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# The effect of family history on screening procedures and prognosis in breast cancer patients - Results of a large population-based case-control study

Katharina Seiffert [a, 1, *], Kathrin Thoene [b, 1], Christine zu Eulenburg [d, e], Sabine Behrens [c], Barbara Schmalfeldt [a], Heiko Becher [b], Jenny Chang-Claude [b, c], Isabell Witzel [a]

[a] University Medical Center Hamburg-Eppendorf, Department of Gynecology, Martinistraße 52, 20246, Hamburg, Germany
[b] Department of Cancer Epidemiology, University Medical Center Hamburg-Eppendorf, Martinistraße 52, 20246, Hamburg, Germany
[c] Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany
[d] University Medical Center Hamburg-Eppendorf, Department of Medical Biometry and Epidemiology, Martinistraße 52, 20246, Hamburg, Germany
[e] University of Groningen, University Medical Center Groningen, Epidemiology, Groningen, the Netherlands

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ABSTRACT

*Background:* The potential benefit of additional breast cancer screening examinations in moderate risk patients (patients with a history of breast cancer in one or two family members) remains unclear.
*Methods:* A large population-based case–control study on breast cancer in postmenopausal women in Germany recruited 2002–2005 (3813 cases and 7341 age-matched controls) was used to assess the association of family history with breast cancer risk. Analysis of family history, participation in screening procedures, and tumor size regarding prognosis in patients was based on follow-up data until 2015.
*Results:* A first degree family history of breast cancer was associated with higher breast cancer risk (OR 1.39, $p < 0.001$). Patients with a first degree family history of breast cancer were more likely to have had >10 mammograms (MG) (42.7% vs. 24.9%, $p < 0.001$) and showed a higher rate of imaging-detected tumors (MG or ultrasound) (45.8% vs. 31.9%, $p < 0.001$). A smaller tumor size at initial diagnosis (below 2 cm) was more likely in patients with a positive family history (OR 1.45, $p < 0.001$) and a higher number of MG (≥10 MG: OR 2.29). After accounting for tumor characteristics, mammogram regularity (HR 0.72, $p < 0.001$) and imaging-assisted tumor detection (HR 0.66, $p < 0.001$) were associated with better overall survival but not with a positive family history.
*Discussion:* Patients with a positive family history had a higher rate of imaging detected tumors with smaller size at initial diagnosis compared to patients without affected family members. Screening was associated with improved survival after a breast cancer diagnosis, irrespective of a positive family history.


## 1. Introduction

There is evidence that public breast cancer screening programs regardless of preexisting risk factors are beneficial in terms of reduced breast cancer mortality for women aged 50–69 years [1]. Besides that, a benefit of additional screening visits has also been documented in high-risk patients (e.g. BRCA 1 or BRCA 2 gene mutations) [2]. However, there is still a high rate of opportunistic screening procedures regardless of screening programs, especially in patients with family history of breast cancer [3]. Although the potential benefit of additional screening examinations in moderate risk patients (patients with a history of breast cancer in one or two family members) remains unclear [4], participation in these additional exams is supported by German statutory health insurances even if only one first-degree family member has a history of breast cancer [5]. Therefore, many women with a first- or second-degree relative with breast cancer are participating more frequently in breast cancer screening procedures outside mammography screening programs that offer screening every 2–3 years.

In this analysis, we first investigated the association of family history of breast cancer with breast cancer risk. We then examined in breast cancer patients the relationships between family history

* Corresponding author.
*E-mail address:* k.seiffert@uke.de (K. Seiffert).
[1] Katharina Seiffert and Kathrin Thoene equally contributed to the paper.

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of breast cancer, frequency of screening procedures in a moderate risk situation (e.g. one or more affected family members), and tumor characteristic. Lastly, we assessed whether more frequent screening due to a positive family history was associated with overall and breast cancer specific survival after accounting for clinical and tumor characteristics.

## 2. Materials and methods

### 2.1. Study population and data source

The cohort consisted of 3813 cases and 7341 controls of the population-based case–control MARIE study (Mamma Carcinoma Risk factor Investigation) [6]. Patients were recruited in two regions of Germany; Hamburg and Rhine-Neckar-Karlsruhe if they were aged 50–74 years at diagnosis and had a histologically confirmed diagnosis of primary invasive (stage I to IV) or in situ breast cancer between January 1, 2001 and September 30, 2005. Two population-based controls without a history of breast cancer matched by age and study region were recruited for each case. Information on pre-diagnostic lifestyle factors, socio-economic status, medical history, and information on specific medications, regimen, and duration of use was collected by a standardized face-to-face interview at recruitment [6]. The histological characteristics of the primary breast cancer were extracted from pathology reports. Treatment and clinical course were abstracted from medical records to verify clinical events either self-reported in the interview or reported by treating physicians during a first follow-up in 2009 and a second follow-up in June 2015 (in total > 90% self-reported events verified) resulting in a cohort study with a follow-up time of >10 years [7].

