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

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Abstract:

This review was done 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 breast cancer 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. In conclusion, different risk factors were prevalent 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.

Keywords: Breast cancer, risk factors, USA women, Pakistani women, Saudi women, Sociodemographic index.

Introduction:

Breast cancer is the most common cancer in females.[1] In the year 2018, more

than two million new cases were reported globally.[2] A variety of modifiable and non-modifiable risk factors are identified for breast cancer (BC). Family history of cancer, ethnicity, and genetic traits are important non-modifiable risk factors.[3] Modifiable risk factors have been identified as obesity,[4] diets,[3] high alcohol consumption,[5] smoking,[6] low physical activity levels,[7] exogenous hormones,[8] and some reproductive factors like low parity, and older age at first pregnancy.[9]

An increase in the socio-demographic index (SDI) of a country seems to cause an increase in attributable behavioral risks for cancer, like tobacco use, alcohol use, and lifestyle factors. SDI is an index calculated from the total fertility rate in women aged 25 years and younger, lag-distributed per capita income, and the mean education for 15 years and older individuals. The index ranges from zero to 100, and quintiles are used to describe low, low-middle, middle, high-middle, and high SDI countries.[10] Similarly, cultural differences between different countries might also influence the attributable risks for BC. From 1980 till the end of the 1990s, breast cancer incidence rates increased to 30% in Western countries. However, since the beginning of the new millennium, the incidence has either declined or has remained the same in many of these countries, like the UK, Canada, the United States, France, and Australia.[11] Also, breast cancer incidence is rapidly increasing in areas that were previously considered low-risk, such as Africa, Asia, and Latin America. This trend is likely due to increased obesity and physical inactivity, delayed pregnancies, fewer children, early menarche, decreased preference to breastfeed, and increasing breast cancer screening.[10] Although Middle Eastern countries have a high SDI, they have developed much later than Western countries and are also culturally different from the West. The number of female breast cancer cases increased by about 378% between 1990 and 2019 in the Middle East and North Africa (MENA) region.[12] and also in the Kingdom of Saudi Arabia (KSA), especially in younger females.[13] Similarly, breast cancer incidence is increasing in lower-SDI countries like Pakistan.

Although both the USA and Saudi Arabia are high-SDI countries,[10] they have wide cultural differences, so they probably have different risk factors. For determining the effect of SDI, Pakistan was included in this review, as it is a developing low-SDI country, [10] however being a Muslim country,

it is culturally similar to Saudi Arabia. This literature review was meant to identify the risk factors in countries with different SDI levels, as well as cultures, with a focus on the USA, Saudi Arabia, and Pakistan, so that recommendations could be suggested for different regions of the world to prevent breast cancer.

Method:

This systematic review was registered with INPLASY on 12th December 2023, under the registration number INPLASY2023120049, with DOI number 10.37766/inplasy2023.12.0049**.** Literature was searched using Google Scholar and PubMed. The search was done using the keywords "breast cancer", "risk factors", "USA women", "Pakistani women", "Saudi women", and "Sociodemographic index". Inclusion criteria were original research articles from the last 10 years, i.e., from January 2013 to April 2023. Review articles and case reports were excluded. A total of 111 articles were extracted. One article was removed as it was a duplicate article and another was removed as it was an animal study. Thirty (30) articles were excluded from the study because they were review articles and not original research. Nine (9) articles were excluded because they only mentioned statistics on breast cancer prevalence but not the risk factors. Three (3) articles were excluded because they only mentioned the sociodemographic index of Pakistan, Saudi Arabia, and Western countries. Eighteen (18) articles were removed because they were from Europe, Australia, Canada, India, Iran, and Iraq. One article was removed as it was only a perspective and not original research. Five (5) articles were removed because they only mentioned the knowledge of the study participants about risk factors for breast cancer. Hence a total of 43 articles were selected, out of which 20 articles were from the USA, 11 articles were from Saudi Arabia, and 12 articles were from Pakistan. AMSTAR 2 was used for the quality assessment of the review. The quality of the review fell in the "Low" category according to the quality assessment.

Results:

Out of 20 studies from the USA, one study[14] showed an association of eight (8) genes (ATM, BARD1, BRCA1, BRCA2, CHEK2, PALB2, PTEN, and TP53) with breast cancer (BC) risk, with odds ratios ranging from two-fold for ATM, and to six-fold for BRCA1 (Table 1).

Two studies from the USA[16,17] showed a protective effect of physical activity (PA) on BC risk. Red meat intake was found to be associated with the risk of BC according to three studies from the USA.[18–20] On the other hand, another study from the USA[20] 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.[22–25] One study from the USA, Europe, and Australia[23] showed cigarette smoke as a risk factor for breast cancer, especially in those with a family history of breast cancer. Five studies from the USA[26–30] showed a relationship between high BMI as well as central obesity with breast cancer risk. One of these studies[29] showed this relationship in premenopausal patients with BRCA1/2 mutations. However, one study[30] from the USA and various Western countries showed a reduced risk of postmenopausal breast cancer with genetically predicted high BMI. One study in the USA and other Western countries[23] showed a relationship between hormonal therapy and BC, in both pre- and post-menopausal women. Two studies[32,33] could find a relationship between hair dye use and BC risk, however, one study[33] could not.

Studies from the Kingdom of Saudi Arabia (KSA) showed that VEGF -2578C>A polymorphism,[34] XRCC1rs1799782 polymorphism,[35] and Val762Ala variant,[36] may play a role in breast cancer in the Saudi population. One study[37] also showed an association of BRCA1gene 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 syndrome[39] and obesity[41,42] were found to be associated with BC risk in Saudi women. Physical inactivity[40] was also found to be associated with BC risk in this population in one study, but another study[42] failed to show this relationship. The use of hormone contraceptives was found to be associated with the risk of breast cancer in Saudi women.[41,44] Early menarche[40] and late menopause[42] 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 relative[42] 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] Smoking[40] was also a risk factor for BC, as found in Western countries.

