

Breast cancer in China

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The health burden of cancer is increasing in China, with more than 1·6 million people being diagnosed and 1·2 million people dying of the disease each year. As in most other countries, breast cancer is now the most common cancer in Chinese women; cases in China account for 12·2% of all newly diagnosed breast cancers and 9·6% of all deaths from breast cancer worldwide. China's proportional contribution to global rates is increasing rapidly because of the population's rising socioeconomic status and unique reproductive patterns. In this Review we present an overview of present control measures for breast cancer across China, and emphasise epidemiological and socioeconomic diversities and disparities in access to care for various subpopulations. We describe demographic differences between China and high-income countries, and also within geographical and socioeconomic regions of China. These disparities between China and high-income countries include younger age at onset of breast cancer; the unique one-child policy; lower rates of provision and uptake for screening for breast cancer; delays in diagnosis that result in more advanced stage of disease at presentation; inadequate resources; and a lack of awareness about breast cancer in the Chinese population. Finally, we recommend key measures that could contribute to improved health outcomes for patients with breast cancer in China.

Introduction

China is the largest low-income or middle-income country and the most populous country in the world according to the World Bank, and is home to about a fifth of the global population.¹ As a result of recent rapid urbanisation at an annual rate of 2·3%, 47% of the Chinese population live in urban areas and disease burden has concomitantly shifted from communicable to non-communicable diseases (including all cancers, but specifically breast cancer).¹ In addition to well known socioeconomic disparities within China,² substantial regional disparities exist, leading generally to insufficient financial resources, infrastructure, and health-care staff in undeveloped regions (figure 1).³

China has a low incidence of breast cancer, but since the 1990s its incidence has increased more than twice as fast as have global rates, particularly in urban areas.⁴ Breast cancer is now the most frequently diagnosed cancer and is the sixth leading cause of cancer-related death in Chinese women.⁵ By 2008, with 169 452 new cases of invasive breast cancer and 44 908 related deaths, China accounted for 12·2% of global cases and 9·6% of related deaths.⁵ Annual diagnoses of breast cancer in China are now about half of those in the European Union (332 000 in 2008; population 498 million⁶), and are similar to the number of cases in the USA (182 000 cases in 2008; population 304 million⁷). Unless this trend is slowed, incidence of breast cancer in China is expected to rise from less than 60 cases per 100 000 women aged 55–69 years to more than 100 cases per 100 000 women by 2021, reaching 2·5 million cases overall by 2021.⁸

In China the average total cost of treatment for each new case of breast cancer is US\$1216, ranking China 103rd of 172 countries (figure 2).⁹ The price of medical services in China (including surgery and nursing) is very low compared with other countries; for example, surgery fees for mastectomy in Shanghai are ¥2200 (\$360),¹⁰ and health professionals in China have long been a group

with low incomes.¹¹ Another reason for the low cost is poor access to patented and new anticancer medicines compared with developed countries. In wealthy coastal regions the average cost is \$2835 per patient with breast cancer, which is twice the national average.¹² Although treatment costs are low in a global context, breast cancer is one of the leading causes of catastrophic medical expenditure in China, and can rapidly impoverish families. In 2012, 12·9% of Chinese households were burdened by catastrophic health expenditure, defined as more than 40% of a household's disposable income.¹³ Despite rapid implementation of universal health coverage in China, low reimbursement continues to result in rising out-of-pocket expenses for cancer patients.¹⁴

We review the status of breast cancer in China; describe key epidemiological, demographic, and socioeconomic factors; and review risk factors, screening efforts, and the state of diagnosis and treatment for breast cancer. We also discuss the substantial disparities between subpopulations and regions within China, which lead to important differences in access to care for Chinese patients with breast cancer. Finally, we explore ways to improve prevention and clinical outcomes for breast cancer in China.

Incidence and mortality of breast cancer in China

A limitation of the data for incidence and mortality of breast cancer in China presented in this Review is that only about 13% of China's population is included in national cancer registries, by contrast with 32% of patients in the European Union and 96% of patients in the USA.^{15–17} This drawback somewhat hampers data interpretation, so that the true burden of cancer in China cannot be estimated solely with use of cancer registration data alone at present. Expansion of China's cancer registry to be more representative of the whole country would improve accuracy of cancer burden estimates. In the absence of such complete or representative data,

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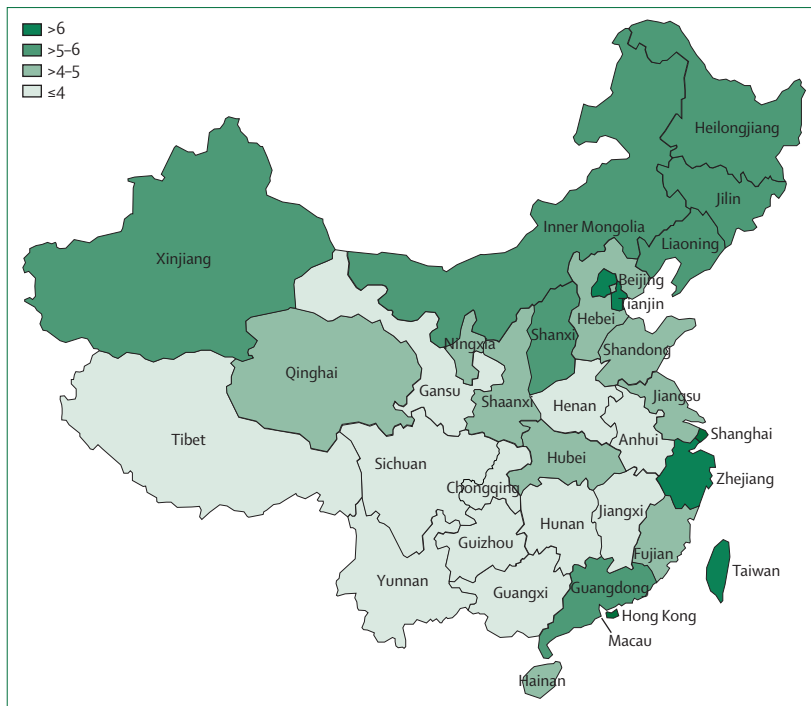