All study participants gave written informed consent. Ethics approval was obtained from the ethics committee of the University of Heidelberg, the Hamburg Medical Council, and the Medical Board of the State of Rhineland-Pfalz. The study was conducted in accordance with the Declaration of Helsinki.

Information on family history of breast cancer was collected by face-to-face interview at recruitment. Participants were asked whether family members were affected by breast cancer and other cancers, and to provide the information separately for mother, sister and daughter (first degree) and for second degree relatives.

### 2.2. Outcome assessment

Study participants were prospectively followed until June 30, 2015. Vital status was assessed via information from population registries. Causes of death were derived from death certificates obtained through the local/regional health offices and coded according to the 10th revision of the International Classification of Diseases (ICD-10-GM). The primary endpoints were overall survival (OS: including death from any cause), breast cancer-specific survival (BCS (non-breast cancer-related deaths were censored), and recurrences (including ipsilateral, contralateral, local/regional invasive recurrence, and distant recurrence). Participants without an event of interest were censored at the date of last contact or on June 30, 2015, whichever came first.

### 2.3. Statistical analysis

Case-control data were reported as mean ± standard deviation (SD) or frequency (percent) for breast cancer cases and controls. Pearson's $Chi^2$-tests and ANOVA were used for comparisons between groups.

To estimate the association between a positive 1st degree and 2nd degree family history and overall breast cancer risk, univariate and multivariable logistic regression models adjusted for diagnosis/interview age (years), number of relatives with BC (1, ≥ 2 or missing) age at first birth (≤21, 22–24, 25–28, 29+ years and missing), mammography ever (no/yes or missing) as well as benign breast disease in the past (y/n) were performed to estimate odds ratios (ORs) and 95% confidence intervals (95% CI). Logistic regression analyses in cases only were performed to estimate associations between the frequency of participation in screening procedures and the tumor size or nodal status, respectively. Having a small tumor (below 2 cm versus above) or being node-negative (pN0 versus other) was the dependent variable. The categorial variable for family history served as adjusting variable.

The Kaplan-Meier method has been used to compare overall survival (OS) and breast cancer specific survival (BCS) with respect to the number of pre-diagnosis performed mammograms and to family history of breast cancer. The log-rank test has been applied to determine differences between the groups. Multivariable Cox proportional hazards regression analysis adjusted for tumor size, nodal status, grading, hormone receptor status, MG regularity, tumor detection mode and family history of breast cancer was conducted to estimate the association of the participation frequency in screening procedures, tumor size and nodal status with OS. To investigate if a positive family history is a potential effect modifier of the association of the frequent participation in screening procedures and OS, an interaction term was included in the Cox model.

All statistical analyses were two-sided at significance level $\alpha = 0.05$.

All analyses were performed on all-available-cases basis. To keep as many observations as possible in the analyses, missing values in categorical variables were assigned an own category.

## 3. Results

### 3.1. Patient characteristics

There were no differences between 3813 cases and 7341 age-matched controls with regard to age (mean age 62 y), menopausal status, age at first delivery, body mass index, education levels and use of contraceptive pills (Table 1). There was a high rate of childbirth in both groups (88.5% vs. 85.9%). There was a higher proportion of cases than controls who never breastfed (never breastfed: cases: 37.6% vs. controls 33.4%, $p < 0.001$, Table 1). On time of study inclusion, there was a higher rate of cases who were currently using hormone replacement therapy compared to controls (46.5%, vs. 33.3%, $p < 0.001$). There was no difference in having clinical examinations like breast palpation, but there was a higher proportion of cases who had regular MG compared to controls (61.5% vs. 53.6% in controls, $p < 0.001$), more than 10 performed MG before diagnosis of breast cancer (>10 MG, cases 28.9%, controls 20.7%, $p < 0.001$) and a history of benign breast diseases (41.9% vs. 34.2%, $p < 0.001$, Table 1).

### 3.2. Association of family history of breast cancer with breast cancer risk

Results of univariate logistic regression model analyses showed a higher proportion of cases with family history of breast cancer of a first degree relative (18.2% vs. 12.2%; OR 1.60, 95% confidence interval (CI) 1.44–1.79, $p < 0.001$) and a second degree relative only (14.1% vs. 11.4%, OR 1.28, 95% CI: 1.14–1.44, $p < 0.001$) compared to controls (data not shown)).

