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European Journal of Cancer 36 (2000) 514–519

European Journal of Cancer

www.elsevier.com/locate/ejconline

Earlier detection of breast cancer by surveillance of women at familial risk

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Received 6 July 1999; received in revised form 15 October 1999; accepted 25 November 1999

Abstract

A positive family history increases the risk for breast cancer which often occurs at a much younger age than in the general population. We studied whether surveillance of these women resulted in the detection of breast cancer in an earlier stage than in symptomatic patients with a family history. Between January 1994 and April 1998, 294 women with 15–25% risk (moderate), mean age: 43.3 (22–75) years, were screened with a yearly physical examination and mammography from 5 years before the youngest age of onset in the family and 384 women with >25% risk (high) for breast cancer, mean age: 42.9 (20–74) years were screened with a physical examination every 6 months and yearly mammography. From September 1995 breast magnetic resonance imaging (MRI) was also carried out for 109 high risk women where mammography showed over 50% density. 26 breast cancers detected under surveillance were significantly more often found in an early T1N0 stage than the 24 breast cancers in patients with a family history referred in that period because of symptoms: 81 versus 46% ($P=0.018$). Patients under surveillance were also less frequently node-positive than the symptomatic group: 19 versus 42% ($P=0.12$). 20 patients with a family history referred by our national screening programme in that period had 21 breast cancers detected, 81% in stage T1N0 and 5% node-positive, which was comparable to the results in our national screening programme T1N0 66%, N+ 24% resulting in a 30% reduction in mortality. The incidence in women under surveillance was 10.1 per 1000 in the 'high' risk group and 13.3 per 1000 in the 'moderate' risk group. Expected incidence in an average risk population aged 40–50 years is 1.5, expected if the group consisted of only gene carriers 15 per 1000. 23% of the breast cancers in the surveillance group were detected at physical examination, but occult at mammography. 38% were detected at mammography and clinically occult. Breast MRI (in the subgroup) detected 3 occult breast cancers. The results of this study show that women with a family history benefit from surveillance as breast cancer was detected significantly more often in a favourable T1N0 stage and a mortality reduction comparable to that obtained in our national screening programme may be expected also in women <50 years of age. Both physical examination and mammography contribute to this result, but the former in this study only contributed in women before menopause. Starting surveillance some years before the youngest age of onset in the family may result in higher detection rates. Screening with MRI can detect breast cancers, still occult at physical examination and mammography.

Keywords: Breast cancer; Screening; Familial risk; Early detection; Surveillance; MRI

1. Introduction

Women with a strong family history of breast cancer not only run a high risk of developing this malignancy, but their risk also increases at a much younger age than in the general population [1]. Highly penetrant mutations in genes like *BRCA1* and *BRCA2* can be detected in women with these family histories and cause approximately 5% of all breast cancers [2]. In carriers of a *BRCA1* mutation, the risk for breast cancer rises sharply from 3% at 30 years of age to 50% at 50 years [2,3]. In *BRCA2* mutation carriers the risk profile develops later [4].

40–80% of healthy women, who after a presymptomatic DNA test appeared to be carriers of *BRCA1* or *2* mutations causing breast cancer in their family, chose primarily surveillance and not (at least for the time being) preventive mastectomy [5,6]. The increased risk of women with a family history is often not attributable to *BRCA1* and *BRCA2* mutations and these women also chose to continue surveillance [7].

In The Netherlands, women with an estimated risk of breast cancer over 25% based on their family history are recommended surveillance with monthly breast

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0959-8049/00/$ - see front matter
PII: S0959-8049(99)00337-8

self examination (BSE), semi-annual examination by a physician (PE) and yearly mammography from 25 years onwards [8]. However, there are not yet sufficient data to prove the effectiveness of surveillance from this age. In this study, we investigated the value of surveillance in patients with a family history. Our central question was whether breast cancer was detected at an earlier stage in patients under surveillance than in patients with a family history, referred because of symptoms of disease.

We also compared the stage of breast cancer of the patients under surveillance with the stage of breast cancers detected during national screening for 50–75 year old women. In this last group, the survival gain and cost–benefit analysis is known.