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, breast cancer 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.[48,49] Older age,[50] unmarried status,[49] nulliparity,[49,51] oral contraceptives,[49] early menarche,[52] late menopause,[49,51] old age of the mother at first delivery,[52] fewer children,[52] a higher number of incomplete pregnancies,[50] and no breastfeeding[49] were also risk factors for breast cancer in Pakistani women. A high fat intake[48] and chicken intake[53] were claimed to be risk factors for BC according to two studies done in Pakistan, but in another study, the diet was not found to be related to the risk of BC.[54] Vitamin D deficiency was found to be associated with an increased risk of breast cancer.[55] Smoking [49] and biomass exposure[56] could also be risk factors for BC in Pakistani women. A non-established risk factor for breast cancer in Pakistani women could be the use of low-quality hair dye or henna.[48]

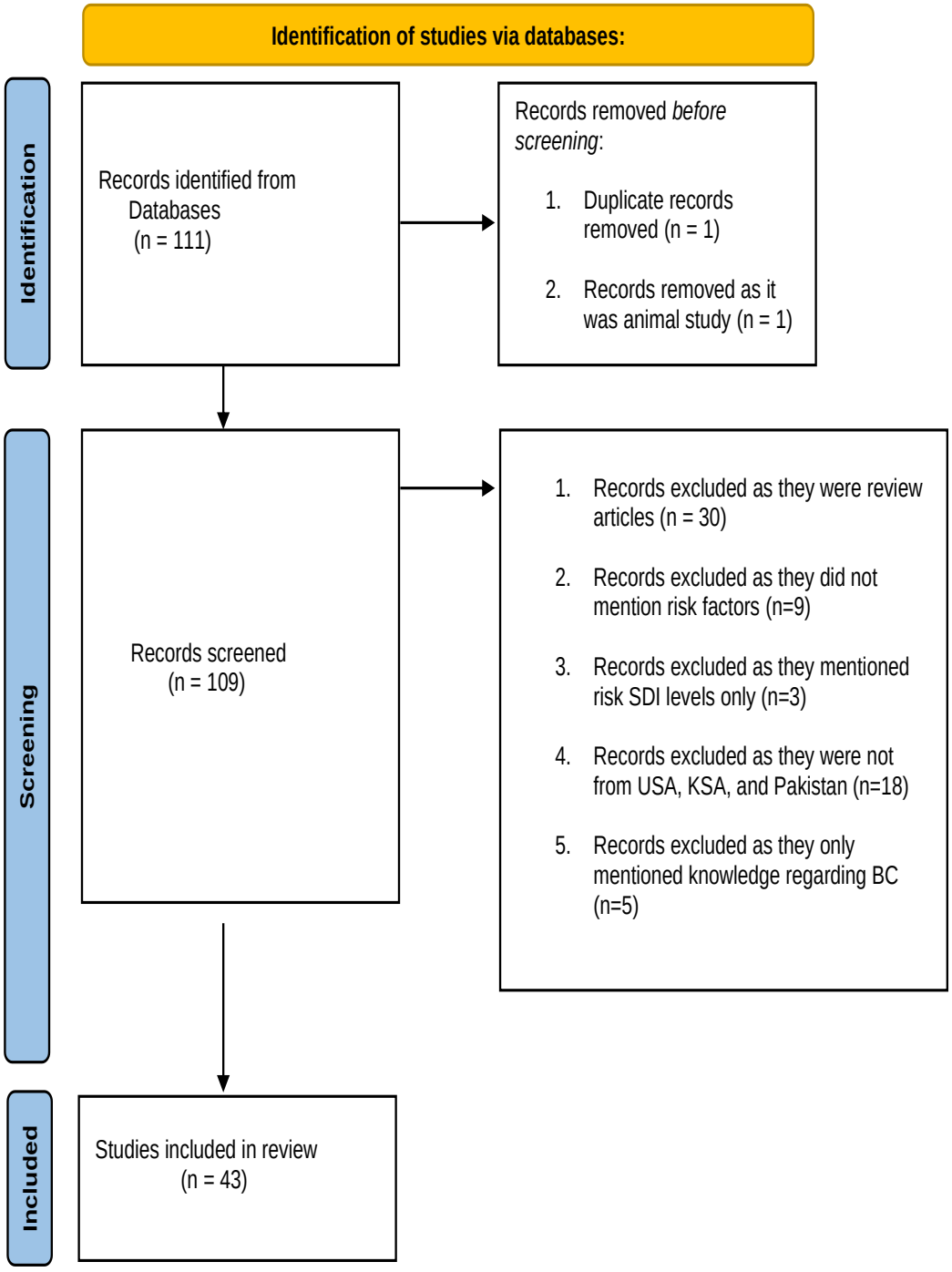

Fig 1: Flow diagram for selection of studies for systematic review:

Table 1: Characteristics and findings of studies from USA:

First author, Year	Country	Study design / Sample size	Inclusion criteria	Findings
Kurian, 2017	USA	Case-control study/ 15,826 cases, 51,200 controls	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
Cao, 2015	USA	Prospective cohort study/ 88,084 women	Pre-and post-menopausal women	Alcohol increases the risk of breast cancer
Jung, 2016	USA	Prospective cohort study/ 1,089,273 women	Pre-and post-menopausal women	Alcohol consumption was positively associated with the risk of breast cancer
White, 2016	USA	Prospective cohort study/ 50,884 women	Pre-and post-menopausal women	Alcohol consumption was positively associated with an increased risk of breast cancer
Neuhouser, 2015	USA	Prospective cohort study/ 67,142 women	Post-menopausal women	High BMI is associated with an increased post-menopausal breast cancer risk
Gaudet, 2014	USA	Prospective cohort study/ 28,965 women	Post-menopausal women	Waist circumference in white women is associated with a higher risk of postmenopausal breast cancer
John, 2015	USA	Case-control study/ 945 cases, 1,418 controls	Cases of breast cancer/Healthy controls	Central obesity throughout the premenopausal years increases breast cancer risk.

White, 2015	USA	Prospective cohort study/ 50,884 women	Pre- and post-menopausal women	Waist circumference is positively associated with both premenopausal and postmenopausal breast cancer risk
Guo, 2016	USA, UK, Europe, Australia, Canada	Case-control study/ 62,328 cases, 83,817 controls	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.
Qian, 2019	USA	Prospective cohort study/ 11,451 cases	Pre- and post-menopausal women	BMI is associated with premenopausal breast cancer in BRCA1/2 mutation carriers.
Maas, 2016	Europe, Australia, and USA	Case-control study/ 17,171 cases and 19,862 controls	Pre- and post-menopausal women	Smoking, alcohol use, high BMI, and hormone therapy in menopause are risk factors for BC
Boeke, 2014	USA	Prospective cohort study/ 75,669 women	Premenopausal women	An inverse association of physical activity was found with premenopausal breast cancer
Hildebrand, 2013	USA	Prospective cohort study/ 73,615 women	Post-menopausal women	Physical activity may lower the risk of breast cancer.
Farvid, 2015	USA	Prospective cohort study/ 44,231 women	Pre- and post-menopausal women	Higher consumption of red meat during adolescence was associated with premenopausal breast cancer
Genkinger, 2013	USA	Prospective cohort study/ 52,062 women	Pre- and post-menopausal women	No associations were observed for intakes of red meat and BC

Inoue-Choi, 2016	USA	Prospective cohort study/ 193,742 women	Post-menopausal women	High consumption of red meat and processed meat may increase the risk of postmenopausal breast cancer.
Lo, 2020	USA	Prospective cohort study/ 42,012 women	Pre- and post-menopausal women	Red meat consumption may increase the risk of invasive breast cancer.
Eberle, 2019	USA	Prospective cohort study/ 46,709 women	Pre- and post-menopausal women	Hair dye can be a risk factor for BC
Llanos, 2017	USA	Case-control study/ 2,280 cases, 2005 controls	Confirmed cases of breast cancer/Healthy controls	Hair dye can be a risk factor for BC
Zhang, 2020	USA	Prospective cohort study/ 1,17,200 women	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				

