Intrinsic Breast Cancer Subtypes depending on Participation in Mammography Screening Program

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Background

Breast cancer in screening participants has shown favorable tumor characteristics and prognostic parameters compared to symptom-detected breast cancer, even including interval cancers. Our aim was to examine the distribution of the molecular breast cancer subtypes considering the proliferation marker Ki-67 in participants (Ps) and non-participants (Non-Ps) of the German Mammography Screening Program (MSP) in a population-based setting.

Methods

This retrospective observational study evaluated population based data from the Epidemiological Cancer Registry Lower Saxony (EKN) (Data completeness > 95%). Reference population was all 285.634 women aged 50–69 years living in the catchment area of the two screening units of Northwest Lower Saxony and Hanover who were invited for screening every two years. The MSP was implemented in these regions from 2005 to 2008. The study included 953 cases of invasive breast cancers (ICD-10 C50) diagnosed in the reference population in 2014 (Ps: 565 cases, Non-Ps: 388 cases, MSP participation-rate = 55%).

The group of the Ps contained screen detected cases and breast cancers that were detected in the interval of 24 month after a negative screening (interval cancer). The group of Non-Ps included all other breast cancers. Excluding criteria: Interval cancers diagnosed later than 24 month after the last unremarkable screening examination because they could not be assigned to one of the groups (n = 78), dropouts from the MSP (n = 7), inadequate data quality (n = 1) and recurrences and metastases (ICD-10 C79.81). Synchronous or metachronous secondary breast cancer were counted multiple times (n = 18).
A modified molecular subtyping of all tumors was performed according to the S3-guideline (categories for Ki-67: ≤ 10% = low, 11-24% = intermediate, ≥ 25% = high) – see **table 1**.

Table 1: Molecular subtypes of breast cancers. Data according to S3 guideline (modified)

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

Table 2: Biological characteristics of breast cancer dependent on screening participation (ICD-10 C50, Yd 2014, 50-69 year old women, Northwest Lower Saxony and Hanover region.

Biological characteristics of breast cancer	Participants (Ps)						Non-participants (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	%	
Invasive carcinomas (ICD-10 C50)	**434**	**100,0**	**131**	**100,0**	**565**	**100,0**	**388**	**100,0**	**953**	**100,0**	
Age at diagnosis	60,3		61,2		60,5		59,2		**60,0**		0,0009
Average age (SD**)	(5,8)		(5,3)		(5,7)		(6,0)		(5,9)		
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	
missing 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	
missing 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	
missing 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	
missing 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	
missing 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
HER2-negative	360	88,0	86	75,4	446	85,3	228	79,4	**674**	83,2	
missing 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 intermed. (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	
missing 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 $B_{HER2-neg}$	(44)		(14)		(58)		(50)		(108)		
Luminal $B_{HER2-pos}$	(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	
missing 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; # Cases with missing data were excluded

For categorical variables, we calculated differences using the chi-squared test; for numerical variables, we used a t-test (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

Considering cases with invasive breast cancer (n = 953) tumours detected in screening Ps 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-Ps – even including interval cancers (see **table 2**).
Regarding grading both groups showed less differences (p = 0,1718), because interval cancers are more comparable with cancers in Non-Ps.
We found distinct differences in distribution of the molecular subtypes between both groups (p < 0,0003): especially in the 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%) and triple-negative (8,8% vs. 12,8%).

Discussion

According to the S3-Guideline an adjuvant chemotherapy can be avoided in the majority of Luminal A subtype 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.
Strengths and limitations: The strong point of this study is the high level of completeness of the EKN Data and 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 (Ps: 92%; Non-Ps: 72%). 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. Otherwise, a high individual risk for breast cancer may also influence the screening status. But if a high-risk woman has screening and curative mammography in alternating years, she will still count as a participant with interval cancer in our study, even though the diagnosis was made in the course of curative care.

References: Mathys B, Urbschat I, Hilbert M, Kieschke J, Hecht G.: Immunhistochemische Tumoreigenschaften bei Mammakarzinomen in Abhängigkeit von der Teilnahme am MSP. Senologie 2022; 19: 140-154

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