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Increased detection of relevant breast cancers with DBT in mammography screening?

Gesteigerte Entdeckung relevanter Mammakarzinome durch DBT im Mammografie-Screening?

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Bibliography

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ABSTRACT

Introduction Screening with digital breast tomosynthesis plus synthetic mammography (DBT+SM) increases invasive breast cancer detection compared to digital mammography (DM). Since a reduction in breast cancer mortality is largely based on the detection of histological grade 2 or 3 breast cancers, a comparison of the detection rates of invasive breast cancers (iCDR), independent of the stage, of grades 2 or 3, was carried out, taking into account breast density, after screening with DBT+SM vs. DM.

Material and Methods The 1:1 randomized, multicenter TOSYMA study recruited participants from 7/2018 to 12/2020 in the German Mammography Screening Program. This explorative subanalysis included 49 479 participants in the DBT+SM arm and 49 689 participants in the DM arm, with complete documentation including visual density categorization (A/B: non-dense parenchyma, C/D: dense parenchyma).

Results The iCDR of grade 2 or 3 was 5.1 per 1000 women screened with DBT+SM vs. 3.6 ‰ screened with DM (difference +1.5 ‰). In the case of non-dense parenchyma, the corresponding DBT+SM rate was 4.5 ‰ (difference to DM + 1.3 ‰), and in dense parenchyma it was 5.7 ‰ (difference to DM + 1.7 ‰).

The iCDR of grade 1 was 2.1 ‰ with DBT+SM (difference to DM + 0.8 ‰). In non-dense parenchyma, the corresponding DBT+SM rate was 1.7 ‰ (difference to DM + 0.7 ‰), in dense parenchyma it was 2.6 ‰ (difference to DM + 1.0 ‰).

Conclusion When screening with DBT+SM, invasive breast cancer detection rates of grade 2 or 3 tumors are higher than with DM. Detection rates and their differences are also higher in women with dense than non-dense parenchyma. These detection rates and their differences are consistently higher for DBT+SM and DM than those for grade 1 cancers. The explorative analyses of this large, randomized trial indicate that DBT+SM screening increases the detection of prognostically more relevant breast cancers.

ZUSAMMENFASSUNG

Einleitung Screening mit digitaler Brust-Tomosynthese plus synthetischer Mammografie (DBT+SM) steigert im Vergleich zur digitalen Mammografie (DM) die Entdeckung invasiver Mammakarzinome. Da eine Senkung der Brustkrebssterblichkeit wesentlich auf der Detektion von Mammakarzinomen der histologischen Grade 2 oder 3 beruht, wurde ein Vergleich der Detektionsraten invasiver Mammakarzinome (iCDR) stadien-

unabhängig von den Graden 2 oder 3, unter Berücksichtigung der Brustdichte, nach Screening mit DBT+SM gegenüber DM vorgenommen.

Material und Methodik Die 1:1 randomisierte, multizentrische TOSYMA-Studie wurde von 7/2018 bis 12/2020 im deutschen Mammografie-Screening-Programm durchgeführt. Die vorliegende explorative Subanalyse umfasste 49 479 Teilnehmerinnen im DBT+SM-Arm und 49 689 Teilnehmerinnen im DM-Arm mit vollständiger Dokumentation, einschließlich visueller Dichtekategorisierung (A/B: nicht dichtes Parenchym, C/D: dichtes Parenchym).

Ergebnisse Die iCDR der Grade 2 oder 3 betrug mit DBT+SM 5,1 pro 1000 gescreenter Frauen vs. 3,6 ‰ mit DM (Differenz + 1,5 ‰). Bei nicht dichtem Parenchym lag die entsprechende DBT+SM-Rate bei 4,5 ‰ (Differenz zur DM + 1,3 ‰), bei dichtem Parenchym bei 5,7 ‰ (Differenz zur DM + 1,7 ‰). Die iCDR des Grades 1 betrug mit DBT+SM 2,1 ‰ (+ 0,8 ‰ vs. DM). Bei nicht dichtem Parenchym lag die entsprechende DBT +SM-Rate bei 1,7 ‰ (Differenz zur DM + 0,7 ‰), bei dichtem Parenchym bei 2,6 ‰ (Differenz zur DM + 1,0 ‰).

