

BREAST CANCER RISK FACTORS IN COUNTRIES WITH DIFFERENT SOCIODEMOGRAPHIC INDICES (SDIS) AND CULTURE: A

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BREAST CANCER RISK FACTORS IN COUNTRIES WITH DIFFERENT SOCIODEMOGRAPHIC INDICES (SDIS) AND CULTURE: A SYSTEMATIC REVIEW

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Abstract

This systematic review was performed to identify breast cancer (BC) risk factors in countries with different sociodemographic indices (SDI) and cultures, with a focus on the USA, Kingdom of Saudi Arabia (KSA), and Pakistan. Inclusion criteria were original articles about BC risk factors from the USA, KSA, and Pakistan, from the last 10 years. A search was done with PubMed and Google Scholar. A total of 43 articles were selected. Different genes were associated with BC in the USA, KSA, and Pakistan. Obesity, low physical activity, cigarette smoking, and hormonal therapy, in both pre- and post-menopausal women were risk factors for BC in studies from USA, KSA, and Pakistan. Red meat intake in the USA, and a high fat intake and chicken in Pakistan were found to be associated with BC. Alcohol was a risk factor for BC in the USA, but no such relationship was found in KSA and Pakistan. Early menarche, late menopause, nulliparity, unmarried status, no breastfeeding, and low Vitamin D levels were also risk factors for BC in Saudi and Pakistani women. Studies from the USA and Pakistan found a relationship between hair dye use and BC risk. The findings of this review provide comprehensive assessment on the prevalence of different risk factors for BC in other cultures and countries of SDI levels. Every country needs to focus on the prevention and control of its respective risk factors.

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1. INTRODUCTION

Breast cancer (BC) is the most prevalent malignancy in women all over the world and it causes more than two million new cases in 2018 alone and is a leading cause of morbidity and mortality in the female population worldwide.^{1,2} The non-modifiable factors are important and include family history, ethnicity and genetic susceptibility, whereas the modifiable factors consist of obesity, dietary habits, alcohol use, smoking, lack of exercise, exogenous hormone use among some reproductive factors such as parity and age at first pregnancy.^{3,9} The burden of BC depends on sociodemographic index (SDI), which is an indicator that integrates fertility rate among women below the age of 25 years, lag-distributed per capita income and average education level among adults aged 15 years and above. There are five countries, namely low, low-middle, middle, high-middle, and high SDI, which have been associated with the escalating exposure to behavioural risks including tobacco and alcohol consumption, sedentary living, and dietary changes. Moreover, the prevalence and expression of these risk factors are affected by the cultural norms as they help to shape the epidemiology of BC in various areas.

From a historical perspective, the occurrence of BC mounted in western countries throughout 1980s-1990s but has witnessed a radical shift because of reduced use of widespread screening and menopausal hormone therapy.¹¹ On the contrary, escalating incidences are experienced in low and middle-income countries (LMICs), led by delayed childbearing, lifestyle changes, obesity, reduced breastfeeding, and rapid urbanisation.¹⁰ In the Middle East and North Africa (MENA) region, the prevalence of BC escalates by 378% between 1990 and 2019, with younger age diagnosed majorly in Saudi Arabia.^{12,13} In particular, Pakistan is witnessing escalating BC cases, usually at a younger median age compared with Western populations.^{2,4,15}

The occurrence of BC has striking cultural contrasts in both the Saudi Arabia and USA despite of their high-SDI countries classifications. On one hand, a major role is played by lifestyle-related exposures including obesity, alcohol consumption, and high red meat intake in the USA. On the other hand, cultural and religious norms drive

risk patterns in the Saudi Arabia. Similar trends and risk patterns are experienced in Pakistan compared with Saudi Arabia, but other key contributors make the Pakistan's case weak in this epidemiology including weak cancer surveillance, resource limitations, weak cancer surveillance, and reliance on biomass fuels, and reliance on biomass fuels.

Thus, this situation warrants a need to understand the roles of socioeconomic development versus cultural practices in driving BC risks and comparing it with high-SDI classified countries (Saudi Arabia and USA). To our knowledge, no previous review has critically examined how SDI and cultural context together determine BC risk factor prevalence and patterns in the USA, Saudi Arabia, and Pakistan. By synthesising genetic, lifestyle, reproductive, and environmental determinants across these settings, we highlight both universal and context-specific risk factors. The insights from this review can guide tailored prevention strategies, strengthen public health education, and inform policymakers in designing interventions that are culturally sensitive and SDI-appropriate.

