



ORIGINAL: Reproductive Risk Factors Associated with Breast Cancer: A Study of Iranian Women (2019-2020)

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ARTICLE INFO

Submitted: 08 Oct 2024
Accepted: 16 Nov 2024
Published: 17 Dec 2024

Keywords:

Breast cancer;
Incidence;
Reproductive risk factors;
Early menarche;
Oral contraceptives

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Citation:

Kord R, Heidari I, Zafari M, Aghamohammadi A. Reproductive Risk Factors Associated with Breast Cancer: A Study of Iranian Women (2019-2020). *Tabari Biomed Stu Res J.* 2024;6(4):11-18.

 10.22034/6.4.11

ABSTRACT

Introduction: Breast cancer constitutes a predominant contributor to cancer-related mortality among women on a global scale, with an observable escalation in incidence rates over recent decades. Principal risk determinants for breast cancer encompass advanced age, obesity, alcohol consumption, hormonal exposure, and genetic susceptibility. This investigation sought to elucidate the correlation between breast cancer and reproductive risk factors among women residing in Golestan Province, Iran, during the period spanning 2019 to 2020.

Material and Methods: A cross-sectional descriptive study was undertaken involving a cohort of 124 patients diagnosed with breast cancer. The research aimed to gather comprehensive data regarding several reproductive health milestones, specifically the age at which menarche occurred, the age at which participants experienced their first and last childbirth, as well as the age at which menopause was reached. To analyze the collected data, descriptive statistical methods were employed.

Results: The mean age of the participants in this study was 47.76 years. Notably, early onset of menarche and the utilization of oral contraceptives were identified as significant risk factors associated with breast cancer. Furthermore, the investigation revealed discernible patterns in both reproductive history and lifestyle factors among the cohort under examination.

Conclusion: The findings presented highlight the significant role of reproductive factors in the etiology of breast cancer. It is imperative that further extensive, multicenter studies be conducted to clarify the intricate relationships between these reproductive factors and the associated risk of developing breast cancer. Specifically, early onset of menarche and the utilization of oral contraceptives merit additional scrutiny as potential focal points for preventive strategies.

Introduction

Breast cancer represents a multifaceted global health challenge characterized by disparate mortality rates across various geographical regions. Although the prevalence of this malignancy is notably higher among women in developed nations,

where it is associated with elevated mortality rates compared to semi-industrialized areas, there is a concerning trend of increasing incidence. Current estimates indicate that breast cancer cases are rising at an approximate rate of 2% annually across

numerous countries. (1,2,3). Clinically, breast cancer is classified into three main categories: 1. Lobular Carcinoma in Situ (LCIS): This condition involves the proliferation of small, loosely connected cells originating from the terminal ductal lobular unit and is associated with an increased risk of bilateral breast cancer (4). 2. Ductal Carcinoma in Situ (DCIS): Characterized by the proliferation of malignant ductal epithelial cells without basement membrane invasion, DCIS accounts for 15-30% of cancers detected through screening mammography (5). 3. Invasive Breast Cancer: This category includes various lesions, most of which originate from the terminal ductal lobular unit, and varies in characteristics (6). Breast cancer is a multifactorial disease that arises from an intricate interplay between genetic predispositions and environmental influences. (7). The principal risk factors associated with the development of breast cancer encompass advancing age, obesity, excessive alcohol consumption, and heightened exposure to estrogenic compounds. (8). A familial predisposition to breast cancer constitutes a significant risk factor, with approximately 20% of breast cancer cases exhibiting a hereditary component. Of these familial cases, it is estimated that around 50% are associated with germline mutations in critical tumor suppressor genes, notably BRCA1 and BRCA2 (9). Key predisposing factors include age, family history, high-fat diet, obesity, and reproductive and hormonal factors such as early menarche, late menopause, infertility, and benign breast disease (10). Recognized as the most common cancer in women and a leading cause of death worldwide, breast cancer's incidence in the United States and Europe is double that in Asian countries, though it is rising in Asia due to lifestyle changes (11,12). Early detection is crucial since tumors are often asymptomatic in the early stages, with a painless lump being a common indicator (13). Risk factors for breast cancer are Unchangeable Factors like Age, gender, family history, early menarche, late menopause, and genetic susceptibility (14). or Modifiable Factors like Obesity, alcohol

