Original Article

Differences in Breast Cancer Characteristics by Mammography Screening Participation or Non-Participation

A Retrospective Observational Study

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Summary

Background: The goal of the German Mammography Screening Program (MSP) is to enable the early detection and less intensive treatment of breast cancer. We compared tumor characteristics and prognostic markers in breast cancers that were detected by screening in the MSP, in the interval after a negative screening, or among non-participants in screening.

Methods: This retrospective series includes all of the 1531 cases of invasive and in situ breast cancer (DCIS, ductal carcinoma in situ) that were newly diagnosed in two certified breast care centers in Münster in the period 2006–2012 among women in the MSP target population. Complete information on the tumor characteristics, tumor biology, and primary surgical treatment were available for all cases. The mode of cancer detection was determined from the state cancer registry of North Rhine–Westphalia. Due to the retrospective design of this case series, there was no randomized allocation.

Results: The 874 cases of breast cancer among MSP participants (714 detected by screening, 160 in the interval after a negative screen) and the 657 cases among non-participants arose in women of similar age (mean, 60.2 versus 59.3 years). MSP participants with breast cancer had DCIS more commonly than non-participants did (23% versus 13%); invasive carcinomas were smaller (74% versus 55% in the T1 stage), less commonly node-positive (25% versus 31%), less commonly high-grade (19% versus 27%), and less commonly triple-negative (7% versus 12%); MSP participants received neoadjuvant treatment less frequently (2% versus 8%) and more frequently underwent breast-conserving surgery (75% versus 62%). They less commonly had a guideline-based indication for adjuvant chemotherapy (46% versus 52%).

Conclusion: MSP participants with invasive breast cancer can generally be treated with less intensive surgical and systemic therapy than non-participants, even if interval cancers are also taken into account. Future studies should also investigate quality of life after a diagnosis of invasive carcinoma in screening participants.

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The mammography screening program (MSP) that has been introduced stepwise in Germany since 2005 is based on the quality requirements of the European guideline (1, 2) and is designed to detect breast cancer at an early stage. To this end, all women aged between 50 and 69 years are invited to a quality assured mammography screening examination every 2 years (3).

Breast cancer is detected among MSP participants not only during the actual screening examination, but also after a negative screening mammography and before the next regular screening appointment; this is referred to as interval cancer. Detecting and assessing the incidence of interval cancers is an important instrument to evaluate the quality of a screening program (1, 2). There are various causes for the occurrence of interval cancers: in addition to radiologically occult cancers that were clinically manifest at the time of radiological imaging yet not visible either on screening mammography or on diagnostic mammography, and the cancers falsely assessed as harmless (false-negative), more than half of these were "true" interval cancers for which there was no visible correlate at the time of screening mammography (4–6). Studies have shown that the prognosis for interval cancer is generally less favorable in terms of tumor stage, grading, and receptor status compared with cancers detected at screening (2, 7–11).

Due to a lack of legislation at the German federal state level, breast cancer cases in the first years of the MSP can only be matched to mode of cancer detection in North Rhine–

Westphalia (NRW) and Lower Saxony (2). Using data from two breast care centers in Münster, Germany, we investigated how the most important clinico-pathological breast cancer prognostic markers (tumor stage, histology, grading, and receptor status) differ when the disease is newly detected in MSP participants or non-participants and whether this influenced the therapeutic approach (surgical therapy, indication for chemotherapy). This was the first time that it was possible for an analysis of the German mammography screening program to take into consideration all interval cancers detected in participants.

