Effectiveness of Breast Cancer Surveillance in *BRCA1/2* Gene Mutation Carriers and Women With High Familial Risk

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Purpose: **Women with a high breast cancer risk due to a familial predisposition may choose between preventive surgery and regular surveillance. The effectiveness of surveillance in high-risk women and especially *BRCA1/2* mutation carriers is unknown. We present first results from a single large family cancer clinic.**

Patients and Methods: **Women with breast cancer risk over 15% were examined by physical examination every 6 months and mammography every year. Detection rates and screening parameters were calculated for the total group and separately for different age and genetic risk groups.**

Results: **At least one examination was performed in 1,198 women: 449 moderate and 621 high-risk women and 128 *BRCA1/2* mutation carriers. Within a median follow-up of 3 years, 35 breast cancers were detected (four ductal carcinoma-in-situ; 31 invasive tumors); the average detection rate was 9.7 per 1,000. Detection rates (95% confidence interval) for moderate and high-risk women and *BRCA1/2* carriers were 3.3 (1.1 to 8.6), 8.4 (5.4 to 13.2), and 33 (17 to 63) per 1,000 person-years, respectively. The ratio of observed cases versus breast cancers expected in an average-risk population of comparable age was 2.7, 7.0 and 23.7 respectively. Overall, node negativity was 65%; 34% of primary tumors were less than 10 mm; sensitivity was 74%. Results with respect to tumor stage and sensitivity were less favorable in *BRCA1/2* carriers and in women under the age of 40.**

Conclusion: **It is possible to identify young women at high risk for breast cancer. The number of cancers detected was significantly greater than expected in an age-matched average-risk population and related to the risk category. Overall, screening parameters were comparable to population screening data, with less favorable results in the youngest age group (< 40) and *BRCA1/2* carriers.**

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RANDOMIZED TRIALS and population-based programs have provided evidence that breast cancer screening can be cost effective in women between 50 and 70 years of age.[1-4] Although results in women between 40 and 50 are more controversial, it was recently found that screening in this age group can also significantly reduce breast cancer mortality.[5] However, in view of the lower incidence of breast cancer and the larger negative screening effects in young women,[6] there is no consensus on the cost effectiveness and the desirability of introducing population-based screening programs for women under the age of 50. It might be more efficient to limit screening in women under age 50 to selected groups of high-risk women, such as women with a positive family history of breast cancer.[7]

The identification of the *BRCA1* and *BRCA2* genes and the possibility of gene mutation testing has caused an increasing demand from high-risk women for genetic testing and counseling about strategies to reduce their risk of breast cancer death. One of the options is intensive surveillance. Because for ethical reasons no randomized trials in genetically susceptible women are to be expected, the effects of surveillance in these women must be evaluated by means of observational studies. To date, a limited number of studies describing experiences and preliminary results of surveillance in women with a family history of breast cancer have been published.[8-11]

In this combined retrospective and prospective follow-up study, we describe the first results of surveillance in proven *BRCA1/2* gene mutation carriers in addition to women with a family history of breast cancer at the Rotterdam Family Cancer Clinic.

Our study sample was large enough to allow subgroup analyses for age and genetic risk group: *BRCA1/2* gene mutation carriers and women with high or moderate familial risk. To our knowledge, thus far, no separate

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Table 1. Risk Groups Defined by DNA-Diagnosis or Genetic-Epidemiologic Tables[15]

	Risk Group	Lifetime Risk of BC (%)	Inclusion Criteria	No. of Women	Age at 1st Surveillance	
					Mean	Range
1	Carriers	60-85	Proven carriers of a *BRCA1/2* mutation (DNA analysis)	128*	37	21-63
2	High	30-50	*HBOC	621	38	22-70
			*≥3 1st- or 2nd-degree relatives with BC			
			*2 1st- or 2nd-degree relatives with BC <50			
3	Moderate	15-30	All others with RR > 2 and not fulfilling the abovementioned criteria	449	38	25-70

Abbreviations: HBOC, hereditary breast and ovarian cancer; BC, breast cancer; RR, relative risk of breast cancer.
*113 *BRCA1* carriers and 15 *BRCA2* carriers.

screening results for proven *BRCA1/2* carriers have been published before.

