

A Scoping Review on the Status of Female Breast Cancer in Asia with a Special Focus on Nepal

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Abstract: This study aimed to provide updated evidence on the status of female breast cancer and cancer treatment facilities in Asia, with a special focus on Nepal. This review used search phrases that included, breast neoplasm or cancer, health status, epidemiology, breast cancer survivors, cancer care facilities, Asia, Nepal. Researchers examined databases from January 2011 to December 2020 (PubMed, PMC, Google Scholar, and the reference lists of included papers). Studies of any design and reviews, were included in the study, except for qualitative studies. The study findings are presented in a narrative synthesis format using Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension for Scoping Reviews. An initial search resulted in 974 papers, and 896 were reviewed after being checked for duplication using the Zotero software. Accordingly, utilizing the inclusion and exclusion criteria, 188 publications were selected, and after review of titles and abstracts, an additional 98 papers were removed for different reasons. Finally, the study looked at 90 female breast cancer papers. Results showed that the number of cases of breast cancer is growing all around the world, including in Asia and Nepal. Age, early menarche, late menopause, nulliparity, positive family history, excessive fat consumption, alcohol, and smoking are all frequent risk factors for breast cancer found in Asian women. Breast self-examination, clinical breast examination, and mammography screening are common methods for detecting breast carcinoma. Chemotherapy, radiation, and modified mastectomy are commonly used options for treatment. The number of breast cancer survivors is growing throughout the world, indicating better clinical care. There is a paucity of survival data in many Asian countries, including Nepal. There is also a scarcity of health workforce specialized in cancer care and treatment, as well as a few health facilities that are available to treat cancer cases in many Asian countries, including Nepal.

Keywords: accessibility to cancer care, epidemiology, incidence, cancer survivors, risk factors, Nepal, treatment

Introduction

Breast cancer (BC) is the most commonly diagnosed malignancy and the foremost cause of death among females. In 2020, an estimated 2.3 million (11.7%) new cases and 684,996 (6.9%) deaths were recorded around the globe.¹ BC, a major women's health issue, has been gaining attention as its incidence and mortality are rising, comprising the fifth leading cause of cancer mortality.²⁻⁴ According to estimates in 2012, around 21.2% of women of Asian countries had breast cancer,⁵ which reached 22.9% in 2020.^{1,6} Breast carcinoma has been identified as the third-ranked cancer among both sexes in Nepal, accounting for 9.6% of total cases, and the second most common cancer among females, comprising of 1973 (17.1%) new cases and 1049 (7.7%) of all female life demises due to breast cancer.⁷

Some changeable and non-controllable risk factors are linked to breast neoplasms.⁸ Factors that cannot be changed, such as hereditary and genetic variables, account for 5% to 10% of mammary carcinoma.⁹ Furthermore, early menarche, late menopause, the use of artificial hormones, alcohol use, obesity, and reduced physical activity are some of the known risk factors for breast carcinoma.^{1,8-10} Screening measures, such as mammography, breast awareness programs, and clinical breast examination, followed by appropriate and timely treatment, are critical to early identification of cases.^{1,11}

Breast cancer cases are managed by a multidisciplinary team, and this multidisciplinary approach in Nepal,¹² has led to an increased survival rate. However, the availability of health facilities is considered very poor,¹³ and recorded data of women living with breast cancer in Nepal¹⁴ is still missing.

The following research questions were formulated:

1. What evidence is available on the status of breast cancer among women in Asia and Nepal?
2. How are the cancer health services delivered in Nepal?

The review's findings are narratively explained and compare the statistics with westernized data, particularly with Europe and the United States. There are very few review articles available in terms of breast cancer status and characteristics in Nepal. Thus, this review reported the broader and systematic picture of breast cancer epidemiology in the context of Asia, especially Nepal, including cancer care delivery and survival status. The information presented in this review was useful to gain a better understanding of the context of breast cancer in Nepal, Asia and would be of value to policymakers in Nepal and some other Asian countries to implement population-based breast cancer registries, improving screening programs, cancer care facilities, as well as, human resources, and research in the next few years. Altogether, those actions will ultimately lead to better access to health facilities, improving the outcomes for breast cancer patients in Nepal.

Materials and Methods

The studies that were mainly focused on the epidemiological characteristics of breast cancer incidence, mortality, risk factors, screening measures, management, breast cancer survivors, cancer care infrastructure, or health care delivery system were included in the review. Academic journal articles published from January 2011 to December 2020, unpublished thesis or reports, written in English, involving women, describing the epidemiological characteristics and concepts of breast cancer survivors were included. Papers that did not focus on epidemiological characteristics of breast neoplasms or qualitative studies were excluded from the review. The review process and final review article followed Peters et al scoping review standards,¹⁵ as well as Tricco et al 2018 recommendation of the "Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist".¹⁶

The literature search was performed in the following databases PubMed Central, Google Scholar, and PubMed to retrieve studies that contained information about the status of breast cancer within Asia and Nepal. To gain access to all related studies, the search was also conducted by nation name. In addition, searches for published papers from the World Health Organization, official websites, as well as bibliographies from included papers were also conducted. As can be seen in Table 1 a search was performed using keywords separately for each database and then combined using "OR" and "AND" Boolean operators. The keywords included the following terms: breast cancer or neoplasm, health status, epidemiology, breast cancer survivors, cancer care facilities, Asia, Nepal and based on three concepts: breast cancer status, breast cancer survivors, and health care delivery services or cancer care facilities, and a combination of these terms separately with publication date limits of last 10 years (2011–2020). A draft search strategy and outcome of the PubMed database searches is provided in Additional file 1.

Results

Out of 974 papers, 896 were chosen for review after being checked for duplication using the Zotero software. Following the first search, 708 articles were eliminated after being screened for title and abstract, 188 publications were chosen, and 98 papers were removed for various reasons.