Table 2: Characteristics and findings of studies from Saudi Arabia:

First author, Year	Country	Study design/ Sample size	Inclusion criteria	Findings
Al Balawi, 2018	Saudi Arabia	Case-control study/ 100 cases, 100 controls	Confirmed cases of breast cancer/Healthy controls	Association of VEGF -2578C>A polymorphism with BC susceptibility in Saudi women
Al-Mutairi, 2013	Saudi Arabia	Case-control study/ 100 cases, 100 controls	Cases of breast cancer/Healthy controls	XRCC1rs1799782 polymorphism may be involved in breast cancer in the Saudi population.
Alanazi, 2013	Saudi Arabia	Case-control study/ 99 cases, 96 controls	Cases of breast cancer/Healthy controls	Val762Ala variant may play a role in breast cancer in the Saudi population.
Mir, 2018	Saudi Arabia	Case-control study/ 100 cases, 100 controls	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, 2013	Saudi Arabia	Case-control study/ 100 cases, 100 controls	Cases of breast cancer/Healthy controls	Lack of association of BRCA1 and BRCA2 variants was found with BC in the Saudi population
Alokail, 2013	Saudi Arabia	Case-control study/ 56 cases, 53 controls	Cases of breast cancer/Healthy controls	Patients with metabolic syndrome have a higher risk of developing BC
Elkum, 2014	Saudi Arabia	Case-control study/ 534 cases, 638 controls	Cases of breast cancer/Healthy controls	Obesity is a risk factor for breast cancer in Arab women
Alsolami, 2019	Saudi Arabia	Case-control study/ 214 cases, 218 controls	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, 2015	Saudi Arabia	Case-control study/ 58 cases, 290 controls	Cases of breast cancer/Healthy controls	Older age at first full-term pregnancy, age at menopause ≥50 years, and 1st-degree family history of breast cancer, but not low PA, were risk factors
Karim, 2015	Saudi Arabia	Case-control study/ 92 cases and 100 controls	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.
Yousef, 2013	Saudi Arabia	Case-control study/ 120 cases, 120 controls	Cases of breast cancer/Healthy controls	Inverse association was found between Vitamin D concentrations and breast cancer risk in Saudi Arabian women.
PA= Physical activity, BC= Breast cancer, BMI=Body mass index				

Table 3: Characteristics and findings of studies from Pakistan:

First author, Year	Country	Study design/ Sample size	Inclusion criteria	Findings
Abbas, 2019	Pakistan	Case-control study/ 100 cases, 100 controls	Cases of breast cancer/Healthy controls	Breast cancer risk was associated with BRCA1/2 variants in the Pakistani population
Bano, 2016	Pakistan	Case-control study/ 1238 cases, 1008 controls	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, 2019	Pakistan	Cross-sectional study/ 80 cases	Cases of breast cancer	High BMI, low PA, high fat intake, and use of low-quality hair dye might contribute to breast cancer
Tariq, 2013	Pakistan	Prospective and	Pre- and post-menopausal women	Higher BMI, older age, and higher number of

		retrospective cohort study/ 100 cases		incomplete pregnancies are risks of BC
Rani, 2022	Pakistan	Retrospective case-control study/ 100 cases, 100 controls	Cases of breast cancer/Healthy controls	Chicken meat can be considered a risk factor for BC
Naqeeb, 2021	Pakistan	Case-control study/ 408 cases, 408 controls	Cases of breast cancer/Healthy controls	Diet was not found to be related to the risk of BC
Shamsi, 2020	Pakistan	Case-control study/ 411 cases, 784 controls	Cases of breast cancer/Healthy controls	Vitamin D deficiency was associated with an increased risk of breast cancer
Nazir, 2015	Pakistan	Case-control study/ 200 cases, 200 controls	Cases of breast cancer/Healthy controls	Nulliparity and age of menopause > 50 years were risk factors for breast cancer
Sufian, 2015	Pakistan	Case-control study/ 108 cases, 108 controls	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
Sultan, 2022	Pakistan	Prospective cohort study/ 500 cases	Pre- and post-menopausal women	Age of presentation in Pakistani cohort was a decade early than the rest of the world
Zahra, 2013	Pakistan	Cross-sectional study/ 200 cases	Pre- and post-menopausal women	Females present with breast cancer at a younger age (<50 years) in Pakistan
Saeed, 2019	Pakistan	Cross-sectional study/ 402 cases	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				

Discussion:

Breast cancer is multifactorial and probably results from interactions of different genetic, environmental, lifestyle, and hormonal factors. A family history of breast cancer is thought to occur due to mutations in tumor suppressor genes BRCA1/2, or other breast cancer susceptibility genes.[11,57,58] 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.[11,57] We will compare these risk factors among countries with different sociodemographic indices (SDI) and cultures with a focus on the USA, Saudi Arabia, and Pakistan.

Genetics and BC risk:

A family history of breast cancer probably occurs due to mutations in tumor suppressor genes.[11,57,58] These mutations predispose an individual to develop breast cancer. One study from the USA showed an association of BRCA1, BRCA2, ATM, BARD1, CHEK2, PALB2, PTEN, and TP53 with breast cancer (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,[34] XRCC1rs1799782 polymorphism,[35] Val762Ala variant,[36] and BRCA1gene mutation[37] might play a role in breast cancer in the Saudi population. However, one study failed to show a relationship of BRCA1 or BRCA2 mutation with BC in the Saudi population.[38] A family history of breast cancer in a first-degree relative[42] 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, breast cancer 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.[60] Similarly, Pakistan shows a consistently high prevalence of consanguinity because of

social, cultural, economic, and religious reasons.[61] This practice can lower BC risk, because homozygosis of mutated genes like BRCA1 and BRCA2 is incompatible with life, and hence is not transmitted to the next generation.[62] 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,[62] as we observed in different studies.[2,47,59]

Obesity and BC risk:

In this review, one study from the USA, Australia, and Europe[23] and five studies from the USA[25–29] showed a relationship between high BMI and central obesity with risk of breast cancer. One of these studies[29] showed a relationship of BC in premenopausal patients with BRCA1/2 mutations. However, one study from various Western countries and the USA[30] 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 syndrome[39] 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.[63]

Alcohol use and BC risk:

Alcohol consumption was found to be significantly associated with breast cancer in the USA.[21,22,24] Although there is 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.[64] 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.[65] Similarly, Pakistani society is an Islamic society and is characterized by low exposure to alcohol as a risk factor for breast cancer.[66]

Smoking and BC risk:

A study from the USA, Europe, and Australia[23] showed that cigarette smoke was a risk factor for breast cancer. In ME, smoking has the largest attribute of breast cancer in females in Lebanon.[12] Smoking was found to be a risk factor for BC in KSA,[40] as well as in Pakistan.[67]

