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Immunohistochemical Tumor Characteristics of Breast Cancer according to Participation in the Mammography Screening Program

Immunhistochemische Tumoreigenschaften bei Mammakarzinomen in Abhängigkeit von der Teilnahme am Mammografie-Screening-Programm

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ABSTRACT

Background Breast cancer detected in participants of the German Mammography Screening Program (MSP) shows a favorable distribution of prognostic parameters and hormone receptor status compared to cancer in non-participants, even including interval cancers. The aim of our study is to examine the distribution of intrinsic breast cancer subtypes considering the proliferation marker Ki-67 in participants and non-participants in a population-based setting and to evaluate the association between Ki-67 and tumour characteristics.

Methods Population based data from the Epidemiological Cancer Registry Lower Saxony is analysed in this retrospectiv observational study. 1115 cases of breast cancer (in situ and invasive, year of diagnosis 2014) among women aged 50–69 years and residing in the regions of two screening units of Lower Saxony are included (n = 285 634 biennially entitled women). The group of the participants containes cancers that are detected by screening or in the interval of 24 month after a negative screening. The group of non-participants includes all breast cancers without match with screening data.

Results Considering cases with invasive breast cancer (n = 953) tumours detected in screening participants are more often diagnosed in early T stage (T1, p < 0,0001), HER2 negativ (p = 0,0336), with lower Ki-67 percentage scores (p < 0,0003) and without loco-regional lymph node involvement (p < 0,0001), compared to tumours in non-participants – even including interval cancers. Regarding grading both groups show less differences (p = 0,1718), because interval cancer are more comparable with cancers in non-participants. We find distinct differences in distribution of the intrinsic suptypes between both groups (p < 0,0003): especially in category Luminal A (38,4 % vs. 26,7 %), but also in the categories Luminal A or B (26,7 vs. 22,1 %), Luminal B (21,1 vs. 30,6 %), HER2 enriched (5,1 vs. 7,8 %) und triple-negative (8,8 vs. 12,8 %). Ki-67 is associated with all analysed prognostic factors, first of all with grading (p < 0,0001).

Discussion According to the S3-Guidelines an adjuvant chemotherapy can be avoided in the majority of Luminal A type breast cancers. Assuming that both groups received a guideline-based therapy MSP participants (including interval cancers) could be treated with less aggressive systemic therapy compared with cancers in non-participants. Our results indicate for both groups that Ki-67 is a prognostic marker, which is not independent of other histopathological factors.

# Britta Mathys and Iris Urbschat contributed equally to this paper.

ZUSAMMENFASSUNG

Hintergrund Mammakarzinome, die bei Teilnehmerinnen des Mammografie-Screening-Programms (MSP) detektiert werden, zeigen auch unter Berücksichtigung der Intervallkarzinome eine günstigere Verteilung der klassischen Prognosefaktoren und des Hormonrezeptorstatus im Vergleich zu Karzinomen bei Nichtteilnehmerinnen. Mit dieser Studie sollen erstmals bevölkerungsbezogene Aussagen zur Verteilung der intrinsischen Subtypen unter Einbeziehung des Ki-67-Proliferationsindex für Teilnehmerinnen und Nichtteilnehmerinnen des MSP vorgelegt werden. Ergänzend wird darüber hinaus untersucht, in welchem Ausmaß der Ki-67-Index mit den tumorbiologischen Eigenschaften assoziiert ist.

Methodik In der retrospektiven Beobachtungsstudie kommen die bevölkerungsbezogenen Daten des epidemiologischen Krebsregisters Niedersachsen (EKN) für das Diagnosejahr (DJ) 2014 zur Auswertung. 1115 Mammakarzinome (ICD-10 C50 + D05 ohne D05.0) der 50–69-jährigen Frauen mit Wohnort in den Regionen der Screening-Einheiten Hannover und Niedersachsen-Nordwest (n = 285 634 2-jährlich anspruchsberechtigte Frauen) werden in die Studie einbezogen. Die Gruppe der Teilnehmerinnen umfasst sowohl Screening-Fälle als auch Intervallkarzinome, die bis 24 Monate nach unauffälligem Screening auftraten. Als Tumoren der Nichtteilnehmerinnen gelten alle Mammakarzinome, die keiner Screening-Teilnehmerin zugeordnet werden konnten.

Ergebnisse Für invasive Tumoren (n = 953) zeigt sich, dass Tumoren von Teilnehmerinnen – auch unter Einbeziehung der Intervallkarzinome – im Vergleich zu Nichtteilnehmerinnen häufiger in einem kleineren T-Stadium (T1) und ohne regionäre Lymphknotenmetastasen (N0) befundet werden (jeweils $p < 0{,}0001$), häufiger HER2-negativ sind ($p = 0{,}0336$) und einen niedrigeren Ki-67-Proliferationsindex aufweisen ($p < 0{,}0003$). Lediglich für das Grading zeigen sich nur geringe Unterschiede zwischen den beiden Gruppen ($p = 0{,}1718$); dies ist auf die Intervallkarzinome zurückzuführen, die eher mit Tumoren der Nichtteilnehmerinnen vergleichbar sind. Die Unterschiede zwischen Teilnehmerinnen und Nichtteilnehmerinnen zeigen sich auch in der Verteilung der intrinsischen Subtypen ($p < 0{,}0003$): besonders deutlich sind diese in der Kategorie Luminal A (38,4 vs. 26,7 %), aber auch die Kategorien Luminal A oder B (26,7 vs. 22,1 %), Luminal B (21,1 vs. 30,6 %), HER-2-positiv (5,1 vs. 7,8 %) und triple-negativ (8,8 vs. 12,8 %) sind unterschiedlich stark vertreten. Ki-67 ist sowohl bei Teilnehmerinnen als auch bei Nichtteilnehmerinnen mit allen Prognosefaktoren assoziiert, besonders ausgeprägt ist die Assoziation mit dem Grading ($p < 0{,}0001$).