A range of screening parameters was calculated and compared with characteristics of breast screening programs and cancer registry data.

PATIENTS AND METHODS

In several specialized centers in the Netherlands, women with a more than two times increased breast cancer risk because of a family history are offered regular surveillance. At our institution, a small group of women with familial risk have been screened since 1978, with rapidly increasing numbers in the 1990s. The screening procedure consists of instructions for monthly breast self-examination, yearly mammography, and clinical breast examination (CBE). This last procedure is generally performed every 6 months except in some moderate-risk women who had a yearly screening interval in the early days of the program. Since 1995, magnetic resonance imaging (MRI) is optionally included in the surveillance program in case of dense mammographic breast tissue and/or *BRCA1/2* gene mutation carriership. When indicated, additional investigation by ultrasound with or without fine-needle aspiration is performed. The minimum age of entry onto the surveillance program is generally 25 years, or younger in women from families with a young age at onset. The general protocol was approved by the medical ethical committee (project DDHK 91-17).

Data Collection and Statistics

To evaluate the effects of surveillance in this specific group of women, a database was set up at our institution collecting from medical file data on family and individual characteristics, surveillance and follow-up data, additional investigations, and final outcome of each examination. Since 1995, data were entered prospectively after each screening visit. Data from before this date were entered retrospectively. To ensure coverage as complete as possible of all breast cancers detected within the program, existing databases of (breast) cancers diagnosed in the hospital were checked to identify breast cancers detected in women with familial risk. All medical records were then reviewed for a possible screening history so that breast cancers detected in screened women, including interval cancers, could be identified. Although it might be that during the course of the program some women were lost to follow-up, we think that in this way severe bias with respect to the incidence of breast cancer could be avoided.

We calculated detection rates of cancers found at the first or subsequent examination as well as the rates of cancers occurring in the interval between two examination rounds, so-called interval cancers. Person-years of risk were calculated from the date of the first examination to the end point of interest: the date of detection of breast cancer (at surveillance or in the interval between two examinations), date of bilateral preventive mastectomy (occurred in 65 women, of whom 52 were proven carriers), or the end of the study period (January 1, 2000). 95% Confidence intervals were computed assuming a Poisson distribution. Observed numbers of invasive breast cancer were compared with expected numbers based on National Cancer Registry data[12]; detection rates and stage distribution were compared with national and international breast screening programs. Sensitivity of the screening test was calculated as the ratio of breast cancers detected by surveillance divided by the total number of breast cancers (screen-detected plus interval cancers).[13,14]

RESULTS

Population and Screening Characteristics

At least one examination was performed at the Dr Daniel den Hoed Cancer Center in 1,198 women with high familial risk, their mean age at first surveillance being 38 years (age range, 21 to 70 years). For 399 women, it was the first examination; for 386 women, screening was done previously in another hospital; and for 413 women, information regarding previous screening examinations elsewhere was missing. By means of DNA testing or genetic-epidemiologic tables,[15] three genetic risk groups were defined: 128 carriers of a *BRCA1*- (n = 113) or *BRCA2*- (n = 15) gene mutation (group 1) and women with a high (group 2; n = 621) or moderate (group 3; n = 449) lifetime risk of breast cancer. In Table 1, inclusion criteria and mean age at the first visit for the three subgroups are shown.