There were no differences in breast cancer subtypes between cases with and cases without positive family history of breast cancer ($p = 0.073$). In this group of postmenopausal breast cancer patients with HR + disease, 18.5% (433/2338) of patients had a positive family history of breast cancer compared with 16.93% (107/

**Table 1**
Characteristics of the MARIE study population.

| | TOTAL N = 11,154 | CONTROL N = 7341 | CASES N = 3813 | P-VALUE |
|---|---|---|---|---|
| Age, years | | | | |
| Mean ± SD | 62±6.03) | 62 ( ±6.02) | 62 ( ±6.05) | 0.274 |
| **Age at Menopause, years** | | | | |
| Mean ± SD | 49 ( ±4.9) | 49 ( ±5.0) | 49 ( ±4.8) | <0.001 |
| **Age at first birth, years** | | | | |
| Mean ± SD | 24 ( ±4.6) | 24 ( ±4.6) | 24 ( ±4.7) | 0.301 |
| **BMI kg/m2** | | | | |
| <22.5 | 4982 (44.7%) | 3286 (44.8%) | 1696 (44.5%) | 0.110 |
| 22.5-<25 | 3453 (31.0%) | 2244 (30.6%) | 1209 (31.7%) | |
| 25-<30 | 2274 (20.4%) | 1494 (20.5%) | 780 (20.5%) | |
| >30 | 439 (3.9%) | 311 (4.2%) | 128 (3.4%) | |
| missing | 6 | 6 | 0 | |
| **Education** | | | | |
| low | 6360 (57.0%) | 4180 (56.9%) | 2180 (57.2%) | 0.881 |
| medium | 3134 (28.1%) | 2074 (28.3%) | 1060 (27.8%) | |
| high | 1658 (14.9%) | 1087 (14.8%) | 571 (15.0%) | |
| **missing** | 2 | 0 | 2 | |
| **Pregnancy ever** | | | | |
| No | 1385 (12.4%) | 847 (11.5%) | 538 (14.1%) | <0.001 |
| yes | 9769 (87.6%) | 6494 (88.5%) | 3275 (85.9%) | |
| missing | 0 | 1 | 0 | |
| **Age at first birth** | | | | |
| no pregnancy | 1844 (16.5%) | 1162 (15.8%) | 682 (17.9%) | 0.015 |
| <21 y | 2697 (24.2%) | 1797 (24,5%) | 900 (23,6%) | |
| 22-24y | 2504 (22,5%) | 1662 (22,6%) | 842 (22,1%) | |
| 25-28y | 2383 (21.4%) | 1609 (21.9%) | 774 (20.3%) | |
| 29 + y | 1722 (15.4%) | 1108 (15.1%) | 614 (16.1%) | |
| missing | 4 | 3 | 19 | |
| **Ever breastfed** | | | | |
| no | 3885 (34.8%) | 2452 (33.4%) | 1433 (37.6%) | <0.001 |
| yes | 7268 (65.2%) | 4889 (66.6%) | 2379 (62.4%) | |
| missing | 1 | 0 | 1 | |
| **Use of contraceptive pill** | | | | |
| no | 3985 (36.1%) | 2610 (35.9%) | 1375 (36.4%) | 0.629 |
| yes | 7066 (63.9%) | 4660 (64.1%) | 2406 (63.6%) | |
| missing | 103 | 71 | 32 | |
| **Use of hormone replacement therapy** | | | | |
| never | 4356 (39.4%) | 3071 (42.2%) | 1285 (33.9%) | <0.001 |
| past | 2524 (22.8%) | 1782 (24.5%) | 742 (19.6%) | |
| current | 4184 (37.8%) | 2425 (33.3%) | 1759 (46.5%) | |
| missing | 90 | 63 | 27 | |
| **Cinical examination/palpation of the breast** | | | | |
| no | 222 (2%) | 105 (1.4%) | 117 (3.1%) | <0.001 |
| yes | 10,923 (98%) | 7229 (98.5%) | 3694 (96.9%) | |
| missing | 9 | 7 | 2 | |
| **Mammogram regularity** | | | | |
| no | 3583 (32.1%) | 2572 (35.0%) | 1011 (26.5%) | <0.001 |
| yes | 6281 (56.3%) | 3935 (53.6%) | 2346 (61.5%) | |
| no mammograms at all | 1245 (11.2%) | 810 (11.0%) | 435 (11.4%) | |
| missing | 45 (0.4%) | 24 (0.3%) | 21 (0.5%) | |
| **Number of mammograms** | | | | |
| 0 | 1245 (11.2%) | 810 (11%) | 435 (11.4%) | <0.001 |
| 1–4 | 4552 (40.8%) | 3259 (44.4%) | 1293 (33.9%) | |
| 5–10 | 2724 (24.4%) | 1745 (23.8%) | 979 (25.7%) | |
| >10 | 2633 (23.4%) | 1527 (20.7%) | 1106 (28.9%) | |
| Missing | 0 | 0 | 0 | |
| **Benign breast diseases** | | | | |
| no | 7024 (63.2%) | 4815 (65.8%) | 2209 (58.1%) | <0.001 |
| yes | 4096 (36.8%) | 2501 (34.2%) | 1597 (41.9%) | |
| missing | 34 | 25 | 25 | |
| **first degree relative with breast cancer** | | | | |
| no | 9009 (85,7%) | 6067 (87,8%) | 2942 (81,8%) | <0.001 |
| yes | 1499 (14,3%) | 843 (12,2%) | 656 (18,2%) | |
| missing | 646 | 431 | 215 | |
| **second degree relative only with breast cancer** | | | | |
| No | 9781 (87.7%) | 6506 (88.6%) | 3275 (85.9%) | <0.001 |
| Yes | 1373 (12.3%) | 835 (11.4%) | 538 (14.1%) | |
| missing | 0 | 0 | 0 | |
| **first and second degree relatives with breast cancer** | | | | |
| **Number of relatives** | | | | |
| 1 | 2591 (23.2%) | 1530 (20.8%) | 1061 (27.8%) | <0.001 |
| 2 | 242 (2.2%) | 131 (1.8%) | 111 (2.9%) | |
| ≥3 | 39 (0.3%) | 17 (0.2%) | 22 (0.6%) | |
| 0 | 7636 (74.3%) | 5232 (77.2%) | 2404 (70.7%) | |
| missing | 646 | 431 | 215 | |

