

RESEARCH ARTICLE

Differences in Incidence, Mortality and Survival of Breast Cancer by Regions and Countries in Asia and Contributing Factors

Yeonju Kim^{1*}, Keun-Young Yoo², Marc T Goodman^{3,4}

Abstract

Although the incidence of breast cancer in Asia remains lower than in North America, Western Europe, and Oceania, rates have been increasing rapidly during the past few decades, and Asian countries now account for 40% of breast cancer cases diagnosed worldwide. Breast cancer mortality has also increased among Asian women, in contrast to decreased mortality in Northern America, Western Europe, and Oceania. These increased rates are associated with higher prevalence of breast cancer risk factors (e.g., reduced parity, delayed childbirth, increased obesity) that have accompanied economic development throughout the region. However, Asian regions (western, south-central, south-eastern, and eastern) and countries differ in the types and magnitude of changes in breast cancer risk factors, and cannot be viewed as a single homogeneous group. The objective of this paper was to contrast the heterogeneous epidemiology of breast cancer by Asian regions and countries, and to suggest potential avenues for future research.

Keywords: Breast cancer - incidence - mortality - survival - epidemiology - risk factor - Asia

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Introduction

Breast cancer is the most common malignancy among women worldwide and in 140 of 184 countries, with an estimated 1.67 million estimated incident cases (Ferlay et al., 2013; Ferlay et al., 2015). The number of women with incident breast cancer in Asia was estimated at 651,000 in 2012, comprising 38.8% of all cases globally, followed by Europe (27.7% of all cases) and North America (15.3% of all cases). Of the 47 Asian countries discussed in this report, breast cancer is the leading malignancy among women in 39 of Asian countries, the second most common malignancy among women in 6 Asian countries, and the fifth most common malignancy in two countries, Mongolia and Bhutan (Ferlay et al., 2013).

Historically, breast cancer incidence has been highest in Northern America, Western and Northern Europe, and Australia/New Zealand, with rates ranging from 85.8 to 96.0 (Figure 1). [Note: All data in this report are expressed per 100,000 women, although only the rates are provided.] Breast cancer incidence rates in Asian countries are estimated at one-fourth to one-third of the rates in the traditionally high-risk countries, with an Asian average rate of 29.1 (Ferlay et al., 2013). However, in contrast to the overall stable rates in England (Westlake and Cooper, 2008), and in the United States (all ages, all race/ethnic groups combined) (DeSantis et al., 2014), breast cancer

incidence has been increasing sharply in Asia (Shin et al., 2010b).

A large body of scientific literature supports the notion that the recent increase in breast cancer incidence among Asian women in Asia is attributable to economic development and adaptation of a more 'westernized' lifestyle, including delayed childbirth, reduced parity and breastfeeding, weight gain, and increased consumption of animal fat (Yoo et al., 2006; Long et al., 2010b; Moore et al., 2010a; Moore et al., 2010b; Moore et al., 2010c; Salim et al., 2010; Forouzanfar et al., 2011; Bhoo-Pathy et al., 2013). While these changes in risk-associated behaviors undoubtedly explain some of the recent elevations in breast cancer rates in Asia, the magnitude of the annual percent change in incidence is discrepant between countries. For example, the age standardized incidence rate (ASIR) for breast cancer among South Korean women increased by 44.9% between 1993 and 2002; whereas, breast cancer rates increased by 24.2% among Singaporean women and 5.2% among Filipinas during the same time period (Shin et al., 2010b). Clearly, Asian countries differ in the types and magnitude of changes in breast cancer risk factors and cannot be viewed as a homogeneous group. In this study, we aimed to examine the heterogeneous characteristics of breast cancer epidemiology by regions and countries in Asia and discuss of the contributing factors of the phenomena.

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Materials and Methods

Data sources for incidence, mortality, and survival

Data from the International Agency for Research on Cancer (IARC) were used primarily in the comparison of breast cancer incidence, mortality, and survival between Asian countries, including GLOBOCAN 2012, Cancer Incidence in Five Continents (CI5), the WHO Cancer Mortality database, and SurvCan (information all available at <http://www-dep.iarc.fr/CancerMondial.htm>). These data were supplemented, where necessary, by national publications and research papers.

GLOBOCAN 2012

GLOBOCAN is a comprehensive cancer registry database which provides contemporary estimates of cancer incidence, mortality and prevalence at the national level for 184 countries (Ferlay et al., 2010; Ferlay et al., 2013). The latest version, GLOBOCAN 2012, was made available for analysis in late 2014 (<http://globocan.iarc.fr/Default.aspx>) (Ferlay et al., 2015). We adapted the GLOBOCAN 2012 categorization scheme which grouped 47 Asian countries into four regions: eastern (5 countries), south-eastern (11 countries), south-central (14 countries), and western (17 countries) (Table 1). Country lists in GLOBOCAN are based on United Nations' criteria, so Taiwan was not included as a separate sovereign nation. We reviewed the breast cancer rates for Taiwan from other sources (Chiang et al., 2010; Shin et al., 2010b) and added Taiwan to the list of eastern Asian countries.

Because GLOBOCAN 2012 compiles and systematically analyzes data from many countries throughout the world, it is the most useful and reliable source for cross-sectional comparisons of cancer incidence and mortality between countries. However, several countries included in GLOBOCAN lack population-based cancer registries and available population-specific information, so cancer rates for these countries were estimated by applying cancer rates and population profiles from neighboring countries (detailed information available at: http://globocan.iarc.fr/Pages/DataSource_and_methods.aspx). We were cautious in interpreting these data.

The comparison of cancer estimates from different versions of GLOBOCAN is not recommended because sources of data have improved and methodology has changed. Thus, CI5 and the WHO cancer mortality database were used to examine time trends in incidence and mortality rates.

Cancer in five continents (CI5)

The CI5 series contain incidence data collected from population based cancer registries deemed to be of acceptable quality (Parkin et al., 2010). In 2006, 12% of the world population and 8% of the Asian population were covered by population based cancer registries, but only 8% of the world population and 4% of the total population in Asia were covered by cancer registries that matched the inclusion criteria of CI5 (Ferlay et al., 2010). The CI5 series began in the 1960s with 32 registries and included Miyagi, Japan and Singapore (Chinese) as the

sole Asian populations. Registries from 17 Asian countries contributed data to CI5 volumes I-X, including Bahrain, China, India, Israel, Japan, Korea, Kuwait, Kyrgyzstan, Malaysia, Oman, Pakistan, Philippines, Qatar, Saudi Arabia, Singapore, Thailand, and Viet Nam. Trends in breast cancer incidence from available registries were calculated using an online analysis tool (<http://ci5.iarc.fr/CI5plus/ci5plus.htm>) available through 'CI5Plus' (Curado et al., 2007; Parkin et al., 2010).

