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Dutch digital breast cancer screening: implications for breast cancer care

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Background: In comparison to other European population-based breast cancer screening programmes, the Dutch programme has a low referral rate, similar breast cancer detection and a high breast cancer mortality reduction. The referral rate in the Netherlands has increased over time and is expected to rise further, mainly following nationwide introduction of digital mammography, completed in 2010. This study explores the consequences of the introduction of digital mammography on the balance between referral rate, detection of breast cancer, diagnostic work-up and associated costs. **Methods:** Detailed information on diagnostic work-up (chart review) was obtained from referred women ($n = 988$) in 2000–06 (100% analogue mammography) and 2007 (75% digital mammography) in Nijmegen, the Netherlands. **Results:** The average referral rate increased from 15 (2000–06) to 34 (2007) per 1000 women screened. The number of breast cancers detected increased from 5.5 to 7.8 per 1000 screens, whereas the positive predictive value fell from 37% to 23%. A sharp rise in diagnostic work-up procedures and total diagnostic costs was seen. On the other hand, costs of a single work-up slightly decreased, as less surgical biopsies were performed. **Conclusion:** Our study shows that a low referral rate in combination with the introduction of digital mammography affects the balance between referral rate and detection rate and can substantially influence breast cancer care and associated costs. Referral rates in the Netherlands are now more comparable to other countries. This effect is therefore of value in countries where implementation of digital breast cancer screening has just started or is still under discussion.

Introduction

In the last decades, several European countries have implemented a population-based mammography screening programme for breast cancer.[1] Early detection of breast cancer through mammographic screening combined with adequate treatment is at present the most effective strategy for reducing mortality from this disease.[2–4] With 14 553 new cases and 3357 deaths in 2008,[5,6] breast cancer is the most common cancer in women in the Netherlands. The Dutch screening programme has played an important role in the reduction of breast cancer mortality with a 28.7% reduction in 2007 compared to the starting point in 1986–88.[7]

There is a substantial variation in performance measures among individual breast cancer screening programmes in European countries and those in the USA.[1,8–10] The referral rate in the Netherlands is still among the lowest in Europe but slowly reaching the European - average.[1,8–10] In contrast, the number of breast cancers detected is comparable[10] and the breast cancer mortality reduction is among the highest.[9,11]

The referral rate is one of the standard performance measures and is defined as the percentage of screening mammograms that requires women to undergo further diagnostic work-up.[1,10] A too low referral rate will potentially result in late detected cancers.[10,12] An adverse consequence of a too high referral rate is the large number of women with a false positive mammogram. This results in unnecessary diagnostic imaging, extra cost and potentially fear and anxiety.[8,13,14]

A study by Otten *et al.*[12] in Nijmegen determined the effect of referral rate on the detection of breast cancer. Results of this study confirmed that more breast cancers could be detected by lowering the threshold of referral for more subtle mammographic abnormalities. Consequently, given that preliminary findings of the study by Otten *et al.* became available early 2000, the National Expert and Training Centre for Breast Cancer Screening (NETCB) recommended raising the referral rate from 9 to 20 per 1000. Since then, we have already observed a nationwide increase in referrals from 9 per 1000 screened women in the year 2000 to 18 per 1000 in 2007.[7] This change in policy has already resulted in approximately 8000 additional referrals per year.[7,12]

An additional factor that has influenced the referral rate over and above the recommended increase by the NETCB has been the introduction of digital mammography in the screening programme, completed in 2010. Digital mammography allows the image to be manipulated and increases the contrast in dense areas of the breast.[15] Other advantages are a better (early) cancer detection, computer-aided diagnosis and an improvement in workflow.[16] One of the Dutch pilot studies that reported on the consequences of the transition from film-screen mammography to digital mammography showed an increased in referrals from 13 to 22 per 1000.[17]

The aim of this study is to determine the effects of the introduction of digital mammography and, consequently, the effects of the changing referral pattern on the number, type and costs of diagnostic hospital procedures for women diagnosed with breast cancer and women

without breast cancer. This information is not yet routinely collected within the national screening programme; therefore, we used data from the well-documented Nijmegen screening programme.[18] The transition from film-screen to digital mammography in Nijmegen occurred in 2007–08. In other European countries, implementation of digital screening has also been shown to influence the referral rates.[19–24] Given the fact that referral rates in the Netherlands are now more comparable to other countries, this effect is of interest to European readers in countries where the implementation of digital screening has just started or is being discussed.