2. Materials and Methods

2.1. Focused Question

The Preferred Reporting Items for Systematic Reviews and Meta-Analyse (PRISMA) guidelines were used. This systematic review was conducted by framing the research question using the Participants, Intervention/Exposure, Comparison, and Outcomes (PICO) strategy. The participants diagnosed with BC were considered and include primary outcome measures such as genetic lifestyles, environmental, reproductive, and dietary risk factors. A comparative analysis was conducted between USA, Saudi Arabia, and Pakistan considering cultural backgrounds and sociodemographic indices. These outcomes help in identifying the prevalence of BC in the chosen regions and country-specific risk factors with attention to the culture and SDI. The following focused research question was framed: *What are the breast cancer risk factors in countries with different SDI levels and cultural settings, and how do these contextual factors influence the prevalence of modifiable and non-modifiable risks?*

This systematic review was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 December 2023 under registration number INPLASY2023120049 (DOI: 10.37766/inplasy2023.12.0049).

2.2. Inclusion and Exclusion Criteria

Clinical trials (both randomized and non-randomised), observational studies (prospective and retrospective), cross-sectional studies, and grey literature (non-academic websites and conference proceedings) were reviewed from January 2013 and April 2023 in the chosen regions. The primary focus behind the selection of these articles was given to the environmental, dietary, lifestyle, and reproductive risk factors for BC. Articles published in English language was considered only and opted out other articles available in other languages. Exclusion criteria were review articles, meta-analyses, case reports, editorials, and studies that focused exclusively on cancer incidence or prevalence without reporting associated risk factors. Articles originating from countries other than the three selected for comparison, and animal studies, perspectives, and studies lacking original data, were also excluded from the analysis.

2.3. Literature Search

Two investigators (MKM and WAH) independently carried out a systematic search of different databases. A combination of keywords and Medical Subject Headings (MeSH) was covered in the search strategy. The following keywords were piloted using MeSH: (Breast Cancer)OR (Risk Factors) AND (USA Women) AND (Saudi Women) AND (Pakistani Women)AND (Sociodemographic Index). Reference lists of relevant articles were also hand-searched to identify additional studies.

The investigators have also conducted cross-referencing of the included articles to explore any suitable article considering the inclusion criteria. Both the investigators have resolved the disparities for the inclusion/exclusion of articles. A Kappa score was used to evaluate the inter-rater reliability of the articles.

2.4. Data Extraction

Screening and data extraction were performed independently by two reviewers. Titles and abstracts were initially screened for relevance, and potentially eligible articles underwent full-text review. A standardized extraction form was used to collect key information, including author names, year of publication, study location, study design, population characteristics, and reported breast cancer risk factors. Extracted data were categorised into genetic, lifestyle, reproductive, dietary, and environmental domains. Outcomes and key findings relevant to risk factor associations were also recorded. Discrepancies between the reviewers were resolved through discussion and consensus.

2.5. Quality Assessment

The methodological quality of the included studies was appraised using AMSTAR 2 (A MeaSurement Tool to Assess Systematic Reviews). This tool evaluates domains such as study selection, data extraction, risk of bias assessment, and the adequacy of reporting. The overall confidence in the results of this review was graded as "low," reflecting limitations in methodological rigor among some of the included studies. Nevertheless, the synthesis of findings across diverse sources allowed meaningful conclusions to be drawn about breast cancer risk factors in the three selected countries.

3. Results

3.1. Literature Search

A total of 111 articles were yielded from the initial database search. Subsequently, 2 articles (one duplicate and one animal study) were removed. Titles and abstracts were assessed for eligibility, which led to the exclusion of 30 review articles, nine papers reporting only prevalence data without risk factors, three studies that described only sociodemographic indices, 18 studies conducted in countries outside the review scope, one perspective article, and five articles that assessed only knowledge and awareness of breast cancer risk factors. In this regard, a total of 43 articles (USA = 20, Saudi Arabia = 11, and Pakistan = 12) met the inclusion criteria and were analysed in this review. The study selection process is presented in the PRISMA 2020 flow diagram (Figure 1).

3.2. General Characteristics of Included Studies

A combination of observational studies, clinical trials, and cross-sectional studies were covered in the final sample of 43 articles. The sample size varies comprehensively from 100 participants to more than 100,000 participants in large population-based cohorts. Multiple risk factors were investigated simultaneously in majority of the studies whereas a few studies emphasised on genetic or dietary relationships.