Methods

Two screening units in Münster, which started operating in October 2005, were the first to implement the MSP in Germany. The retrospective case series presented here included all eligible women aged 50–69 years that were treated in two Münster breast care centers (the University Hospital and the St. Franziskus Hospital) for breast cancer between 2006 and 2012. Data on pathological prognostic markers, tumor biology, and primary surgical therapy were available in the breast care centers with more than 95% completeness. The indication for adjuvant chemotherapy was established by the authors according to the current S3 guideline (12). For all cases of breast cancer that occurred during the study period, the state cancer registry of North Rhine–Westphalia holds valid information on the mode of detection (by screening, during the interval after a negative screening mammography, or in the case of no previous screening participation). Almost all cases of breast cancer (over 95%) were registered in the state cancer registry for the study period (2, 13). The rate of screening participation for this period was 55% (14). The local ethics commission gave its approval for the study.

Chi-square tests were calculated to compare the frequencies of categorized variables, while factors measured on a continuous scale were compared using t-tests. The p-values provided in the tables were derived from multiple exploratory comparisons; they should not be interpreted as an indicator of statistical significance that cannot be determined in exploratory studies. Analyses were performed using the SAS 9.4 software.

A detailed description of the methodological approach can be found in the *eMethods* section.

Results

The study included 1534 women aged between 50 and 70 years who had been treated for incident breast cancer in two breast care centers in Münster (University Hospital [n = 958] and St. Franziskus Hospital [n = 576]) between 1 January 2006 and 31 December 2012. Patients with synchronous or metachronous bilateral breast cancer were deemed to be one case. In order to compare participants and non-participants in the MSP, those for whom the mode of cancer detection could not be clearly identified (n = 3) were excluded, leaving 1531 women in the analysis.

TABLE 1

Baseline breast cancer characteristics in the study population (diagnosis during the period 2006–2012)

	N	%
Breast cancer cases	**1531**	**100.0**
Age at diagnosis, mean (SD)	59.8 (6.1)	
Years of diagnosis		
2006–2009	810	52.9
2010–2012	721	47.1
Ductal carcinoma in situ (DCIS)	285	18.6
Invasive cancer	1246	81.4
Invasive cancers	**1246**	**100.0**
of which:		
T stage 1	812	65.2
T stage 2+	373	29.9
Treated neoadjuvantly	61	4.9
N stage 0	836	67.1
N stage 1+	346	27.8
Treated neoadjuvantly	61	4.9
Missing	3	0.2
Grading:		
Grade I	327	26.2
Grade II	631	50.6
Grade III	284	22.8
Missing	4	0.3
Receptor status:		
Hormone receptor-positive, HER2-negative	901	72.3
HER2-positive	213	17.1
Triple-negative	118	9.5
Missing	14	1.1
Type of surgery:		
Breast-conserving therapy	862	69.2
Breast-conserving therapy + mastectomy	96	7.7
Mastectomy	281	22.6
Missing	7	0.6
Indication for chemotherapy:		
Yes	608	48.8
No	577	46.3
Treated neoadjuvantly	61	4.9
Type of surgery (including DCIS):	**1531**	**100.0**
Breast-conserving therapy	1049	68.5
Breast-conserving therapy + mastectomy	134	8.8
Mastectomy	341	22.3
Missing	7	0.5

HER2, human epidermal growth factor receptor 2; SD, standard deviation

The average age of patients diagnosed with breast cancer was 59.8 years; 81.4% of patients had invasive cancer (*Table 1*). At the time of primary surgery, 65.2% and 67.1% were stage T1 and N0, respectively; approximately 5% were treated neoadjuvantly. In all, 72.3% of breast cancers were luminal-like tumors and just under 10% were triple-negative. Almost 70% of patients were primarily treated with breast-conserving surgery.