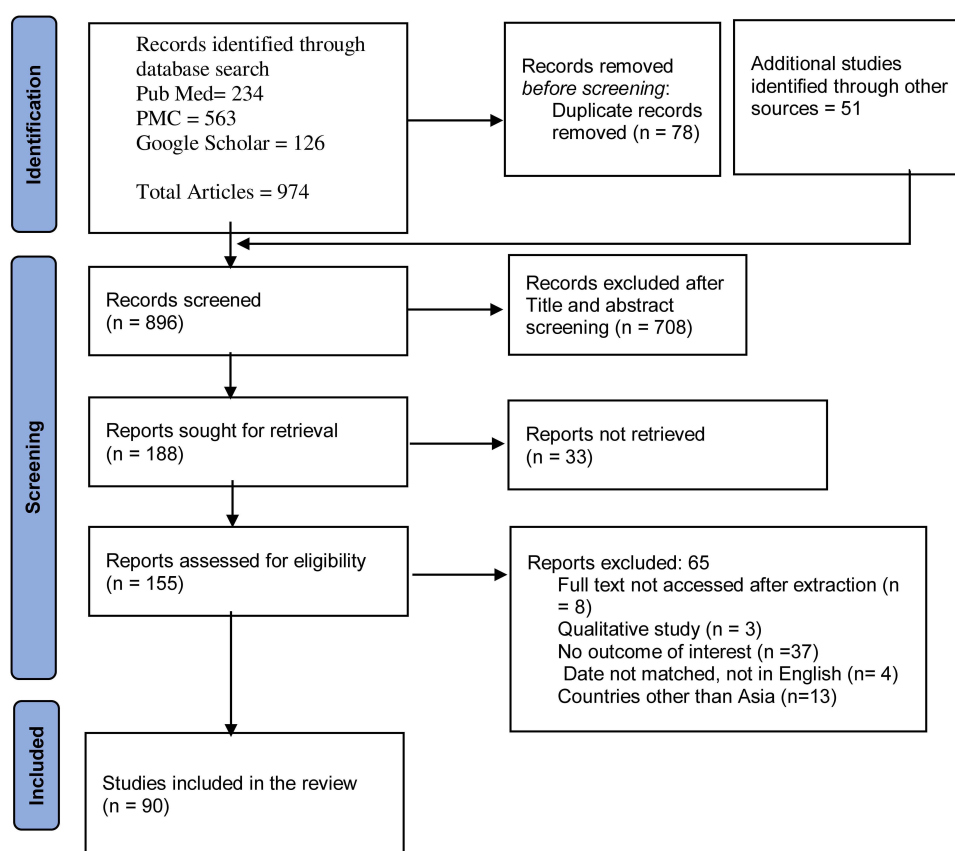
Finally, the study looked at 90 female breast cancer papers that were published in English between 2011 and 2020. Key trends are narrated in the seven categories: incidence or prevalence, mortality, risk factors, screening, treatment, survival, and cancer care facilities or delivery systems. Figure 1 depicts the literature evaluation and selection.

Table I Search Strategy Details

Search Strategy	Details
Inclusion criteria	Participants (P): Female BC of any age, stage, treatment Concepts (C): (concept 1) status of breast cancer or health status indicators of breast cancers (mortality, incidence or prevalence, risk factors, screening, treatment) Concept 2: Breast cancer survivors or survivors' trends Concept 3: Access to health services or cancer care facilities Context (C): Asia, Nepal
Exclusion criteria	P: Pediatric population C: not mentioned epidemiological features of breast carcinoma, awareness study and study that does not talk about trends of breast cancer survivors status and health care delivery services or access to a cancer care facility C: Europe, Africa, South America, North America, Antarctica, Oceania
Language filter	English
Time filter	2011–2020
Sex	Human, Female

Incidence or Prevalence

Breast carcinoma was identified as the most prevalent cancer in females in 2012, with an projected 1.7 million new cases, accounting for 25% among all malignant cases globally. In many nations, such as South America, Africa, and Asia, the

**Figure 1** Flow diagram of the study selection process.

incidence of breast cancer is on the rise. In the year 2012, 793,700 breast cancer cases were diagnosed in developed countries, while developing countries had 882,900 cases of breast tumors.¹⁷

Breast carcinoma is the most frequent malignancy among women in East Asia, Southeastern Asia, and Pacific Islands countries.¹⁸ There were 651 thousand new cases of breast cancer have been documented in Asia. The highest new cases were reported in Eastern Asia (277.1 thousand), followed by South Central (223.9 thousand). Furthermore, the south-eastern region had the second lowest number of breast cancer cases (107.5 thousand), whereas Western Asia reported the lowest number of cases (42.5 thousand).^{19–21} In Europe, 464.2 thousand new cases were reported in 2012, and the lowest reported cases were from Northern Europe (78.2 thousand). Western Europe had the second highest number of cases of breast cancer (161.5 thousand), followed by Central and Eastern Europe. Southern Europe had the second lowest number of new cancer cases (100.8 thousand).^{19,20} Western Asia had the highest age-specific incidence rate (ASIR) for breast cancer (42.8), followed by south-eastern Asia (34.8), south-central Asia (28.2), and eastern Asia (27.0). Overall, the Asian region had 29.1 ASIR.).^{19–21} Moreover, in Europe, Western Europe had the highest age-specific incidence rate (96.0) followed by Northern Europe (89.4), Southern Europe (74.5) and the lowest one in the central and eastern European regions. Overall, on an average, European region had the 71.1 ASIR in 2012 (Table 2).^{17,20,22}

The UN regions divide Asia into different sub-regions that include Eastern, Southern, South-Eastern, Central, Western, and South Central Asia. In Southern Asia, there are nine countries: Afghanistan, Bangladesh, Bhutan, India, Iran (the Islamic Republic of), Maldives, Nepal, Pakistan, and Sri Lanka.²³ Nepal is in the South-central Asia according to UN Regions in Global Cancer Observatory Survey (GLOBOCAN).

As shown in Table 3, among the southern Asian countries, India recorded the highest number of cases of breast cancer (144,937), followed by Pakistan (34,038), Bangladesh (14,836), Iran (9795), Sri Lanka (3955), Afghanistan (3108),

Table 2 Comparison of Age-Standardized Incidence Rate and New Cancer Cases of the Breast by Regions in 2012

Area	New Cases	ASIR	Area	New Cases	ASIR
Asia	651.0 ²²	29.1 ^{19–21}	Europe	464.2 ^{19,20}	71.1 ^{17,20,22}
Eastern Asia	277.1 ^{19–21}	27.0 ^{19–21}	Central and Eastern Europe	123.6 ^{19,20}	47.7 ^{17,20,22}
South-Central Asia	223.9 ^{19–21}	28.2 ^{19–21}	Northern Europe	78.2 ^{19,20}	89.4 ^{17,20,22}
South-Eastern Asia	107.5 ^{19–21}	34.8 ^{19–21}	Southern Europe	100.8 ^{19,20}	74.5 ^{17,20,22}
Western Asia	42.5 ^{19–21}	42.8 ^{19–21}	Western Europe	161.5 ^{19,20}	96.0 ^{17,20,22}

Abbreviation: ASIR, age-standardized incidence rate (per 100,000), new estimated cases (thousands).

Table 3 Age Standardized Incidence Rate and New Breast Cancer Cases by Country of Southern Asia, 2012

Country Name	Cases	ASIR
Pakistan	34,038	50.3 ²⁴
Afghanistan	3108	35.1 ²⁴
Maldives	41	31.6 ²⁴
Sri Lanka	3955	30.9 ²⁴
Iran (Islamic Republic of)	9795	28.1 ²⁴
India	144,937	25.8 ²⁴
Bangladesh	14,836	21.7 ²⁴
Nepal	1716	13.7 ²⁴
Bhutan	13	4.6 ²⁴

Abbreviation: ASIR, age-standardized incidence rate.