Exposure to environmental tobacco smoke also increases the risk of breast cancer. Many women are exposed to secondhand smoke by their husbands or partner.[68] Second-hand smoke is attributed to breast cancer in all of the Middle East and North African (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 for those of Middle Eastern descent in Western countries. Waterpipe smoking is socially acceptable for women compared to cigarette smoking in ME.[69] University and school students use it due to peer pressure, and fashion in ME as well as in Pakistan.[70] The water pipe is used to smoke tobacco and is known by different names, like hookah, and shisha. It is claimed that the harmful effects of water pipe smoking are reduced by using filters in mouthpieces, water additives, and mesh fittings.[71] But, waterpipe smoke contains nitrosamines and glycerol nicotine, and it produces chemical substances like carbon monoxide and many polyaromatic hydrocarbons, which are transmitted while smoking. Hence it appears to increase the risk of several cancers.[70] As water pipe smoking is a social activity, non-smokers are likely to be exposed to secondhand smoke from the water pipe itself, as well as to smoke exhaled by users.[71]

The incomplete combustion of biomass for energy production produces Polycyclic Aromatic Hydrocarbons (PAHs), according to the Agency for Toxic Substances and Disease Registry,[72] 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.

Diet and BC risk:

Certain diets might also be related to the risk of BC. 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 breast cancer, 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] On the other hand, another study from the USA[20] could not show any relationship between red meat intake and BC.

The MENA region has been undergoing a shift in dietary patterns from the healthy traditional Mediterranean diet, to a more Westernized diet, which is rich in energy and fat. Middle Eastern countries also have high intakes of red meat and most of these countries cross the recommended amounts.[65] 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 breast cancer risk.[65] A literature review showed a positive association between dietary fat and breast cancer in Saudi women. The review showed that high consumption of red meat during adolescence was associated with premenopausal breast cancer.[7] Some studies showed a weak positive association between saturated fat intake and breast cancer risk, even among those postmenopausal women who did not have a history of using hormonal therapy. However, no individual study in KSA showed a relationship between BC risk and an intake of meat or fat.

In Pakistan also, Westernized diets are important risk factors for breast cancer.[67] Although cereals are the basic constituent of the Pakistani diet which accounts for more than 60% of total energy consumption and 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.[73] One study[53] showed a possible relationship of chicken meat with BC risk. Yet, another study[50] suggested a possible relationship of high fat intake with BC risk. However, according to a case-control study,[54] the diet was not found to be related to the risk of BC.

Physical activity level and BC risk:

Two studies from the USA[15,16] showed an effect of physical activity (PA) on BC risk. Low PA was found to be associated with the risk and PA was found to be protective against BC. More than 75% of Saudi women are physically less active.[59] Physical inactivity was found to be associated with increased BC risk in this population according to one study, but another study[42] failed to show this association. A rise in the incidence of breast cancer in Pakistan has occurred due to risk factors associated with changes in lifestyle and socioeconomic development. Physical inactivity is an important risk factor for breast cancer in this region.[67] Physical inactivity was found to be a risk factor for BC in the Pakistani population according to two studies.[48]

Age and BC risk:

Advancing age is an important risk factor for cancer.[74] Older age was found to be a risk factor for BC in a Pakistani study.[48] 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.[75] However, in Middle Eastern (ME) countries, breast cancer occurs in women at an average age of <50 years, which is about 10 years earlier than it appears in Western countries.[65] Similarly, the median age of breast cancer is 49 years in Pakistani women. This is a very young age compared with other populations.[45,46] This might have happened due to economic and cultural changes occurring in ME countries,[59] as well as in developing countries in Asia,[10] like Pakistan.

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.[76] Similarly, no such details were found in the literature about Pakistani women.

Hormones and BC risk:

Circulating endogenous estrogens and androgens are positively associated with the risk of breast cancer in premenopausal women.[77] Early menarche and late menopause increase breast cancer risk because of longer estrogen exposure to the breast.[78] However, pregnancy, breastfeeding, and higher parity are associated with a lower risk of breast cancer.[79] During pregnancy, there is a great increase in total estrogen secretion, but estriol levels increase much

more than those of estrone or estradiol. Estriol might have less carcinogenic potential than other estrogens.[78] However, incomplete pregnancies or abortions have not been associated with BC risk.[79] Oral contraceptives initiated prior to age 25, can cause an early initiation of BRCA1-associated breast cancers.[80] Similarly, post-menopausal estrogen and progestin therapy significantly increase breast cancer incidence.[81]

One study in the USA[23] showed a relationship between hormonal therapy and BC, in both pre- and post-menopausal women. The use of hormone contraceptives was also found to be associated with the risk of breast cancer in Saudi women.[40,42] Similarly, oral contraceptives were also risk factors for breast cancer in Pakistani women.[49] Early menarche[42] and late menopause also seemed to be related to BC risk in the Saudi population. Nulliparity[42] was also a probable risk factor for BC in Saudi women. Having fewer children compared to the past, the late age of marriage, a decline in breastfeeding, and an increase in the use of external hormones in Saudi Arabia have increased the risk of BC.[59] Similarly, unmarried status,[49] nulliparity,[49,51] oral contraceptives,[49] early menarche,[52] late menopause,[49,51] old age of the mother at first delivery,[52] fewer children,[52] and no breastfeeding[49] were risk factors for breast cancer in Pakistani women. A higher number of incomplete pregnancies was also found to be a risk factor in Pakistani women,[48] a finding not in agreement with findings in the USA.[79]

High plasma glucose and BC risk:

High fasting plasma glucose is an attributable risk factor for breast cancer.[82] It is the largest attribute of breast cancer in all of the Middle East and North African (MENA) countries.[12] High glucose levels were found to be associated with BC risk in Saudi women.[39] However, no studies could be found from the USA and Pakistan in this regard.

Vitamin D deficiency and BC risk:

Although high serum levels of vitamin D have been found to have a protective effect on breast cancer risk in both premenopausal and postmenopausal women.[83,84] No study was found from the USA showing an effect of low vitamin D levels on BC risk, since the year 2013. However, an inverse relationship was found between Vitamin D levels and the risk of BC in Saudi women.[44] Similarly, Vitamin D

deficiency was found to be associated with an increased risk of breast cancer in Pakistani women.[55]

Hair dyes and BC risk:

No positive association was found between the use of hair dye and the risk of most cancers.[33] However, a higher breast cancer risk was found to be associated with the use of permanent hair dye in two studies from the USA.[31,32] Dye constituents, like 2,4-diaminoanisole sulfate, para-phenylenediamine, and aromatic amines like 4-aminobiphenyl-(ABP) might be risks for BC.[32] No such study could be found in KSA. However, there was a belief in a study in KSA,[85] regarding knowledge about BC risk factors, which suggested hair dye could be a risk factor for BC. A risk factor for breast cancer in Pakistani women could be the use of low-quality hair dye or henna.[50] Lack of checks on personal care cosmetics in Pakistan, like cheap local hair-dye brands containing paraphenylenediamine could be a cause.[2]