WHO cancer mortality database

The WHO cancer mortality database, managed by IARC, contains selected cancer mortality statistics by country. The data were extracted from the WHO mortality databank, which includes deaths registered in national databases along with the underlying cause of death, as coded by the International Classification of Diseases (ICD). Trends in breast cancer mortality rates were illustrated using an online analysis tool available through the IARC website (<http://www-dep.iarc.fr/WHODb/WHODb.htm>).

Survival data: Survcan

The IARC published survival rates (SurvCan) from 27 cancer registries in 14 countries in Africa, Asia, the Caribbean and Central America. (Sankaranarayanan et al., 2011b) The objective of SurvCan is to provide a baseline for the evaluation of future improvement in cancer diagnosis and care in developing countries.

Results

Incidence overall in Asia

The ASIR for breast cancer among Asian women was highest in western Asia (42.8), followed by south-eastern

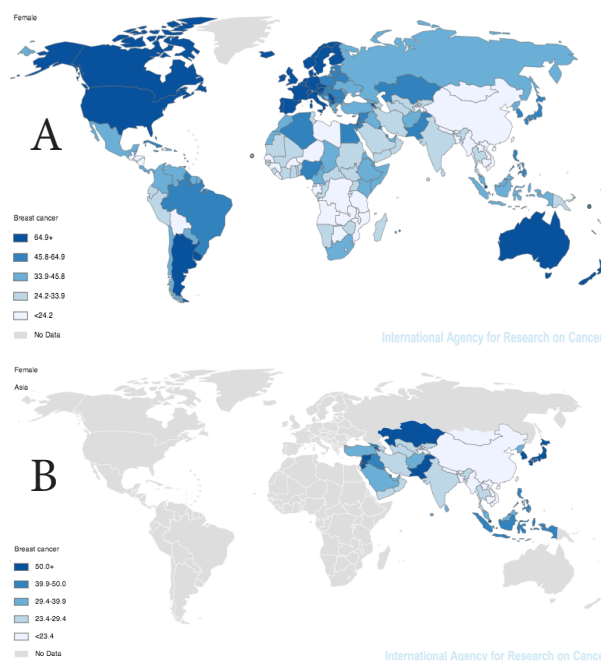


Figure 1. Age Standardized Incidence Rates (Per 100,000) of Breast Cancer among Women of All Ages Mapped by Countries and Colored by Quintiles from Globocan 2012 . (A) World (B) Asia

Asia (34.8), south-central Asia (28.2), and eastern Asia (27.0) (Table 1) (Ferlay et al., 2013). Countries with the highest ASIR for breast cancer in Asia were Israel (80.5), Lebanon (78.7), Armenia (74.1), Singapore (65.7), Kazakhstan (63.0), Jordan (61.0), Syria (52.5), South Korea (52.1), Japan (51.5), and Pakistan (50.3); and countries with the lowest ASIR were Mongolia (9.4) and Bhutan (4.6). Based on CI5, among several Asian countries with reliable trend data, breast cancer incidence has increased steadily in all countries including South

Korea, Taiwan, China, Singapore, Thailand, Japan and Philippines (in order of increasing rates) (Parkin et al., 2010; Shin et al., 2010b; Jung et al., 2013), with the notable exception of breast cancer incidence among Israeli Jews which has generally been decreasing since 1999 after a period of increase (Figure 2) (Keinan-Boker et al., 2013).

Eastern Asian countries

Countries in eastern Asia had the lowest overall breast cancer incidence by region (27.0), although this rate was

Table 1. Breast Cancer Incidence in 47 Asian Countries^a

Region	Country	No. Cases	CR	ASIR
Eastern Asia		277,054	36	27
	Korea, Republic of	17,140	70.3	52.1
	Japan	55,710	85.9	51.5
	Korea, Democratic Republic of*	5,707	45.7	36.8
	China	187,213	28.6	22.1
South-Eastern Asia	Mongolia	125	8.7	9.4
		107,545	35.3	34.8
	Singapore	2,524	96.8	65.7
	Brunei	83	40.6	48.6
	Philippines	18,327	38.1	47
	Indonesia	48,998	39.9	40.3
	Malaysia	5,410	37.4	38.7
	Timor-Leste*	108	18.6	32.6
	Thailand	13,653	38.4	29.3
	Viet Nam	11,067	24.4	23
	Myanmar*	5,648	22.9	22.1
	Cambodia*	1,255	17	19.3
	Lao PDR*	472	14.8	19
South-Central Asia		223,899	25.3	28.2
	Kazakhstan*	6,252	73.5	63
	Pakistan	34,038	38.4	50.3
	Afghanistan*	3,108	19.3	35.1
	Maldives	41	25.5	31.6
	Sri Lanka	3,955	36.8	30.9
	Iran, Islamic Republic of	9,795	26.3	28.1
	Kyrgyzstan*	662	24	27.3
	Uzbekistan*	3,370	23.9	27.1
	Turkmenistan*	656	25	26.8
	India	144,937	23.8	25.8
	Bangladesh	14,836	19.7	21.7
	Tajikistan*	520	14.4	20.4
	Nepal*	1,716	11	13.7
	Bhutan	13	3.7	4.6
Western Asia		42,485	36.6	42.8
	Israel	4,010	103	80.5
	Lebanon	1,934	88	78.7
	Armenia*	1,704	102.5	74.1
	Jordan	1,237	39.4	61
	Syrian Arab Republic*	4,140	39.7	52.5
	Kuwait	314	26.9	46.7
	Qatar	148	31.6	46.1
	State of Palestine	1,541	67.7	44
	Georgia*	578	27.5	44
	Iraq *	4,542	27.1	42.6
	Bahrain	177	34.7	42.5
	United Arab Emirates*	568	22.8	39.2
	Turkey	15,230	40.8	39.1
	Saudi Arabia	2,791	21.7	29.5
	Yemen	1,963	15.5	27.4
	Oman	195	16.4	26
	Azerbaijan*	1,413	29.7	25.4