2. Patients and methods

In this study, we included the group of consecutive women who visited the outpatient breast clinic of the Rotterdam Cancer Centre between January 1994 and April 1998 with a family history of breast cancer. Some of these women were registered together with the patients of the Rotterdam Family Cancer Clinic in the Rotterdam/Leiden genetic working group. We included in this study only the group of women under surveillance at the breast clinic, as this group can be compared with the consecutive group of women referred to this clinic during the same time period because of symptoms or because of an abnormality detected at the national screening programme. Women were considered under surveillance, if they consented with the proposed surveillance scheme and no breast cancer was detected at clinical examination nor at two view mammography during the first visit. Risk estimation was performed by two breast clinic doctors or by the geneticist using the tables of Houlston and Claus [9,10]. Risk estimates were higher, with an increasing rate of affected relatives, decreasing age of onset in the relatives and/or one or more cases of ovarian cancer. A woman was considered at moderate risk, with for instance, 1 affected first degree relative or 2 second degree relatives < 50 years of age. High risk estimates were made for instance for patients with 2 first degree relatives < 50 years of age with breast cancer; 1 or more first degree relatives with breast cancer plus 1 or more with ovarian cancer. According to the estimated risk two surveillance schemes were proposed.

294 women under surveillance with moderate risk (15–25%) got instructions on carrying out a monthly BSE and were scheduled for a yearly physical examination and mammography, starting 5 years before the age at which the youngest family member had got breast cancer (age of onset).

384 women under surveillance with high risk ($> 25\%$) were scheduled for surveillance according to the national guidelines. From September 1995 onwards breast MRI in addition to normal surveillance was performed in women with high risk and over 50% density at mammography ($n = 109$).

We investigated and compared the stage in which breast cancers were detected in three groups of patients all with a positive family history:

Group 1: Patients who developed breast cancer whilst under surveillance because of their family history ($n = 26$). The surveillance group.

Group 2: Patients with breast cancer, referred by the general practitioner in the same period because of symptoms of their disease who appeared to have a positive family history ($n = 24$). The symptomatic group. Patients could be referred because of a palpable mass, skin or nipple retraction, nipple discharge, inflammatory breast disease or pain.

Group 3: Patients detected at the national screening programme and referred to our clinic in that period who appeared to have a positive family history ($n = 20$). The screening group.

We also evaluated the contribution of BSE, physical examination, mammography and fine needle aspiration cytology (FNAC). Statistical differences in stage between groups were analysed using the two-sided Fisher's exact tests.

2.1. Technique

Mammography was performed on a General Electric Senographe 600T unit (Milwaukee, USA), focus 0.3 mm and Kodak screens (min RE). Standard oblique and craniocaudal projections were obtained during the first visit and alternated thereafter with mediolateral oblique projections only. There was dual reading of all mammograms by experienced radiologists. For ultrasound an Acuson 128XP/10 (ART) system with a 7.5 mHz linear array transducer was used. Breast MRI examination was performed with a 1.5 Tesla magnetic resonance imaging system (Vision, Siemens, Erlangen, Germany).

3. Results

From January 1994 to April 1998, 384 women were under surveillance because of their family history with an estimated risk for breast cancer over 25% (high), mean age 42.9 (20–74) years in April 1998. We screened 200 women in 1994; 228 in 1995; 284 in 1996; 372 in 1997; 105 women in 1998 until April. In total in this period in this group 1189 women years at risk.

294 women with an estimated risk between 15 to 25% (moderate), mean age 43.3 (22–75) years in April 1998, were under yearly control. 184 women in 1994; 226 in 1995; 274 in 1996; 286 in 1997; 80 women in 1998 until April. In total in this period in this group 1050 women

years at risk. In 26 of these women under surveillance, breast cancer was detected during follow-up (surveillance group). 12 were at high risk (H) and 14 moderate (M). 13 were $\leqslant 50$ years of age and 4 >70 years of age. In the same period breast cancer was detected in 198 patients referred with symptoms to our department. 24 had a family history (symptomatic group). 11 were at high risk (1 *BRCA1* carrier) and 13 moderate.

