

Current Status and Future Projections of Breast Cancer in Asia

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Summary

Asia is the world's largest continent comprising about 3/5 of the human population. Breast cancer is the most common type of cancer and the second leading cause of cancer-related deaths among women in Asia, accounting for 39% of all breast cancers diagnosed worldwide. The incidence of breast cancer in Asia varies widely across the continent and is still lower than in Western countries, but the proportional contribution of Asia to the global breast cancer rates is increasing rapidly in parallel to the socioeconomic development. However, the mortality-to-incidence ratios are much higher for Asia than for Western countries. Most Asian countries are low- and middle-income countries (LMICs) where breast cancer presents at a younger age and a later stage, and where patients are more likely to die from the disease than those in Western countries. Moreover, diagnostic workup, treatment and palliative services are inadequate in most Asian LMICs. In this review, we present an overview of the breast cancer risk factors and epidemiology, control measures, and cancer care among Asian countries.

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Introduction

Asia as the world's largest and most populous continent comprises roughly 30% of the earth's land area and 60% of the human population. It includes 6 regions and 48 countries, most of which are classified as low- and middle-income countries (LMICs). Asia is a region with diverse ethnicities and cultures, large socioeconomic disparities, and greatly varying healthcare systems. Wide variations in breast cancer incidence and mortality exist between and within Asian countries. Overall, the incidence of breast cancer in Asia is still lower than in Western countries, but the proportional contribution of Asia to the global breast cancer rates is increasing rapidly due to rapid economic growth and urbanization and a rise in the population's socioeconomic status. Moreover, while the age-standardized incidence rate (ASR) of breast cancer in Asia is still only about 1/3 of that in the USA (29.1/100,000 in Asia versus 92.9/100,000 in the USA), the mortality-to-incidence ratios are much higher for Asia (0.35 vs. 0.16, respectively) [1].

The goal of this review is to highlight key areas of breast cancer epidemiology, care and outcomes in Asia.

Cancer Prevalence and Epidemiology in Asia

Breast Cancer Incidence

When discussing cancer incidence in Asia, it is important to note that only 20% of all Asian countries have population-based cancer registries, of which only 4 (8%), i.e. Japan, Korea, Singapore and Taiwan China, cover the entire population [2]. In the absence of representative data, informed use of the available data can still be a valuable tool for the development of cancer control policies.

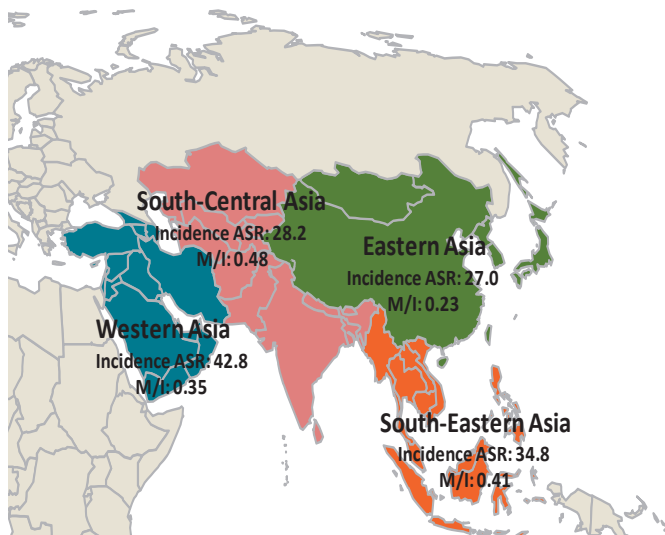


Fig. 1. Incidence and M/I ratio of breast cancer in the Asia region. Data are adapted from [1]. ASR = Age-standardized rate (per 100,000 women), M/I = mortality-to-incidence rate ratio.

For example, comparable age-specific incidence rates and trends have been observed in several Asian countries [3–5], indicating that rough patterns showing regional or rural/urban differences as well as trends over time are likely to be valid.

In 2012, > 600,000 new breast cancer cases were reported in Asia, accounting for 39% of all breast cancers diagnosed worldwide. Based on these estimated numbers, breast cancer is certainly the most common cancer among women in Asia, accounting for 21.2% of all cancer cases in women [6]. The overall incidence of breast cancer is lower in Asia (ASR of 29.1/100,000) compared to the average world level (ASR of 43.1/100,000), and even more so compared to some developed regions such as the European Union (EU; ASR 80.3/100,000) or the USA (ASR 92.9/100,000).

