Estimating the Breast Cancer Burden in Germany and Implications for Risk-based Screening

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ABSTRACT

In Germany, it is currently recommended that women start mammographic breast cancer screening at age 50. However, recently updated guidelines state that for women younger than 50 and older than 70 years of age, screening decisions should be based on individual risk. International clinical guidelines recommend starting screening when a woman's 5-year risk of breast cancer exceeds 1.7%. We thus compared the performance of the current age-based screening practice with an alternative risk-adapted approach using data from a German population representative survey. We found that 10,498,000 German women ages 50–69 years are eligible for mammographic screening based on age alone. Applying the 5-year risk threshold of 1.7% to individual breast cancer risk estimated from a model that considers a woman's reproductive and personal characteristics, 39,000 German women ages 40–49 years would additionally be eligible. Among those women, the number needed to screen to detect one breast cancer case, NNS, was 282, which was close to the NNS = 292 among all 50- to 69-year-old women. In contrast, NNS = 703 for the 113,000 German women ages 50–69 years old with 5-year breast cancer risk <0.8%, the median 5-year breast cancer risk for German women ages 45–49 years, which we used as a low-risk threshold. For these low-risk women, longer screening intervals might be considered to avoid unnecessary diagnostic procedures. In conclusion, we show that risk-adapted mammographic screening could benefit German women ages 40–49 years who are at elevated breast cancer risk and reduce cost and burden among low-risk women ages 50–69 years.

Prevention Relevance: We show that a risk-based approach to mammography screening for German women can help detect breast cancer in women ages 40–49 years with increased risk and reduce screening costs and burdens for low-risk women ages 50–69 years. However, before recommending a particular implementation of a risk-based mammographic screening approach, further investigations of models and thresholds used are needed.

Introduction

Breast cancer is the most common female cancer in developing and developed countries (1). In Germany, 68,950 women were diagnosed with breast cancer and 18,570 women died of the disease in 2016 (2). The number of breast cancer cases in Germany is projected to increase (3), due to aging of the population and changes in reproductive behavior, for example, a higher proportion of childless women, later ages at first birth, and lower breastfeeding rates, and changes in lifestyle, including diet and exercise habits (2).

The German mammographic screening program (MSP), established in 2009, invites all women ages 50–69 years for a mammogram every 2 years. The program aims to reduce breast cancer–related mortality by detecting cancers early, but there is ongoing debate about efficacy of screening mammography, the potential of overdiagnosis, the optimal age to initiate screening, screening intervals, and potential harmful effects (4, 5). Recently updated German guidelines state that for women younger than 50 and older than 70 years "screening decisions based on individual risk" should be considered, and recommend screening women ages 40–49 years who are at "moderate breast cancer risk" by ultrasound and mammography (6).

These recommendations acknowledge that the current age-based eligibility criteria for the German MSP for a woman from the general population do not account for other well-established breast cancer risk factors, for example, a woman's breast cancer family history, her history of benign breast

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disease, her reproductive history, use of hormone replacement therapy (HRT), and other lifestyle factors (7). Recently developed risk models take some of these factors into account (7–9) and can facilitate implementing risk-adapted screening approaches. Eligibility for screening based on risk can reduce unnecessary diagnostic procedures for women at low breast cancer risk and target more intensive diagnostic procedures to women at elevated risk (6). These ideas also motivated two ongoing screening trials. The WISDOM trial was designed to compare annual mammography with a risk-based screening schedule in 100,000 U.S. women ages 40–74 years (10). Breast cancer risk is estimated with the Breast Cancer Surveillance Consortium (BCSC) model that uses information from 76 SNPs in addition to personal and clinical characteristics. MyPeBS (My Personal Breast Screening; https://mypebs.eu/) is an ongoing randomized study of 85,000 women ages 40–70 years to assess the effectiveness of a risk-based breast cancer screening strategy compared with screening according to regional guidelines in several European countries and Israel. Breast cancer risk is calculated with the BCSC and Tyrer-Cuzick models.

