in the three centers (P = 0.6). These results remained similar when using only the 60 tumors with two or more real measurements for the analyses. In addition, comparing measurements obtained with MRI and mammography, no influence of modality was found (P = 0.81).

When the limit of detection at MRI was set at <0.01 cm^3 instead of <0.004 cm^3, reanalysis showed little change in the independent effects of age and risk group on DT. When recalculated with the adapted threshold, the mean DTs in the BRCA1/2 group in the ≤40, 41 to 50, and >50 age groups were 30, 73, and 98 days, respectively. In the high-risk group, they were 89, 123, and 175 days, respectively.

Discussion

A finding unique to our study is that, at the same age, the average growth rate of the tumors of women with a BRCA1 or BRCA2 mutation was twice as fast as that of high-risk patients (DT ratio, 0.5). This mutation effect on tumor growth was consistent in the three countries. The mean tumor DT of 46 days in the BRCA1 group and 52 days in the BRCA2 group

Table 2. Patient and tumor characteristics in the three risk groups

	Total (*N* = 100)	BRCA1 (*n* = 43)	BRCA2 (*n* = 16)	High risk (*n* = 41)	*P*
Mean age, y (range)	45 (27-67)	43 (27-60)	48 (37-67)	46 (32-59)	0.04
Menopausal status					
Premenopause	67	29 (67%)	10 (63%)	28 (69%)	
Postmenopause (BPSO)	10	8 (19%)	1 (6%)	1 (2%)	0.07
Postmenopause (natural)	23	6 (14%)	5 (31%)	12 (29%)	
Mean density at mammography	2.4	2.3	2.7	2.4	0.5
Cancers by age (y)					
≤40	31	20 (46%)	3 (19%)	8 (20%)	0.02
>40	69	23 (54%)	13 (81%)	33 (80%)	
Cancer detection					
Interval	11	9 (21%)	0	2 (5%)	0.03
Screening	89	34 (79%)	16 (100%)	39 (95%)	
Median size at pathology, mm (range)					
In the total group	11 (4-42)	13 (4-40)	8 (4-15)	11 (4-42)	<0.001
≤40 y	15 (4-40)	18 (4-40)	11 (7-15)	12 (4-20)	0.003*
>40 y	9 (4-42)	12 (4-35)	7 (4-10)	10 (5-42)	
Grade					
1	11 (12%)	1 (3%)	1 (7%)	9 (24%)	
2	38 (43%)	12 (32%)	9 (60%)	17 (46%)	<0.001
3	40 (45%)	24 (65%)	5 (33%)	11 (30%)	

NOTE: Data are number of patients (%) unless otherwise indicated.
Abbreviation: BPSO, bilateral preventive salpingo-oophorectomy.
*P value for difference in tumor size ≤40 and >40 y in the total group.

Table 3. Number and modality of the measurements used for DT calculations according to risk group

	MRI ≥2	Mx ≥2	MRI 1 + n.v.t.	Mx 1 + n.v.t.	Total ≥2	Total 1 + n.v.t.	P*
Total no.	35	25	27	13	60	40	
BRCA1	14	9	15	5	23	20	
BRCA2	6	2	7	1	8	8	0.2
High risk	15	14	5	7	29	12	

NOTE: ≥2, two or more real measurements.
Abbreviations: Mx, mammography; n.v.t., no visible tumor.
*P value for the difference between the three risk groups in number of DT calculated with uncensored (≥2) versus censored (1 + no visible tumor) measurements.

in this multinational study is very similar to the 45 days in the 30 women with a BRCA mutation reported in the previous Dutch-only study (12). With twice as many carriers in the current analysis, this finding seems robust. We could not show a difference between BRCA1 and BRCA2 mutations in effect on tumor growth rate. Tumors in women with either BRCA1 or BRCA2 mutations tend to appear at a younger age than sporadic cancers and are more often high grade (8, 16–18). Clear differences between BRCA1- and BRCA2-related cancers have been described in hormonal receptor status. BRCA1-related tumors are commonly estrogen receptor negative and progesterone receptor negative (often her2neu negative, basal type). BRCA2-related tumors are usually estrogen receptor positive and progesterone receptor positive, similar to sporadic or high-risk patients (16–18). The significantly faster tumor growth in both mutation groups compared with high-risk women makes it highly unlikely that growth rate is associated with the estrogen receptor or progesterone receptor status.

Despite pooling the multinational data of the three largest MRI high-risk screening studies, only three tumors detected before age 40 in women with BRCA2 mutations could be assessed. And although the faster growth in women with BRCA1 mutations below the age of 40 was reflected by their larger tumor size at detection and the occurrence of interval cancers, BRCA2-related tumors were small and no interval cancers occurred. To confirm DTs in tumors with BRCA2 mutations, a larger study would therefore be desirable.