Nepal (1716), Maldives (41) and Bhutan (14). Further, with regard to the Age Standardized Incidence Rate (ASIR), Pakistan had the highest (50.3) followed by Afghanistan (35.1), Maldives (31.6), Sri Lanka (30.9), Iran (28.1), India (25.8) and Bangladesh (21.7). Nepal had the second lowest ASIR (13.7) of breast cancer and Bhutan had the lowest (4.6) in the year 2012.²⁴

As seen in Figure 2, in 2012, breast cancer was found in significant numbers in some west Asian populations, with the highest ASIR in Lebanon (78.7), Jordan (61), and Kuwait (46.7) respectively, and the lowest ASIR was found in Oman (26.0).²⁵

As depicted in Figure 3, among the 50 most populous nations, globally, breast carcinoma ranked 1st by number of incident cases in 2013, 3rd ranked among developed nations, and 1st ranked in developing countries. In Asian countries, breast cancer is the fifth most common cancer in China and fourth cancer in North Korea, and Vietnam, third most common cancer in Thailand, Afghanistan, and Bangladesh, whereas it was the first most common cancer in India, Nepal, Pakistan, Indonesia, Malaysia, Myanmar, and Philippines.²⁶

Breast cancer was detected in 17,877 (15.5%) of 108,894 individuals in Korea before the age of 40. It is prevalent among both the young and the elderly. However, an increase in breast cancer cases was seen among those over age 40.²⁷

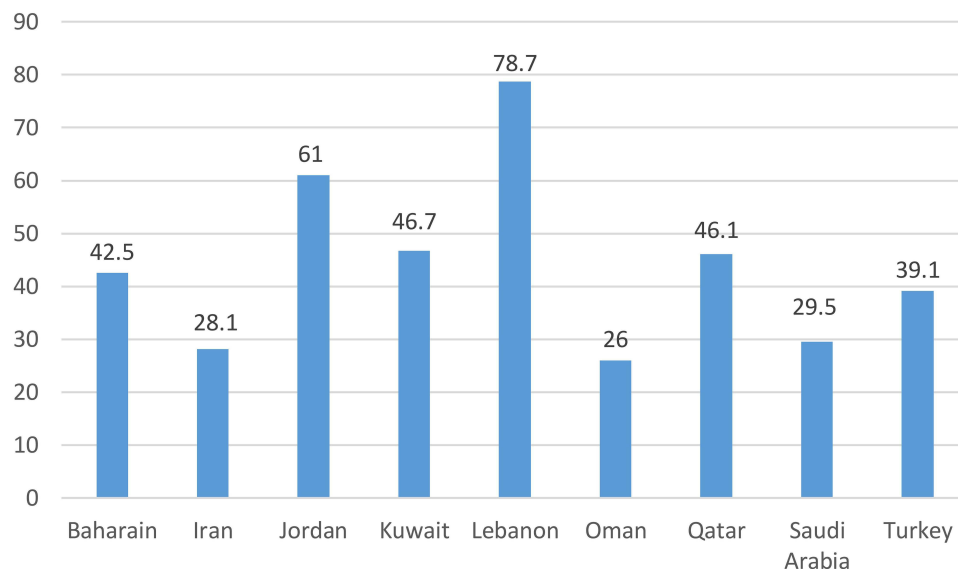


Figure 2 Age standardized rate of female breast cancer incidence in the West Asian countries, 2012.

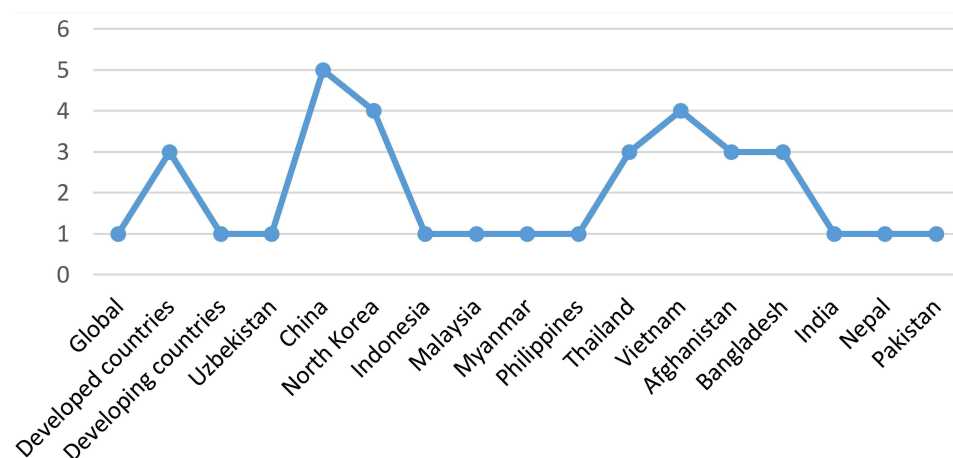


Figure 3 Breast cancer ranked globally and in Asian Regions in 2013.

According to a study from the National Institute of Cancer Research Hospital (NICRH), Bangladesh, there were 5255 recognized breast cancer cases between 2005 and 2010 and the average age of the patients was 41.8 years.²⁸ An article published in 2012 on the causes of breast cancer in China found that exposure to reproductive factors in 2001 accounted for 9671 (6.74%) breast cancer cases and 2769 (6.90%) fatalities.²⁹ In China, an estimated 268.6 thousand new cases of female breast carcinoma were diagnosed in 2015³⁰ and in Pakistan's 18 nuclear energy cancer centers across four province, 4486 female patients were diagnosed with mammary cancer in the 2015–16 year.³¹ Mongolia had a low incidence rate of mammary tumor in 2008 with 92 cases. The age-standardized rate of breast malignancy was 8/100,000, the lowest in the world.³² Breast carcinoma is the most prevalent form of malignancy in women there in Western Pacific. High-income nations and territories, as well as Pacific Island countries and places, have a particularly high prevalence.³³

Breast malignancy was discovered in 3062 Afghan women (15.7%) in 2018. A study conducted in Afghanistan between 2015 and 2019 from 650 patients with breast lesions, 24% were diagnosed with breast cancer when cytology tests were performed, with an average age of cancer diagnosis being 43.6 years and the earliest age being 20 years.³⁴ Breast cancer has been more common among Arab women over the last 26 years, with 45,980 new cases and 20,623 deaths reported in 2016 in the region.³⁵ Aggressive breast tumors were reported 19,755 in Sri Lankans in the years 2001–10. The patients were 53.1 years old on average. Breast cancer incidence has increased from 9.2% in 2001 to 12.9% in 2010.³⁶

Accordingly, based on the data from India's cancer registries, the incidence of breast cancer rose from 1982 to 2010. Thiruvananthapuram has a higher three-year moving average age-adjusted incidence rate (33.9) than any other city from 2003 to 2011, followed by Delhi with 29.6.³⁷ Between 1990 and 2016, the age-standardized incidence rate of breast cancer in India grew by 39.1%. In 2016, breast cancer was the primary or secondary major cause of cancer-related death among women in 28 Indian states.³⁸ The crude incidence of BC in Chelyabinsk region increased from 67.8 in 2006 to 93.9 in 2015, and urban prevalence being higher.³⁹

In 2017 and 2018, the global figure of breast cancer was also a leading cause of death among women,^{1,9,40–42} and this was equally true for Asian territories, with a high frequency in East Asia,^{40,42,43} with younger women in Southeast Asia being the most affected one in 2017.