A comparison of the 874 incident breast cancers in screening program participants (diagnosed at screening or during the screening interval) with the 657 breast cancers in non-participants (*Table 2*) shows that the number of new-onset breast cancers in the MSP implementation phase between 2006 and 2009 was similar to the 3 years from 2010 to 2012 in which the MSP was fully implemented. On the other hand, the number of breast cancer cases among non-participants in the 2010–2012 period was markedly lower compared with the previous period. Age at diagnosis was similar in participants and non-participants. The percentage of ductal carcinomas in situ was considerably higher among MSP participants ($p<0.0001$) compared with non-participants (12.8%). Invasive breast cancer in MSP participants was also more frequently stage T1 ($p<0.0001$) and node-negative ($p = 0.005$). The percentage of cases treated neoadjuvantly was lower among screening participants (2.4% versus 7.9%). Although there were virtually no differences in tumor histology, the proportion of high-grade tumors found at invasive breast cancer grading was clearly lower among MSP participants compared with non-participants ($p<0.0001$). Triple-negative (7.3%) and HER2-positive (15.6%) cancers were also found less frequently among participants compared with non-participants (12.0% and 18.9%, respectively). In terms of the primary type of surgery, MSP participants with invasive breast cancer were treated by means of breast-conserving surgery significantly more often ($p<0.0001$) than were non-participants (75.2% versus 62.1%). The proportion of surgical approaches remained unchanged if ductal carcinomas in situ were included. According to guideline recommendations, either an adjuvant chemotherapy was indicated or women were treated with a neoadjuvant chemotherapy in 48.8% of all MSP participants with invasive breast cancer, whereas the same was true in 59.6% of non-participants with cancer.

In order to estimate biases in the comparison between participants and non-participants due to the initial prevalence screening and the lower frequency of interval cancers at the beginning of the study period, a sensitivity analysis was performed for the period 2010–2012 (*Table 3*). The percentage of interval cancers in MSP participants diagnosed with breast cancer was 23% during this period of routine operation of the MSP following the implementation phase (*eTable*). Nevertheless, differences of similar magnitude were confirmed for tumor size and grading (*Table 2*) ($p<0.0001$). In contrast, differences in node and receptor status were less pronounced. The percentage of breast-conserving surgery in MSP participants had continued to rise.

A more in-depth analysis compared the 160 interval cancers with the 714 breast cancers detected during screening examinations (*eTable*). As expected, the percentage of in situ tumors in interval cancers was notably lower ($p<0.0001$), and TNM staging, grading, and receptor status were less favorable ($p = 0.045$ or less). In terms of breast-conserving procedures, interval cancers behaved similarly to breast cancer in non-participants; indeed, chemotherapy was indicated slightly more frequently here.

Discussion

The retrospective case series presented here compares the clinicopathological characteristics of incident breast cancer cases in participants—taking into account interval cancers—with incident cases among non-participants for the first time since the introduction of the German mammography screening program. It was revealed that the characteristics of breast cancers in participants were prognostically more favorable compared with those in non-participants; accordingly, breast-conserving surgical approaches were more frequent in participants and chemotherapy more rarely indicated.

The study design needs to be taken into account when appreciating these results: this observational study examines a breast cancer case series and does not represent a randomized comparison of participants and non-participants; it is therefore not free from possible biases (confounding). Additionally, these cases were not derived from a well-defined population-based cohort. These and other important aspects will be critically examined below.

The distinctive feature of the analysis presented here lies in the fact that the inclusion of interval cancers—which are methodologically challenging to determine and have a less favorable prognosis—provides a broader perspective: thus, the patient-relevant effects of the MSP are evaluated in terms of the type and extent of cancer treatment for all screening participants—and not just for those cancers detected at screening. Even when interval cancers were included, it was shown that cancer in MSP participants required overall less intensive treatment compared with non-participants. The number of breast-conserving procedures for invasive cancer observed at the start of the MSP in this study is consistent with a German analysis of nationwide data from the period 2005–2009: there, the total rate of breast-conserving approaches was reported to be 66.9% (15), whereas the corresponding percentage for the period studied in the present study (2006–2012) was 68.5%. The sensitivity analysis in *Table 3* shows that this percentage rose to almost as much as 80% in participants between 2010 and 2012, whereas it remained constant in non-participants.