Schlussfolgerung Im Screening mit DBT+SM liegen die Detektionsraten für alle Mammakarzinome Grad 2 oder 3 höher als mit DM. Bei dichtem Brustparenchym zeigen sich höhere entsprechende Detektionsraten und Differenzen der Detektionsraten als bei nicht dichtem Parenchym.

Diese Detektionsraten, wie auch ihre Differenzen, sind mit DBT+SM und mit DM konsistent höher als für Karzinome mit Grad 1. Die explorativen Analysen dieser großen randomisierten Studie deuten darauf hin, dass der Einsatz von DBT+SM im Screening zu einer gesteigerten Entdeckung prognoserelevanter Mammakarzinome führt.

Introduction

Early-stage breast cancer detection aims to reduce advanced tumour stages by diagnosing breast cancer earlier, thus enabling potential therapeutic advantages and reducing breast cancer-specific mortality [1]. Mammography is an evidence-based method for systematic early-stage cancer detection with a proven reducing effect on breast cancer mortality [2, 3]. In Germany, a mammography screening programme (MSP) based on the European Guidelines for women aged between 50 and 69 years has been implemented nationwide, starting in 2005 [4]. With breast cancer being the most common cause of cancer-related death in women, research into innovative screening strategies is warranted [5].

By reducing superimpositions, made possible by X-ray tube arching and reconstruction of layers parallel to the detector surface, digital breast tomosynthesis (DBT) achieves higher breast cancer detection rates compared to digital mammography (DM), the current standard in population-basted early detection [6].

The large, randomized controlled TOSYMA study, which was embedded in the German mammography screening programme, showed that DBT plus reconstructed, synthetic mammography (DBT+SM) was superior to the current standard screening method (DM) in the detection of invasive breast cancers [7, 8]. The higher cancer detection rate when using DBT+SM was observed with non-advanced, invasive breast cancers (UICC stage I) in particular, among those with histological grades 2 or 3 [9].

It is known that the effect of screening on breast cancer mortality not only depends on early-stage cancer detection but also on tumour biology. The latter determines both the speed of tumour growth and the risk of metastasis.

The histological grade is an independent strong prognostic factor for breast cancer, reflecting tumour biology; it is associated with breast cancer-specific survival and disease-free survival [10, 11]. Genome expression profile studies have deciphered additional useful factors of breast cancer biology and significantly deepened our understanding of the biology of the disease; the utility of these factors as prognostic and predictive tools is currently being evaluated. At the same time, these studies have provided further evidence of the high level of relevance of the biological characteristics reflected in the histological grade [12, 13, 14]

The relative reduction in breast cancer-specific mortality attributable to tumour detection in screening varies depending on tumour grade, as shown in the Swedish screening programme [11]. Of the breast cancers detected in the UK screening programme that had a fatal outcome, 6 %, 37 % and 47 % were classified as grade 1, grade 2 or grade 3, respectively [15].

Since the desired reduction in breast cancer mortality is largely based on the detection of histological grade 2 or 3 breast cancers in a screening setting, the aim of this study was to provide an explorative comparison of the rates of detection of invasive breast cancers of grades 2 or 3, independent of the stage, between the DBT+SM arm and the DM arm of the TOSYMA study, while also taking into account breast density.

Materials and Methods

Study design

The multicentre TOSYMA study was conducted in 17 screening units in the German federal states of North Rhine-Westphalia and Lower Saxony from July 2018 to December 2020. A total of 99 689 women were randomly assigned (1:1) to the test arm (DBT+SM) or the control arm (DM). The study protocol was approved by the responsible ethics committee (2016–132-f-S) and assessed by two further ethics committees. A written consent was obtained from all study participants [16]. The study is registered on the publicly accessible database ClinicalTrials.gov (NCT 03377036). The study protocol, the results of the first primary end point with secondary endpoints as well as subanalyses have already been published [7, 8, 9, 16, 17].