With a median follow-up period of 3.0 years (range, 0 to 22 years), 35 breast tumors (including four ductal carcinomas-in-situ [DCIS]) were detected. With the total number of follow-up years being 3,607, the average breast cancer detection rate (invasive breast cancer and DCIS) was 9.7 per 1,000; excluding DCIS, it was 8.6 per 1,000 person-years. Twenty-six of the 35 tumors were detected at screening (three at the first examination and 23 at a subsequent examination), making the rate of screen-detected cancers 7.2 per 1,000. Nine cancers were detected in the interval between screens (interval cancer rate 2.5 per 1,000). The time interval from the last negative screen until diagnosis ranged from 8 weeks to 10 months. Four cancers, diagnosed

Table 2. Observed and Expected Numbers of Invasive Breast Cancer per Risk Group

Risk Group	No. of Women	Observed No. of Invasive Breast Cancers*	No. of Person-Years At Risk	Detection Rate per 1,000 (95% CI)	Expected No. of Breast Cancers†	Ratio of Observed to Expected (95% CI)
BRCA1/2 carriers (1)	128	9	268	33 (17-63)	0.38	23.7 (1.2-483)
High risk (2)	621	18	2,146	8.4 (5.4-13.2)	2.57	7.0 (1.9-26.1)
Moderate risk (3)	449	4	1,193	3.3 (1.1-8.6)	1.47	2.7 (0.4-17.6)
Overall/total	1,198	31	3,607	8.6 (5.8-11.8)	4.42	7.0 (2.6-18.9)

Abbreviation: CI, confidence interval.
*Four patients with DCIS excluded.
†For age-matched population according to National Cancer Registry 1990-1995.

at the time of the scheduled surveillance visit, were already symptomatic: these women had experienced symptoms for several weeks or months without calling in for an earlier check-up, as had been advised to them.

The mode of diagnosis of the 26 screen-detected cancers was as follows: 12 cancers were not palpable at the time of detection and found by mammography (n = 9) or MRI (n = 3): in one case, MRI was used as a screening modality instead of mammography because of dense breast tissue; in the two other cases (proven *BRCA1* carriers), MRI was alternated with mammography (every 6 months). Twelve cases were detected by CBE and mammography, one case by CBE and MRI (a *BRCA1* carrier), and one by clinical examination only.

Relationship With Risk and Age Categories

In Table 2, observed and expected numbers of breast cancer are shown for each risk group, as defined in Table 1. In the group of proven carriers, nine breast tumors were detected (all in *BRCA1* carriers). The mean age at diagnosis was 40 years. In the high-risk group, 24 tumors were found (including four cases of DCIS); the mean age at diagnosis was 48 years. In the moderate-risk group, four tumors were detected. The mean age at diagnosis was 50 years. The detection rates of invasive breast cancer were 33 per 1,000 person-years (95% CI, 17 to 63) in *BRCA1/2* gene mutation carriers, 8.4 (5.4 to 13.2) per 1,000 in the high-risk group, and 3.3 (1.1 to 8.6) per 1,000 in the moderate-risk group. Thus, although a clear trend of a decreasing detection rate was seen, the confidence intervals of the risk categories 2 and 3 overlapped. The ratio of observed versus expected breast cancer cases varied from 23.7 (95% CI, 1.2 to 483) in proven carriers to 7.0 (1.9 to 26.1) in the high-risk group and 2.7 (0.4 to 17.6) in the moderate-risk group, with an overall observed-expected ratio of 7.0 (2.6 to 18.9).

In Table 3, observed and expected numbers of invasive breast cancer are presented per age category. Detection rates varied from 3.6 (1.9 to 7.2) per 1,000 in women under the age of 40 years to 11.8 (6.6 to 21.1) per 1,000 in the age group 40 to 49 years and 26.1 (15.1 to 45.7) per 1,000 in women older than 50 years of age: a clear trend of an increasing detection rate with age, due to the rising incidence of breast cancer with age. Again, 95% confidence intervals partly overlapped. The ratio of observed versus expected breast cancer cases was 5.6 (0.9 to 33.4) in women under the age of 40, 6.2 (1.3 to 29.7) in the age group 40 to 49 years, and 9.8 (1.5 to 62.2) in women over the age of 50.