3.3. Risk Factors Reported in the USA

Out of 20 studies from the USA, Kurian¹⁴ showed an association of 8 genes (ATM, BARD1, BRCA1, BRCA2, CHEK2, PALB2, PTEN, and TP53) with BC risk, with odds ratios ranging from two-fold for ATM, and to six-fold for BRCA1. Boeke¹⁵ and Hildebran¹⁶ showed a protective effect of physical activity (PA) on BC risk. Red meat intake was found to be associated with the risk of BC.¹⁷⁻¹⁹ However, Genkinger²⁰ could not show any relationship between red meat intake and BC. Alcohol was also found to be a risk factor for BC according to four studies from the USA.²²⁻²⁴ Mass²¹ showed cigarette smoke as a risk factor for BC, especially in those with a family history of BC. Five studies²⁵⁻²⁹ showed a relationship between high BMI and central obesity with BC risk. Qian²⁹ showed the similar relationship in premenopausal patients with BRCA1/2 mutations. However, Guo³⁰ showed a reduced risk of postmenopausal BC with genetically predicted high BMI. Mass²¹ showed a relationship between hormonal therapy and BC, in both pre- and postmenopausal women. Eberle³¹ and Llanos³² could find a relationship between hair dye use and BC risk, however, no relationship was identified by Zhang³³ (Table 1).

Table 1: Study Characteristics (USA)

First author, Year	Country	Study design	Inclusion criteria	Findings
Kutian ¹²	USA	Case-control study	Confirmed cases of breast cancer/Healthy controls	Eight genes (ATM, BARD1, BRCA1, BRCA2, CHEK2, PALB2, PTEN, and TP53) were associated with breast cancer, with odds ratios ranging from two-fold for ATM, and to six-fold for BRCA1
Boeke ¹⁸	USA	Prospective cohort study	Pre-menopausal women	An inverse association of physical activity was found with premenopausal breast cancer
Hildebrand ¹⁶	USA	Prospective cohort study	Post-menopausal women	Physical activity may lower the risk of breast cancer.
Inoue-Choi ¹⁷	USA	Prospective cohort study	Post-menopausal women	High consumption of red meat and processed meat may increase the risk of postmenopausal breast cancer.
Lo ⁸	USA	Prospective cohort study	Pre- and post-menopausal women	Red meat consumption may increase the risk of invasive breast cancer.
Farvid ¹⁹	USA	Prospective cohort study	Pre- and post-menopausal women	Higher consumption of red meat during adolescence was associated with premenopausal breast cancer
Genkinger ²⁰	USA	Prospective cohort study	Pre- and post-menopausal women	No associations were observed for intakes of red meat and BC
Maas ²¹	Europe, Australia, and USA	Prospective cohort study	Pre- and post-menopausal women	Smoking, alcohol use, high BMI, and hormone therapy in menopause are risk factors for BC
White ²²	USA	Prospective cohort study	Pre-and post-menopausal women	Alcohol consumption was positively associated with an increased risk of breast cancer
Cao ²³	USA	Prospective cohort study	Pre-and post-menopausal women	Alcohol increases the risk of breast cancer
Jung ²⁴	USA	Prospective cohort study	Pre-and post-menopausal women	Alcohol consumption was positively associated with the risk of breast cancer
White ²¹	USA	Prospective cohort study	Pre- and post-menopausal women	Waist circumference is positively associated with both premenopausal and postmenopausal breast cancer risk
John ²⁶	USA	Case-control study	Cases of breast cancer/Healthy controls	Central obesity throughout the premenopausal years increases breast cancer risk.
Gaudet ²⁷	USA	Prospective cohort study	Post-menopausal women	Waist circumference in white women is associated with a higher risk

Neuhouser ²⁶	USA	Prospective cohort study	Post-menopausal women	High BMI is associated with an increased post-menopausal breast cancer risk
Qian ²⁹	USA	Prospective cohort study	Pre- and post-menopausal women	BMI is associated with premenopausal breast cancer in BRCA1/2 mutation carriers
Gao ³⁰	USA, UK, Europe, Australia, Canada	Case-control study	Women from two large consortia of BCAC and DRIVE Project	BMI predicted by Genome-wide association studies (GWAS) is inversely associated with the risk of both pre- and postmenopausal breast cancer
Elbert ³¹	USA	Prospective cohort study	Pre- and post-menopausal women	Hair dye can be a risk factor for BC
Llano ³²	USA	Case-control study	Confirmed cases of breast cancer/Healthy controls	Hair dye can be a risk factor for BC
Zhang ³	USA	Prospective cohort study	Pre- and post-menopausal women	No positive association was found between the use of hair dye and the risk of any cancer

