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ACCURACY OF THE GAIL MODEL IN INVASIVE BREAST CANCER

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Abstract

Objective:

This study evaluates the predictive ability of the Gail Model specifically in the detection of invasive ductal carcinoma.

Materials and methods:

The study was approved by the institutional review board, enrolled nulliparous patients, aged 35-85 years, attending the outpatient department of the hospital with complaints of a breast lump, on a non-probability consecutive basis. All patients provided informed voluntary informed consent after they were informed about the pros and cons of participating in the study. The 5-year and lifetime risk score were calculated via Gail calculator. Its effectiveness was assessed using metrics such as sensitivity, specificity, and are under the curve. All the participants then underwent histopathological examination for the confirmation of the presence of invasive ductal carcinoma.

Results:

As per the inclusion criteria, a total of 124 females were enrolled into the study. As per the Gail model, females at high risk (>1.67%) to develop invasive ductal carcinoma in the next 5 years were 9.6%. The sensitivity, specificity, and AUC of the Gail score in detecting the carcinoma was evaluated to be 35.3%, 100%, and 0.885 respectively.

Conclusion:

The Gail Model serves as a valuable component in the multifaceted approach to breast cancer risk assessment, particularly for IDC. However, integrating genetic, lifestyle, and additional clinical factors could enhance its predictive accuracy, ultimately improving early detection and intervention strategies for invasive ductal carcinoma in breast cancer screening protocols.

INTRODUCTION

Breast cancer ranks as one of the most prevalent cancers affecting women globally and is the second leading cause of fatalities among women, following lung cancer (Gibberd, 2000). Annually,

approximately 2.09 million women receive a breast cancer diagnosis, with around 627,000 succumbing to the illness (WHO, 2021).

The incidence of breast cancer is increasingly on the rise in Asia, significantly contributing to the overall global disease burden. A staggering 39% of all breast cancer cases diagnosed worldwide occur in this region (Fan et al., 2015). In Pakistan, the situation is particularly alarming, with the country reporting the highest prevalence of breast cancer in Asia—approximately 1 in every 9 women is affected by the disease (Ghoncheh et al., 2015). Furthermore, a report by the International Agency for Research on Cancer in 2018 indicated that there were 34,066 newly diagnosed cases of breast cancer among women in Pakistan (WHO, 2019).

A recent study highlighted that, in Pakistani women, breast cancer typically manifests in their 30s (Soomro et al., 2018). This suggests that earlier screening is essential to detect the disease before symptoms arise. The mortality rate for females suffering from breast cancer in Pakistan is alarmingly high, at approximately 30.8% (GLOBOCAN, 2018). Notably, around 20% of these cases are classified as Triple-negative breast cancer, a more aggressive and recurrent form of the disease (Boyle, 2012). Among four major Asian countries—India, China, and Thailand—Pakistan has the highest rate of breast cancer incidence. Moreover, the age-standardized death rate for breast cancer patients in Pakistan is projected to rise dramatically, reaching 62% by the year 2030 (Mubarik et al., 2022).

Sadly, the country experiences a higher incidence of breast cancer-related fatalities, primarily attributed to late diagnoses and delays in referrals to suitable medical facilities (Begum, 2018). Various factors contribute to the risk of developing breast cancer, including biological sex, age, timing of menarche and menopause, childbirth history, previous hormonal therapy, family history—particularly involving first-degree relatives—exposure to radiation, smoking, and other lifestyle choices. Additionally, significant genetic considerations, such as mutations in the BRCA1 and BRCA2 genes, are also critical (Bray et al., 2018). Raising awareness about the symptoms of breast cancer and promoting early screening are crucial strategies for mitigating associated risks. The American Cancer Society has established guidelines to prevent and detect breast cancer early. They recommend that women at moderate to high risk begin regular screening mammograms at 45 years of age (Oeffinger et al., 2015; Saslow et al., 2007).

Numerous models exist for assessing the risk of breast cancer in women, including the Gail Model, Claus Model, BRCAPRO Model, and Cuzick–Tyrer Model (McTiernan et al., 2001; Bondy et al., 1994; Gail and Mai, 2010; Armstrong et al., 2000). Among these, the Gail Model is particularly prevalent because it estimates both the risk of developing breast cancer over the next five years and the lifetime risk. This assessment takes into account various factors such as the woman's age, the onset of menstruation, the age of her first childbirth, her family medical history, and the number of biopsy procedures she has undergone (Gail and Mai, 2010; Gail et al., 1989).

The primary objective of this study is to evaluate the performance of the Gail model to estimate the risk (five-year and lifetime) for the development of invasive ductal carcinoma in women of age 35 to 85 years.

Materials and Methods:

The study was conducted after approval from CPSP and IRB. Verbal consent was taken from participants before starting data collection. Females aged between 25-85 years presenting with breast lump and nulliparous were enrolled in the study. At the time of enrollment complete details of the study were explained to the patient and written inform consent was taken. After taking consent, baseline demographics and clinical details were noted in a predesigned proforma (Appendix I).

Gail model score of risk stratification was calculated. Patient underwent histopathology for confirming the diagnosis of invasive ductal carcinoma. This study was based on the collection of data related to the patient's history and thorough examination. The variables included for evaluation were age of patient, age at first live birth, age of menarche, family history (1st degree relatives with breast cancer) was noted in a predesigned proforma.

Data was analyzed using SPSS version 25. Quantitative variables such as age, age at first live birth, age of menarche, and duration of breast lump were reported as median (IQR), while qualitative

variables such as residence, marital status, family H/o breast cancer, ethnicity and breast cancer were reported as frequency and percentage. Receiver operator characteristic (ROC) curve was constructed and area under the curve (AUC) was obtained along with best cut-off values for sensitivity and specificity of the Gail model score. Confounding variables such as age, residence and duration of breast lump were controlled through stratification. Post stratification (ROC) curve were constructed and area under the curve (AUC) were obtained.

Results:

As per the inclusion criteria, a total of 124 females were enrolled in the study. The median age of the participants was 43.0 years (38.0-51.8 years) (**Table 3**). The categorization of the female patients based on the age is shown in **Figure 1**. The majority of the patients belonged to the age category of 35-50 years.