consumption, and cumulative estrogen exposure (7). And Additional Factors like High-fat diet and reproductive elements like early menarche and infertility (10). Studies emphasize the importance of genetic and environmental factors in breast cancer development. Research by Newman et al. established a direct link between mutations in BRCA1 and BRCA2 genes and an increased risk of breast cancer, with individuals carrying these mutations showing a significantly higher susceptibility (6,9). Smith et al. found that prolonged hormone replacement therapy (HRT) after menopause could elevate breast cancer risk, while early menarche and delayed menopause due to extended estrogen exposure also increase risk (7,10). Epidemiological studies highlight the impact of lifestyle factors, with Johnson et al. noting an increased risk of breast cancer in women with low physical activity and a high-fat diet. Obesity, particularly post-menopause weight gain, is a significant risk factor (7,8). Research into reproductive factors has garnered significant attention, with Brown et al. elucidating that a postponement of the initial pregnancy or a reduction in the number of pregnancies correlates with an elevated risk of breast cancer. Conversely, prolonged breastfeeding appears to confer a protective effect against the development of this malignancy (15,16). In light of the critical significance associated with comprehending the risk factors and implementing preventive measures for breast cancer, it is imperative that further extensive research is conducted. This investigation seeks to evaluate the incidence rates and reproductive risk determinants among individuals diagnosed with breast cancer in Golestan Province during the years 2019-2020. The objective is to augment our understanding of the disease, facilitate early detection, and enhance treatment outcomes.

Methods

Study Design and Population

This study employed a cross-sectional descriptive methodology with a practical focus. The cohort comprised individuals diagnosed

with breast cancer in Golestan Province.

Sampling Method and Sample Size

Participants were selected through the method of convenience sampling. Given that the objective of the study was to ascertain prevalence, it was not deemed necessary to establish a pre-determined sample size.

Inclusion and Exclusion Criteria

Inclusion Criteria

- A confirmed diagnosis of breast cancer

Exclusion Criteria

1. Individuals with a suspected but unconfirmed diagnosis of breast cancer.
2. Patients with incomplete medical records

Data Collection and Analysis

Data were gathered from the hospital records of patients who had been admitted, utilizing a checklist that was specifically developed by the researcher. Upon receiving approval from the pertinent authorities, patients who

fulfilled the inclusion criteria were identified. The data that were collected were systematically documented, categorized, and subsequently analyzed employing SPSS-18 software. This analysis encompassed descriptive statistical methods, which included the creation of tables and graphs, as well as various measures of central tendency and dispersion.

Results

Demographic Statistics

The ages of the participants varied between 28 and 69 years, yielding a mean age of 47.76 years. The average age at which menarche occurred was 12.70 years, with a range extending from 9 to 16 years. The mean ages for first and last pregnancies were recorded at 25.71 years and 35.94 years, respectively. Furthermore, the average age at menopause was determined to be 45.51 years, with a range from 39 to 53 years (**Table 1**).

Table 1. Descriptive Statistics of Quantitative Variables.

Variable	Mean	Standard Deviation	Minimum	Maximum
Age (years)	47.76	11.76	28.00	69.00
Age at Menarche (years)	12.70	1.58	9.00	16.00
Age at First Pregnancy (years)	25.71	8.39	15.00	40.00
Age at Last Pregnancy (years)	35.94	5.06	28.00	46.00
Age at Menopause (years)	45.51	5.61	39.00	53.00

Qualitative Variables

Marital Status and History of Pregnancy

Among the cohort of 124 patients, 116 individuals (93.54%), were married, whereas a minority of 8 individuals (6.45%) were single (**Table 2**). Within the subset of married patients, it was observed that 111 individuals (89.51%) reported a history of pregnancy, while 13 individuals (10.49%) indicated the absence of such a history. (**Table 3**).

Age at First and Last Pregnancy

For the age at first pregnancy: 14 patients (12.06%) were between 15 and 20 years old, 56 (48.27%) were between 20 and 25 years old, 30 (25.86%) were between 25 and 30 years old, 12 (10.34%) were between 30 and 35 years old, and 4 (3.44%) were between 35 and 40 years old. For the age at last

pregnancy: 20 patients (17.24%) were between 25 and 30 years old, 41 (35.34%) were between 30 and 35 years old, 49 (42.24%) were between 35 and 40 years old, 4 (3.33%) were between 40 and 45 years old, and 2 (1.72%) were between 45 and 50 years old. (**Table 4**).

Table 2. Frequency Distribution of Marital Status

Marital Status	Frequency	Percentage
Married	116	93.54%
Single	8	6.45%
Total	124	100%

Table 3. Frequency Distribution of Pregnancy History

Pregnancy History	Frequency	Percentage
Yes	113	89.51%
No	11	10.49%
Total	124	100%

Table 4. Frequency Distribution of Age at First and Last Pregnancy Among Study Participants

Age Rang (Years)	First Pregnancy	Percentage(%)	Last Pregnancy	Percentage(%)
15-20	14	12.06	-	-
20-25	56	48.27	-	-
25-30	30	25.86	20	17.24
30-35	12	10.34	41	35.34
35-40	4	3.44	49	42.24
40-45	-	-	4	3.44
45-50	-	-	2	1.72
Total	116	100	116	100

Table 5. Frequency Distribution of Age at Menarche and Menopause Among Participants.

