Purpose: Women with high breast density (HBD) carry an increased risk for breast cancer (BC). The aim of the study was to provide data on awareness and knowledge gaps among women with vs w/o HBD about BC risk factors (BCRFs), which is the basis for effective communication about screening.

Patients and Methods: This was a web-based survey of 3000 women aged ≥30 and ≤70 from six countries. It comprised of 45 questions. T-tests and chi-square tests with False Discovery Rate adjustments were conducted as applicable, with significant differences reported at α=0.05.

Results: Three-thousand women were included in the analysis, 733 (24.4%) had HBD. Overall, 39% of women were familiar with the concept of HBD in the context of BC. Thirty-one percent of women were aware of HBD as BCRF and for 24% of women HBD was personally applicable. A significantly higher proportion of women with HBD were aware of almost all BCRFs compared to women w/o HBD (p ≤ 0.05). Similarly, a significantly higher proportion of women with HBD have undergone screening procedures compared to women w/o HBD (p ≤ 0.05). A total of 1617 women underwent mammography, 904 ultrasound and 150 MRI during their last screening. The most relevant source of information about BC was the health care professional, as reported by 63% of women.

Conclusion: Overall 39% of women were familiar with HBD as BCRF. Lack of BCRF awareness may contribute to delayed screenings, missed opportunities for early detection, and potentially poorer outcomes for individuals with dense breast tissue. Thus, this information should be communicated more widely.

Keywords: breast cancer risk factors, dense breast, screening, imaging modalities, sources of information

Introduction
Breast cancer (BC) is the most frequently diagnosed cancer in women. In 2020, about 2.3 million women were newly diagnosed and 685,000 die globally each year. By the end of 2020, 7.8 million women diagnosed with BC in the past 5 years were alive, thus making BC the world’s most prevalent cancer. Over the last three decades, BC incidence and death rates have increased due to the change in risk factor (RF) profiles (eg, age > 50, sex hormone intake, high breast density [HBD], obesity, alcohol/nicotine consumption, physical inactiveness, etc.), better cancer registration, and better cancer detection. Treatment of breast cancer is complex and involves a combination of different modalities including surgery, radiotherapy, chemotheraphy, hormonal therapy, or biological therapies delivered in diverse sequences.

Breast cancer risk factors (BCRFs) can be categorized as modifiable factors and non-modifiable factors. Non-modifiable RFs include, but are not limited to, female sex, older age, family history of breast or ovarian cancer, late first pregnancy, no full-term pregnancy, no breastfeeding, late menopause, HBD and previous history of chest radiation therapy. Modifiable RFs include but are not limited to obesity, alcohol intake, smoking, low physical activity, and hormone replacement therapy. The knowledge of RFs is a key parameter for BC awareness and thus screening participation. This knowledge might depend on age, education, income, country, and ethnicity.
HBD is one of the strongest independent BCRFs. Women with extremely dense breast tissue (ACR Category D) have a 4.6-fold increased BC risk compared to women with almost totally fatty breast (<5% density). It is postulated that just the abundance of fibro-glandular tissue might increase the probability of proliferative lesions, potential precursors of BC. In addition, HBD and accumulations of cancer cells attenuate x-rays to a similar degree so that cancer lesions might “hide” behind the dense tissue. This masking effect might be the reason why x-ray mammography (MMG) loses sensitivity with increasing breast density (BD).

Regular self-examination, physical examination by the doctor, MMG and ultrasound are screening procedures used for clinical diagnosis. While MMG is the most common basic imaging tool for BC screening worldwide, the National Cancer Institute also recommends breast magnetic resonance imaging (BMRI) for screening women with an elevated risk of BC, eg BRCA1/2 mutation carriers and women with a strong family history. Similarly, the European Society of Breast Imaging recommends that women with extremely dense breast tissue be screened with BMRI. Also, the American Cancer Society screening guidelines recommend for certain women at high risk for BC, a screening BMRI along with a yearly MMG.

Awareness of BCRFs and screening procedures in women with vs w/o HBD has not been investigated yet in such a large and diverse population. The results should support effective communication about BC screening and increase screening participation.

**Materials and Methods**

**Study Design**

This was a cross-sectional study utilizing quantitative research methods to collect holistic data on BC awareness.