In Middle Eastern (ME) countries and Pakistan, breast cancer occurs in women at an average age of <50 years, which is around 10 years earlier than in Western countries.[45,46,65] In the USA BRCA1, BRCA2, ATM, BARD1, CHEK2, PALB2, PTEN, and TP53 gene mutations, in the KSA VEGF -2578C>A, XRCC1rs1799782, Val762Ala, and BRCA1gene mutations, and in the Pakistani population BRCA1/2 variants were found to be associated with BC. After considering the prevalence of various risk factors in these three countries, it could be observed that not only the SDI level, but the culture of a country could also influence these factors. It could be seen that consanguinity in Islamic countries could both increase or decrease the risk of different cancers.[62] Although early marriage, multiparity, and breastfeeding are still prevalent in these countries, Westernization after economic development has affected these traditions also and resulted in an increase in BC risk. Similarly, this economic development has taken its toll in the form of obesity, unhealthy diet, physical inactivity, and smoking. Alcohol use is still not prevalent in Islamic countries despite differences in SDI levels, but smoking waterpipe has flourished, especially in the younger generation. On the other hand, the use of sex hormones has declined in Western countries due to the high awareness of cancer risk related to these products. Similarly, strict bans on public smoking in Western countries

have also impacted the cancer risks beneficially.

Reducing exposure to modifiable risk factors could decrease the cancer rate, and policies should be devised following the local cancer risk factors.[10] Saudi society is conservative and most women refrain from seeking medical advice due to shyness. This causes the disease to become advanced.[86] Similar cultural circumstances and low socioeconomic status of individuals as well as the country are the hindrances in diagnosing and treating BC in Pakistan.[2] A rise in the rates of BC cases, especially among younger women, along with obesity calls for action in all countries of ME.[65] It is important to note that public health interventions are impeded due to the scarcity of research and data collection.[65] Similarly, there is an uncertainty of risk-attributable 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.[86] The development of a cancer registry is integral to cancer control efforts.[10] Some steps are now being taken by the Government of Pakistan. One such step is taken by the Pakistan Health Research Committee (PHRC) which works under the Government of Pakistan to build a cancer registry by bridging all cancer hospitals in Pakistan.[2] Lack of resources and expert oncologists, and the absence of proper reporting about the cases are the reasons that prevent the evaluation of risk factors for breast cancer in Pakistani women. The limitation of resources is the main problem for Pakistani researchers in evaluating the errors in gene functions. Poor legal control over the production of unhealthy hair dyes and poor management of fuel and hence high use of biomass fuel needs to be checked by the government.

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. Firstly, there is a lack of data collection quality in low-income countries like Pakistan, hence the results from some studies might be biased. Secondly, we mentioned the overall trends for each country but did not describe the regions of each country. Thirdly, as it was not a meta-analysis, the quality of its results could be biased.

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.

Acknowledgments: None

Conflict of interests: None

References:

1. Idrees R, Fatima S, Abdul-Ghafar J, Raheem A, Ahmad Z. Cancer prevalence in Pakistan: meta-analysis of various published studies to determine variation in cancer figures resulting from marked population heterogeneity in different parts of the country. *World J Surg Onc*. 2018;16(1):129. doi:10.1186/s12957-018-1429-z

2. Khan NH, Duan SF, Wu DD, Ji XY. Better Reporting and Awareness Campaigns Needed for Breast Cancer in Pakistani Women. *CMAR*. 2021;Volume 13:2125-2129. doi:10.2147/CMAR.S270671

3. Kazemi A, Barati-Boldaji R, Soltani S, Mohammadipoor N, Esmaeilinezhad Z, Clark CTC et al. Intake of Various Food Groups and Risk of Breast Cancer: A Systematic Review and Dose-Response Meta-Analysis of Prospective Studies. *Adv. Nutr*. 2021;12(3):809-849. doi:10.1093/advances/nmaa147

4. Seiler A, Chen MA, Brown RL, Fagundes CP. Obesity, Dietary Factors, Nutrition, and Breast Cancer Risk. *Curr Breast Cancer Rep*. 2018;10(1):14-27. doi:10.1007/s12609-018-0264-0

5. Key TJ, Balkwill A, Bradbury KE, Reeves GK, Kuan AS, Simpson RF et al. Foods, macronutrients and breast cancer risk in postmenopausal women: a large UK cohort. *Int. J. Epidemiol*. 2019;48(2):489-500. doi:10.1093/ije/dyy238

6. Park HA, Neumeyer S, Michailidou K, Bolla MJ, Wang Q, Dennis J et al. Mendelian randomisation study of smoking exposure in relation to breast cancer risk. *Br J Cancer*. 2021;125(8):1135-1145. doi:10.1038/s41416-021-01432-8

7. Taha Z, Eltom SE. The Role of Diet and Lifestyle in Women with Breast Cancer: An Update Review of Related Research in the Middle East. *BioResearch Open Access*. 2018;7(1):73-80. doi:10.1089/biores.2018.0004

8. Santen RJ, Heitjan DF, Gompel A, Lumsden MA, Pinkerton JV, Davis SR et

al. Underlying Breast Cancer Risk and Menopausal Hormone Therapy. *J. Clin. Endocr*. 2020;105(6):e2299-e2307. doi:10.1210/clinem/dgaa073

9. Yedjou CG, Sims JN, Miele L, Noubissi F, Lowe L, Fonseca DD et al. Health and Racial Disparity in Breast Cancer. In: Ahmad A, ed. *Breast Cancer Metastasis and Drug Resistance*. Vol 1152. Advances in Experimental Medicine and Biology. Springer International Publishing; 2019:31-49. doi:10.1007/978-3-030-20301-6_3

10. Tran KB, Lang JJ, Compton K, Xu R, Acheson AR, Henrikson HJ et al. The global burden of cancer attributable to risk factors, 2010–19: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet*. 2022;400(10352):563-591. doi:10.1016/S0140-6736(22)01438-6

11. American Cancer Society. *Global Cancer Facts & Figures 4th Edition*.; 2018.

12. Safiri S, Noori M, Nejadghaderi SA, Sullman MJM, Bragazzi NL, Almasi-Hashiani A et al. Burden of female breast cancer in the Middle East and North Africa region, 1990–2019. *Arch Public Health*. 2022;80(1):168. doi:10.1186/s13690-022-00918-y

13. Elasbali AM, Mohammed EME, Alonzi Z, Al-Ruwaili HAA, Alsharari AH, Alshammari A et al. Factors Associated with the Prevalence of Breast Cancer Risk: Perception of Northern Saudi Civic. *JCT*. 2019;10(03):245-256. doi:10.4236/jct.2019.103020

15. Kurian AW, Hughes E, Handorf EA, Gutin A, Allen B, Hartman A et al. Breast and Ovarian Cancer Penetrance Estimates Derived From Germline Multiple-Gene Sequencing Results in Women. *JCO Precision Oncology*. 2017;(1):1-12. doi:10.1200/PO.16.00066

