

Reduction of Advanced Breast Cancer Stages at Subsequent Participation in Mammography Screening

Abnahme fortgeschrittener Brustkrebsstadien bei wiederholter Teilnahme am Mammografie-Screening

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Key words

- breast cancer
- population-based screening
- digital mammography
- interval cancer
- effectiveness

Zusammenfassung



Ziel: Die Abnahme fortgeschrittener Brustkrebsstadien ist der relevanteste Surrogatparameter eines Früherkennungsprogramms. Er stellt den letzten Parameter der kausalen Kaskade dar mit einem zu erwartenden Effekt auf die Brustkrebs-spezifische Mortalität. Um die Effektivität des populationsbezogenen Mammografie-Screenings zu bewerten, wurden die 2-Jahresinzidenzraten fortgeschrittener Brustkrebsstadien nach initialer und erster Folgerunden-Teilnahme analysiert.

Material und Methoden: Die Studie schließt 19563 initiale und 18034 erste Folgeuntersuchungen einer digitalen Screening-Einheit ein (2008–2010). Die Brustkrebsstadien, diagnostiziert im Programm oder im nachfolgenden zweijährigen Intervall (2-Jahresinzidenz), wurden durch das epidemiologische Krebsregister erhoben. Raten aller und kombinierter UICC-Stadien 2, 3 und 4 (fortgeschrittene Stadien) wurden für eine 2-Jahresperiode analysiert. Die Proportionen wurden auf Signifikanz durch den chi-Quadrat-Test getestet ($p < 0,001$).

Ergebnisse: Die 2-Jahresinzidenzrate aller Stadien lag bei Frauen der Folgerunde im Vergleich zur Erstrunde signifikant niedriger (0,85 vs. 1,29 pro 100 Frauen (%); $p < 0,0001$). Im Folgerunden-Screening wurde eine signifikant niedrigere 2-Jahresinzidenz fortgeschrittener Stadien im Vergleich zum Erstrunden-Screening beobachtet (0,26% vs. 0,48%; $p = 0,0007$); bei Frauen von 50 bis 59 Jahren war der Inzidenzunterschied geringer (0,21% vs. 0,35%; $p = 0,07$) als bei Frauen von 60 bis 69 Jahren (0,31% vs. 0,70%; $p = 0,0008$).

Schlussfolgerung: Im Übergang von der Prävalenz zur Inzidenzphase des Mammografie-Screenings ist eine Programmwirksamkeit anhand einer niedrigeren 2-Jahresinzidenz fortgeschrittener Brustkrebs-erkrankungen unter Folgerunden- im Vergleich zu Erstrunden-Teilnehmerinnen, insbesondere zwischen 60 und 69 Jahren, zu verzeichnen.

Abstract



Purpose: The decline in advanced breast cancer stages is presumably the most relevant surrogate parameter in mammography screening. It represents the last step in the causal cascade that is expected to affect breast cancer-related mortality. To assess the effectiveness of population-based screening, we analyzed the 2-year incidence rates of advanced breast cancers between women participating in the initial and in the first subsequent round.

Materials and Methods: The study included data from 19563 initial and 18034 subsequent examinations of one digital screening unit (2008–2010). Data on tumor stages, detected by screening or within the following interval of two years (2-year incidence), were provided by the epidemiological cancer registry. Rates of all and combined UICC stages 2, 3 and 4 (advanced stages) were reported for a two-year period. Proportions were tested for significance by using chi-square tests ($p < 0.001$).

Results: The 2-year incidence rate of all stages was significantly lower in participants in subsequent screening than in initial screening (0.85 vs. 1.29 per 100 women (%); $p < 0.0001$). A significantly lower 2-year incidence of advanced stages was observed for subsequent screening compared to initial screening (0.26% vs. 0.48%; $p = 0.0007$). Among women aged 50 to 59 years, the incidence of advanced stages was less clearly different (0.21% vs. 0.35%; $p = 0.07$) than in women aged 60 to 69 years (0.31% vs. 0.70%; $p = 0.0008$).

