Cost-effectiveness of Breast Cancer Screening Programme for Women in Rural China

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Abbreviation: ductal carcinoma in situ, DCIS; gross domestic product, GDP; incremental cost-effectiveness ratio, ICER; quality-adjusted life year, QALY.

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Novelty and Impact: Our study analysed the cost-effectiveness of breast cancer screening programme in rural China with clinical breast examination coupled with ultrasound as the primary tool. With reduction in health-related quality of life from false-positives considered, breast cancer screening does harm to health. Priority should be given to ensure that symptomatic women have proper access to diagnosis and treatment at an early stage which leads to mortality reductions but without the usual harms associated with screening. †

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ABSTRACT

In low and middle-income countries mammographic breast cancer screening is prohibitively expensive and a cheaper alternative option is to use ultrasound as the primary screening test. In 2009, China launched a breast cancer screening programme for rural women aged 35-64 years with clinical breast examination coupled with ultrasound as the primary tool. This study aimed to analyse the cost-effectiveness of breast screening compared with no screening among Chinese rural women. We developed a Markov model to estimate the lifetime costs and effects for rural women aged 35 years from a societal perspective. Asymptomatic women in the intervention arm were screened every three years before age 64 years. Breast cancer in the non-screening arm can only be diagnosed on presentation of symptoms. Parameter uncertainty was explored using one-way and probabilistic sensitivity analyses. Compared to no screening, breast cancer screening cost $186.7 more and led to a loss of 0.20 quality-adjusted life years (QALYs). Breast screening was more expensive and did harm to health among rural women with an incremental cost-effectiveness ratio (ICER) of $-916/QALY. The sensitivity analysis identified utility loss from false positives as the factor that most influenced the results, but this did not affect the conclusions. In a rural setting with such low incidence, screening for asymptomatic disease is not cost-effective with current screening tools. Priority should be given to ensure that symptomatic women have proper access to diagnosis and treatment at an early stage as this will lead to mortality reductions without the usual screening harms.

INTRODUCTION

Breast cancer is the most common cancer among women worldwide. Globally, 1.67 million new cases of breast cancer were diagnosed in 2012, contributing more than 25% of female cancer incident cases [1]. Breast cancer is potentially a curable disease if diagnosed and treated early. In the US, as in other high-income countries, patients diagnosed at an early stage (Stage I/II) have a better prognosis (5-year survival rate of 85%-98%). In contrast, cases diagnosed with advanced breast cancer (Stage III/IV) have a poor 5-year survival rate of 30%-70% [2]. But breast cancer disparities have been observed between urban and rural regions. Whilst the incidence of breast cancer is lower among women residing in rural areas, mortality from the disease is higher due to poorer survival [3]. The poorer survival among rural women is mainly related to the rural disadvantage in access to screening, diagnosis and treatment [3]. A systematic review of 41 studies reported that rural women were more likely to mention difficulties in breast cancer health service access such as a greater distance to breast cancer specialists [4]. Some women tend to seek medical services only when experiencing acute illness or pain, leading to delay in diagnosis and poorer prognosis among rural patients. Late diagnosis of breast cancer also contributes to higher care costs due to the need for more intensive and expensive treatments [5].

In China, breast cancer is the most frequently diagnosed cancer and the fifth leading cause of cancer-related deaths [6]. Marked urban-rural differences in breast cancer stage at diagnosis [7] and survival have been reported [8], with rural women being diagnosed at an advanced stage and thus having poorer five-year survival (51.9%–60.3%) than their urban counterparts (75.7%–79.9%) [8]. Therefore, the priority for breast cancer control activities in rural China is to develop strategies to ensure that women with breast cancer are diagnosed and treated early.