Methods

Screening setting and study population

The Dutch breast cancer screening programme has been evaluated annually since the start of the programme. The diagnosis is considered part of the screening outcome and referred women are monitored with respect to final diagnosis, staging, treatment and long-term outcome. False negatives are identified by linking the screening registry to the cancer registry. However, since assessment is not considered part of the screening programme, there is no detailed information from the hospitals on the specific work-up of referred women in terms of possibly different assessment procedures and costs. The Nijmegen screening programme is part of the Dutch national screening programme. Details on both the national programme and the Nijmegen programme have been described previously.[18,25,26] In short, women aged 50–75 years are invited for a screening examination every two years. Two-view (mediolateral oblique and craniocaudal) mammography is used at initial screens; at subsequent screens, a mediolateral oblique view is standard. Additional craniocaudal views are performed only on indication, for example, in the case of architectural distortion, new or increased asymmetry, no previous screening examination available for comparison and referral in the previous screening round. This is decided by the radiographer at the time of screening. At present, an additional view is performed at 50% of all subsequent screens. The mammograms are independently read by two certified screening radiologists who must reach consensus about referral for further diagnostic assessment. If consensus is not reached, a third reader will decide.

All screening radiologists in the Netherlands complete a dedicated education and training programme of several weeks. After finishing this training programme, they all read more than the minimum required number of 3000 screening mammograms a year (on average, a Dutch screening radiologist reads 12 000 screening mammograms a year). Before the start of digital screening, all screening radiologists completed an additional training course to make them aware of the potential impact on referral rates. This course was developed taking full advantage of our experiences in one of the Dutch digital pilots.[17,27] In the Netherlands, there is a continuous system of feedback to screening radiologists. The outcomes of all women referred and interval carcinomas detected are regularly evaluated. Also, the screening radiologists work in a Dutch hospital as a clinical radiologist where they assess the referred women in their daily work. There were no major changes in the number of screening radiologists between 2000 and 2007 in the region of Nijmegen.

This study included all women living in Nijmegen who were referred to hospital on the basis of a positive screening mammography in the period 2000–07 ($n = 988$). The Nijmegen screening programme used film-screen mammography in the period 2000–06; the transition from film-screen to digital mammography in the Nijmegen screening programme occurred in 2007–08. In 2007, circa 75% of the women were screened using digital mammography. Data on screening examinations, referrals, diagnostic procedures undertaken after referral, surgical procedures and final diagnosis were collected from patient records (chart review). Initial screens and subsequent screens are reported separately because of expected differences in detection and referral rates. An initial screen is the first screening examination of an individual woman in the screening programme. All screening examinations following the first screening examination are subsequent screens. Two women were excluded from the study population due to missing data.

Table 1 Reimbursement rates and cost price (€) of diagnostic procedures upon referral in the Netherlands (2000 and 2007)

Diagnostic procedure[a]	Costs 2000 (€)[b]	Costs 2007 (€)[b]
Mammography	68	79
Ultrasound	64	74
Cytology or histology procedure	128	152
MRI	174	206
Open surgical biopsy	1041	1166
Multidisciplinary breast cancer team[c]	238	273

a: Reimbursement rates according to the Dutch Health Care Authority (NZA).[30]
b: Cost per procedure, using the consumer price index for indexation.
c: Cost price, including hospital costs and surgical consultation.[31]

Diagnostic work-up upon referral

All women with a positive screening mammography are referred to the multidisciplinary breast cancer team via their GP, and further assessment is performed in either of two hospitals (one academic and one general). Only occasionally do women not follow their GP's advice or seek the help of a hospital outside the region. The breast cancer team consists of a radiologist, surgical oncologist, pathologist, radiation oncologist, internal oncologist and a nurse practitioner or a mamma care nurse.[28] The diagnostic work-up may include a physical examination, mammography of both breasts (including local compression or magnification views if required), ultrasound, magnetic resonance imaging, cytology (percutaneous fine-needle biopsy), histology (core biopsy) and open surgical biopsy (only if the diagnosis could not be determined after repeated biopsy procedures).[28,29]

Costs

The reimbursement rates of diagnostic work-up upon referral are defined by the Dutch Healthcare Authority[30] (Table 1). Reimbursement rates include hospital costs and consultations with medical specialists. All women visit the multidisciplinary breast cancer team, so these visits are also included in the definition of the cost price.[31] We indexed the reimbursement rates and cost prices using the consumer price index from Statistics Netherlands.[6] Costs associated with the screening programme are not included in this study.