632) in the HER2 positive subgroup and 15.58% (62/398) in the triple-negative subgroup.

Multivariate analysis showed a significantly higher breast cancer risk for participants with a positive family history of breast cancer (1 affected family member: OR 1.39, 95% CI: 1.26–1.54, p < 0.001, 2 or more affected family members: OR 1.75, 95% CI: 1.45–2.11, p < 0.001) and for women with a history of benign breast diseases (OR 1.40, 95% CI: 1.29–1.52, p < 0.001, Table 2). Reduced breast cancer risk was shown for patients with lower age at first birth (25–28 years: OR 0.80, 95% CI 0.71–0.91: p = 0.001) and also for patients who ever had a MG (OR 0.83, 95% CI: 0.73–0.94, p = 0.004, Table 2). There was no significant association for age (Table 2).

### 3.3. Relationship between family history of breast cancer and performed screening procedures as well as tumor detection

Among breast cancer patients, those with a first degree positive family history received a higher number of MG than those without positive family history of breast cancer (>10 MG: 42.7% vs. 24.9%, p < 0.001, Table 3). Also patients with a second degree positive family history of breast cancer received a higher number of MG (>10 MG: 34.0% vs. 27.2%, p = 0.009, Table 3) compared to patients without positive family history of breast cancer.

Breast cancer was imaging-detected by MG or ultrasound in 35.5% of all cases with a higher rate of imaging-detected cancers in patients with positive family history of breast cancer compared to patients without positive family history (first degree family history 48.6% vs. 33.1%, p < 0.001; second degree family history 42.7% vs. 34.3%, p = 0.001,Table 3).

### 3.4. Family history of breast cancer and screening effect

Patients with a positive family history (OR 1.45, 95% CI: 1.27–1.66, p < 0.001) and patients who received a higher number of MG (≥10 MG: OR 2.29, 95% CI: 1.88–2.81, p < 0.001) were more likely to be diagnosed with smaller tumor size at initial diagnosis (tumor size below and above 2 cm) compared to patients without positive family history and patients without any performed MG (Suppl. Table 1). These patients were also more likely to be diagnosed with node-negative than node-positive disease (with positive family history (OR 1.38, 95% CI 1.216–1.568, p < 0.001) and with higher number of MG (≥10 MG: OR 1.58, 95% CI 1.329–1.873 p < 0.001)) *(data not shown)*.

Kaplan-Meier estimates showed significantly improved overall survival rates (5-year-cumulative risk of death 5 vs. 20%, p < 0.001, Fig. 1) and breast cancer specific survival rates in patients with a higher number of performed MG (5-year-cumulative risk of death 5 vs. 15%, p < 0.001). Patients with relatives with breast cancer also had improved overall survival rates (5-year-cumulative risk of death 5 vs. 12%, p = 0.006, Fig. 2) and breast cancer specific survival rates (5-year-cumulative risk of death 3 vs. 6%, p = 0.025).