As shown in Table 4, In terms of ASIR, in the Asian regions, Western Asia recorded the highest with 45.3, followed by Eastern Asia (39.2), South-eastern (38.1) and South-central Asia (25.9), whereas among European regions, Western Europe recorded the highest ASIR (92.6), followed by the Northern area (90.1), Southern Europe (80.3). The lowest was in Central and Eastern Europe (54.5) in 2018.⁹

When comparing the worldwide breast cancer incidence in 1990 to 2017, the incidence of breast cancer in 2017 was double that of 1990. Furthermore, ASIR in high socio-demographic index (SDI) nations stayed at the uppermost in 2017, reaching up to 40.99, almost quadruple that of low SDI nations, which remained at 11.62.⁴⁴

Every year, the actual and anticipated cancer incidence in Nepal showed a rising trend. The female cancer rates were higher than the male cancer rates.⁴⁵ A retrospective study conducted in Nepal in the year 2012 of five major hospitals found that breast cancer had the second-highest incidence and age-standardized rate (5.70) per 100,000 in females. The greatest risk of having breast cancer was found in the 45–49 years age group.¹³ According to hospital registries, breast cancer was the second most prevalent malignancy^{13,46} among Nepalese women between 2003 and 2013, consisting of

Table 4 Burden of Breast Cancer in the Asian and European Region in 2018

Asian Region	ASIR	European Region	ASIR
Eastern	39.2 ⁹	Central and Eastern	54.5 ⁹
South-Central	25.9 ⁹	Northern	90.1 ⁹
South-Eastern	38.1 ⁹	Southern	80.3 ⁹
Western	45.3 ⁹	Western	92.6 ⁹

Abbreviation: ASIR, age-standardized incidence rate.

15.6% in 2003 and 15.4% in 2013.^{46,47} Breast cancer incidence rates were 2.4 per 100,000 in 2003 and 5.1 per 100,000 in 2013.⁴⁶

In Nepal, an estimated 1700 new cases of breast cancer were detected in 2012, with an ASR of 13.7 new cases per 100,000 women,¹⁴ whereas an estimated 1973 (17.1%) new cases diagnosed in 2020,⁷ with an ASR of 13.9 new cases per 100,000 women.

Mortality

Breast tumor was one of the topmost causes of cancer-related fatalities in 2012, contributing for 521,900 fatalities globally, or 15% of all cancer mortality in women.¹⁷

As seen in Table 5, the number of people who died from breast cancer in industrialized nations was 197.5 thousand compared to 324.3 thousand in developing countries, indicating a high fatality rate.¹⁹ Breast cancer takes the lives of 231 thousand Asian women, with 104.7 thousand deaths recorded in South-central Asia, followed by eastern Asia with 68.5 thousand, South-eastern Asia with 43 thousand and the lowest in the western Asia 14.8 thousand.^{20,21} Furthermore, as seen in Table 5, European countries have a lower number of fatalities from breast carcinoma compared to Asian Countries. In the Asian regions, a high number of deaths was observed in south central Asia, while in Europe it was seen in Central and Eastern Europe (48.7 thousand). The second largest number of case fatalities was recorded in Western Europe (37.2 thousand), followed by the south (27.5 thousand) and Northern Europe (17.8) in the year 2012.¹⁹ In addition to this, age-standardized rates of mortality (ASRM) in 2012 showed that the high number observed in developed nations was 14.9 per 100,000 people compared to 11.5 in developing countries. Among Asian regions, the greatest number was found in western Asia (15.1), followed by south-eastern (14.1), south-central (13.5) and eastern Asia (6.1)^{20,21} whereas in Europe, the Central-eastern region recorded the highest ASRM at 16.5 per 100,000 people, followed by North (16.3), West (16.1) and Southern Europe 14.9.^{20,21}

As seen in Table 6, Pakistan had the highest Age Standardized Mortality Rate (ASMR), followed by Afghanistan, whereas Bhutan had the lowest standardized mortality of breast carcinoma. In terms of mortality, India had the most deaths, followed by Pakistan, and Bhutan had the fewest deaths, followed by the Maldives.²⁴ Breast cancer was the fifth biggest cause of female death worldwide in 2013. Furthermore, in South Asia, breast carcinoma is the ninth leading cause of death in Bangladesh, fifth in India, fourth in Nepal, third in Afghanistan, and second in Pakistan.²⁶

Breast neoplasm was the major cause of mortality among Chinese women in 2015, with 69.5 thousand cases.³⁰

As shown in Figure 4, in 2018, low Human Development Index (HDI) countries had the highest ASRM of breast cancer compared to high HDI countries. The HDI represents the overall picture of the country average accomplishment in key dimension of human progress in terms of life expectancy, education, and income levels, and can greatly affect provision of health care and standard of living.⁴⁸ Eastern and Western Europe had similar numbers of age-standardized deaths. Among the Asian regions, Southeastern Asia had the highest age-standardized death rate in the same year.⁹

Projections of breast cancer mortality (BCM) in five Asian nations showed that BCM increased over time. Aging was the most critical factor contributing to the increase in BCM in Asian Countries. According to BCM forecasts, mortality

Table 5 Estimated Breast Cancer Fatalities (Thousands) and Age-Standardized Rates Mortality by Region in 2012

Area	Mortality	ASRM	Area	Mortality	ASRM
Developing countries	324.3 ¹⁹	11.5 ^{19,21}	Developed countries	197.5 ¹⁹	14.9 ¹⁹
Asia	231.0 ¹⁹	10.2 ^{19,21}	Europe	131.3 ¹⁹	16.1 ¹⁹
South-Central Asia	104.7 ¹⁹	13.5 ^{19,21}	Central and Eastern Europe	48.7 ¹⁹	16.5 ¹⁹
Eastern Asia	68.5 ¹⁹	6.1 ^{19,21}	Western Europe	37.2 ¹⁹	16.1 ¹⁹
South-Eastern Asia	43.0 ¹⁹	14.1 ^{19,21}	Southern Europe	27.5 ¹⁹	14.9 ¹⁹
Western Asia	14.8 ¹⁹	15.1 ^{19,21}	Northern Europe	17.8 ¹⁹	16.3 ¹⁹

Abbreviation: ASRM, age-standardized rates mortality.