In addition, the indication for adjuvant chemotherapy resulting from the constellation of clinicopathological

TABLE 2

A comparison of breast cancer characteristics in women that participated in the mammography screening program and women that did not participate (diagnosis in the years 2006–2012)

	Participants		Non-participants		p-Value
	N	%	N	%	
Breast cancer cases	**874**	**100.0**	**657**	**100.0**	
Age at diagnosis, mean (SD)	60.2 (6.1)		59.3 (6.0)		0.765
Years of diagnosis					
2006–2009	430	49.2	380	57.8	0.001
2010–2012	444	50.8	277	42.2	
Ductal carcinoma in situ (DCIS)	201	23.0	84	12.8	<0.0001
Invasive	673	77.0	573	87.2	
Invasive cancers	**673**	**100.0**	**573**	**100.0**	
of which:					
T stage 1	498	74.0	314	54.8	<0.0001
T stage 2+	159	23.6	214	37.4	
Treated neoadjuvantly	16	2.4	45	7.9	
N stage 0	485	72.1	351	61.3	0.005
N stage 1+	170	25.3	176	30.7	
Treated neoadjuvantly	16	2.4	45	7.9	
Missing	2	0.3	1	0.2	
Grading:					
Grade I	213	31.7	114	19.9	<0.0001
Grade II	331	49.2	300	52.4	
Grade III	128	19.0	156	27.2	
Missing	1	0.2	3	0.5	
Receptor status:					
Hormone receptor–positive, HER2-negative	513	76.2	388	67.7	0.002
HER2-positive	105	15.6	108	18.9	
Triple-negative	49	7.3	69	12.0	
Missing	6	0.9	8	1.4	
Type of surgery:					
Breast-conserving therapy	506	75.2	356	62.1	<0.0001
Breast-conserving therapy + mastectomy	42	6.2	54	9.4	
Mastectomy	124	18.4	157	27.4	
Missing	1	0.2	6	1.1	
Indication for chemotherapy:					
Yes	312	46.4	296	51.7	<0.0001
No	345	51.3	232	40.5	
Treated neoadjuvantly	16	2.4	45	7.9	
Type of surgery (including DCIS)	**874**	**100.0**	**657**	**100.0**	
Breast-conserving therapy	645	73.8	404	61.5	<0.0001
Breast-conserving therapy + mastectomy	66	7.6	68	10.4	
Mastectomy	162	18.5	179	27.3	
Missing	1	0.1	6	0.9	

HER2, human epidermal growth factor receptor 2; SD, standard deviation

prognostic markers shows that non–MSP participants with breast cancer require chemotherapy more frequently, although the indication was most frequently made for interval cancers (12, 16). Although detailed information on the types of chemotherapy frequently administered in the outpatient sector is lacking in the the documentation of the two inpatient facilities, the guideline adherence demonstrated at the two certified breast care centers gives reason to assume that the recommendations of the current S3 guideline (12) were reliably implemented. The results of the German mammography screening program confirm the findings from a 2002 Canadian study conducted in a comparable setting (17) and a recent review article (18) has raised the question of how often chemotherapy could be avoided as a result of early cancer detection: based on the data presented here, this applies to approximately 8%–10% of all cases of breast cancer.