Results of multivariate cox-proportional hazard regression analyses showed that prognostic factors like small tumor size, node-negative disease, lower grading (G1, G2), positive hormone receptor status and older age were associated with improved overall survival. Even after adjustment for tumor characteristics,

**Table 2**
Univariate and multivariate logistic regression analysis of breast cancer risk.

| | UNIVARIATE | | MULTIVARIATE | |
|---|---|---|---|---|
| Variable | OR (95% CI) | p-value | OR (95% CI) | p-value |
| **Age, years** | 1.00 (0.98–1.01) | 0.274 | 1.00 (0.99–1.01) | 0.138 |
| **Number of relatives with breast cancer** | | | | |
| Ref.: no relatives with BC | | | 1.00 | |
| 1 | 1.41 (1.28–1.56) | <0.001 | 1.39 (1.26–1.54) | <0.001 |
| ≥2 | 1.77 (1.47–2.12) | <0.001 | 1.75 (1.45–2.11) | <0.001 |
| missing | 1.06 (0.89–1.25) | 0.522 | 1.05 (0.89–1.25) | 0.53558 |
| **Mammography ever** | | | | |
| Ref.: no | | | 1.00 | |
| yes | 0.96 (0.85–1.09) | 0.550 | 0.83(0.73–0.94) | 0.004 |
| Missing | 1.24 (0.21–7.55) | 0.813 | 1.17 (0.19–7.25) | 0.866 |
| **Age at first birth** | | | | |
| Ref.: no pregnancy | | | 1.00 | |
| ≤21 y | 0.85 (0.75–0.97) | 0.012 | 0.86 (0.75–0.98) | 0.019 |
| 22-24y | 0.86 (0.76–0.98) | 0.022 | 0.86 (0.76–0.97) | 0.017 |
| 25-28y | 0.82 (0.72–0.93) | 0.002 | 0.80 (0.71–0.91) | 0.001 |
| 29 + y | 0.94 (0.82–1.08) | 0.410 | 0.93 (0.81–1.07) | 0.324 |
| Missing | 0.57 (0.06–5.48) | 0.624 | 0.58 (0.06–5.57) | 0.635 |
| **Benign breast disease** | | | | |
| Ref.: no | | | 1.00 | |
| yes | 1.39 (1.28–1.51) | <0.001 | 1.40 (1.29–1.52) | <0.001 |
| missing | 0.79 (0.37–1.68) | 0.534 | 0.81 (0.38–1.75) | 0.598 |

**Table 3**
Breast cancer detection in association with family history of breast cancer.

| Number of Mammograms | Cases with | Cases without | p-value |
|---|---|---|---|
| | **1st degree positive relative** | **1st degree positive relative** | <0.001 |
| **0** | 38 (5.8%) | 374 (12.7%) | |
| **1–4** | 171 (26.0%) | 1040 (35.3%) | |
| **5–9** | 161 (24.5%) | 769 (26.1%) | |
| **10+** | 280 (42.7%) | 733 (24.9%) | |
| **missing** | 6(1,0%) | 26 (0.9%) | |
| **Number of Mammograms** | **Cases with 2nd degree positive relative only** | **Cases without 1st and 2nd degree positive relative** | 0.009 |
| **0** | 46 (8.5%) | 389 (11.9%) | |
| **1–4** | 169 (31.4%) | 1124 (34.3%) | |
| **5–9** | 136 (25.3%) | 843 (25.7%) | |
| **10+** | 183 (34.0%) | 890 (27.2%) | |
| **missing** | 4 (0.8%) | 29 (0.9%) | |
| | **Cases with** | **Cases without** | |
| **Detection of breast cancer by** | **1st degree positive relative** | **1st degree positive relative** | p < 0.001 |
| **Palpation** | 334 (50.9%) | 1959 (66.6%) | |
| **Mammogram/ultrasound** | 319 (48.6%) | 979 (33.1%) | |
| **missing** | 3 | 10 | |
| **Detection of breast cancer by** | **Cases with 2nd degree positive relative only** | **Cases without 1st and 2nd degree positive relative** | p = 0.001 |
| **Palpation** | 306 (56.9%) | 2139 (65.3%) | |
| **Mammogram/ultrasound** | 230 (42.7%) | 1122 (34.3%) | |
| **missing** | 2 | 14 | |

mammogram regularity (HR 0.72, p < 0.001) and imaging-assisted tumor detection (HR 0.66, p = 0.002, Table 4) were associated with improved overall survival in multivariate analysis. After adjusting for screening and tumor characteristics, a positive family history itself was not associated with improved survival (Table 4). There was no significant interaction between family history and screening frequency with respect to overall survival.

## 4. Conclusion

Our analysis showed that family history of breast cancer was associated with higher breast cancer risk and resulted in a higher participation frequency in breast cancer-screening procedures like MG and ultrasound. Even in a moderate risk situation according to family history of breast cancer (e.g. one affected family member), patients participated more often in screening procedures and had a higher number of performed MG before diagnosis. Consecutively, there was also a higher rate of imaging-detected tumors in this moderate risk cohort, which resulted in smaller tumor size, less affected lymph nodes and better prognosis. However, there was no direct association between a positive family history of breast cancer and survival after adjusting for screening and tumor characteristics in the multivariate analysis.