Figure 1: Number of medical technical personnel per 1000 people
Figure based on data from the China health statistics yearbook (2011).³

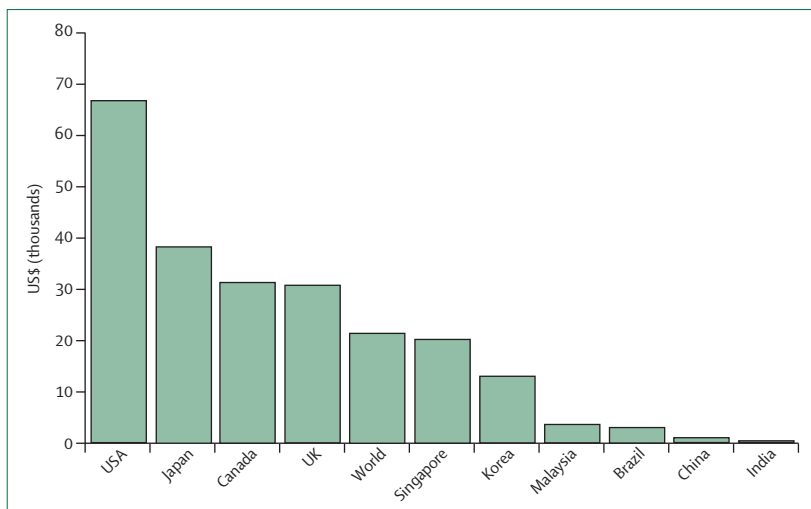


Figure 2: Average cost per breast cancer case
Figure based on data from the Economist Intelligence Unit (2009).⁹

informed use of the available data, with appropriate statistical methods, can be a valuable instrument for development of a cancer control policy in China.¹⁸ Additionally, very similar age-specific incidences and trends have been reported in other areas in the region (eg, Hong Kong and Taiwan¹⁹⁻²¹), suggesting that patterns of regional or rural-urban differences and trends over time are probably valid.

Incidence

GLOBOCAN estimates that breast cancer is the most frequent cancer in Chinese women, with an age-standardised rate (ASR) of 21.6 cases per 100 000 women.⁵ According to the Chinese National Central Cancer Registry, the disease is the most common cancer among urban women and the fourth most common cancer in rural areas. The ASR is twice as high in urban areas (34.3 cases per 100 000 women) as in rural areas (17.0 cases per 100 000 women; figure 3). The highest rates occur in eastern coastal urban areas that are socioeconomically well developed, with an ASR of 46.6 cases per 100 000 women reported in Guangzhou,¹⁵ which is similar to that in Japan (42.7 cases per 100 000 women).⁵ By contrast, in some less developed regions in western or central China the ASR for breast cancer is estimated to be as low as 7.94 cases per 100 000 women.

The mean age at diagnosis of breast cancer in China is 45–55 years, which is considerably younger than for western women. Data from both Shanghai and Beijing show two age peaks, one at 45–55 years and the other at 70–74 years, with an increasing shift towards an older median age at diagnosis.⁴ In 2008, 16.6% of patients with breast cancer were aged 65 years or older in China (compared with 42.6% of patients in the USA); by 2030, 27.0% of patients with breast cancer in China are estimated to be 65 years or older (figure 4).²²

The peak in age-specific incidence in women aged 45–55 years might be due to a birth cohort effect, resulting from changes in menstrual and reproductive patterns and other lifestyle and environmental factors that are prevalent in more recent birth cohorts.⁸ Similar cohort effects have been reported in areas such as Taiwan and Hong Kong,¹⁹⁻²¹ and have been attributed to shifts in risk-factor profiles of younger women.^{21,23,24}

Mortality

In 2008, GLOBOCAN reported breast cancer to be the sixth leading cause of death from cancer in Chinese women, after lung, gastric, liver, oesophageal, and colorectal cancer, with an ASR of 5.7 cases per 100 000 women.⁵ Mortality from breast cancer rose progressively during the past three decades in both rural and urban areas; this increase might partly be explained by improved quality of cancer registry data.¹⁵ The ASR in urban areas (7.2 cases per 100 000 women) is now 46.9% higher than in rural areas (4.9 cases per 100 000 women; figure 5).¹⁵ In urban areas mortality doubled between 2002 and 2008, whereas in rural areas mortality did not increase, resulting in a reversed urban-rural difference (from –2.3 cases per 100 000 women in 2002 to +3.6 cases per 100 000 women in 2008).²⁵ This reversal is due to a substantial increase in the number of urban women aged 55–59 years and in those aged 75 years and older in urban centres.²⁵ We calculated the mortality-to-incidence ratio using data from 32 Chinese

cancer registries. In urban areas, the ratio continuously decreased, from 0·22 in 2003 to 0·18 in 2007; in rural areas, the ratio decreased from 0·32 in 2003 to 0·28 in 2007. This finding suggests that, despite a sharp increase in age-adjusted incidence rates, increases in mortality relative to incidence have not been as substantial.²⁶

5-year survival for patients with breast cancer in Shanghai (the most industrialised city in China) was shown to be 78% as early as 1992–95,²⁷ compared with 89% reported for US women in 1999–2005,²⁸ suggesting that improvements in control and care of breast cancer are achievable in China. However, in Qidong (a rural neighbouring area of Shanghai) 5-year survival was still only 58% in 1992–2000,²⁹ pointing to substantial disparities within the country that need to be addressed. We speculate that survival for patients with breast cancer might be inferior in disadvantaged areas and socio-economic groups of China, similar to these data from Shanghai and its rural hinterland. More research is needed to identify causal factors for these disparities and strategies to eliminate them.