Breast cancer ASRs vary around 10-fold across Asian regions, with reported rates ranging from 27.0/100,000 in eastern Asia to 42.8/100,000 in western Asia (fig. 1, table 1). Japan and South Korea report the highest incidence rates of breast cancer for eastern Asia (51.5 and 52.1 per 100,000, respectively), whereas for south-eastern Asia the highest rate is noted in Singapore (65.7/100,000). The observed increase in breast cancer incidence rates also varies between different Asian countries, with increases of 6% per year seen in Japan compared to 3–4% per year in Shanghai China, Singapore and Thailand [7, 8].

Even within countries, there are notable differences in the incidence of breast cancer: In China, the highest rate occurs at the socioeconomically developed east coast region (e.g., an ASR of 46.6/100,000 in Guangzhou) [9]. By contrast, the ASR is estimated to be as low as 7.9/100,000 in the less developed south-western regions. In addition, the breast cancer incidence rates also vary by ethnicity: In Malaysia, a multi-ethnic country, the incidences rates are 59.7/100,000 in the Chinese population, 55.8/100,000 in Indians, and 33.9/100,000 in native Malaysians [10].

Table 1. Incidence and mortality of breast cancer

	Incidence ASR	Mortality ASR	M/I
World	43.1	12.9	0.30
High human development	45.2	14.7	0.33
Medium human development	26.5	9.8	0.37
Low human development	32.6	17.0	0.52
Asia	29.1	10.2	0.35
Eastern Asia	27.0	6.2	0.23
South-East Asia	34.8	14.1	0.41
South-Central Asia	28.2	13.5	0.48
Western Asia	42.8	15.1	0.35

ASR = Age-standardized rates (per 100,000 women), M/I = mortality-to-incidence rate ratio.

Data are adapted from [1].

Age at Diagnosis

In Asian countries, the age at diagnosis of breast cancer is substantially lower than in high-income countries [11], with a median of 53.9 years in Japan, 51 years in Korea [12], 48–50 years in China [8], and 48.3 years in Thailand [13]. For Asian-Arab countries, the median age at breast cancer diagnosis is even below 50 years, with 48 years in Oman [14], 45 years in Saudi Arabia [15], and 44 years in Jordan [16]. In Saudi Arabia, 26.4% of the breast cancers are diagnosed before the age of 40 years, compared to 6.5% in the USA [15].

The age at presentation has increased over time in Asian countries, which may be due to the fact that women of successive generations are increasingly exposed to risk factors, as well as to the introduction of mammography and ultrasound in women older than 50 years and an increased life expectancy. In Japan, the median age at diagnosis increased from 48 years in 1946–1959 to 53.9 years in 2000–2001. Similarly, in China, the median age at diagnosis increased from 47.5 years in 1990 to 50 years in 2007 [8], and the median age at diagnosis in Saudi Arabia increased from 40 years in 1981–1990 [17] to 45 years in 2002 [15].

Breast Cancer Mortality

In 2012, an estimated 231,013 women in Asia died from breast cancer, accounting for 7% of all deaths, and 40.8% of the cancer deaths, ranking second behind lung cancer in women. The age-standardized mortality rate of breast cancer in Asia is 10.2/100,000, which is lower than the global level of 12.9/100,000 and matching countries with medium human development. Similar to the differences in the incidence rates there are also large differences in the breast cancer mortality rates across Asia, ranging from 6.2/100,000 in eastern Asia to 15.1/100,000 in western Asia (fig. 1, table 1) [6]. In Malaysia (25%), the Philippines (23%), Indonesia (22%), Singapore (20%), and Japan (19%), breast cancer is the leading cause of cancer-related deaths. In these countries, the breast cancer mortality rates have been stable in recent years. In contrast, the mortality rates have increased in several countries, with the highest recorded increases noted in Thailand (7% per year from 2000 to 2006) and Malaysia (6% per year from 1997 to 2008) [18].