Screening for breast cancer aims to reduce mortality from this cancer, as well as the morbidity associated with advanced stages of the disease, through early detection in asymptomatic women. There is still controversy about the benefit of breast cancer screening programs and concerns regarding overdiagnosis. Recently published data of 323,719 women participating in the German mammography screening program between 2003 and 2014 showed an increase of early stage breast cancer and a decrease in breast cancer mortality [8]. Also an independent panel of experts evaluated the screening benefit in 2015 and showed that women 50–69 years of age who were invited to attend mammographic screening had, on average, a 40% reduction in the risk of death from breast cancer irrespective of preexisting risk factors [1].

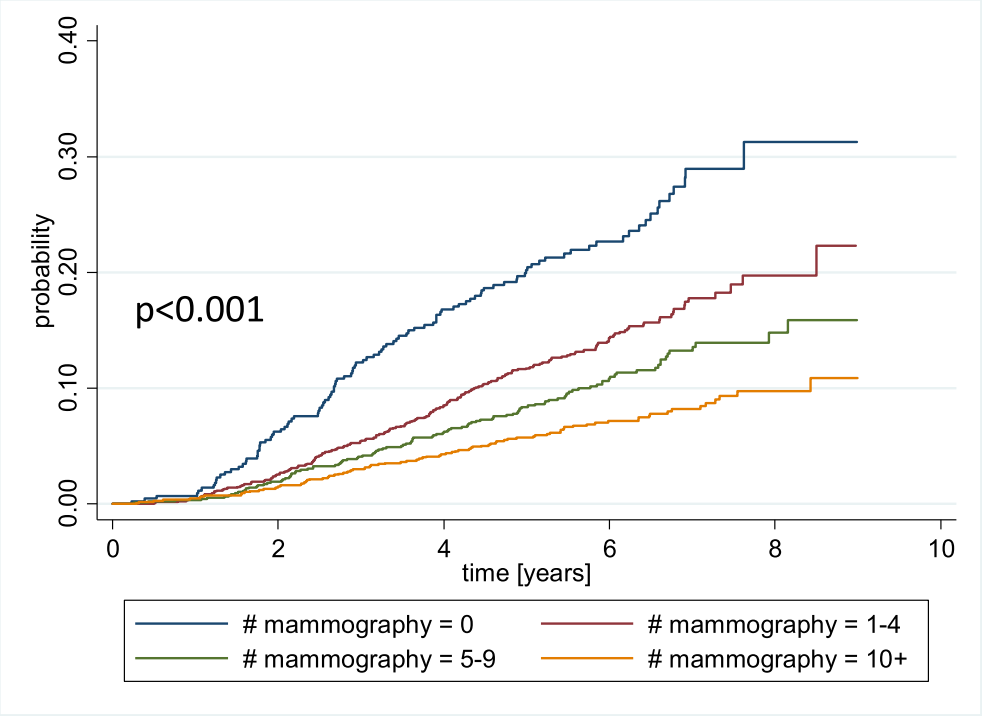


**Fig. 1.** Kaplan-Meier curves for 10-years cumulative risk of death, stratified by pre-diagnosis performed mammograms.

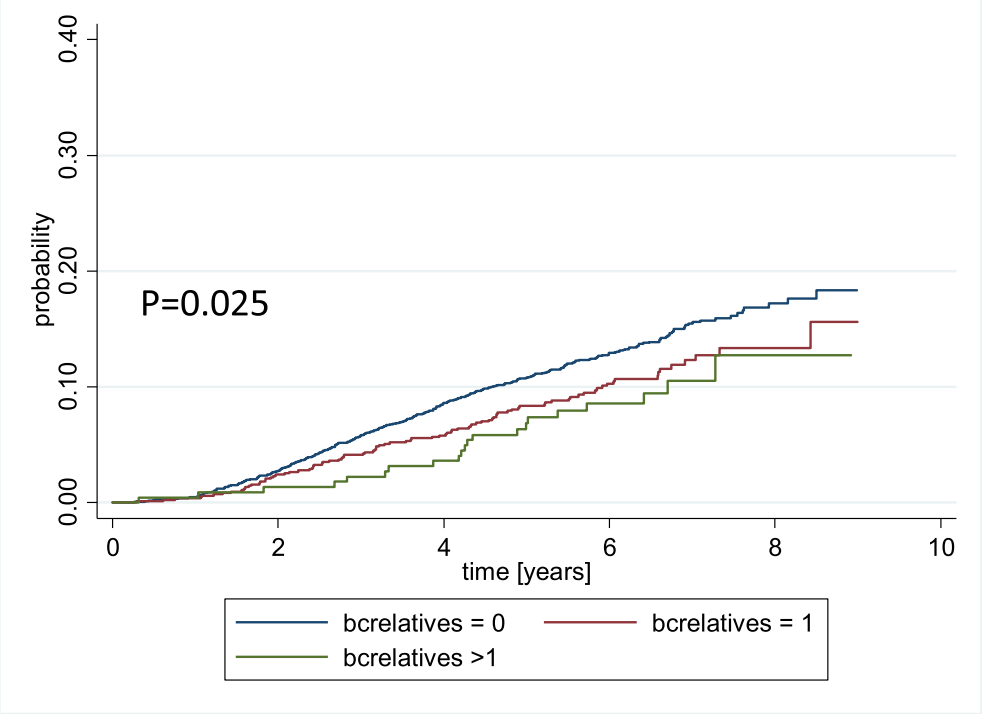


**Fig. 2.** Kaplan-Meier curves for 10-years cumulative risk of death, stratified by family history of breast cancer.

The German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC) established since 1996 a panel of clinical criteria for genetic testing of individuals in a clinical setting, based on familial history of breast and ovarian cancer [9]. A "high risk" is defined as a lifetime risk of breast cancer of more than 30%, whereas other guidelines define a risk of more than 20% as elevated [10]. A benefit of additional screening visits has been documented in "high-risk" patients (e.g. BRCA 1, BRCA 2 gene mutations) [2]. But it remains unclear how to advise patients, who are not "high-risk" patients but still have a family history of breast cancer, especially in a first or second degree relative. As a consequence of this, there is a high rate of opportunistic screening procedures regardless of

**Table 4**
Overall survival and risk factors (multivariate Cox-proportional hazard regression analysis).

| Variable | HR (95% CI) | p-value |
|---|---|---|
| | Overall survival | |
| **Tumor size** | | |
| pT1 (<2 cm) | 1.00 | |
| pT2 (2–5 cm) | 1.30 (1.04–1.63) | 0.023 |
| pT3+4 (>5 cm, …) | 2.40 (1.77–3.25) | <0.001 |
| missing | 2.21 (1.52–3.20) | <0.001 |
| **Nodal status** | | |
| pN0 | 1.00 | |
| pN1 (1–3) | 1.72 (1.30–2.13) | <0.001 |
| pN2 (≥4) | 2.88 (2.34–3.72) | <0.001 |
| missing | 7.54 (4.06–13.98) | <0.001 |
| **Grading** | | |
| G1 | 1.00 | |
| G2 | 1.99 (1.34–2.95) | 0.001 |
| G3 | 2.81 (1.86–4.25) | <0.001 |
| G4 | 7.65 (1.72–34.11) | 0.008 |
| missing | 3.21 (1.61–6.41) | 0.001 |
| **Hormone Receptor Status** | | |
| ER/PR positive | 1.00 | |
| ER + or PR+ | 1.60 (1.28–2.01) | <0.001 |
| ER/PR negative | 1.81 (1.44–2.27) | <0.001 |
