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A REVIEW ON THE PREVALENCE OF BREAST CANCER IN PAKISTAN

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ABSTRACT

Breast cancer is frequently diagnosed cancer of females all over the world. The most common cancer in Pakistan also is breast cancer. Breast cancer incidence in Pakistan i490[4944ut58u95[4o[-qwl[21[3p[p3`]3p1'3[4pv os 2.5 times greater than that in nearby countries like India and Iran. The breast cancer-associated risk factors are age, early menarche, family history, alcohol consumption, and low socioeconomic status. Breast cancer accounts for 23% of all cancer cases worldwide. In Asia Pakistan has the highest incidence rate of breast cancer except that in Jews and Israel. In Pakistan every year minimum of 90,000 females are exposed to breast cancer. The breast cancer frequency in Karachi Pakistan is 69.1 per 100,000. This review article aims to provide updated knowledge and comparative analysis of the prevalence, risk factors, and incidence rate of breast cancer in Pakistan.

Keywords: Breast Cancer, Prevalence, Pakistan, Distribution**.**

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INTRODUCTION

Breast cancer is frequently diagnosed malignancy of females in the biosphere **[1].** Breast cancer is highly prevalent in women because of late marriages, obesity, post-menopausal actions, and late diagnosis of breast cancer by X-ray **[2].** The existence of malignant lumps in breast tissues indicates breast cancer, growth of cancer cells is continued with time, and new defective cells are made. Nearby tissues are also invaded by tumorous cells **[3].** Cancer is becoming a hazardous disease, as time passes, In the world specifically in emerging countries like Pakistan cancer distribution is very fast. Breast cancer is frequently diagnosed cancer in females in Karachi in addition to other parts of Pakistan **[4].** In Pakistan record-keeping system at the national level is not appropriate, so breast cancer data in Pakistan is not accurate **[5].** Studies relating to epidemiology indicate that the association between breast cancer and the VDR (vitamin D receptor) gene can be changed by cultural characteristics shown by a population with a mutual heritage and values **[6].**

As information on molecular biology is increased, breast cancer is nowadays identified as a diverse disease with various environmental, cultural, and traditional differences **[7].** The elements that increase the risk of breast cancer are early menarche, first-live birth in older age, and no breastfeeding **[8].** Oxytocin is secreted by nipple stimulation which results in generating nerve impulses to start milk ejection **[9].** Breast tissue is the site from where breast cancer is devised, usually, it is devised from the inside layer of milk channels**[10].** Every year more than 1.2 million individuals with breast cancer are identified globally, as stated by WHO (World Health Organization) records. Multi-factor molecular tests can define

Table 1: Prevalence of breast cancer according to disease stage.

Hospital	Total No.	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	References
INMOL	200	--	Negligible number	26.5%	37.5%	35.5%	[14]
INMOL & Mayo Hospital	563	--	9%	33%	36%	22%	[15]
INMOL	5939	01%	10%	32%	35%	23%	[16]
SKMCH & RC	5018	02%	07%	43%	23%	08%	[17]
Retrospective Audit	100	--	1.3%	70.3%		17%	[18]
INMOL & Mayo hospital	1101	--	9%	37%	39%	15%	[15]
INMOL & SHL	261	--	3%	33%	52%	12%	[19]

subtypes of breast cancer like Blue Print **[11]**. For the choice of chemotherapy, the important factor is the difference of triple-negative breast cancer, in which carboplatin is as effective as docetaxel in the basal-like subtype but not as effective in other intrinsic subtypes **[12].** Tumor-infiltrating lymphocytes are frequently present in triple-negative, rapidly growing, and other human epidermal growth receptor 2 (HER2) positive breast cancers **[13],** and have been related to developed complete persistence, amplified PCR free of other analytical aspects, and longer uninfected existence. The patients of Aggressive breast ca*n*cer with overexpression of HER2 protein are treated with trastuzumab; the HER2 extracellular area is targeted by a recombinant monoclonal antibody to overpower the downstream signaling pathways **[20**]. In women sheltering BRCA1/2 germline alterations have increased lifetime risk of developing breast cancer. Pakistani women detected with triple-negative breast cancer (TNBC), Hereditary BRCA1 analysis should be considered **[21].** Suggestions for hereditary BRCA1/2 testing for patients with TNBC are not universally acknowledged and differ between certified civilizations. In recent times, a harmful alteration (c.5101C>T) in the FANCM gene was recognized in BRCA1/2-negative familial patients with TNBC from Finland **[22]**. In INMOL and Mayo Hospital Lahore, the total number of breast cancer registered is 563 from Jan 2009- Dec 2009 and the percentage of stages is 9% in stage 1, 33% in stage 2, and 36%, 22% in stage 3 and stage 4 respectively **[15].** Badar et al **[17]** Conducted a study in SKMCH & RC during Jan 2003-Dec 2009 which revealed the 5018 total number of breast cancer cases and percentage in different stages 2%, 7%,43%, 23%,08% as stage 0, stage 1, stage 2, stage 3, stage 4 respectively**.** Similarly, the retrospective audit of 100 breast cancer patients shows the percentage in different stages 1.3% stage 1, 70.3% stage 2, 17% stage 4 **[18]**. In 2009 total of 1101 breast cancer cases were registered in INMOL & Mayo Hospital and the percentages of disease stages are 9% stage 1, 37% stage 2, 39% stage 3, and 15% stage 4 **[16].** During 2012-2015 a total 261 number of breast cancer cases were recorded in INMOL & SHL and the percentages of stages are 3% stage 1, 33% stage 2, 52% stage 3, and 12% stage 4. During July- Dec 2009, 5939 breast cancer recorded at INMOL and the percentage at different stages were 1%, 10%, 32%, 35%, and 23% at stage 0, stage 1, stage 2, stage 3, stage 4 respectively **[19].** A total 200 number of breast cancer cases were registered and the percentages of the stage are negligible number at stage 1, 26.5% at stage 2, 37.5% at stage 3, 35.5% at stage 4 **[14].**