PA=Physical activity, BC= Breast cancer, BMI=Body mass index

PA=Physical activity, BC= Breast cancer, BMI=Body mass index

3.4. Risk Factors Reported in Saudi Arabia

The eleven Saudi studies underscored the dual influence of genetics and cultural practices on breast cancer risk. Studies showed that VEGF -2578C>A polymorphism,³⁴ XRCC1rs1799782 polymorphism,³⁵ and Val762Ala variant,³⁶ may play a role in BC in the Saudi population. Mir et al.³⁷ also showed an association of BRCA1 gene mutation with BC in Saudi women but another study failed to show a relationship of either *BRCA1* or *BRCA2* mutation with BC in Saudis.³⁸ Metabolic syndrome³⁹ and obesity^{40,41} were found to be associated with BC risk in Saudi women. Physical inactivity was also found to be associated with BC risk in this population in Alsolami et al.⁴¹ but Al-Amri et al.⁴² failed to show this relationship. The use of hormone contraceptives was found to be associated with the risk of BC in Saudi women.⁴³ Early menarche⁴¹ and late menopause⁴² also seemed to be related to BC risk. Nulliparity, older age at first full-term pregnancy,⁴² and a family history of breast cancer in a first-degree relative⁴² were also probable risk factors for BC in Saudi women. An inverse relationship was found between Vitamin D levels and the risk of BC.⁴⁴ Smoking⁴¹ was also a risk factor for BC as found in Western countries (Table 2).

Table 2: Study Characteristics (Saudi Arabia)

Study	Country	Study design	Inclusion criteria	Findings
Al Balawi ¹²	Saudi Arabia	Case-control study	Confirmed cases of breast cancer/Healthy controls	Association of VEGF -2578C>A polymorphism with BC susceptibility in Saudi women
Al-Mutairi ¹⁸	Saudi Arabia	Case-control study	Cases of breast cancer/Healthy controls	XRCC1 rs1799782 polymorphism may be involved in breast cancer in the Saudi population.
Alanazi ¹⁶	Saudi Arabia	Case-control study	Cases of breast cancer/Healthy controls	Val762Ala variant may play a role in breast cancer in the Saudi population.
Mir ²⁷	Saudi Arabia	Case-control study	Cases of breast cancer/Healthy controls	Mutation in BRCA1 gene was found to be responsible for the susceptibility to breast cancer in the Saudi population
Hasan ³⁴	Saudi Arabia	Case-control study	Cases of breast cancer/Healthy controls	Lack of association of BRCA1 and BRCA2 variants was found with BC in the Saudi population
Alokail ³⁹	Saudi Arabia	Case-control study	Cases of breast cancer/Healthy controls	Patients with metabolic syndrome have a higher risk of developing BC
Elkum ⁴⁰	Saudi Arabia	Case-control study	Cases of breast cancer/Healthy controls	Obesity is a risk factor for breast cancer in Arab women
Alsolami ⁴¹	Saudi Arabia	Case-control study	Cases of breast cancer/Healthy controls	Obesity, physical inactivity, smoking, hormonal contraceptive use, and early menarche were risk factors for women in Saudi Arabia.
Al-Amri ⁴²	Saudi Arabia	Case-control study	Cases of breast cancer/Healthy controls	Older age at first full-term pregnancy, age at menopause ≥ 50 years, and 1 st degree family history of breast cancer, but not low PA, were risk factors
Karim ⁴³	Saudi Arabia	Case-control study	Cases of breast cancer/Healthy controls	Use of oral contraceptives (for more than 10 years) may be associated with the risk of breast cancer in Saudi women.
Youssef ⁴⁴	Saudi Arabia	Case-control study	Cases of breast cancer/Healthy controls	Inverse association was found between Vitamin D concentrations and breast cancer risk in Saudi Arabian women.
1	PA= Physical activity, BC= Breast cancer, BMI=Body mass index			

3.5. Risk Factors Reported in Pakistan

In Pakistani women, the age of presentation of BC in the Pakistani women was a decade earlier than in the rest of the world.^{45,46} In Pakistan, BC risk was associated with BRCA1/2 variants.⁴⁷ A high BMI was found to be related to the risk of BC in Pakistani women in three studies.^{48,50} Physical inactivity was also found to be a risk factor for BC in two studies on the Pakistani population.^{47,48} Older age,⁵¹ unmarried status,⁴⁸ nulliparity,^{48,52} oral contraceptives,⁴⁸ early menarche,⁵¹ late menopause,^{48,52} old age of the mother at first delivery,⁵¹ fewer children,⁵¹ a higher number of incomplete pregnancies,⁵⁰ and no breastfeeding⁴⁸ were also risk factors for BC in Pakistani women. A high fat intake⁴⁹ and chicken intake⁵³ were claimed to be risk factors for BC in Pakistan but Naqeeb et al.⁵⁴ did not show any relationship between diet and the risk of BC. Vitamin D deficiency was found to be associated with an increased risk of BC.⁵⁵ Smoking⁴⁸ and biomass exposure⁵⁶ could also be risk factors for BC in Pakistani women. A non-established risk factor for BC in Pakistani women could be the use of low-quality hair dye or henna (Table 3).⁴⁹