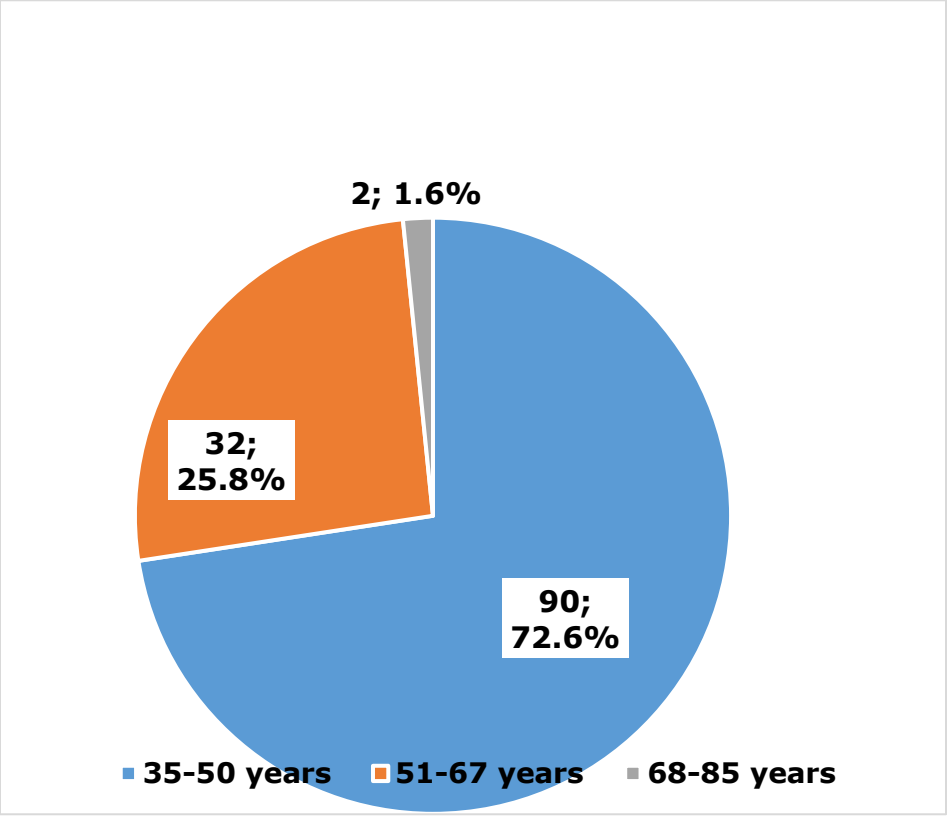

Figure 1: Distribution of patients based on age

Table 1: Distribution of continuous variables in the study

	Mean (±SD)	Median (IQR)	Min-Max
Age (years)	45.4 (±9.2)	43.0 (38.0-51.8)	35.0–69.0
Age of menarche (years)	11.4 (±2.1)	11.0 (10.0–13.0)	7.0–15.0
Age at first live birth (years)	22.2 (±4.2)	22.0 (19.0-25.0)	15.0-32.0
Duration of breast lump (days)	109.5 (±64.1)	90.0 (60.0-160.5)	20.0-300.0
Gail model 5-years	0.90 (±0.59)	0.80 (0.50-1.10)	0.20-2.90

risk score (%)			
Lifetime risk score (%)	10.2 (±3.6)	9.2 (7.9-11.2)	4.4-21.1

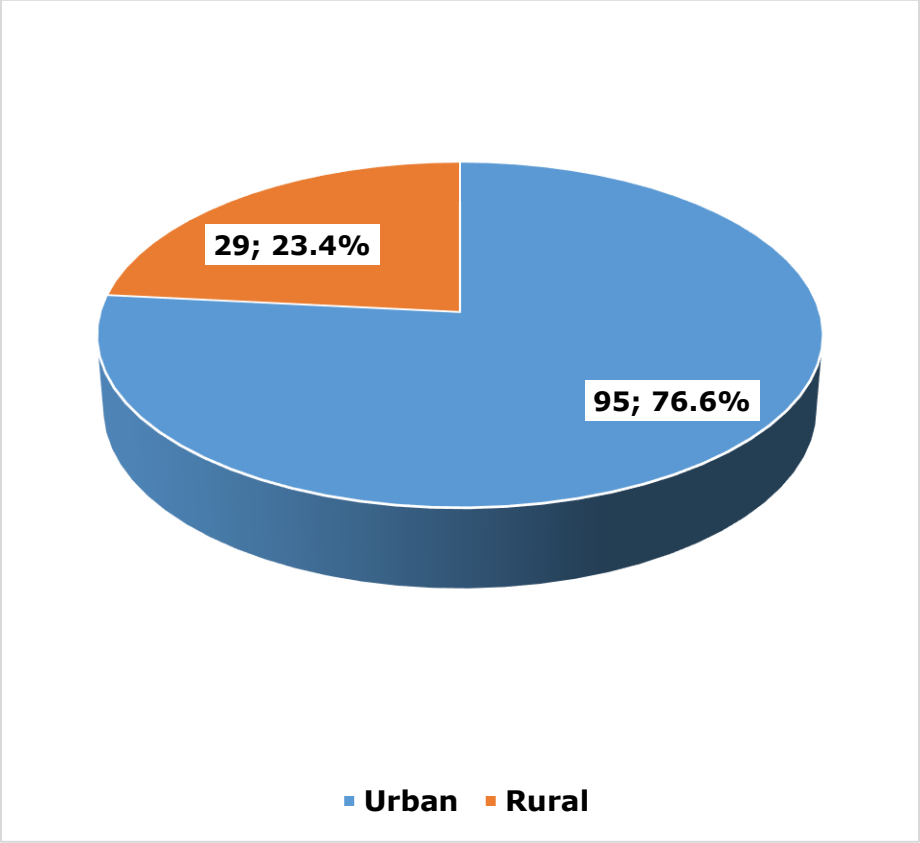

Figure 2: Residential distribution of the study participants

Most of the study participants i.e. 76.6% (n=95) had an urban dwelling (Figure 2).