In a multiple logistic regression model Status of TNBC and the presence of BRCA1 alterations have no relation to the simultaneous consideration of tumor histology, family phenotype, and tumor grade **[6]**. Overexpression of the HER2 gene causes 15-30% of the invasive breast cancer. For invasive breast tumor patients, the selection of anti-HER2 therapy effective clinical results, and correct assessment of human epidermal growth factor receptor 2 (HER2) status is quite essential **[23].** The increasing list of mutations and other genetic defects in patients with recurring breast cancer has been shown by several current studies. Cycloxygenase-2 enzyme produces Prostaglandins which have a role in breast carcinogenesis. In Pakistani patients, the mutual COX-2 single nucleotide polymorphism (SNP) haplotype is associated with breast cancer-related risk **[24)**. The immunohistochemistry (IHC) procedure is not able to explain the chromosomal and genetic alterations but it is regularly used to assess the HER2 oncoprotein overexpression **[23].** The cells that are positive for estrogen and progesterone receptors known as malignant cells can urge their growth by identifying signals from their respective hormones. Almost two tests are positive for hormone receptors for every three

breast cancer patients**.** SNPs bring about genetic variances in breast cancer (BC) vulnerability between females from different societies. In Pakistan Breast cancer is a distinct disease affecting younger women with a high frequency of violent molecular kinds **[16].**

RISK FACTORS

The identified leading contributing factors for breast cancer comprised: radiation exposure to the chest at an age less than 30, family history, genetics, no exercise, race, overweight, gestation, use of hormone replacement therapy, alcohol consumption, age, heavy breast, and smoking **[25]**. Current statistics have emphasized that a risk factor for breast cancer incidence is benign pathology with atypia and even without atypia. The factors related to breast cancer are early menarche, delayed parity, and lack of breastfeeding. These factors are being observed in low- and middle-income countries like Pakistan, Bangladesh, and India. Delayed parity is also a risk factor for evolving breast cancer. Assisted reproductive technology (ART) associated Hormonal exposure and Breast cancer-related risk factors are family history (First degree relative) early menarche, age, consumption of joint estrogen and progestin menopausal hormones, drinking alcohol, lack of awareness, lack of exercise, and low socioeconomic status regarding the disease. Pre-menopausal breast cancer and postmenopausal breast have many common risk factors, but less parity is a risk factor only for post-menopausal breast cancer. Menopausal age of greater than 50 years and Nulliparity are the factors that increase breast cancer risk. Age fewer than 25 years at first live birth and Breastfeeding was not defensive against breast cancer. There is a Lack of knowledge in the Pakistani population about breast cancer epidemiology and etiology, but struggles until now have also brought information about genetic origins in various cultural groups inside Pakistan. The recurrent factor is the variation in genetic information between all possible risk factors of breast cancer **[26].** The presence of human papillomavirus 16 (HPV16) has a positive correlation, which is found with estrogen receptor/ progesterone receptor (ER/PR) and HER2-positive breast cancers. Our understanding of genetic predisposition to breast cancer has been improved by worldwide research efforts on various civilizations but despite these findings, 75% of the familial risk of breast cancer rests unsolved**.** The risk factors described by different studies are COX-2 SNP haplotype **[**BRSA ½, human interferon a2b **[27],** smoking 20 packs/year and use of oral contraceptives **[28]** in family history the consanguineous Marriage, first-degree relative **[29]** old age at first pregnancy **[30].**

INCIDENCE RATE

The most populated city of Pakistan is Karachi; in this city, during 1998-2002 age-standardized rate of breast cancer was 69.1 out of 100,000 females, which is the maximum documented rate in Asia. In Pakistan, the incidence of breast cancer is approximately 2.5 times greater than that in the nearby countries India and Iran. [**31]**. The major health issue for females in Pakistan and also worldwide is breast cancer. Worldwide one-fourth of all cancer cases are breast cancer with a standardized incidence rate of 38.9 **[32].**

