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SCREENING

Trends in surgical treatment for breast cancer in Germany after the implementation of the mammography screening program

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Abstract

In Germany, the nationwide population-based mammography screening program (MSP) was introduced in 2005 and is full-running since 2010. By 2014, incidence rates for invasive breast cancer were very similar to those of the pre-screening era. Therefore, the ongoing effect of the MSP on breast cancer surgery rates can now be investigated. We analyzed population-based breast-conserving (BCS) and mastectomy (MET) surgery rates (per 100,000) among women aged < 50, 50–69 (eligible for the MSP), and 70+ years among women with in situ and invasive breast cancer during 2005–2015. For invasive breast cancer, both BCS and MET rates slightly increased in the age group < 50 years (38.3 in 2005 vs 42.5 in 2015 and 15.7 vs 18.2, respectively). In contrast, MET rates considerably decreased among women aged 50–69 and 70+ years (92 vs 65.4 and 155.4 vs 122.1, respectively), while BCS rates increased in both age groups (210.6 vs 254.4 and 147.2 vs 187, respectively). For in situ breast cancer, MET rates slightly increased in all age groups. BCS rates slightly increased in women aged < 50, but nearly doubled for women aged 50–69 (26.9 vs 49.1) and markedly increased in the 70+ age group (11.5 vs 16.1). During and after the implementation of MSP, there was a strong shift towards BCS within the screening-eligible age group and for women aged 70+ . Women with invasive breast cancer in these age groups may profit from screening with a decline of MET rates in favor of BCS rates at the expense of higher surgery rates for in situ breast cancer.

Keywords Breast neoplasms · Mastectomy · Breast-conserving surgery · Germany · Mammography · Screening

Introduction

After non-melanotic skin cancer, breast cancer is the most frequently diagnosed cancer and the most frequent cause of cancer deaths in women in Germany, with over 69,000 newly diagnosed cases and about 18,000 deaths in 2014. In this calendar year, the crude incidence rate of breast cancer in Germany was about 168 per 100,000 person-years and the age-specific incidence rates for women aged < 50 years, 50–69 years, and 70+ years were about 52, 284 and 346 per 100,000 person-years, respectively [1]. The German guideline for the treatment of breast cancer recommends breast-conserving therapy for in situ cancers with limited size, for invasive breast cancers with favorable relation of tumor size to breast volume, and invasive breast cancers with negative margins (R0) after surgery. In contrast, mastectomy is recommended for incompletely resected cancers (R1), inflammatory breast cancers, contraindications for the adjuvant radiation therapy, and patients' preference [2]. In addition, surgical treatment for breast cancer is intrinsically driven by stage at diagnosis. Apart from reducing breast cancer

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mortality on the long run, the implementation of an organized mammography screening program (MSP) for breast cancer is also expected to permit less invasive breast cancer therapies due to detection in early stage.

According to the German early cancer detection guidelines that were adapted from the European Guidelines for Quality Assurance in Breast Cancer Screening and Diagnosis [3], women aged 50–69 years in Germany are biennially invited to undergo mammography screening. In 2005, the nationwide population-based MSP started with six out of 94 planned screening units and in 2009 all planned 94 screening units had been set up. Since 2010, the MSP is full-running with a coverage of roughly 50% of an eligible population of 10.5 million women, which corresponds to about 2.7 million women nationwide who undergo screening per calendar year. Supplementary Table 1 shows the percentages of women who were actually screened from 2005 to 2015 by calendar year and Federal State [4]. During the introduction phase of a MSP in a population, a transitory increase of incidence and, as a result, of surgery rates for breast cancer is expected due to the detection of clinically unapparent cancers at the first screening round (prevalence screening). Thereafter, these rates usually decline considerably. In Germany, incidence rates for invasive breast cancer, after initially increasing, declined by 2014 nearly down to the levels of the pre-screening era [1, 5]. Thus, it is reasonable to assume that the transitional effect of the prevalence screening on incidence rates is no longer relevant and, consequently, that these rates will remain relatively stable over the next years. Now it is therefore possible to estimate the impact of the full-running MSP on surgical treatment of breast cancer.

The aim of this study was to assess the ongoing effect of the implementation of a nationwide MSP on surgery rates for invasive and in situ breast cancer in Germany based on nationwide hospitalization data of the years 2005 up to 2015.