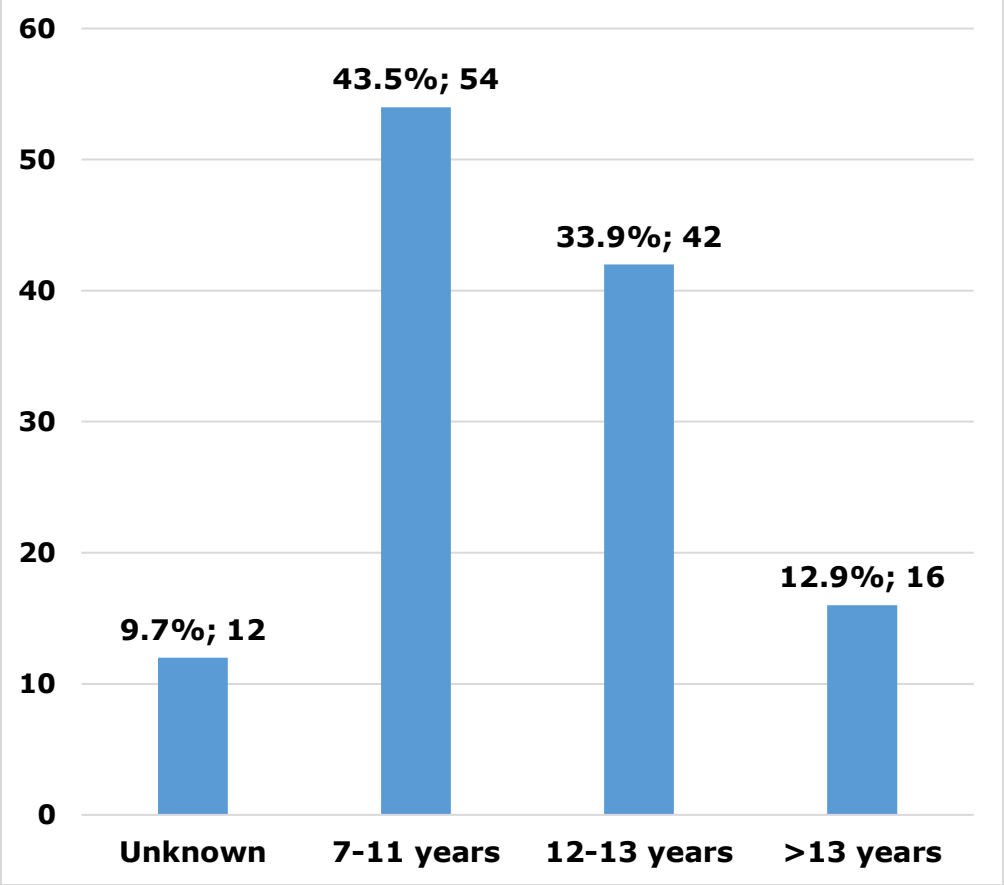

Figure 3: Distribution of the patients as per their age of menarche

In the current study, the majority of the patients (54; 43.5%) had their menarche between the ages of 7 to 11 years (Figure 3). The median (IQR) age of the menarche of the study participants was 11.0 years (10.0-13.0 years) (Table 3).

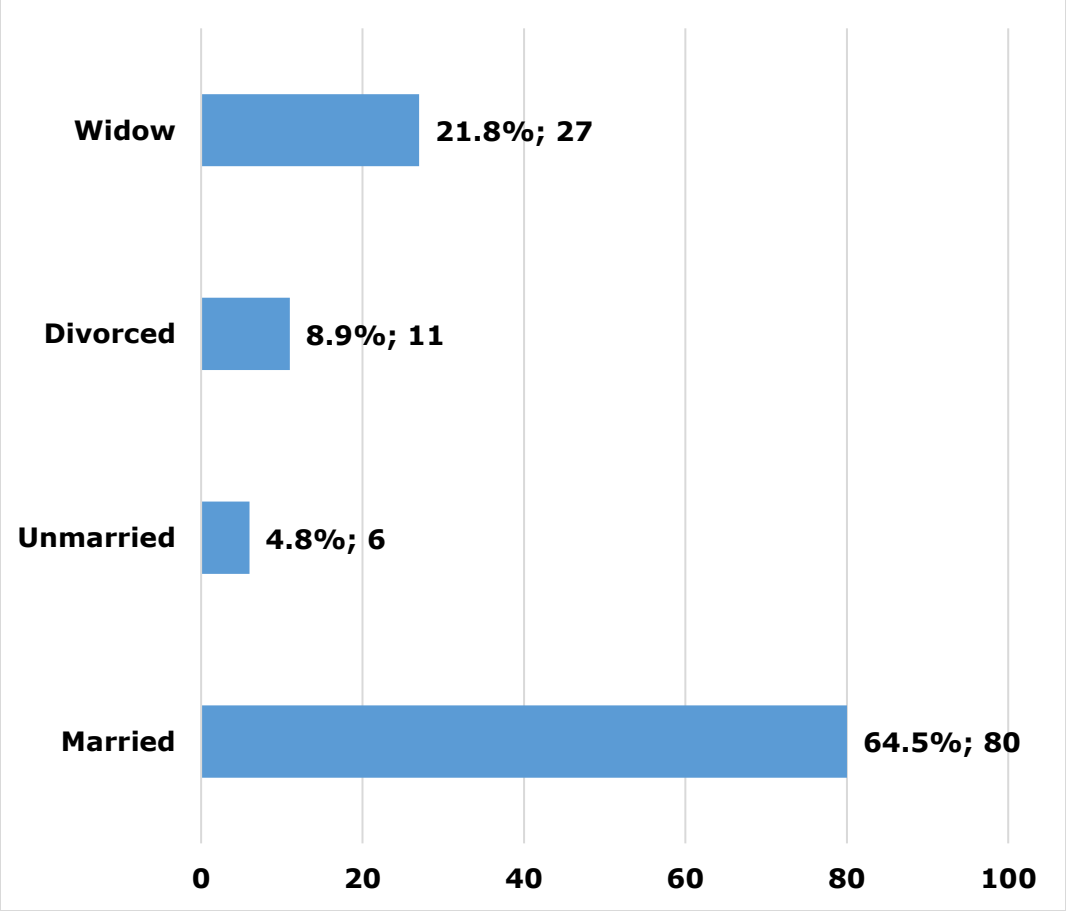

Figure 4: Frequency of the marital status of the study participants

In the present study, a major proportion of the patients was formed by married ladies (80.0; 64.5%) (Figure 4).