Tumor Characteristics at Diagnosis and Sensitivity

In Tables 4 and 5, tumor and screening characteristics are described for the total group and separately per risk group (Table 4) and age group (Table 5). Overall, four (11%) of the 35 breast tumors were DCIS. All cases of DCIS were detected in women over the age of 50, being part of the high-risk subgroup. Histology of the 31 invasive tumors was as follows: 28 were ductal, two were lobular invasive, and one was medullary. Ten (34%) of 29 invasive tumors with known tumor size were smaller than 10 mm, eight

Table 3. Age-Specific Observed and Expected Numbers of Invasive Breast Cancer

Age at First Surveillance	No. of Women	Observed No. of Invasive Breast Cancers*	No. of Person-Years At Risk	Detection Rate per 1,000 (95% CI)	Expected No. of Breast Cancers†	Ratio of Observed to Expected (95% CI)
<40 years	739	8	2,213	3.6 (1.9-7.2)	1.42	5.6 (0.9-33.4)
40-49 years	302	11	935	11.8 (6.6-21.1)	1.78	6.2 (1.3-29.7)
>50 years	157	12	459	26.1 (15.1-45.7)	1.22	9.8 (1.5-62.2)
Overall/total	1,198	31	3,607	8.6 (5.8-11.8)	4.42	7.0 (2.6-18.9)

*DCIS excluded.
†For age-matched population according to National Cancer Registry 1990-1995.

Table 4. Tumor and Screening Characteristics per Risk Group

	Risk Group								
	BRCA1/2 Carriers		High Risk		Moderate Risk		Total		
Variable	No.	%	No.	%	No.	%	No.	%	*P**
DCIS	0/9	0	4/22	18	0/4	0	4/35	11	.26
N+ tumors†	5/9	56	6/18	33	1/4	25	11/31	35	.45
T ≤ 10 mm‡	2/9	22	7/16	44	1/4	25	10/29	34	.51
Interval cancers	4/9	44	5/22	23	0/4	0	9/35	26	.21
Sensitivity	5/9	56	17/22	77	4/4	100	26/35	74	.21

*P = the difference between subgroups.
†Invasive tumors only.
‡Two invasive tumors with missing tumor size (T).

(28%) were between 10 and 15 mm, and 11 (38%) were greater than 15 mm (range, 16 to 40 mm). The size of two invasive tumors was missing because of multifocality (one case) or ill-defined border (one case).

Twenty (65%) of 31 invasive tumors were node-negative and 11 (35%) were node-positive. Two (66%) out of three cancers detected at the prevalent screen were node-positive, but this was 31% (six of 19) of the incident screen-detected and 33% (three of nine) of the interval cancers, respectively. Risk group– and age-specific results showed high node positivity, especially in proven carriers and the youngest age group: 56% (five out of nine) of the invasive tumors in carriers already node-positive and 62% (five out of eight) of the tumors in women under the age of 40. Differences between the subgroups were not significant.

The overall sensitivity of the screening test was 74% (26 of 35), including the four symptomatic screen-detected tumors in the numerator, or 63% (22 of 35) excluding these four tumors from the numerator. Although insignificant, a remarkable difference in sensitivity between risk groups was seen, as interval cancers were detected especially in proven carriers, rendering a low sensitivity (56%) in this subgroup. This might not (only) be due to their young age: although age-specific results showed, as expected, an increasing sensitivity with age of 63% in the youngest age group, 73% in the age group 40 to 49, and 81% in the oldest age group (Table 5), sensitivity in the youngest age group increased to 100% (four of four cases) when proven carriers in this age group were excluded (results not shown because of small numbers).

Follow-Up

Two out of the 31 patients (one BRCA1 carrier and one patient from the high-risk group) with an invasive tumor relapsed; both died of metastatic disease 2.5 and 4 years, respectively, after the diagnosis. One additional patient died of another cause (chronic myeloid leukemia).