Table 6 Incidence and Age-Standardized Rate of Mortality Breast Cancer by Country of Southern Asia, 2012

Country Name	Deaths	ASRM
India	70,218 ²⁴	12.7 ²⁴
Pakistan	16,232 ²⁴	25.2 ²⁴
Bangladesh	7142 ²⁴	11.0 ²⁴
Iran	3304 ²⁴	9.9 ²⁴
Afghanistan	1695 ²⁴	20.6 ²⁴
Sri Lanka	1361 ²⁴	10.3 ²⁴
Nepal	865 ²⁴	7.2 ²⁴
Maldives	14 ²⁴	11.5 ²⁴
Bhutan	5 ²⁴	1.8 ²⁴

rates in Asian nations may continue to rise over time, particularly among the elderly. In comparison to other countries, Pakistan has the highest predicted BCM rates.⁴⁹ Breast cancer killed 870 women in Nepal in 2012, with an ASR of 7.2 deaths per 100,000 women,¹⁴ and 1049 died in 2020, with an ASR of 7.7 deaths per 100,000 women.⁷

Risk Factors

Many factors exacerbated women's susceptibility to breast cancer. According to Malaysian study, breast carcinoma in the family members; usually a first-degree relative (19%) and post-menopausal women (52%) were more likely to develop breast cancer.⁵⁰ A case-control study from Seoul (Korea) found that the menarche at a young age raised the risk of breast malignancy and the advanced age of the pregnancy, and that longer estrogen exposure prior to a full-term pregnancy was associated with a higher risk of hormone receptor-positive breast carcinoma.⁵¹ In Kolkata, India,⁵² researchers reported an increased breast cancer risk in women who were not getting adequate sleep or working night shifts.

One study from India showed that the highest number of breast carcinoma patients were seen in the age group of 40–49 years, seen highly in pre-menopause, high blood pressure, and high random blood sugar measurements.⁵³ According to the findings, from a meta-analysis of observational studies, postmenopausal women, following western dietary patterns⁵⁴ had an increased risk for breast cancer. Also, increased dietary fat consumption,⁵⁵ intake of meat, fat, and processed meat⁵⁶ raised the possibility of having breast carcinoma in Taiwanese women. Early menarche, late

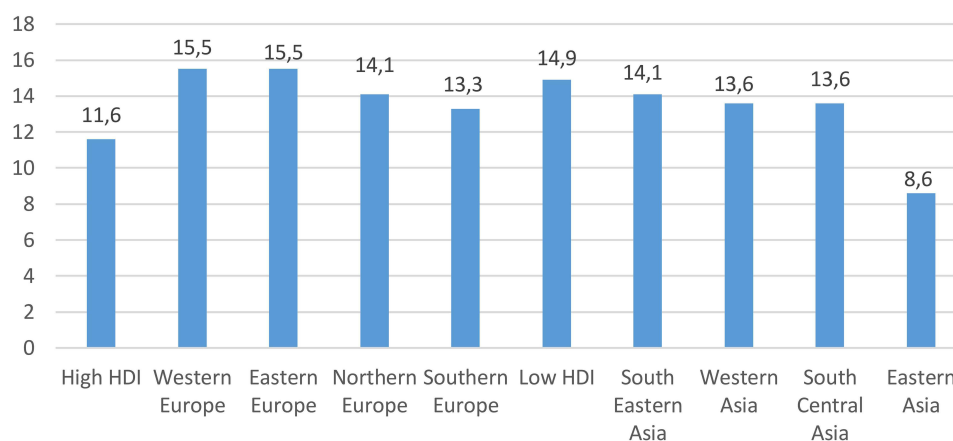


Figure 4 Distribution of age specific breast cancer deaths by region in 2018.

Abbreviation: HDI, Human Development Index.

menopause, delayed first child,^{5,14,57} high dietary fat intake, excessive alcohol consumption, hormone replacement therapy, smoking, and radiation exposure,^{5,58,59} Early first menstruation and pre-menopausal women,^{28,60} are some additional factors that raised the possibility of having breast cancer among Asian women. Also, women who are adopting Western lifestyles and dietary changes, shorter periods of breastfeeding and late first child birth are all of which are key predictors of a higher incidence of breast cancer in developing regions.^{14,61}

According to the clinical profile of Nepalese women with breast carcinoma, incidence was highest in Perimenopausal women (34.2%) between the ages of 41 to 50.⁶² In a study of Korean women, the dietary inflammatory index (DII) was found to be highly correlated with mammary cancer risk, with having high DII values associated to a greater threat of developing breast cancer in estrogen-positive and progesterone-positive individuals.⁶³ BRCA1, BRCA2, TP53, and CDH1 are genetic risk factors for invasive breast tumors.⁵⁷ According to a study conducted in Assam, India, showed that chewers of betel quid had a 2.35 fold increased risk of breast cancer than non-chewers.⁶⁴

Breastfeeding had the strongest anti-cancer effect, with mothers who had ever breastfed their child having a 35% lower risk of developing mammary carcinoma. After controlling for other risk factors, Malaysian women with a BMI of 23.0–27.4 kg/m² had a 33% lower risk of breast carcinoma, and those with a BMI of 27.5 kg/m² had a 53% less risk. One cup or more soy milk or soy product consumption per week also reduces the risk of breast cancer.⁵⁰ A plant based diet was reported to protect against breast malignancy in a study of Taiwanese women.⁵⁶ Another review stated that high levels of soy consumption and physical exercise that begin in adulthood lowered the risk of breast cancer. Also, evidence suggests that childhood food, adolescent alcohol consumption, and other characteristics are linked with breast cancer and premalignant proliferative benign lesions thus, preventive measures should begin at an early age.⁶⁵

Positive family history of breast cancer, younger age at menarche, older age at first live childbirth, estrogen users has significantly associated risk factors with breast cancer in a study from Singapore.⁶⁶ In addition, non-Malay ethnicity, parental histories of breast tumor, diagnosed of non-cancerous mammary illness, earlier age at first menstruation, fewer live births, bigger breast density, and a high BMI were all connected to an increased chance of getting breast cancer, according to study from Singapore.⁶⁷

A study among Asian and white British women in the UK found that Asian women had a lower risk of breast cancer related to reproductive and hormonal factors than British women. The cause could be that British women had earlier first menstruation, were nulliparous, used hormone therapy, and drank more alcohol than Asian women.⁶⁸

Furthermore, breast cancer is very common in premenopausal Nepalese women. Breast cancer is usually related to young premenopausal women, late menarche, early first-term pregnancy, high dietary fat, excessive alcohol consumption, hormone replacement treatment, smoking, and radiation exposure are all linked to an elevated risk of breast cancer in Nepalese women, almost similar with other Asian countries.¹⁴

Screening

As frequency of breast carcinoma is increasing in Southeast Asian women, there is a need for early diagnosis and high-quality techniques.⁶⁹ Only 2.2% of women aged 40–69 years who took part in the 2003 World Health Survey from 15 developing countries underwent breast cancer screening in the past five years. Breast cancer screening rates vary by country, ranging from 0% in Mali to 26% in Congo.⁷⁰

There are many countries that do not have country-wide population-based breast cancer screening programs in Asia. Some Asian countries, such as Korea, Japan, Singapore, China, and Taiwan, have begun population-based breast cancer screening services; Biennial mammographic screening is suggested in Korea starting at the age of 50.⁵ Breast self-examination (BSE), Clinical Breast Exam (CBE), and mammography are the most common screening modalities used in low-income countries to identify breast cancer.^{71,72} According to the World Bank 2020, Afghanistan is categorized as a low-income country. Sri Lanka, Bangladesh, Pakistan, India, and Nepal are low-middle income countries, whereas China, Thailand, and Malaysia are upper middle-income countries, while Singapore and Taiwan are high-income countries.⁷³ Table 7 show the common screening modalities based on Low-to high income countries below.