CR, crude rate; ASIR, age standardized incidence rate; *Rates are expressed per 100,000 women; the Data source is GLOBOCAN 2012; *represents that no incidence rates from the countries were available

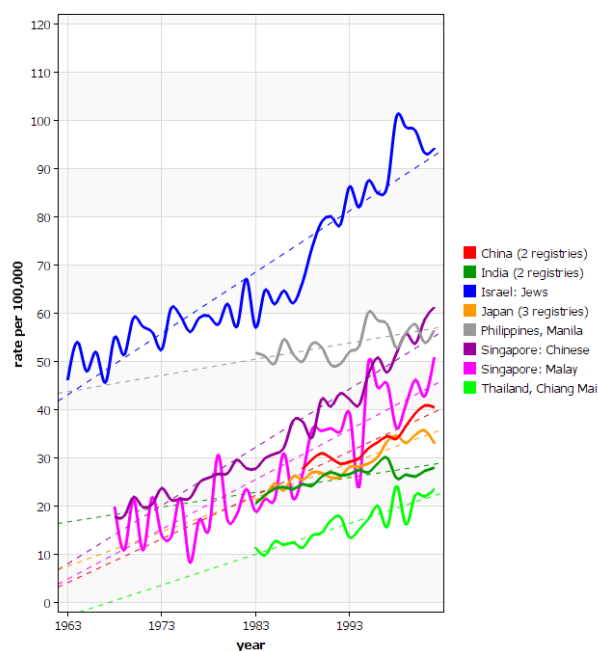


Figure 2. Trends of Age Standardized Breast Cancer Incidence Rates in Several Asian Countries from 1963 to 2002 in the CI5

heavily influenced by China with an ASIR of 22.1, much lower than that in South Korea (52.1) and Japan (51.5). South Korean women experienced the sharpest increase in breast cancer incidence during the past decade, with a 47.5% change from 1999 through 2010 (Jung et al., 2013). By contrast, breast cancer incidence increased by 30.8% in China (including Hong Kong and Shanghai) between 1988 and 2002, and 12.0% in Japan between 1983 and 2002 (Figure 2). The increasing incidence of breast cancer in China between 1993 and 2002 appeared much more modest in rural China (14.6%) than in urban Shanghai (29.3%) (Shin et al., 2010b). Breast cancer ASIR among Taiwanese women was increased from 12.75 during the period 1980-1984 to 44.45 during the period 2000-2006 (35.7%) (Chiang et al., 2010).

South-eastern Asian countries

South-eastern Asian countries had moderate rates for breast cancer (34.8 by region), with higher incidence in Singapore, Brunei, Philippines, Indonesia, and Malaysia than in Viet Nam, Myanmar, Cambodia, and Laos (Table 1). In Singapore, the rate for breast cancer has been

increasing rapidly, with substantial changes in incidence among both Chinese (71.0) and Malay (61.1%) women between 1968 and 2002 (Figure 2). Increases in breast cancer incidence among women in Manila (4.7%) and Chiang Mai (12.1%), were much smaller during the observation period.

South-central Asian countries

Breast cancer incidence rates in south-central Asian countries were divergent, with a high of 63.0 in Kazakhstan to a low of 4.6 in Bhutan (Table 1). These data must be treated with some caution, however, as 7 of the 14 south-central Asian countries had no cancer registry data on which to base rates.

Western Asian countries

The ASIR for breast cancer in western Asian countries was higher than the Asian average of 29.1, with the exception of Yemen, Oman, and Azerbaijan (Table 1). Moreover, breast cancer rates in Israel (80.5) and Lebanon (78.7) are comparable to rates in Canada (79.8) and Australia/New Zealand (85.8) (Ferlay et al., 2013). Breast cancer incidence among Kuwaiti women increased from 15.9 during the period 1979-1982 to 41.3 during the period 1998-2002 (Muir et al., 1987; Parkin et al., 1992; Parkin et al., 1997; Parkin et al., 2002; Curado et al., 2007). By contrast, breast cancer incidence among Israeli Jews has increased irregularly since 1963, with a slight downturn in more recent years (Figure 2). A join-point analysis using data from the Israel National Cancer Registry from 1996 to 2007, suggested that the incidence of invasive breast cancer decreased by 3% among Jewish women, while rates increased by 98% among Arab women (Keinan-Boker et al., 2013). Nonetheless, breast cancer incidence among Palestinians (44.0) remains about half that observed among Jewish Israeli women.

Age-specific incidence rates in Asian countries

Distinct patterns were apparent in the age-specific incidence rates for breast cancer in Asian countries between 2003 and 2007 (Figure 3). In general, the incidence rates increased sharply to a peak at menopause and then were decreased or were stable. This is in contrast to age-specific breast cancer rates in the US, UK, Denmark and New Zealand in which the rates increased according to age. In Japan, China (Jiashan) and South Korea, the

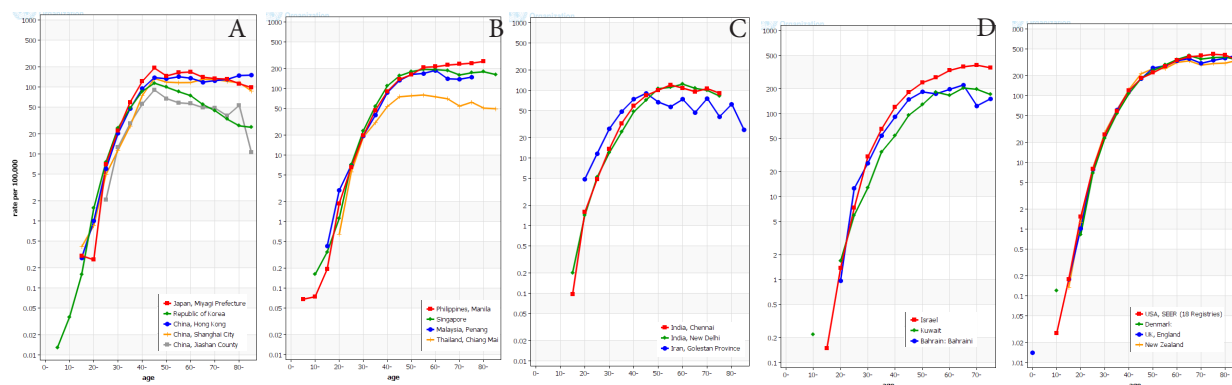


Figure 3. Age-specific Cancer Incidence Rates (per 100,000) of Breast Cancer in Asian Countries from 2003 to 2007 in CI5X. (A) Eastern Asia (B) South-eastern Asia (C) South-central Asia (D) Western Asia (E) America, Europe and Oceania