Results

Screening outcomes

A total number of 77 969 screening invitations and 57 874 screening examinations were registered in Nijmegen during the period 2000–07; 8286 were initial screens and 49 588 subsequent screens (Table 2). The attendance rates increased slightly from 68% (2000) to 77% (2006). In 2007, the attendance rate was 74%. In the period 2000–06, the screening test was performed using film-screen mammography. On average, 25 per 1000 initially screened women and 13 per 1000 subsequently screened women were referred (15 per 1000 for all women). The average breast cancer detection rate was 5.5 per 1000 women screened between 2000–06, 6.1 for initial screens and 5.3 for subsequent screens. During this period, 37% of the women with a positive screening examination were diagnosed with breast cancer (positive predictive value), 24% for initial screens and 42% for subsequent screens.

After the partial implementation of digital screening in Nijmegen in 2007 (75% digital), the average referral rate went up to 34 per 1000 in that year, 69 per 1000 in initial screens and 28 per 1000 in subsequent screens. The breast cancer detection rate increased to 7.8 per 1000, 9.6 for initial screens and 7.5 for subsequent screens. This results in a decrease in

Table 2 Breast cancer screening programme in Nijmegen: screening outcomes for initial and subsequent examinations (2000–07)

Year of screening	Invitation (*n*)	Screening examination (*n*)		Attendance (%)	Referral rate (‰)			Breast cancer detection rate (‰)			Positive predictive value (%)		
		Initial	Subsequent		Initial	Subsequent	Overall	Initial[a]	Subsequent	Overall	Initial	Subsequent	Overall
2000	9486	1313	5202	68	25	11	14	10.7	5.4	6.4	42	48	46
2001	9959	767	6443	72	18	7	9	1.3	5.0	4.6	7	67	53
2002	9101	1273	5431	74	12	9	9	6.3	4.8	5.1	53	54	54
2003	10 426	729	7005	74	18	15	16	5.5	5.4	5.4	31	35	35
2004	9459	1326	5853	76	41	19	23	6.0	5.6	5.7	15	29	24
2005	9243	685	6297	76	26	13	14	7.3	4.6	4.9	28	37	35
2006	10 603	1252	6949	77	32	14	17	4.0	6.5	6.1	13	45	36
Total	**68 277**	**7345**	**43 180**	74	**25**	**13**	**15**	**6.1**	**5.3**	**5.5**	**24**	**42**	**37**
Introduction of digital screening mammography in 2007 (75% digital mammography)													
2007	9692	941	6408	76	69	28	34	9.6	7.5	7.8	14	26	23

a: Small numbers.

positive predictive value to 23%, 14% for initial screens and 26% for subsequent screens.

Diagnostic work-up upon referral: absolute and relative numbers

A total of 91 women were referred in 2000 versus 247 in 2007 (Table 3). We found an increase in true positive referrals of 36%: 42 women were diagnosed with breast cancer in 2000 and 47 women in 2007. In the same period, we found an increase of 288% in false positive referrals: 49 women in 2000 versus 190 women in 2007 had no breast cancer.

The total number of diagnostic work-up procedures performed in the Nijmegen hospitals increased from 250 to 614 during the study period. The number of procedures rose from 125 to 188 among true positive referrals and from 125 to 426 among false positive referrals. Mammography and ultrasound were performed in almost all cases (true and false positives). The number of mammograms increased by 168% for all referred women, with an increase of 33% among women with breast cancer and 284% among women with no breast cancer. We found similar results regarding ultrasound. The number of cytology and histology procedures performed for all referred women increased by 36% and 400%, respectively. This is especially the case among false positive referrals for whom an increase of cytology (43%) and histology (500%) was observed. In 2007, 61% of all women classified with a false positive screening mammography only received a clinical mammography and/or ultrasound; this was 39% in 2000.

Per 100 referred women, the number of biopsy procedures (histology and cytology) procedures declined from 61 to 51; an increase was seen among the true positives (from 81 to 104 per 100 referrals) and a decrease among the false positives (from 45 to 36). Similar results were obtained for MRI. Surgical biopsies, however, were performed less frequently in both true and false positives; rates strongly declined from 16 to 3 procedures per 100 referrals.

Despite the increase in absolute numbers, the number of procedures performed per 100 referrals declined from 273 in 2000 to 248 in 2007, with an increase among true positives from 297 to 331 per 100, and a decrease among false positives from 255 to 223 per 100.