16. Hildebrand JS, Gapstur SM, Campbell PT, Gaudet MM, Patel AV. Recreational Physical Activity and Leisure-Time Sitting in Relation to Postmenopausal Breast Cancer Risk. *CEBP*. 2013;22(10):1906-1912. doi:10.1158/1055-9965.EPI-13-0407

16. Boeke CE, Eliassen AH, Oh H, Spiegelman D, Willett WC, Tamimi RM. Adolescent physical activity in relation to breast cancer risk. *Breast Cancer Res Treat*. 2014;145(3):715-724. doi:10.1007/s10549-014-2919-5

17. Farvid MS, Cho E, Chen WY, Eliassen AH, Willett WC. Adolescent meat intake and breast cancer risk: Adolescent meat intake and breast cancer risk. *Int J Cancer*. 2015;136(8):1909-1920. doi:10.1002/ijc.29218

19. Inoue-Choi M, Sinha R, Gierach GL, Ward MH. Red and processed meat, nitrite, and heme iron intakes and postmenopausal breast cancer risk in the NIH-AARP Diet and Health Study. *Int J Cancer*. 2015;138(7).

19. Lo JJ, Park YM, Sinha R, Sandler DP. Association between meat consumption and risk of breast cancer: Findings from the Sister Study. *Int J Cancer*. 2020;146(8):2156-2165. doi:10.1002/ijc.32547

20. Genkinger JM, Makambi KH, Palmer JR, Rosenberg L, Adams-Campbell LL. Consumption of dairy and meat in relation to breast cancer risk in the Black Women's Health Study. *Cancer Causes*

Control. 2013;24(4):675-684. doi:10.1007/s10552-013-0146-8

21. Cao Y, Willett WC, Rimm EB, Stampfer MJ, Giovannucci EL. Light to moderate intake of alcohol, drinking patterns, and risk of cancer: results from two prospective US cohort studies. *BMJ*. Published online August 18, 2015:h4238. doi:10.1136/bmj.h4238

23. Jung S, Wang M, Anderson K, Baglietto L, Bergkvist L, Bernstein L et al. Alcohol consumption and breast cancer risk by estrogen receptor status: in a pooled analysis of 20 studies. *Int J Epidemiol*. 2016;45(3):916-928. doi:10.1093/ije/dyv156

24. Maas P, Barrdahl M, Joshi AD, Auer PL, Gaudet MM, Milne RL et al. Breast Cancer Risk From Modifiable and Nonmodifiable Risk Factors Among White Women in the United States. *JAMA Oncol*. 2016;2(10):1295. doi:10.1001/jamaoncol.2016.1025

25. White AJ, DeRoo LA, Weinberg CR, Sandler DP. Lifetime Alcohol Intake, Binge Drinking Behaviors, and Breast Cancer Risk. *Am. J. Epidemiol*. 2017;186(5):541-549. doi:10.1093/aje/kwx118

25. White AJ, Nichols HB, Bradshaw PT, Sandler DP. Overall and central adiposity and breast cancer risk in the sister study: Adiposity and Breast Cancer Risk. *Cancer*. 2015;121(20):3700-3708. doi:10.1002/cncr.29552

27. John EM, Sangaramoorthy M, Hines LM, Stern MC, Baumgartner KB, Giuliano AR et al. Overall and Abdominal Adiposity and Premenopausal Breast Cancer Risk among Hispanic Women: The Breast Cancer Health Disparities Study. *Cancer Epidemiology, Biomarkers & Prevention*. 2015;24(1):138-147. doi:10.1158/1055-9965.EPI-13-1007-T

27. Gaudet MM, Carter BD, Patel AV, Teras LR, Jacobs EJ, Gapstur SM. Waist circumference, body mass index, and postmenopausal breast cancer incidence in the Cancer Prevention Study-II Nutrition Cohort. *Cancer Causes Control*. 2014;25(6):737-745. doi:10.1007/s10552-014-0376-4

29. Neuhouser ML, Aragaki AK, Prentice RL, Manson JE, Chlebowski R, Carty CL et al. Overweight, Obesity, and Postmenopausal Invasive Breast Cancer Risk: A Secondary Analysis of the Women's Health Initiative Randomized Clinical Trials. *JAMA Oncol*. 2015;1(5):611. doi:10.1001/jamaoncol.2015.1546

30. Qian F, Wang S, Mitchell J, McGuffog L, Barrowdale D, Leslie G et al. Height and Body Mass Index as Modifiers of Breast Cancer Risk in *BRCA1* / *2* Mutation Carriers: A Mendelian Randomization Study. *JNCI.* 2019;111(4):350-364. doi:10.1093/jnci/djy132

31. Guo Y, Andersen SW, Shu XO, Michailidou K, Bolla MN, Wang Q et al. Genetically Predicted Body Mass Index and Breast Cancer Risk: Mendelian Randomization Analyses of Data from 145,000 Women of European Descent. Beck AH, ed. *PLoS Med*. 2016;13(8):e1002105. doi:10.1371/journal.pmed.1002105

32. Llanos AA, Rabkin A, Bandera EV, Zirpoli G, Gonzalez BD, Xing CY et al. Hair product use and breast cancer risk among African American and White women. *Carcinogenesis*.

2017;38(9):883-892. doi:10.1093/carcin/bgx060

32. Eberle CE, Sandler DP, Taylor KW, White AJ. Hair dye and chemical straightener use and breast cancer risk in a large US population of black and white women. *Int J Cancer*. 2020;147(2):383-391. doi:10.1002/ijc.32738

34. Zhang Y, Birmann BM, Han J, Giovannucci E, Speizer F, Stampfer MJ et al. Personal use of permanent hair dyes and cancer risk and mortality in US women: prospective cohort study. *BMJ*. Published online September 2, 2020:m2942. doi:10.1136/bmj.m2942

34. Al Balawi IA, Mir R, Abu-Duhier FM. Potential Impact of Vascular Endothelial Growth Factor Gene Variation (-2578C>A) on Breast Cancer Susceptibility in Saudi Arabia: a Case-Control Study. *Asian Pac J Cancer Prev*. 2018;19(4). doi:10.22034/APJCP.2018.19.4.1135

36. Al Mutairi FM, Alanazi M, Shalaby M, Alabdulkarim HA, Pathan AAK, Parine NR. Association of XRCC1 Gene Polymorphisms with Breast Cancer Susceptibility in Saudi Patients. *Asian Pac J Cancer Prev*. 2013;14(6):3809-3813. doi:10.7314/APJCP.2013.14.6.3809

37. Alanazi M, Pathan AAK, Arifeen Z, Shaik JP, Alabdulkarim HA, Semlali A et al. Association between PARP-1 V762A Polymorphism and Breast Cancer Susceptibility in Saudi Population. Schönbach C, ed. *PLoS ONE*. 2013;8(12):e85541. doi:10.1371/journal.pone.0085541