Diskussion Für Mammakarzinome des Luminal-A-Subtyps kann nach aktuellen Empfehlungen der S3-Leitlinie überwiegend auf eine Chemotherapie verzichtet werden. In der Annahme einer leitliniengerechten Therapie dürfte die Gesamtgruppe der Teilnehmerinnen (inklusive derer mit Intervallkarzinomen) somit deutlich häufiger eine schonendere Therapie erfahren haben als die Gruppe der Nichtteilnehmerinnen. Die Analysen zu Ki-67 weisen für beide Gruppen darauf hin, dass der Proliferationsindex ein Prognosefaktor ist, der jedoch nicht unabhängig ist.

Background

Breast cancer accounts for the largest proportion of cancer deaths in women in Germany, amounting to 17.7% [1]. Aimed at diagnosing breast cancer at an early stage, the quality-assured Mammography Screening Program (MSP) has been implemented in Germany since 2005, following the European guidelines [2]. In this program, all eligible women aged 50–69 years are invited for a screening examination every 2 years. Early detection of carcinoma is associated with improved prognosis and more conservative therapy [3]. Several studies have shown that MSP participants with invasive breast cancer had more favorable prognostic factors and tumor characteristics than non-participants [4–6]].

Besides the classical prognostic factors (such as age, grading, tumor size, nodal status), treatment strategies in early breast carcinoma are also influenced by the hormone receptor status, the HER2 status and the proliferation marker Ki-67. As an alternative to the analysis of gene expression profiles, a simplified classification of intrinsic subtypes of breast carcinoma based on these immunohistochemically determinable tumor characteristics can be performed, which demonstrates differences in their course and response to therapy: whereas in the case of a tumor of the luminal A subtype, adjuvant endocrine therapy alone is usually sufficient, chemotherapy is predominantly recommended for the other subtypes, supplemented if necessary by anti-HER2 therapy [7, 8]. In this context, the level of the Ki-67 proliferation index influences the decision whether the implementation of adjuvant chemotherapy is considered to improve the prognosis of an early hormone receptor-positive and HER2-negative tumor. Moreover, Ki-67 is considered an independent prognostic factor, with the level of the Ki-67 proliferation index influencing disease-free survival and overall survival [9, 10]. Data from a meta-analysis suggest that a high Ki-67 positivity of ≥ 25% can be expected to result in lower overall survival compared with lower expression levels [11].

The aim of the present study is to compare the tumor biological characteristics of breast carcinomas in participants and non-participants of the MSP in Lower Saxony on the basis of cancer registry data and to use this information to derive conclusions about therapy for these two groups. For the participants, we will consider both carcinomas detected during screening and carcinomas diagnosed during the interval. To our knowledge, this will be the first time that the comparative evaluation of molecular subtypes using the Ki-67 proliferation index will be performed on a population-based level in Germany. The extent to which the Ki-67 proliferation index is associated with the biological characteristics of the tumor will also be shown in a supplementary analysis. Therefore, tumors from participants and non-participants will be considered separately.

▶ **Table 1** Molecular subtypes of breast carcinomas. Data according to S3 guideline [7, modified]

Molecular subtypes	ER*	PR**	HER2	Ki-67
Luminal A	ER-positive and/or PR-positive (≥ 1 % or IRS > 2)		Negative	Low (≤ 10 %)
Luminal A or B***	ER-positive and/or PR-positive (≥ 1 % or IRS > 2)		Negative	Intermediate (11–24 %)
Luminal $B_{HER2\text{-}neg}$	ER-positive and/or PR-positive (≥ 1 % or IRS > 2)		Negative	High (≥ 25 %)
Luminal $B_{HER2\text{-}pos}$			Positive	Any Ki-67
HER2-positive****	Negative	Negative	Positive	Any Ki-67
Triple-negative	Negative	Negative	Negative	Any Ki-67

* ER = estrogen receptor;
** PR = progesterone receptor;
*** cannot be classified as luminal A or luminal B due to intermediate Ki-67;
**** HER2-positive = score 3 or score 2 and positive FISH.

Methods

This retrospective observational study evaluates population-based data from the Epidemiological Lower Saxony Cancer Registry (EKN). Our reference population was all 285,634 women aged 50–69 years living in the catchment area of the 2 screening units (SU) of Northwest Lower Saxony and Hannover who were invited for screening every two years. The German Mammography Screening Program (MSP) was implemented in these regions from 2005 to 2008.

The study included 1,115 cases of invasive and in situ breast carcinomas (ICD-10 C50 and D05, excluding D05.0) diagnosed in the reference population in 2014. Synchronous or metachronous secondary breast carcinomas were counted multiple times (n = 18). Data completeness for breast cancer is over 95 %, according to Robert Koch-Institute estimates for the year of diagnosis 2014. The EKN data status is October 2020. The mammography screening participation rate for 2014 was 55 %; 18 % of the participants were first-time participants, and 82 % were repeat participants.

Through Record-Linkage of all MSP participant data with the cancer registry data the cause of cancer detection for all breast carcinomas were determined in the EKN. We made a distinction between participants and non-participants. The latter were tumor patients for whom there was no match with the screening data. For the group of MSP participants, tumors were further differentiated into cases detected at screening (screening cases) and interval carcinomas (IC). We defined IC as a breast carcinoma diagnosed outside the MSP in a participant who was unremarkable at screening during the interval 0–24 months after the last screening examination. We excluded the following cases: carcinomas diagnosed later than 24 months after the last unremarkable screening examination because they could not be assigned to one of the screening groups (n = 78); dropouts from the MSP for whom no further diagnostic clarification could be performed after abnormal screening mammography (n = 7); and tumors with inadequate data quality (n = 1). Recurrences and metastases (ICD-10 C79.81) were not included in the study. For tumors treated neoadjuvantly, the distribution of TNM stage refers to the primary clinical TNM stage.