Risk factors for breast cancer in Chinese women

Patterns of breast cancer risk for Chinese women are only partly aligned with known risk factors for women in high-income countries.³⁰ Similar to western women, reproductive and hormonal factors—eg, a long menstrual life (mainly based on early age at menarche and later age at menopause), nulliparity, increased age at first live-birth, and limited breastfeeding—are associated with a modestly increased risk of breast cancer in the Chinese population.^{31–34} The fall in the fertility rate, partly due to the one-child policy, might also have affected breast cancer risk through these factors (eg, by reducing lifetime duration of breastfeeding). In China, increased numbers of births per woman have indeed been associated with a reduced risk of breast cancer (odds ratio [OR] 0·69, 95% CI 0·52–0·91) for postmenopausal women.³⁴ China's total fertility rate (the average number of children that would be born to a woman over her lifetime) fell from about 6·0 in 1950–55 to 1·6 in 2010.^{35,36} The wealthy eastern coastal regions have the lowest total fertility rate (figure 6). In urban Shanghai the total fertility rate is the lowest of any city in the world (0·81 in 2010), far lower than in most industrialised countries.³⁷ However, other areas in the region (eg, Hong Kong and Taiwan) have reported similar increases in breast cancer incidence without implementation of the one-child policy.¹⁹

Obesity in premenopausal and postmenopausal women and low levels of physical activity, both known as westernised or urban lifestyle risk factors for breast cancer, also probably contribute to the increasing incidence of breast cancer in China.³⁸ In particular, the healthy traditional dietary pattern (consumption of rice, fresh vegetables, soy, pork, and wheat flour) has changed to a western diet,³⁹ with 25·4% of Chinese women reported as being overweight (body-mass index ≥ 25) and another

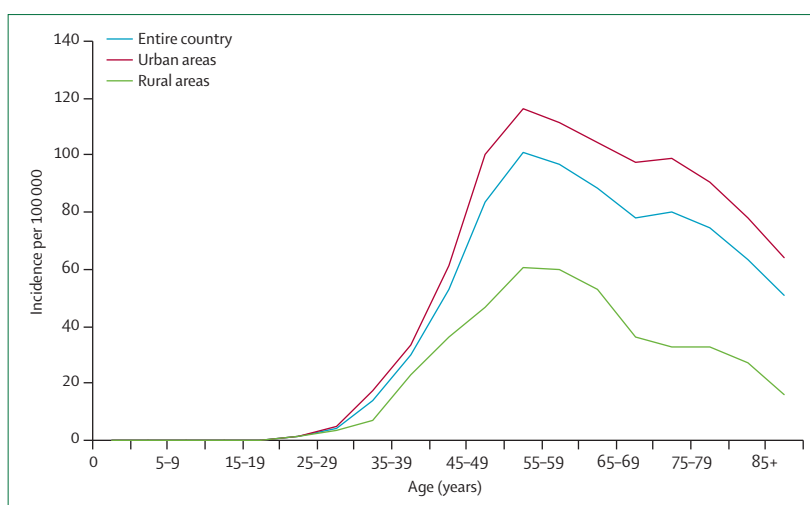


Figure 3: Age-specific incidence of female breast cancer in all registry areas, 2009

Figure based on data from the Chinese Cancer Registry annual report.¹⁵

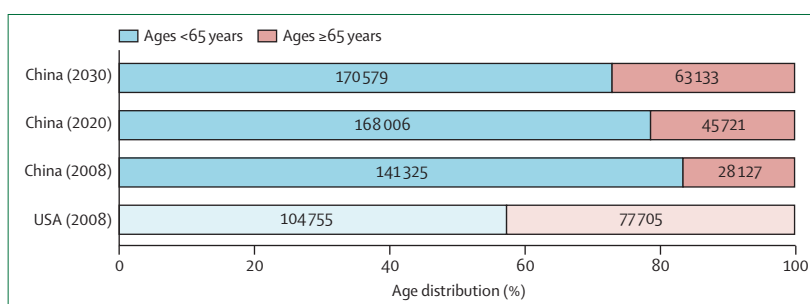


Figure 4: Age distribution of patients with breast cancer

Figure shows age distribution in China and the USA in 2008, and estimated distributions in China in 2020 and 2030; based on data from the WHO China country profile.²²