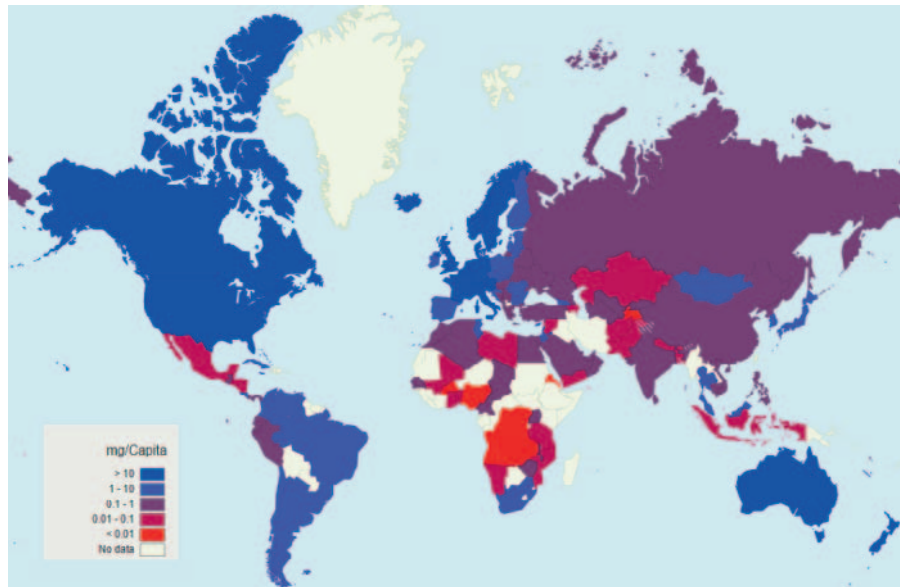


Fig. 2. Opioid consumption maps – morphine, mg/capita, 2012 [79].

The most suitable measure to compare outcomes for patients across countries is the age-standardized mortality-to-incidence rate (M/I) ratio. For breast cancer in Asia, it is 0.35, which is higher than the world average of 0.30, and also higher than expected from Asia’s human development index (0.33; see fig. 1, table 1) [6].

Breast Cancer Survival

Similar to incidence data, cancer survival data are not widely available for many Asian countries, and concerns regarding data accuracy apply as discussed above for incidence.

A recent worldwide cancer survival study compared the 5-year survival of cancer from 67 countries, including 16 Asian countries [19]. For women diagnosed from 2005 to 2009, the 5-year survival from breast cancer was 80% or higher in 5 countries within Asia, including China (80.9%), Israel (86.7%), Japan (84.7%), Korea (82.7%), and Qatar (85.3%). Survival was lower than 70% in Malaysia (67.8%) and India (60.4%), and very low in Mongolia (56.5%). The greatest increase in survival was observed in China, rising from 53.8% in 1995–1999 to 80.9% in 2005–2009. Survival increased little in Malaysia from 64.8% in 1995–1999 to 67.8% in 2005–2009, and similarly slowly, but starting at a much higher level, in Japan (81.8% in 1995–1999, 84.2% in 2000–2004, and 84.7% in 2005–2009) [19]. The breast cancer survival rates across Asia were consistent with the development of cancer health services and the gross national income (GNI) per head in the countries or regions.

Apart from between-country differences, disparities in survival can also be observed between different socioeconomic regions within Asian countries. For example, in China, the 5-year survival of breast cancer in Qidong was 58% in 1992, compared to 78% in its rural neighboring area of Shanghai [20]. In India, large differences were likewise noted in the survival of most cancers between rural, semi-urban, or small urban areas, whereas no differences were noted between different metropolitan areas, where healthcare

services are more generally available [21]. These large variations in survival within populations reflect large geographic, rural/urban, and socioeconomic disparities with varying levels of development of cancer health services. In addition, ethnic differences in breast cancer survival exist: In South-East Asia, the 5-year breast cancer overall survival is highest in Chinese women (75.8%), followed by Indians (68.0%) and Malaysians (58.5%) [22].

Risk Factors

In Asian populations, breast cancer is associated with some of the risk factors known from Western populations [23], including early menarche, late menopause, older age at first full-term pregnancy, and no breast-feeding, regardless of the region [24–29]. However, not all of these factors are similarly relevant in Asian populations. For example, a recent meta-analysis suggests that, although hormone replacement therapy is an important risk factor in Caucasians (odds ratio (OR) 1.13, 95% confidence interval (CI) 1.05–1.22), it is not associated with an elevated breast cancer risk in Asian women (OR 0.96, 95% CI 0.44–2.09) [30].

As for lifestyle factors, 2 meta-analyses have implicated soy and high isoflavone to be associated with a decreased risk of breast cancer [31, 32], with the greatest protective effects for hormone receptor-positive tumors [33]. Diabetes mellitus (OR 1.52, 95% CI 1.30–1.78) [30] and smoking were reported to increase the breast cancer risk [34], but not to a similar extent for all regions [35]. In contrast to reports from developed countries [36, 37], a higher body mass index is not associated with premenopausal breast cancer, but is linked to postmenopausal breast cancer in Asian populations [38].