In addition to the hormone receptor status and the HER2 status, the Ki-67 proliferation index was captured subsequently for this study from the diagnostic texts available in the cancer registry and classified into three groups according to the open recommendations of the S3 guideline group: Ki-67 low (≤ 10 %), intermediate (11–24 %), and high (≥ 25 %). All tumors were categorized into the molecular subtypes luminal A, luminal A or B, luminal B, HER2-positive, and triple-negative based on immunohistochemical parameters and the Ki-67 index (▶ **Table 1**).

Tumors with missing data were excluded from the relevant calculations. They are included as case numbers in the tables.

We followed the Good Epidemiological Practice guidelines when evaluating the data.

We performed the evaluations using Access (2016). For categorical variables, we calculated differences using the chi-squared test; for numerical variables, we used a t-test. We performed the tests using Excel (2016). We presented the differences by means of the p-value. However, due to the partially exploratory nature of the study and the large number of tests performed, the p-values should not be seen as having statistical significance.

Results

In the study population, 1,115 breast carcinomas (ICD-10 C50 + D05, excluding D05.0) were diagnosed. Of these carcinomas, 698 were diagnosed in screening participants and 417 in non-participants (▶ **Table 2**). The proportion of carcinomas in situ was 19.1 % in participants. This was significantly higher than the proportion of 7.0 % in non-participants ($p < 0.0001$). The difference is mainly due to screening cases (in situ proportion 22.8 %). The mean age of onset was 1.2 years higher for participants at 60.3 years than for non-participants at 59.1 years ($p < 0.0023$). A detailed analysis (not shown) demonstrates that, among non-participants, younger women (50–52 years) are significantly more likely represented compared to participants.

▶ **Table 2** Biological characteristics of breast carcinomas dependent on screening participation (Yd 2014, 50–69-year-old women, NW Lower Saxony and Hanover region).

Biological characteristics of the tumor	Participants (Ps)						Non-Ps		Total		p-value (cf. Ps to Non-Ps)
	Screening cases (A)		Interval carcinomas* (B)		Ps total (A + B)						
	n	%	n	%	n	%	n	%	n	%	
Breast cancer cases in total (ICD-10 C50 + D05)	**562**	**100.0**	**136**	**100.0**	**698**	**100.0**	**417**	**100.0**	**1,115**	**100.0**	
Carcinomas in situ (D05)	128	22.8	5	3.7	133	19.1	29	7.0	**162**	14.5	<0.0001
Invasive carcinomas (C50)	434	77.2	131	96.3	565	80.9	388	93.0	**953**	85.5	
Age at diagnosis Average age (SD**)	60.1 (5.9)		60.9 (5.5)		60.3 (5.8)		59.1 (6.0)		**59.8** (5.9)		0.0023
Invasive carcinomas (ICD-10 C50)	**434**	**100.0**	**131**	**100.0**	**565**	**100.0**	**388**	**100.0**	**953**	**100.0**	
of which:											
T stage 1	315	73.6	51	40.5	366	66.1	159	48.9	**525**	59.7	<0.0001
T stage 2 +	113	26.4	75	59.5	188	33.9	166	51.1	**354**	40.3	
No data	6		5		11		63		**74**		
N stage 0 (incl. N1mi)	349	82.5	82	66.1	431	78.8	202	65.6	**633**	74.0	<0.0001
N stage 1 +	74	17.5	42	33.9	116	21.2	106	34.4	**222**	26.0	
No data	11		7		18		80		**98**		
M stage 0	386	99.0	121	98.4	507	98.8	239	87.2	**746**	94.8	<0.0001
M stage 1	4	1.0	2	1.6	6	1.2	35	12.8	**41**	5.2	
No data	44		8		52		114		**166**		
Grading I	64	14.8	7	5.6	71	12.7	40	11.0	**111**	12.1	0.1718
Grading II	244	56.5	65	51.6	309	55.4	185	51.1	**494**	53.7	
Grading III	124	28.7	54	42.9	178	31.9	137	37.8	**315**	34.2	
No data	2		5		7		26		**33**		
ER+ PR+	310	74.5	73	64.0	383	72.3	194	66.7	**577**	70.3	0.0747
ER+ PR-	58	13.9	14	12.3	72	13.6	38	13.1	**110**	13.4	
ER- PR+	1	0.2	1	0.9	2	0.4	0	0.0	**2**	0.2	
ER- PR-	47	11.3	26	22.8	73	13.8	59	20.3	**132**	16.1	
No data	18		17		35		97		**132**		
HER2-positive	49	12.0	28	24.6	77	14.7	59	20.6	**136**	16.8	0.0336

▶ **Table 2** (Continuation)

Biological characteristics of the tumor	Participants (Ps)						Non-Ps		Total		p-value (cf. Ps to Non-Ps)
	Screening cases (A)		Interval carcinomas* (B)		Ps total (A + B)						
	n	%	n	%	n	%	n	%	n	%	
HER2-negative	360	88.0	86	75.4	446	85.3	228	79.4	**674**	83.2	
No data	25		17		42		101		**143**		
Ki-67 high (≥ 25 %)	94	23.1	52	46.4	146	28.1	117	41.6	**263**	32.9	0.0003
Ki-67 intermediate (11–24 %)	134	32.9	29	25.9	163	31.4	80	28.5	**243**	30.4	
Ki-67 low (≤ 10 %)	179	44.0	31	27.7	210	40.5	84	29.9	**294**	36.8	
No data	27		19		46		107		**153**		
Molecular subtypes											
Luminal A	169	41.9	28	25.5	197	38.4	75	26.7	**272**	34.3	0.0003
Luminal A or B***	113	28.0	24	21.8	137	26.7	62	22.1	**199**	25.1	
Luminal B	76	18.9	32	29.1	108	21.1	86	30.6	**194**	24.4	
• of which:											
▪ Luminal $B_{HER2\text{-}neg}$	(44)		(14)		(58)		(50)		(108)		
▪ Luminal $B_{HER2\text{-}pos}$	(32)		(18)		(50)		(36)		(86)		
HER2-positive	17	4.2	9	8.2	26	5.1	22	7.8	**48**	6.0	
Triple-negative	28	6.9	17	15.5	45	8.8	36	12.8	**81**	10.2	
No data	31		21		52		107		**159**		