We recently showed that two models, BCRAT (11) and BCmod (12), that predict breast cancer risk for women in the general U.S. population, were well-calibrated in German women ages 40–70 years using data from the prospective EPIC Germany cohort, and 1-year breast cancer predicted model risks estimated for all German women using the "German Health Interview and Examination Survey for Adults" (DEGS) agreed well with overall German breast cancer incidence (13). Both models use questionnaire-based risk factor information that is easy and inexpensive to obtain.

In this article, we use BCmod risk estimates from the DEGS survey to compare the current age-based screening strategy in Germany with a risk-based one. We applied recommendations of the National Comprehensive Cancer Network (NCCN) guidelines (14), that annual mammographic screening should start when a woman's 5-year risk of invasive breast cancer exceeds 1.7%, but also show results obtained when using lifetime risks, which were the basis of the German guidelines (6). We compare the numbers of women eligible for screening, the numbers of breast cancer cases screened, and the numbers of women needed to be screened to detect one breast cancer case (NNS) in Germany for age- and risk-based screening approaches to inform future screening recommendations.

Materials and Methods

German health interview and examination survey for adults (DEGS)

We evaluated the distribution of breast cancer risk using data on 3,705 women participating in the cross-sectional DEGS survey, a nationally representative health survey (15). Using a two-stage stratified cluster sampling design, DEGS data were collected using standardized personal interviews, self-administered questionnaires, and standardized measurements. Primary sampling units (PSUs) in the two-stage design were communities, stratified by districts and measures of urbanization. Within PSUs, random samples of individuals, stratified by 10-year age groups, were drawn from local population registers. Further details on the design and sampling procedures are provided in (15). The DEGS study protocol was approved by the Charite-Universitätsmedizin Berlin (Berlin, Germany) Ethics Committee in September 2008 (No. EA2/047/08). The women sampled into DEGS can be weighted to represent the general German adult female population at the time of recruitment (2008–2011). Supplementary Table S1 shows the distribution of several breast cancer risk factors in women in DEGS ages 40 years or older.

Risk model

BCmod (12) predicts a woman's risk of developing invasive breast cancer over a specified time period (e.g., 5 years or lifetime), given her age, reproductive history and breast cancer family history, her past history of biopsy and diagnosis of benign hyperplasia, her current body mass index, HRT use, and alcohol consumption (12). The probability of developing breast cancer is computed by combining RR estimates for a woman's risk factors with attributable risk estimated from two large U.S. cohorts and age-specific breast cancer incidence and competing mortality rates from the Surveillance, Epidemiology, and End Results Program. The model was well-calibrated in German women (13).

Imputation of missing values and statistical analysis

Information on some predictors used in BCmod was not collected in DEGS, including age at first live birth, type and duration of HRT use, a past diagnosis of benign breast disease, and breast cancer family history. As described previously (13), we used multiple imputation with chained regression equations (IVEware; ref. 16) and information on missing variables from 27,934 women in the German EPIC cohort study to generate five complete datasets (17). While EPIC is not representative of the overall German female population, its utilization for imputation is likely adequate, as the assumption underlying imputation is missing at random, that is, conditional on the observed data, the missing data in DEGS are similar to those in EPIC. We further compared the DEGS risk factor distributions after imputation with those from population-based controls sampled into two population-based German breast cancer case–control studies and found generally good agreement, suggesting unbiasedness of the imputation approach (Supplementary Table S2). Estimates were obtained for each imputed dataset accommodating the complex survey design, and then combined across imputed datasets. Variances of the final estimates were computed using Rubin formula, thus fully incorporating the variability in estimates across imputed datasets. All analyses were performed with SAS 9.4 (SAS Institute; procedures SURVEYMEANS, SURVEYFREQ, and MIANALYZE).

The NNS was computed as the total number of women divided by the number of projected cases within 1 year of follow-up, overall, or within groups. The number of cases was obtained by summing 1-year projected risk estimates overall or in subgroups.