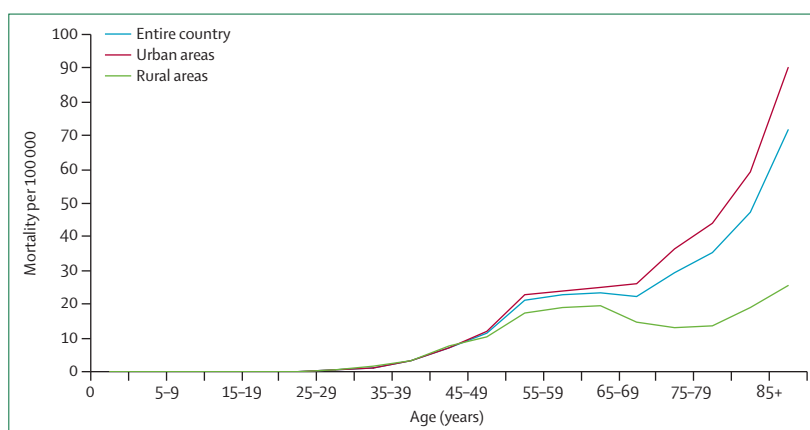


Figure 5: Age-specific mortality for female breast cancer in all registry areas, 2009

Figure based on data from the Chinese Cancer Registry annual report.¹⁵

6·7% as being obese (body-mass index ≥ 30).⁴⁰ Even the number of 13-year-old students reported as being overweight (up to 19·2%) or obese (9·5%) is increasing.⁴¹ In high-income countries, high body-mass index has been

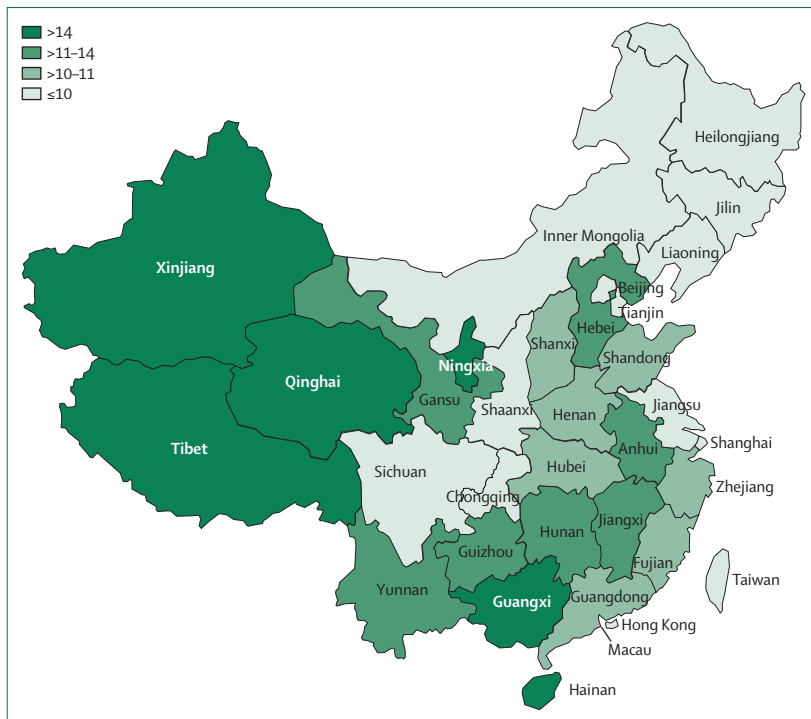


Figure 6: Chinese birth rate by region per 1000 population, 2010
Figure based on data from the China health statistics yearbook (2011).³

consistently associated with increased risk of breast cancer in postmenopausal women,⁴² whereas in premenopausal women it is associated with a reduced risk of breast cancer.⁴³ However, the association between weight and risk of breast cancer in low-risk populations (such as that in China) might be different from that reported in high-income countries, with a lack of association for premenopausal breast cancer and a stronger association for postmenopausal breast cancer.⁴⁴ Findings from a large nationwide study³⁰ lend support to this hypothesis, showing that Chinese women (both premenopausal and postmenopausal) with a body-mass index of 24 kg/m² or higher had a four-times increased risk of breast cancer compared with women with a body-mass index of less than 24 kg/m², which is somewhat higher than would be expected on the basis of accumulated evidence in non-Chinese populations.^{45,46} Thus, the present trends of overweight and obesity in young women in China could contribute to an increase in prevalence of breast cancer (probably postmenopausal) in the future. However, despite these statistics there are no operational public policies or incentives in place to reduce unhealthy diets, address obesity, or increase physical activity in the population.⁴⁷

These data show that, although identification of country-specific patterns and trends for risk and incidence of breast cancer is important, most risk factors are similar between different countries and ethnic groups around the world. This suggestion is supported

by findings from an international case-control study⁴⁸ and data from a multiethnic cohort,⁴⁹ which showed that despite variations in the overall incidence of breast cancer, associations between risk factors and incidence were similar across ethnic groups. For example, the known effects of height, use of hormone replacement therapy, family history, and weight gain have all been shown for Chinese women living in Singapore and Shanghai.^{31,38,50}

Screening and early diagnosis for breast cancer

The benefit of mammography remains controversial in women younger than 50 years;⁵¹ however, 57% of Chinese patients with breast cancer are within this age range.⁵² This finding might account in part for why cost-effectiveness studies of mammography screening have not been as convincing for Chinese women as for western women.^{53,54} At present, there is no nationwide screening programme for breast cancer in China. Barriers to implementation of a population-based mammography screening programme include insufficient convincing cost-effectiveness data; the large, widely dispersed population; insufficient mammography equipment; and inadequate insurance coverage for such a programme.⁵⁵ A national screening programme for breast cancer was attempted in 2005, with a goal of screening 1 000 000 women with both mammography and ultrasound, but was terminated because of lack of funding and concern about false-positive diagnoses.⁵⁶ Despite these concerns, national guidelines established in 2007 recommend annual mammography for women aged 40–49 years, and every 1–2 years for those aged 50–69 years.⁵⁷ By 2012, 530 000 women had been screened, which was 19·2% of women aged 40–69 years, 16·4% of women in urban areas, and 20·6% in rural areas.⁵⁸ Only 2% of the poorest quintile of women are screened, compared with 35·9% of the wealthiest quintile.⁵⁸ Apart from organisational and funding obstacles, inherent reluctance from cultural barriers and cancer fatalism in Chinese women hampers screening efforts, particularly in older women and those from groups with low socioeconomic status.^{59–61} In rural areas, most women are unwilling to spend ¥20 (\$3·20) on a screening package for breast and cervical cancer, despite the true cost of a mammogram being ¥200 (\$32).⁶² Findings from a study⁶³ in Beijing showed that only 5·2% of new cases were detected by routine mammographic screening, whereas 82·1% of women who were diagnosed experienced obvious symptoms; the proportion of breast cancers detected through screening is about 60% in the USA.⁶⁴