Following sociocultural changes towards Westernized lifestyles, Asian women are now characterized by delayed childbearing and fewer children [8], less breast-feeding, a more sedentary workforce, and other Westernized dietary and lifestyle patterns [39]. These

changes increase the relevance of 'Western' breast cancer risk factors. Modifiable health behaviors in Asian populations thus include the maintenance of a traditional dietary pattern (high in rice, fresh vegetables, and soy) thought to be protective, in addition to enhanced physical activity and maintaining body weight [40].

Screening and Early Detection

As discussed, Asian populations display a peak in breast cancer incidence between 40 and 49 years of age. Therefore, screening programs that have been shown to be successful in Western countries probably cannot be implemented in a similar way in Asia because the efficacy of mammographic screening might be questionable in populations with a different epidemiology of breast cancer regarding age, risk factors, and ethnicity. In addition, cost also needs to be addressed in less developed populations with different cost-effectiveness thresholds. Finally, even if theoretically (cost-)effective, inadequate resources for a population-based screening equipment and the lack of human resources and quality control might still hamper the implementation of effective screening [23]. Finally, compliance with a population-based mammographic screening program is needed before showing a reduction in breast cancer mortality (as in Canada), and it is therefore unlikely for age, biologic and compliance reasons to achieve a reduction in mortality in Asia rivaling that shown in Western countries from these programs.

In most Asian countries, there are no national population-based breast cancer screening programs [23]. However, some Asian countries, including Korea [41], Japan [42], Singapore [43], China [44], and Taiwan [44, 45], have initiated population breast cancer screening programs: In Korea, biennial mammographic screening starting at age 50 years is being recommended [46]. Chinese recommendations include annual mammography for women aged 40–49 years, and every 1–2 years for those aged 50–69 years [47].

Chinese patients are often reluctant to visit doctors for regular health screening, frequently presenting only when advanced symptoms arise [48]. In several regions of Asia, including, for example, China and Malaysia, delayed presentation of breast cancer is often due to cancer fatalism, which leads to difficulties in the uptake of healthcare interventions, particularly those targeted at primary prevention [21, 49]. In addition, the belief in traditional and alternative therapies is widespread and sometimes hampers effective therapies [21, 49]. Reluctance to adopt the available healthcare is prevalent not only in eastern Asia: For example, in Saudi Arabia, 92% of the women aged above 50 years have never had a screening mammogram although health services are free of charge [50].

Strategies to improve early diagnosis of breast cancer in Asian populations are needed. In a study from India, clinical breast examination (CBE) done annually for women aged 40–60 years was estimated to reduce the mortality by 23.3%, similar to reductions achieved by biannual mammographic screening (25.8% for the same age group), but potentially at half the cost [51]. On the other

hand, a randomized trial from Shanghai reported no reduction in mortality from breast self-examination (BSE) after 10–11 years of follow-up, but a costly increase in benign breast biopsies [52]. Overall, most researchers agree that teaching BSE is useful for promoting the benefits of early diagnosis via enhancing public awareness [53].

If screening is found to be a cost-effective way of early diagnosis for specific Asian populations, different screening techniques from those used in Western populations might be indicated. In particular, it has been reported that a higher breast density in Asian populations might limit the sensitivity of mammography screening so that ultrasound screening, which is superior in dense breast tissue, might be more sensitive in Asian populations. However, evidence is scarce to support its use within a national screening strategy. A nationwide randomized trial in China has been undertaken comparing efficacy and cost in high-risk women aged 30–65 years screened by mammography, ultrasound, or both. Although ultrasound was shown to be superior in terms of accuracy and sensitivity [54], there is presently no sound evidence to justify the routine use of ultrasonography as an adjunct screening tool in Asian women at an average population risk for breast cancer [55]. Population-based studies of clinical breast examination combined with diagnostic ultrasound are ongoing in China [56].

Taken together, these factors indicate that mammography screening should be adopted prudently in Asian countries, considering regional risk factors, patterns of healthcare uptake, epidemiologic characteristics, and human and financial resources. In the current transition period of Asian economies, birth-cohort effects should be incorporated to quantify risk and identify high-risk groups. Furthermore, known regional, socioeconomic and particularly urban-rural disparities need to be addressed when screening programs are designed and implemented throughout Asia [21].