Furthermore, Middle-resource countries (MRCs) frequently used BSE and CBE as early detection screening methods to identify breast cancer. However, evidence suggests BSE has not improved breast cancer mortality and suggests BSE

Table 7 Most Common Breast Cancer Screening Modalities in Asian Countries

Low-Income Countries	Middle-Income Countries	High-Income Countries	Nepal
BSE, Clinical Breast Exam, Mammography ^{71,72,124} Breast Ultrasound ¹²⁴	Breast Self-Examination, Clinical Breast Exam ^{74,75}	CT Scan, MRI, PET ⁷⁴ Mammogram, ^{125,126} Breast USG FANC, CNB, VAB ¹²⁷ Genetic testing ¹²⁶	BSE, Ultrasound Mammography, Breast Ultrasound ¹⁴ FNAC, Biopsy

Abbreviations: FNAC, Fine Needle Aspiration Cytology; VAB, Vacuum-Assisted Biopsy, CNB; Core Needle Biopsy; USG, Ultrasound.

should be a part of breast cancer awareness program. BSE and CBE are recommended in the absence of mammography screening in low-and middle-income countries (LMICs) countries.^{74–76}

Breast self-examination, ultrasonography, MRI, and mammography are the most commonly used screening methods in Nepal.¹⁴ In addition with this, positron emission tomography (PET) scan, and diagnostic immunohistochemistry (IHC) services also available in Nepal.⁷⁷ A study from Tokyo, Japan regarding seeking cancer-related information and screening behavior found that out of 200 Nepalese migrants, 29 (14.5%) performed cancer screening, among them 8 (4%) performed mammography screening for breast cancer.⁷⁸

Treatment

Breast surgery, breast-conserving surgery, sentinel node biopsy, radiation therapy, brachytherapy, cytotoxic drugs like anthracyclines, and endocrine therapy are commonly available treatments in lower-MRCs.⁷⁴ Table 8 describes the commonly utilized treatment modalities based on low to high income Asian countries and Nepal.

An analysis of data from 1990–2007 of two teaching hospitals of Malaysia and Singapore found that 97% of women received loco-regional, systemic, or a combination of both treatments for breast cancer. Surgery was used to treat non-metastatic breast cancer stages 0 to III, with 70% of cases requiring a mastectomy and 30% requiring breast conserving surgery.⁷⁹ According to a Hong Kong study, out of 7449 breast cancer patients treated between 1997 and 2001, 55.8% were treated with chemotherapy. Radiation therapy was given to 60.2% of the patients, while tamoxifen was given to 85.7% of those with ER-positive tumors.⁸⁰ The most prevalent treatment strategies utilized in Nepal include modified radical mastectomy, breast-conserving surgery with post-radiation, radiation to the chest wall after mastectomy, systemic therapy with cytotoxic drugs, hormone therapy, Tamoxifen for hormone receptor-positive cases, and immunotherapeutic agents. Palliative treatments such as opiate analgesics for pain relief, glucocorticoids for inflammation or discomfort caused by nerve compression, non-steroid anti-inflammatory drugs are used to manage the cancer case.¹⁴ In Nepal, B.P Koirala Memorial Cancer Hospital offer services for all types of cancer, as well as radio-diagnosis imaging and nuclear medicine.⁸¹

Table 8 Breast Cancer Treatment Modalities Used in Low-Middle to High Income Countries in Asia

Low- Middle Income Country	High Income Country	Nepal
BCS ^{36,74} Brachytherapy ⁷⁴ Cytotoxic drugs ¹²⁸ Endocrine therapy ⁷⁴ Mastectomy ^{33,36,74,128} Radiation therapy ^{33,36,74} Sentinel node biopsy ^{33,36} Axillary node dissection ¹²⁸ Lumpectomy ¹²⁹	BCS ^{79,87} Mastectomy ^{83,87} Chemotherapy, Neo- adjuvant chemotherapy ⁸⁰ Radiation therapy ⁸⁷ Hormone therapy, Tamoxifen ^{80,87}	BCS ^{14,62} Radical or simple mastectomy ¹⁴ Radiation therapy ^{14,62,77} Systemic therapy with cytotoxic drugs ^{14,62} Hormone therapy, Tamoxifen ¹⁴ Immunotherapeutic agents ¹⁴

Abbreviation: BCS, Breast Conserving Surgery.

In a study in Pakistan in 2016, the age range of women with breast cancer was between 26–64 years, with a peak around 46–55 years. The clinical staging of the cancer in these patients T3N1M0 (31.5%), T4N0M0 (14.6%), T3N0M0 (12.4%) and T3N2M0 (11.2%).⁸² A study from Nepal showed that out of 114 patients with breast cancer, the majority of women were aged between 41–50 years. Regarding receptor status, the majority (64.0%) were Estrogen receptor (ER) and Progesterone receptor (PR) negative, 21.9% were both ER and PR positive, and 9.6% were ER negative and PR positive, while 4.4% of patients were ER positive and PR negative. Clinical staging of their breast cancer showed that 26.3% of patients were at stage III, 42.1% at stage II, 6.1% at stage IV and only 5.4% of cases were at stage I.⁶²

Survival

Female breast cancer has a greater survival rate than most other forms of female cancer, with most patients in industrialized nations living for at least 5 years after diagnosis. There is limited information available for Asia, which generally indicates much lower rates of survival compared to developed countries.⁸³ Underdeveloped countries have limited survival statistics, and the available ones are consistent with observed variations in incidence and death. In comparison to the United States and Sweden, LMICs such as Brazil, India, and Algeria have considerably lower five-year survival rates for breast cancer.⁶¹

Female breast cancer survivors or “Pink Warriors” numbers vary within Asia. China, Korea, and Japan had the highest five-year relative survival rates for breast cancer (>80%), followed by Taiwan, Singapore, and Turkey (75–80%), Thailand, Israel (non-Jews), Jordan, Saudi Arabia (60–65%), Philippines (58–59%), and India (51%).²⁰ Also, a study from Malaysia and Singapore⁷⁹ found that breast cancer stage 0 to II has 82.5% 5 year-survival compared to 30.2% in women with other stages of cancer. Another Malaysian study found that patients with stage I, II, and IV breast cancer had a five-year survival rate of 98%, 95%, and 36%, respectively.⁸⁴