Table 2. Age Standardized Incidence Rate, Mortality Rate, and Mortality-to-Incidence Ratio of Breast Cancer by Regions in the World^a

Region/ Category	Incidence (per 100,000)	Mortality (per 100,000)	Mortality-to-Incidence ratio
World	43.3	12.9	0.3
Asia	29.1	10.2	0.35
Eastern Asia	27	6.1	0.23
South-Central Asia	28.2	13.5	0.48
South-Eastern Asia	34.8	14.1	0.41
Western Asia	42.8	15.1	0.35
America	-	-	-
Caribbean	46.1	15.1	0.33
Central America	32.8	9.5	0.29
South America	52.1	14	0.27
Northern America	91.6	14.8	0.16
Europe	71.1	16.1	0.23
Central and Eastern Europe	47.7	16.5	0.35
Northern Europe	89.4	16.3	0.18
Southern Europe	74.5	14.9	0.2
Western Europe	96	16.2	0.17
Oceania	79.2	15.6	0.2
Australia/New Zealand	85.8	14.5	0.17
Melanesia	41	19.7	0.48
Micronesia/Polynesia	59.7	13.1	0.22
Africa	36.2	17.3	0.48
Eastern Africa	30.4	15.6	0.51
Middle Africa	26.8	14.8	0.55
Northern Africa	43.2	17.4	0.4
Southern Africa	38.9	15.5	0.4
Western Africa	38.6	20.1	0.52
Less developed regions	31.3	11.5	0.37
More developed regions	74.1	14.9	0.2
Low Human Development	32.6	17	0.52
Medium Human Development	26.5	9.8	0.37
High Human Development	45.2	14.6	0.32
Very High Human Development	79	14.1	0.18

^aData source: GLOBOCAN 2012

age-specific incidence rates increased steeply to age 45-49 years and declined thereafter. A similar pattern was observed in Iran. In contrast, in Shanghai and Hong Kong, age-specific incidence rates increased to age 45-49 years and stabilized thereafter. In most south-eastern and western Asian countries, except the Philippines and Israel, the incidence for breast cancer peaked at 50-54 years followed by a plateau. In the Philippines and Israel, age-specific breast cancer incidence rates increased by age identical to the patterns observed in western countries. This data may reflect the earlier westernization in the Philippines and the large European population in Israel compared to other Asian countries.

Mortality

The age-standardized mortality rate (ASMR) for breast cancer is 12.9 worldwide, with an average ASMR for breast cancer in Asia of 10.2. Similar to breast cancer incidence, there is substantial heterogeneity in breast cancer mortality by region, with the highest mortality in western Asia (15.1), followed by south-eastern Asia (14.1), south-central Asia (13.5), and eastern Asia (6.1). Importantly, among the four Asian regions, only eastern

Asia had a lower mortality rate than the world average. Breast cancer mortality rates steadily increased in Korea, Japan, and Taiwan from 1975 to 2006 (Figure 4), while the rates slightly decreased after 1990 in Hong Kong and Singapore among women ≥ 70 years (Shin et al., 2010a). Similarly, breast cancer mortality increased in south-eastern Asian countries, especially among Filipino women who experienced a sharp increase in death rates from 1995 through 2009 (Figure 4). Mortality trends during the 30-year period 1980 to 2009 were divergent in south-central Asian countries with large increases in breast cancer mortality in Kazakhstan, more modest increases in Turkmenistan and Uzbekistan, and only slight increases in Kyrgyzstan. In western Asian countries, mortality in Israel has been decreasing since 1995; whereas, mortality rates in other countries increased slightly or were too unstable for evaluation. In contrast to the increasing trend of mortality observed in most Asian countries, mortality rates for breast cancer have been declining among all age groups in Australia, Denmark, the United States, and the United Kingdom since the late-1990s.

In addition to the upswing in breast cancer mortality, an emerging concern in some parts of Asia is the high

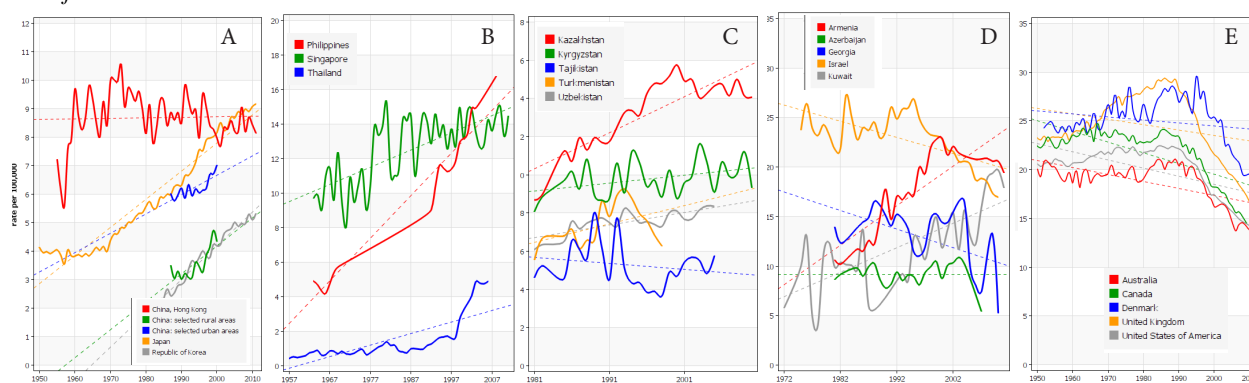


Figure 4. Trend of Age Standardized Mortality Rate (per 100,000) among Selected Countries from the WHO Cancer Mortality Database. (A) Eastern Asia (B) South-eastern Asia (C) South-central Asia (D) Western Asia (E) America, Europe and Oceania

Table 3. Five-Year Relative Survival Rate of Breast Cancer Estimated from Population Registry Data in Selected Asian Countries