Conclusion: During the change from prevalent to incident phase mammography screening, a program impact is seen by a lower 2-year incidence of advanced breast cancers within subsequent compared to initial participants, predominately in women aged 60 to 69 years.

received 28.9.2015
accepted 16.10.2015

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DOI <http://dx.doi.org/10.1055/s-0041-107835>
Published online: 20.10.2015
Fortschr Röntgenstr 2016; 188: 33–37 © Georg Thieme Verlag KG Stuttgart · New York · ISSN 1438-9029

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Kernaussagen:

- ▶ Die Evaluation der Inzidenz fortgeschrittener Tumorstadien stellt den relevantesten Surrogatparameter für Brustkrebs-Früherkennungsprogramme dar.
- ▶ Erstmals wurde die 2-Jahresinzidenz fortgeschrittener Brustkrebsstadien nach Teilnahme am Folgerunden-Screening analysiert.
- ▶ Wir beobachteten einen signifikanten Einfluss des Screenings auf die 2-Jahresinzidenz fortgeschrittener Tumorstadien, vorrangig in der Altersgruppe 60 – 69 Jahre.

Key Points:

- ▶ The incidence of advanced tumor stages represents the most relevant surrogate parameter for screening effectiveness.
- ▶ For the first time the 2-year incidence of advanced breast cancer stages after subsequent mammography screening was analyzed.
- ▶ We observed a significant effect of screening on the 2-year incidence of advanced stages, predominately in the age group 60 to 69 years.

Citation Format:

- ▶ Weigel S, Heindel W, Heidrich J et al. Reduction of Advanced Breast Cancer Stages at Subsequent Participation in Mammography Screening. *Fortschr Röntgenstr* 2016; 188: 33–37

Purpose

The major aim of population-based mammography screening is the reduction of mortality from breast cancer. This can inevitably only be achieved in a long-term perspective and requires follow-up of the screened cohorts over extended periods of time [1]. As an alternative to awaiting breast cancer mortality reduction, early surrogate indicators can be identified and analyzed in their development over time [1]. Surrogate parameters that have been found to predict breast cancer mortality reduction are overall breast cancer detection rate, proportion of screen-detected cancers that are invasive, proportion of screen-detected invasive cancers ≤ 10 mm and interval cancer rate [1].

Previous reports have shown that the implementation of the mammography screening program in Germany resulted in the expected increase in breast cancer incidence rates in the target population of women aged between 50 and 69 years. Moreover, the characteristics of screen-detected breast cancers fulfilled the requirements of the European guidelines and were significantly more favorable compared to breast cancers diagnosed outside the program [2, 3]. Accordingly, interval cancer rates of the implementation phase, defined as breast cancers occurring within an interval of two years after a negative screening examination, compared favorably with those of other established European programs [4].

The ultimate concept behind mammography screening is to detect breast cancer in an early localized stage in order to prevent progression into an advanced, potentially fatal stage. Thus, effective screening should lead to a decline of advanced tumors among screened women as early as after the first screening round [1]. This decline is presumably the most relevant surrogate parameter of the influence of screening participation as it represents the last step in the causal cascade that is expected to affect mortality. To assess the reduction of advanced breast cancer, screen-detected as well as interval cancers among all participants of the mammography screening have to be identified.

Based on data for interval cancers from the initial and the first subsequent screening round, we compared for the first time in Germany the 2-year incidence rates of advanced breast cancers between women participating in the initial and in the first subsequent round of the mammography screening program.

Materials and Methods

This study included data from 19563 examinations of the initial round and 18034 examinations of the first subsequent round conducted within one screening unit. All women underwent digital

mammography screening in one screening unit. Data on tumor incidence and stages were provided by the population-based epidemiological cancer registry for screen-detected as well as interval-detected cancers (2-year incidence rate).

Screening process

The screening unit of this study is enrolled in the German mammography screening program which adheres to the European guidelines [1, 5]. The target population is defined as women aged 50 to 69 years; the screening interval is two years. All eligible female residents in the catchment area of the screening unit were invited by a personal letter offering a specific examination date. Screening mammograms were graded independently by two readers. Any suspicious abnormalities were discussed with an adjudicator to define cases for further assessment. The entire screening process, including histology of breast lesions, is documented and retrievable via dedicated screening software (MaSc; KV-IT, Dortmund and Düsseldorf, Germany) which is linked with the epidemiological cancer registry.

