



A framework for personalized mammogram screening

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ABSTRACT

Breast cancer screening guidelines serve as crucial evidence-based recommendations in deciding when to begin regular screenings. However, due to developments in breast cancer research and differences in research interpretation, screening guidelines can vary between organizations and within organizations over time. This leads to significant lapses in adopting updated guidelines, variable decision making between physicians, and unnecessary screening for low to moderate risk patients (Jacobson and Kadiyala, 2017; Corbelli et al., 2014).

For analysis, risk factors were assessed for patient screening behaviors and results. The outcome variable for the first analysis was whether the patient had undergone screening. The risk factors considered were age, marital status, education level, rural versus urban residence, and family history of breast cancer. The outcome variable for the second analysis was whether patients who had undergone breast cancer screening presented abnormal results. The risk factors considered were age, Body Mass Index, family history, smoking and alcohol status, hormonal contraceptive use, Hormone Replacement Therapy use, age of first pregnancy, number of pregnancies (parity), age of first menses, rural versus urban residence, and whether or not patients had at least one child.

Logistic regression analysis displayed strong associations for both outcome variables. Risk of screening nonattendance was negatively associated with age as a continuous variable, age as a dichotomous variable, being married, any college education, and family history. Risk of one or more abnormal mammogram findings was positively associated with family history, and hormonal contraceptive use. This procedure will be further developed to incorporate additional risk factors and refine the analysis of currently implemented risk factors.

1. Introduction

Among women, breast cancer is the second most common cancer and is second only to lung cancer as the leading cause of cancer death (Facts About Breast Cancer In The United States, xxxx; Breast Cancer Statistics, xxxx). The incidence of breast cancer has remained relatively stable, as demonstrated by a report from the American Cancer Society, which noted a 2.1% per year decline in pre-invasive breast cancer incidence and a 0.3% per year increase in invasive breast cancer incidence from the years 2012 to 2016 (American Cancer Society, 2019). Studies utilizing Surveillance, Epidemiology, and End Results (SEER) cancer

registry data indicated a downward trend in breast cancer mortality rates (How Common Is Breast Cancer, xxxx). However, the overall incidence remains high, with 276,489 new invasive breast cancer diagnoses and 42,170 deaths expected throughout 2020 (National Cancer Institute Surveillance, xxxx). Siegel et al. asserted that the increase in incidence implies a decrease in mortality, but since 2010 the decline in the breast cancer mortality has slowed compared to other cancers (Siegel et al., 2020).

Several studies have emphasized the benefit of regular breast cancer screening in reducing mortality (Cancer.org. ACS Breast Cancer Early Detection Recommendations [online] Available at, 2020; Coldman Jan,

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2015; Saei Ghare Naz, 2018; Puvanesarajah et al., 2019; Stang and Jöckel, 2018). Breast cancer detected through screening had lower mortality rates than cancer detected by symptom (Puvanesarajah et al., 2019), and lower breast cancer mortality was observed in women in screening programs (Stang and Jöckel, 2018; Beau et al., 2018). Cancer screening is not without risk, so the decision to begin regular screening is often based on age and evidence-based risk factors. Several organizations publish guidelines for regular breast cancer screening, including the American Cancer Society (ACS), the United States Preventative Services Task Force (USPSTF), and the American Academy of Family Physicians (AAFP). Although they are a valuable clinical tool, these guidelines frequently contradict one another on the appropriate age to begin and frequency of regular screenings (Brown et al., 2018; Tyagi and Dhesy-Thind, 2018). Additionally, as research continues, newly published guidelines for a given organization can contradict guidelines from the same organization three to five years prior (Peppercorn et al., 2017).