Results

Distribution of 5-year risk based on BCmod in age groups of German women

Figure 1 shows the estimated distribution of 5-year individual BCmod risks in German women for different age groups. The mean 5-year breast cancer risk increased with increasing age group, ranging from 0.63% for women ages 40–44 years old to 2.32% for women ages 65–69 years. Among 40–44 years old women, the 5-year breast cancer risk ranged from 0.37% to 1.49%, and no woman had a breast cancer risk ≥1.7. However, among women ages 45–49 years old, 5-year breast cancer risks ranged from 0.53% to 2.24%. The median risk was 0.83% for women ages 45–49 years, and we, therefore, used a risk of <0.8% to define "low risk." Among those ages 50–54 years, risks ranged from 0.65% to 3.01%. The mean 5-year risk of women ages 55–59 years was 1.68% (range, 0.79%–4.35%) and 2.06% for women ages 60–64 years. The median 5-year risk for women ages 60–64 years was 1.91% (range, 0.95%–5.92%) and it was 2.15% for women ages 65–69 years (range, 1.07%–6.45%; **Fig. 1**).

On the basis of BCmod estimates, 67% of the 6,721,000 German women ages 40–49 years had a 5-year breast cancer risk higher than the lowest 5-year risk (0.65%) among 50-year-old women (**Table 1**). These 40–49 years old women are currently not eligible for mammographic screening, while a 50-year-old woman with breast cancer risk of 0.65% is.

Comparison of the age-based and risk-based screening strategies

According to the current age-based screening program, 10,498,000 German women ages 50–69 years are eligible for biennial mammograms. Of those, 35,900 are expected to have a breast cancer diagnosis within 1 year following risk assessment, corresponding to NNS of 292 (**Table 2**).

Using a risk-based approach, 39,000 German women ages 45–49 years with 5-year risks >1.7% would be additionally eligible for mammographic screening; 140 of those are expected to be diagnosed with breast cancer within 1 year (NNS = 282; **Table 2**). This NNS is very close to that of women ages 50–69 years, and much lower than the NNS values for women ages 45–49 years with 5-year risks <0.8% and 0.8%–1.7% (NNS =