Study participants

In Germany, all women between the ages of 50 and 69 years receive an invitation letter every two years to take part in the Mammography Screening Programme (MSP). In the catchment areas of the study centres, they received a personal study invitation with information material in addition to the regular MSP invitation letter. Women diagnosed with breast cancer within the last 5 years or with a mammogram within the last 12 months were not eligible for MSP participation. Breast implants and repeated TOSYMA participation were specific exclusion criteria for the TOSYMA study [7, 8, 9, 16, 17].

Set-up of the screening examination

The opportunity to participate in the study was offered in 17 screening units at 21 sites: Lower Saxony Northwest (Wilhelmshaven), Hannover, Lower Saxony North (Stade), Lower Saxony Central (Vechta), Lower Saxony Northeast (Lüneburg), Duisburg, Krefeld/Mönchengladbach/Viersen, Wuppertal/Solingen (Bergisches Land/Mettmann district), Aachen-Düren-Heinsberg, Cologne (Bergisch Gladbach), Münster-South/Coesfeld, Bottrop, Gelsenkirchen, Recklinghausen, Minden-Lübbecke/Herford, Bielefeld/Gütersloh, Hamm/Unna/Märkischer Kreis (Schwerte), Höxter, Paderborn, Soest (Lippstadt), Münster-North/Warendorf).

Seven different manufacturers of mammography systems were used to provide the DBT+SM or DM examination: Fujifilm Cooperation, Amulet Innovality, Tokyo, Japan (n = 10 075); IMS Giotto, Class Tomo, Sasso Marconi, Italy (n = 7970); Hologic, Lorad Selenia 3Dimensions, Marlborough, US (n = 10 955); Hologic, Lorad Selenia Dimensions, Marlborough, US (n = 40 645); Siemens Healthineers, MAMMOMAT Inspiration, Erlangen, Germany (n = 6759); Siemens Healthineers, MAMMOMAT Revelation, Erlangen, Germany (n = 12 917); GE Healthcare, Senograph Essential, Chicago, US (n = 10 237).

In both study arms, the examinations comprised the craniocaudal and the mediolateral oblique views of each breast. In addition to synthetic, 2-dimensional mammograms (SM), stacked slices of ≤ 1 mm thickness were reconstructed to create the images for reading (DBT) [7, 8, 9, 16, 17].

Reading of the screening examination and diagnostic work-up

As in the current MSP, independent double reading was performed in both study arms by the same certified readers. The screening study comprised a total of 83 experienced readers with at least 2 years of prior screening experience and more than 5000 screening readings per year. DBT training was provided prior to the start of the TOSYMA study in the Reference Centre for Mammography Münster. Based on the DM and SM images, breast density was visually assigned to the categories A (fatty), B (fibroglandular), C (heterogeneously dense), D (extremely dense) [18, 19]. There were 4 to 8 readers at each site. They received their list of study examinations in a mixed sequence of the two study arms without being able to identify the study arm prior to selecting the examination in the screening software. In the case of suspicious findings, the results were discussed in the consensus conference with the physician responsible for the programme to decide whether a further diagnostic work-up was indicated. The diagnostic work-up after study participation was not different from the established procedure of the MSP and comprised, besides the clinical examination, additional mammography views (e. g., magnification mammograms or DBT), ultrasonography, MRI scans, and invasive diagnostic interventions.

Each of the 32 pathologists involved produced at least 100 screening diagnoses per year and took part in a mandatory continuing education course every 2 years, in addition to the self-auditing procedures. The training focused on the internationally recommended Nottingham Grading System, based on semi-quantitative scoring (1 to 3) of glandular differentiation, nuclear pleomorphism and mitotic rate per square millimetre (G1: scoreΣ 3–5, G2: scoreΣ 6–7, G3: scoreΣ 8–9) [4, 20, 21].

All screening data were stored in the screening documentation system MaSc (KV-IT GmbH, Dortmund, Germany) [8, 9, 16, 17].