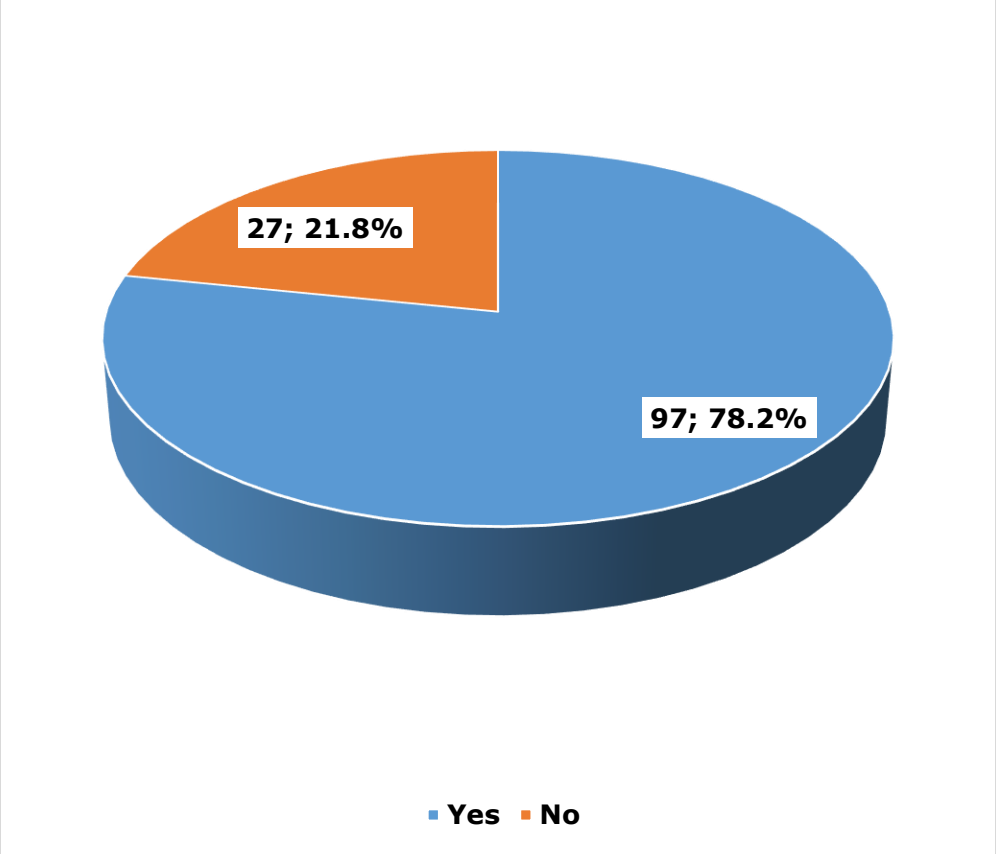

Figure 5: Frequency of the participants who had children

In the present study, 78% (n=97) of the patients were mothers (Figure 5).

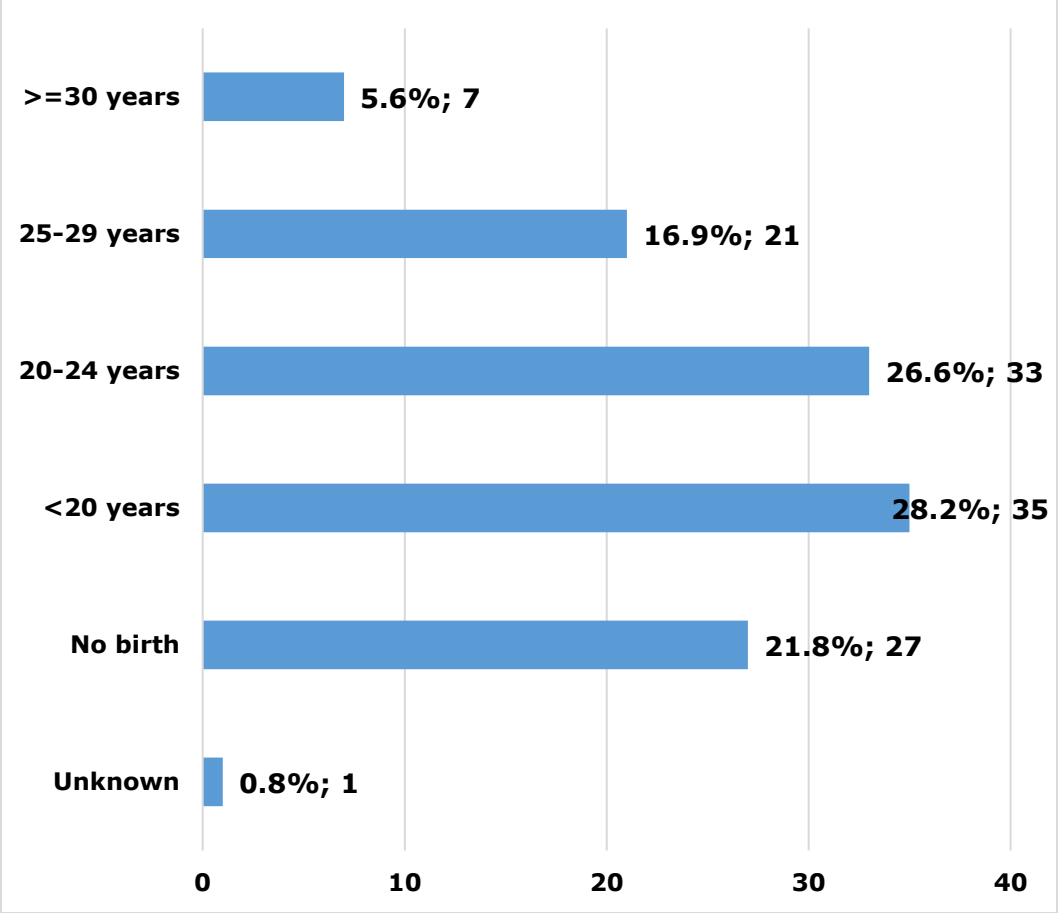

Figure 6: Frequency of the age groups of patients at first live birth

The majority of the patients (n=33; 26.6%) belonged to the age group of 20-24 years at the time of their first live birth (Figure 6). The median (IQR) age of the study participants at the time of their first live birth was 22.0 years (19.0-25.0 years) (Table 3).