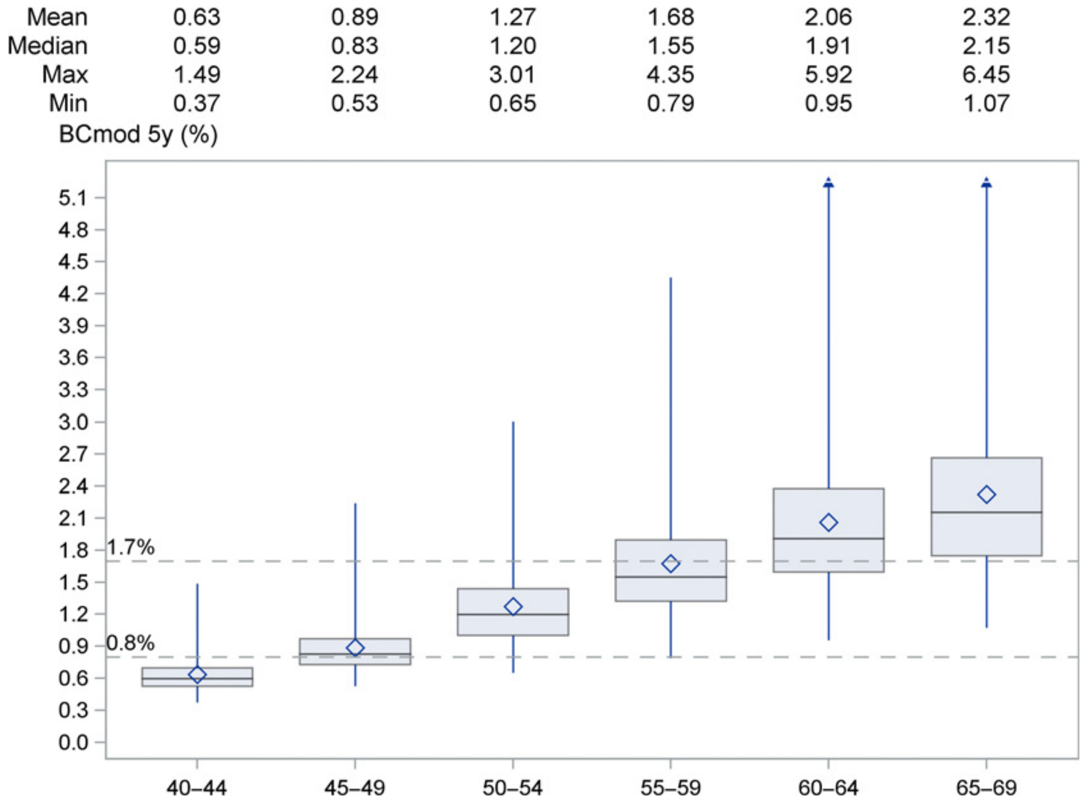

Figure 1.
Distribution of 5-year risk based on BCmod in age groups of German women (projected from DEGS). Boxplots: the boxes are drawn from the first to third quartile with the horizontal line in the middle denoting the median, the diamond denoting the mean value, and the whiskers ranging from minimum to maximum (except for ages 60+).

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Table 1. Numbers and percentage with 95% CIs in parentheses of German women ages 40–49 years with 5-year risk estimates (BCmod) below and above 0.6488%, the lowest estimated 5-year risk among women ages 50+ years.

Risk group	Age 40–49 years	(95% CI)
5-year risk <0.65%		
Total count	2,250,000	(1,777,850–2,721,957)
Percent	33%	(27%–40%)
Number of BC cases expected within 1 year from risk assessment	2,100	(1,645–2,540)
5-year risk ≥0.65%		
Total count	4,471,000	(3,870,548–5,071,674)
Percentage	67%	(60%–73%)
Number of BC cases expected within 1 year from risk assessment	6,800	(5,905–7,721)
Total		
Number of BC cases expected within 1 year from risk assessment	8,900	(8,026–9,784)

Abbreviations: BC, breast cancer; CI, confidence interval.

772 and NNS = 566, respectively; **Table 2**). For women ages 40–44 years, NNS = 1,021 for those with 5-year risks <0.8% and NNS = 637 for those with risk between 0.8% and 1.7% (**Table 2**).

Only 45% of German women ages 50–60 years had a 5-year BCmod risk ≥1.7%. As depicted in **Fig. 1**, after age 55, most women had 5-year risk estimates ≥0.8%. There were 5,624,000 women ages 50–69 years old with risks between 0.8% and 1.7%, and 4,761,000 women with risk ≥1.7%, with expected numbers of breast cancer cases of 13,800 and 22,000 and NNS = 408 and NNS = 217, respectively. However, 113,000 women ages 50–69 years had a 5-year risk <0.8%; 160 breast cancer diagnoses would be expected in the year following risk assessment, corresponding to NNS = 703. These women might consider delaying screening until their 5-year risk (computed during annual routine checks) rises above 0.8% (**Table 2**).

Table 2. Total number of German women in each age group, percentage in risk stratum, and number of predicted BC cases within 1 year of risk assessment estimated from the DEGS survey and the BCmod BC risk prediction model.