Study data and statistical analyses

This subanalysis included 49 479 participants in the DBT+SM arm and 49 689 participants in the DM arm with complete screening documentation, including visual density categorization (▶ **Fig. 1**). Descriptive analyses with stratification of invasive detection rates (iCDRs) by histological grade (grade 1 vs. grade 2 or grade 3) and breast density (A+B: non-dense breast vs. C+D: dense breast) were performed for each study arm [18, 19]. When the two breasts differed in density, the higher category was documented; when independent double reading led to discordant categorization of breast density, the highest density category was used [9, 16, 17, 18, 19].

The findings are presented as the absolute number of invasive breast cancers and as invasive breast cancer detection rates (iCDR, per 1000 women screened) in the two study arms as well as their respective differences. The resulting estimates of the risk difference are reported with a 95 % Wald confidence interval (CI). Given the explorative nature of these analyses, no adjustments for multiple comparisons were made and no p-values are provided. The statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

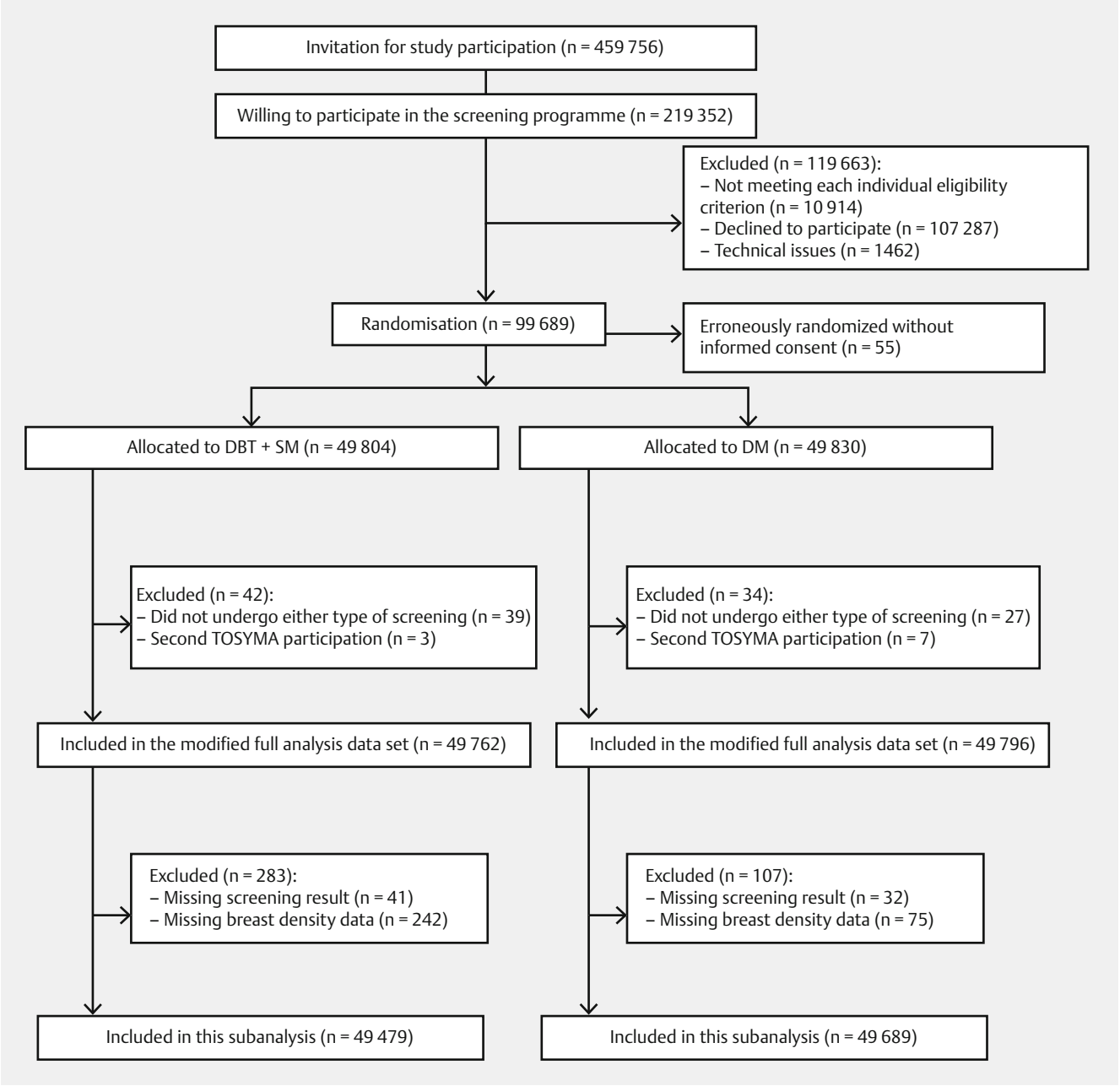
Results

In the DM arm, 240 invasive breast cancers were detected among 49 689 participants included; in the DBT+SM-Arm, 354 invasive breast cancers were diagnosed among 49 479 participants included.

Invasive breast cancer detection stratified by histological grade

In the DM arm, the iCDR of grade 1 breast cancers was 1.3 per 1000 women screened (63/49 689); the ICDR of grade 2 or grade 3 breast cancers was 3.6 per 1,00 women screened (177/49 689).

In the DBT+SM arm, the iCDR of grade 1 tumours was 2.1 per 1000 women screened (104/49479); the ICDR of grade 2 or grade 3 tumours was 5.1 per 1000 women screened (250/49 479).



▶ **Fig. 1** Flowchart of randomization in der TOSYMA study and inclusion in this subanalysis. TOSYMA: TOmosynthesis plus SYnthesized MAmmography trial; DBT+SM: digital breast tomosynthesis and synthetic mammography; DM: digital mammography.

The number of examinations with detected breast cancers, the iCDRs and the resulting differences (with confidence intervals) between the study arms are shown in ▶ **Table 1**.

Invasive breast cancer detection stratified by histological grade and mammographic density