At present there is no consensus about the role of clinical breast examination for early detection in the diverse Chinese population, but population-based studies of clinical breast examination combined with diagnostic ultrasound are in progress.⁶⁵ Hope for earlier-stage detection through clinical breast examination is

supported findings from a study⁶⁶ in India, which showed clinical breast examination to be as cost effective as mammography in this regard. This technique is potentially important for all populations in China, where advanced-stage presentations and neglected breast cancer are more frequent than in high-income countries. Although the investigators of the Shanghai study concluded that “intensive BSE [breast self-examination] instruction in the absence of mammography would be unlikely to reduce breast cancer mortality”, most researchers agree that self-examination probably improves awareness and might play a part in nationwide programmes for earlier-stage detection in China.^{67–69}

There remains a need to improve public awareness, to continue studying the benefits of mammography and clinical breast examination in earlier-stage detection, and provide more accessible health services for Chinese women willing to undergo screening.

Clinical diagnosis

Age at diagnosis

The median age at diagnosis of breast cancer is 48–50 years in China compared with 64 years in the USA, with 57·4% of women diagnosed before 50 years, and 62·9% of women diagnosed while still premenopausal.^{4,52} However, median age at presentation continues to increase.⁴

Stage at diagnosis and delayed early detection

More frequent presentation with advanced-stage breast cancer is the main reason for disparities in survival between African American and white women in the USA.⁷⁰ Findings from a multicentre nationwide study⁵² 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 disease; more women from upper socioeconomic groups presented with stage I and II disease than did disadvantaged women, many of whom presented with stage III or IV disease.⁵² Because most data about stage at presentation are collected from surgical departments, disease presentations at stage IV (triaged to medical oncologists) are probably substantially underestimated in China; findings from a business survey^{71,72} suggested that nearly two thirds of patients with breast cancer in China were diagnosed with advanced disease. By contrast, 60% of women in the USA present with localised stage I and II disease, 33% present with regional stage III disease, and only 5% present with stage IV disease.⁷³

Long waiting times before initiation of treatment for newly diagnosed breast cancer are of prognostic concern, especially if delay leads to stage progression and disease worsening, or to more treatment complications. Investigators of a 2013 study⁷⁴ reported that waiting times to initiate surgical treatment of more than 6 weeks resulted in 5-year survival of 80% compared with 90% for waiting times of less than 2 weeks. Because of disparities in public awareness, substantial delays in diagnosis have

been reported for different regions of China. The median time from symptoms to visiting a doctor is 1 month in wealthy areas of China,⁶³ compared with 94 days in less developed western and central regions.⁷⁵ Two studies have reported that delays of more than 3 months occur in 39·2–50·2% of patients, and worrisome delays of longer than 1 year occur in 11·7–17·3% of patients in some less developed regions of China.^{75,76}

Diagnosis and pathological reports

Although image-guided core needle biopsy is the gold standard method to diagnose primary breast cancer, data from Beijing suggest that only 34·1% of patients are diagnosed by core needle biopsy in China, whereas 19·0% are diagnosed with use of fine needle aspiration, and 46·9% by fresh frozen-section excision biopsy.⁶³ Although not representative for all of China, these data from a well-developed urban region suggest deficits in diagnostic workup for primary breast cancer.

Overall, breast tumours from women in Asian countries have similar molecular and genetic characteristics as do those in white women.⁷⁷ The lower prevalence of hormone-receptor positivity—about 50–60% in Chinese women compared with more than 70% in white women—reported from several studies might be due to a younger age of the affected population in China.^{4,78–80} This suggestion is supported by the fact that the incidence of oestrogen-receptor-positive disease is increasing in China, similar to the increasing age at diagnosis of breast cancer; findings from one study⁷⁹ showed oestrogen-receptor-positive disease to increase from 49·0% of cases to 59·4% between 1999 and 2008. Similar trends have been reported in Malaysia, where oestrogen-receptor positivity increased by 2% for every 5-year cohort between 1994 and 2008.⁸¹ Oestrogen-receptor positivity correlates with age in Chinese women,⁸⁰ similar to the pattern reported in the USA.⁸²

Available data suggest that the incidence of breast cancers positive for HER2 is similar for Chinese and US women; up to 25% of Asian patients could therefore potentially benefit from HER2-targeted treatment.^{52,83–85}

Because comparisons across studies are hampered by variations in inclusion criteria and by changing methods of oestrogen-receptor measurement over time, direct evidence showing complete similarity in histopathological features of breast cancer between Chinese and white women is not available. Findings from a survey⁶³ of 101 hospitals in Beijing showed that basic pathological information that typically guides treatment choices—eg, tumour size, histological grade, and nodal status—was missing for up to 67·2% of newly diagnosed cases. For example, 25·9% of patients treated with breast-conserving surgery did not have surgical margins reported by pathology laboratories.⁶³ Anti-HER2 therapy significantly improves survival in patients with HER2 positive disease, but because it is costly and potentially toxic, false-positive and false-negative laboratory results