This study was conducted in accordance with the current version of the Declaration of Helsinki and applicable national and local requirements for good pharmacovigilance practices. Institutional Review Boards and Ethics Committees were approached for review and approval. The US IRB (ADVARRA) issued an exemption notice, provided that each investigator will meet the ethical standards of the institution, will maintain the confidentiality of any identifiable data, will inform subjects about the research nature of the study and the fact that participation is voluntary. In Germany, this type of study does not require approval.

The study was a self-administered, web-based survey. No diagnostic or therapeutic intervention was performed. The survey was conducted by Trinity Life Sciences, recruited by Kantar Health, and programmed by M3 Global Research.

The target sample size was 3000 women from 6 countries, ie, the United States (US), Germany, Italy, South Korea, Brazil and Mexico (500 in each country).

Kantar Health recruited the sample for this study from its proprietary online panel of potential research participants in each country. This panel, called “LifePoints”, is open to anyone who passes the company’s quality checks, which are designed to exclude fraudulent participants. Participation on the panel is voluntary, but efforts are made to ensure panels are inclusive and representative of the general population. The panel size was as follows: the United States 22.1 million, Germany 3.7 million, Italy 2.4 million, South Korea 1.6 million, Brazil 12.8 million and Mexico 6.4 million with about 50% of women. The large size of the panel helps reduce selection bias in research.

About ~700–1000 female panellists were invited in each country to participate in the research. The invited women were chosen randomly. The number of invitees depended on the number deemed necessary to achieve the target sample of n = 500 in each country, which in turn was based on its calculation of the expected response rate (of those invited, % who respond to invites) and incidence rate (of those who complete the screener designed to determine eligibility, % who qualify for the research) in each country. Invitations were sent via email.

Of the ~700–1000 female panellists invited to participate in the research in each country, 500 qualified on the age criteria and completed the survey.

**Study Population**

Women aged ≥30 and ≤70, irrespective of BC diagnosis and treatment, were recruited. Eligible age ranges were identified based on BC screening guidelines in each country (the United States and Brazil 30–70 years, Germany and Italy 49–69 years, South Korea 40–69 years, and Brazil 30–69 years).
years, South Korea and Mexico 30–69 years). Women had to be able to complete the web-based structured questionnaire in their primary local language. They were asked to respond according to the best of their knowledge.

Participants remained completely anonymous. Personally identifiable information remained with the recruiting firm and was not shared with Trinity or Bayer.

Participants provided informed consent electronically via specific questions in the screening questionnaire, compliant with the stipulations of the General Data Protection Regulation (GDPR). Participants received an appropriate honorarium in their local currency upon completion of the survey.

**Questionnaire**

No pre-existing, pre-validated survey with the desired questions was found. The newly developed questionnaire was fielded in the main local language in each country. It comprised 45 questions and 251 context-sensitive sub-questions, which could be answered in about 10 minutes. The sub-questions were defined as the unique values respondents could choose in answer to a given question. The focus of the questionnaire was on three main areas: 1). Awareness of and experience with BC screening, in particular screening procedures and dynamics of the screening journey (eg, reason for undergoing screening, screening frequency/timing, type of health care provider (HCP) seen, burden of out-of-pocket cost, and experience with BC screening). 2). Knowledge of BCRFs and self-perceived risk of BC; 3). Sources of information, ie, resources used to learn more about women’s health and BC screening.

Two pilot interviews with eligible English-speaking women from the United States were conducted to ensure that all sections of the survey reflected study objectives and instrument questions were appropriately timed, appropriately sensitive to participant experiences, and able to capture the rationale behind survey responses ([Supplementary Material 1 – Questionnaire](#)).

**Statistics**

Descriptive statistics were used to describe the study population including means, medians, maximum/minimum ranges, and frequencies. Ninety-five percent confidence intervals for study outcomes were provided to permit informal statistical comparisons between subgroups.

Outcome variables were as follows: demographics, awareness of BCRFs, awareness and experience of screening procedures, additional attitudes, and sources of information. All variables were completely de-identified.

A t-test with False Discovery Rate (FDR) adjustment was conducted for all continuous variables, and a chi-square test with FDR adjustment was conducted for all categorical variables. Specifically, the FDR adjustment was applied to any comparison made in the study when more than two groups were compared. All statistically significant differences were reported at α = 0.05.