In recent times, the incidence rate of breast cancer reported by Shaukat Khanum Memorial Cancer Hospital is 21.5% among all and 45.9% among female patients**.** The incidence of breast cancer in women living in the United States from Asia is 1.5-4 times more than that of women living in the United States from other particular countries of origin **[33].** Among Asians the incidence of breast cancer in Pakistan is highest After Jews in Israel, accounting for 34.6% of women's cancers. The incidence rates of breast cancer increased with age for all available years in Karachi. The incidence rates become higher sequentially and among people aged 15-50 years the rates are comparatively high but after the age of 50 years, these rates show variation. Of all incidents breast cancer premenopausal breast cancer included a considerably greater percentage in developing countries (average 47.3%) as compared to established countries (average 18.5%) **[34]**. A study conducted in Quetta and Larkana shows the age-specific incidence rate (ASIR) of female breast cancer is 11.8 in Quetta and 20.6 in Larkana. The data from the Agha Khan University Pathology-based cancer registry (APCR) during the period of (1998-2002) shows the age-specific incidence rate in females is 22.4 **[35]**. Badar et al reported the ASIR of female breast cancer in Globocan during the period of (2012) is 50.3. In Karachi, the ASIR of female breast cancer during (2010-2015) was 87.9 which is the highest incidence rate in Pakistan **[36]**. During the period of (2010-2012), the ASIR of female breast cancer in Lahore was 47.6. Bhurgri et al revealed the ASIR of female breast cancer at 51.7 during (1995-1997) in South Karachi **[37]**.