DISCUSSION

Nowadays, a number of countries, including the Netherlands, offer the opportunity of selective breast cancer surveillance to women with a family history of breast cancer. The current policy in 16 European Family Cancer Clinics was recently reviewed by Vasen et al.[16] Current surveillance modalities are breast self-examination, clinical examination, and mammography. MRI is performed only in research settings.

Most clinics recommend a mammographic examination every year instead of every 2 years, as the growth rate is higher and the mammographic visibility of breast tumors lower in younger women.[17,18] There is no consensus on the minimum age at entry: mammography generally is per-

Table 5. Tumor and Screening Characteristics per Age Group

	Age Group								
	<40 Years		40-49 Years		≥50 Years		Total		
Variable	No.	%	No.	%	No.	%	No.	%	*P**
DCIS	0/8	0	0/11	0	4/16	25	4/35	11	.07
N+ tumors†	5/8	62	2/11	18	4/12	33	11/31	35	.13
T ≤ 10 mm‡	2/7	33	3/10	30	5/12	42	10/29	34	.79
Interval cancers	3/8	37	3/11	27	3/16	19	9/35	26	.61
Sensitivity	5/8	63	8/11	73	13/16	81	26/35	74	.61

*P = the difference between subgroups.
†Invasive tumors only.
‡Two invasive tumors with missing tumor size (T).

Table 6. Characteristics of Breast Cancer Surveillance Trials in Women With Familial Risk

First Author (ref)	Country	No. of Women (total/*BRCA1/2* carriers)	Inclusion Criteria	Age at Entry (years)		Screening Method	Screening Interval	Mean Follow-Up
				Mean	Range			
Saetersdal[8]	Norway	537/?	"Dominant inheritance"	42.5	20-76	X-mam + CBE	(1st-round results)	
Moller[19]	Norway	1194/?	FH+ (see ref)	42.9		X-mam	Annual	1.8 years
Chart[11]	Canada	1044/?	FH+ or combination of other BC risk factors	39.5/42.7 (2 pop)		X-mam + CBE	Annual (high risk: 6-monthly CBE)	21.9 months
Lalloo[10]	UK	1259/?	FH+: lifetime risk BC > 1 in 6	39.1	28-49	X-mam	Annual	30 months
Kollias[9]	UK	1371/?	FH+: lifetime risk > 1 in 9	41	18-49	X-mam + CBE	Annual CBE + biennial x-mam	22 months
Lai[20]	Taiwan	2629/?	Relative of BC case	? (> 35)		X-mam + CBE	Annual	?
Tilanus-Linthorst[21]	The Netherlands	678/?	> 15% lifetime risk	42.9/43.3	20-75	X-mam* + CBE	Annual (high risk: 6-monthly CBE)	3.3 years
Brekelmans (this study)	The Netherlands	1198/128	FH+: RR > 2	38	21-70	X-mam* + CBE	6-monthly CBE + annual x-mam*	36 months

Abbreviations: FH+, positive family history; BC, breast cancer; RR, relative risk; X-mam, mammography; CBE, clinical breast examination; ?, unknown.
*MRI in selected cases (dense breast tissue or *BRCA1/2* carriership).

formed for the first time at age 25 to 35 or 5 to 10 years younger than the youngest affected relative in case of young age at onset (< 30 to 35 years).

In Tables 6 and 7, characteristics and first preliminary results of published surveillance projects in genetically susceptible women in different countries are presented. Although inclusion criteria and minimum age at entry vary between countries and centers, detection rates are uniformly similar or even higher than in population screening programs aimed at women aged 50 to 70.[8-11,19-21]

Our results and those of others thus show that it is clearly possible to identify young women at high familial risk: the number of breast cancers detected in our population was on average seven times greater than expected in an average-risk population of comparable age. Our study sample was large enough and the follow-up period long enough to calculate age-specific screening parameters and results for three separate genetic risk groups: proven *BRCA1/2* carriers and women with a high or moderate familial risk of breast cancer. With respect to detection rates, we found, as expected, clear trends with age and genetic risk groups.