* Interval carcinomas 0–24 months after screening examination;
** SD = standard deviation.
*** Cannot be classified as luminal A or luminal B due to intermediate Ki-67.

Further consideration of biological tumor characteristics concerns invasive carcinomas (n = 953, of which 565 were participants and 388 were non-participants). Invasive interval carcinomas accounted for 23.2 % of all invasive carcinomas in participants (131 out of 565 cases). As regards the distribution of the classical prognostic factors, the following differences between the groups are evident: Participants overall had a more favorable distribution of classical prognostic factors compared to non-participants, with a greater number of smaller tumors in stage T1 (66.1 % vs. 48.9 %; p < 0.0001), which were more frequently node-negative (78.8 % vs. 65.6 %; p < 0.0001) and occurred more frequently without distant metastases (98.8 % vs. 87.2 %; p < 0.0001). It is only in grading that the differences between participants and non-participants appear less pronounced (p = 0.1718). Moreover, tumors from participants were more likely to be hormone receptor-positive (86.2 % vs. 79.7 %; p = 0.0747), HER2-negative (85.3 % vs. 79.4 %; p = 0.0336) and more often had low Ki-67 indices (40.5 % vs. 29.9 %; p = 0.0003). ▶ **Table 2** also shows that the differences between participants and non-participants were mainly due to screening cases. In terms of the biological characteristics of the tumor, interval carcinomas tend to correspond to non-participants.

Complete data were available for categorizing subtypes by immunohistochemical algorithm (▶ **Table 1**), for 83 % (794 of 953) of all invasive carcinomas (participants: 91 %; non-participants: 72 %). After excluding tumors with missing data, the distribution of subtypes differed significantly between participants and non-participants (p < 0.0003). Luminal A subtype tumors were more common in participants than non-participants (38.4 % vs. 26.7 %). Our analysis could not unambiguously classify luminal A or B category tumors (26.7 % vs. 22.1 %) because of their intermediate Ki-67 values. Additional tumor characteristics (grading, T stage, nodal status) or the use of a multigene signature would be required in clinical practice to make a therapeutic decision [12, 13]. The result of a multigene test is usually not available in the EKN. Tumors of the luminal B subtype (21.1 % vs. 30.6 %), HER2-positive (5.1 % vs. 7.8 %), and triple-negative (8.8 % vs. 12.8 %) were observed less frequently in participants as compared with non-participants.

The results in ▶ **Table 3, 4** indicate the extent to which the Ki-67 proliferation index is associated with the biological characteristics of the tumor. Total participants (▶ **Table 3**) and non-participants (▶ **Table 4**) are shown separately. Ki-67 proliferation index data completeness was 84 % (participants 92 %, non-participants 72 %), which was slightly higher than the values reported for intrinsic subtypes. Cases with missing values are not included in the calculation of the p-value.

The results show an increasingly unfavorable distribution of prognostic factors with increasing Ki-67 positivity. In the group of participants, the association between Ki-67 and T stages (Ki-67 low: T1 = 78.8 % vs. Ki-67 high: T1 = 51.4 %; p < 0.0001) was even slightly more pronounced than for N stages (Ki-67 low: N0 = 84.5 % vs. Ki-67 high: N0 = 72.3 %; p = 0.0230) and M stages (Ki-67 low: M0 = 100 % vs. Ki-67 high: M0 = 97 %; p = 0.0316). This correlation was also found in the group of non-participants to a similar extent; the correlation was less pronounced only for M stages (p = 0.1761).

There was a particularly strong association between Ki-67 and the grading distribution (p = 0.0001). For participants, high Ki-67 positivity of ≥ 25 % was associated with fast-growing, undifferentiated tumors (grading III) in 80.7 % of cases. In contrast, only 4.3 % of tumors with a low Ki-67 positivity of ≤ 10 % were grading III. The results for non-participants differed only slightly from those for participants.

Sensitivity analysis

It is well known that screening is associated with a stage shift. In particular, screening helps advance the diagnosis of slow-growing and biologically less aggressive carcinomas. Assuming that these tumors, which have a favorable prognosis, are diagnosed earlier in all participant age groups (from the over-70 age group to the 65–69 screening age group; 65–69 → 60–64; 60–64 → 55–59; 55–59 → 50–54), we can conclude that bringing forward the diagnosis in the youngest age group of 50–54 years may result in more tumors with prognostically favorable characteristics. This could bias the overall results.

Another bias is possible in the group of non-participants. This group is expected to include a higher number of patients with a greatly increased risk of breast cancer, who have a genetically determined younger age at onset of the disease. It can be assumed that they are more often represented in the youngest age group of 50–54-year-olds.

Therefore, in a sensitivity analysis, we tested whether the effect of the more favorable distribution of molecular subtypes in participants compared with non-participants which we described in ▶ **Table 2** would be maintained even if we excluded the youngest age group, 50–54 years, from the study. This sensitivity analysis showed that, for the remaining age group of 55–69 years, there is still a more favorable distribution of molecular subtypes for the group of participants (p = 0.0065). The proportion of luminal A carcinomas in this group is 12.1 percentage points higher than that of non-participants (37.0 % vs. 24.9 %; see ▶ **Table 5**).