Stage at Presentation and Delayed Detection

Presenting with more advanced stages of breast cancer is related to poor prognosis and higher treatment cost [57]. The stage at presentation of breast cancer varies widely throughout Asian countries and within these countries. In less developed regions and countries, late stage at presentation is very common: For example, in India, more than half of all breast cancer patients present with stage III–IV disease [58]; a nationwide study in China showed that 15.7% of patients were diagnosed at stage I, 44.9% at stage II, 18.7% at stage III, and 2.4% at stage IV [59]. The proportion of stage IV patients in this study was likely greatly underestimated, as the presenting stage of disease is generally kept within surgical databases, which do not keep records of stage IV presentations. As another example of late-stage presentations, in Oman, 34.9% and 15.8% of patients were reported to have stage III or IV disease, respectively [14]. In contrast, in more developed countries or regions of Asia, women present with earlier stages of breast cancer: In Korea, 56% of breast cancers are diagnosed at a localized stage [60], and in Japan 90% of patients present with stages 0–II [61].

Across Asia, data on the stage at presentation from within countries also reflect large regional, ethnic, and socioeconomic disparities: In China, women living in Beijing are more likely to present with stage I breast cancer (27%) and are less likely to have stage IV disease (0.3% – which again is likely underestimated) compared to less developed regions (3% stage I and 5% stage IV) [62].

As Asian countries develop socioeconomically, offering better education and access to healthcare, a shift in stage at breast cancer diagnosis can be noted: For example, in Shanghai, cases detected early are increasing, with the proportion of stages 0–II rising from 78.6% in 1990 to 93.3% in 2007, whereas the share of stage III breast cancer gradually decreases. Correspondingly, the proportion of asymptomatic breast cancer gradually increased from 0.94% in 1990 to 6.8% in 2007, and non-invasive breast cancers increased markedly, representing 14.7% of all cases in 2007 [8].

Besides delays in diagnosis in less developed regions, long waiting times before initiation of treatment for newly diagnosed breast cancer are common in Asia. In Thailand, 17% of patients report a delay in medical consultation of longer than 3 months, and 42% of longer than 3 months, before seeing a doctor. Family income, education, previous breast symptoms, self-treatment, and travel time to the hospital were associated with a delay of treatment initiation [63]. In China, the median time delay for treatment is 1 month in wealthy areas, compared to 94 days in less developed western and central regions. In some undeveloped regions of China, delays of more than 1 year occur in up to 12–17% of patients [64–66]. These numbers are causing concern, as any effort to increase awareness and early diagnosis of breast cancer becomes irrelevant if timely treatment cannot be offered to patients.

Breast Cancer Treatment

Because of its cost and the need for specialized multimodality infrastructure and human resources, the variability in treatment standards offered to breast cancer patients in Asia is even greater than that of screening options. Of a total of 51 Asian countries, only 20 have some form of national cancer center, with research capacities in only a minority of these [2]. Treatment standards are strongly associated with socioeconomic development, whereby Asian countries can be classified into 3 categories according to per capita GNI income level: low-resource, middle-resource, and high-resource countries.

In low-resource countries such as Nepal, Pakistan, Mongolia, and Iraq, cancer diagnosis and treatment facilities are extremely scarce [2] and prognosis is correspondingly poor [67]. The biggest challenges in these countries are little community awareness of breast cancer, inadequate pathology facilities, and fragmented care systems with respect to radiotherapy and systemic treatment [68]. In Nepal, for example, there is only 1 national cancer hospital in addition to 5 specialized cancer hospitals, for a population of ~30 million people [69]. Half of all breast cancer patients present at late stages, with only 1% in situ cancers, 7% stage I, 41% stage II, 40%

stage III, and 10% stage IV [70]. Only 4 hospitals in the country have radiation equipment, which is available at very high cost to patients, and novel diagnostic procedures and targeted therapies are unavailable [69].