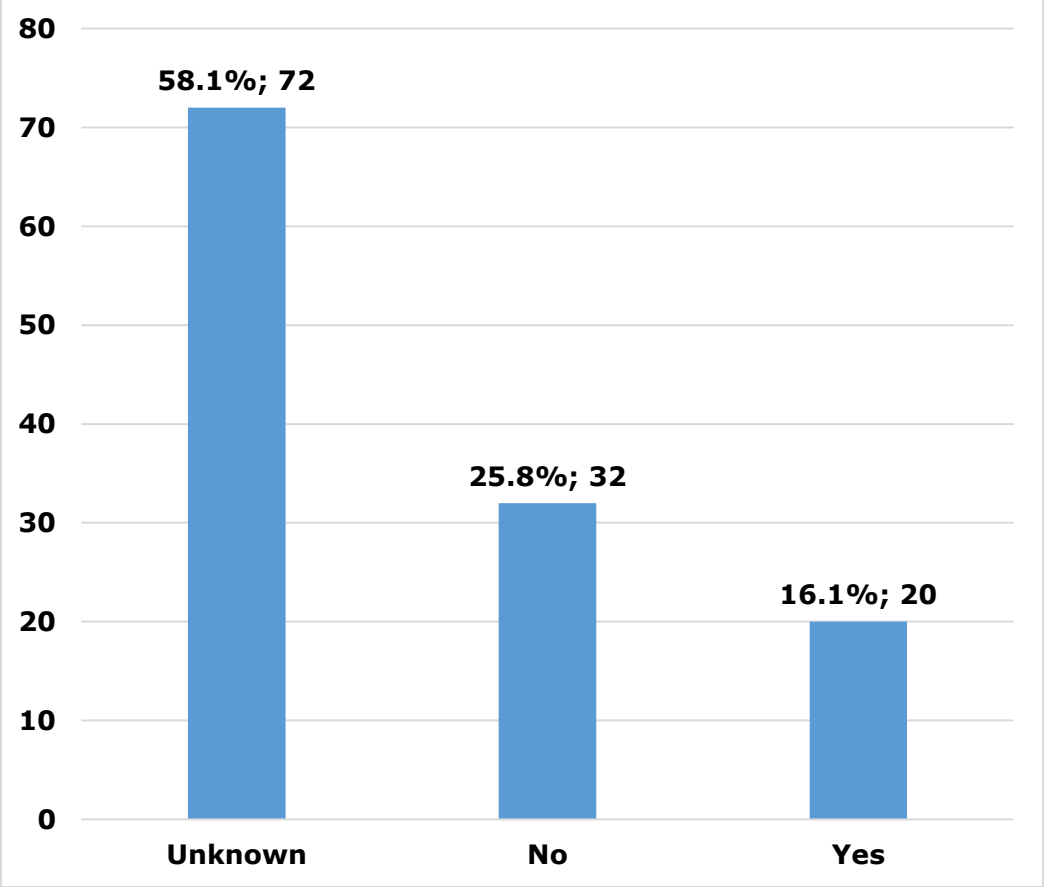

Figure 7: Frequency of patients with a family history of breast cancer

There were only 20 patients (16.1%) in the present study who had a positive family history of breast cancer (Figure 7).

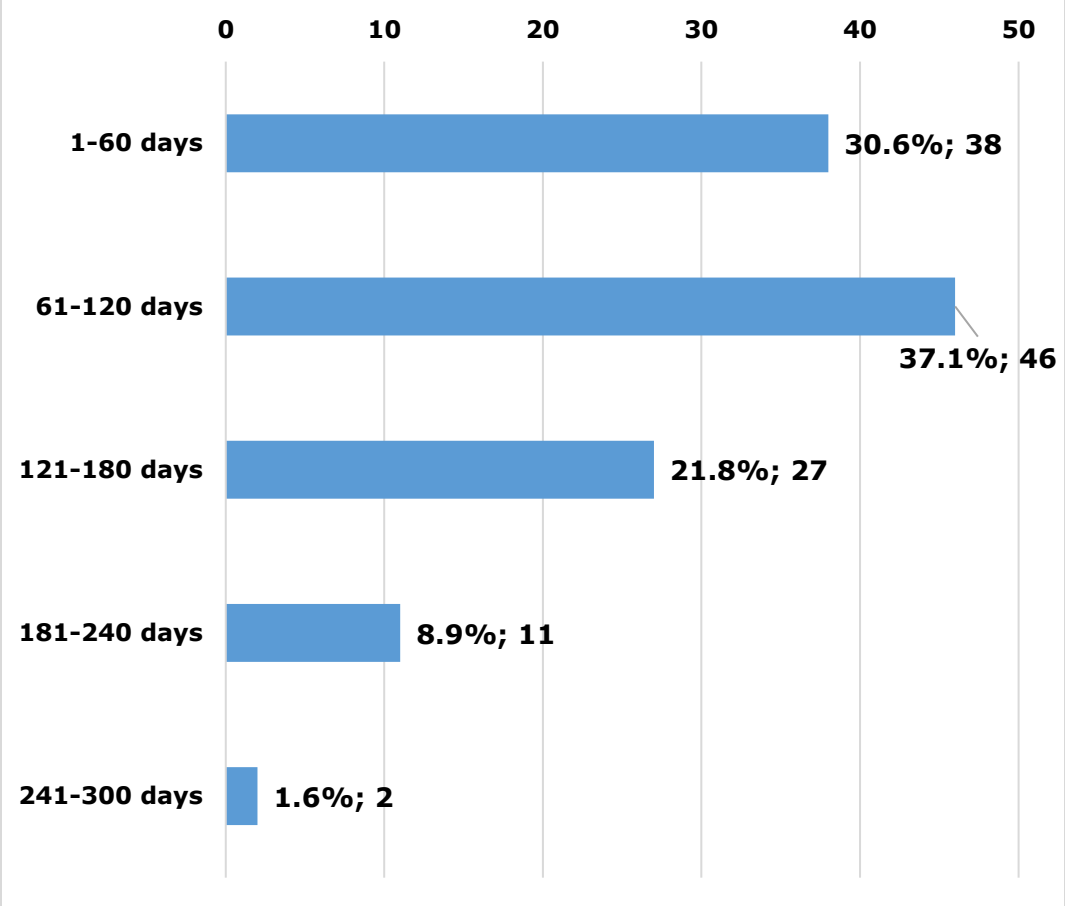

Figure 8: Frequency of duration of the presence breast lump

In the present study, the majority of the patients (n=46; 37.1%) had the breast lump for a range of 81 to 120 days (Figure 8). The median (IQR) duration of the presence of breast lump in the study participants was 90.0 days (60.0-160.5 days) (Table 3).