Discussion

Our study is a retrospective analysis of cancer registry data on the biological characteristics of breast carcinomas in women after the comprehensive implementation of the German Mammography Screening Program in Lower Saxony.

This is the first population-based comparison of breast cancer characteristics between screening participants and non-participants, taking into account the proliferation marker Ki-67. Even including the interval carcinomas, which have a less favorable prognosis and accounted for 23.2 % of tumors in the participant group (131 out of 565 invasive tumors), the results showed a more favorable distribution of classical prognostic factors and intrinsic subtypes and lower levels of Ki-67 in participants compared with non-participants. In terms of tumor characteristics, interval carcinomas are more comparable to tumors in the non-participant group. To minimize a bias effect due to a potential overdiagnosis during screening, which is expected, especially in the case of low-grade carcinomas in situ [14], the biological tumor characteristics results in this study refer to invasive tumors.

▶ **Table 3** Biological characteristics of breast carcinomas dependent on the Ki-67 proliferation index for participants of the German Mammography Screening Program (Yd 2014, 50–69-year-old women, NW Lower Saxony and Hanover region).

Participants*	**Ki-67 proliferation index**								**Total**		**p-value (Comparison, columns A to C)**
	High (≥ 25 %) (A)		**Intermediate (11–24 %) (B)**		**Low (≤ 10 %) (C)**		**Ki-67 No data (D)**				
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
Invasive breast cancer cases (ICD-10 C50)	**146**		**163**		**210**		**46**		**565**		
T stage 1	73	51.4	103	64.0	164	78.8	26	60.5	**366**	66.1	< 0.0001
T stage 2 +	69	48.6	58	36.0	44	21.2	17	39.5	**188**	33.9	
No data	4		2		2		3		**11**		
N stage 0 (incl. N1mi)	102	72.3	124	78.5	174	84.5	31	73.8	**431**	78.8	0.0230
N stage 1 +	39	27.7	34	21.5	32	15.5	11	26.2	**116**	21.2	
No data	5		5		4		4		**18**		
M stage 0	130	97.0	146	99.3	188	100.0	43	97.7	**507**	98.8	0.0316
M stage 1	4	3.0	1	0.7	0	0.0	1	2.3	**6**	1. 2	
No data	12		16		22		2		**52**		
Grading I	1	0.7	13	8.0	51	24.3	6	14.6	**71**	12.7	< 0.0001
Grading II	27	18.6	115	71.0	150	71.4	17	41.5	**309**	55.4	
Grading III	117	80.7	34	21.0	9	4.3	18	43.9	**178**	31.9	
No data	1		1		0		5		**7**		
ER+ PR+	66	45.2	134	83.2	175	83.3	8	61.5	**383**	72.3	< 0.0001
ER+ PR-	19	13.0	20	12.4	30	14.3	3	23.1	**72**	13.6	
ER- PR+	2	1.4	0	0.0	0	0.0	0	0.0	**2**	0.4	
ER- PR-	59	40.4	7	4.3	5	2.4	2	15.4	**73**	13.8	
No data	0		2		0		33		**35**		
HER2-positive	47	32.4	20	12.6	7	3.4	3	25.0	**77**	14.7	< 0.0001
HER2-negative	98	67.6	139	87.4	200	96.6	9	75.0	**446**	85.3	
No data	1		4		3		34		**42**		

▶ **Table 3** (Continuation)

Participants*	Ki-67 proliferation index								Total		p-value (Comparison, columns A to C)
	High (≥ 25 %) (A)		Intermediate (11–24 %) (B)		Low (≤ 10 %) (C)		Ki-67 No data (D)				
	n	%	n	%	n	%	n	%	n	%	
Molecular subtypes											
Luminal A	0	0.0	0	0.0	197	95.2	0	0.0	**197**	38.4	< 0.0001
Luminal A or B**	0	0.0	137	86.2	0	0.0	0	0.0	**137**	26.7	
Luminal B	86	59.3	15	9.4	6	2.9	1	50.0	**108**	21.1	
• of which:											
▪ Luminal $B_{HER2\text{-}neg}$	(58)		(0)		(0)		(0)		(58)		
▪ Luminal $B_{HER2\text{-}pos}$	(28)		(15)		(6)		(1)		(50)		
HER2-positive	19	13.1	5	3.1	1	0.5	1	50.0	**26**	5.1	
Triple-negative	40	27.6	2	1.3	3	1.4	0		**45**	8.8	
No data	1		4		3		44		**52**		

* The participant group includes screening cases and interval carcinomas 0–24 months after screening.
** Cannot be classified as luminal A or luminal B due to intermediate Ki-67.

▶ **Table 4** Biological characteristics of breast carcinomas dependent on Ki-67 proliferation index for non-participants of the German Mammography Screening Program (Yd 2014, 50–69-year-old women, NW Lower Saxony and Hanover region).