In the DM arm, the iCDR of grade 1 breast cancers was 1.0 per 1000 women screened for the categories A/B (28/28 009) and 1.6 for the categories C/D (35/21 680). The corresponding rates were higher for grade 2 or grade 3 breast cancers with 3.2 per 1000 women screened for the categories A/B (90/28 009) and 4.0 for the categories C/D (87/21 680).

In the DBT+SM arm, the iCDR of grade 1 tumours was 1.7 per 1000 women screened for the categories A/B (46/26 767) and 2.6 for the categories C/D (58/22 712). The highest iCDRs were found for grade 2 or grade 3 breast cancers with 4.5 per 1000 women screened for the categories A/B (120/26 767) and 5.7 for the categories C/D (130/22 712).

The number of examinations with detected breast cancers, the iCDRs and the resulting differences (with confidence intervals) between the study arms are shown in ▶ **Table 2**.

▶ **Table 1** Comparative invasive breast cancer detection rates with stratification by histological grade for the two study arms of the TOSYMA RCT.

	DM	DBT+SM	iCDR difference (DBT+SM – DM) (95 % Wald confidence interval)
Invasive cancers	240	354	114
G1	63	104	41
iCDR G1	1.3‰	2.1‰	0.8‰ (0.31–1.37)
G2+G3	177	250	73
iCDR G2+3	3.6‰	5.1‰	1.5‰ (0.66–2.30)

DM: digital mammography; DBT+SM: digital breast tomosynthesis and synthetic mammography; iCDR: invasive breast cancer detection rate; G: histological grade

▶ **Table 2** Comparative invasive breast cancer detection rates with stratification by histological grade and breast density for the two arms of the TOSYMA RCT.

	DM	DBT+SM	Difference iCDR (DBT+SM – DM) (95 % Wald confidence interval)
Invasive breast cancers G1			
Invasive cancers A+B	28	46	18
iCDR A+B	1.0‰	1.7‰	0.7‰ (0.06–1.38)
Invasive cancers C+D	35	58	23
iCDR C+D	1.6‰	2.6‰	1.0‰ (0.05–1.80)
Invasive breast cancers G2+3			
Invasive cancers A+B	90 (69+21)	120 (96+24)	30 (27+3)
iCDR A+B	3.2‰	4.5‰	1.3‰ (0.20–2.35)
Invasive cancers C+D	87 (72+15)	130 (106+24)	43 (34+9)
iCDR C+D	4.0‰	5.7‰	1.7‰ (0.38–3.06)

DM Digital mammography; DBT+SM: digital breast tomosynthesis and synthetic mammography; iCDR: invasive breast cancer detection rate; G: histological grade; A+B: non-dense breast; C+D: dense breast

▶ **Fig. 2** shows the iCDRs with stratifications by tumor grade and breast density, comparing the study arms DM and DBT+SM (▶ **Fig. 3**).