The screening unit in this study started operations in October 2005 with one unit that was complemented by a second unit in October 2006. During the observed screening period 2008 to 2010, digital screening examinations were obtained by both mammography units (MicroDose Mammography MDM, L30, Sectra Medical Systems, recently Philips Healthcare, The Netherlands, 54% of included examinations; Mammomat 3000 Nova, Siemens Healthcare, Germany, DirectView CR 975 EHR, General Electric, US, with DirectView CR 975, Carestream Health, Germany, 46% of included examinations). For assessment additional imaging was performed with a full-field digital mammography unit (Selenia; Hologic, US) and a dedicated breast ultrasound system (10 – 14 MHz) (Acuson S2000; Siemens Healthcare, Germany).

Data retrieval

A notification of each case of breast cancer detected during a screening examination is digitally submitted to the responsible epidemiological cancer registry. In addition, the doubly encrypted personal identifiers of each screening participant are regularly linked to the records of the cancer registry by a probabilistic linkage procedure to identify matches [4]. Interval cancers are defined as breast cancer matches occurring in women who had a negative screening mammography but developed breast cancer during the following 24 months. Screen-detected and interval-detected cancers comprised a diagnosis of ductal carcinoma in situ (DCIS) as well as invasive breast cancers [1, 4].

The screening period was chosen from January 2008 to December 2010 as it represents the fully implemented routine screen-

ing program, permits the inclusion of both, a round of initial screening examinations and a full subsequent screening round, and comprises also the identification of all interval cancers until December 2012. There were a total of 19 563 initial and 18 034 first subsequent round participants. Examinations carried out during a second subsequent screening round were not considered. We excluded cases for which the categorization according to the UICC classification was incomplete, i.e., 7 cancer cases (2.8%) in the initial screening group and 3 cancer cases (1.9%) in the subsequent screening group [6].

Statistical analysis

The age distribution of the participants in the initial and first subsequent round is described as frequency and the detection rates of the UICC stages 0 (pTis), 1 (pT1, N0, M0) and the combined stages 2, 3 and 4 (stage II+, advanced stages) are reported per 100 women screened for a two-year period, that is, summarizing cancers detected during the screening mammography plus those detected in the subsequent 24-month interval. The latter proportions were compared by chi-square tests. To account for multiple testing, a Bonferroni correction was applied and a nominal level of $p < 0.001$ was accepted as statistically significant for single comparisons.

Results

The numbers and proportions of participating women per five-year age group, separated according to initial screening and first subsequent screening round, are presented in **Table 1**. It reveals that women who attended the mammography screening

for the first time (initial round) were younger than those coming back for a follow-up screening examination, while the latter group reflected fairly well the age distribution in the target population of the state. A particularly high proportion of first-time attenders belonged to the age group 50 to 54 years (43.7%).

Overall, the breast cancer incidence rate over 2 years, composed of the screen-detected plus the interval cancers, was significantly lower in women participating in the subsequent screening round (154/18 034 = 0.85 per 100 women screened) as compared to those from the initial screening (253/19 563 = 1.29 per 100 women; $p < 0.0001$). This rate included 39 vs. 35 incident interval cancers which accounted for interval cancer rates of 0.20 per 100 women in the initial round and 0.19 per 100 women in the first subsequent round.

A significantly lower 2-year incidence of stage 0 (ductal carcinoma in situ) was seen for the subsequent screening round in comparison to the initial screening round (0.16 (29/18 034) vs. 0.27 (52/19 563) per 100 women; $p = 0.029$) in contrast to the 2-year incidence of stage 1 (0.42 (75/18 034) vs. 0.52 (101/19 563) per 100 women; $p = 0.18$).

As shown in **Table 2**, a significantly lower 2-year incidence of advanced stage breast cancer (II+) was observed for the subsequent screening round in comparison to the initial screening round (0.26 (47/18 034) vs. 0.48 (93/19 563) per 100 women; $p = 0.0007$). The rates of screen-detected advanced stage cancers were significantly lower in the subsequent screening group than in the initial screening group (0.17 (30/18 034) vs. 0.33 (64/19 563) per 100 women; $p = 0.0001$) as was the difference in advanced stage interval cancers (0.09 (17/18 034) vs. 0.15 (29/19 563) per 100 women; $p < 0.001$).