Methods

According to the hospital financing law (Krankenhausentgeltgesetz, KHEntG), general hospitals in Germany annually transfer their individual hospitalization data to a DRG (diagnosis related group) data center (Institute for the Hospital Remuneration System, InEK). The DRG data center undertakes a plausibility check of the data and forwards anonymised data to the Federal Bureau of Statistics. Based on confidentiality regulations (Bundesstatistikgesetz, BStatG), individual hospitalization data are available for scientific use. DRG-based hospitalization data include one primary diagnosis and up to 89 secondary diagnoses coded by ICD-10 (International Classification of Diseases, 10th edition). Up to 100 medical procedures coded according to a national classification of operations and procedures (OPS) can be documented for each hospitalization case.

Principles of the analysis of this hospitalization file have been described previously [6–9]. In brief, we identified all hospitalizations of women from 2005 through 2015 with a main diagnosis of primary malignant invasive (ICD-10: C50) or in situ breast cancer (ICD-10: D05) that included surgery of the breast (OPS-Codes: 5-870 to 5-879), regardless of whether these women had participated in the MSP or not. Breast surgery was subdivided into breast-conserving surgery (BCS), (OPS: 5-870, 5-871), mastectomy (MET) (5-872 to 5-876), and other surgeries (5-879). As several codes for surgical procedures of interest may have been assigned, we checked first whether a code for a MET was used and, only if not, whether a code for a BCS was used. We excluded few hospitalizations (less than 0.5%) for the following reasons: missing sex of the patient, place of residence outside Germany, homeless people and unknown places of residence, resulting in a final data set of 919,461 hospitalization cases.

Statistical methods

We estimated nationwide annual surgery rates (per 100,000 person years) from 2005 through 2015 by dividing the number of breast cancer-related hospitalizations associated with a surgical treatment of the breast by the midyear population of women. Population data were provided by the Federal Bureau of Statistics. We were especially interested in surgery rates among women aged < 50 years, 50–69 years (eligible for MSP), and 70+ years. Although even narrower age bands would be of interest, we were not allowed to produce these rates due to data protection regulations. In addition, we calculated relative rate changes (in percentage) between 2005 and 2015 with 95% confidence intervals (95%CI).

We used additive regression models to estimate absolute differences of surgery rate changes over time across age groups accounting for overdispersion by using a negative binomial likelihood [10]. Models were computed separately for diagnoses (C50 and D05) and type of surgery (BCS and MET). As the outcome in these models we used the absolute number of hospitalizations in the strata that were defined by year (11 categories; 2005–2015), age group (3 categories; < 50 years, 50–69 years, and 70+ years), and Federal State (16 categories). As covariates, all of them categorical, we used year, age group, Federal State, and the interaction of year and age group. For parameter estimation [10], each covariate (including the intercept) was multiplied by the midyear population in the respective stratum of year, age group, Federal State, and the interaction of year and age group. The parameters of actual interest, that is, the differences of rate differences were then estimated as simple linear

Table 1 Surgery rates (per 100,000) for invasive breast cancer (ICD-10: C50), observed and estimated changes

	Nationwide analysis				Model-based differences in rate change		
	Rate 2005 (SE)	Rate 2015 (SE)	Rate changes 2015–2005	Relative rate changes (%) (95%CI)	Comparison (age-) groups	Rate difference 2015–2005	95%CI
BCS							
0–49 years	38.3 (0.4)	42.5 (0.4)	4.2	11.0 (7.9; 14.2)			
					50–69 versus < 50	41.0	23.4; 58.6
50–69 years	210.6 (1.4)	254.4 (1.5)	43.8	20.8 (18.7; 22.9)			
					50–69 versus 70+	7.6	− 14.1; 29.2
70+ years	147.2 (1.5)	187.0 (1.6)	39.8	27.0 (23.7; 30.3)			
MET							
0–49 years	15.7 (0.3)	18.2 (0.3)	2.5	15.9 (11.0; 21.1)			
					50–69 versus < 50	− 28.7	− 35.0; − 22.5
50–69 years	92.0 (0.9)	65.4 (0.8)	− 26.6	− 28.9 (− 31.0; − 26.7)			
					50–69 versus 70+	5.7	− 6.4; 17.7
70+ years	155.4 (1.5)	122.1 (1.3)	− 33.3	− 21.4 (− 23.6; − 19.2)			

SE standard error; 95%CI 95% confidence interval, BCS breast-conserving surgery, MET mastectomy