As mentioned above, observational studies can be subject to biases. Thus, it could be that tumors with more favorable characteristics are found among participants partly as a result of potential overdiagnosis and overtreatment (19, 20). Since this applies in particular to ductal carcinoma in situ, such tumors were excluded in order to restrict comparisons to incident invasive cancer alone. However, it is not possible on the basis of the available data to determine the extent to which the more frequent T1 tumors detected in participants may also be attributable to overdiagnosis. Furthermore, it is known that social differences are reflected in participation rates (21). These differences can impact the use of reconstructive breast surgery (22); however, the authors found no evidence in the literature that this effect can also be assumed for the decision regarding the type of surgical treatment (i.e., for mastectomy or against breast-conserving surgery). The question also arises whether risk factors for the development of breast cancer were operating in participants and non-participants to varying degrees of frequency and extent, and whether this had an effect on the clinicopathological characteristics at diagnosis. However, recent analyses of the Norwegian screening program show that although alcohol and smoking increase the incidence of breast cancer, this increase was confined to the more prognostically favorable luminal-A and luminal-B tumors as well as to HER2-negative tumors (23). Since alcohol consumption and smoking can be expected more frequently in non-participants tending to be of lower social status, it is more likely that the extent of differences observed for the receptor-related markers have been underestimated. In the authors' opinion, differences in tumor stage primarily indicate that the lack of earlier diagnosis was the principal reason for the differences observed. Since women of higher social status are generally more likely to utilize preventive and medical services (21, 24), diagnosis at an earlier point in time could have been expected among participants even without the introduction of an MSP. It is not possible to assess, based on the available data, the extent to which the systematic invitations integral to the MSP have increased the reach-out to other social classes.

Data on tumor progression are undoubtedly essential in a comparative assessment of patient-relevant endpoints. Since insufficient prospective information on disease course was available in the study database, it is important to refer here to the ongoing studies on the effects of MSP on breast cancer mortality carried out on the basis of a larger database (25). The same applies to evaluating the importance of overdiagnosis and overtreatment. Here again, the data from this case series fail to provide any reliable information.

From a methodological perspective, it should also be borne in mind that between 2006 and 2009 primarily prevalence screening was conducted, in which a higher number of breast cancer cases were diagnosed than in subsequent screening rounds (26). In addition to the in situ tumors and small invasive tumors typical of screening that would have remained clinically undetected for some time, the breast cancer cases found in the prevalence screening also included those prevalent breast cancers that would soon have been detected even without the screening program. From 2009 onwards, once the prevalence round had been completed (27), most MSP participants underwent incidence screening. Therefore, it must be borne in mind with regard to the comparisons performed here that the prevalent breast cancer cases initially "contaminated" the characteristics of MSP participants: this led to an increase in the number of tumors not typical in screening and with less favorable clinicopathological characteristics. On the other hand, the incidence of interval cancers was lower during the period in which the program was being introduced, since these are only detected up to 30 months after a negative screening mammography. Therefore, as expected, interval cancers accounted for only a small percentage (13.5%) of cancers in participants diagnosed with breast cancer in the period 2006–2009. In contrast, the sensitivity analysis in *Table 3* in conjunction with the *eTable*, which corresponds more closely to the routine operation of the MSP following the implementation phase, shows a rate of 23% for interval cancers, and thus corresponds to comparable data relating to a 24-month period (1).

Although results from a limited study region cannot simply be extrapolated to other regions, one can assume comparable conditions in other screening regions due to the extremely high level of quality assurance in the mammography screening program as well as similar participation rates (14). The study period of 7 years was sufficiently long to balance out the effect of the prevalence round following the introduction of the MSP, which was confirmed by the sensitivity analysis. One can also suppose that the results are equally suited to describing the current situation in the MSP, assuming a consistent level of quality assurance (28). Special emphasis should be put on a particular strength of the study, i.e., the

TABLE 3

A comparison of breast cancer characteristics in women that participated in the mammography screening program and women that did not participate (diagnosis in the years 2010–2012)