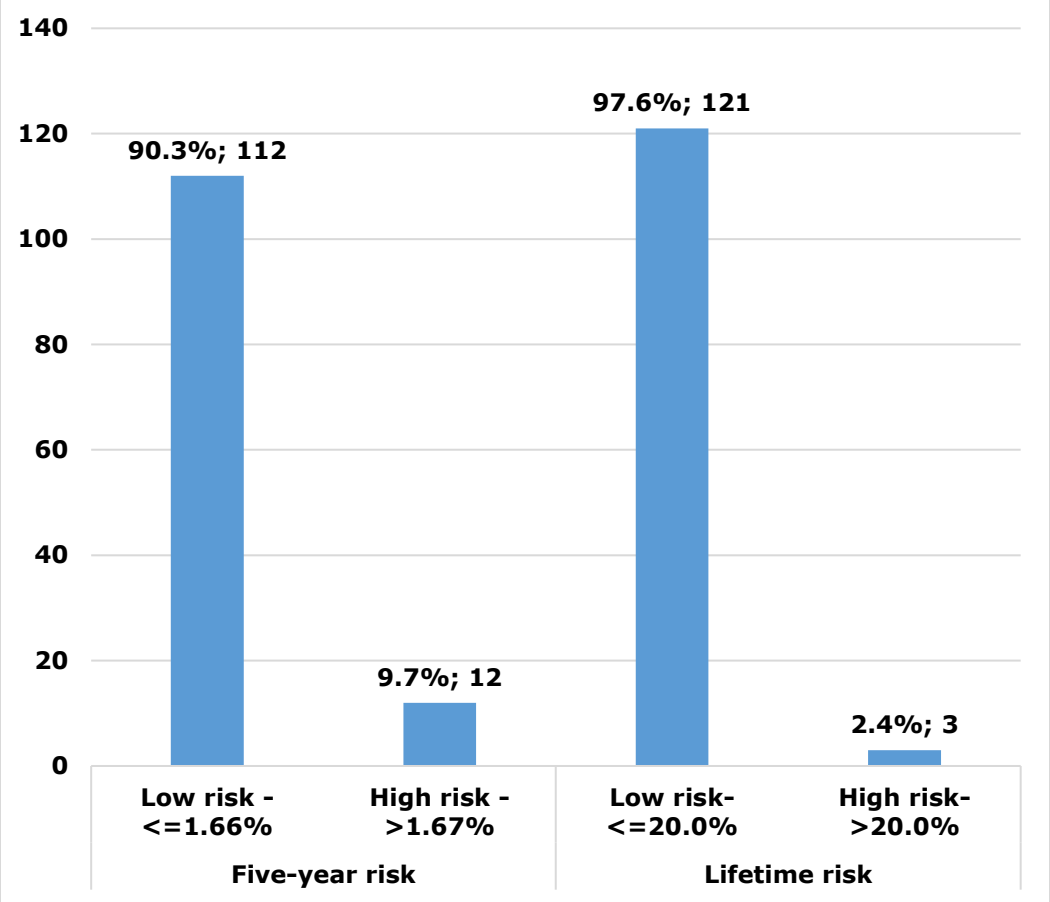

Figure 9: Five-year and lifetime risk of the study participants as per the Gail model

As per the Gail model. 90.3% (n=112) and 97.6% (n=121) of the patients in the present study had low 5-year and lifetime risk respectively (Figure 9). The median (IQR) five-year and lifetime risk score as per the Gail score was reported to be 0.80% (0.50-1.10%) and 9.2% (7.9-11.2%) respectively (Table 3).

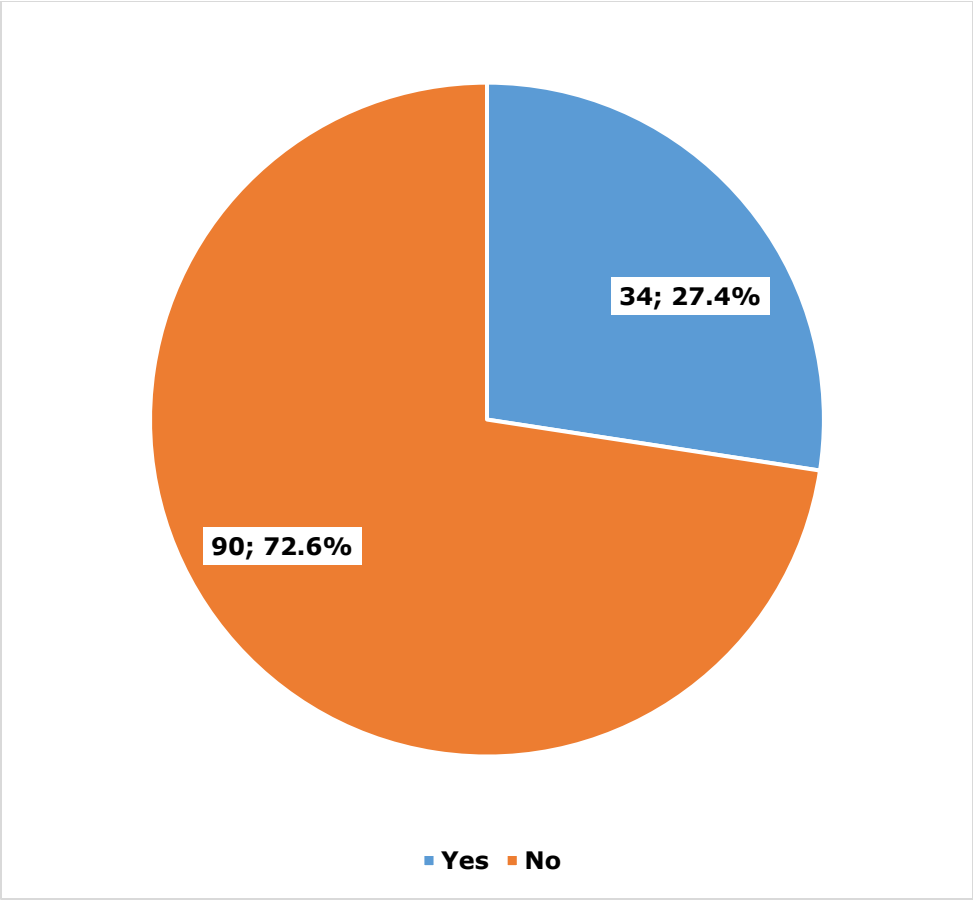

Figure 10: Frequency of invasive ductal carcinoma as per the histopathology

The histopathological analysis of the breast lump revealed the presence of invasive ductal carcinoma in 27.4% (n=34) of the cases **(Figure 10)**.