Age Rang (Years)	Menarche	Percentage (%)	Menopause	Percentage (%)
5-10	22	17.74	-	-
10-15	84	67.74	-	-
15-20	18	14.51	-	-
35-40	-	-	4	5.79
40-45	-	-	19	27.53
45-50	-	-	37	53.62
50-55	-	-	9	13.04
Total	124	100	69	100

Age at Menarche and Menopause

The age at menarche was distributed as follows: 22 patients (17.74%) started menstruating between ages 5-10 years, 84 (67.74%) between ages 10-15 years, and 18 (14.51%) between ages 15-20 years (Table 5). Of the 124 patients, 69 (55.64%) had experienced menopause. The distribution of age at menopause was: 4 patients

(5.79%) aged 35-40 years, 19 (27.53%) aged 40-45 years, 37 (53.62%) aged 45-50 years, and 9 (13.04%) aged 50-55 years (Table 5).

History of Oral Contraceptive Use

Among the 124 patients, 96 (77.41%) had used oral contraceptives, while 28 (22.58%) had not (Table 6).

Table 6. Frequency Distribution of Oral Contraceptive Use Among Participants.

Oral Contraceptive Use	Frequency	Percentage (%)
Yes	96	77.41
No	28	22.58
Total	124	100

Breastfeeding History

Within the 124 patients, 85 (68.54%) had a history of breastfeeding, and 39 (31.45%) did not (Table 7).

Table 7. Frequency Distribution of Breastfeeding History among Study Participants

Breastfeeding History	Frequency	Percentage(%)
Yes	85	68.54
No	39	31.45
Total	124	100

History of Smoking and Alcohol Consumption

Out of the 124 patients, 21 (16.93%) had a history of smoking, while 103 (83.06%) did not. Additionally, 6 patients (4.83%) had a history of alcohol consumption, and 118

(95.16%) did not (Table 8).

Table 8. Distribution of Smoking and Alcohol Consumption History Among Participants.

Variable	Frequency	Percentage(%)
Smoking History		
Yes	21	16.93
No	103	83.06
Total	124	100
Alcohol Consumption History		
Yes	6	4.83
No	118	95.16
Total	124	100

Educational Level

In terms of educational achievement: 23 patients (18.54%) had not completed high school, 28 (22.58%) had graduated from high school, 39 (31.45%) held a bachelor’s degree,

16 (12.90%) possessed a master's degree, and 18 (14.51%) earned a doctorate or higher. (Table 9).

Table 9. Distribution of Educational Attainment Among Participants.

Education Level	Frequency	Percentage (%)
Below Diploma	23	18.54%
Diploma	28	22.58%
Bachelor's Degree	39	31.45%
Master's Degree	16	12.90%
Doctorate or Higher	18	14.51%
Total	124	100%

Discussion

Breast cancer is the most common cancer among women in developed nations (1). Many studies show an increasing trend in breast cancer cases worldwide. This disease is complicated, resulting from a combination of genetic and environmental influences that cause genetic and epigenetic alterations in breast cells. Important risk factors include age, obesity, alcohol intake, and lifetime exposure to estrogen, with a strong family history of breast cancer being the most critical risk factor (5). About 20% of breast cancer cases are hereditary, indicating a particular genetic risk. Research studies have found several significant risk factors, including age, family history, high-fat diet, obesity, and reproductive and hormonal influences such as early onset of menstruation, late onset of menopause, infertility, benign breast conditions, and elevated estrogen levels from hormone replacement therapy after menopause. Additionally, there is a noted connection with previous occurrences of uterine, ovarian, and colon cancers. (7). is a significant factor in breast cancer risk, with postmenopausal women facing a sixfold increase in incidence compared to premenopausal women. Early onset of menstruation and late onset of menopause heighten the risk of breast cancer due to extended exposure to estrogen and

progesterone. The timing of a woman's first pregnancy also affects her risk; those who have their first child after age 35 are at greater risk than those who have never been pregnant. Recent childbirth is linked to a lower risk compared to childbirth that occurred more than ten years ago, and extended breastfeeding can decrease risk by postponing regular ovulation. (8). The highest rates of breast cancer deaths occur in individuals aged 30 to 60 years, highlighting the disease's significant effect during crucial family and work periods, as well as among the increasing elderly female population. (9). Previous research has primarily concentrated on Western populations, which are notably different in terms of geography, economy, and social context compared to our study area. Consequently, this study aimed to explore reproductive risk factors in breast cancer patients in Golestan Province during 2019-2020, taking into account the specific characteristics of Iranian women, especially those from the northern region. The study involved 124 breast cancer patients from the Golestan Province Health Centre, with ages ranging from 28 to 69 years and an average age of 47.76 years. The average age at which menstruation begins was 12.70 years, with a range from 9 to 16 years. The average ages for first and last pregnancies were 25.71 and 35.94 years, respectively. The average age at which menopause occurred was 45.51 years, with a range from 39 to 53 years (17). Sirati et al. reported an average menopause age of 46.9 years, with participants aged between 26 and 81 years. Basharat et al. found an average menopause age of 42.96 years, with menarche occurring at an average of 13.13 years in the case group and 13.42 years in the control group; menopause occurred at an average of 45.81 years in the case group and 48.31 years in the control group (18). Abdollahian et al. reported an average menopause age of 43.9 years, with participants ranging from 30 to 60 years (19). In our study, 89.51% of patients had a history of pregnancy, while 10.49% did not have such a history. First pregnancies occurred between the ages of 15-20 in 12.06% of cases,