The overall sensitivity found in our study was 74%, which is comparable to the results of the Dutch Breast Screening Programme.[22] As expected, a trend of increasing sensitivity with age was seen. With respect to risk group, a low sensitivity was found in the group of proven *BRCA1/2* carriers: four out of nine cases detected in this group were interval cancers. Although this result is based on small numbers and awaits confirmation by others, it might be that this reflects a true characteristic of *BRCA*-associated tumors. Although the true sensitivity of screening (the number of missed cases) is a theoretical parameter that cannot be measured, there are several methods to approximate this.[13,14] In our study, "sensitivity" was estimated by the number of cancers appearing between screens. This group of so-called interval cancers consists not only of missed cancers, caused for instance by poor mammographic visibility, but also of incident tumors with a high tumor growth rate. In *BRCA1* carriers, there are indications for both possibilities: mammographic visibility might be lower in these women,[23] and histopathologic studies have found a consistently higher proliferation rate, a marker for growth rate, in *BRCA1* carriers.[24,25] Nevertheless, we found no differences in disease-free and overall survival between women with *BRCA1/2*-associated and sporadic tumors matched for age and year of diagnosis.[26,27]

The percentage of DCIS found in our study (11%) was also comparable to that of the Dutch Breast Screening Programme. Most "high-risk" surveillance studies find a higher percentage of DCIS, which is to be expected, as DCIS is generally found more often in younger women,[18] with the possible exception of proven carriers of a *BRCA1* mutation.[28] This last observation might explain why in our study no cases of DCIS were found in women under the age of 50, an age group that includes a high percentage of *BRCA1/2* carriers.

The overall percentage of tumors with positive lymph nodes was 35% (11 of 31), whereas this was 31% (six of 19) in cancers detected at an incident screening round. This last percentage is comparable to the Dutch National Breast Screening Programme[4] and within the acceptable level suggested for population screening programs in women over the age of 50.[29] Although it is important to use population-based standards to monitor surveillance results in women with a positive family history, for a valid comparison it is also useful to compare screening results, such as node positivity to symptomatic tumors in familial breast cancer patients, as it might be that the natural history

Table 7. Results of Breast Cancer Surveillance Trials in Women With Familial Risk

First Author	Detection Rate* per 1,000	Observed-Expected Ratio	% DCIS	% N+ or ≥ Stage II*	Sensitivity (%)	Additional Remarks
Saetersdal	15	5	11	12.5		Only 1st-round results
Moller	5.8	5	30	10	?	
Chart	7.3	?	39	29 ≥ stage II	91	
Lalloo	5.5	5	23	45	87	
Kollias	9.1	5	21	35	66	
Lai	5.7	34	?	32	?	MST 1,9 years
Tilanus-Linthorst	9.3	6	19	24	92	
Brekelmans	8.6	7	11	35	74	Includes *BRCA1/2* carriers

Abbreviations: MST, mean sojourn time; N+, lymph node–positive tumors; ?, unknown.
*For invasive breast cancers only.

and tumor characteristics differ from those of sporadic breast cancer patients.[30,31] Kollias et al[9] found no differences between screened and symptomatic women (matched for age and family history) with respect to invasive tumor size, grade, or lymph node stage, whereas Tilanus-Linthorst et al[21] found a more favorable tumor stage in "high-risk" women screened within a breast clinic as compared with a symptomatic group of comparable age and a positive family history. Especially with respect to lymph node status, other surveillance studies of high-risk women show a large variability, ranging from 10% to 45% node positivity (Table 7). Reasons for these varying results might be different population characteristics, such as age range and percentage of genetically susceptible women, or screening schemes and modalities (Table 6).