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are an important issue. Findings from a nationwide survey⁶¹ of the quality of HER2 testing by immunohistochemistry in 45 Chinese hospitals suggested that only 28 (62%) met acceptable reporting standards. Even in Beijing 8.9% of patients have no access to HER2 testing, and almost 10% of patient samples with uncertain immunohistochemistry results failed to have further HER2 testing done with in-situ hybridisation.⁶³ Guidelines for standardisation of HER2 testing have now been published in China,⁸⁶ and an online system has been established to improve the diagnostic accuracy of HER2 testing, but much work remains to achieve accurate measurement.

Genetic risk and counselling

Familial clustering of breast cancer is frequent in China, and genetically inherited susceptibility to breast cancer due to germline *BRCA1/2* mutations is similar for women of Chinese and western European descent.⁸⁷ Although genetic testing and counselling are provided routinely for women in developed countries, they are not generally approved in China despite the fact that many Chinese women accept these services when available.^{88,89}

Treatment for breast cancer

Surgery

Access to and timely delivery of optimum care for breast cancer affect clinical outcomes but important disparities in both exist across China.⁹⁰ Patterns of practice for breast surgery vary considerably between regions and between hospitals. Since the 1990s, breast-conserving surgery (whenever possible) has become the guideline-recommended surgical treatment. However, findings from a nationwide survey⁵² in China showed that mastectomy continues to account for 88.8% of surgery for primary breast cancer, by contrast with 36% of surgical cases in the USA.⁹¹ Even in developed urban areas such as Beijing or Shanghai, incidence of breast-conserving surgery were only 12.1% in 2005,⁹² climbing to 24.3% by 2008.⁶³ An explanation for the low frequency of breast-conserving surgery in China is a shortage of resources for radiation therapy (which needs to be given as part of breast-conserving surgery), most notably in less developed regions of the country.⁹³ Complete axillary lymph node dissection, with its attendant complication risk of lymphoedema and other local morbidities, is done in 84.1% of patients in Beijing, 57.6% of whom have no lymph node involvement.⁶³ By contrast, 59% of US patients with breast cancer can avoid axillary lymph node dissection (with its associated morbidities) by receiving upfront sentinel lymph node biopsy dissection.⁹⁴ A continuing Chinese study⁹⁵ by the Chinese Breast Cancer Study Group (CBCSG001) aims to improve rates of sentinel lymph node biopsy, with secondary study endpoints including safety and efficacy of preoperative lymphoscintigraphy and pathological reporting of sentinel lymph node biopsies.⁹⁵

Radiation therapy

Findings from Chinese retrospective epidemiological studies suggest that only 27% of patients with breast cancer nationwide receive radiation therapy as part of their primary treatment, which is lower than in other countries (eg, 40% in South Korea,⁹⁶ 58–68% in the Netherlands,⁹⁷ and 76% in Brazil⁹⁸). However, similar to incidence of breast-conserving surgery in China, use of radiation therapy is also increasing. However, the availability of breast-conserving surgery is poor in China because the country has only 0.8 radiotherapy centres, 0.8 clinical accelerators, and 0.2 CT scanners per million people, by sharp contrast with the USA, which has 9.3 radiotherapy centres, 13 clinical accelerators, and 1.3 CT scanners per million people.⁹⁹ Implementation of breast-conserving surgery across China is also hampered by a shortage of trained radiation oncologists and technologists. Of patients who are treated by breast-conserving surgery, 16.3% do not receive radiation therapy as per standard guidelines,¹⁰⁰ suggesting an urgent need to improve and standardise radiation therapy for breast cancer in China.

Systemic treatment and personalised medicine

Adjuvant chemotherapy for breast cancer is popular in China, with about 81.4% of all patients with invasive breast cancer starting chemotherapy.⁶³ By contrast, completion of adjuvant chemotherapy is suboptimal, with 12.1% of treated patients in one report⁶³ having received less than four cycles (less than the minimum recommended standard). Investigators of a Beijing study⁶³ noted that only 80.1% of hormone-receptor-positive patients received adjuvant endocrine therapy; worryingly, 9.2% of patients with hormone-receptor-negative tumours were also prescribed endocrine therapy, a treatment known to be ineffective in this subset of patients.⁵²

Drug reimbursement policies in China strongly affect the availability of optimum systemic therapies. Many drugs are not covered by insurance, frequently resulting in prohibitively high out-of-pocket expenses for patients.^{72,101} Lack of access to new drugs also limits systemic treatment options for metastatic disease.¹⁰² For example, only 40% of patients with metastatic breast cancer receive second-line treatment, and only a quarter receive third-line therapies⁷¹—significantly lower than in Japan or the USA, where 80% of patients with breast cancer receive second-line treatment and 65% receive third-line treatment.⁷¹ Reasons for this low use of later treatments include the lack of available therapies in China and the burden of cost of new treatments. As their metastatic disease progresses, patients also frequently lose confidence in their doctors and western medicine, and often turn to traditional Chinese medicine.⁷²

For example, despite the improvement in outcomes for breast cancer with anti-HER2 treatment,^{103,104} access to trastuzumab is not possible in most of China, and none of the newer targeted agents are covered by insurance. Only