Table 3: Study Characteristics (Pakistan)

Study	Country	Study design	Inclusion criteria	Findings
Sultani ³⁶	Pakistan	Prospective cohort study	Pre- and post-menopausal women	Age of presentation in Pakistani cohort was a decade early than the rest of the world
Zahra ³⁸	Pakistan	Cross-sectional study	Pre- and post-menopausal women	Females present with breast cancer at a younger age (<50 years) in Pakistan
Abbas ³⁷	Pakistan	Case-control study	Cases of breast cancer/Healthy controls	Breast cancer risk was associated with BRCA1/2 variants in the Pakistani population
Bano ³⁹	Pakistan	Case-control study	Cases of breast cancer/Healthy controls	High BMI, smoking, physical inactivity, unmarried status, nulliparity, oral contraceptive use, no breastfeeding, and late menopause were risk factors for breast cancer in Pakistani women
Hissam ⁴⁰	Pakistan	Cross-sectional study	Cases of breast cancer	High BMI, low PA, high fat intake, and use of low-quality hair dye might contribute to breast cancer
Tariq ⁴⁰	Pakistan	Prospective and retrospective cohort study	Pre- and post-menopausal women	Higher BMI, older age, and higher number of incomplete pregnancies are risks of BC
Sufian ⁴¹	Pakistan	Case-control study	Cases of breast cancer/Healthy controls	Family history of breast cancer, early menarche, old age of the mother at first delivery, and fewer children were risk factors for breast cancer in Pakistani women
Nazir ²⁵	Pakistan	Case-control study	Cases of breast cancer/Healthy controls	Nulliparity and age of menopause > 50 years were risk factors for breast cancer
Rani ³⁷	Pakistan	Retrospective case-control study	Cases of breast cancer/Healthy controls	Chicken meat can be considered a risk factor for BC
Naqeeb ⁴²	Pakistan	Case-control study	Cases of breast cancer/Healthy controls	Diet was not found to be related to the risk of BC
Shams ³⁸	Pakistan	Case-control study	Cases of breast cancer/Healthy controls	Vitamin D deficiency was associated with an increased risk of breast cancer
Saeed ⁴³	Pakistan	Cross-sectional study	Pre- and post-menopausal women	Biomass exposure could be a risk factor for breast cancer

PA= Physical activity, BC= Breast cancer, BMI=Body mass index

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3.6. Quality Assessment Findings

The quality of methodology of 43 articles included was evaluated with AMSTAR 2. The majority of the studies have adequately described their objectives and populations, but some of them have not indicated a detailed description of participant selection and confounding adjustment. Genetic association studies were usually well-designed but were usually constrained by small samples. Studies on lifestyle and diet were often based on self-reported information, which created a bias in recall. Few studies were given specific follow-up information or prospective design, and thus the information could not be used to make the conclusion of causality. The available evidence base could be considered as of low quality, which is associated with inconsistent design and reporting criteria. However, comparison of results of various studies made the findings in this review stronger.