Although the average node-positivity rate in our study was 35%, there were differences between the three risk categories and age groups: in the groups of proven carriers and women under the age of 40 (categories that partly overlapped), 56% and 62%, respectively, already were node-positive. There are indications from other studies that breast cancer in young patients might be more aggressive than in older patients.[32,33] For instance, in a population of 136 clinically diagnosed patients from Nijmegen, 42% of the cases under the age of 50 with a tumor smaller than 1 cm already had positive lymph nodes, whereas this was 15% in patients in the age group 50 to 69.[33] It seems, therefore, that to reduce breast cancer mortality in these young women, a substantial proportion of small cancers has to be detected.

In conclusion, in *BRCA1/2* mutation carriers, the highest cancer detection rates and observed-expected ratio were found, as well as the lowest sensitivity in addition to a relatively unfavorable tumor stage at diagnosis. Especially in this group and in women under the age of 40, a more intensive screening scheme might be warranted. Alternatively, the current screening methods, such as mammography and CBE, might be insufficiently effective in preventing death of breast cancer. New technologies, such as MRI, might offer better possibilities. In several countries, including the Netherlands, studies were recently started that will evaluate the value of MRI in the early detection of breast cancer in high-risk women.[34,35]

REFERENCES

1. Fletcher SW, Black W, Harris R, et al: Report of the International Workshop on screening for breast cancer. J Natl Cancer Inst 85:1644-1656, 1993

2. Kerlikowske K, Grady D, Rubin SM, et al: Efficacy of screening mammography: A meta-analysis. JAMA 273:149-154, 1995

3. Tabar L, Fagerberg G, Cehn H-H, et al: Efficacy of breast cancer screening by age: New results from the Swedish Two-County trial. Cancer 75:2507-2517, 1995

4. Fracheboud J, de Koning HJ, Beemsterboer PMM, et al: Nationwide breast cancer screening in the Netherlands: Results of initial and subsequent screening 1990-1995. Int J Cancer 75:694-698, 1998

5. Report of the Organizing Committee and Collaborators, Falun Meeting, Sweden (21 and 22 March, 1996): Breast-cancer screening with mammography in women aged 40-49 years. Int J Cancer 68:693-699, 1996

6. Elmore JG, Barton MB, Moceri VM, et al: Ten-year risk of false positive screening mammograms and clinical breast examinations. N Engl J Med 338:1089-1096, 1998

7. Kerlikowske K, Grady D, Barclay J, et al: Positive predictive value of screening mammography by age and family history of breast cancer. JAMA 270:2444-2450, 1993

8. Saetersdal A, Dorum A, Heimdal K, et al: Inherited predisposition to breast carcinoma: Results of first round examination of 537 women at risk. Anticancer Res 16:1989-1992, 1996

9. Kollias J, Sibbering DM, Blamey RW, et al: Screening women aged less than 50 years with a family history of breast cancer. Eur J Cancer 34:878-883, 1998

10. Lalloo F, Boggis CRM, Evans DGR, et al: Screening by mammography, women with a family history of breast cancer. Eur J Cancer 34:937-940, 1998

11. Chart PL, Franssen E: Management of women at increased risk for breast cancer: Preliminary results from a new program. Can Med Assoc J 157:1235-1242, 1997

12. Visser O, Coebergh JWW, Schouten LJ, et al (eds): Incidence of Cancer in the Netherlands 1995. Utrecht, the Netherlands, 1998

13. Day NE: Estimating the sensitivity of a screening test. J Epidemiol Community Health 39:364-366, 1985

14. Brekelmans CTM, Westers P, Faber JAJ, et al: Age specific sensitivity and sojourn time in a breast cancer screening programme (DOM) in the Netherlands: A comparison of different methods. J Epidemiol Community Health 50:68-71, 1996