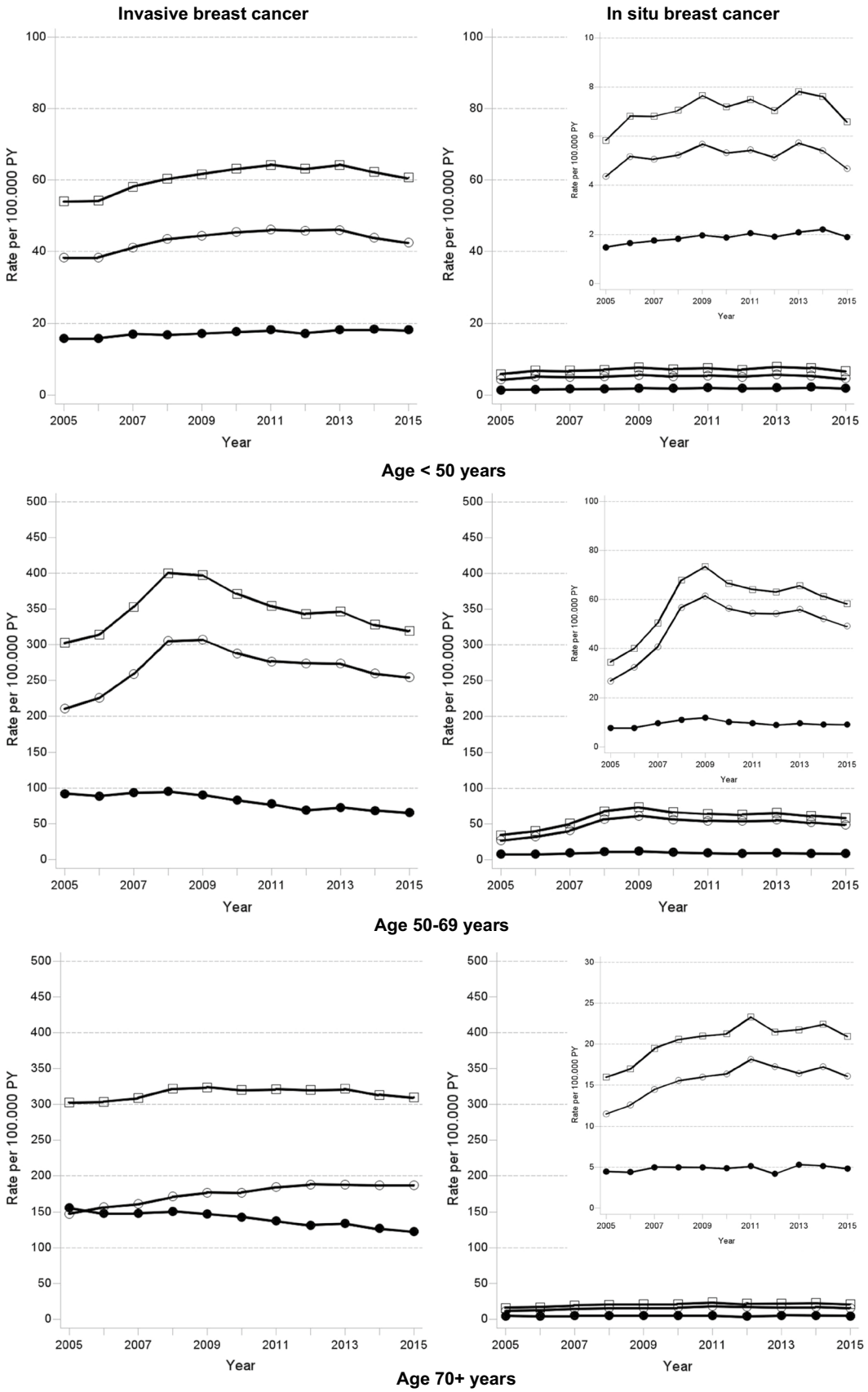
The estimated differences of rate changes are estimated from an additive negative binomial regression model with Federal State, calendar year, age group, and the interaction of calendar year and age group as covariates

combinations of the respective model parameters and are reported with their 95% confidence intervals. This means especially that the reported differences between 2005 and 2015 use information from the complete time course. The additive negative binomial models were estimated by the NLMIXED procedure in SAS, because only this procedure allows for estimating the necessary customized linear combinations of parameters. However, we double-checked the results for the main parameters by using the GENMOD procedure, with the code given in [10]. Hospitalizations classified as "other surgeries" (N = 2598, 0.3%) were excluded from these additive regression analyses. All analyses were performed with SAS® (SAS Inc., Cary, NC, USA), Version 9.4.