38. Mir R, Javid J, Al Balawi IA,Alkharsah KR, Hadi MA, Rahman MA et al. A Germline Mutation in the BRCA1 3'UTR Variant Predicts Susceptibility to Breast Cancer in a Saudi Arabian Population. *Asian Pac J Cancer Prev*. 2018;19(3). doi:10.22034/APJCP.2018.19.3.859

39. Hasan TN, Shafi G, Syed NA, Alsaif MA, Alsaif AA, Alshatwi AA. Lack of Association of BRCA1 and BRCA2 Variants with Breast Cancer in an Ethnic Population of Saudi Arabia, an Emerging High-Risk Area. *Asian Pac J Cancer Prev*. 2013;14(10):5671-5674. doi:10.7314/APJCP.2013.14.10.5671

40. Alokail MS, Al-Daghri N, Abdulkareem A, Draz HM, Yakout SM, Alnaami AM et al. Metabolic syndrome biomarkers and early breast cancer in Saudi women: evidence for the presence of a systemic stress response and/or a pre-existing metabolic syndrome-related neoplasia risk? *BMC Cancer*. 2013;13(1):54. doi:10.1186/1471-2407-13-54

41. Alsolami FJ, Azzeh FS, Ghafouri KJ, Ghaith MM, Almaimani RA, Almasmoum HA et al. Determinants of breast cancer in Saudi women from Makkah region: a case-control study (breast cancer risk factors among Saudi women). *BMC Public Health*. 2019;19(1):1554. doi:10.1186/s12889-019-7942-3

42. Elkum N, Al-Tweigeri T, Ajarim D, Al-Zahrani A, Amer SMB, Aboussekhra A. Obesity is a significant risk factor for breast cancer in Arab women. *BMC Cancer*. 2014;14(1):788. doi:10.1186/1471-2407-14-788

43. Al-Amri FA, Saeedi MY, Al-Tahan FM, Ali AM, Alomary SA, Arafa M et al. Breast cancer correlates in a cohort of breast screening program participants in

Riyadh, KSA. *JENCI.* 2015;27(2):77-82. doi:10.1016/j.jnci.2015.04.002

44. Karim SM, Baeshen W, Neamatullah SN, Bin B. Oral Contraceptives, Abortion and Breast Cancer Risk: a Case Control Study in Saudi Arabia. *Asian Pac J Cancer Prev*. 2015;16(9):3957-3960. doi:10.7314/APJCP.2015.16.9.3957

45. Yousef FM, Jacobs ET, Kang PT, Hakim IA, Going S, Yousef JM et al. Vitamin D status and breast cancer in Saudi Arabian women: case-control study. *AJCN*. 2013;98(1):105-110. doi:10.3945/ajcn.112.054445

46. Sultan N, Memon SA, Mooghal M, Wali S, Khan W, Tahseen H et al. Ethnic predisposition, risk factors and breast cancer presentation; a 10-year data. Single centered prospective cohort study from Karachi. *Ann. Med. & Surg*. 2022;82. doi:10.1016/j.amsu.2022.104612

47. Zahra F, Humayoun F, Yousaf T, Khan NA. Evaluation of Risk Factors for Carcinoma Breast in Pakistani Women. *JFJMC*. 2013; 07(01): 34-8

47. Abbas S, Siddique A, Shahid N, Khan RT, Fatima W. Breast cancer risk associated with BRCA1/2 variants in the Pakistani population. *Breast Cancer*. 2019;26(3):365-372. doi:10.1007/s12282-018-0932-y

49. Tariq R, Huma S, Butt MZ, Amin F. Risk factors leading to high prevalence of breast cancer. *J. Appl. Pharm*. 2013; 04(01): 706-12

50. Bano R, Ismail M, Nadeem A, Khan MH, Rashid H. Potential Risk Factors for Breast Cancer in Pakistani Women. *Asia Pac J Cancer Prev.* 2016; 17(9): 4307-12

51. Hisam Z, Soomro NM, Lakhiar RA. Evaluation of risk factors for breast cancer in Pakistani women. *PJPH*. 2020;9(3):139-143. doi:10.32413/pjph.v9i3.168

52. Nazir N, Waheed A, Farhat K, Ismail M, Mansoor Q, Javed G. A case-control study of risk factors associated with female breast cancer. *Pak Armed Forces Med J.* 2015; 65(3):391-96

53. Sufian SN, Masroor I, Mirza W, Butt S, Afzal S, Sajjad Z. Evaluation of Common Risk Factors for Breast Carcinoma in Females: a Hospital Based Study in Karachi, Pakistan. *Asian Pac J Cancer Prev*. 2015;16(15):6347-6352. doi:10.7314/APJCP.2015.16.15.6347

54. Rani DK, Laghari Z, Warsi J, Memon SF, Bhatti U, Bai K. Breast cancer in relation with vegetarian and non-vegetarian diet. *Journal of Xi'an Shiyou University*. 2022;18(12): 407-20

55. Naqeeb H, Siraj S, Iqbal Z, Khan I. Dietary patterns and risk of breast cancer among women: A case-control study. *Pak J Physiol.* 2021; 17(4): 35-8

14. Shamsi U, Khan S, Azam I, Khan AH, Maqbool A, Hanif M et al. A multicenter case control study of association of vitamin D with breast cancer among women in Karachi, Pakistan. Moran JM, ed. *PLoS ONE*. 2020;15(1):e0225402. doi:10.1371/journal.pone.0225402

56. Saeed S, Khan JA, Iqbal N, Irfan S, Shafique A, Awan S. Cancer and how the patients see it; prevalence and perception of risk factors: a cross-sectional survey from a tertiary care centre of Karachi, Pakistan. *BMC Public Health*. 2019;19(1):360. doi:10.1186/s12889-019-6667-7

57. Momenimovahed Z, Salehiniya H. Epidemiological characteristics of and risk factors for breast cancer in the world. *BCTT*. 2019;Volume 11:151-164. doi:10.2147/BCTT.S176070

58. Armstrong N, Ryder S, Forbes C, Ross J, Quek RG. A systematic review of the international prevalence of BRCA mutation in breast cancer. *CLEP*. 2019;Volume 11:543-561. doi:10.2147/CLEP.S206949

59. Chaudhri E, Fathi W, Hussain F, Hashmi SK. The Increasing Trends in Cases of the Most Common Cancers in Saudi Arabia: *JEGH*. 2020;10(4):258. doi:10.2991/jegh.k.200515.001

60. El Goundali K, Chebabe M, Zahra Laamiri F, Hilali A. The Determinants of Consanguineous Marriages among the Arab Population: A Systematic Review. *ijph*. Published online February 13, 2022. doi:10.18502/ijph.v51i2.8679

61. Iqbal S, Zakar R, Fischer F, Zakar MZ. Consanguineous marriages and their association with women's reproductive health and fertility behavior in Pakistan: secondary data analysis from Demographic and Health Surveys, 1990–2018. *BMC Women's Health*. 2022;22(1):118. doi:10.1186/s12905-022-01704-2