UNDER PEER REVIEW IN IJAR

Table 4: Risk-summary table (AMSTAR-informed) for the 43 included studies

#	Study	Country	Design (as per Manuscript 2)	Protocol registered	Clear objectives	Methods described	Confounding adjustment reported	Study-level RoB reported	Funding reported	COI reported	Overall quality (pragmatic)
1	Kurian ¹⁴	USA	Cohort / genetic sequencing	NR	Yes	Yes	Yes	NR	NR	NR	Moderate
2	Becke ¹⁵	USA	Prospective cohort	NR	Yes	Yes	Yes	NR	NR	NR	Low–Moderate
3	Hildebrand ¹⁶	USA	Prospective cohort	NR	Yes	Yes	Yes	NR	NR	NR	Low–Moderate
4	Inoue-Choi ¹⁷	USA	Cohort (diet)	NR	Yes	Yes	Partial/NR	NR	NR	NR	Moderate
5	Lo ¹⁸	USA	Cohort	NR	Yes	Yes	Partial/NR	NR	NR	NR	Moderate
6	Farvid ¹⁹	USA	Cohort	NR	Yes	Yes	Partial/NR	NR	NR	NR	Moderate
7	Genkinger ⁸	USA	Case-control	NR	Yes	Yes	Partial/NR	NR	NR	NR	Moderate–High
8	Mase ²¹	USA/Europe	Pooled cohort / multiregion	NR	Yes	Yes	Yes	NR	NR	NR	Low–Moderate
9	White ²³	USA	Cohort	NR	Yes	Yes	Yes	NR	NR	NR	Low–Moderate
10	Cao ³¹	USA	Cohort	NR	Yes	Yes	Yes	NR	NR	NR	Low–Moderate
11	Jung ³²	USA	Cohort	NR	Yes	Yes	Yes	NR	1	NR	Low–Moderate
12	Park ⁶	USA	Mendelian randomisation	NR	Yes	Yes	N/A (MR)	NR	NR	NR	Low–Moderate
13	Eliassen et al.	USA	Cohort	NR	Yes	Yes	Yes	NR	NR	NR	Moderate

2	Bano et al. ⁴¹	Pakistan	Case-control	NR	Yes	Partial/NR	NR	NR	NR	Moderate- Unclear
8	1 Hsaini et al. ⁴⁹	Pakistan	Cross-sectional	NR	Yes	No	NR	NR	NR	High / Unclear
9	Tariq et al. ⁵⁰	Pakistan	Descriptive / survey	NR	Yes	Partial/NR	NR	NR	NR	High (limited causal inference)
3	1 Sufian et al. ⁵¹	Pakistan	Hospital-based study	NR	Yes	Partial/NR	NR	NR	NR	High / Unclear
1	1 Nazir et al. ⁵²	Pakistan	Case-control	NR	Yes	Partial/NR	NR	NR	NR	Moderate
3	1 Rani et al. ⁵³	Pakistan	Dietary case-control	NR	Yes	Partial/NR	NR	NR	NR	Moderate- Unclear
3	1 Nageeb et al. ⁵⁴	Pakistan	Case-control	NR	Yes	Partial/NR	NR	NR	NR	Moderate- Unclear
4	1 Shamsi et al. ⁵⁵	Pakistan	Multicenter case-control	NR	Yes	Partial/NR	NR	NR	NR	Moderate
5	1 Saeed et al. ⁵⁶	Pakistan	Cross-sectional survey	NR	Yes	No	NR	NR	NR	High (limited causal inference)
6	1 Armstrong et al. ⁵⁸	International	Review / meta (context)	N/A	Yes	N/A	N/A	NR	NR	Not applicable
7	1 Chaudhri et al. ⁵⁹	KSA	Epidemiologic trend analysis	NR	Yes	Partial/NR	NR	NR	NR	Unclear
8	1 Alfashdi et al. ⁶⁴	KSA	Knowledge/perception	NR	Yes	No	NR	NR	NR	High (for causal inference)
9	1 Momenovahed & Salehimiya ⁶¹	Intl	Review (background)	N/A	Yes	N/A	N/A	NR	NR	Not applicable

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4. Discussion

BC is multifactorial and probably results from interactions of different genetic, environmental, lifestyle, and hormonal factors. A family history of BC is thought to occur due to mutations in tumor suppressor genes BRCA1/2, or other BC susceptibility genes.^{11,27,58} Some potentially modifiable risk factors are overweight or obesity, postmenopausal use of combined estrogen and progestin, physical inactivity, smoking, and alcohol use. Reproductive factors including a long menstrual history (early menarche and/or late menopause), no offspring, having a first child after age 30, and use of oral contraceptives also increase the risk of breast cancer.^{11,58} We will compare these risk factors among countries with different SDIs and cultures with a focus on the USA, Saudi Arabia, and Pakistan.

A family history of BC probably occurs due to mutations in tumor suppressor genes.^{11,27,58} These mutations predispose an individual to develop BC. One study from the USA showed an association of BRCA1, BRCA2, ATM, BARD1, CHEK2, PALB2, PTEN, and TP53 with BC risk, with the effect ranging from two-fold for ATM, to six-fold for BRCA1.¹⁴ Studies from KSA showed that VEGF -2578C>A polymorphism,⁵⁴ XRCC1rs1799782 polymorphism,⁵⁵ Val762Ala variant,⁵⁶ and BRCA1 gene mutation⁵⁷ might play a role in BC in the Saudi population. However, one study failed to show a relationship of BRCA1 or BRCA2 mutation with BC in the Saudi population.⁵⁸ A family history of breast cancer in a first-degree relative⁵⁹ was also a risk factor for BC in Saudi women. Genetic factors causing breast cancer are common among consanguineous groups of people in Saudi Arabia's western part.⁵⁹ In the Pakistani population, BC risk was associated with BRCA1/2 variants.⁴⁷ A study has also suggested the relationship of consanguinity (genetic relatedness) with the risk of breast cancer in Pakistani females.²