	Participants		Non-participants		p-Value
	N	%	N	%	
Breast cancer cases	**444**	**100.0**	**277**	**100.0**	
Age at diagnosis, mean (SD)	59.8 (6.0)		59.1 (6.0)		0.927
Ductal carcinoma in situ (DCIS)	93	20.9	36	13.0	0.007
Invasive	351	79.1	241	87.0	
Invasive cancers	**351**	**100.0**	**241**	**100.0**	
of which:					
T stage 1	263	74.9	138	57.3	<0.0001
T stage 2+	75	21.4	85	35.3	
Treated neoadjuvantly	13	3.7	18	7.5	
N stage 0	241	68.7	154	63.9	0.624
N stage 1+	97	27.6	68	28.2	
Treated neoadjuvantly	13	3.7	18	7.5	
Missing	0	0.0	1	0.4	
Grading:					
Grade I	98	27.9	46	19.1	0.001
Grade II	177	50.4	113	46.9	
Grade III	75	21.4	81	33.6	
Missing	1	0.3	1	0.4	
Receptor status:					
Hormone receptor positive, HER2-negative	272	77.5	169	70.1	0.117
HER2-positive	53	15.1	42	17.4	
Triple-negative	26	7.4	28	11.6	
Missing	0	0.0	2	0.8	
Type of surgery:					
Breast-conserving therapy	280	79.8	150	62.2	<0.0001
Breast-conserving therapy + mastectomy	15	4.3	22	9.1	
Mastectomy	56	16.0	66	27.4	
Missing	0	0.0	3	1.2	
Indication for chemotherapy:					
Yes	169	48.2	126	52.3	0.042
No	169	48.2	97	40.3	
Treated neoadjuvantly	13	3.7	18	7.5	
Type of surgery (including DCIS)	**444**	**100.0**	**277**	**100.0**	
Breast-conserving therapy	355	80.0	174	62.8	<0.0001
Breast-conserving therapy + mastectomy	23	5.2	27	9.8	
Mastectomy	66	14.9	73	26.4	
Missing	0	0.0	3	1.1	

HER2, human epidermal growth factor receptor 2; SD, standard deviation

Key messages

- This study is the first Germany-wide analysis of clinicopathological tumor characteristics according to the mode of breast cancer detection (at screening, during intervals after a negative screen, or in the case of no previous participation in screening) using data from the German mammography screening program (MSP).
- Invasive breast cancers in participants of the mammography screening program were more frequently stage T1 and less frequently node-positive, triple-negative, and grade III compared with non-participants
- Participants in the mammography screening program with invasive breast cancer—also taking interval cancer into account—were able to undergo less intensive surgical and systemic treatment compared with non-participants.
- This is confirmed by a sensitivity analysis for a period following full implementation of the mammography screening program (2010–2012). The same analysis also shows a further increase in the percentage of breast-conserving surgical procedures.

database, which does not yet exist in this form anywhere in Germany: not only the modes of detection, particularly the data on interval cancers provided by the state cancer registry, but also the prognostic markers from the breast care centers were available in their entirety over a long period of time for a large number of patients.

Conclusion

This retrospective observational study reveals for the first time that participants in the German MSP with invasive breast cancer—even including interval cancers—could undergo less intensive surgical and systemic treatment compared with cancers in non-participants. No analyses of MSP data on quality of life are available as yet. Therefore, future investigations need to show whether the differences in surgery and treatment observed here are also reflected in a comparatively better quality of life following the diagnosis of invasive cancer.

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Conflict of interest statement

The authors state that there are no conflicts of interest.

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► **Supplementary material**
eMethods, eTable:
www.aerzteblatt-international.de/18m0520

CLINICAL SNAPSHOT

Amour Fou at Age 77

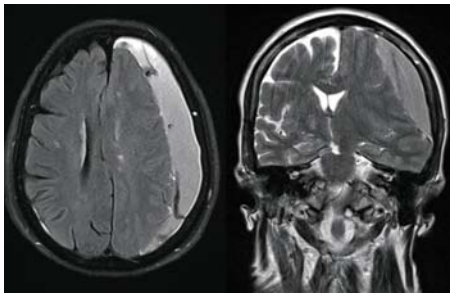

Figure: Preoperative MRI scan of the head, T2-flair axial and T2 frontal images. The postoperative head CT (not shown) shows residual hygroma and a cerebral parenchymal defect (enlargement of the lateral ventricle on the affected side).