All results were reported based on non-missing data, and there was no imputation for missing values. Total N and non-missing n were reported in the deliverable. Not all survey respondents saw all questions – some questions were presented only if applicable to a given respondent based on responses to earlier questions.

All data were reported at the individual country level as well as at an aggregate cross-country (“global”) level. Country-level data were weighted using the following methodology.

Weights were assigned to each respondent based on 3 demographic factors: age, education and geography. 1). Firstly, the sample for each country was divided into age groups using a class interval of 10 years. These age groups were then weighted to accurately reflect the distribution of age groups within each country’s population. 2). Secondly, the sample for each country was divided into three education groups: women with less than a bachelor’s degree, women with only a bachelor’s degree, and women with a degree higher than a bachelor’s degree. Each group was assigned weights based on its representation in the true population. 3). Thirdly, the sample for each country was weighted to reflect the size of the country’s true population. 4). Lastly, the final weight was calculated by multiplying the weights obtained from the previous steps to arrive at the “global” results. Additionally, the final weights were constrained within a range of 0.2 as the lower limit and 5 as the upper limit, to prevent significant under- or over-representation of any individual respondent.

All designs and analyses were conducted in SPSS 24.0 and Q Research Software.
Results
Study Population
At total of 4804 respondents entered the screener, 3101 (65%) qualified for participation, and 3000 were included in the analysis. Of these, 733 (24.4%) women had known HBD. Women w/o HBD include 1834 women who reported not to have HBD and 433 women who did not know their BD or preferred not to answer (Figure 1).

Demographics
The age distribution was not substantially different in all 6 countries except for the elderly (60–70 years), who formed the smallest portion of the sample in Mexico (MX).

The percentage of women with below undergraduate education was lowest in the United States (US) (35%), the percentage of women with postgraduate education was highest in the United States (US), Germany (DE), and Italy (IT). Only 121 (4%) of women in the sample had been diagnosed with BC; 43 (1%) were on treatment at the time of the research (Table 1).

The demographics of women with vs w/o HBD differed remarkably. Women with HBD were significantly older (fewer in the age group 30–39 years, more in the age group 50–59 years), better educated (fewer below undergraduates, more postgraduates) and had more often BC in their medical history (Table 2).

Familiarity with Concept of “HBD” in the Context of BC
Overall, 39% of women were familiar with the concept of BD. Women from the United States were best informed (49%), German women were least familiar with this concept (19%) (Figure 2).

About half (52%) of 1200 women familiar with the BD concept knew that women with HBD have a higher risk of developing BC (data not shown).

Awareness of BCRFs
The awareness of the RF “family history of breast or ovarian cancer” or “personal history of BC” was highest, ie, 72% and 58%, respectively. Forty-three percent of the participants were aware of the BCRFs “age” and “hormone intake”. All other RFs were known by about a third of the population or less. The RF “HBD” was known by 31%. The most
important personally applicable BCRF was “physical inactiveness, mentioned by 48% of women. All other RFs applied to ≤28%. “HBD” was applicable to 24% (Figure 3).

A total of 63% women either have no knowledge or would like to know more about BCRFs (data not shown).

### Awareness of BCRFs by BD

Apart from the RF “personal history of BC”, women with HBD were significantly more aware of all other BCRFs than women w/o HBD (p ≤ 0.05). The highest awareness levels were seen for RFs “family” and “personal history of BC” for both groups. For women with HBD, awareness of HBD as a RF was as high as awareness of personal history as a RF (58%). The largest difference between the two groups was for RF “HBD”, which was known by 58% of women with HBD and only 22% of women w/o HBD (Figure 4).
Screening Procedures Undergone by BD

Women with HBD are significantly more likely to have undergone screening procedures than women not having HBD (p ≤ 0.05). “Self-examination” was the most popular screening procedure followed by “physical examination by doctor” and MMG. Eighty percent of women with HBD had experienced MMG (vs 53% of women w/o HBD), 51% had experienced ultrasound (vs 29% of women w/o HBD). Less than 20% of women in both groups underwent MRI or biopsy (Figure 5).