Consanguineous marriage is customary in most Arab communities.⁵⁹ Similarly, Pakistan shows a consistently high prevalence of consanguinity because of social, cultural, economic, and religious reasons.⁶⁰ This practice can lower BC risk because homozygosity of mutated genes like BRCA1 and BRCA2 is incompatible with life and hence is not transmitted to the next generation.⁶¹ However, parents with a low risk of cancer can produce offspring with a higher cancer risk. Hence, different consanguineous populations can show both an increase and a decrease in the risk of different cancers,⁶⁰ as we observed in different studies.^{2,47,58}

In this review, one study from the USA, Australia, and Europe³⁰ and five studies from the USA²⁵⁻²⁹ showed a relationship between high BMI and central obesity and with risk of BC. One of these studies²⁹ showed a relationship of BC in premenopausal patients with BRCA1/2 mutations. However, one study from various Western countries and the USA³⁰ showed that there was a reduced risk of postmenopausal breast cancer with genetically predicted BMI, a finding which differs from the positive relationship of BMI with BC, from studies using measured adult BMI. Metabolic syndrome³⁹ and obesity^{40,41} were also found to be associated with BC risk in Saudi women. Similarly, a high BMI was found to be related to the risk of BC in Pakistani women in three studies.⁴⁸⁻⁵⁰

Obesity has increased in Saudi Arabia as well as in Pakistan. With a rapid change in the economy, people in ME have changed their traditional lifestyle diet to a more Westernized one, by adopting eating out habits, and an increase in food portion sizes, along with a very sedentary lifestyle.⁷ Similarly, fast-food consumption and physical inactivity have also increased dramatically in Pakistan due to industrialization, urbanization, and the nutritional transition, like in other low-income developing countries.⁶²

Alcohol consumption was found to be significantly associated with BC in the USA.²²⁻²⁴ Although there has been a relatively increased cancer incidence in Arab countries and low-SDI countries like Pakistan during the last few years, it is still much lower than in Western countries. These lower figures for cancer in Arab countries could be attributed to several factors.⁶³ One of these factors is the negligible use of alcohol by women in most Arab countries, especially in KSA, due to cultural and religious reasons.⁶⁴ Similarly, Pakistani society is an Islamic society and is characterized by low exposure to alcohol as a risk factor for BC.⁶⁵

A study from the USA, Europe, and Australia²¹ showed that cigarette smoke was a risk factor for BC. In middle eastern regions, smoking is the largest attribute of BC in females in Lebanon.¹² Smoking was found to be a risk

factor for BC in KSA,⁴¹ as well as in Pakistan.⁶⁶ Exposure to environmental tobacco smoke also increases the risk of BC. Many women are exposed to second-hand smoke by their husbands or partners.⁶⁷ Second-hand smoke is attributed to BC in all of the Middle East and North Africa (MENA) countries in about 3.5% of cases.

Waterpipe smoking is meant for socializing, and pleasure. It is also an expression of cultural identity for people in the Middle East and those of Middle Eastern descent in Western countries. Waterpipe smoking is socially acceptable for women compared to cigarette smoking in ME.⁶⁸ University and school students use it due to peer pressure, and fashion in ME as well as in Pakistan.⁶⁹ The water pipe is used to smoke tobacco and is known by different names, like hookah, and shisha. Bhatnagar et al.⁷⁰ claimed that the harmful effects of water pipe smoking are reduced by using filters in mouthpieces, water additives, and mesh fittings. Hence it appears to increase the risk of several cancers.⁶⁹ As water pipe smoking is a social activity, non-smokers are likely to be exposed to secondhand smoke from the water pipe itself, and to smoke exhaled by users.⁷⁰

The incomplete combustion of biomass for energy production produces Polycyclic Aromatic Hydrocarbons (PAHs), according to the Agency for Toxic Substances and Disease Registry,⁷¹ and biomass fuel is classified as a probable carcinogen by the International Agency for Research on Cancer (IARC).⁵⁶ PAHs might be a risk factor for BC. Biomass exposure was found to be the most neglected risk factor among patients in a Pakistani study.⁵⁶ Due to the lack of electricity and gas supply in most areas of Pakistan, people are forced to utilize biomass as a fuel.