Non-participants	Ki-67 proliferation index								Total		p-value (Comparison, columns A to C)
	High (≥ 25 %) (A)		Intermediate (11–24 %) (B)		Low (≤ 10 %) (C)		Ki-67 No data (D)				
	n	%	n	%	n	%	n	%	n	%	
Invasive breast cancer cases (ICD-10 C50)	**117**		**80**		**84**		**107**		**388**		
T stage 1	27	28.7	34	47.9	53	69.7	45	53.6	**159**	48.9	< 0.0001
T stage 2 +	67	71.3	37	52.1	23	30.3	39	46.4	**166**	51.1	
No data	23		9		8		23		**63**		
N stage 0 (incl. N1mi)	56	61.5	37	56.1	56	76.7	53	67.9	**202**	65.6	0.0277
N stage 1 +	35	38.5	29	43.9	17	23.3	25	32.1	**106**	34.4	
No data	26		14		11		29		**80**		
M stage 0	69	84.1	47	85.5	61	93.8	62	86.1	**239**	87.2	0.1761
M stage 1	13	15.9	8	14.5	4	6.2	10	13.9	**35**	12.8	
No data	35		25		19		35		**114**		
Grading I	1	0.9	3	3.8	23	28.0	13	15.5	**40**	11.0	< 0.0001
Grading II	26	22.2	63	79.7	54	65.9	42	50.0	**185**	51.1	
Grading III	90	76.9	13	16.5	5	6.1	29	34.5	**137**	37.8	
No data	0		1		2		23		**26**		
ER+ PR+	51	44.0	63	81.8	74	88.1	6	42.9	**194**	66.7	< 0.0001
ER+ PR-	20	17.2	9	11.7	7	8.3	2	14.3	**38**	13.1	
ER- PR+	0	0.0	0	0.0	0	0.0	0	0.0	**0**	0.0	
ER- PR-	45	38.8	5	6.5	3	3.6	6	42.9	**59**	20.3	
No data	1		3		0		93		**97**		
HER2-positive	37	32.2	12	15.8	4	4.9	6	42.9	**59**	20.6	< 0.0001
HER2-negative	78	67.8	64	84.2	78	95.1	8	57.1	**228**	79.4	
No data	2		4		2		93		**101**		

▶ **Table 4** (Continuation)

Non-participants	Ki-67 proliferation index								Total		p-value (Comparison, columns A to C)
	High (≥ 25 %) (A)		Intermediate (11–24 %) (B)		Low (≤ 10 %) (C)		Ki-67 No data (D)				
	n	%	n	%	n	%	n	%	n	%	
Molecular subtypes											
Luminal A	0	0.0	0	0.0	75	91.5	0	0.0	**75**	26.7	< 0.0001
Luminal A or B*	0	0.0	62	81.6	0	0.0	0	0.0	**62**	22.1	
Luminal B	70	60.9	9	11.8	4	4.9	3	37.5	**86**	30.6	
• of which:											
▪ Luminal $B_{HER2\text{-}neg}$	(50)		(0)		(0)		(0)		(50)		
▪ Luminal $B_{HER2\text{-}pos}$	(20)		(9)		(4)		(3)		(36)		
HER2-positive	17	14.8	3	3.9	0	0.0	2	25.0	**22**	7.8	
Triple-negative	28	24.3	2	2.6	3	3.7	3	37.5	**36**	12.8	
No data	2		4		2		99		**107**		

* Cannot be classified as luminal A or luminal B due to intermediate Ki-67.

▶ **Table 5** Sensitivity analysis – distribution of molecular subtypes for participants and non-participants after excluding the youngest age group of 50–54-year-old women.

Sensitivity analysis	55–69-year-old women only						p-value
	Participants (Ps)		Non-Ps		Total		
	n	%	n	%	n	%	
Molecular subtypes							
Luminal A	148	37.0	46	24.9	**194**	33.2	0.0065
Luminal A or B*	106	26.5	42	22.7	**148**	25.3	
Luminal B	90	22.5	60	32.4	**150**	25.6	
HER2-positive	22	5.5	13	7.0	**35**	6.0	
Triple-negative	34	8.5	24	13.0	**58**	9.9	
No data	37		81		**118**		

* Cannot be classified as luminal A or luminal B due to intermediate Ki-67

Classical prognostic factors

Prognostic factors, such as tumor size, nodal status, grading, hormone receptor status, and HER2 status are considered key factors in deciding whether adjuvant therapy for breast carcinoma is required and, if so, what type of treatment is needed. [7, 13].

As expected, in our evaluation of invasive carcinomas, participants had more favorable TNM stages than non-participants, with a higher proportion of small carcinomas (T1: 66.1 % vs. 48.9 %) and carcinomas without lymph node involvement (N0: 78.8 % vs. 65.6 %). Other national and international studies have reported similar results [6, 15–17]. For screening cases, they are within the recommendations of the European guidelines for subsequent screening [2].

Tumor size correlates with the likelihood of lymph node involvement. However, it is also considered an independent prognostic factor with the recurrence rate increasing with increasing tumor size [15, 18]. An excellent prognosis was observed for node-negative hormone receptor-positive tumors smaller than 1 cm [19]. Previous studies have shown a significant difference in the tumor stage distribution between carcinomas detected within and outside a screening process, with a more favorable tumor stage distribution in screening cases [5, 20].

Histological grading has an impact on both the therapeutic procedure and the further outcome [18]. Our results show little difference in the grading distribution between participants and non-participants. This is due to unfavorable differentiation in interval carcinomas with a high proportion of grading III tumors. Thus, the present results differ from the results of a retrospective case series from North Rhine-Westphalia (NRW) [6], which can be justified by the fact that the present study is population-based whereas the study population in NRW comes from two breast centers. Moreover, interinstitutional differences in the classification of pathologies may lead to discrepancies [21].

Intrinsic subtypes

In early breast carcinoma, molecular subtypes are highly important in determining whether adjuvant chemotherapy should be given. The aim of the therapeutic decision is to avoid overtreatment or undertreatment [8, 22].

For the luminal A subtype, which has a low Ki-67 index (≤ 10 %), the present study showed significant differences between participants and non-participants (38.4 % vs. 26.7 %). According to the current recommendations of the S3 guideline, chemotherapy is not required for most luminal A tumors [7]. Thus, assuming that the treatment complied with the guidelines, the entire group of participants (including those with interval carcinomas) was likely to have received less aggressive therapy significantly more often than the non-participants. The difference of 11.7 percentage points between these two study groups confirms the results of the study from NRW, in which the difference between participants and non-participants with regard to the presence of an indication for (neo) adjuvant chemotherapy was 10.8 percentage points [6]. Lower tumor stages and longer disease-free survival were observed for luminal A tumors with high hormone receptor positivity (PR > 20 %) and low Ki-67 index (< 20 %) compared with luminal B tumors [23].