	Age 40–44 years (95% CI)	Age 45–49 years (95% CI)	Age 50–69 years (95% CI)
Total population			
Total count[a]	3,261,000	3,461,000	10,498,000
Number of BC cases expected within 1 year from risk assessment	3,400	5,500	35,900[b]
NNS	953	631	292
5-year BC risk <0.8%			
Total count[a]	2,871,000 (2,399,498–3,343,261)	1,494,000 (1,157,169–1,831,468)	113,000 (38,486–187,825)
Percentage	88% (79%–97%)	43% (35%–51%)	1% (0%–2%)
Number of BC cases expected within 1 year from risk assessment	2,800 (2,355–3,268)	1,900 (1,508–2,365)	160 (53–269)
NNS	1,021	772	703
5-year BC risk 0.8%–1.7%			
Total count[a]	389,000 (93,249–685,016)	1,927,000 (1,535,413–2,318,348)	5,624,000 (5,005,871–6,241,407)
Percentage	12% (3%–21%)	56% (47%–64%)	54% (49%–58%)
Number of BC cases expected within 1 year from risk assessment	600 (158–1, 064)	3,400 (2,694–4,120)	13,800 (12,309–15,280)
NNS	637	566	408
5-year BC risk >1.7%			
Total count[a]	0	39,000 (0–145,620)	4,761,000 (4,150,573–5,371,914)
Percentage	0%	1% (0%–4%)	45% (41%–50%)
Number of BC cases expected within 1 year from risk assessment	0	140 (0–510)	22,000 (19,261–24,709)
NNS	NA[c]	282	217

Note: The number needed to screen (NNS) was derived as the ratio of the total count and the number of expected BC cases.
Abbreviations: BC, breast cancer; CI, confidence interval.
[a]Estimated from weighted survey data.
[b]Differences due to rounding.
[c]No data available for estimation.

On the basis of remaining lifetime risks (RLR) >16%, which is currently used in German guidelines (6), 78,000 women ages 40–49 years would be eligible for screening; 220 of those are expected to be diagnosed with breast cancer, corresponding to NNS = 358 (Supplementary Table S3).

Discussion

The current age-based mammography screening program in Germany is being reevaluated (4, 5) and recent guidelines (6) recommend considering individualized risk in screening decisions for women <50 and >70 years old. This recommendation acknowledges that some younger women might benefit from screening (18) and that some unnecessary diagnostic procedures in older low-risk women could be avoided.

On the basis of NCCN guidelines (14), annual mammographic screening for a woman <50 years should start when her 5-year invasive breast cancer risk exceeds 1.7%. This risk threshold corresponds to the average risk of a 60-year-old U.S. woman, for whom it is agreed upon that mammography screening is beneficial. The mean 5-year risks in 55- to 59- and 60- to 64-year-old German women were similar, 1.68% and 2.06%, respectively (**Fig. 1**).

We, therefore, compared the numbers of women screened, the expected numbers of breast cancer cases screened, and the NNS in Germany when using the eligibility risk cutoff of 1.7% for women 40–50 years old. We used the BCmod risk model for the risk-based calculations, as it was well-calibrated in German women ages 40–77 years and thus, provides unbiased breast cancer risk estimates (13). We calculated risk using DEGS survey data and found that 39,000 women (1%) ages 45–49 years would be eligible for mammographic screening. Using RLR > 16% as a basis for screening recommendation as suggested in the recent German guidelines (6), 78,000 German women ages 40–49 years would be eligible. However, using RLR is problematic, as a young woman can have a low short-term risk, but large RLR based on the long remaining lifetime alone; in addition, risk models are typically validated only for shorter projection intervals (9).

The median 5-year risk among 45-to 49-year-old women, who are currently not invited to screening, was 0.8%. Similar to the reasoning of the NCCN guidelines, one could thus also consider delaying screening for the 113,000 women ages 50–59 with risk estimates lower than 0.8%, as their risk is as low or lower than that of the median 45- to 49-year-old for whom screening is currently not recommended. The low number of breast cancer cases in this group is also reflected in the high number needed to screen, NNS = 703. Risk estimates were almost universally above 0.8% for all women around age 55, suggesting a maximum delay of 5 years to screening initiation for women ages 50–59 years with risk <0.8%.

Of note, risk-adapted screening is already implemented in Germany for women with high breast cancer risks due to a strong family history of breast or ovarian cancer. They are offered intensified breast cancer surveillance, including MRI starting at age 25–30 years (19).