The patient, a 77-year old woman, was a retired bookkeeper in good physical health. She had been in psychotherapy for decades because of anxiety and marital problems and suffered from a low-dose benzodiazepine dependence. She was widowed after 43 years of monogamous marriage and then, 1¼ years later, developed an amorous relationship with an 80-year-old married man living next door, with obsessive infatuation and an intense experience of sexual revelation. Her feelings of guilt and egodystonic experience and behavior were treated during depth-psychological sessions with a psychiatrist. The affair ended when her lover turned away from her; the ensuing emotional preoccupation and suicidal thoughts led to two psychiatric hospitalizations and to the need for intensive outpatient psychotherapy. She was not suffering from a dementia syndrome, delusions, or any clinically evident neurologic deficits. Therapy resistance, cognitive rigidity, and alien nature of her sexual obsession motivated referral for an MRI scan of the head, which yielded the unexpected finding of a subdural hematoma with older and newer components, midline shift, and incipient transtentorial herniation. She was operated on immediately (burr-hole trepanation and hematoma evacuation); the hematoma consisted of old and acute parts. There had been no prior history of anticoagulation, a fall, or other head trauma. An organic personality disorder was diagnosed (ICD-10:F07.0). By the time of follow-up 2½ months after surgery, the patient had only partly distanced herself from her sexual-amorous preoccupation but had not resumed contact with her neighbor.

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Supplementary material to:

Differences in Breast Cancer Characteristics by Mammography Screening Participation or Non-Participation

A Retrospective Observational Study

by Bettina Braun, Laura Khil, Joke Tio, Barbara Krause-Bergmann, Andrea Fuhs, Oliver Heidinger, and Hans-Werner Hense

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eMETHODS

In October 2005, two screening units in Münster were the first in Germany to start the mammography screening program (MSP). The retrospective case series presented here included all eligible women aged 50–69 years who were treated in two Münster breast care centers (the University Hospital and the St. Franziskus Hospital) for breast cancer between 2006 and 2012. The participation rate during this period was approximately 55% (14). The local ethics commission gave their approval for the study.

The Breast Care Center at the University Hospital Münster and the Breast Care Center at St. Franziskus Hospital Münster are independently certified by the certification board of the Westfalen–Lippe Medical Association (*ÄKzert*)[*1]. All breast cancers are documented in both centers using the ONDIS[*2] tumor documentation system. As is usual in most breast care centers, regular comparisons are made with the respective hospital information system to check for internal completeness, whereby access is available to medical reports, surgical reports, tumor conference documents, and pathologists' findings.

The following data were available in both breast care centers with more than 95% completeness: cancer diagnosis (invasive breast cancer [ICD-10: C50] or ductal carcinoma in situ [ICD-10: D05, without D05.0]); date of diagnosis; post-operative tumor status (pTNM) or information on preceding neoadjuvant treatment; tumor histology and grading; hormone receptor and HER2 status. Tumor biology was divided into the following subtypes: luminal-like (estrogen and/or progesterone receptor–positive, HER2 receptor–negative), HER2-positive (HER2 receptor–positive, estrogen and progesterone receptor–negative or –positive), and triple-negative (estrogen, progesterone, and HER2 receptor–negative) (16). Information was also available on primary surgical treatment. The indication for adjuvant chemotherapy was established by the authors according to the current German S3 guideline (12); this specifies that adjuvant chemotherapy is indicated in HER2 receptor–positive or estrogen and progesterone receptor–negative tumors, as well as in node-positive tumors or high-grade tumors (12).