Lack of consistency between guidelines significantly undermines the potential benefit of cancer screenings and leads to noncompliance, lapses in adopting updated guidelines, disagreement between physicians, and patient confusion (Jacobson and Kadiyala, 2017; Corbelli et al., 2014; Siegel et al., 2020). These issues are illustrated by the period following the USPSTF 2009 guideline update, during which the USPSTF recommended women begin regular screening at age 50 and be screened biennially. This was in stark contrast to their previous guidelines, which recommended initiating regular screening at age 40 and screening annually. Physician recommendations and patient behaviors appeared to change very little in the five years following the update. Screenings among women 40–49 declined in the months following the update but quickly returned to pre-update levels (Brown et al., 2018). Most internal medicine providers in 2012 were still recommending annual screening initiating at the age of 40 (Corbelli et al., 2014). Considering these issues, it may be necessary for large health systems to interpret guidelines in the context of their patient population. Several models for assessing the risk of breast cancer have been developed and can act alongside screening guidelines to inform patient care. However, these risk assessment models can vary significantly in which risk factors they incorporate and their applicability to different population sizes (Brentnall and Cuzick, 2020; Evans and Howell, 2007). There can also be significant variation between patient populations due to demography, environmental factors, and local health policy (Januszewski et al., 2014).

Per the ACS, the current guidelines are that women between ages 40 and 44 have the option to start annual breast cancer screening with. Women between the ages of 45 and 54 are advised to have mammograms annually, and women aged 55 and older are advised to either switch to biennial mammograms or continue yearly mammograms at

their discretion (Cancer.org, 2020).

Despite the importance of breast cancer screening, noncompliance is common, especially among low-income patients (Khaliq et al., 2013). Among 210 hospitalized women aged 50–75, 13% had never received a mammogram, and 39% were overdue for screening. Common causes of noncompliance in cancer screening include financial concerns, lack of awareness, lack of healthcare access, and cultural or religious beliefs (Peppercorn et al., 2017; Roetzheim et al., 1996; Halpern et al., 2007; Falomo et al., 2018; Alharbi et al., 2019). This study seeks to establish a process whereby health systems assess the relevance of common risk factors in screening attendance and mammography results and evaluate the relevance of those factors to their patient population (see Table 1).

2. Methods

To access and utilize the data, approval from the University of Kansas Medical Center's (KUMC) Internal Review Board was obtained. The data analyzed in this study was a subset of the broader dataset collected via a self-reported Health History Questionnaires (HHQs; Andrew Godwin, PhD, PI). The survey, initially developed by Dr. Godwin and Dr. Mary Daly (Fox Chase Cancer Center), was distributed to patients registered with The University of Kansas Cancer Center's (KUCC) Biospecimen Repository Core Facility (BRCF) through The University of Kansas Health System (TUKHS) breast imaging clinic or KUCC. The HHQ was designed to gather data related to patient health history and family history. This is beneficial because a patient's health and family history can be difficult to extract from health records and standardize for analysis.

The electronic version of the HHQ began in 2017. Prior to 2017, the HHQ was collected solely in paper form. For this manuscript, we utilized data captured from January 2017 through May 2020. The response rate during this period was approximately 45.82%. The data capture workflow is described below in Fig. 1.

Analysis was conducted using logistic regression through the STATA statistical package (StataCorp, 2019). In the first iteration of analysis, the outcome variable for logistic regression was the screening variable (mam_s), in which two groups were compared. Group 1 consisted of patients who had not undergone screening, and group 2 consisted of patients who had undergone screening. The question in the HHQ used reads as follows: "Have you ever had any of the following breast cancer screenings?" Within this question, the subsection of "Mammogram" was used. There were four possible responses to this subsection, including "No, I've never been screened for breast cancer in this manner" (7.85% of overall response); "Don't remember having this breast cancer screening" (0.41%); "Yes, all results were normal" (53.09%); and "Yes, one or more of the results was abnormal" (38.66%). The dichotomous

Table 1
Guidelines for Mammography Screening: Changes Over Time.

Year	United States Preventative Services Task Force		American Cancer Society		American Academy of Family Physicians		American College Of Obstetricians and Gynecologists	
	Age 40-49	Age ≥50	Age 40-49	Age ≥50	Age 40-49	Age 50-74	Age 40-49	Age ≥50
2006	Biennial	Biennial	Annual	Annual	Biennial	Biennial	Biennial	Annual
2009	Case by Case ^a	Biennial	Annual	Annual	Case by case	Biennial	Annual	Annual
2016	Case by Case	Biennial	Annual ^b	Biennial	Case by Case ^c	Biennial	Annual	Annual
2020	Case by Case	Biennial	Annual	Biennial	Case by Case	Biennial	Case by Case ^d	Annual

a. As of 2016, the US Preventative Services Task Force recommends that the decision for biennial screening in women younger than 50 years should be made on an individual basis, with consideration of the potential harms and benefits of screening. Additionally, the USPSTF recommends biennial screening mammography for women aged 50 to 74 years.