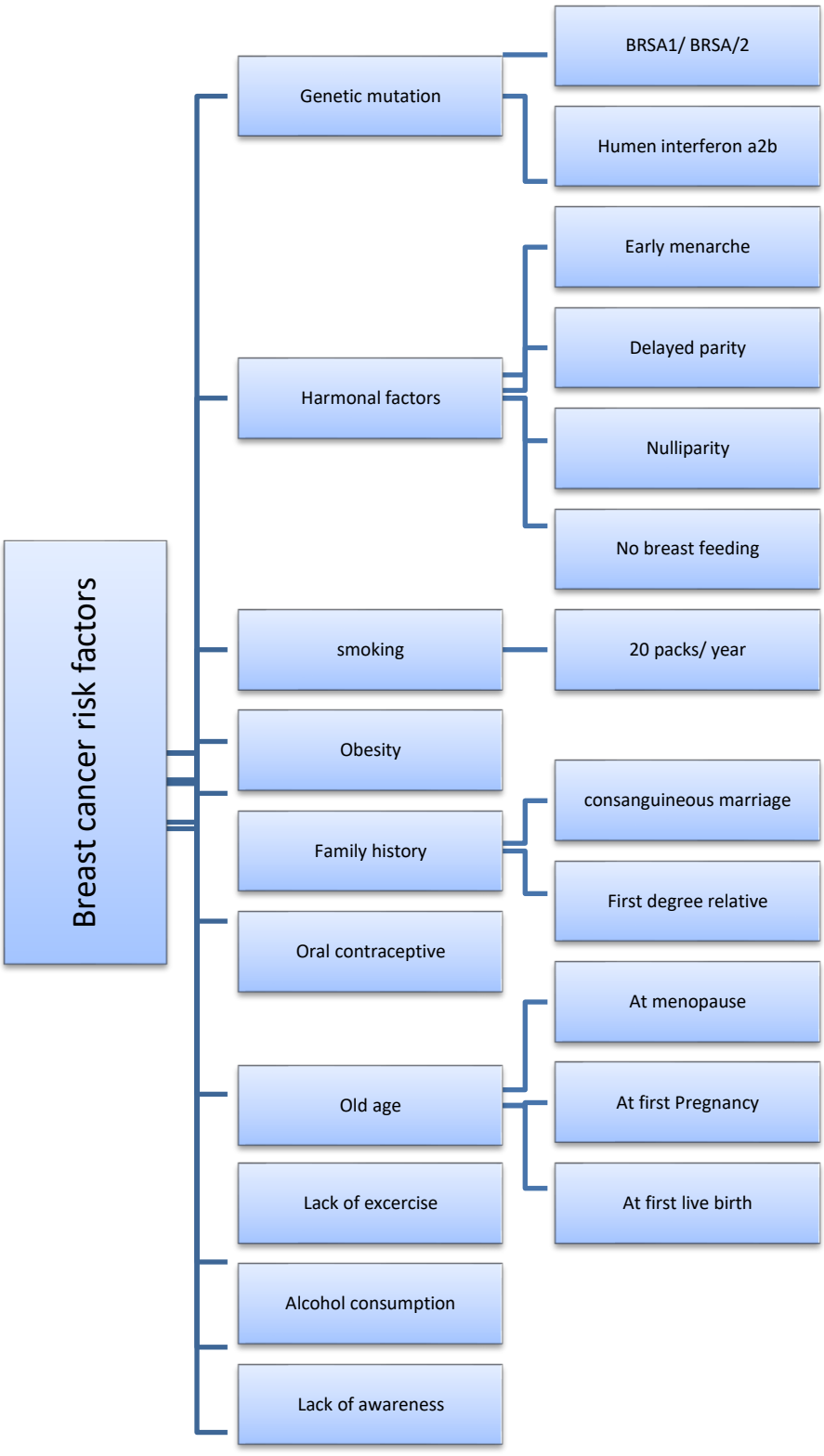
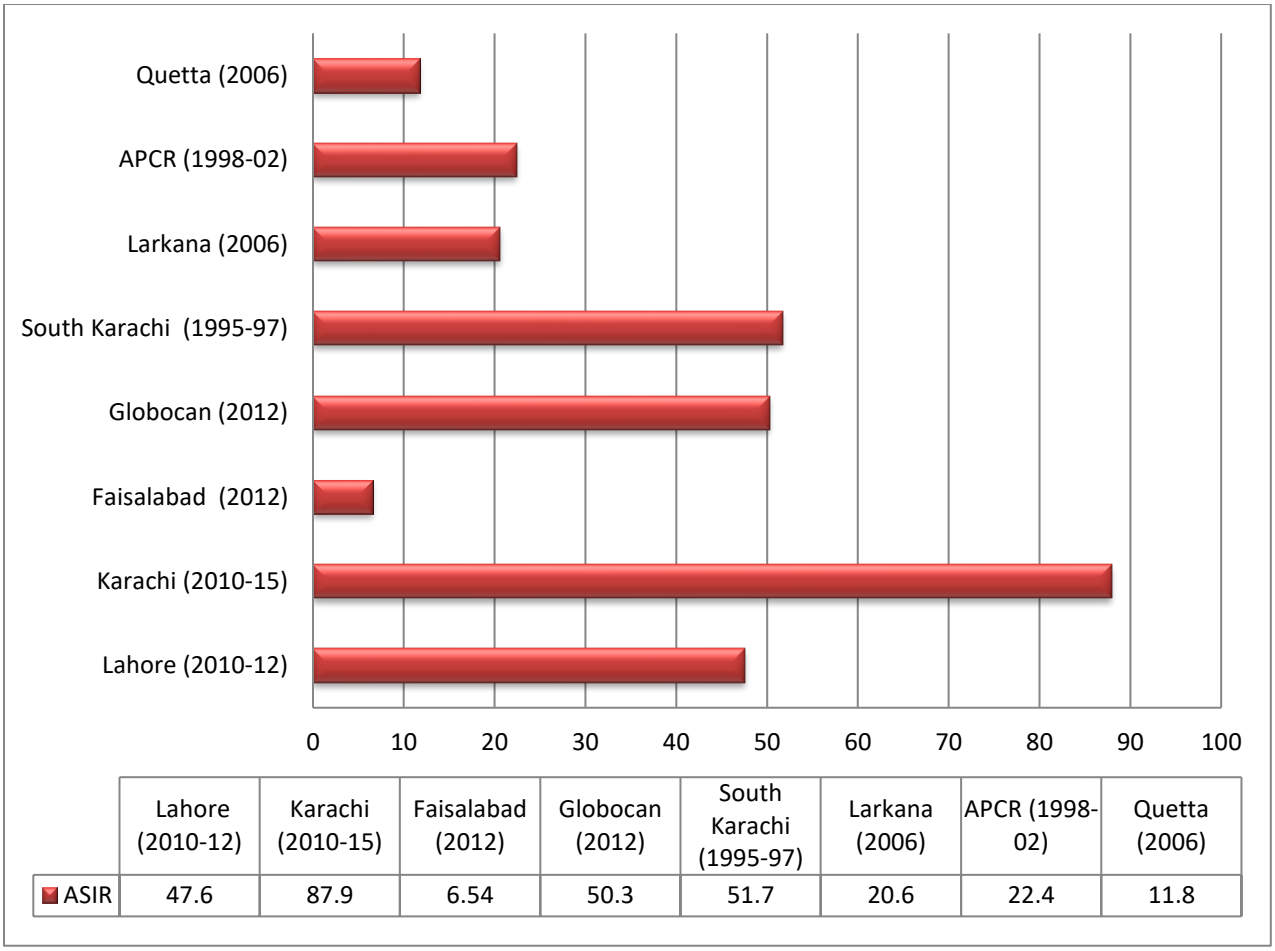


Figure 1: Risk factors associated with breast cancer.



	Lahore (2010-12)	Karachi (2010-15)	Faisalabad (2012)	Globocan (2012)	South Karachi (1995-97)	Larkana (2006)	APCR (1998-02)	Quetta (2006)
ASIR	47.6	87.9	6.54	50.3	51.7	20.6	22.4	11.8

Figure 2: Age-specific incidence rate of breast cancer in females.