Luminal A or B subtype (Ki-67 index 11–24 %), which cannot be further differentiated based on the EKN data, is also more prevalent in participants than non-participants (26.7 % vs. 22.1 %). For these tumors, further clinical-pathological parameters, such as the tumor size, grading, number of affected lymph nodes, or results of gene expression analyses, would be required for unambiguous classification [12, 13]. For the latter variable, in particular, the EKN does not have any data that could be evaluated using routine procedures. A subanalysis of the luminal A or luminal B category was performed to provide a rough estimate of the distribution of these tumors between the luminal A or luminal B subtypes (not shown). For this category, the frequency of tumors with an unfavorable T stage (T3 +) or grading (III) was found to be

slightly lower in participants compared to non-participants (20.4 % vs. 27.4 %). It can be concluded that the difference between participants and non-participants is still underestimated in the luminal A category discussed previously.

In the present study, the subtype distribution of interval carcinomas was largely comparable to the distribution of tumors in non-participants.

Ki-67 proliferation marker

There is a clear association between Ki-67 and the classical prognostic factors. To our knowledge, the present evaluation is the first to show that this association was observed to the same extent in both screening participants and non-participants (▶ **Table 3, 4**). The association between the level of Ki-67 and the grading distribution was particularly pronounced ($p < 0.0001$ in each case): both participants and non-participants had a high proportion of grading III tumors when the Ki-67 expression was high (≥ 25 %) (80.7 % and 76.9 %, respectively). The results indicate that Ki-67 is a prognostic factor; however, it is not independent.

Both parameters provide information about the growth rate of tumor cells: the antigen Ki-67 is formed and can be detected only during the active phases of the cell cycle, whereas it is not expressed in resting cells (G0 phase) [24]. Histological grading evaluates the degree of differentiation of tumor cells based on their growth pattern, nuclear pleomorphism, and frequency of mitosis. The mitotic count primarily influences the prognostic value of the grading and is particularly elevated in poorly differentiated (G3) tumors [25].

Accordingly, our data also shows an association between Ki-67 and the tumor size ($p < 0.0001$), with a higher proportion of high-proliferation tumors to low-proliferation tumors in tumor stage T2 +, both in participants and non-participants.

However, it is remarkable that in the T2 + category in the group of participants, the ratio of absolute case numbers of high-proliferation tumors to low-proliferation tumors was 1: 0.64 (n = 69 to 44). The ratio for non-participants deviates clearly from this at 1:0.34 (n = 67 to 23) (▶ **Table 3, 4**). Participants thus appear to have a lower Ki-67 proliferation index more often than the non-participants, even if they have larger tumors. This result is consistent with the assumption that large but slow-growing tumors are less likely to be clinically conspicuous and, therefore, are more likely to be detected by screening than large and highly proliferative tumors. The latter are more likely to be associated with clinical changes due to more rapid growth and are more likely to appear outside of screening.

Similar effects can be observed for the N1 + category. A modeled analysis could provide further insight in this regard.

Several studies have shown comparable associations between Ki-67 and other prognostic factors [10, 26–28] or investigated the prognostic value of Ki-67 [10, 11, 29]. A multicenter analysis of cancer registry data by Inwald et al. revealed an association between Ki-67 expression and other clinical and histopathological parameters, again primarily between Ki-67 and the grading distribution [10]. Moreover, Ki-67 proved to be an independent prognostic factor for disease-free survival and overall survival, with a significant decrease in both parameters starting from a Ki-67 index of > 25 %.

Given the clinical utility of Ki-67 for therapeutic decision-making, the consensus recommendation of a 2019 international working group on Ki-67 advocates Ki-67 testing in early ER-positive/HER2-negative breast carcinoma and recommends refraining from adjuvant chemotherapy if the Ki-67 index is < 5 % and performing chemotherapy if the Ki-67 index is > 30 %. In the intermediate range, on the other hand, the interobserver concordance is not considered sufficient for Ki-67 determination [30]. In their statement on the current St. Gallen International Consensus Guidelines, a German expert group advises using further criteria for risk assessment for the tumors mentioned above with intermediate Ki-67 between 10 and 25 % [12]. This classification of "cut points" is virtually the same as the definition of the intermediate range of Ki-67 in the present study.

A final look at the subgroup of interval carcinomas (▶ **Table 2**) shows that the proportion of highly proliferative tumors (Ki-67 index ≥ 25 %) is 2-fold higher than in screening cases (46.4 % vs 23.1 %) and higher than that of non-participants (41.6 %). Comparative data on the distribution of Ki-67 in interval carcinomas have been sparse. In a paper by Cabioglu published in 2020, the proportion of interval carcinomas with high Ki-67 expression (≥ 20 %) was nearly twice as high as in tumors detected by screening [31].

This may be due to a differing clustering of phenotypes, with a higher proportion of rapidly growing and, therefore, clinically conspicuous triple-negative and HER2-positive subtypes in the interval [32, 33]. Accordingly, in the study by Alanko et al. (2021), histological examinations detected high grading, predominantly with grading III, in interval carcinomas of both subtypes and higher Ki-67 index medians than in luminal tumors [34].

Strengths and limitations

The strong point of the present study is the high degree of completeness of the EKN data. With more than 95 % of all expected breast carcinomas, it is almost equivalent to a population survey. The reference population comprises approximately 25 % of all eligible 50–69-year-old women in the MSP in Lower Saxony. We can, therefore, assume that the results are representative for Lower Saxony. Another positive aspect is the population-based registration of interval carcinomas, which the EKN has performed since 2005 [35]. Thus, these interval carcinomas, which have a worse prognosis than screening cases, can be included in the group of screening participants.