Awareness of Basic Facts About BC by Density

Women with HBD were significantly more likely to be aware of all BCRFs (p ≤ 0.05). About two-thirds of women (65% of women w/o HBD vs 75% of women with HBD) knew that regular MMGs help with early detection of BC. Fifty-seven
percent of women with HBD knew that “MMG can fail to detect BC” and 41% knew that “MRI can be better than MMG in women with HBD” (Figure 6).

### Challenges with Imaging Procedures
A total of 1617 women underwent MMG, 904 women underwent ultrasound and 150 women underwent MRI as part of their most recent round of screening. The percentage of women having any challenges with the imaging procedure was highest for MRI, followed by ultrasound and MMG. Only “long-term side effects” were lowest for ultrasound. The biggest challenge for all modalities was “anxiousness in the days leading up to the procedure” (Figure 7).

However, overall women’s satisfaction with imaging-based screening (“highly” or “somewhat satisfied”) was almost similar for all three modalities, ie, for MMG 86% (n = 1617), ultrasound 91% (n = 904) and MRI 89% (n = 150) (data not shown).
The most relevant source of information about BC used in the past was the “health care professional”, mentioned by 63% of women. In the future, women wished to obtain more information from “health and wellness phone apps”, “women’s health blogs and forums” and “support groups relating to women’s health” (Figure 8).

Discussion

A survey among 3000 women from 6 countries about their BCRF awareness and screening procedures was conducted. A total of 733 women (24%) with known HBD were identified. These women with HBD were much more aware of BCRFs, had undergone more screening procedures, and were better informed about basic facts on BC.

The recruiting firm Kantar Health picked potentially participating women from its proprietary online panel using convenience sampling, with the best efforts to attain a demographically representative sample. This way it was aimed that the women’s ethnic/racial identification, level of education, and household income was representative of the demographic mix of the true population of women in each country. In addition, we weighted each country sample to reflect the age and education mix of the national population.

The specific age range of ≥30 to ≤70 years was applied to capture the full range of screening programs in all 6 countries and also to capture data on women who will start screening in the near future. Although country-specific
evaluations were performed, the focus of this report was on the global level. This global data pool includes 3000 women and was weighted to reflect the population sizes of countries.

A total of 733 women (24%) reported having HBD. This percentage is higher than expected from the literature, where usually 3–13% of women were reported to have HBD, depending on age. However, this might be due to the age distribution of the cohort, which encompassed women aged 30–70 years, with 50% of the sample under the age of 50 years (Table 1). Prevalence of HBD decreases with age, particularly after menopause (± 50 years). Also, women reported “to the best of their knowledge” about their BD and this information was not validated for this study.

In addition, the demographics of women with vs w/o HBD differed in some respects. Women with HBD were older, better educated and more often had a history of BC (Table 2). Both education and age impact BD. After menopause, fibro-glandular tissue is replaced by fatty tissue and consequently BD decreases. As a result, an inverse distribution of RF “HBD” was expected with higher prevalence of HBD in the younger age brackets. However, better educated women often get pregnant at older age and breastfeed shorter, both factors are related to higher breast density. The higher prevalence of the RF “Personal history of BC” in women with HBD (7% in women with HBD vs 3% in women w/o HBD) was expected, as BD is a RF for BC. Although the difference was just 4%, this might explain the positive association between age and BD in our sample.

The highest RF awareness was found for the RFs “family” or “personal history of BC”, 72% and 58%, respectively. Forty-three percent of the participants were aware of the BCRFs “age” and “hormone intake”. All other BCRFs were known by around a third of the cohort or less (Figure 3). Beidler et al also identified “family history” as the most known BCRF (93%) in a survey cohort of 1858 women (40–76 years old). Similarly, Khushalani et al found that 88% of their 10,940-women cohort was aware of the RF “family history”.

In Beidler et al’s study, about half of respondents thought BD to be a greater risk than nulliparity (52%), having more than 1 alcoholic drink per day (53%), or having a prior breast biopsy (48%). Most respondents felt BD was a lesser risk than having a first-degree relative with BC (93%) or being overweight (65%). Our findings suggest a similar hierarchy, but there are some differences as well. Notably, frequent consumption of alcohol or nicotine is slightly more likely to be
seen as a risk factor than HBD in this study (35% vs 31%). Obesity after menopause is less often recognized as a risk factor than HBD (28% vs 31%) (Figure 3).