Among women aged 50 to 59 years, the 2-year incidence of advanced breast cancers was less clearly different (0.21 (20/9440) vs. 0.35 (45/12 746) per 100 women; $p = 0.07$) than in women aged 60 to 69 years (0.31 (27/8590) vs. 0.70 (48/6817) per 100 women; $p = 0.0008$ **Table 2**).

Among the stage II+ cancers, categories T3 and T4 were clearly less frequent than T1 plus N1 and T2. Notably, this was observed in both screening-detected as well as interval-detected breast cancers. Likewise, the proportion of M0 tumors rose from the initial to the subsequent screening round for both screen-detected and interval cancers (**Table 3**).

Discussion

The objective of screening for breast cancer is to reduce mortality from the disease without adversely affecting the health status of those who participate in cancer screening. The effectiveness of a

Table 1 Distribution of 5-year age groups of the state-wide target population of the mammography screening program in comparison to initial and subsequent round participants of one unit in 2008 – 2010.

Tab. 1 Verteilung der 5-Jahres-Altersgruppen der landesweiten Zielpopulation des Mammografie-Screening-Programmes im Vergleich zu Erst- und Folgerunden-Teilnehmerinnen einer Einheit.

	total	50 – 54 yrs.	55 – 59 yrs.	60 – 64 yrs.	65 – 69 yrs.
population	100 %	28.6 %	25.6 %	20.7 %	24.9 %
50 – 69 years ¹					
initial round participants	19 563 (100 %)	8528 (43.7 %)	4218 (21.6 %)	3185 (16.1 %)	3632 (18.5 %)
first subsequent round participants	18 034 (100 %)	4230 (23.5 %)	5214 (28.9 %)	4113 (22.7 %)	4477 (24.7 %)

¹ Age distribution of the official target population for December 2008.

	participating women		detection rates per 100 women: screening plus interval			detection rates stage II+ per 100 women: screening plus interval		
	initial round	first subsequent round	initial round	first subsequent round	p-values	initial round	first subsequent round	p-values
50 – 69 yrs.	19 563	18 034	1.29	0.85	0.0001	0.48	0.26	0.0007
50 – 54 yrs.	8528	4230	1.00	0.50	0.0005	0.39	0.17	0.056
55 – 59 yrs.	4218	5214	1.19	0.71	0.02	0.28	0.25	0.93
60 – 64 yrs.	3185	4113	1.54	1.00	0.0495	0.69	0.15	0.005
65 – 69 yrs.	3632	4477	1.76	1.23	0.06	0.72	0.47	0.18
50 – 59 yrs.	12 746	9444	1.06	0.61	0.0005	0.35	0.21	0.074
60 – 69 yrs.	6817	8590	1.66	1.12	0.005	0.70	0.31	0.0008

Table 2 2-year incidence rates of all breast cancer stages and of advanced breast cancer stages.

Tab. 2 2-Jahresinzidenzraten aller Brustkrebsstadien und der fortgeschrittenen Brustkrebsstadien.

stage II+	initial screening round				first subsequent screening round			
	screen- detected cancers n	screen- detected cancers %	interval- detected cancers n	interval- detected cancers %	screen- detected cancers n	screen- detected cancers %	interval- detected cancers n	interval- detected cancers %
	total	64	100.0	29	100.0	30	100.0	17
T1 (N1)	17	26.7	3	10.3	11	36.7	8	47.1
T2	34	53.1	22	75.9	17	56.7	9	52.9
T3	9	14.1	2	6.9	1	3.3	–	–
T4	4	6.3	2	6.9	1	3.3	–	–
N0	22	34.4	12	41.4	12	40.0	4	23.5
M0	55	86.0	25	86.2	28	93.3	16	94.1

Table 3 Number (n) and frequency (%) of tumor categories (T), nodal status (N) and distant metastasis (M) of advanced breast cancer cases.

Tab. 3 Anzahl (n) und Häufigkeiten (%) der Tumorkategorien (T), des Nodalstatus (N) und der Fernmetastasierung (M) fortgeschrittener Brustkrebsstadien.

program is a function of the quality of multiple individual components. Epidemiology is the fundamental guiding and unifying discipline throughout the entire process of a screening program including evaluation and assessment of impact [1].