PREVALENCE

In Pakistan record keeping system at the national level is not appropriate, so breast cancer data in Pakistan is not accurate. In Pakistan, the most frequently diagnosed cancer among females is also breast cancer, accounting for nearly one in nine female patients **[26].** Breast cancer accounts for about 23% of all cancers worldwide, and about two-thirds of breast cancer cases are estrogen and progesterone receptor-positive, according to the American Cancer Society. Breast cancer incidence in young age women is increasing day by day in Pakistan. According to the data of Shaukat Khanum Memorial Cancer Hospital and Research Center (SKMCH & RC), the breast cancer incidence rate is high at 45.42% for the age group 45-49 years. In Pakistani females, not many studies discovered the high expression of ER, PR, and HER-2/neu. The worldwide mortality rate of women due to breast cancer was around 508,000 in 2011. It is thought that breast cancer most frequently occurs in established countries, but the truth is that, in unestablished countries, 50% of breast cancer cases and a 58% mortality rate were found. Screening and early diagnosis of breast cancer are not good in Pakistan. More than 30% of breast cancer is detected in stages III and IV, according to the record of (SKMCH & RC) **[17].** Breast cancer is the most commonly diagnosed cancer in Pakistan. Among the registered cancer cases Karachi has the maximum rate of breast carcinoma (38%) in women (MuN, 2015). Every year in Pakistan a minimum of 90,000 women are exposed to breast cancer. From 1998 to 2002, the frequency of breast cancer in Karachi was 69.1 out of 100,000 **[38]**. The South Asian population-based cancer registry data revealed that the highest age-standardized rate at 69 per 100,000 of breast cancer is in Pakistan. Worldwide breast cancer is the most commonly diagnosed cancer in females and in many countries, its frequency is increasing progressively. The low-risk Asian countries including Pakistan have

been observed with an increase in breast cancer over the recent three decades **[14]**. Breast cancer is the most commonly diagnosed cancer and the major reason for cancer death among women, accounting for 14% of the cancer deaths and 23% of the total cancer cases **[39].** The 8 years period 2000-2008 data of Karachi Institute of Radiotherapy & Nuclear Medicine (KIRAN) was published in 2009, it revealed ASIR of 0.40 in males and 38.2 in females of age limit 0-75 years with a percentage of 0.97 and 38.2 respectively **[40].**

The study of Faisalabad shows a total 3275 number of breast cancer patients registered in 2012 with an ASIR rate of 0.02 in males and 6.54 in females with an age limit of 15-35 **[41].** In Pakistani females different types of breast cancer are present. In Karachi, during the period of (2010-2015), the total number of breast cancer cases was 3930 the number of breast cancer in females of age limit 0-75 years is 3889 with a percentage of 49.5 and ASIR of 87.9. In Pakistan, TNBC occurs most commonly, 636 cases from SKMCH & RC were analyzed their 10-year outcome analysis revealed (56.2 %) had their diagnosis made at less than 40 years of age; 30.5 % of the cases had TNBC **[42].** During the period of (2010-12), a study in Lahore showed the total breast cancer patients of age limit 0-75 are 4152 among these 4082 are females and 70 are males with ASIR of 0.8 and 47.6 respectively. **[43].** The data from 7 7-year period (2004-2011) of the Karachi Institute of Radiotherapy & Nuclear Medicine (KIRAN) was published in 2014 and shows 5331 breast cancer registries. **[31]**. The study conducted at SKMCH during the period of (1995-2005) shows the 8915 number of breast cancer registries **[17].** The study conducted by Kareem et al in Faisal Abad in 2012 revealed that 245 breast cancer registries **[41].** Karachi Cancer Registry (KCR) shows the 709 number of breast cancer during (1995-1997) (38].

Table 2: Age-specific incidence rate of breast cancer in Pakistan [17,39,10].

Study population	**Age Specific Incidence Rate (A S I R)**							**Period**
	Age Limit	Male			Female			
		Total	%among all	ASIR	total	%among all	ASIR	
Lahore	0-75	70	1.0	0.8	4082	45.0	47.6	2010-12
Karachi	0-75	-	-	-	3889	49.5	87.9	2010-2015
Faisalabad	15-35	4.05	0.7	0.02	6.83	43.8	6.54	2012
KIRAN	0-75	32	0.97	0.40	3243	99.0	38.2	2000-2008
SKMCH & RC	0-75	-	-	-	-	45.9	-	1995-2009
INMOL	-	-	-	-	-	41	-	2002-2009

Table 3: The frequency of cancer in different areas of Pakistan.

Study Population	**No. of all cancers**			**No. of breast cancer**			**Data duration**
	Total population/ year	Male %	Female %	Total no.	Male %	Female %	
Lahore	100,000	57.2	42.7	4152		-	2010-2012
Karachi	100,000	41.9	58.1	3930	1.04	98.9	2010-2015
Faisalabad	100,000	35.9	64.1	245	0.41	99.5	2012
INMOL	100,000	43.6	56.4	6718	2.05	97.5	2002-2009
KIRAN	100,000	48.1	51.9	3275	0.98	99.0	2000-2008
Agha Khan	100,000	-	-	53,012	0.09	99.9	1991-2001
APCR	100,000	91.6	96.0	-	-	22.4	1992-2002
Northern Pakistan	100,000	-	-	2397	5.88	94.1	1992-2001
IRNUM Peshawar	100,000	61	39	-	-	-	2000-2004
Karachi South	100,000	50.6	49.4	-	-	-	1995-1997
AUKH, Quetta	100,000	-	-	-	0.7	13.0	1998-1999
SKMCH & RC	100,000	-	-	34038	-	-	1995-2009