The RF “HBD” was known by 31% and applicable to 24% of women (Figure 3). These results are totally in line with Tran et al who reported a study on 1609 Korean women aged 40–69 years, of whom 29.7% had good BD knowledge.20

In the United States, the knowledge of the concept of breast density was highest (49%) (Figure 2). Even higher results were recorded by Santiago-Rivas et al in a study with 264 women in New York. Sixty-nine percent knew about this RF but only 30.4% knew their breast density.21 These more favorable results in the United States are most probably due to the federal legislation to standardize density reporting in all 50 states and US Territories in February 2019.22

Women with HBD were significantly more aware of almost all BCRFs than women w/o HBD (p ≤ 0.05). Still, a high proportion, >40% of women, who know they have HBD do not know that this is a BCRF (Figure 4). Tran et al concluded that awareness of one’s BD and knowledge about BD were positively associated with perceptions of absolute and comparative risk and cancer worry.20

Women in all age groups with HBD were significantly more likely to have undergone screening procedures than women w/o HBD (p ≤ 0.05) (Figure 5). This also supports the findings by Tran et al that women aware of their breast density and women with a good level of breast density knowledge were more likely to undergo future BC screening.20 Interestingly, de Lange et al reported that only 5276 of 8061 invited women (66%) with extremely high BD and knowing about the inherited risk for BC were interested in undergoing additional cancer screening with MRI. Only 4783 women (59%) finally completed the Dutch “DENSE” trial (Dense Tissue and Early Breast Neoplasm Screening)23 though they knew that MRI provides significantly higher sensitivity to detect BC in women with HBD.24 Reasons for non-participation were mostly emotional, ie, “procedure-related inconveniences” and “anxiety regarding the result”.23

Only 31% of women were familiar with the fact that HBD is a BCRF (Figure 3). Even more than 40% of women knowing to have HBD do not know that this is a BCRF (Figure 4). Since HBD is of paramount clinical importance, this information should be spread more widely. HCPs are a key source of information, mentioned by 63% (Figure 8). However, Lunsford et al found that many doctor-women-conversations about BC, BC screening and self-examination were brief and unsatisfying due to a lack of detail. Few women took action or changed lifestyle behaviors with the intent to reduce BC as a result of their conversations.25 This study cohort suggested - in addition to the HCP - to leverage “medical websites”, “public health awareness campaigns”, “health phone apps” and “women’s health blogs, forums and support groups” (Figure 8). As women with HBD were significantly more knowledgeable about BC, personalized risk-based BC screening and prevention might be a way forward.27,28

A number of limitations/biases need to be addressed: 1). Recall bias: Respondents might not have been able to accurately remember previous events or experiences, omit details, or memories may be influenced by subsequent events and experiences. Therefore, respondents were asked to provide responses “to the best of their ability”. 2). Selection bias: Respondents were recruited using a convenience sampling approach, with best efforts to attain a representative sample to mitigate selection bias. 3). Social desirability bias: Responses might have tended to underreport socially undesirable attitudes and overreport socially desirable attributes. Care was taken in framing the questions included in the instrument to help mitigate this bias. 4). There might have been important differences in behaviors and perceptions for certain subgroups of women (eg, women with a history of BC, women assigned to a follow-up breast MRI or women with a positive screening result) that are worth understanding in detail. However, as these sub-groups were rather small, a robust subgroup analysis was not possible. 5). The group of 433 women who did not know their BD or preferred not to answer were included in the “women w/o HBD” group. As these women might also have HBD, the true differences between the two groups might be even larger than what our findings suggest. 6). The questionnaire was validated by only two women.

Conclusion
Overall 39% of women were familiar with HBD as BCR. Lack of BCRF awareness may contribute to delayed screenings, missed opportunities for early detection, and potentially poorer outcomes for individuals with dense breast tissue. Thus, this information should be communicated more widely not only by HCPs but also by using modern forms of communication, ie, campaigns, apps, blogs, and support groups.
Acknowledgments

Bayer commissioned Trinity Life Sciences to help gather and analyze the information presented in this manuscript. We thank Anuj Chopra, Ankit Saurabh, and Tanvee Thakur from Trinity Life Sciences for their support with study execution and data analysis.

Disclosure

JE and NS are Bayer employees. BO reported professional fees for conducting the study from Bayer. The other authors report no conflicts of interest in this work.

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