15. Claus EB, Risch N, Thompson WD: Autosomal dominant inheritance of early-onset breast cancer: Implications for risk prediction. Cancer 73:643-651, 1994

16. Vasen HFA, Haites NE, Evans DGR, et al: Current policies for surveillance and management in women at risk of breast and ovarian cancer: A survey among 16 European Family Cancer Clinics. Eur J Cancer 34:1922-1926, 1998

17. Brekelmans CTM: Natural history and epidemiology of interval breast cancer in the DOM screening programme. Thesis, Utrecht, 1995

18. Kerlikowske K, Grady D, Barclay J, et al: Effect of age, breast density and family history on the sensitivity of first screening mammography. JAMA 276:33-38, 1996

19. Moller P, Maehle L, Heimdal K, et al: Inherited breast carcinoma: Prospective findings in 1194 women at risk. Acta Oncol 35:7-11, 1996 (suppl 8)

20. Lai M, Yen M, Kuo H, et al: Efficacy of breast-cancer screening for female relatives of breast-cancer-index cases: Taiwan multicentre cancer screening (TAMCAS). Int J Cancer 78:21-26, 1998

21. Tilanus-Linthorst MMA, Bartels CCM, Obdeijn AIM, et al: Earlier detection of breast cancer by surveillance of women at familial risk. Eur J Cancer 36:514-519, 2000

22. Fracheboud J, de Koning HJ, Beemsterboer PMM, et al: Interval cancers in the Dutch breast cancer screening programme. Br J Cancer 81:912-917, 1999

23. Chang J, Yang WT, Choo HF: Mammography in Asian patients with BRCA1 mutations. Lancet 353:2070-2071, 1999

24. Lakhani SR, Jacquemier J, Sloane JP, et al: Multifactorial analysis of differences between sporadic breast cancers and cancers involving BRCA1 and BRCA2 mutations. J Natl Cancer Inst 90:1138-1145, 1998

25. Eisinger F, Stoppa-Lyonnet D, Longy M, et al: Germline mutation at BRCA1 affects the histoprognostic grade in hereditary breast cancer. Cancer Res 56:471-474, 1996

26. Verhoog LC, Brekelmans CTM, Seynaeve C, et al: Survival and tumour characteristics of breast-cancer patients with germline mutations of BRCA1. Lancet 351:316-321, 1998

27. Verhoog LC, Brekelmans CTM, Seynaeve C, et al: Survival in hereditary breast cancer associated with germline mutations of BRCA2. J Clin Oncol 17:3396-3402, 1999

28. Jacquemler J, Eisinger F, Guinebretiere J-M, et al: Intraductal component and BRCA1-associated breast cancer. Lancet 348:1098, 1996 (letter)

29. Day NE, Williams DRR, Khaw KT: Breast cancer screening programmes: The development of a monitoring and evaluation system. Br J Cancer 59:954-958, 1989

30. Claus EB, Risch N, Thompson WD, et al: Relationship between breast histopathology and family history of breast cancer. Cancer 71:147-153, 1993

31. Fukutomi T, Kobayashi Y, Nanasawa T, et al: A clinicopathological analysis of breast cancer in patients with a family history. Jpn J Surg 23:849-954, 1993

32. Walker RA, Lees E, Webb M'B, et al: Breast carcinomas occurring in young women (< 35 years) are different. Br J Cancer 74:1796-1800, 1996

33. Peer PGM: Screening for breast cancer in women under age 50. Thesis, Nijmegen, 1996

34. Leach M: National study of magnetic-resonance imaging to screen women at genetic risk of breast cancer. Lancet 350:6, 1997

35. Kriege M, Brekelmans CTM, Boetes C, et al: MRI screening for breast cancer in women with high familial risk. Second European Breast Cancer Conference, Brussels, Belgium, September 26-30, 2000. Eur J Cancer 36:5137, 2000 (suppl 5, abstr 467)