Results

Among all age groups, the overall surgery rates (BCS plus MET rates) for both invasive and in situ breast cancer showed an increase during the introduction phase of the MSP which was only partially offset by a decrease in the rates during the following phase of the full-running program. However, for invasive breast cancer, overall surgery rates at the end of the study period were only slightly higher than the rates in the pre-screening period for all three age groups. In contrast, overall surgery rates for in situ breast cancer remained markedly elevated in the age groups 50–69 and 70+, while there was only a slight increase over time in the age group < 50. BCS rates showed widely the same trend as the overall surgery rates. MET rates for invasive breast cancer in women aged 50–69 years and 70+ years decreased continuously during the whole study period, while MET rates for invasive breast cancer in women aged < 50 and for in situ breast cancer in all age groups showed little change over time (Fig. 1).

For invasive breast cancer, different trends in surgical treatment between 2005 and 2015 can be observed among the three age groups. For the youngest age group there was a slight increase in both rates, BCS and MET (from 38.3 to 42.5 and from 15.7 to 18.2 per 100,000, respectively). In contrast, BCS rates increased considerably among women aged 50–69 and 70+ years from 210.6 to 254.4 per 100,000 and from 147.2 to 187 per 100,000, respectively. The model-based comparison of the differences between BCS rate changes over time in the screening eligible women aged 50–69 with the differences in women aged < 50 and 70+ showed a 41 per 100,000 (95%CI: 23.4; 58.6) and 7.6 per 100,000 (95%CI: − 14.1; 29.2) larger absolute increase of the BCS rate among women aged 50–69, respectively. MET rates for invasive breast cancer decreased considerably in women aged 50–69 years and 70+ years from 92 to 65.4 per 100,000 and from 155.4 per 100,000 to 122.1 per 100,000, respectively. The comparison of MET rate changes over time showed a 28.7 per 100,000 (95%CI: − 35; − 22.5) larger decrease of the rates among women aged 50–69 compared to women aged < 50 years. In comparison to women aged 70+ years, women aged 50–69 showed a 5.7 per 100,000 (95%CI: − 6.4; 17.7) smaller decrease of the MET rates (Table 1).


Invasive breast cancer
In situ breast cancer
Rate per 100.000 PY
Year
Age < 50 years
Age 50-69 years
Age 70+ years

◂**Fig. 1** Age-specific surgery rates (per 100,000) of in situ and invasive breast cancer in Germany 2005–2015. Squares: breast surgery including breast-conserving surgery and mastectomy, unfilled circles: breast-conserving surgery, filled circles: mastectomy, PY person-years. The inset graph shows a more detailed version of the overall graph up to a rate of 10, 100, or 30 per 100,000 respectively

While the BCS rate for in situ breast cancer among women aged < 50 years did not vary substantially, among women aged 50–69 and 70+ years these rates were considerably higher in 2015 compared to 2005 (49.1 vs 26.9 per 100,000 and 16.1 vs 11.5 per 100,000, respectively). Using additive regression models to compare the BCS rate changes between 2005 and 2015 among women aged 50–69 with those among women aged < 50 and 70+ revealed a 20.3 per 100,000 (95%CI: 15.5; 25) and 15.5 per 100,000 (95%CI: 10.3; 20.6) larger absolute increase of the BCS rate among women aged 50–69 respectively. Finally, MET rates for in situ breast cancer increased slightly over time in all three age groups (Table 2).

From 2005 through 2015, overall 815,703 and 103,758 breast surgeries for invasive and in situ breast cancer, respectively, were performed in Germany. The annual surgery numbers increased during the implementation phase of the MSP and thereafter decreased. The proportion of MET among all breast surgeries for both cancer types was lower in 2015 than in 2005 (28.3 vs 36.3% and 18.9 vs 23.8%, respectively) (Supplementary Table 2). Supplementary Tables 3, 4 and 5 give an overview of surgery rates for invasive and in situ breast cancer by surgical treatment, age group and calendar year.