between ages 20-25 in 48.27%, between ages 25-30 in 25.86%, between ages 30-35 in 10.34%, and between ages 35-40 in 3.44%. Recent pregnancies occurred in the following age groups: 25-30 years in 17.24% of cases, 30-35 years in 35.34%, 35-40 years in 42.24%, 40-45 years in 3.33%, and 45-50 years in 1.72% (20). The age at which participants began menstruating was distributed as follows: 17.74% started between ages 5-10 years, 67.74% between ages 10-15 years, and 14.51% between ages 15-20 years. Early onset of menstruation was not found to be a risk factor in the study by Wahidin et al. (21). Among the group of 124 patients, 55.64% had reached menopause, with the following age breakdown: 5.79% at ages 35-40 years, 27.53% at ages 40-45 years, 53.62% at ages 45-50 years, and 13.04% at ages 50-55 years. A case-control study conducted by Yuan et al. in China in 2018, which included 794 cases and 805 controls, indicated that a history of medical abortion, multiple surgical abortions, or a combination of both was linked to an increased risk of breast cancer among postmenopausal women. (22). In our research, 77.41% of patients reported using oral contraceptives, while 22.58% did not. Wahidin et al. found odds ratios of 1.93 for those who had used oral contraceptives for less than six years and 2.90 for those who had used them for more than six years. This suggests a positive link between the use of oral contraceptives and the occurrence of breast cancer, with an increased risk associated with longer usage. A notable portion of participants, 68.54%, had a history of breastfeeding, whereas 31.45% did not. However, Wahidin et al.'s study in Indonesia from 2018 indicated no significant relationship between breastfeeding and the risk of breast cancer (21). Among the participants, 16.93% reported a history of smoking, while 83.06% did not. Additionally, 4.83% had a history of alcohol consumption, while 95.16% did not. Due to the limited number of cases in studies by Basharat et al. and Abdollahian et al., a thorough risk assessment was not feasible (18,19). However, Roohparvarzadeh et al. identified

exposure to tobacco smoke as a major risk factor for breast cancer (19). In terms of educational attainment, 18.54% had not completed high school, 22.58% held a high school diploma, 31.45% possessed a bachelor's degree, 12.90% had a master's degree, and 14.51% earned a doctorate or higher. Consistent with our findings, Hashemi et al. and Grevena et al. did not find a clear link between socioeconomic status, educational attainment, and breast cancer (20,23). Basharat et al. noted a slightly increased risk of breast cancer among individuals without a university degree; however, this difference was not statistically significant (18).

Conclusion

The results of this investigation reveal a heightened incidence of breast cancer among individuals in their forties. Notably, the early onset of menstruation and the utilization of oral contraceptives were prevalent among the women diagnosed with this malignancy, suggesting a potential correlation between these factors and an increased risk of developing breast cancer. Furthermore, there were no significant disparities in educational attainment within the studied cohort. A principal limitation of this research lies in its concentration on a singular institution and the relatively modest sample size, which was constrained by temporal limitations. This restricted sample size further impeded the capacity to categorize participants into distinct groups for comprehensive statistical analysis. To enhance the robustness and generalizability of the findings, subsequent investigations should encompass multiple institutions with larger participant cohorts to enable a more exhaustive exploration of the variables under consideration. Furthermore, subsequent investigations should prioritize the collection of data regarding familial histories of malignancies and implement screening protocols for patients concerning these particular risk factors. In light of the significant influence that pharmacological agents may exert on the etiology of cancer, it

is imperative that future studies meticulously catalog all medications administered to patients and conduct analyses based on their respective classifications.

Acknowledgments

We wish to extend our sincere appreciation to Islamic Azad University – Sari Branch for their significant contributions to the present study.

Conflicts of interest

The authors hereby declare the absence of any conflicts of interest.

Authors' contributions

All authors participated in the conceptualization and design, analysis and interpretation of the data, drafting of the manuscript, and critically revising it for intellectual content. They have all approved the final version for submission and have agreed to assume accountability for all facets of the work.

Funding

This research did not receive any external funding.

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