b. As of 2015, the American Cancer Society recommends annual screening for women who are 45 to 54 years old and biennial screening for women who are 55 years or older.

c. As of 2015, the American Academy of Family Physicians recommends that for women who are 40 to 49 years old, the decision to start screening should be an individual one. For women 50–74, they recommend biennial screening with mammography.

d. As of 2017, the American College of Obstetricians and Gynecologists recommends that women of average risk should be offered annual screening starting at age 40; if a woman decides not to start annual screening at that time, regular screening should start at age 50. They included that the decision should be made individually by each woman after discussing the issue with her doctor.

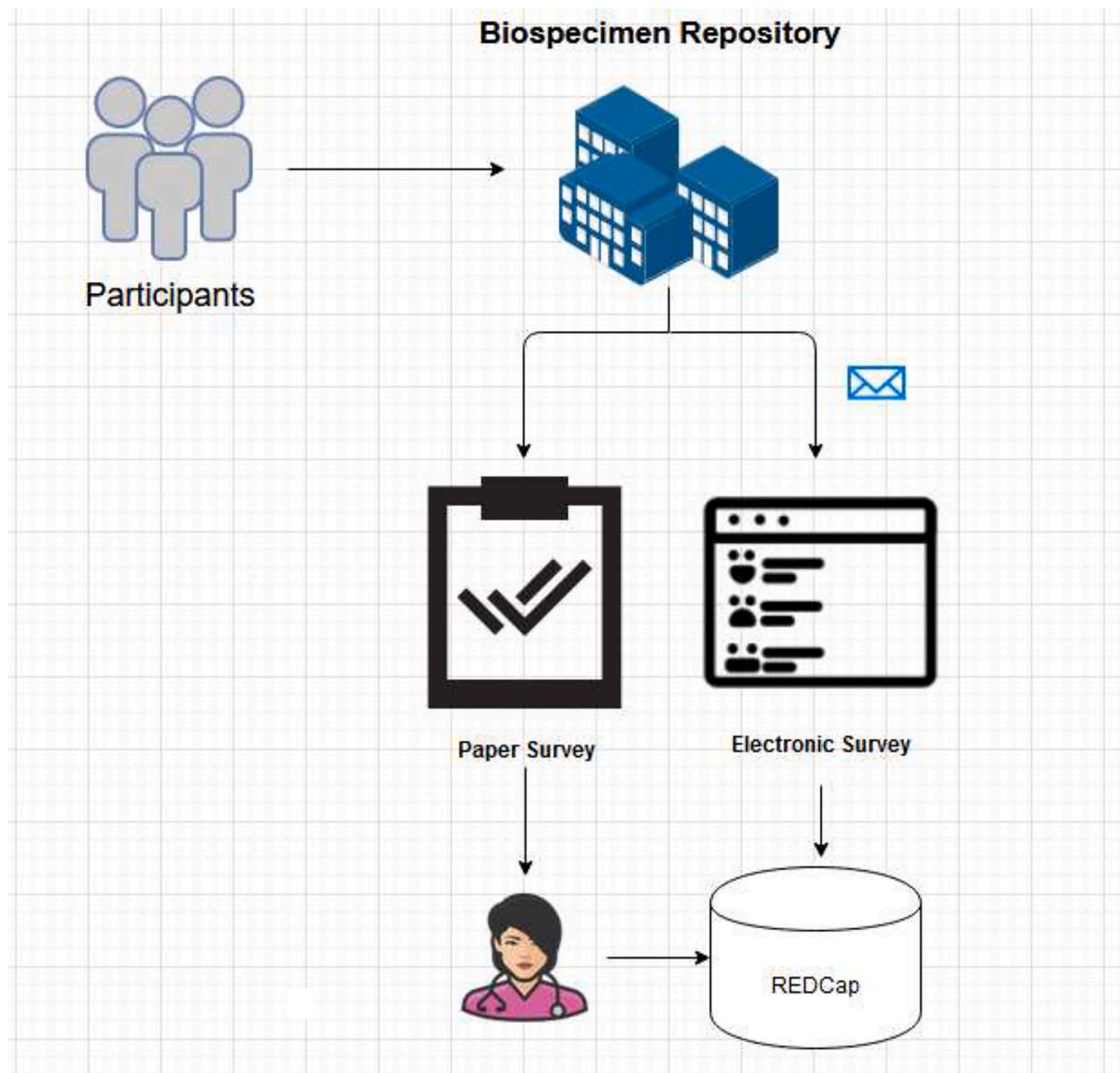


Fig. 1. Survey Capture Workflow.

