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


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 = 0,0008). 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-Erkranungen 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 19 563 initial and 18 034 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 = 0,0008). 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.
Materials and Methods

This study included data from 19 563 examinations of the initial round and 18 034 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).

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.

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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). 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.

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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

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**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.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Total</th>
<th>50 – 54 yrs.</th>
<th>55 – 59 yrs.</th>
<th>60 – 64 yrs.</th>
<th>65 – 69 yrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>100 %</td>
<td>28.6 %</td>
<td>25.6 %</td>
<td>20.7 %</td>
<td>24.9 %</td>
</tr>
<tr>
<td>Initial round participants</td>
<td>19 563</td>
<td>8528</td>
<td>4218</td>
<td>3185</td>
<td>3632</td>
</tr>
<tr>
<td>First subsequent round participants</td>
<td>18 034</td>
<td>4230</td>
<td>5214</td>
<td>4113</td>
<td>4477</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Age group</th>
<th>Initial round</th>
<th>First subsequent round</th>
<th>Detection rates per 100 women: screening plus interval</th>
<th>Detection rates stage II+ per 100 women: screening plus interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-values</td>
<td>p-values</td>
<td>p-values</td>
<td>p-values</td>
<td>p-values</td>
</tr>
<tr>
<td>-----------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>50 – 69 yrs.</td>
<td>19 563</td>
<td>18 034</td>
<td>1.29</td>
<td>0.85</td>
</tr>
<tr>
<td>50 – 54 yrs.</td>
<td>8528</td>
<td>4230</td>
<td>1.00</td>
<td>0.50</td>
</tr>
<tr>
<td>55 – 59 yrs.</td>
<td>4218</td>
<td>5214</td>
<td>1.19</td>
<td>0.71</td>
</tr>
<tr>
<td>60 – 64 yrs.</td>
<td>3185</td>
<td>4113</td>
<td>1.54</td>
<td>1.00</td>
</tr>
<tr>
<td>65 – 69 yrs.</td>
<td>3632</td>
<td>4477</td>
<td>1.76</td>
<td>1.23</td>
</tr>
<tr>
<td>50 – 59 yrs.</td>
<td>12 746</td>
<td>9444</td>
<td>1.06</td>
<td>0.61</td>
</tr>
<tr>
<td>60 – 69 yrs.</td>
<td>6817</td>
<td>8590</td>
<td>1.66</td>
<td>1.12</td>
</tr>
</tbody>
</table>

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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 classified 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 where 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-

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<table>
<thead>
<tr>
<th>stage II+</th>
<th>initial screening round</th>
<th>first subsequent screening round</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>screen-detected cancers</td>
<td>screen-detected cancers</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>total</td>
<td>64</td>
<td>100.0</td>
</tr>
<tr>
<td>T1 (N1)</td>
<td>17</td>
<td>26.7</td>
</tr>
<tr>
<td>T2</td>
<td>34</td>
<td>53.1</td>
</tr>
<tr>
<td>T3</td>
<td>9</td>
<td>14.1</td>
</tr>
<tr>
<td>T4</td>
<td>4</td>
<td>6.3</td>
</tr>
<tr>
<td>N0</td>
<td>22</td>
<td>34.4</td>
</tr>
<tr>
<td>M0</td>
<td>55</td>
<td>86.0</td>
</tr>
</tbody>
</table>

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Tab. 3 Anzahl (n) und Häufigkeiten (%) der Tumorkategorien (T), des Nodalstatus (N) und der Fernmetastasierung (M) fortgeschrittener Brustkrebsstadien.
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, predominately in women aged 60 to 69 years.

References

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