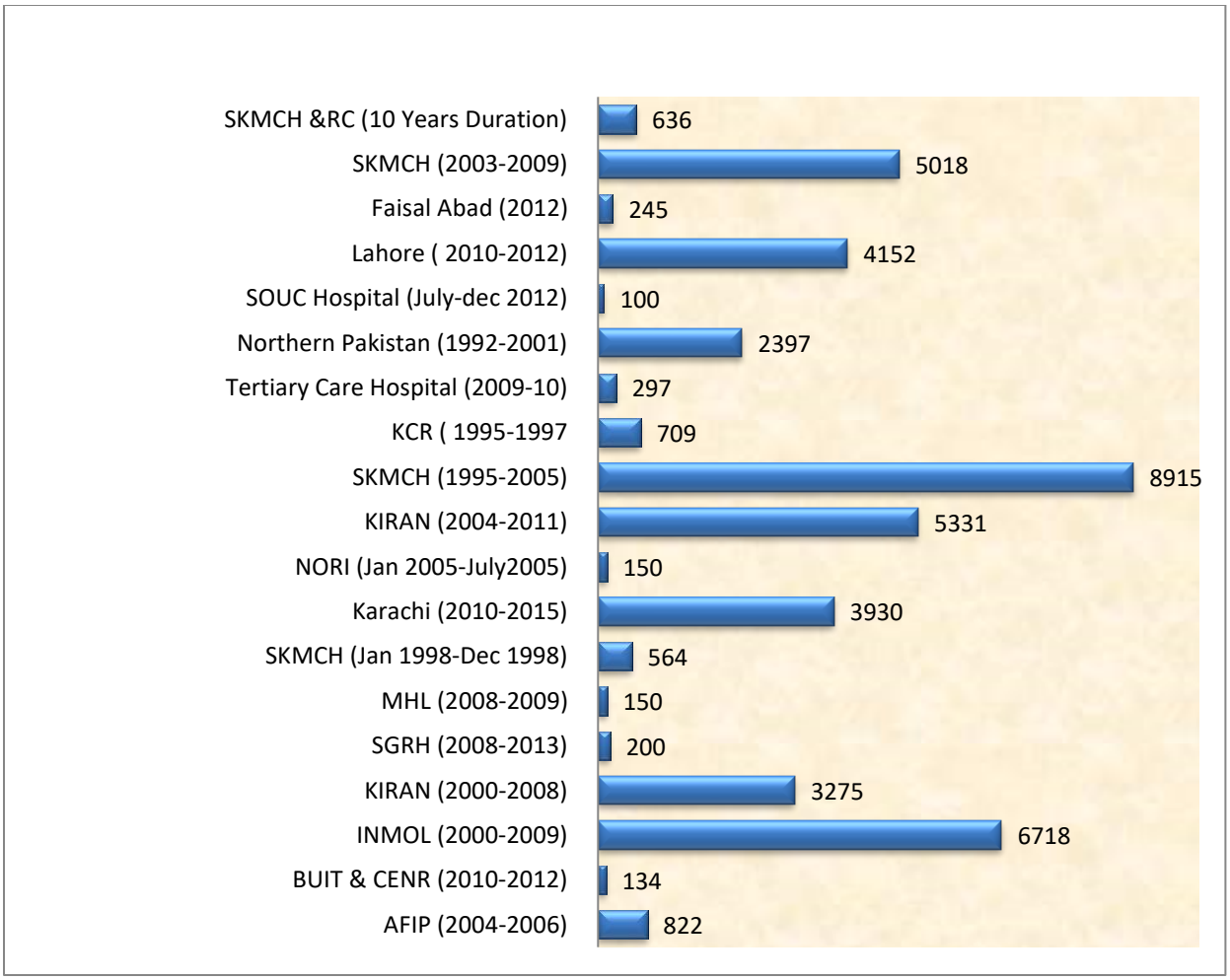


Figure 3: The registries of breast cancer in different areas of Pakistan**.**

Data from 9 years period (2000-2009) of the Institute of Nuclear Medicine and Oncology Lahore (INMOL) was published in 2012, it shows the 6718 number of breast cancer **[16]**. In Balochistan University of Information Technology (BUIT) and Center of Excellence for Nuclear Medicine (CENR), 134 breast cancer cases were registered during the period of (2010-2012) [44]. A two-year data of Armed Forces Institute of Pathology Rawalpindi (AFIP) during (2004-2006) revealed 822 breast cancer patients registered. Figure 1 shows the prevalence of heterogeneous subtypes of breast cancer in different areas of Pakistan. Infiltrating ductal carcinoma 37% (40-49 years) and 81% in the age range of (48 years) ductal carcinoma in situ 16.25% mucinous carcinoma 0.52% in filtering lobular carcinoma 0.34% papillary carcinoma 0.17% in the age range of (48 years). Another study conducted in Peshawar revealed the percentage of subtypes as infiltrating ductal carcinoma 82.60% mucinous carcinoma 2.17% filtering lobular carcinoma 6.50% papillary carcinoma 4.35% invasive lobular carcinoma 6.50% medullary carcinoma 2.17% in the age range of (40-59 years). Another clinical survey at the National Cancer Institute Karachi revealed the prevalence of infiltrating ductal carcinoma in the age group of (30-66 years) is 91%. Afridi and Ahmad revealed in their findings the prevalence of invasive intraductal carcinoma in the age group of (31-53 years) is 94% in Karachi. A study conducted in Karachi by Bhurgri revealed the prevalence of breast cancer subtypes in the age group (48-95 years) 92.10% benign lumps and 1% ductal carcinoma in situ **[45].**