Another strong point is the high level of completeness of the characteristics recorded by the EKN. For example, the Ki-67 data is available in 84 % of studied cases for the year of diagnosis 2014 (participants: 92 %; non-participants: 72 %). As in the above-mentioned study by Inwald et al. (78 % complete Ki-67 data, [10]), the high level of data completeness underscores the importance of Ki-67 in routine clinical practice, even though adding Ki-67 to conventional prognostic factors is not recommended unreservedly [7].

The expression 'no information' is distributed unequally between the study groups to some extent. A distortion of the results for most parameters is unlikely for the 50–69 age group. Cases with missing data were excluded from the relevant calculations; for the sake of transparency, however, they are included as case numbers in the tables. For Ki-67, excluding these cases may be

associated with a slight bias in the results toward underestimating the frequency of triple-negative and HER2-positive carcinomas because Ki-67 was not always determined for these subtypes. The S3 guidelines state the following on the subject: "*Triple-negative and HER2-positive carcinomas are usually treated neoadjuvantly. In this situation the Ki-67 level is no longer necessarily relevant.*" ([7], *S. 130)*. Unfortunately, the data on neoadjuvant treatment were not available for this analysis. In the study by Braun et al., the proportion of breast carcinomas treated with neoadjuvant therapies was 3.7 % for participants and 7.5 % for non-participants [6].

This study was conducted as a retrospective observational study based on routine data. One possible bias is a healthy screen participation bias, which states that healthier women with a lower risk of mortality are more likely to participate in screening [36, 37]. For example, Czwikla et al. (2019), using routine data from BARMER, have shown that barriers to participation are particularly apparent in the case of severe diseases that have a major negative impact on daily life [37]. On the other hand, less severe diseases could cause increased concerns for one's health and provide additional motivation for participating in the MSP.

Individual risk profiles may also influence the screening status. Women with a greatly increased risk of breast cancer (for example, BRCA1/2 carriers) are recommended to receive regular preventive care in specialized centers of the German Consortium for Hereditary Breast and Ovarian Cancer. If a breast carcinoma occurs, these high-risk patients are then more likely to belong to the non-participant group. A certain overestimation of the differences cannot therefore be ruled out. These high-risk patients cannot be identified from the EKN data. In general, hereditary breast cancer is estimated to account for 5–10 % of all breast cancers [38].

On the other hand, the Recommendations for Medical Imaging Procedures from the German Commission on Radiological Protection (SSK) [39] recommend that women at a moderately increased risk participate in the mammography screening program together with supplementary procedures based on a risk-benefit analysis. In practice, it has been shown that high-risk women who are recommended to have an annual mammography often take it in rotation (curative application one year, screening participation the next year). The above is also confirmed by the data of an EKN survey on the cause of breast cancer detection among breast cancer patients in Lower Saxony in the year of diagnosis 2008 [40], which we have reevaluated concerning this issue (unpublished results). Of the 1917 participants in this study, 17.5 % (n = 335) of all patients reported an increased risk of breast cancer (defined as previous incidence of breast cancer or breast cancer in 1st-degree relatives). Of these 335 high-risk patients, 44 % (n = 148 of 335) reported that their disease was detected in an organized screening. At 48 % (n = 160), the proportion of high-risk patients whose breast cancer was first detected in outpatient or inpatient care was only slightly higher. In 8 % of cases (n = 27), the cause of cancer detection could not be identified. Moreover, if a high-risk woman has screening and curative mammography in alternating years, she will still count as a participant if an interval carcinoma is diagnosed within 24 months of an unremarkable screening examination, even though the diagnosis was made in the course of curative care. In our study, this counteracts an overestimation of the differences between the study groups to a certain extent.

Further bias is possible in the group of screening participants due to bringing forward the diagnosis, particularly of slow-growing carcinomas, and in the group of non-participants due to the younger age of disease onset in the high-risk patients due to genetic factors. Thus, our data also shows a lower average age of onset for non-participants (59.1 years) than participants (60.3 years). Since the youngest age group, 50–54, should be particularly affected by the corresponding bias in both study groups, we conducted a sensitivity analysis to determine the extent to which the exclusion of this age group would change the results. The sensitivity analysis shows that the more favorable distribution of molecular subgroups in participants than non-participants is maintained when the 55–69-year-old women are analyzed separately.

Conclusions

Breast carcinomas in MSP participants are more likely to have more favorable tumor characteristics and prognostic factors than carcinomas in non-participants. This is reflected in our study's distribution of intrinsic subtypes, with a higher proportion of luminal A tumors in the participants. Thus, our results confirm previous findings, including at the population level, even though a possible bias due to different risk constellations in both groups with a potential impact on the tumor biology cannot be excluded. The results suggest that participants with breast cancer may be more likely to receive less aggressive therapy than non-participants with breast cancer, even after accounting for interval carcinomas that have a worse prognosis. Further studies on this issue using incidence rates, such as stage-specific incidence of advanced tumors, would be desirable. A methodological study on this would be preferable because it is difficult to determine the number of non-participants in the population eligible for screening every two years (denominator calculation). The extent to which there are also differences in disease management (especially in the perceived quality of life) and survival parameters between the two groups should also be the subject of further studies.

Ethical aspects

This article did not involve studies on humans or animals.

Conflicts of interest

BM serves as a reporting physician in mammography screenings. IU and JK have no conflicts of interest to declare. As head of the Mammography North Reference Center, GH is in charge of quality assurance for the mammography screening program. GH is also head of the NW Lower Saxony screening unit. MH is an information specialist at the Mammography North Reference Center.

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