Retrospective analysis of 1997–2001 data from Hong Kong, Southern China found that relative survival, cancer-specific survival, and disease-free survival in patients with invasive breast cancer were 84%, 85.2%, and 81.2% respectively. Furthermore, at 5 years, stage-specific relative survival was 97.5%, 87.8%, 66.2%, and 19.3% for stages I, II, III, and IV, respectively.⁸⁰

For the years 2000 to 2005, the overall 5-year survival rate of breast cancer patients in Malaysia was poor. It was 49.4% with an average of 68.1 months. Furthermore, among the ethnic groups, Indian women had a better survival (54.2%) compared to Chinese women (49.1%), and Malays (45.1%) recorded the lowest survival.⁸⁵ Malaysian women had a lower survival rate of 69% compared to Singapore’s 80%. The survival rate increased from 1993 to 2007 in both Malaysian and Singaporean women, from 62 to 79% and 73 to 81%, respectively, in a study reported by Sexana et.al.⁸⁶ Another Singaporean study discovered that the 1, 3, and 5 years overall survival (OS) rates were 99.8%, 98.7%, and 97.1%, respectively.⁸⁷

Between January 2005 and December 2009, 868 women were diagnosed with breast cancer in Malaysia, with an overall survival rate of 43.5%, with Chinese, Indians, and Malays having 5-year survival rates of 48.2%, 47.2%, and 39.7%, respectively. The percentage of survivors decreased as the phases progressed, with Malays (46%) being the most affected, followed by Chinese (36%) and Indians (34%).⁸⁸

Also, a study from Asian-American ethnic groups found that there were variations in the survival rate. Southeast Asian and Japanese women had better survival than Filipinos. Asian women had better survival rates than whites.⁸⁹ Another Southeast Asian study discovered that Chinese women had the highest five-year overall survival rate, followed by Indians and Malays.⁹⁰ In the years 2012–15, a Chinese study discovered a high survival rate of breast cancer of >60%. Female breast cancer patients’ survival rates increased from 73% in 2003–05 to 78.8% in 2006–08, 79.5% in 2009–11, and 82% in 2012–15. Surprisingly, patients with breast cancer in rural settings have a higher survival rate than those in urban ones.⁹¹

In a study from Kazakhstan, they found that out of 253 cases, 5-year survival was 18.2%.⁹² In a study in Korea, the overall cohort’s 3-year survival rate was 56.4%, with a median survival of 44 months. Over 24 years, the survival pattern altered dramatically, with a substantial increase in total survival. For patients with breast cancer diagnosed, the three-year survival rate increased from 38.7% in the 1990s to 50.5% in 2000–2004, 57.3% in 2005–2009, and 70.1% in 2010–2014.⁹³

According to a Jordanian survey, a total of 533 individuals with breast cancer over the age of 50 had a 5-year survival rate of 67.6%, with survival being greater for patients with non-metastatic illness.⁹⁴

Cancer Care Facilities

As the prevalence of breast cancer rises, there is an urgent need for the implementation of preventive and treatment services. There is a need that every woman has equitable access to cancer care, from testing to effective therapy.⁹⁵ Cancer care facilities include a specialized multidisciplinary public and private health cancer center that provides comprehensive oncology services.⁷⁴

According to Hossain et al.^{28,96}, there are 14 functional radiotherapy centers, and around 500 beds are allocated for cancer treatment, which is insufficient for Bangladeshi patients. All cancer patients in Bangladesh are diagnosed and treated in two public hospitals, a few private hospitals, and 14 oncology units of public medical teaching hospitals. In 1960s, the Pakistan Atomic Energy Commission (PAEC) established a several hospitals within the country that provide cancer treatment. There were 21 dedicated cancer specialist hospitals that offered treatment for all cancer types and 50 general hospitals where only chemotherapy and radiation services are available.⁹⁷ Cancer care is provided by the National Cancer Institute of Sri Lanka, a specialist cancer hospital, along with, seven university-affiliated and eleven general hospitals.⁹⁸

A population-based cancer registry was established in 2018, and it now includes around 20% of Nepal's population. In 2003, the first hospital-based registers were established, and there are now 12 such registries across the nation. Nepal has three Government financed cancer hospitals. They are: 1. B.P Koirala Memorial Cancer Hospital, 2. Bhaktapur Cancer Hospital 3. Sushil Koirala Prakhari Cancer Hospital.^{77,81} A few public hospitals also offer cancer treatment, including surgery and basic chemotherapy. Only two private clinics provide positron emission tomography (PET) scan services throughout the nation. Several private hospitals provide cancer care services and some private diagnostic facilities that typically provide CT scan and MRI imaging services. There is just one public multispecialty hospital in Kathmandu, Civil Service Hospital, which treats hematologic malignancies and offers bone marrow transplantation.⁷⁷

Three specific oncology palliative care centers are also available in Nepal. Nepal has been classified as Group C Category 1 by the Hospice Palliative Care Alliance. The National Academy of Medical Sciences also offers radiotherapy, teletherapy, brachytherapy and palliative therapy. Now most cancer hospitals have their own palliative service section. B.P. Koirala Memorial Cancer Hospital and Tribhuvan University Teaching Hospital, Nepal's largest interdisciplinary academic medical institution. One private laboratory, offers diagnostic immunohistochemistry (IHC) services. The majority of IHC requests are handled by some private laboratories which send the sample to Indian laboratories and receive the results in a couple of weeks.⁷⁷

Both the public and private health sectors are providing health services in Nepal. Public health services are delivered through district, zonal, and regional hospitals. There are district public health offices and centers. Also, primary health care centers, health centers, and health posts are offering public health services. Private hospitals, medical colleges, and other institutes offer private health services. So, generally, patients visit any of the nearest health centers and receive consultation from healthcare providers or doctors. Patients are referred to oncology hospitals when their health care providers suspect they have cancer. There is a lack of a uniform strategy for referring cancer patients.⁸¹ The Nepal government provides nearly \$1000 USD to each cancer patient as a financial help which is directly transferred to the cancer hospital.⁷⁷

Discussion

Breast cancer rates and mortality are both high in many Asian nations, and they fluctuate over time. Similarly, high frequency is observed in Sub-Saharan Africa, which is due to a lack of awareness and late-stage detection, as well as gender norms and spirituality,⁹⁹ almost the same reasons that are present in Asian countries.