| missing | 0.79 (0.19–3.33) | 0.745 |
| **Age** | 1.03 (1.02–1.04) | <0.001 |
| **Mammogram regularity** | | |
| No | 1.00 | |
| yes | 0.72 (0.59–0.89) | <0.001 |
| missing | 1.16 (0.91–1.48) | 0.236 |
| **Detection tumor by** | | |
| Palpation (patient/doctor) | 1.00 | |
| Mammogram/Ultrasound | 0.66 (0.50–0.85) | 0.002 |
| missing | 0.38 (0.05–2.91) | 0.353 |
| **Relatives with breast cancer** | | |
| 0 | 1.00 | |
| 1 | 0.95 (0.75–1.20) | 0.654 |
| ≥2 | 0.84 (0.54–1.31) | 0.447 |
| missing | 1.41 (1.03–1.94) | 0.032 |

screening programs in patients with a moderate risk situation with regard to family history of breast cancer [11]. Even if it is well-known that there is a higher risk for patients in terms of developing breast cancer even if they have just one affected family member [12], the effect of additional screening procedures in this moderate risk cohort remains unclear [3,13].

In our analysis, we could identify a group of patients with moderate risk with regard to family history of breast cancer who were not eligible according to the guidelines for genetic counselling [14,15]. In this group, number of MG before diagnosis and imaging-assisted tumor detection was also associated with improved overall survival. There was no difference in the magnitude of association of MG regularity, number of MG and imaging-assisted tumor detection with improved overall survival in patients with a moderate family history and those without a family history of breast cancer. A limitation of our study is the retrospective nature of the collected information. We could not exactly determine the age at breast cancer diagnosis in affected family members in our cohort. Thus, we were not able to differentiate between familial and hereditary breast cancer by the reported family history. Although we found a beneficial screening effect also in patients with a family history of breast cancer, based on the available data we cannot assess which screening method was superior or should be offered. It also remains unclear why patients with a family history of breast cancer in our cohort had a higher rate of performed screening procedures compared to patients without a family history of breast cancer. One reason might be a higher awareness of developing breast cancer by the patients themselves or by their physicians. Also, based on our data, we cannot conclude at what age screening procedures in a moderate risk group should start, although the median age of included patients in our study was 62 years and many patients had more than 10 performed MG before the diagnosis of breast cancer. This is in line with other data, showing low benefit of intensified screening procedures in high-risk patients without BRCA 1 or BRCA 2 gene mutations before the age of 50 [13].