outcome variable *mam_s* was then derived, which coded patients who had not undergone screening (Group 1) as 1, and patients who had undergone screening (Group 2) as 0. Risk factors for screening attendance include age, marital status, education level, rural versus urban residence, and family history of breast cancer.

Age was evaluated both as a continuous variable and as a dichotomous variable. Age, as a dichotomous variable, was evaluated where patients over the age of 50 were coded as 1 and patients under the age of 50 were coded as 0 (Sun et al., 2017). Other variables that were coded dichotomously included: rural vs urban residence as assessed by rural-urban continuum codes (Ursin et al., 1998; Ers.usda.gov., 2020), marital status, level of education assessed by patients having any college education, and family history of breast cancer.

The second round of analysis centered on breast cancer screening results and analyzed a subset of Group 2 in the previous analysis. Analysis was performed using logistic regression with screening results as the outcome variable (*mam_abn*). Patients within this subset were dichotomized into patients who had one or more abnormal mammogram results (Group 2a) and patients who only received normal mammogram results (Group 2b). Group 2a patients with one or more abnormal results were coded as 1, and Group 2b patients with no

abnormal results were coded as 0. Due to focusing on a subset of Group 2, patients who did not remember if they had received a mammogram and patients who had not received a mammogram were dropped for analysis ($n = 2,147$). The outcome variable for the second set of analyses was compared against the selected risk factors for abnormal mammography results. Risk factors for mammography result included age, Body Mass Index (BMI), family history, smoking and alcohol status, hormonal contraceptive use, Hormone Replacement Therapy (HRT) use, age of first pregnancy, number of pregnancies (parity), age of first menses, rural versus urban residence, and whether or not patients had at least one child (Leysen et al., 2017; Kim et al. Sep, 2018; Shieh et al., 2019).

Participant BMI was calculated utilizing the height (in inches) and weight (in pounds) and was categorized based upon the Centers for Disease Control guidelines into the following categories: overweight, obese, normal, and underweight (Centers for Disease Control and Prevention, 2020). Family history was coded as a dichotomous variable where patients with at least one family member who had been diagnosed with breast cancer were coded as 1. Hormonal contraceptive use was coded into two separate variables with the first (*contra*) being a continuous variable representative of the age when the patient began using hormonal contraceptives and the second (*hormonal_use*) being a

dichotomous variable where patients who were current or former users of hormonal contraceptives were coded as 1 and otherwise as 0. Smoking status was coded as a dichotomous variable where current or former smokers were coded as 1 and patients who were neither were coded as 0. Alcohol status was coded as a dichotomous variable where patients who currently drink at least one alcoholic drink per week were coded as 1 and those who did not were coded as 0. Hormone Replacement Therapy use was evaluated using a dichotomous variable where patients who currently or formerly used HRT were coded as 1. An article by Kelsey and colleagues, on the correlation of reproductive factors with breast cancer suggested we also investigate the age of first pregnancy, age of first menses, and number of pregnancies before participants responded to the HHQ survey (Kelsey et al., 1993).

3. Results

Over three years, we had 3,667 participants: 2,743 female, 885 male, and 39 who declined to define their gender. For our analyses we excluded partial survey responses and male responses, bringing down our sample size to n = 2,354. Participant characteristics are described in Table 2 below:

Most participants (70%) were 45 years of age or older. While this can affect the generalizability of results across all age groups, it also allows analysis to center on women who are most relevant to the broader discussion. New breast cancer diagnoses rise sharply from the 35–44 age group (8.3%) to the 45–54 age group (19.7%) and continue to rise in the 55–64 age group (SEER, 2020). Additionally, screening guidelines frequently utilize ages 40, 45, and 50 as crucial milestones in the decision to begin regular breast cancer screening (Tyagi and Dhesy-Thind, 2018).