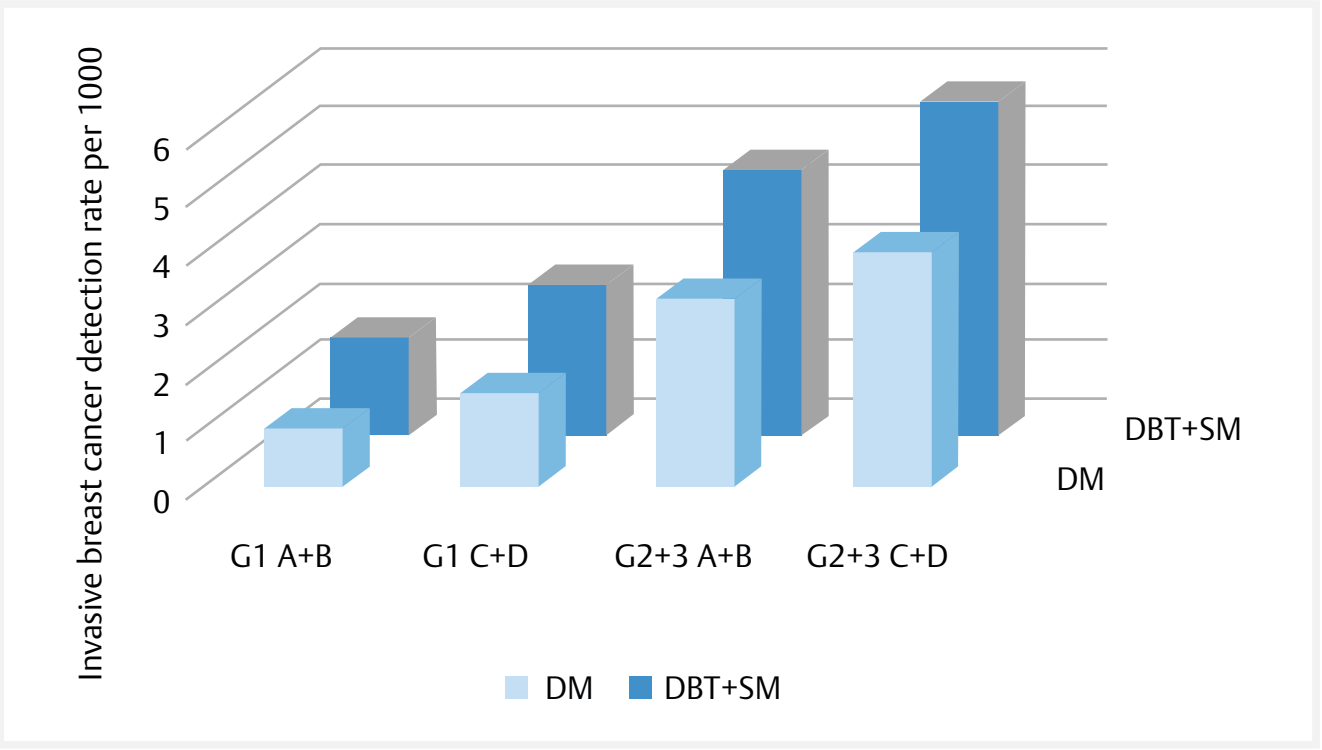
Discussion

The first primary endpoint of the first phase of the randomized, controlled TOSYMA trial investigated whether a clinically relevant increase in the detection rate of invasive tumours is achieved when DBT+SM is used for breast cancer screening compared to DM, the standard imaging modality [7].