The main strength of this large population-based patient sample with long-term follow-up is the availability of detailed information about family history of breast cancer and participation in screening procedures. To our knowledge, this is the first observational study that was able to show that patients with moderate breast cancer risk are more likely to have received a mammography screening, which is associated with a clinical benefit.

Our analysis showed an association between positive family history and participation in screening procedures, higher number of performed MG, higher rate of imaging-detected tumors as well as better prognostic factors in screen-detected breast cancer. This could be valued as positive screening effect which could support the role of screening even in a cohort of women with elevated breast cancer risk defined by family history of breast cancer. However, our results only show that ever mammography screening is beneficial with respect to survival and this holds whether or not the women had a positive family history. Regular mammography screening (which is only ever MG here) is associated with improved survival because of the more favourable tumor characteristics of screen-detected tumors.

## Conclusion

Women with a family history of breast cancer are at higher risk of developing breast cancer. Additional screening procedures showed a benefit in terms of smaller tumor size, less affected lymph nodes at time of diagnosis and better prognosis in this group of breast cancer patients. However, it remains unclear when to start additional procedures and which screening method should be favored.

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## Ethical approvements

Ethics approval was obtained from the ethics committee of the University of Heidelberg, the Hamburg Medical Council, and the Medical Board of the State of Rhineland-Pfalz. The study was conducted in accordance with the Declaration of Helsinki.

## Declaration of competing interest

All authors declare that they have no conflict of interest.

## References

[1] Lauby-Secretan B, et al. 'Breast-Cancer screening — viewpoint of the IARC working group'. N Engl J Med Jun. 2015;372(24):2353–8.
[2] Grann VR, et al. Comparative effectiveness of screening and prevention strategies among BRCA1/2-affected mutation carriers. Breast Canc Res Treat Feb. 2011;125(3):837–47.
[3] Destounis SV, et al. Comparison of breast cancers diagnosed in screening patients in their 40s with and without family history of breast cancer in a community outpatient facility. Am J Roentgenol Apr. 2014;202(4):928–32.
[4] Müller D, et al. Cost-effectiveness of different strategies to prevent breast and ovarian cancer in German women with a BRCA 1 or 2 mutation. Eur J Health

Econ Apr. 2018;19(3):341–53.
[5] https://www.tk.de/techniker/service/gesundheit-und-medizin/praevention-und-frueherkennung/brust-und-gebaermutterhalskrebsfrueherkennung/mammografie-2013626'. .
[6] Flesch-Janys D, et al. Risk of different histological types of postmenopausal breast cancer by type and regimen of menopausal hormone therapy. *Int. J. cancer* Aug. 2008;123(4):933–41.
[7] Jung AY, et al. Pre- to postdiagnosis leisure-time physical activity and prognosis in postmenopausal breast cancer survivors. Breast Cancer Res Dec. 2019;21(1):117.
[8] Katalinic A, Eisemann N, Kraywinkel K, Noftz MR, Hübner J. Breast cancer incidence and mortality before and after implementation of the German mammography screening program. Int J Canc 2020 Aug 1;147(3):709–18. https://doi.org/10.1002/ijc.32767. Epub 2019 Dec 4.
[9] Meindl A, Ditsch N, Kast K, Rhiem K, Schmutzler RK. Hereditary breast and ovarian cancer: new genes, new treatments, new concepts. Dtsch. Arztebl. Int. May 2011;108(19):323–30.
[10] National Collaborating Centre for Cancer. Familial breast cancer, classification and care of people at risk of familial breast cancer. Nice 2013;Jun(57).
[11] Ferrat E, et al. 'Understanding barriers to organized breast cancer screening in France: women's perceptions, attitudes, and knowledge'. Fam Pract Aug. 2013;30(4):445–51.
[12] Pharoah PDP, Day NE, Duffy S, Easton DF, Ponder BAJ. Family history and the risk of breast cancer: a systematic review and meta-analysis. Int. J. cancer May 1997;71(5):800–9.
[13] Bick U, et al. 'High-risk breast cancer surveillance with MRI : 10-year experience from the German consortium for hereditary breast and ovarian cancer'. Breast Canc Res Treat 2019;175(1):217–28.
[14] Kast K, et al. Prevalence of BRCA1/2 germline mutations in 21 401 families with breast and ovarian cancer. J Med Genet Jul. 2016;53(7):465–71.
[15] Clinical N, Guidelines P, Guidelines N. 'Genetic/Familial high-risk Assessment. Breast and Ovarian'; 2018.