Logistic regression analysis suggested that age as a continuous variable (OR = 0.812, 95% CI = 0.788 – 0.835, p < 0.001), age as a dichotomous variable (OR = 0.309, 95% CI = 0.258 – 0.360, p < 0.001), marital status (OR = 0.541, 95% CI = 0.371 – 0.787, p = 0.001), education (OR = 0.512, 95% CI = 0.311 – 0.845, p = 0.009), age of first pregnancy (OR = 0.970, 95% CI = 0.952–0.987, p = 0.001), and family history (OR = 0.437, 95% CI = 0.321 – 0.763, p = 0.001) were associated with increased odds of attending a mammogram screening. Therefore, results can be interpreted thusly because patients who had not attended a mammogram screening (Group 1) were coded as 1, and thus an Odds Ratio < 1 indicates that the presence of these risk factors would lead to increased odds of mammogram attendance than their

Table 2
Participant Characteristics.

	(n, %)
Ethnicity (n, %)	
White (n, %)	2183, 92.7%
Black or African American (n, %)	100, 4.6%
Mexican, Mexican American (n, %)	45, 1.9%
Other (n, %)	26, 1.1%
Current smoker (n, %)	794, 33.7%
Married (n, %)	1,728, 73.4%
Current alcohol use (n, %)	1,096, 46.6%
Ever used contraceptive pill (n, %)	2,030, 86.2%
Rural residence (n, %)	274, 11.6%
BMI (mean, SD)	28.5 (7.1)
Age, years (mean, SD)	56.4 (12.7)
Age, years (n, %)	
0–20 years old	4, 0.16%
21–30 years old	55, 2.31%
31–40 years old	222, 9.34%
41–50 years old	501, 21.07%
51–60 years old	624, 26.24%
61–70 years old	658, 27.67%
71–80 years old	276, 11.61%
80 years or older	38, 1.60%
Age of first pregnancy, years (mean, SD)	19.8 (11.1)
Number of times pregnant (mean, SD)	2.2 (1.7)

absence (Bland and Altman, 2000). The interpretation of these results is that a patient with a family history of breast cancer is 2.29 times more likely to attend breast cancer screening. The variable assessing rural or urban setting did not reach statistical significance (OR = 1.36, 95% CI = 0.695–2.660, p = 0.37). Results from the first analysis have been summarized below in Table 3.

The second set of logistic regression analysis on mammography results suggests that family history (OR = 1.47, 95% CI = 1.175 – 1.839, p = 0.001) and hormonal contraceptive use (OR = 1.38, 95% CI = 1.072 – 1.773, p = 0.012) were associated with increased risk of one or more abnormal mammography result(s). Additional factors such as BMI (OR = 0.998, 95% CI = 0.98 – 1.006, p = 0.305), smoking status (OR = 0.943, 95% CI = 0.779 – 1.142, p = 0.547), alcohol status (OR = 1.02, 95% CI = 0.848 – 1.226, p = 0.837), parity (OR = 1.00, 95% CI = 0.932 – 1.072, p = 0.992), age of first menses (OR = 0.965, 95% CI = 0.912 – 1.021, p = 0.217), age of first pregnancy (OR = 1.002, 95% CI = 0.987 – 1.018, p = 0.78), age of initial hormonal contraceptive use (OR = 1.254, 95% CI = 0.959 – 1.638, p = 0.098), rural living status (OR = 1.292, 95% CI = 0.989–1.689, p = 0.068), and having at least one child (OR = 1.05, 95% CI = 0.643 – 1.715, p = 0.845) failed to reach statistical significance. Results from the second analysis have been summarized below in Table 4.

4. Conclusion

The key findings of this study can be grouped according to factors in screening attendance and in abnormal mammography results. Among screening factors it was found that older patients, those who were married, those who had a college education, those with a family history of breast cancer, and those who had a first pregnancy at a later age were all more likely to have attended a breast cancer screening. Among the abnormal mammography results it was found that those with a family history of breast cancer and hormonal contraceptive use were at an increased risk of abnormal results. Additionally, there was a small population (8.28%) of survey participants who have never utilized mammogram screening, including people of different ages.