Table 2: Association of understudy variables with the presence of invasive ductal carcinoma on histopathological examination

Parameter		Frequency	Invasive Ductal Carcinoma		
			Yes [n=34]	No [n=90]	p-value
Age, years	35-50	90	16 (47.1)	74 (82.2)	**0.000¥***
	51-67	32	16 (47.1)	16 (17.8)	
	68-85	2	2 (5.9)	0	
Residence	Urban	95	23 (67.6)	72 (80.0)	0.160β
	Rural	29	11 (32.4)	18 (20.0)	
Age of menarche, years	Unknown	12	4 (11.8)	8 (8.9)	0.431¥
	7-11	54	16 (47.1)	38 (42.2)	
	12-13	42	8 (23.5)	34 (37.8)	
	>13	16	6 (17.6)	10 (11.1)	
Marital status	Married	80	14 (41.2)	66 (73.3)	**0.000¥***

	Unmarried	6	0	6 (6.7)	
	Divorced	11	5 (14.7)	6 (6.7)	
	Widow	27	15 (44.1)	12 (13.3)	
Age at first live birth, years	Unknown	1	0	1 (1.1)	0.435¥
	No birth	27	5 (14.7)	22 (24.4)	
	<20	35	14 (41.2)	21 (23.3)	
	20-24	33	7 (20.6)	26 (28.9)	
	25-29	21	6 (17.6)	15 (16.7)	
	≥30	7	2 (5.9)	5 (5.6)	
Family history of breast cancer	Yes	20	14 (41.2)	6 (6.7)	**0.000β***
	No	32	5 (14.7)	27 (30.0)	
	Unknown	72	15 (44.1)	57 (63.3)	
Period of breast lump, days	1-60	38	11 (32.4)	27 (30.0)	0.907¥
	61-120	46	11 (32.4)	35 (38.9)	
	121-180	27	9 (26.5)	18 (20.0)	
	181-240	11	3 (8.8)	8 (8.9)	
	241-300	2	0	2 (2.2)	
Any children	Yes	97	29 (85.3)	68 (75.6)	0.331β
	No	27	5 (14.7)	22 (24.4)	

¥-Fisher-Exact test; β- Chi-Square test; *statistically significant

Age (p-value: 0.000), marital status (p-value: 0.000), and positive family history of breast cancer (p-value: 0.000) were found to have a statistically significant difference in patients who had invasive ductal carcinoma on histopathological examination.

Table 3: Association of understudy variables with the five-year and lifetime risk for invasive ductal carcinoma

Parameter		Frequency	5-year risk			Lifetime risk		
			Low risk (≤1.66) [n=112]	High risk (>1.66) [n=12]	p-value	Low risk (≥20%) [n=121]	High risk (>20%) [n=3]	p-value
Age, years	35-50	90	88 (78.6)	2 (16.7)	**0.000¥***	87 (71.9)	3 (100)	0.587¥
	51-67	32	24 (21.4)	8 (66.7)		32 (26.4)	0	
	68-85	2	0	2 (16.7)		2 (1.7)	0	
Residence	Urban	95	88 (78.6)	7 (58.3)	0.149¥	92 (76.0)	3 (100)	1.000¥
	Rural	29	24 (21.4)	5 (41.7)		29 (24.0)	0	
Age of menarche, years	Unknown	12	9 (8.0)	3 (25.0)	0.058¥	12 (9.9)	0	0.452¥
	7-11	54	47 (42.0)	7 (58.3)		51 (42.1)	3 (100)	
	12-13	42	41 (36.6)	1 (8.3)		42 (34.7)	0	
	>13	16	15 (13.4)	1 (8.3)		16 (13.2)	0	
Marital status	Married	80	77 (68.8)	3 (25.0)	**0.003¥***	77 (63.6)	3 (100)	0.725¥
	Unmarried	6	6 (5.4)	0		6 (5.0)	0	
	Divorced	11	10 (8.9)	1 (8.3)		11 (9.1)	0	
	Widow	27	19 (17.0)	8 (66.7)		27 (22.3)	0	
Age at first live birth,	Unknown	1	1 (0.9)	0	0.562¥	1 (0.8)	0	**0.041¥***
	No birth	27	26 (23.2)	1 (8.3)		27 (22.3)	0	
	<20	35	29 (25.9)	6 (50.0)		35 (28.9)	0	

years	20-24	33	30 (26.8)	3 (25.0)		33 (27.3)	0	
	25-29	21	19 (17.0)	2 (16.7)		19 (15.7)	2 (66.7)	
	≥30	7	7 (6.3)	0		6 (5.0)	1 (33.3)	
Family history of breast cancer	Yes	20	12 (10.7)	8 (66.7)	**0.000¥***	17 (14.0)	3 (100)	**0.004¥***
	No	32	31 (27.7)	1 (8.3)		32 (36.4)	0	
	Unknown	72	69 (61.6)	3 (25.0)		72 (59.5)	0	
Period of breast lump, days	1-60	38	34 (30.4)	4 (33.3)	0.709¥	37 (30.6)	1 (33.3)	0.527¥
	61-120	46	42 (37.5)	4 (33.3)		45 (37.2)	1 (33.3)	
	121-180	27	23 (20.5)	4 (33.3)		27 (22.3)	0	
	181-240	11	11 (9.8)	0		10 (8.3)	1 (33.3)	
	241-300	2	2 (1.8)	0		2 (1.7)	0	
Any children	Yes	97	86 (76.8)	11 (91.7)	0.460¥	94 (77.7)	3 (100)	1.000¥
	No	27	26 (23.2)	1 (8.3)		27 (22.3)	0	

¥-Fisher-Exact test; *statistically significant

Age (p-value: 0.000), and marital status (p-value: 0.003) were found to have a statistically significant impact on the 5-year risk to develop invasive ductal carcinoma. Age at first live birth (p-value: 0.041), was a statistically significant factor to impact the lifetime risk to develop invasive ductal carcinoma. Positive family history of breast cancer significantly impacted the patient's chances of 5-year (p-value: 0.000) and lifetime risk (p-value: 0.004) to develop invasive ductal carcinoma respectively.

Table 4: Association of five-year and lifetime risk as per the Gail model with the presence of invasive ductal carcinoma on histopathological examination

Risk				Invasive ductal carcinoma on histopathology		p-value
			Frequency	Yes **(n=34)**	No **(n=90)**	
Five-year	High risk	>1.67%	12	12 (35.3)	0	0.000¥*
	Low risk	≤1.67%	112	22 (64.7)	90 (100)	
Lifetime	High risk	>20.0%	3	2 (5.9)	1 (1.1)	0.182¥
	Low risk	*≤20.0%*	*121*	*32 (94.1)*	*89 (98.9)*	

¥-Fisher-Exact test; *statistically significant

The patient's five-year risk to develop invasive ductal carcinoma was observed to be statistically significant.