Costs

During the study period, the total costs of the diagnostic work-up for all referrals more than doubled from €53 241 in 2000 to €134 241 in 2007 (Table 4). The total costs for true positive referrals rose from €24 884 to €37 841. The total costs for false positive referrals however more than tripled (from €28 357 to €96 400). The average cost of diagnostic work-up per woman referred is €585 (2000) and €543 (2007). The cost of diagnostic work-up per woman diagnosed with breast cancer is €592 (2000) and €664 (2007). For false positive referrals, the cost per woman is €579 (2000) and €507 (2007). The cost per woman who only received imaging is €121 (2000) and €137 (2007).

Discussion

This study was designed to assess the impact of the introduction of digital mammography on the referral rate, the number of false positive referrals, breast cancers detected, diagnostic work-up procedures and costs. In Nijmegen, the average referral rate for subsequent screens between 2000 and 2006 was 13 per 1000 screened women and 28 per 1000 in 2007. The high number of referrals in 2007 is mainly a consequence of the introduction of digital mammography and has, together with the higher referral rate, resulted in a higher detection rate. The improved detection is not in proportion to the increase in referral rate. Roughly 1 in 4 referrals led to the detection of cancer, resulting in a decreased positive predictive value of 23%.

National programme

The results of the Nijmegen screening programme are consistent with those of the national screening programme and can therefore be used to calculate the impact of predicted increases in referral rate for the Netherlands in relation to the implementation of digital mammography. There were no other changes in policy during the study period. The average referral rate for subsequent screens in Nijmegen is comparable to the general referral rates in the Netherlands (13 compared to 13.8 between 2000 and 2006).[7] The results of the national screening programme show an increase in detected breast cancers among subsequently referred women from 4.2 per 1000 (2000) to 5.2 (2007).[7] Furthermore, the number of biopsies performed as a result of screening fell from 63 (2000) to 46 (2007) per 100 referred women.[7] Therefore, almost 60% of women received additional imaging only. Similar results were seen in the Nijmegen screening programme.

Resource use and cost of diagnostic work-up

A steep rise in the number and, subsequently, in absolute costs of diagnostic work-up was seen in the period after the introduction of digital mammography. The cost of a single diagnostic work-up slightly decreased, which can be partly explained by the shift from surgical biopsies to core biopsy procedures as described in the guidelines on screening and diagnosis;[28] the diagnosis should be established pre-operatively by means of histological assessment (core needle biopsy). The sharp drop in the number of surgical biopsies which require operating room facilities and anaesthesiology has had a great impact on our figures and can be placed on the positive side of the equation. A study performed by Duijm *et al.*[32] in 2000–05 showed similar results regarding the number of imaging procedures following a positive screening mammography. In their study, the number of surgical biopsies steeply declined from 34.7 to 4.6 per 100 referrals. A large increase, from 2.1 to 26.8 per 100 referrals, was noted for histology procedures, and they also recorded a decrease in costs per referral.

Table 3 Breast cancer screening programme in Nijmegen, The Netherlands: utilization of diagnostic work-up procedures (*n*) following referral (2000 and 2007)

Diagnostic follow up	Referral from 91 to 247 women (increase 171%)						Breast cancer (TP[a]) from 42 to 47 women (increase 36%)						No breast cancer (FP[a]) From 49 to 190 women (increase 288%)					
	2000		2007		Change		2000		2007		Change		2000		2007		Change	
	n[b]	per 100	*n*[b]	per 100	%	per 100	*n*[b]	per 100	*n*[b]	per 100	%	per 100	*n*[b]	per 100	*n*[b]	per 100	%	per 100
Mammography	91	100	244	99	168	−1	42	100	56	98	33	−2	49	100	188	99	284	−1
Ultrasound	83	91	207	84	149	−7	42	100	57	100	36	0	41	84	150	78	263	−6
Cytology[c]	42	46	57	23	36	−23	28	67	37	65	32	−2	14	29	20	11	43	−18
Histology[d]	14	15	70	28	400	13	6	14	22	39	267	25	8	16	48	25	500	9
MRI	5	5	28	11	460	6	1	2	14	25	1300	23	4	8	14	7	250	−1
Open surgical biopsy[e]	15	16	8	3	−47	−13	6	14	2	4	−67	−10	9	18	6	3	−33	−15
Total number of procedures	**250**	**273**	**614**	**248**	**146**	**−25**	**125**	**297**	**188**	**331**	**50**	**34**	**125**	**255**	**426**	**223**	**240**	**−32**
Breast cancer team	91	100	247	100	171	0	42	100	57	100	36	0	49	100	190	100	288	0
Imaging only	19	20	115	47	505	27							19	39	115	61	505	22

a: TP, FP, true positive and false positive screening examination, respectively.
b: Number of procedures.
c: Fine needle aspiration biopsy (FNAB) or diagnostic biopsy using ultrasound.
d: Core needle biopsy (CB). Biopsy using stereotactic guidance.
e: Local excision using general anaesthetic for PA purposes. No treatment.