Country - Registry	Year	No. Cases	5YR Relative Survival, %	Source
Eastern Asia				
China - Hong Kong SAR	1996-2001	10,112	89.8	(Sankaranarayanan et al., 2011b)
China - Qidong	1992-2000	651	59.4	(Sankaranarayanan et al., 2011b)
China - Shanghai	1992-1995	5,184	78.7	(Sankaranarayanan et al., 2011b)
China - Tianjin	1991-1999	5,863	84.8	(Sankaranarayanan et al., 2011b)
Korea	1999	5,537	83.7	(Tanaka et al., 2009)
Japan - Miyagi	1997-1999	2,029	88.1	(Tanaka et al., 2009)
Taiwan	1997-1999	11,723	79.7	(Tanaka et al., 2009)
South-eastern Asia				
Singapore	1993-1997	3,204	76.2	(Sankaranarayanan et al., 2011b)
Philippines - Manila&Rizal	1993-2002	1,615	58.6	(Tanaka et al., 2009)
Thailand - Chiang Mai	1993-1997	544	62.1	(Sankaranarayanan et al., 2011b)
Thailand - Lampang	1990-2000	830	64.9	(Sankaranarayanan et al., 2011b)
South-central Asia				
India - Mumbai	1992-1994	7,294	51.4	(Sankaranarayanan et al., 2011b)
Western Asia				
Israel (Jews)	1990-1992	6,131	71	(Ministry of Health Israel, 2000)
Israel (non-jews)	1990-1992	171	63.1	(Ministry of Health Israel, 2000)
Jordan	1997-2002	838	64.2	(Arkoob et al., 2010)
Saudi Arabia - Riyadh	1994-1996	298	64.5	(Sankaranarayanan et al., 2011b)
Turkey - Izmir	1995-1997	1,329	76.7	(Sankaranarayanan et al., 2011b)

mortality-to-incidence rate (MI) ratio for breast cancer. The MI ratio is calculated by dividing the mortality rate by the incidence rate and is an indirect measure of cancer survival - the higher the MI ratio, the lower the survival rate. Compared to the low MI ratio in North America (0.16), the lowest MI ratio in Asia was 0.23 in eastern Asia and the highest was 0.48 in south-central Asia (Table 2). This two-fold difference in the MI ratio between Asian regions might be explained by differences in economic development, i.e., higher MI ratio in less developed countries and lower MI ratio in more developed countries. While 8.8% of new breast cancer cases were diagnosed in less developed countries, 14.4% of deaths were reported from those countries. In contrast, 61.7% of incident breast cancer cases were diagnosed in highly or very highly developed countries, but only 50.8% of deaths were reported from these countries (Ferlay et al., 2013).

Survival

Breast cancer survival also varies within Asia (Sankaranarayanan et al., 2011b), which is consistent with regional differences by stage at diagnosis. In Table

3, the 5-year relative survival rates (%) from breast cancer calculated from population-based registries in several Asian countries/cities are summarized (Ministry of Health Israel, 2000; Tanaka et al., 2009; Arkoob et al., 2010; Sankaranarayanan et al., 2011b). The five-year relative survival rate for breast cancer was highest in Hong Kong, Tianjin, Korea, and Japan (>80%), followed by Shanghai, Taiwan, Singapore, Izmir (75-80%), Israel (Jews) (71%), Thailand, Israel (non-Jews), Jordan, Saudi Arabia (60-65%), Qidong, Philippines (58-59%), and India (51%). Stages of breast cancer in each country are described in the Discussion

Discussion

Breast cancer rates remain comparatively low among women in Asia, but the secular trends show a rapid increase in incidence in most of the region, with the exception of Israel. A higher mortality-to-incidence ratio, more advanced stage at diagnosis, and reduced survival were observed in less developed countries than in more developed countries in Asia. The increase in breast cancer

incidence is likely associated with changes in reproductive factors, obesity and, perhaps, enhanced medical care and breast cancer screening. A detail description of epidemiologic and clinical factors that are associated with breast cancer statistics in Asian countries are discussed in this section.

In terms of risk factors of breast cancer among Asian women, reproductive and hormone-related factors are the most studied. Results from large case-control and cohort studies conducted among women in China, Taiwan, Singapore, Japan, and South Korea suggest that women who are unmarried, nulliparous or with a reduced number of full-term pregnancies, older at first full-term pregnancy, have not breastfed, or who had an early menarche or late menopause, are at increased risk for postmenopausal breast cancer (Kato et al., 1992; Yoo et al., 1992; Chie et al., 1997; Chie et al., 1998; Chie et al., 2000; Gao et al., 2000; Zheng et al., 2000; Tamakoshi et al., 2005; Wu et al., 2006b; Kim et al., 2007; Kawai et al., 2012; Huang et al., 2013; Sugawara et al., 2013). Similar findings have been observed in smaller case-control studies conducted in other Asian countries such as Malaysia, Philippines, Thailand, India, Pakistan, and Israel (Ratanawichitrasin et al., 2002; Faheem et al., 2007; Shema et al., 2007; Gajalakshmi et al., 2009; Long et al., 2010b; Moore et al., 2010a; Moore et al., 2010b; Moore et al., 2010c; Salim et al., 2010; Lodha et al., 2011; Matalqah et al., 2011; Sulaiman et al., 2011; Bhadoria et al., 2013; Shamsi et al., 2013). Few large well-designed epidemiologic studies were conducted in countries from south-central and western Asian regions.

However, an association of oral contraceptive pill (OC) use or hormone replacement therapy (HRT) with breast cancer risk has been inconsistent between studies: an increased risk among women with a history of OC use was reported in a Taiwanese study (Chie et al., 1998) and with HRT use in a Singaporean study (Ng et al., 1997), although no association with HRT use was found among women in Japan (Saeki et al., 2008; Kawai et al., 2010), or Thailand (Ratanawichitrasin et al., 2002). Although it is likely that HRT is a risk factor for breast cancer in Asian women, as in women from other countries (Fournier et al., 2005; Chlebowski et al., 2013), in countries that have limited resources and research funding, ecologic and cross-sectional studies may assist with risk stratification (Hoel et al., 1983; Koo et al., 1997; Zhang et al., 2012).