Most Asian countries such as China, India, Malaysia, Turkey, and Iran are categorized as middle-resource countries [2]. For these countries, the main challenges include the low quality of data registries, inadequate multidisciplinary coordination, and a lack of resource-appropriate prioritization of breast cancer control programs [68]. In parallel to the growing socioeconomic status, promising improvements in breast cancer treatment have been recorded in these countries over the past few decades. For example, in China, less invasive surgical modalities have been adopted and doxorubicin-based regimens are increasingly being used so that 81.4% of all patients with invasive breast cancer receive adjuvant chemotherapy [64], and the rate of breast-conserving surgery has climbed from 12.1% in 2005 to 24.3% by 2008 [64, 71]. However, treatment often does not concur with current international guidelines: Of those patients who receive breast-conserving surgery, 16.3% do not receive radiation therapy as per standard guidelines [72], and in China, 12.1% of the patients who receive adjuvant chemotherapy are given less than 4 cycles of therapy [64]. A Beijing study also reported that only 80.1% of hormone receptor-positive patients receive adjuvant endocrine therapy, while 9.2% of patients with hormone receptor-negative tumors are improperly prescribed endocrine therapy [59, 64].

Many drugs are not covered by insurance, leading to prohibitively high out-of-pocket expenses [73, 74] and limited treatment options, particularly for metastatic disease [75]. For example, ~80% of Chinese patients with human epidermal growth factor receptor 2 (HER2)-positive disease are not offered trastuzumab and newer targeted agents are not covered by insurance [64]. Consequently, patients with metastatic breast cancer have limited options, with only 40% receiving second-line treatment, and only 15% receiving third-line therapy for metastatic breast cancer. In comparison, 80% of breast cancer patients receive second-line treatment in Japan and 65% third-line therapy in the USA [76].

With these limitations and a lack of implementation of standardized management, the survival rates of breast cancer in Asia's middle-resource countries are considerably lower than those in high-resource countries. In addition, wide disparities between subpopulations within middle-resource countries remain, so that numbers on a national level often neither reflect the poor outcomes of a large share of disenfranchised populations nor the good outcomes of urban elites.

Japan, Korea, Singapore, and Taiwan belong to the group of high-resource Asian countries, with high breast cancer incidences and relatively favorable breast cancer survival rates [2]. These countries have well-established cancer control and cancer care systems with sufficient financial resources at the national level. The clinical characteristics and outcomes of breast cancer in these countries are quite similar to those in Western countries and treatment is standardized to a large extent [77].

Palliative Care

Although palliative care has become an integral component of healthcare systems in many developed countries of the world, it has yet to be established in most low- and middle-resource countries. The most recent global classification of palliative care provision categorizes countries into 6 groups. Within Asia, only Japan, Singapore, Taiwan, and Hong Kong have achieved advanced palliative care integration, while most Asian countries offer either limited or no palliative care services. China and India, which comprise about 2/5 of the world population, are categorized under Group 4a ('preliminary integration') and Group 3b ('generalized palliative care provision'), respectively. As yet, no Asian country offers ambulatory palliation, which has been shown in the Western literature to provide better quality of life for patients and their families, to be more cost effective and to prolong survival when compared to established in-patient palliation. Afghanistan, Bhutan, North Korea, and Laos have no known palliative care activities [78]. Even within countries offering some extent of palliative care on a national level, palliative services may only be available to urban populations [23].

One measure for the quality of palliative care across the world is opioid consumption, which is used by the World Health Organization (WHO) as a surrogate for pain management, particularly in cancer patients with severe pain. The morphine equivalence (ME) metric by WHO region (adjusted for population) allows for equi-analgesic comparisons between countries of the aggregate consumption of major opioids. These data show that opioid consumption in any Asian country has not nearly reached the extent of use in Europe or North America and it is particularly low in southern Asia (fig. 2).

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Conclusion

In parallel to the socioeconomic development in Asia and the subsequent shift from socio-communicable to non-communicable diseases, cancer is moving to the forefront of health threats to Asian middle-resource populations. With respect to breast cancer, the incidence rates are increasing, while healthcare systems are often ill prepared to deal with diseases such as this, requiring multidisciplinary, comprehensive care. While cancer care in some developed countries is comparable to US or European standards, late stage at presentation, cancer fatalism, poor diagnostic workup, and inadequate treatment and palliative services hamper most low- and middle-resource Asian countries.

Women with breast cancer in developing Asian countries present at a younger age, at later stages, and are more likely to die from the disease than those in Western countries. Furthermore, discrepancies in incidence, mortality, age at diagnosis, and stage at presentation exist within and between Asian countries. Breast cancer control efforts therefore need to be tailored to the local breast cancer epidemiology and healthcare resources and should include not only healthcare delivery but also promote awareness and early detection. In addition, breast cancer control strategies in developing Asian countries need to address the existing vast geographic and urban/rural disparities and specifically focus on the needs of underserved populations.

Disclosure Statement

The authors declare no conflicts of interest.

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