62. Denic S, Agarwal MM. Breast cancer protection by genomic imprinting in close kin families. *BMC Med Genet*. 2017;18(1):136. doi:10.1186/s12881-017-0498-0

63. Templin T, Cravo Oliveira Hashiguchi T, Thomson B, Dieleman J, Bendavid E. The overweight and obesity transition from the wealthy to the poor in low- and middle-income countries: A survey of household data from 103 countries. Popkin BM, ed. *PLoS Med*. 2019;16(11):e1002968. doi:10.1371/journal.pmed.1002968

64. Arafa MA, Farhat KH. Why cancer incidence in the Arab counties is much lower than other parts of the world? *J Egypt Natl Canc Inst*. 2022;34(1):41. doi:10.1186/s43046-022-00142-3

65. Naja F, Nasreddine L, Awada S, El Sayed Ahmad R, Hwalla N. Nutrition in the Prevention of Breast Cancer: A Middle Eastern Perspective. *Front Public Health*. 2019;7:316. doi:10.3389/fpubh.2019.00316

66. Nayab A, Fatima S, Rustam SA, Gul A, Khan AU, Bibi A et al. Alcohol consumptions and prevention of underage alcohol consumption in Pakistan. *RRJoLS*. 2022; 01(01): 014-021

67. Zaheer S, Shah N, Maqbool SA, Soomro NM. Estimates of past and future time trends in age-specific breast cancer incidence among women in Karachi, Pakistan: 2004–2025. *BMC Public Health*. 2019;19(1):1001. doi:10.1186/s12889-019-7330-z

68. Szkiela M, Kusideł E, Siwińska-Beck E, Makowiec-Dąbrowska T. Smoking Tobacco – a Risk Factor for Breast Cancer. *J Health Study Med*. 2021; 2 :43-60. doi:10.36145/JHSM2021.09

69. Akl EA, Jawad M, Lam WY, Co CN, Obeid R, Irani J. Motives, beliefs and attitudes towards waterpipe tobacco smoking: a systematic review. *Harm Reduct J*. 2013;10(1):12. doi:10.1186/1477-7517-10-12

70. Salih S, Shaban S, Athwani Z, Alyahyawi F, Alharbi S, Ageeli F et al. Prevalence, Predictors, and Characteristics of Waterpipe Smoking Among Jazan University Students in Saudi Arabia: A Cross-Sectional Study. *Ann. Glob. Health*. 2020;86(1):87. doi:10.5334/aogh.2912

71. Bhatnagar A, Maziak W, Eissenberg T, Ward KD, Thurston G, King BA et al. Water Pipe (Hookah) Smoking and Cardiovascular Disease Risk: A Scientific Statement From the American Heart Association. *Circulation*. 2019;139(19). doi:10.1161/CIR.0000000000000671

72. Korsh J, Shen A, Aliano K, Davenport T. Polycyclic Aromatic Hydrocarbons and Breast Cancer: A Review of the Literature. *Breast Care*. 2015;10(5):316-318. doi:10.1159/000436956

73. Ali A, Manzoor MF, Ahmad N, Adil RM, Qin H, Siddique R et al. The Burden of Cancer, Government Strategic Policies, and Challenges in Pakistan: A Comprehensive Review. *Front Nutr*. 2022;9:940514. doi:10.3389/fnut.2022.940514

74. Kresovich JK, Xu Z, O'Brien KM, Weinberg CR, Sandler DP, Taylor JA. Methylation-Based Biological Age and Breast Cancer Risk. *JNCI*. 2019;111(10):1051-1058. doi:10.1093/jnci/djz020

75. Lei S, Zheng R, Zhang S, Wang S, Chen R, Sun K et al. Global patterns of breast cancer incidence and mortality: A population-based cancer registry data analysis from 2000 to 2020. *Cancer Communications*. 2021;41(11):1183-1194. doi:10.1002/cac2.12207

76. Al-Shamsi HO, Alrawi S. Breast cancer screening in the United Arab Emirates: is it time to call for a screening at an earlier age? *JCPCR*. 2018;9(3). doi:10.15406/jcpcr.2018.09.00334

77. Folkerd E, Dowsett M. Sex hormones and breast cancer risk and prognosis. *The Breast*. 2013;22:S38-S43. doi:10.1016/j.breast.2013.07.007

78. Song SS, Kang S, Park S. Association of Estrogen-Related Polygenetic Risk Scores with Breast Cancer and Interactions with Alcohol Intake, Early Menarche, and Nulligravida. *Asian Pac J Cancer Prev*. 2022;23(1):13-24. doi:10.31557/APJCP.2022.23.1.13

79. Terry MB, Liao Y, Kast K, Antoniou AC, McDonald JA, Mooij TM et al. The Influence of Number and Timing of Pregnancies on Breast Cancer Risk for Women With BRCA1 or BRCA2 Mutations. *JNCI Cancer Spectrum*. 2018;2(4):pky078. doi:10.1093/jncics/pky078

80. Kotsopoulos J, Lubinski J, Moller P, Lynch HT, Singer CF, Eng C et al. Timing of oral contraceptive use and the risk of breast cancer in BRCA1 mutation carriers. *Breast Cancer Res Treat*. 2014;143(3):579-586. doi:10.1007/s10549-013-2823-4

81. Chlebowski RT, Anderson GL. Changing Concepts: Menopausal Hormone Therapy and Breast Cancer. *JNCI*. 2012;104(7):517-527. doi:10.1093/jnci/djs014

82. Sun X, Gustat J, Bertisch SM, Redline S, Bazzano L. The association between sleep chronotype and obesity among black and white participants of the Bogalusa Heart Study. *Chronobiol. Int*.

2020;37(1):123-134. doi:10.1080/07420528.2019.1689398

83. Estébanez N, Gómez-Acebo I, Palazuelos C, Llorca J, Dierssen-Sotos T. Vitamin D exposure and Risk of Breast Cancer: a meta-analysis. *Sci Rep*. 2018;8(1):9039. doi:10.1038/s41598-018-27297-1

84. Bauer SR, Hankinson SE, Bertone-Johnson ER, Ding EL. Plasma Vitamin D Levels, Menopause, and Risk of Breast Cancer: Dose-Response Meta-Analysis of Prospective Studies. *Medicine*. 2013;92(3):123-131. doi:10.1097/MD.0b013e3182943bc2

85. Alrashidi AG, Ahmed HG, Alshammeri KJK, Alrashedi SA, ALmutlaq BA, Alshammari NM et al. Knowledge and Perceptions of Common Breast Cancer Risk Factors in Northern Saudi Arabia. *Asian Pac J Cancer Prev*. 2017;18(10). doi:10.22034/APJCP.2017.18.10.2755

86. Majeed FA, Azeem AR, Farhan N. Lung cancer in Pakistan, where do we stand? *J Pak Med Assoc*. 2019;69(3).