Obesity is an established risk factor for postmenopausal breast cancer among Asian women in eastern Asia and in some countries in south-eastern Asia (Ng et al., 1997; Shu et al., 2001; Yoo et al., 2001; Li et al., 2006; Jee et al., 2008; Shin et al., 2009; Shi et al., 2010; Bao et al., 2011; Sueta et al., 2012; Kawai et al., 2013; Miyagawa et al., 2013; Sangrajang et al., 2013; Suzuki et al., 2013). Data from large prospective and case-control studies conducted in Shanghai, China, Japan, Korea, Taiwan, Singapore, and Thailand suggest that women with higher body mass indices (BMI) have a 1.5- to 2.0-fold higher risk of breast cancer compared to women with a normal BMI (Ng et al., 1997; Shu et al., 2001; Li et al., 2006; Wu et al., 2006b; Jee et al., 2008; Shin et al., 2009; Shi et al., 2010; Kawai et al., 2013; Sangrajang et al., 2013;

Suzuki et al., 2013). Moreover, higher BMI has been associated with a higher risk of ER+/PR+ and/or luminal type cancer among Chinese and Japanese women (Yoo et al., 2001; Bao et al., 2011; Sueta et al., 2012; Miyagawa et al., 2013). In studies among Chinese women, overweight/obesity explained 9% of the variation in postmenopausal breast cancer risk in urban areas and 6% of the variation in breast cancer risk among women in rural areas (Wang et al., 2012a). Furthermore, weight reduction improved breast cancer survival (Chen et al., 2010).

While adolescent obesity may be related to an increased risk of postmenopausal breast cancer, epidemiologic studies conducted in Asia have produced limited data in this regard. Further research regarding the role of body fat accumulation or overweight/obesity among teenagers in the development of premenopausal breast cancer among Asian women is needed for health planning purposes, since about half of the breast cancers are detected among women ≤ 50 years in most Asian countries. Although large prospective studies of breast cancer incidence have been conducted in several eastern Asian countries, prospective studies with sufficient power to identify risk factors for premenopausal breast cancer are generally lacking.

Aside from body weight, physical activity has been associated with a reduced risk of postmenopausal breast cancer among Chinese and Japanese women (Matthews et al., 2001; Adams et al., 2006; Suzuki et al., 2008; Gao et al., 2009; Shin et al., 2009; Pronk et al., 2011; Suzuki et al., 2011; Kawai et al., 2013). Population-based intervention studies to measure the impact of weight control and exercise on risk reduction and management of breast cancer in Asian populations are needed.

The association between dietary factors and breast cancer risk among Asian women has been a interesting research topic due to the rapid changes and unique culture of dietary habits among Asians. Based on time-trend analyses of national health data or ecologic studies, it has been posited that changes in dietary habits to a more western style (i.e., higher intake of calorie, fat, animal protein) correlate with an increased breast cancer incidence among women residing in Asian countries (Kim et al., 2009; El-Basmy et al., 2012; Mizota and Yamamoto, 2012). In large cohort studies however, this association has not been consistent: an increased risk of breast cancer was observed among Shanghai women in association with a higher intake of animal-derived fat (Kallianpur et al., 2008); whereas, fat consumption was not associated with breast cancer risk among Japanese women (Wakai et al., 2005). In a prospective study in Korea, serum total cholesterol level was associated with a 31% higher risk of breast cancer among postmenopausal Korean women (Ha et al., 2009).

Unique dietary habits that can be observed traditionally among eastern Asian women are higher intake of soy products and green tea. In the Shanghai Women's health study, breast cancer risk was inversely associated with the intake of soy products (Lee et al., 2009). Among Japanese, a similar inverse association was observed in three cohort studies (Yamamoto et al., 2003; Iwasaki et al., 2008; Wada et al., 2013), but the association was not significant in two other cohort studies (Key et al., 1999; Nishio et al., 2007).

Among Korean women, an inverse relation between soy intake and breast cancer was observed in two case-control studies (Do et al., 2007; Cho et al., 2010). In addition, higher soy intake contributed to both reduced recurrence and mortality from breast cancer in a large population-based case-control study among Chinese women (Shu et al., 2009). A higher intake of green tea was associated with a reduced risk of breast cancer among Chinese (Dai et al., 2010), but not among Japanese women (Iwasaki et al., 2010a; Iwasaki et al., 2010b; Iwasaki et al., 2014). Dietary intervention studies with soy and green tea among high consumers will provide information on the acute effects of constituent compounds on endogenous hormone concentrations associated with breast cancer development.

Genetic factors, such as polymorphisms, family history, and BRCA mutation, and their relation to breast cancer risk among Asian women were reported from previous studies. In a consortium including 23,637 breast cancer patients and 25,579 controls of East Asian ancestry, a replication study was conducted of 70 single-nucleotide polymorphisms (SNPs) in 67 independent breast cancer susceptibility loci identified by genome-wide association study (GWAS) primarily in European-ancestry populations (Zheng et al., 2013). In the study (Zheng et al., 2013), only half of the genetic risk variants initially reported in whites were associated with breast cancer risk in the East Asian population; whereas five breast cancer associated SNPs initially identified among Asians (Zheng et al., 2009; Long et al., 2010a; Cai et al., 2011; Long et al., 2012), were replicated in samples of whites which were variants at 6q25, 10q21, 11q24, and 16q12. In other GWAS studies among Asians, new breast cancer risk variants at 6q14, 10q25, and 2q34 were discovered (Kim et al., 2012; Shi et al., 2013). SNPs in several genes (i.e., XRCC1, EGFR, ATM, TP53) may be associated with breast cancer risk among Asian women, but sample sizes have been limited (Park et al., 2003; Hirose et al., 2004; Lee et al., 2005; Yuan et al., 2005; Hong et al., 2009; Faghani et al., 2011; Bag et al., 2012; Han et al., 2012; Al Mutairi et al., 2013). Although results from small case-control studies suggest gene-environment interactions for breast cancer risk among Asian women, no significant interactions were observed with a cumulative genetic risk score of 20 susceptibility loci for breast cancer and known risk factors (reproductive factors, BMI, waist-to-hip ratio, etc.) in the Shanghai Breast Cancer Genetics Study (Li et al., 2013). It will be necessary to investigate the ethnic-specific impact of SNPs on breast cancer development and treatment with substantially larger datasets in order to produce reliable and valid information specific to Asian race/ethnicity. A further challenge is that genetics may vary substantially across Asian subgroups that have lived in geographically isolated areas.

A strong scientific consensus exists that family history of breast cancer is associated with an increased risk of breast cancer, although the risk estimates differ by country, ranging from a 1.5- to 2.0-fold increased risk among Chinese, Japanese, and Korean women (Kato et al., 1992; Kim et al., 2007; Kilfoy et al., 2008) and a 4.0- to 5.0-fold increased risk of breast cancer among Taiwanese and Indian women (Yang et al., 1997; Lodha et al.,

2011). Studies with higher risk estimates were generally smaller case-control studies, suggesting that the familial associations may have been overestimated.