Red meat consists of heterocyclic amines, n-nitroso compounds, and polycyclic aromatic hydrocarbons, which are potential human carcinogens. Meat also contains animal fats and saturated fats, which are associated with an increased risk of BC, especially the ER+/ER- and HER2 subtypes.⁴ Red meat intake was found to be associated with the risk of BC according to three studies from the USA.¹⁷⁻¹⁹ However, another study from the USA³⁰ could not show any relationship between red meat intake and BC. Middle Eastern countries also have high intakes of red meat and most of these countries cross the recommended amounts.⁶⁴ There is a higher intake of Western diets due to cultural changes occurring in Saudi Arabia.⁵⁹ A positive correlation has been found between protein, fats, and calorie intake and BC risk.⁶⁴

In Pakistan also, Westernized diets are important risk factors for BC.⁶⁶ Although cereals are the basic constituent of the Pakistani diet which accounts for more than 60% of total energy consumption, there is a lack of fish and meat consumption, and fruit and fresh vegetables are also limited due to the country's poorly established marketing.⁷² A rise in the incidence of BC in Pakistan has occurred due to risk factors associated with changes in lifestyle and socioeconomic development. Physical inactivity is an important risk factor for BC in this region.⁶⁶ Physical inactivity was found to be a risk factor for BC in the Pakistani population according to one study.⁴⁸

Advancing age is an important risk factor for cancer.⁷³ In the USA, patients mostly presented with BC at age >70 years, but the trend of breast cancer incidence decreased in the USA between 2000 and 2012, especially in women aged 50-59 years, which was probably largely attributed to the decreased use of menopausal hormone therapy.⁷⁴ Features of BC in the Arab population have been described, but the cause of the younger onset of BC has not been evaluated in the literature.⁷⁵ Similarly, no such details were found in the literature about Pakistani women.

Circulating endogenous estrogens and androgens are positively associated with the risk of BC in premenopausal women.⁷⁶ Early menarche and late menopause increase BC risk because of longer estrogen exposure to the breast.⁷⁷ However, pregnancy, breastfeeding, and higher parity are associated with a lower risk of BC.⁷⁸ During pregnancy, there is a great increase in total estrogen secretion, but estradiol levels increase much more than those of estrone or estradiol. Estradiol might have less carcinogenic potential than other estrogens.⁷⁷ However, incomplete pregnancies or abortions have not been associated with BC risk.⁷⁸ Oral contraceptives initiated before age 25, can cause an early initiation of BRCA1-associated breast cancers.⁷⁹ Similarly, postmenopausal estrogen and progestin therapy significantly increase BC incidence.⁸⁰

1 Although high serum levels of vitamin D have been found to have a protective effect on BC risk in both premenopausal and postmenopausal women.^{82,83} 2 study was found from the USA showing an effect of low vitamin D levels on BC risk, since the year 2013. No such study could be found in KSA. However, there was a belief in a study in KSA,⁸⁴ regarding knowledge about BC risk factors, which suggested hair dye could be a risk factor for BC. A risk factor for BC in Pakistani women could be the use of low-quality hair dye or henna.⁴⁹ Lack of checks on personal care cosmetics in Pakistan, like cheap local hair-dye brands containing paraphenylenediamine could be a cause.²

1 Saudi society is conservative and most w 1 men refrain from seeking medical advice due to shyness. This causes the disease to become advanced.⁸⁵ Similarly, there is an uncertainty of attributable risk factors for cancer burden in many lower SDI countries because there is no proper data available at a national level. Pakistan, too, does not have a valid national cancer registry at present to provide us with correct data.⁸⁵

1 The strength of this review was the comparison of SDI and culture of the three countries, to look for risk factors for BC, which has not been done before. There were certain limitations of this study. First, there is a lack of data collection quality in low-income countries like Pakistan, hence the results from some studies might be biased. Second, we mentioned the overall trends for each country but did not describe the regions of each country. Third, as it was not a meta-analysis, the quality of its results could be biased.

5. Conclusion

In conclusion, gene mutations including BRCA1 mutations were risk factors for BC. Consanguinity could either increase or decrease the risk of cancer. Obesity, unhealthy diet, physical inactivity, alcoholism, and smoking were also risk factors for BC. Early marriage, multiparity, and breastfeeding were found to be protective in Pakistan and the KSA. All these facts should be kept in mind and the public should be educated about these risk factors. The fact that smoking and the use of sex hormones have declined in Western countries and so has BC prevalence, should be utilized in educating the public in developing countries.

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BREAST CANCER RISK FACTORS IN COUNTRIES WITH
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