Of the 111 women referred by the national screening programme with breast cancer in that period, 20 had a family history (screened group). One patient had a bilateral carcinoma. 4 patients were at high risk and 16 moderate.

3.1. Characteristics of the patients and the means of detection

Characteristics of the patients and means of detection in the 3 groups are summarised in Table 1. The mean age of the patients in the surveillance and symptomatic group was lower than in the screened group, 52 (27–86), 52 (31–86) versus 58 (49–69) years of age.

Cancers were more often palpable in symptomatic patients (18; 75%) than in the patients under surveillance (13; 50%). Other signs of malignancy at physical examination were: one nipple retraction in the surveillance group; two nipple retractions and one inflammatory breast cancer in the symptomatic group; three cases of dimpling of the skin in the screening group. 2 of the patients under surveillance at moderate risk, both 51 years old, presented in the interval between two screens with a palpable tumour detected at BSE, which proved to be T1cN0 and T1cN1 breast cancer. 4 other patients noticed the tumour themselves at BSE, but did not come earlier. Breast cancer was detected clinically but not suspected at mammography in 6 (23%) women under surveillance and 5 (21%) symptomatic women. These tumours were suspicious at ultrasound guided FNAC in 3 women. FNAC on palpation was suspicious in the other 8.

Table 1
Means of detection of cancer in the three groups

	Surveillance ($n=26$)	Symptomatic ($n=24$)	Screening ($n=20$) (21 cancers)
Mean age (range) years	52 (27–86)	52 (31–86)	58 (49–69)
	n (%)	*n* (%)	*n* (%)
Palpable tumour	13 (50)	18 (75)	15 (71)
Mammography malignant/ suspicious	16 (62)	18 (75)	21 (100)
Detect MRI[a]	3 (11)	1 (4)	
FNAC malignant/ suspicious[b]	18/20 (90)	18/22 (81)	14/16 (87)

[a] In subgroup only.
[b] Per cent malignant/suspicious of performed cytologies. FNAC, fine needle aspiration cytology.

Mammography results were considered malignant in more symptomatic patients (75%) than in patients under surveillance (62%). Malignancy was detected at mammography and clinically occult in 10 (38%) patients under surveillance and 1 (4%) symptomatic patient. In 2 of the 10 clinical occult patients under surveillance the mammographic abnormality was not classified as malignant, but proved to be so at ultrasound guided FNAC (Table 2).

MRI detected three breast cancers, occult at mammography and without a new palpable tumour in the surveillance group, but 1 patient showed nipple retraction at PE. In 1 symptomatic patient breast MRI was performed because of axillary metastasis, of a clinically and mammographically occult breast tumour and MRI showed the primary breast cancer. Thereafter these malignancies could be recognised at ultrasound and proven by ultrasound guided FNAC.

3.2. Stage at detection

Table 3 shows the stage of the cancers in the three groups. In the surveillance group, patients were 81 versus 46% significantly more often detected in a favourable T1N0 stage ($P=0.018$) than in the symptomatic group. Patients under surveillance were also more often node negative compared with the symptomatic group, 81–54% ($P=0.12$).

Tumour stage in the patients under surveillance was comparable to the results in our national screening with T1No 81 versus 66% at the national screens and N+ in the invasive cancers 24% (5/21) versus 24% [11]. Tumour stage in our screened group was not significantly different from the surveillance group.

Table 2
Stage and means of detection in the surveillance group according to age ($n=26$)

	$\leqslant 50$ years	>50 years
PE+ Ma+	3 T1cN0 34[a], 47, 50 years	1 T1aN0 65 years 2 T1cN0 51[b], 61 years 2 T1b+c N1 51[b], 61 years
PE+ Ma−	2 Tis 39, 48[a] years 1 T1bN0 36[a] years 1 T2N1 27[a] years	1 T2N1 51 years
PE− Ma+	1 Tis 37 years 3 T1a+bN0 32,[c] 46, 50 years	2 Tis 70, 78 years 2 T1a+bN0 75, 78[c] years 1 T1cN0 72 years 1 T1bN1 55 years
MRI+ Ma−	2 T1b+cN0 29, 42 years	1 T1bN0 53 years (nipple retraction, PE+)

PE, physical examination; Ma, mammography; MRI, magnetic resonance imaging; FNAC, fine needle aspiration cytology; Underlined $>$T1n0.
[a] Noticed at Breast Self Examination (BSE).
[b] Noticed at BSE and came at interval.
[c] Tumour noticed at mammography, but no malignant classification proven at ultrasound guided FNAC.