The participation rate for the German MSP is 56%, below the European Union's benchmark of acceptable participation (>70%; ref. 20). Focusing resources, for example, regularly assessing and discussing breast cancer risk, could help to specifically motivate higher risk women to participate in screening and lower breast cancer mortality.

A strength of our study is combining a well-calibrated risk prediction model with a population representative survey to obtain numbers representative for Germany. However, there are some limitations. One is the modest sample size of the DEGS survey and imputation of some model predictors based on the EPIC cohort study. As EPIC is conducted in only two German locations (Heidelberg and Potsdam), the imputation could have biased the risk factor distribution compared with the overall German female population. However, when we compared the distribution of risk factors in DEGS after imputation with that observed in population-based controls from two German breast cancer case–control studies, there were few noticeable differences (Supplementary Table S2). Another limitation is that BCmod predicts incidence, while the most relevant quantity for screening is the prevalence of clinically detectable breast cancer. However, data from the BCSC suggest that prevalence is proportional to incidence in previously unscreened women. Under this proportionality assumption, one can, therefore, use models that predict incidence to determine who should get screened. A limitation of BCmod is its modest discriminatory accuracy, with an area under the receiver operator characteristics curve, AUC of around 0.6 in German women (13). For a model with a higher AUC, the NNS would be further reduced (21). Thus, models that add genetic and other molecular information, for example, a polygenic risk score (PRS), are useful (22), with the trade-off that such data are more costly to obtain and some women might not agree to genetic measurements. A minor limitation is that BCmod does not include an important predictor of breast cancer risk, breast density, as this information would not be available at the time a woman wants to decide when to start mammographic screening. However, it would be important to incorporate breast density information into decision-making regarding screening intervals following an initial screen and deciding on the most appropriate screening modality. Both, PRS and breast density could help to further risk stratify the 113,000 women ages 50–59 years with BCmod risk estimates lower than 0.8%. However, importantly, as BCmod was well-calibrated in German women (13), all our population-level calculations are unbiased and valid.

In summary, we showed that risk-adapted mammographic screening could benefit women ages 40–49 years who are at elevated breast cancer risk, and reduce screening costs and burdens for low-risk women ages 50–69 years compared with the current age-based screening practice. A possible screening strategy might be to regularly compute a woman's 5-year breast

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cancer risk starting at age 40 and then recommend screening when her risk surpasses a risk level common among older women (e.g., 1.7%, mean risk for ages 55–60 years). A model that additionally includes mammographic density could be used to update and refine risk estimates after a woman's first mammogram (23) to help adapt screening intervals and to decide on the most appropriate modality. Considering all possible scenarios here goes beyond the scope of this article and more work is needed to identify the optimal screening strategy and risk cutoffs with careful balancing of risks, benefits, and costs. Such an analysis was conducted by Pashayan and colleagues (24), who compared age-based screening for United Kingdom women every 3 years to targeted screening on the basis of a model that contains age and a PRS and found a higher benefit-to-harm ratio for the risk-based strategy than the age-based approach.

We found that by using age-based screening, 10,498,000 biennial mammograms are administered and 35,900 breast cancer cases are detected among screened German women. Using a risk-based approach 10,424,000 mammograms (74,000 fewer) would lead to almost the same number of detected breast cancer cases. However, risk-adapted screening may be administratively more challenging and a careful weighing of potential costs, benefits, and harms is needed before recommending its implementation in Germany.

Authors' Disclosures

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Authors' Contributions

A.S. Quante: Conceptualization, methodology, writing–original draft, project administration, writing–review and editing. **A. Hüsing:** Conceptualization, formal analysis, methodology, writing–original draft, project administration, writing–review and editing. **J. Chang-Claude:** Writing-review and editing. **M. Kiechle:** Writing-review and editing. **R. Kaaks:** Writing–review and editing. **R.M. Pfeiffer:** Conceptualization, formal analysis, validation, visualization, methodology, writing–original draft, project administration, writing–review and editing.

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