Table 4 Breast cancer screening programme in Nijmegen: costs (€) for all referrals, true positive and false positive referrals (2000 and 2007)

Costs of diagnostic work-up	2000	2007
All referrals	53 241	134 241
Per referred woman	585	543
All breast cancers detected	24 884	37 841
Per breast cancer detected	592	664
All false positives	28 357	96 400
Per false positive referral	579	507
Per false positive referral, imaging only[a]	121	137

a: No visit to the multidisciplinary breast cancer team.

Several other published studies[33–35] lead to a better understanding of the economic consequences of a higher referral rate. These studies also estimated the resource use and costs associated with a diagnostic work-up for suspected breast cancer. International comparison, however, is difficult due to differences in the screening programmes. The USA, for example, has one of the highest rates for positive screening mammography (9%).[10,33] Chubak *et al.* (2010) found that 87% of the recalled women only received imaging procedures.[33] This is almost twice as high as in our study. Also, an average cost of $286 [€210, (2011 exchange rate: 1 USD = Euro 0.73)] was found for a diagnostic work-up with imaging only.[35] We calculated a rate of €121 for each diagnostic work-up. Both studies come to the same conclusion: that the costs of false positive screening mammograms are high and may be significant for a healthcare system.[33–35]

Adverse consequences

The introduction of digital screening mammography in 2007 in Nijmegen clearly caused a peak in the referral rate, surpassing the NETCB recommendation of 20 per 1000. A similar effect has previously been reported in detail for one of the Dutch digital pilots.[17,27] Experiences from this first digitization period in the Netherlands show that at first the referral rate peaked at 73 per 1000 screened women but then stabilized around 22 per 1000.[17] If the results of this study are extrapolated to a national level, we expect 6000 extra referrals per year, based on an increase from 14 000 referrals in 2006 (886 000 screening examinations) to 20 000 referrals in 2008 (918 000 screening examinations). This is likely to result in the detection of 1500 additional breast cancers (based on an estimated increase in referrals from 16 to 22 in 2006 per 1000 screened women and a PPV of 25%).[7] The total number of referrals in The Netherlands would then increase from 16 000 to 22 000[7] at an extra cost of €3.3 million per year. The incremental cost per breast cancer detected will be €2200. The total costs for additional work-up have been estimated at €12 million, which is 5% of the total budget spent on breast cancer care in the Netherlands.[36] Of this total, an estimated €8.5 million would be spent on false positive referrals only.

Conclusions

We believe that our study shows that the low referral rate in combination with the introduction of digital screening affects the balance between referral rate and detection rate and can substantially influence breast cancer care and associated costs.

On the positive side, improved detection is expected to lead to the diagnosis of an additional 1500 extra breast cancers per year possibly leading to fewer recurrent and metastatic cancers. On the negative side, due to the increase in the numbers of false positive referrals, hospitals are likely to face a considerable increase in diagnostic procedures and costs. Hospitals have been forced to cope with an increase in referrals and associated work-up. Policy makers and hospital management should be aware of these changes and review current policy. In other European countries, implementation of digital screening has also been shown to influence the referral rates.[19–24] Other European studies have also reported the impact of digital screening on referral and detection rates, but to our knowledge, this is the first study to report on implications for breast cancer care.

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Conflicts of interest: None declared.

Key points

- More women have been referred to hospital for diagnostic work-up after the implementation of digital mammography in a breast cancer screening programme. More breast cancers have

been detected, but there is a disproportionate increase in the number of women referred with no breast cancer.
- As a result, there has been an increase in the number of diagnostic procedures in hospitals. As a consequence, costs of referral have increased comparably.
- Policy makers and hospital management should consider the consequences of an increased number of women being referred to hospitals. More false positive women will be referred and the overall breast cancer care costs will increase.

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