Table 3
Stage of detection of breast cancer in the three groups

	Surveillance (H) $n=26$	Symptomatic (H) $n=24$	Screening (H) $n=21$[a]
Tis	5 (3)	5 (1+1 *BRCA1*)	3
T1a+bNo	9 (2)	3 (1)	9 (3)
T1c No	7 (5)	3 (1)	5
T2-3 No		2 (1)	3 (1)
T1 N1	3 (1)	3 (2)	
T2-3 N1-2	2 (1)	5 (4)	1
Tx N1		1	
T2 Nx		1	
T4 M1		1	
	n (%)		
Tis-1 No	21 (81)	11 (46)	17 (81)
P0.018			
Tis1a+bNo	14 (54)	8 (33)	12 (57)
N+	5 (19)	10 (42)	1 (5)
P0.12			

H, women at high risk.
[a] In the screened group are 20 patients with 21 cancers.

Table 2 shows the stage of the cancers and means of detection in the surveillance group for patients $\leqslant 50$ years and >50 years. The stage of detection in the 13 patients $\leqslant 50$ years of age was at least as favourable as in the total surveillance group. Of the surveillance patients >50 years of age, 4 were above the age for national screening, with their tumours detected in an early stage primarily by mammography. PE contributed substantially in patients $\leqslant 50$ years of age whilst in only 2 patients >50 years of age the malignancy was occult at mammography. In a 51 year old patient the tumour was detected at PE in a late stage. In a patient of 53 years of age the tumour was visible at MRI, whilst there was slight nipple retraction at PE.

4. Discussion

This study showed that in patients under surveillance significantly more breast cancers are detected in a favourable Tis-1 N0 stage than in symptomatic patients with a family history. In the patients under surveillance $\leqslant 50$ years of age detection was at least as often early as in the patients over 50 years of age. For the evaluation of breast cancer screening programmes, the percentage Tis-1-N0 cancers is considered a good predictor of mortality [12–14]. At this stage we can expect an 80–87% (dependent on tumour grade) 15 year survival rate compared with 83% survival of age-matched females in the general population [14]. In the 54% of patients detected in stage $\leqslant$T1a-bN0 under surveillance, we can even expect a 7 year survival rate of 96% [15].

Disease free and overall survival in patients with *BRCA1* or *2* mutations or hereditary cancer does not differ significantly from survival in sporadic patients in most studies [16–19]. This makes the effort to detect breast cancer at an early stage worthwhile in these patients.

Our study showed no differences apart from MRI in means and stage of detection between women at high or at moderate risk in the three groups. In the surveillance group, 6 of the 13 palpable tumours were noticed at BSE, but only 2 of these women came during the interval despite strong encouragement for women to do so at any possible suspect clinical sign. We could not demonstrate earlier detection by BSE in patients under surveillance in this study. Coebergh and colleagues demonstrated an earlier stage of breast cancer detection in the general population in the last decades due to better awareness of women of suspect clinical signs or less hesitation to visit a physician [20]. Because of this we give instructions to all women pre- and postmenopausal on BSE and indeed often see symptomatic patients who detect very small tumours.

The 23% clinically detected mammographically occult tumours in the surveillance group were suspicious at ultrasound guided FNAC or at FNAC on palpation. This underlines the necessity of FNAC in all palpable tumours. Physical examination, if followed by the right consequences, seems a useful addition to mammography certainly in the surveillance of premenopausal high risk women. However, PE hardly contributed to early detection in patients >55 years under surveillance. Menopause seems a better indicator for the effectiveness of PE than a fixed age (for instance $\leqslant 50$ years of age). In our mostly postmenopausal patients detected at the national screening programme 71% had a clinically manifest tumour. Their tumour stage was as good as in the surveillance group. Screening with only BSE and mammography 2-yearly may also be sufficient after menopause in women with a family history, although the percentage of women at high risk was too small to draw such a conclusion in this study.