The mutation rate of BRCA1 and BRCA2 genes among high risk breast cancer patients who were suspected to have hereditary breast/ovarian cancer also varies by country, ranging from 3.8% in Hong Kong (BRCA1) (Tang et al., 1999), 5.1% in Iran (BRCA1) (Kooshyar et al., 2013), 7.6% in northwest China (BRCA1/2) (Ou et al., 2013), 7.8% in Indonesia (BRCA1/2) (Purnomosari et al., 2007), 8.6%-12.7 % in Korea (BRCA1/2) (Ahn et al., 2004; Son et al., 2012), and 26.7% in Japan (BRCA1/2) (Sugano et al., 2008). The BRCA1 and BRCA2 mutation rates among all breast cancer cases were 1.1% in Shanghai (Suter et al., 2004) and 2.8% in Korea (Ahn et al., 2004).

Based on the observed increases in the incidence and mortality from breast cancer, guidelines for breast cancer screening have been implemented in clinics throughout Asia, generally including bi-annual mammography screening among women older than 40 years (Leong et al., 2010). Moreover, some countries such as Korea, Singapore, and Taiwan have implemented nationwide screening programs managed by the government (Wang, 2003; Wu et al., 2006a; Kim et al., 2011). Breast cancer mammography screening rates differ by countries in Asia: 21.7% in China in 2010 (Wang et al., 2013), 26.4% in Taiwan in 2009 (Wu et al., 2012), 23.8% in Japan in 2009, and 51.4% in Korea in 2009 (OECD, 2011). However, facilities for routine mammographic breast screening are lacking in middle- and low-resource countries such as India (Khokhar, 2012; Shetty, 2012).

Some studies examined the effectiveness of mammography among Asians. A study from Taiwan tested the validity of a two-stage mammography screening programme, and the area under the receiver (AUC) operating characteristic curve was acceptable at 71% (Wu et al., 2006a). Moreover, the positive predictive value of recall after mammography was 14%, much higher than the 8% recall for selective screening and 2% recall for physical examination (Wu et al., 2006a). More cases were detected at a lower stage among mammography users than non-users in a Singapore study (Ng et al., 1998). Asian women tend to have denser breasts which might increase the false-negativity of mammography. Test sensitivity was increased with the use of supplementary ultrasonography in Taiwan and Singapore (Hou et al., 2002; Leong et al., 2012). In a study of 14,483 Thai women, the addition of ultrasonography to mammography increased the breast cancer detection rate, especially among women aged 40-59 years with non-fatty, dense breasts (Korpraphong et al., 2013).

In many Asian countries, mammographic screening is available only in a limited number of hospitals and it is affordable only to a small fraction of people in the country. In those countries, annual clinical breast examination alone may be another cost-effective option. A randomized trial to evaluate the efficiency of clinical breast examination (CBE) has been conducted in India, and showed that ASIR for advanced-stage breast cancer was higher among those who didn't have CBE after 3.5 years of follow-up (Sankaranarayanan et al., 2011a). In

a cost-effective analysis based on data from India, CBE performed annually from ages 40 to 60 was predicted to be nearly as efficacious as biennial mammography screening for reducing breast cancer mortality while incurring only half the net costs (Okonkwo et al., 2008).

Training health staff and raising public awareness were useful and cost-effective in down-staging of breast cancer in a study conducted in Malaysia (Devi et al., 2007). However, breast self-examination didn't reduce mortality from breast cancer in China (Thomas et al., 2002). For women who live in countries/territories with limited resources and/or have strong cultural barriers to getting screened for breast cancer, such as reliance on alternative medicine, public education is necessary to reduce the morbidity and mortality from breast cancer (Seow et al., 1997; Anderson et al., 2011; Erwin et al., 2011; Huang et al., 2011; Shaheen et al., 2011; Wee and Koh, 2011).

Some researchers developed breast cancer prediction models among Asian women. Mathematical models to estimate breast cancer risk specific to Asian women have been developed among Korean women and a multi-ethnic population in Singapore (Gao et al., 2012; Park et al., 2013). A Korean model was independently developed using the risk estimates extracted from a large Korean case-control study and was assessed in two Korean cohort studies, which showed AUCs of 0.61 and 0.89 (Park et al., 2013). The Singapore model, which was a modified Gail model, found that the inclusion of age at menarche, age at first birth, and the number of first degree relatives with breast cancer performed fairly well with associated concordance statistics of 0.60 (Gao et al., 2012). In addition to the known factors, 12 SNPs were included to a risk assessment model among Chinese women, with a c-statistic of 0.63 after adjustment for over-fitting (Zheng et al., 2010). Asian-specific breast cancer risk assessment models would be useful especially in less developed countries with meager resources (Lertkhachonsuk et al., 2013), but the role of such models in counseling women regarding their risk of breast cancer needs to be validated in several diverse Asian populations. It is likely that risk assessment will ultimately need to be tailored to particular countries or regions.

Clinical factors of breast cancer, such as median age at detection, distribution of stage at diagnosis, and prevalence of estrogen and/or progesterone receptor, were different in Asian countries. The median age at diagnosis for breast cancer among women in Asian countries is generally between 49-50 years. In large size case studies or population registry data, the median age at diagnosis for breast cancer was 49-50 years in South Korea, Singapore, Malaysia, and Hong Kong, China, India (Tan et al., 2009; Ghosh et al., 2011; Jung et al., 2011; Kwong et al., 2011), but 57 years among Japanese women (Sonoo and Noguchi, 2008). In some countries, such as Indonesia, women are diagnosed at a younger age (median 47 years) (Ng et al., 2011). Ranges of median ages reported from western Asian countries are between 45 and 52 years (El Saghir et al., 2007; Najjar and Easson, 2010), and the weighted median age among 8 Arab countries was 49 years (Najjar and Easson, 2010). Asian women were about 6-18 years younger at breast cancer diagnosis than non-Hispanic