Discussion

In Germany, about 5 years after the complete implementation of the nationwide population based MSP the incidence rates for invasive breast cancer were very similar to those before starting the program. Among women in the age group eligible for screening, the overall surgery rate for invasive breast cancer after 5 years of full-running MSP was only slightly higher than the rate of the pre-screening era. However, in the age groups 50–69 and 70+ years, BCS rates for invasive breast cancer were considerably higher than before the implementation of the program, while the MSP was associated with a considerable decrease in mastectomy surgeries.

Many previous studies mainly investigated the effect of MSPs on surgery rates during the introduction phase of the program but only few population-wide studies assessed the influence of a well-running MSP on the changes of surgery rates. In Norway, from the pre-screening (1993–1995) to the full-running phase of the MSP (2005–2008), the overall surgery rates for invasive or in situ breast cancer among screening-eligible women increased from 180 to 305 per 100,000 whereas the corresponding rates among women aged 40–49 years and 70–79 years showed only little change over time. However, mastectomy rates for breast cancer (invasive plus in situ) were considerably lower than during the pre-screening period in all age groups [11]. Increasing trends in BCS rates were found also in an analysis that compared data on invasive or in situ breast cancer from Northern Ireland that started a MSP program for women aged 50–64 years in 1993 with data from the Republic of Ireland that began MSP in 2000. In addition, MET rates increased in both populations only among women aged 65+ years [12]. Data from Denmark showed that, among women aged 50–69 years eligible for screening, MET rates in areas of the country where the MSP was full-running since many years were very similar to those found in areas where the program had not been implemented at all [13]. Finally, a recent analysis of surgery data from women aged 50–75 years who underwent biennial screening in the Netherlands between 1997 and 2011 showed that BCS rate did not substantially vary, whereas MET rate increased gradually from 0.9 to 1.9 per 1000 [14]. Data from the population-based epidemiological cancer registry in North Rhine-Westphalia, a Federal state in the northwest of Germany, have shown that, among women aged 50–69 years, the introduction phase of the MSP was associated with an increase of incidence rates of advanced-stage breast cancer followed by a considerable decrease of these rates, whereas the incidence rates of early-stage breast cancer remained elevated also during the full-running phase of the MSP, suggesting a stage shift of breast cancer incidence [15]. Similar effects were reported by the Robert-Koch-Institute (RKI) on the aggregated data of the German cancer registries. Within the screening-eligible ages group rates of breast cancer in UICC stages II + III increased with the implementation of the MSP and afterwards dropped below the rates of the pre-screening era [16]. Our data show that the implementation of the MSP among women aged 50+ years is associated with increases in BCS rates for both invasive and in situ breast cancer. At the same time, MET rates for invasive breast cancer decreased among women aged 50–69 and 70+ and were considerably lower in 2015 if compared to those of the pre-screening era. Our findings are therefore highly consistent with those of Simbrich et al. [15] and strongly support the proposition within the RKI report, that women in the target population might have profited from early detection by less aggressive treatment options.

To assess the independent effect of the MSP on the surgical treatment modality of breast cancer, we have to consider the influence of non-MSP related factors, including temporal changes over time of treatment protocols, which are influenced by guidelines as well as underlying temporal trends in background incidence rates and the use of opportunistic

Table 2 Surgery rates (per 100,000) for in situ breast cancer (ICD-10: D05), observed and estimated changes

	Nationwide analysis				Model-based differences in rate change		
	Rate 2005 (SE)	Rate 2015 (SE)	Rate changes 2015–2005	Relative rate changes (%) (95%CI)	Comparison (age-) groups	Rate difference 2015–2005	95%CI
BCS							
0–49 years	4.4 (0.1)	4.7 (0.1)	0.3	6.8 (−1.8; 16.2)			
					50–69 versus < 50	20.3	15.5; 25.0
50–69 years	26.9 (0.5)	49.1 (0.7)	22.2	82.5 (74.4; 91.0)			
					50–69 versus 70+	15.5	10.3; 20.6
70+ years	11.5 (0.4)	16.1 (0.5)	4.6	40.0 (27.8; 53.4)			
MET							
0–49 years	1.5 (0.1)	1.9 (0.1)	0.4	26.7 (10.3; 45.6)			
					50–69 versus < 50	1.3	0.0; 2.6
50–69 years	7.7 (0.3)	9.1 (0.3)	1.4	18.2 (7.8; 29.7)			
					50–69 versus 70+	1.3	−0.3; 2.8
70+ years	4.5 (0.3)	4.8 (0.2)	0.3	6.7 (−8.6; 24.5)			