Also, the USA has a high rate of invasive breast cancer 232,340 with a mortality rate of 39,620 in 2013,¹⁰⁰ which increased in 2015,¹⁰¹ and 2017.¹⁰² One in eight (12.8%) women in the United States are at risk of getting breast cancer during their lifetime, and 1 in 39 (2.8%) will die.¹⁰³ Overall, there are 268, 600 invasive breast cancer cases and 41,700 death in the United States in 2019, and, it is the second largest cause of cancer fatalities among women,¹⁰³ and incidence

of female mammary carcinoma and death rates are expected to rise in 2021, with 281,500 new cases and 43,600 deaths,¹⁰⁴ similarly breast cancer cases and deaths are expected to rise in coming years. It is the second most common cancer among females.⁷ In 2018, South Central Asia had the highest death rate due to breast cancer, with 123,060 cases. China was the leading country, with 97,972 deaths, followed by India 87,090.¹⁰⁵ In the year 2020, among the European region, Western Europe (15.6) had the highest ASR of mortality due to breast cancer per 100,000 females. Also, in the same year, among the Asian regions, Western Asia (16.0) had the highest ASR of deaths due to breast carcinoma.¹

As a consequence of improved medication and diagnosis, breast cancer mortality has reduced in many high-income countries,¹⁰⁶ but for many low and middle-income nations, this is not the case where the death rate is still high due lack of diagnostic setup and adequate treatment facilities. Age, early menarche, late menopause, first child beyond 30 years, high dietary fat intake, excessive alcohol consumption, hormone replacement treatment, smoking, and radiation exposure are all variables that raise the risk of breast cancer in Asian and Nepalese women,^{1,5,14,28,35,57,59} similar with the western countries. In the UK, it was found that a genetic history of breast cancer was found to increase the risk of breast cancer when compared to individuals those who did not have a family history,¹⁰⁷ another study from the UK found that smoking was linked to an increased risk of breast cancer, with a significantly higher risk associated with women who had a family history of breast cancer.¹⁰⁸ Also, Breast cancer risk is linked to age, menarche, smoking, and a family history of cancer, according to an Afghanistan survey.¹⁰⁹

In Queensland, Australia, insufficient physical activity, a high BMI, alcohol use, and being on hormone replacement treatment are all risk factors for invasive breast cancer in women aged 45 to 69 years.¹¹⁰ In research from the United States, women with previous in situ breast cancer who were older at menarche had a higher chance of getting a second primary breast tumor.¹¹¹ Breast cancer is linked to earlier pubertal development and menarche in UK.¹¹²

The Asian population's peak mammary carcinoma age is 40–49 years, which is different from that of Western nations. Screening programs used in industrialized countries may not be practical in Asia.⁵ In comparison to Western countries, only a few Asian nations have population-based breast cancer screening programs. CBE, BSE, USG, mammography screening are the common screening measures used in India,¹¹³ and Nepal¹⁴ whereas the imaging diagnosis of BC includes bilateral mammography and ultrasonography of the breast and surrounding lymph glands, and triple assessment is recommended (clinical assessment, mammography and/or ultrasound and biopsy) during the initial consultation to the breast clinics in many European states.¹¹⁴ Almost every European country has adopted digital mammography as a screening tool. Mammography screening programs for aged 50 to 74 years old in Europe reduce breast cancer mortality by 25–30%. Switzerland, Cyprus, Austria, Denmark, Germany, and Finland are some examples that have nation-wide breast cancer screening programs.¹¹⁵

In America, breast cancer is treated with breast-conserving surgery, mastectomy, chemotherapy, radiation therapy, and targeted therapy.^{116,117} In Asian countries, practically all women are treated with the same therapeutic management, although it is not accessible to everyone. Breast cancer is treated in India using a modified radical mastectomy, radiation, chemotherapy, and adjuvant treatment,¹¹³ also Nepal has used multidisciplinary treatment strategies similar as India.¹⁴ Targeted cancer therapy using immuno-modulatory medicines is one of the most advanced therapeutic options for breast cancer in developed countries like USA.¹¹⁸

The recovery rate of breast carcinoma around the world has varied. A study from the US found that insurance status increases the accessibility to screening services and treatment facilities that improve the survival rate.^{119,120} In Asian American women, the number of breast cancer survivors is also increasing.¹²¹ The five-year survival rate from a study by Yip et al⁷⁵ from 2000 to 2014 data revealed an increase in breast cancer warriors in China, Korea, Japan, India, and Thailand in succeeding years, but a drop in survival in the years 2010–14 in Malaysia compared to 2005–09. Asian Americans have 91.1% survival in the US compared to other ethnicities such as African Americans, American Indians.¹⁰⁰ Because of advancements in treatment and earlier detection, the overall five-year relative survivability rate of female patients with breast cancer has enhanced. Breast carcinoma has a 5-year, 10-year, and 15-year relative survival rate of 89%, 83%, and 78%, respectively.¹²²

Cancer care services are delivered in Nepal through cancer specific public hospital and some general public and private hospitals. But, there is a lack of data on the survival of breast cancer.⁸¹ There is a need for well-developed cancer

related facilities in Low-and Middle-income countries. These countries also require an additional specialties like diagnostic radiology, cardiac, respiratory medicine and psychiatric units.¹²³

The cancer survival data for many Asian nations is scarce. Many Asian countries do not have sufficient cancer treatment centers, human resources, equipment, and prices are not affordable for many people. This review has many strengths and limitations. The review examines the descriptive epidemiology of female breast cancer in Asia and Nepal. This study gives an overall insight into breast cancer epidemiology. This type of review study was conducted in Nepal for the very first time. Also, this study helps to identify the gaps in breast cancer status and provide future research areas. The study's limitation is that the results are limited by narrative synthesis rather than critical analysis.

Conclusion

The incidence rates of breast cancer and death are rising in many Asian countries that threatens the health of Asian population. Increased age, early menarche, delayed first menstruation, peri menopausal women and family history positive are common major risk factors associated with breast cancer in Nepal and Asia. In many Asian nations, including Nepal, there are no clear recommendations for breast carcinoma management, no national screening program, and a lack of breast survivor data. BSE, CBE, breast ultrasound and mammography are common diagnostic tests used for early identification and detection in Nepal. Unfortunately, when it comes to cancer care, health services and delivery systems in Nepal they are still in the early stages. Both public and private health facilities try to provide best possible cancer screening and treatment. There is a need to raise awareness and develop a community-wide early detection program, as well as a national screening program that covers the whole population of Nepal. Also, there is an immediate need for strengthening the existing screening and treatment facilities across the country, implementation of population-based breast cancer registries; and required a more trained oncologists and onco-nurses for improving patient care in Nepal. Further, research is suggested on individual components of the status of breast cancer so that evidence-based practices can be implemented in oncology centers to facilitate the treatment of breast cancer.

Abbreviations

ASIR, Age-Standardized Incidence Rate; ASMR, Age-Standardized Mortality Rate; BSE, Breast Self-Examination; CBE, Clinical Breast Examination; CT Scan, Computer Tomography Scan; HDI, Human Development Index; MRI, Magnetic Resonance Imaging; SDI, Socio-demographic Index.

Acknowledgments

All of the authors whose work was reviewed in the development of this manuscript are gratefully acknowledged. We would also like to thank Dr. Paul Johnson for his critical review and English proof reading.

Funding

There was no financial support received.

Disclosure

The authors report no conflicts of interest in relation to this work.

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