The decreasing growth rate of breast cancers with increasing age was confirmed in both women with BRCA1/2 mutations and in high-risk patients in this combined study. On average, invasive tumors doubled in volume in 1 month in mutation carriers diagnosed up to age 40 compared with 2 months for carriers ages 41 to 50 and 3 months for carriers diagnosed after age 50. The corresponding DTs in high-risk patients in these three age categories were 3, 4, and 6 months, respectively. When a tumor doubles its volume four times, tumor size at imaging will increase from 2 to 5 mm or from 4 to 10 mm. This is a detectable change, and although in studies the rate of distant metastases increased much faster with increasing tumor size in high-grade cancers (as often seen in BRCA1/2-related tumors) than in low grade cancers, as long as the tumor was detected in the 2- to 10-mm size range the prognosis was excellent (8–10, 18). In our BRCA1 group under age 40, however, mean tumor pathology size was 18 mm, a size at which the risk of metastases is relatively high for these usually high-grade cancers (29, 30).

Table 4. Multivariate analysis of tumor volume DT in 100 invasive tumors in relation to age and risk group (with adjustment for center)

Factor	DT ratio	95% CI of DT ratio	P
Age	1.6*	1.2-2.1	0.004
BRCA1	0.5†	0.3-0.8	0.003
BRCA2	0.5†	0.2-0.9	0.03

Abbreviation: 95% CI, 95% confidence interval.
*Effect of an increase of age with 10 y.
†Versus high risk.

We cannot compare the growth rates in our study directly to the growth rate of tumors of women in the average-risk population as screening is not offered below age 40 years. Peer et al. (26) calculated a median tumor volume DT of 80 days in patients ages <50 years not selected for risk and a DT of 160 days for women ages >50 years, very similar to our finding of 183 days for high-risk women ages >50 years. Large-scale population mammography screening studies have also shown that the sojourn time (the time interval during which a tumor can be detected at imaging, but not yet clinically) is longer for women ages >50 years than for women ages between 40 and 50 years (13–15, 30–32).

Dense breast tissue was not associated with enhanced growth rate and did not explain the larger tumor size in our younger age groups at multivariate analysis. Therefore, dense breast tissue does not seem a valid reason to increase screening frequency. This is consistent with the findings by White et al. (32). We could not show an influence of tumor grade or menopausal status on tumor growth rate independent of age.

We can recognize some limitations to our study as a consequence of the combination of material from three different national trials. The inclusion criteria were similar but not identical, resulting in different contributions to the three risk groups and the older age profile of the Canadian participants. The image review processes were undertaken separately by the three national groups, and although methods were precisely described and discussed, one cannot be sure that these were exactly comparable. The gain from combining the material to give greater statistical power for the subset analysis, however, outweighs these limitations. In tumors measurable only at detection, but not at previous imaging, tumor size was estimated to be below the limit of detection. Varying this threshold in a sensitivity analysis generated very similar DTs, however. Our study is to our knowledge the first breast cancer growth rate study with results that are partly based on three-dimensional imaging of tumor volume at MRI. These measurements may be

Table 5. Numbers of patients, mean DT, average breast density, and tumor pathology size of the 100 cancers per age and risk group

	≤40 y (*n* = 31)	41-50 y (*n* = 42)	>50 y (*n* = 27)	*P**
No. BRCA1/2	23	24	12	
No. high risk	8	18	15	
Mean DT days (95% reference)				
BRCA1/2	28 (4-222)	68 (9-553)	81 (10-653)	0.004
High risk	83 (12-593)	121 (17-850)	173 (25-1,202)	0.06
Mean density				
Total group	2.6	2.5	2.0	0.03
Median pathology size, mm (range)				
In the total group	15 (4-40)	10 (4-42)	9 (4-27)	0.009
BRCA1/2	15 (4-40)	9.5 (4-35)	8.5 (4-25)	0.016
High risk	11.5 (4-20)	10 (6-42)	9 (5-27)	0.45

*P for the difference in mean DT between the three age groups (adjusted for study center).

more accurate than the calculated volume from two-dimensional studies such as mammography. Our results, however, did not show a difference between the two modalities.

Our data suggest that, in women ages <40 years with a BRCA1 mutation, breast tumors are relatively common, grow quickly, and are often high grade. Moreover, with annual screening, these tumors are larger at diagnosis and interval cancers may be more common than in other high-risk women. When screening very young women, however, the false-positive rate may be higher and this could reduce the cost-effectiveness. This study has shown that age and mutation status should be considered together with other factors when developing recommendations for screening high-risk women.

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