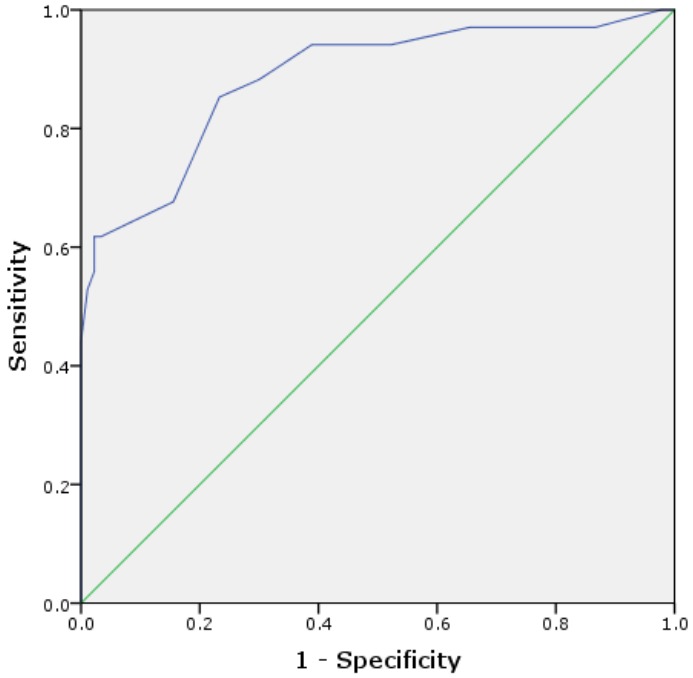

Figure 11: ROC analysis for the five-year risk to develop invasive ductal carcinoma in study participants

	95% CI	p-value
AUC	0.885 (0.814-0.957)	0.000*

For a cutoff of >1.67, the sensitivity, and specificity was observed to be 35.3% and 100% respectively.

Discussion:

The significant increase in breast cancer cases underscores the need for effective strategies to identify risk factors and assess how much these factors contribute to breast cancer in the affected population. This study investigated the influence of various factors, including age, the age at which menstruation begins, the age at which first childbirth occurs, family history, and biopsy results. The analysis revealed that breast cancer incidence rises with age, with the highest number of cases occurring among premenopausal women. These findings align with previous reports from India, which indicate a trend of earlier breast cancer diagnosis compared to Western countries, where the majority of cases are typically diagnosed in individuals over 50 years old (DeSantis et al., 2017).

The age at which menstruation begins, known as menarche, is often considered a reproductive risk factor for breast cancer. However, the current study did not find a significant link between the timing of menarche and breast cancer development. Research findings on this topic have been mixed. Some studies conducted in Western countries and India suggest that there is no connection between the age of onset of menstruation and the risk of breast cancer. Conversely, other researchers indicate that an earlier onset of menarche may be associated with a higher incidence of breast cancer (Khalis et al., 2018; Collaborative Group on Hormonal Factors in Breast, 2012). This discrepancy may be due to the fact that the control group consisted primarily of participants under the age of 40, indicating that a longer follow-up period would be necessary to draw definitive conclusions regarding the relationship between menarche and breast cancer risk based on this study.

The age at which a woman experiences her first live birth plays a significant role in influencing breast cancer rates. In a particular study, 28.2% and 26.6% of participants reported having their first live birth at ages below 20 and between 20 to 24 years, respectively, with the average age being 22.2 years.

Another research conducted by Tam et al. in 2010 found that the average age for Caucasian women having their first live birth was 24.3 years, while for recent Chinese immigrants, it was 25.5 years. Having children at a younger age, particularly before turning 20, is linked to a significantly lower risk of developing breast cancer, according to Vogel (2000). Some studies suggest that this protective effect is only present in pregnancies that result in the birth of a viable infant, as noted by Sakorafas et al. (2002). Conversely, delaying childbirth may raise the likelihood of breast cancer later in life. Consistent findings have been reported across various studies conducted both in Western countries and in India (Khalis et al., 2018; Collaborative Group on Hormonal Factors in Breast, 2012; Albrektsen et al., 2005; Li et al., 2008). While the precise mechanisms remain somewhat unclear, early pregnancy has been linked to reduced levels of estrogen and lasting alterations in the development of breast cancer, which occur independent of estrogen exposure (Russo et al., 2005; Lee et al., 2008).

Research has indicated that individuals with a family history of breast cancer, particularly among first-degree relatives, are at a higher risk for developing the disease themselves. This observation is consistent with findings from various studies conducted both in India and internationally (Ahern et al., 2017; Saxena et al., 2005; Lodha et al., 2011). The current research highlights that having a family history of breast cancer notably increases the risk of developing invasive ductal carcinoma, both over a five-year period and across a lifetime. Earlier studies have indicated that the Gail model tends to significantly undervalue the impact of familial factors on the likelihood of breast cancer occurrence (Pankratz et al., 2008). Research indicates that, after adjusting for age, having a family history of breast and/or ovarian cancer is typically linked to the highest risk increase. However, the specific risk level is influenced by several factors, including the number of affected relatives, their type, and their age at diagnosis (Ferrer et al., 2005). Generally, the chances of inheriting breast cancer are significantly greater when the affected individual is a first-degree relative, such as a mother or sister, as opposed to a second-degree relative like a grandmother or aunt (Smith et al., 2003). Risk can be inherited from both maternal and paternal sides of the family. When the risk comes from the paternal side, it may not be obvious among first-degree relatives who are affected (Smith et al., 2003).

The research had several constraints. Data was gathered through personal interviews, which may have influenced responses due to social desirability bias and potential inaccuracies in memory recall. A significant issue was the inability to achieve a satisfactory response rate, largely due to the participation challenges faced by the local community in rural regions. Furthermore, the study was limited by inadequate information regarding the racial and ethnic backgrounds of the participants, as well as incomplete family histories of breast cancer. As a result, the risk scores produced by the modified Gail model could be somewhat lower than what might actually be expected.

Conclusion:

In conclusion, the current study comprehensively examined the predictive ability of the Gail model in identifying invasive ductal carcinoma of the breast. Through a detailed analysis of patient data and various risk factors, the findings underscore the Gail model's utility as a valuable tool for early detection and risk assessment. While the model demonstrated significant predictive capabilities, its effectiveness is enhanced when used in conjunction with other diagnostic methods and personalized patient histories.

The implications of this study extend beyond academic interest; they highlight the potential for improved screening protocols and personalized risk stratification in clinical practice. Future research should focus on refining the Gail model by incorporating additional biomarkers and genetic data, thereby enhancing its accuracy and applicability across diverse populations.

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