While this is consistent with previous studies on breast cancer screening attendance factors, the degree to which these associations exist can vary significantly between studies and populations (Shah et al., 2014). For example, a study analyzing breast cancer attendance factors in Sweden found that unmarried women were 2.4 times more likely to not attend breast cancer screening (Manjer et al., 2015). In comparison to our patient population where unmarried women were 1.848 times more likely to not attend screening, the association in their population appears more significant. These comparisons cannot account for differences in methodology, HHQs, and statistical analysis. As variable as patient populations can be, there is currently no reliable means to compare the relevance of risk factors in either breast cancer screening attendance or breast cancer risk to other populations.

This study acts as the first iteration to provide a standardized data gathering and analysis process to compare risk factors in breast cancer screening attendance and risk between patient populations and within demographics of individual patient populations. The aim is to eventually develop a breast cancer risk factor application that would combine

Table 3
Logistic Regression Analysis Table: comparing participants who have undergone mammogram screening versus participants who have not undergone screening.

Screening Nonattendance	Odds Ratio	P-value	[95% Conf. Interval]	
Age (Continuous)	0.812*	>0.001	0.788	0.835
Age 50+	0.037*	>0.001	0.002	0.061
Marital Status	0.767*	0.285	0.894	1/358
Level of Education	0.512*	0.009	0.311	0.845
Rural Residence	1.360	0.370	0.695	2.66
Family History	0.495*	0.001	0.695	0.763

*Statistical significance at P < 0.05.

Table 4
Logistic Regression Analysis Table Comparing the Abnormal Group with the Normal Group.

Abnormal Mammogram Result	Odds Ratio	P-value	[95% Conf. Interval]	
Age (Continuous)	0.998	0.578	0.989	1.006
Age 50+	1.077	0.083	0.888	1.308
Body Mass Index	0.993	0.305	0.980	1.006
Family History	1.470*	0.001	1.175	1.839
Smoking Status	0.943	0.547	0.779	1.142
Alcohol Status	1.020	0.837	0.848	1.226
Hormonal Contraceptive	1.379*	0.012	1.072	1.773
Age at First Contraceptive Use	1.254	0.098	0.959	1.638
Hormone Replacement Therapy	1.085	0.419	0.890	1.324
Age of First Pregnancy	1.002	0.780	0.987	1.018
Number of times Pregnant	1.000	0.992	0.932	1.072
Age of First Menses	0.965	0.217	0.912	1.021
Rural residence	1.292	0.068	0.981	1.703
At least one child	1.050	0.845	0.643	1.715

*Statistical significance at $P < 0.05$.

established risk algorithms with the data gleaned from the local patient population. In this way, breast cancer risk assessment could be tailored to patient populations while still utilizing the high-quality data behind currently available options. With an openly available template for assessing local breast cancer risk factors, other healthcare systems would be enabled in developing their own similar tools. There were several limitations to this study including patient participation, low sample sizes in mammography results, the utilization of a questionnaire not specifically designed for the purposes of the study, and the fact that answers were self-reported by patients. Our patient population was also predominantly patients visiting TUKHS breast imaging clinic and KUCC, with a patient population that consists heavily of those living in urban areas (88.29%; Williams and Thompson, 2016). This limits our ability to accrue an adequate sample size to assess rural populations. While the assessment of rural vs urban living status can provide some insight into healthcare access, this study was limited in its assessment of more direct socioeconomic measures such as the MUA/HPSA status of patient residence and historical county level poverty rates. These factors will be developed for implementation in further iterations to flesh out the socioeconomic aspects of patient residence. We were limited in our ability to assess risk factors among and between ethnic backgrounds, as our patient population and participants were predominantly white (92.73%). We are hopeful that further data gathering among minority populations will allow for more robust analysis. Lastly, the HHQ response rate (Jan 2017–May 2020) was approximately 45.82%. Despite these limitations, there are several planned improvements to enhance the generalizability of findings as well as the standardization of the procedure.