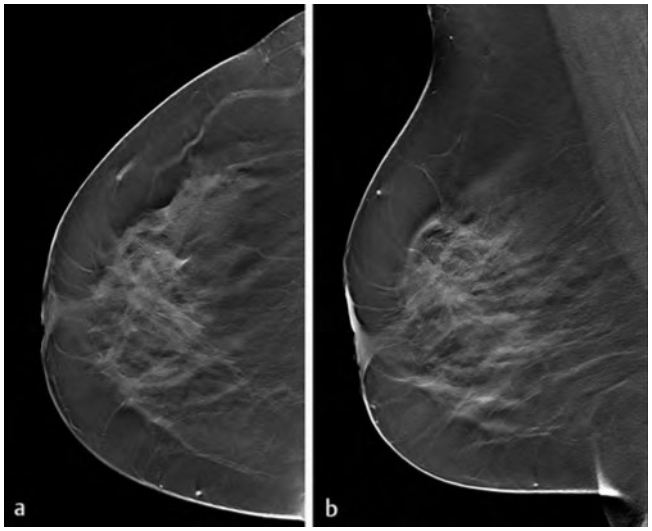
After recruitment had closed in 12/2020, 354 invasive breast cancers were documented in 49 715 women of the DBT+SM arm (invasive detection rate: 7.1 per 1000 women screened) und 240 invasive breast cancers in 49 762 women of the DM arm (invasive detection rate: 4.8 per 1000 women screened). The invasive breast cancer detection rate was significantly higher in the intervention arm compared to the control arm (odds ratio [OR] 1.48; 95 % confidence interval [CI] 1.25–1.75; $p<0.0001$) [8]. The detection rate for invasive tumours up to 20 mm in diameter was substantially higher in the intervention arm compared to the control arm (OR 1.73; 95 % CI 1.41–2.13) [8]. These results were achieved with no marked difference in the recall rates between the two study arms (DBT+SM: 4.9 %; DM: 5.1 %). The PPV1 was higher with DBT+SM compared to DM (DBT+SM: 17.2 %, DM: 12.3 %) [8] (TOSYMA-1).

As yet, there is no conclusive evidence in the literature to suggest that DBT screening is more effective compared to DM screening, particularly in reducing breast cancer-specific mortality. The increase in detection rates observed with DBT+SM screening could be attributable to an increasing level of overdiagnosis, i. e. cancer diagnoses that would not have progressed to a symptomatic or life-threatening disease during the patient's lifetime [21, 22]. Therefore, the TOSYMA study was supplemented by a second phase, investigating the incidence rates of invasive interval breast cancers diagnosed within 24 months after the screening examination (TOSYMA-2). Interval cancers are considered an important clinical surrogate endpoint for the evaluation of breast cancer screening [23]. Results for this second primary endpoint of the TOSYMA study are expected to become available by 2024/2025 [7].

In addition, it would be useful to carry out a supplementary assessment closer to screening based on prognostic tumour parameters [9]. Several studies have shown an association between histological grade, a well-established indicator of



▶ **Fig. 2** Comparative invasive breast cancer detection rates with stratification by histological grade and breast density for the two arms of the TOSYMA study. DM: digital mammography; DBT+SM: digital breast tomosynthesis and synthetic mammography; G: histological grade; A+B non-dense breast; C+D: dense breast.



▶ **Fig. 3** Digital breast tomosynthesis of the right breast in **a** craniocaudal (cc) and **b** mediolateral oblique (MLO) views. In the individual slices, an architectural distortion is noted in the right upper lateral aspect in both views. Histology: invasive lobular breast cancer, pT2 (31 mm), pN0, cM0, G2.

tumour growth rates, and prognosis [11, 24, 25]. According to the results of the Swedish Two County Trial, the histological tumour grade at the time of diagnosis has a long-term effect on later survival, similar to nodal status and tumour size [26].

This prognostic significance of the histological grade is also reflected in the differences in reduction of breast cancer-specific mortality due to screening detection in the Swedish Two County trial. The reduction in screening-detected grade 3 tumours is 35 %, in grade 2 tumours 32 %, but in grade 1 tumours only 6 % [11]. This grading-related effect is long-term in nature and contributes to the fact that the impact of screening programmes on breast cancer mortality can still be observed many years later; while the effect is strongest in the first 5 years, it can last for up to 15 years [26].