20.6% of patients with HER2-positive breast cancer in Beijing receive HER2-targeted therapy, despite approval of trastuzumab in 2002 in China.⁶³ Trastuzumab is often not included in national or local reimbursement listings, which again results in prohibitively unaffordable out-of-pocket expenses for many patients.¹⁰¹ Having no access to other new drugs approved in high-income countries (eg, trastuzumab emtansine and pertuzumab) further limits systemic treatment options for Chinese patients.^{101,102}

Palliative care for patients with breast cancer

Health care in general and end-of-life care specifically are inadequately supported in China.¹⁰⁵ According to findings from a study by the Economist Intelligence Unit,¹⁰⁶ China ranks 37th of 40 countries for palliative-care programmes and end-of-life health care. Frequent strong taboos against discussion of death and an accompanied refusal to accept its inevitability in Chinese culture make alignment of modern treatment plans with traditional cultural beliefs difficult.¹⁰⁷ Chinese physicians are often undertrained in palliative care and thus unable to provide adequate end-of-life care.¹⁰⁸ There is both a need and an opportunity for China to implement modern ambulatory palliative-care programmes, which improve quality of life for patients and families and are more cost effective than is admission to hospital for end-of-life care.^{109,110}

Traditional Chinese medicine

Traditional Chinese medicine, mainly the use of combinations of herbs, represents about 40% of the Chinese pharmaceutical market with annual sales of \$21 billion.¹¹¹ About 80% of cancer patients have used traditional Chinese medicine and 90% of oncologists have prescribed herbs.¹¹² More than 100 formulations of traditional Chinese medicine are available for patients with breast cancer in China.⁷² Findings from a business survey report⁷² suggested that proportions of patients using traditional Chinese medicine in combination with medical treatments are 37.9%, 42.2%, and 39.5% for stage 0–II, stage III, and stage IV breast cancer, respectively. The widespread use of traditional medicine is related to beliefs that it can alleviate toxic effects associated with other treatments and improve immune function and quality of life.¹¹²

Breast cancer research

High-quality scientific evidence is crucial for decision making for the care of patients with breast cancer. However, the quantity and quality of research and scientific evidence is inadequate in China. At present, 162 Chinese clinical trials of breast cancer are registered on ClinicalTrials.gov, which is far less than for other industrialised countries (particularly for investigator-initiated trials; table). Although breast-cancer oncology groups in China have participated in international multicentre clinical trials, so far China has not joined any international cooperative group for breast cancer.

	Number of ongoing trials*	Total number of publications†	Number of publications in 2012†
China	162 (mainland)	7110	1296
Japan	80	7986	609
South Korea	149	2714	444
India	76	1957	272
UK	329	6086	424
USA	3097	46 959	2800
Canada	448	8149	588

*Retrieved from ClinicalTrials.gov (March 12, 2013) with search term "breast cancer" and country. †Retrieved from PubMed (Sept 20, 2013) with medical subject heading "breast cancer" in "all fields" and "country" in "all fields" not in "text word".

Table: Number of publications and trials in progress for breast cancer

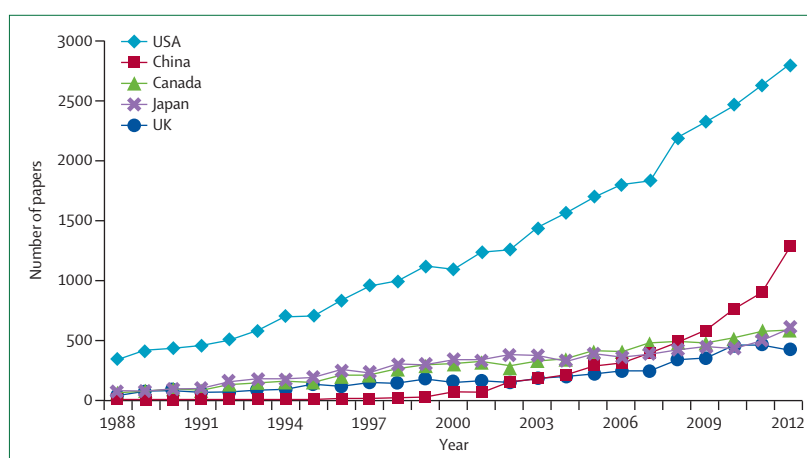


Figure 7: Breast-cancer-related research papers by country

Figure shows trends of breast-cancer-related research papers listed on PubMed. We retrieved papers from PubMed on Sept 20, 2013, with the medical subject heading "breast cancer" and country in "all fields" not in "text word".

Scientific publications from China related to breast cancer have steadily increased (figure 7). In 2012, the total number exceeded that of Canada, the UK, or Japan, and was second only to the USA (table). Researchers from China have published the most clinical research articles about breast cancer of all low-income or middle-income countries (18% of all papers), followed by Turkey, India, Poland, and Brazil.¹¹³ However, concurrent with a surge of scientific publications originating from China, there is a growing concern that many publications are of poor quality and could contain falsified data.¹¹⁴

Conclusions and recommendations

As in other low-income or middle-income countries, breast cancer is common in China and incidence is increasing. The disease occurs at a younger median age in Chinese women than in western white women,^{115,116} which might be due to differences in genetics or risk factors. Although women in China overall have a lower risk of breast cancer than do women in high-income countries, young Chinese women nowadays have a higher risk of breast cancer than did young Chinese

Panel: Recommendations for control of breast cancer in China**Comprehensive and balanced health-care system**

- Financial support to reduce out-of-pocket medical expenses
- Ensure that resources for cancer control are allocated with attention to disenfranchised populations