WORLDWIDE DISTRIBUTION

Globally breast cancer (BC) is the frequently occurring malignancy of females. In all study populations breast cancer incidence rates are progressively high with time. In Southeastern Asia

rates were relatively increased and became gradually lower alongside a south-to-north slope. The most frequently diagnosed cancer in females is breast cancer worldwide; it is the malignancy of breast tissue. Breast cancer is stated in 23% of all cancer cases globally. Breast cancer is the most frequently diagnosed female cancer in the United States cancer, 1 of 8 females are affected by it. Through different people there is extensive variation in the incidence of age-standardized breast cancer globally, in Western Europe, the incidence is 89.9 per 100,000 women, and in Eastern Africa 19.3 per 100,000 women. Breast cancer is the most frequently occurring malignancy and a principal reason for death in females all over the biosphere. According to a current inspection, in Asian countries about 25 % of all cancer cases have been recognized as transmissible factors. Women's breast cancer incidence is intensely associated with age, signifying a relation with hormonal prominence. Pakistani females between ages 20 to 35 years are recurrently stated with advanced stages of breast cancer in Karachi hospitals in contrast to worldwide studies. Globally Breast cancer among women is the second most principal cancer among females. In Pakistan breast cancer is the most commonly identified cancer, with the maximum mortality rate in the Asian population next to the Israeli Jews. The breast cancer incidence rate is analogous to the uppermost risk areas in the biosphere. The most frequent malignancy is breast cancer because of the overall risk of its development among white women with approximations of 1 out of 8 American women and 1 out of 12 British **[46].**

ASR of female breast cancer in Pakistan as compared to the Asian population is described in different studies. According to the studies conducted the ASR of female breast cancer in Pakistan is 69 per 100,000 **[31]** In Kuwait 46.7/100,000, in Philippines 47/100,000, in Malaysia 38.7/100,000, in Russia 45.6/100,000, in Japan 51.5/100,000 in China 22.1/100,000 in Israel (Jews) 80.5/100,000 in Singapore 65.7/100,000, in Bahrain 42.5/100,000, in Turkey Izmir 22.4/100,000, in India 22.9/100,000, Iran 28.1/100,000, in Cyprus, Bangladesh and Afghanistan ASR is 78.4/100,000, 21.7/100,000 and 35/100,000 respectively **[47]**

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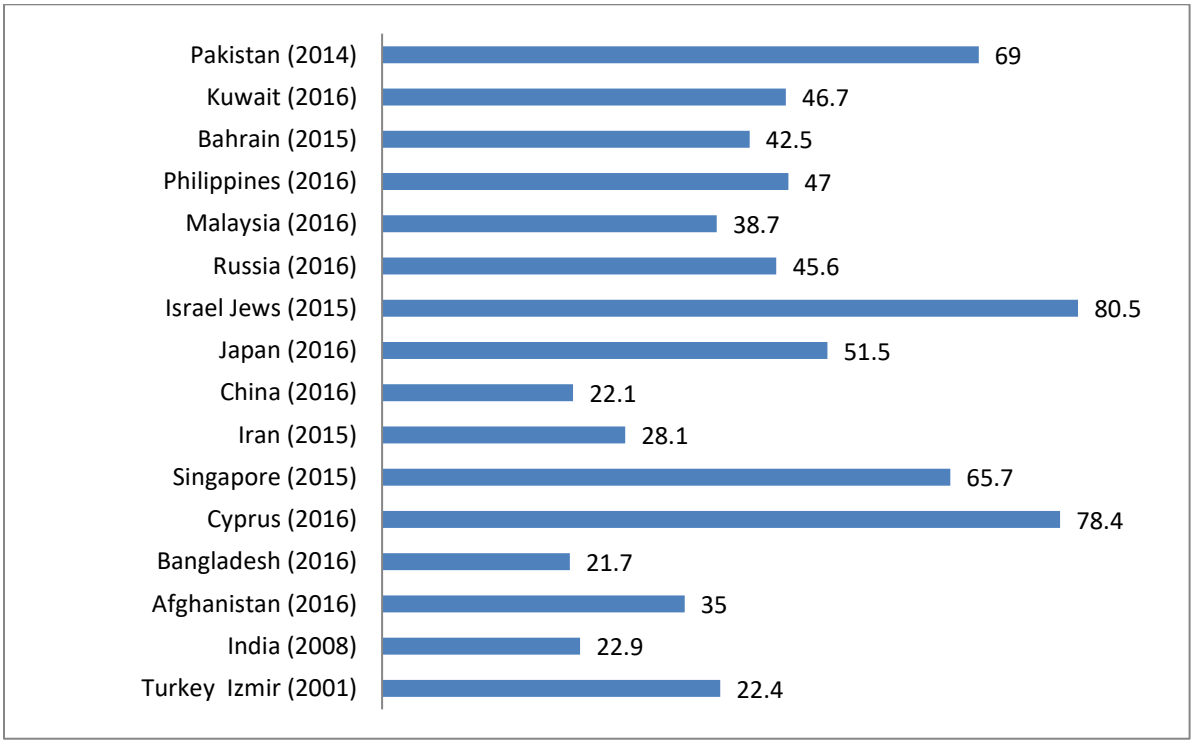