For all cases of breast cancer that occurred during the study period, the state cancer registry of North Rhine–Westphalia (NRW) holds valid information on mode of cancer detection (at screening, during intervals after a negative screening mammography, or in the case of no previous screening participation). At over 95%, virtually all cases of breast cancer were registered in the NRW state cancer registry for the study period (2, 13). The retrospective classification used here for the period 2006–2012 is only possible in the federal states of North Rhine–Westphalia and Lower Saxony due to the lack of legislation elsewhere in Germany (2). Breast cancer was classified as detected at screening if it was discovered during a mammography screening examination. Cases of breast cancer occurring in women that had undergone a negative screening examination and had been diagnosed with breast cancer within the subsequent 30 months, prior to participating in the next regular MSP examination, were classified as interval cancers. In women whose radiologically abnormal screening findings remained unexplained, breast cancer occurring 4–30 months following the unexplained screening examination was also classified as interval cancer (n = 3). All cancers diagnosed in women who had never participated in the MSP or whose previous screening examination lay more than 30 months in the past were defined as breast cancer in non-participants.

Chi-square tests were calculated to compare the frequencies of categorized variables, while factors measured on a continuous scale were compared using t-tests. The p-values provided in the tables were obtained by means of multiple exploratory comparisons and serve merely as an indication of the probability with which the differences in frequency found would have been expected if there had in fact been no differences between participants and non-participants. They should not be misinterpreted as an indicator of statistical significance that cannot be determined in exploratory studies. Analyses were performed using the SAS 9.4 software.

[*1] www.aekzert.de/index.php?id=aekzert-home (last accessed on 2 March 2018)
[*2] www.kvwl.de/arzt/kv_dienste/it/ondis.htm (last accessed on 28 February 2018)

eTABLE

A comparison of breast cancer characteristics in MSP participants whose cancer was discovered at screening mammography, and of MSP participants that were negative at screening mammography but in whom cancer was diagnosed in the ensuing interval of 30 months prior to the next screening (interval cancers) (diagnosis during the period 2006–2012)

	Discovered at screening		Discovered during the interval after screening		p-Value
	N	%	N	%	
Breast cancer cases	**714**	**100.0**	**160**	**100.0**	
Age at diagnosis, mean (SD)	60.2 (6.2)		60.1 (5.7)		0.276
Years of diagnosis					
2006–2009	372	52.1	58	36.3	<0.001
2010–2012	342	47.9	102	63.7	
Ductal carcinoma in situ (DCIS)	188	26.3	13	8.1	<0.0001
Invasive cancer	526	73.7	147	91.9	
Invasive cancers	526	100.0	147	100.0	
of which:					
T stage 1	412	78.3	86	58.5	0.0001
T stage 2+	109	20.7	50	34.0	
Treated neoadjuvantly	5	1.0	11	7.5	
N stage 0	397	75.5	88	59.9	0.008
N stage 1+	123	23.4	47	32.0	
Treated neoadjuvantly	5	1.0	11	7.5	
Missing	1	0.2	1	0.7	
Grading:					0.001
Grade I	182	34.6	31	21.1	
Grade II	256	48.7	75	51.0	
Grade III	87	16.5	41	27.9	
Missing	1	0.2	0	0.0	
Receptor status:					0.045
Hormone receptor-positive, HER2-negative	410	78.0	103	70.1	
HER2-positive	79	15.0	26	17.7	
Triple-negative	32	6.1	17	11.6	
Missing	5	1.0	1	0.7	
Type of surgery:					0.016
Breast-conserving therapy	407	77.4	99	67.4	
Breast-conserving therapy + mastectomy	33	6.3	9	6.1	
Mastectomy	85	16.2	39	26.5	
Missing	1	0.2	0	0.0	
Indication for chemotherapy:					<0.0001
Yes	229	43.5	83	56.5	
No	292	55.5	53	36.1	
Treated neoadjuvantly	5	1.0	11	7.5	
Type of surgery (including DCIS)	714	100.0	160	100.0	
Breast-conserving therapy	537	75.2	108	67.5	0.039
Breast-conserving therapy + mastectomy	55	7.7	11	6.9	
Mastectomy	121	17.0	41	25.6	
Missing	1	0.1	0	0.0	

HER, human epidermal growth factor receptor 2; MSP, mammography screening program; SD, standard deviation