Considering the association between hormonal contraceptive use and abnormal mammogram findings, future studies would explore the duration of hormonal contraceptive use in our population, as this factor has been well documented in literature (Mørch et al., 2017; Schneyer and Lerma Dec, 2018; Grandi et al., 2018). As the smoking status and alcohol status factors relied on dichotomous variables, future studies should incorporate analysis that accounts for cigarettes smoked during a typical day, average drinks per week, secondhand smoke exposure, calculated variables for pack years, and the age at which patients began smoking or drinking (Leysen et al., 2017). There are significant differences between ethnicities in breast cancer screening attendance, incidence, and survival rates (Helvie et al. Sep 1, 2014; DeSantis et al., 2016). Future studies we would assess risk factors as they relate to specific ethnicities, as this can be a significant factor in patient population variation. In consideration of this, we plan to expand our outreach by partnering with the Mason Cancer Alliance, the outreach network of KUCC, to reach rural and minority patients (Maskarinec et al., 2011; Masoniccanceralliance.org, 2020). It is also important to consider that abnormal mammogram results do not equate to a breast cancer

diagnosis, as there can be several reasons for an abnormal result. Further studies could incorporate breast cancer diagnosis, breast cancer type, and treatment as considerations.

While it is vital to consider that despite the strong predictive power of risk factors such as breast density and family history, most women diagnosed with screen-detected breast cancer did not exhibit these risk factors (Neal et al., 2018). As such, evaluating the significance of additional risk factors in individual patient populations could inform healthcare providers in how heavily to weigh those additional factors, especially in patients who present with many of them. As risk relates to age, we assessed age as a continuous and dichotomous variable and found significance in both. This was performed with the consideration that a significant proportion (16.7%) of screen-detected breast cancer diagnoses are made in women ages 40–49 (Neal et al., 2018). Gathering evidence may reinforce the concept that age as a risk factor should be treated as a scale rather than a dichotomy that is activated at a target age and could potentially lead to improvements in breast cancer mortality rates in not only the 40–49 age group but others as well (Hendrick and Helvie, 2011). Future analysis could include discretize variables in age group and comparisons between age groups to further investigate this factor. Lastly, participants who did not attend screening were not asked further questions on why they did not attend screening, which would be beneficial in assessing risk factors of nonattendance.

As an immediate next step, we will focus on cross validating this data against participants' medical records. Further studies could incorporate medical record information from participants to track subsequent breast cancer diagnoses and adherence to breast cancer screening guidelines (Corbelli et al., 2014; Alvarez et al., 2019). This could provide longitudinal data to supplement current findings and examine how screening attendance may change as individual patients get older.

After further refinement, we intend to develop a breast cancer risk factor app for our patient population using established risk assessment methods informed by the results of our population specific analysis. This app would allow individuals to assess their risk based on age, BMI, smoking status, alcohol status, contraceptive use, age of first pregnancy, and additional risk factors that were included in this analysis or will be implemented in future analysis. Using the patient's information, the app would provide recommendations based on both national standards and population-specific data to inform patients of their overall risk and assist patients in deciding when to begin regular screening (Shieh et al., 2019).

While still in its early stages, it is the aim of this process that with iterative improvement and collaboration with other health systems, we could develop a tool for healthcare providers to assess the risk of breast cancer in their patient population. The applicability of this insight could potentially be utilized by several organizations outside of local health systems. Local governments could use this information to inform health policy and direct resources toward addressing the most pressing risk factors for breast cancer among their population. Individual patients could utilize more accessible tools such as apps or web-based assessments to consider their own risk within their population as an adjunct to established guidelines and tools. Physicians could account for variation in their patient population directly to inform their care. One example of this may be if a physician with a higher proportion of black female patients observed from their report that members of this demographic experienced a higher Odds Ratio of screening nonattendance due to a certain risk factor, the physician could consider that in discussions with patients. Lastly, with the eventual development of a standardized process of data gathering and analysis, public health officials could draw comparisons between their patient population and others. This would allow them to consider the contribution of environmental factors specific to their sample population.

5. Limitations

As alluded to at the beginning, breast cancer is still an incredibly common and pervasive disease. While breast cancer screening

guidelines are a valuable and ever-evolving tool for clinical decision making, the confusion and non-adherence that can result from frequent shifts in recommendations can result in needless death or unnecessary testing. Breast cancer screening is a vital life-saving tool when utilized appropriately. It is our hope that through the refinement of this procedure, health systems will be able to tailor the process of regular screening to the needs of their patient population (Hendrick et al., 2019).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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