SE standard error, 95%CI 95% confidence interval, BCS breast-conserving surgery, MET mastectomy

The estimated differences of rate changes are estimated from an additive negative binomial regression model with Federal State, calendar year, age group, and the interaction of calendar year and age group as covariates

screening, which is mammography screening outside an organized MSP. As the organized MSP in Germany began relatively late compared to most European countries, the changes in treatment protocols with shift to BCS may have contributed to a lowering of MET rates. To assess the potential influence of non-MSP associated secular trends, our statistical models for estimating differences in temporal changes in surgical rates used the age groups < 50 years and 70+ years as reference groups. In the younger age group < 50, we observed only slight changes in surgical rates during the study period. Both rates, BCS and MET, were slightly higher in 2015 compared to 2005 for invasive and in situ breast cancer. These results indicate that there were no substantial changes over time of standard treatment protocols for breast cancer in Germany, independent of screening activities. On the other hand, with the exception of the prevalence peak, surgical rates showed similar trends in the older age group 70+ as in the screening-eligible age group. In particular, for invasive breast cancer, BCS rates were considerably higher by the end of the study period than in 2005 while MET rates had dropped during the study period. For in situ breast cancer, an increase in BCS rates could be observed during the introduction phase of the MSP, which was not offset by a decrease in MET rates. As a result, overall surgery rates for in situ breast cancer stayed elevated in comparison to the pre-screening era in both age groups 50–69 and 70+. However, the similarity of surgery rates between the two age groups is restricted to a direct comparison of the pre-screening era with the end of the study period. Surgical trends in women aged 70+ showed no intermediate peak of surgical rates as a result of the incidence peak of prevalence screening. The temporal pattern of surgery rates in women aged 70+ years deserves some comments. First, we assume that this increase is due to screening activity in this age group as in situ breast cancers are typically detected by mammography screening. The lack of an increase of surgery rates for invasive breast cancer in combination with a lack of a prevalence peak during introduction of the MSP may indicate that the increase of surgery rates for in situ breast cancer among women aged 70+ years is mainly due to ongoing mammography screening outside the MSP among women who previously participated in the MSP. Second, an unknown fraction of in situ cancers undergoing breast surgery reflect overdiagnosis and consequently overtreatment. It is unresolved to which extent treatment of in situ breast cancer can prevent the development of invasive breast cancer. Detection rates of in situ breast cancer in the MSP are highest for high-grade in situ carcinoma [17]. Data from the UK National Health Services Breast Screening Programme (NHSBSP) obtained from women who attended the mammography screening over four screening years showed that the detection rate of in situ breast cancer was negatively associated with the incidence rate of invasive interval breast cancer [18]. Mammographies coded as diagnostic most

likely contain a fraction of opportunistic mammographies. A time trend analysis of health-insured (AOK, Allgemeine Ortskrankenkasse) women aged 50–69 in Germany showed that in the period 2007–2009 18% of all insured women received diagnostic mammography, whereas this percentage was only 10% in the period 2014–2016 [19, 20]. We cannot answer how much this decrease is caused by the decrease in opportunistic screening. However, the fact that we observed this decline at all suggests that mammography screening outside the organized MSP took place in Germany and may have slightly influenced our results.

Although we present the largest nationwide study of the association between the organized MSP and surgery rates for breast cancer in Germany, there are several factors that limit our results. First, the reference age groups < 50 years and 70+ years provide only a rough estimation of the surgery rates among the counterfactual population of women in the screening age group had the MSP not been implemented. Second, we were not able to distinguish between first- and subsequent screening rounds. Third, only about half of the women aged 50–69 participate in MSP [4], limiting the possible effects of the screening program on the population. Finally, due to the anonymization of the data and a lack of pseudonyms, women that are hospitalized more than once with a diagnosis of breast cancer during the study period could not be re-identified.

In conclusion, we showed that, after the complete implementation of MSP and 5 years of full-running, there was a strong shift from MET towards BCS within the screening-eligible age group and for women aged 70+. While after 5 years of the full-running MSP the incidence rates for invasive breast cancer in Germany were very similar to those of the pre-screening era, our results suggest that women in the target population may profit from the MSP with a reduction in the need for aggressive surgical treatments for invasive cancer at the expense of higher surgery rates for in situ breast cancer.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval For this type of study formal consent is not required.

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