Malignancies were detected at mammography exclusively in 38% during surveillance and in 4% of symptomatic patients. In young women >25 years of age mammography is of great value in our experience. This has also been described by Liberman in the screening of women of 35–39 years old [21]. Even in young women mammography is the most sensitive examination for the detection of *in situ* carcinoma. In only 28% (109/384) of our screened women at high risk did mammography results show $>50\%$ dense breast tissue which is likely limiting its sensitivity. Both Feig and Brekelmans showed that in premenopausal women mammography should be performed yearly, not 2-yearly, to prevent too high (50%) a rate of carcinomas developing during the intervening time period [22,23]. They explained this by

faster growth rate of tumours occurring in patients at a younger age.

MRI detected three breast cancers in T1N0 stage during surveillance which were in two cases clinically occult and all mammographically occult. In the 109 women screened with MRI, no carcinomas were detected by palpation or mammography even 1 year after closing this study.

4.1. Results of surveillance

In our high risk group the detection rate was 10.1 per 1000 person-years; expected rate in an average risk population aged 40–50 years is 1.5 per 1000. If this group had consisted only of gene carriers a breast cancer incidence of 15 per 1000 would have been expected (2% per year between 25–50 years of age and 1% per year between 50–75 years of age). The risk estimation in our group seems realistic. Screening women at familial risk with physical examination and yearly mammography was shown to be effective and seems worthwhile in women before menopause, when this incidence can be expected.

In our moderate risk group the detection rate was 13.3 per 1000 person-years. Our risk estimation may have been somewhat low. The explanation of the higher incidence could also be explained by the fact that we screened this group only from 5 years younger than the youngest age of onset of cancer in the family. Maybe we should also start surveillance closer to the youngest age of onset in women at high risk.

The stage of tumours detected in women with a family history during the national screening programme, was as good as those amongst the younger patients of the surveillance group. For postmenopausal women at moderate risk the national screening scheme with only mammography 2-yearly together with BSE may be sufficient.

Between October 1988 and December 1995 Kollias and colleagues (1998) screened 1371 women under 50 years of age with a family history with an annual clinical examination and 2-yearly mammography [24]. Their incidence rate was 3.3 per 1000 visits. They detected a higher proportion of DCIS in the family history surveillance group compared with an age-matched symptomatic group; 21 versus 4%, but no differences for invasive tumour size or lymph node stage. This difference compared with our study could be due to the interval of the screening mammography in premenopausal women; 2-yearly versus yearly in our study.

Between September 1992 and May 1997 Lalloo and colleagues screened 1259 women under 50 years of age who had a 4-fold increased risk with annual breast examination and mammography. They detected 9 incident + interval cancers, with an incident rate of 4.8 per 1000. The stage of detection was 1 LCIS, T1 7 out of 9, node-positive 4 out of 9 and 2 where the nodal status was unknown [25].

Multicentre trials have started in Great Britain, Germany and The Netherlands to determine the cost effectiveness of screening woman at high risk with different surveillance schemes.

5. Conclusion

In this study we demonstrated a significant earlier detection of breast cancer in women at increased risk under surveillance compared with symptomatic patients. The stage of detection was as favourable in the patients $\leqslant 50$ years of age under surveillance as in the >50 years of age patient group. The incidence in the high risk group was seven times the incidence in an average risk population (40–50 years of age). Both physical examination and mammography made an important contribution to this result in patients <55 years of age. Physical examination made no contribution in postmenopausal women with a family history. Screening with MRI can detect tumours occult at PE and mammography.

Acknowledgements

We thank Cecile T.M. Brekelmans (epidemiologist) for statistical analysis and advice, Leon Verhoog for his advice, Ada van Eekelen for data management and Marijke Westerhout-Kersten.

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