The results of the explorative TOSYMA subanalysis presented here show that in both study arms the breast cancer detection rates were higher for grade 2 or 3 breast cancers compared to grade 1 tumours. The difference achieved with DBT+SM vs. DM is greater for iCDR of tumours with grades 2 or 3 compared to grade 1. Early grade 1 breast cancers are more likely to contribute to overdiagnosis than grade 2 or grade 3 tumours; therefore, its rates among early tumour diagnoses in stage UICC I are of interest.

Unlike the above mentioned earlier TOSYMA subanalysis which assessed grade-dependent detection for the early UICC I tumour stage [9], this subanalysis includes screening-detected breast cancers of all tumour stages. The results are consistent: Screening leads to a higher detection rate of grade 2 or 3 tumours compared to grade 1 tumours, both in the detection of the early tumour stage and also when advanced tumour stages are included. DBT +SM achieved higher detection rates than DM, with the highest rates being observed with dense breast parenchyma [9]. Supplementary information of the TOSYMA study on prognostic param-

eters indicates that in the DBT+SM arm the higher iCDR in women with dense parenchyma is primarily based on the detection of screening-relevant grade 2 or grade 3 breast cancers and not on the detection of grade 1 tumours [27, 28]. While DBT+SM also increased the detection of grade 1 cancers compared to DM, the magnitude of the effect is smaller compared to that on the detection rate of more prognosis-relevant grade 2 or 3 cancers.

With almost 100 000 participants, TOSYMA is the largest randomized controlled screening trial evaluating DBT+SM vs. DM conducted so far. It provides the opportunity to carry out supplementary analyses on the basis of a successful randomization. The pragmatic approach offers a high degree of external validity and also demonstrates its real-world feasibility, especially due to the inclusion of numerous screening units and device technologies. Radiology staff and physicians underwent special training prior to the start of the study. All investigators were experienced, with no differences between the two study arms or between the study and routine screening [17].

This study has limitations. TOSYMA analysed only one screening round; consequently, it is possible that the differences between the study arms are influenced by an initial prevalence screening effect with DBT+SM. In addition, there might be a learning curve in reading tomosynthesis images. Having access to the screening examination via the screening software, the TOSYMA readers were not blinded with regard to the study arm [17].

Conclusion

The explorative analyses of this large, randomized trial indicate that DBT+SM screening increases the detection of prognostically more relevant breast cancers (TOSYMA-1). Once the follow-up data have been analysed in 2024/2025 (TOSYMA-2), we will be able to evaluate whether the higher breast cancer detection rates achieved with DBT+SM result in measurable differences in invasive interval cancer rates, an important surrogate indicator, between the two study arms.

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Conflict of Interest

S.W. Payments for lectures from the Reference Center for Mammography Münster; leadership role at the Reference Center for Mammography in Muenster and the associated Reference Screening Unit; board member of the AG Mammadiagnostik of the German Röntgen Society and German Society for Senology; before starting the TOSYMA trial, received training cases from all vendors without charge for reader training at the Reference Center for Mammography Münster. V.W.E. No relevant relationships. H.W.H. No relevant relationships. T.D. No relevant relationships. J.G. Consulting fees from Dr August Wolff, Ecker + Ecker, QUIRIS Healthcare, and TESARO; honoraria for lectures from Roche and TESARO; participation on a data and safety monitoring board or advisory board for the TOMAHAWK trial (University Medical Center Schleswig-Holstein, Campus Lübeck) and Ruxo-BEAT trial (RWTH Aachen University). W.H. Payments for lectures from the Reference Center for Mammography Münster; leadership role of the Reference Center for Mammography in Muenster and the associated Reference Screening Unit; board member/member of the European Society of Radiology, German Röntgen Society, European Society of Breast Imaging, German Society for Senology, and German Röntgen Museum; before starting the TOSYMA trial, received training cases from all vendors without charge for reader training at the Reference Center for Mammography Münster.

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