A national control plan for breast cancer

- Integrate the medical, economic, educational, and environmental sectors to develop strategies for cancer control

Breast cancer registries and data collection

- Improve national and regional cancer registries
- Collect accurate hospital-based data from different disciplines and centres
- Complete studies of health outcomes and cost effectiveness for cancer control

Prevent stage IV disease

- Increase public awareness
- Encourage physical activity and obesity reduction
- Explore screening methods suitable for Chinese women
- Implement clinical downstaging programmes
- Reduce delays to treatment
- Improve the quality of surgery, radiation, essential medicines, and clinical trials

Improve care for stage IV cancer

- Improve availability and quality of anticancer therapies
- Accelerate approval of new drugs
- Improve quality control of generic drugs
- Implement ambulatory palliative-care plans

Breast cancer research and education

- Expand training of cancer care personnel
- Fund multidisciplinary workshops for breast cancer care
- Establish guidelines and training programmes for pathology and biomarker testing
- Promote clinical and laboratory research for Chinese populations
- Expand international collaboration

Refine breast cancer guidelines

- Take into account inadequate medical resources and poor access to new drugs in treatment approaches
- Define minimum clinical recommendations

women of previous generations, even when reporting bias is taken into account. Findings from a study reported by Linos and colleagues⁸ suggest that these demographic changes in China are mainly due to reproductive changes. In fact, reproductive patterns that affect concentrations of sex hormones (eg, older age at first fullterm pregnancy, fewer children, and less breastfeeding) have changed radically in Chinese women, in addition to changes in lifestyle and environment that are associated with an increased risk of breast cancer (panel).

Because breast cancer in China occurs at a lower median age than in high-income countries, screening and early detection are probably not cost effective;¹¹⁷ age-specific incidence is similar to that reported in high-income countries, where screening has not been shown to reduce mortality in women younger than 50 years. Routine annual screening has been suggested to begin at 40 years of age, but only further research will establish whether this measure will be beneficial.⁵⁷ In some large cities, a double incidence peak has been reported, and both age-related incidence and average (and median) age at diagnosis of breast cancer are increasing in China.⁴ Some researchers speculate that the incidence curve will be similar to that in high-income countries in the future, which argues against defining at-risk populations by specific age groups, especially in the context of China's ageing population and the birth cohort effect.^{4,8} With no nationwide screening programme, resources might be best allocated for earlier stage detection by increasing of patient awareness (including breast self-examination), and treatment of patients in a timely manner if a palpable breast lump is noticed.

In view of the increasing incidence of breast cancer in China, detection, diagnosis, and treatment for breast cancer urgently need to be improved.⁷⁴ The Chinese Government has implemented several important measures to tackle the challenges faced at the turning point of this health transition. For example, since 2009 the Chinese Government has developed an affordable and accessible health-care system covering both urban and rural residents. As a result, the percentage of the population enrolled in the national medical insurance system increased to near-universal coverage by 2012, with out-of-pocket expenses falling to about 35% of general medical costs.^{14,118} Additionally, breast cancer was included in a list of 20 diseases of utmost priority, for which 70% of inpatient medical expenses are now covered by the national insurance scheme,¹¹⁹ and many drugs used in oncology are made available through the National Essential Drugs List established in 2009.¹⁰¹

To improve national incidence and mortality statistics, special emphasis needs to be placed on patients with little or no access to care. Improved initiatives for secondary prevention have promoted minimally invasive surgical procedures—eg, breast-conserving surgery and sentinel lymph node biopsy—that are associated with improved cosmetic outcomes and reduced morbidity.⁴ However, most Chinese patients are still being overtreated with aggressive surgery (eg, mastectomy and axillary lymph node dissection), and, paradoxically, unnecessary chemotherapy. By contrast, some patients are undertreated, do not receive guideline-recommended radiotherapy after lumpectomy, or are given insufficient chemotherapy even in the presence of adverse clinicopathological prognostic features. Increased investments in health-care systems, education, and assessment are needed to upgrade the

Search strategy and selection criteria

We searched Medline and the China National Knowledge Infrastructure database with the terms “breast cancer” and “China”. Articles published in either English or Chinese between January, 1990, and March, 2013, were included. Abstracts from the American Society of Clinical Oncology annual meetings and from the San Antonio Breast Cancer Symposia from 2005 to 2012 were included when relevant.

quality of care and to reduce morbidity and mortality from breast cancer.

Drug costs account for the largest proportion of all medical expense in China.^{12,120} Non-medical expenses are also high, particularly for patients from remote areas and by comparison with the income of these populations.¹²¹ The application of treatment guidelines for high-resource countries can therefore be cost prohibitive in low-income or middle-income countries such as China. Guidelines and minimum clinical recommendations are needed that take into account disparities between regions and socioeconomic groups in the country. The disparities within the country can be reduced by financial redistribution and the introduction of initiatives for early detection and public awareness to detect breast cancer at earlier stages.³⁷ Cost-effective ambulatory palliative-care programmes probably represent the best way forward to manage quality of life for patients with advanced disease and their families. Breast-cancer control efforts should include not only health-care delivery (ie, early detection, diagnosis, and treatment), but also public participation to increase awareness and promotion of early detection. Because the disparity of access to treatment for breast cancer will remain for some time, great effort is needed to expand insurance benefits and cancer-care infrastructure to underserved women in China.

Contributors

All authors planned and wrote the Review. LF, KS-W, and PEG did the literature search and prepared the figures and tables.

Declaration of interests

We declare no competing interests.

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