Interval cancer rates after the first subsequent round of the mammography screening program were provided by the epidemiological cancer registry. The data now allow for the first time the evaluation of the total breast cancer incidence rates of participants of the subsequent screening round comprising screen-detected tumors as well as those identified during the subsequent two-year interval up to the next regular invitation to screening.

A prerequisite for a reduction in breast cancer mortality is a more favorable stage distribution in cancers detected among screening participants such that a decline of advanced tumors should be observed among the screened women already early after the first screening round [1]. We report here that the 2-year incidence of advanced breast cancer stages (II+) was significantly lower in the group of participants of the subsequent screening round as compared to those of the initial screening. This appeared attributable to lower rates of screen-detected cancers as well as interval-detected cancers. A subgroup analysis revealed that the effect was most prominent and statistically significant for women aged 60 to 69 years, while the difference in those aged 50 to 59 was still modest and not significant.

One recent study investigated the effect of randomized breast screening trials on the incidence of advanced stage disease and on the subsequent breast cancer death rate. In the trials that achieved a 20% or greater reduction in advanced stage disease, there was an average breast cancer mortality reduction of 28% among women invited to screening (attenders and non-attenders combined). In the trials that achieved a reduction in advanced stage disease of less than 10%, there was no reduction in breast cancer mortality among women invited to screening [7]. Another study evaluated mortality from breast cancer and reported that cancers classed as stages II-IV comprised 33% of cancers in the screening study group and 52% in the control group [8]. Within the subsequent screening group, we found regarding the 2-year incidence a proportion of advanced breast cancer stages in relation to all cancer diagnoses of 30.6% (detection rates 0.26 and 0.85 per 100 women screened).

The European guidelines suggest an epidemiological approach. For the assessment of the reduction, the advanced interval cancers from the interval after the first screening round and the advanced screen-detected cancers of the second screening round have to be summed up and compared with the background incidence rate of advanced tumors, starting after the prevalent screening [1]. State-wide evaluation according to the guidelines is a future project.

While the overall interval cancer rate between both screening rounds was comparable (subsequent vs. initial screening: 0.19 vs. 0.20 per 100 women), the interval cancer rate of advanced tumor stages was significantly lower in the subsequent screening group compared to the initial screening group (0.09 vs. 0.15 per 100 women). The subanalysis of advanced tumor stages showed that a lower 2-year incidence rate of advanced breast cancer stages was not mainly based on a reduction of large non-metastasized tumors but on a reduction of tumors diagnosed with axillary metastasis (N0: initial 34.4% vs. subsequent 40.0% of all stage II+ cancers) or distant metastasis (M0: initial 86.0% vs. subsequent 93.3% of all stage II+ cancers).

The strength of our study is that the epidemiological cancer registry was able to provide data of screen-detected cancers as well as of interval cancers including subsequent screening at an early point. Therefore, the data enabled a comparison over a screening period of three years including a further two years for interval cancer occurrence plus another two years for completeness of data submissions in the epidemiological cancer registry. The evaluation of a reduction of advanced tumor stages represents the last surrogate parameter before subsequent reduction of breast cancer-related mortality will be assessable [9]. According to a recent publication of the working group of the International Agency for Research on Cancer (IARC), mammography screening needs ongoing evaluation with respect to the benefits and adverse effects [10]. As a limitation, results from one screening unit are probably not transferable to other screening units. Data to create stages of breast cancer disease were not available for a small percentage of screen-detected cancers (2.8%) and interval cancers (1.9%), which were therefore excluded from the study and not further specified in detail. Further subsequent round screening might lead to different results. The age distribution of participants of the initial and first subsequent screening round was different, and this may influence cancer detection rates. Since the frequency of younger women was higher in the initial screening group compared to the subsequent screening group in combination with the result that the incidence of advanced breast cancer stages was lower in younger than older age groups, the different age distribution is less likely the reason for a significantly lower 2-year incidence rate of advanced stages in the subsequent screening group.

Conclusion

With new data including interval cancers after subsequent screening participation, screening effectiveness can be assessed on a higher level. During the change from the prevalent to inci-

dent phase, the impact of digital mammography screening has been shown by a lower 2-year incidence rate of advanced breast cancers in subsequent compared to initial participants, predominantly in women aged 60 to 69 years.

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