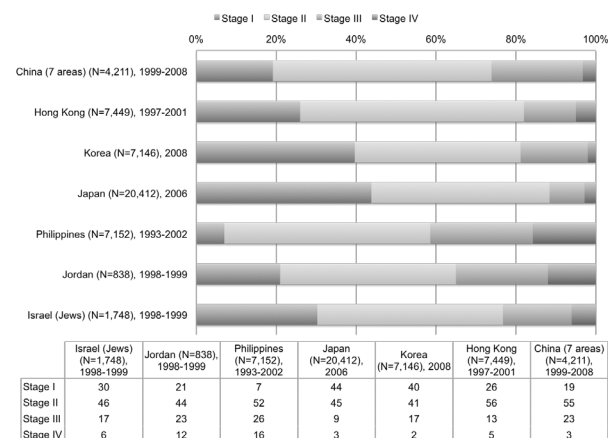


Figure 5. Distribution of Stage at Diagnosis of Breast Cancer in China, South Korea, Japan, Philippines, Jordan, and Israel (Jews). Stage distribution was calculated among cases of stages reported; data sources: China (Wang et al., 2012b), Hong Kong (Kwong et al., 2011), Korea (Jung et al., 2011), Japan (Sonoo and Noguchi, 2008), Philippines (Laudico et al., 2009), Jordan (Arkoob et al., 2010), Israel (Rennert et al., 2007)

whites (median age 63), and are younger than Asians (median age 56) in the United States (Yi et al., 2012). It has been suggested that the early onset of Asian women is explained by an age-period-cohort effect: the rapid change of breast cancer risk profiles allied to westernized lifestyle such as low parity, insufficient breastfeeding, and weight gain are observed among younger and more recently born women, which have resulted in a higher increase of breast cancer in the generation (Minami et al., 2004; Chia et al., 2005; Shen et al., 2005; Dhillon et al., 2011; Mousavi-Jarrarhi et al., 2013).

Stage at diagnosis reflects access to and sophistication of medical care, cancer screening, as well as tumor aggressiveness. The distribution of breast cancer cases by stage at diagnosis differs considerably between Asian countries (Figure 5). The percentage of breast cancers diagnosed at an early stage (stage I and II) was relatively high in Japan (89%), Hong Kong (82%), and Korea (81%), followed by Israel (Jews) (76%) and China (74%), but lower in Jordan (66%) and the Philippines (59%) (Rennert et al., 2007; Sonoo and Noguchi, 2008; Laudico et al., 2009; Arkoob et al., 2010; Ghosh et al., 2011; Jung et al., 2011; Kwong et al., 2011; Wang et al., 2012b). Population-based data are difficult to obtain from less developed countries. A case series study from a single center in Indonesia including 637 breast cancer cases, suggested that many women were diagnosed at advanced stages: 41% stage III and 22% stage IV (Ng et al., 2011). In population registry data from Singapore and Thailand, the proportion of local, regional, and distant cancer was 53%, 39%, and 9% in Singapore compared with 30%, 50%, and 9% in Thailand, respectively (Tan et al., 2009; Kotepui and Chupeerach, 2013). The percentage of women diagnosed with breast cancer at an 'unknown' stage was higher in less developed countries: 34% in Indonesia and 28% in the Philippines compared with 14% to 17% in Hong Kong, Mainland China, Israel, Jordan, and <10% in Japan and Korea. Studies conducted in less developed countries in Asia show that women diagnosed with breast cancer at a

late stage tend to be older, lower socioeconomic status, lower family income, less educated, live in rural areas, and have a greater time to referral and greater number of consultations with a surgeon before diagnosis (Wang et al., 2012b; Poup et al., 2014).

Estrogen positive (ER+) breast cancer was the most common subtype among women in Japan (76%), Korea (67%), Hong Kong (66%), Israeli Jews (59%), and Malaysian and Singaporean Chinese (57%) (Rennert et al., 2007; Sonoo and Noguchi, 2008; Jung et al., 2011; Kwong et al., 2011; Bhoo-Pathy et al., 2012). Malay and Indians in Malaysia and Singapore had a relatively smaller proportion of ER+ cancer (53% in both race/ethnic groups) (Bhoo-Pathy et al., 2012). Similarly, ER+ cancer constituted 52% of breast cancer cases among Indonesian women (Ng et al., 2011). Estrogen and progesterone positive (ER+/PR+) tumors represented 51% of breast cancer cases among Indian women and 48% of cases among Mainland Chinese women (Ghosh et al., 2011; Wang et al., 2012b). In contrast, estrogen negative cancer was predominant among Kuwaiti women (69%) (Saleh and Abdeen, 2007).

In contrast to ER status, the distribution of HER2 status is more complex in Asian countries and is not consistent with survival expectation. The proportion of HER2+ breast cancer was lowest among Japanese (15%), followed by Indians (17%), Mainland Chinese (23%), Malaysians (26%), Koreans (31%), Hong Kong Chinese (43%), and Indonesians (45%) (Sonoo and Noguchi, 2008; Ghosh et al., 2011; Jung et al., 2011; Kwong et al., 2011; Ng et al., 2011; Wang et al., 2012b). While HER2 positivity is generally associated with reduced breast cancer survival, HER2 status was poorly correlated with an intra-country ranking rate of breast cancer survival probabilities in Asia (see table 3). For example, HER2 positivity was generally low in India (17% of cases), a country with comparatively poor breast cancer survival, but high in Korea (31% of cases) and Hong Kong (43%), the country/city with the most favorable breast cancer survival probability in Asia. Although it is unclear whether the discrepancy in HER2 status between countries is biological or spurious resulting from inconsistent immunohistochemistry, ecological comparisons cannot account for other factors, such as enhanced medical care, that may also account for these putative inconsistencies.

In summary of the clinical characteristics, in contrast to less developed countries, breast cancer in more developed countries tended to be diagnosed at an earlier stage, with fewer unstaged cases, and was more likely to be ER+, suggesting that earlier detection, improved diagnosis, and better treatment options in higher resource countries contribute (Jemal et al., 2011), at least in part, to higher breast cancer survival rates.

In conclusion, breast cancer incidence in Asian countries has rapidly increased in most of the region. It is likely that morbidity and mortality from breast cancer in Asia will continue to grow, and demand for the implementation of population-based, community programmes for breast cancer prevention will expand. Increasing breast cancer awareness through health education, increasing the availability of clinical breast

examination and the identification of high-risk women may be cost-effective strategies for secondary prevention in less developed regions and countries. For example, in resource-poor rural China, breast cancer rates will continue to grow among the cohort of women who reached reproductive age under the one child policy. Pilot programmes might be implemented in these areas that evaluate the efficacy of risk-stratification in the identification of women at greatest risk for a breast cancer diagnosis. An additional challenge to cancer control efforts in low resource Asian countries is to improve the quality of cancer registration, epidemiologic research, and breast cancer treatment. These efforts might be facilitated by sustained government support, health worker training programmes, and promotion of multidisciplinary treatment options utilizing available resources.

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