Figure 4: Age-standardized incidence rates (ASR)/100,000 for breast cancers in Pakistan compared to the Asian population.

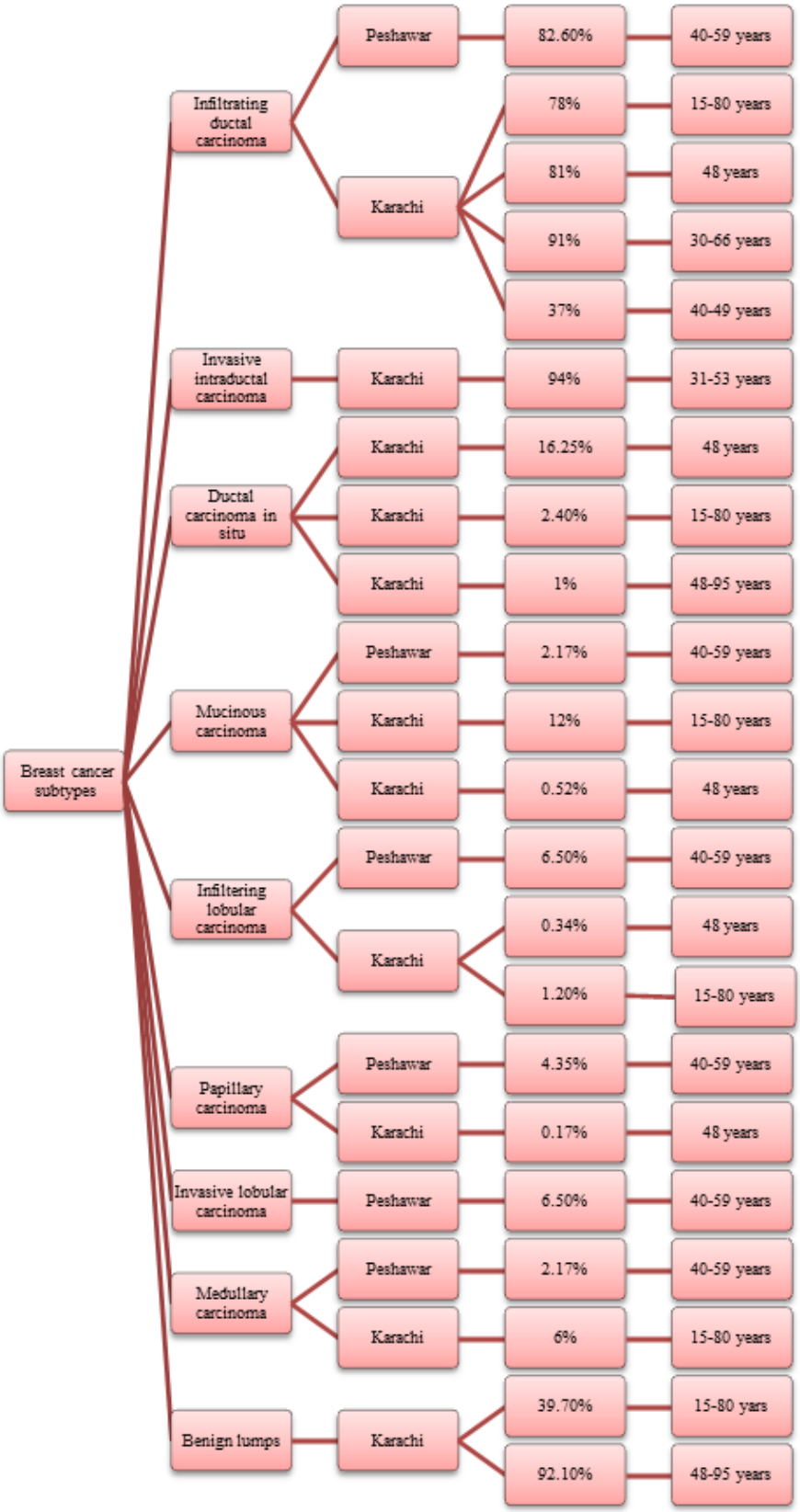

Figure 5: Subtypes of breast cancer.

CONCLUSION

Breast cancer is a major health burden. It persists despite many research studies conducted to understand and evaluate the genetics and risk factors behind breast cancer and to control the breast cancer incidence rate. In conclusion, this review article established the fact that many breast cancer risk factors are involved in increasing the prevalence of breast cancer in Pakistan.

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