The Chinese government launched a breast cancer screening programme based on clinical breast examination coupled with ultrasound as the primary screening tool for rural women aged 35-64 years in 31 provinces [9]. However, the impact of this programme is still unknown and the cost-effectiveness evidence is lacking. The low incidence in rural areas may challenge the utility and cost-effectiveness of screening programmes in such settings. To date there is only very limited evidence from rural Iran and Egypt on the cost-effectiveness of breast cancer screening among rural populations in low and middle-income countries [10, 11]. However, China is unique in that it is the only country to recommend ultrasound, as opposed to mammography, coupled with clinical breast examination as the primary screening test. Ultrasound permits the detection of small, otherwise occult, breast cancers in women with dense breasts [12]. Ultrasound may be cheaper and logistically more viable in rural areas but its accuracy is highly dependent on the level of training and performance of the operator. Furthermore, there is no evidence that screening average-risk women with clinical breast examination or ultrasound leads to a reduction in breast cancer mortality [13].

In this study, we aimed to compare for the first time the lifetime effects, costs, and cost-effectiveness of breast cancer screening using clinical breast examination coupled with ultrasound as a primary screening test compared with no screening in rural China. We used the current policy of screening rural women aged 35-64 years in order to provide the economic evidence to policy-makers.

METHODS

Screening strategy

We compared the current strategy of the rural breast cancer screening programme with no screening. In the screening group, the Breast Imaging Reporting and Data System (BI-RADS) [14] was employed to report breast cancer screening results where BI-RADS I and II indicate negative results, BI-RADS III suspicious results, BI-RADS IV and V positive results, and BI-RADS 0 insufficient information. Participants in the screening programme undergo a clinical breast examination and ultrasound. Those women found to have a positive result are further tested by biopsy for diagnostic confirmation whereas those with a suspicious result, or with insufficient information, undergo mammography. If the mammography result is positive a biopsy is performed for diagnostic confirmation. If the mammography result is suspicious or provides insufficient information, doctors will use their clinical judgment to decide whether a biopsy is required to reach a final conclusion [9]. The screening flow is shown in Figure 1.

In the non-screening arm, breast cancer patients can only be diagnosed on presentation of symptoms. Breast cancer patients in the screening arm can be diagnosed while they are still asymptomatic, thus at an earlier stage of the disease when prognosis is better. We assumed all breast cancer patients diagnosed by biopsy received treatment.

Modelling strategy

We developed a natural history Markov model for breast cancer screening in Chinese women [15] using the TreeAge software (TreeAge software Inc. Williamstown, United States of America), to inform a long-term decision model. Our model predicted the lifetime costs and quality-adjusted life years (QALYs) of screening and no screening for Chinese rural women with no previous history of breast cancer, from 35 years to death. We used a triennial screening frequency (once every three years) in the baseline analysis, and we explored the scenarios of screening every year and every five years.

Natural history

Figure 2 illustrates the various health states and the potential transitions between them [15]. Healthy women can transition to ductal carcinoma in situ (DCIS), stage I, or remain cancer-free. Women with DCIS are at a higher risk of developing invasive breast cancer (relative risk=2.02) [2]. Patients at stage I can progress to stage II, stage III and stage IV in turn. All women can die from non-breast cancer causes during disease progression but only patients at stage IV can die from breast cancer. The state progression transition probabilities used in this analysis are from models described in the literature [16-18].

We estimated the probability of symptoms in an unscreened population by calibrating the model. In the non-screening arm, incident cases are only detected on presentation of symptoms; the distribution of incidence cases by stage is therefore a function of the probability of transitions and the probability of symptoms [19]. We adjusted the probability of symptoms until the distribution of cases presented at each stage was similar to the distribution of reported incidence cases [17]. Our estimates of transition probabilities are provided in Table 1.

Epidemiological and clinical data

Estimates of the age-specific invasive breast cancer incidence in rural areas were extracted from the 2012 Chinese Cancer Registry Annual Report [6]. DCIS incidence was not directly reported in China so we estimated the DCIS incidence based on the ratio of invasive and non-invasive breast cancer cases among 3,838 unselected Chinese breast cancer patients in a hospital setting [20]. Age-specific non-breast cancer mortality figures (i.e. excluding mortality from breast cancer) in rural areas were calculated by subtracting age-specific breast cancer mortality rates [21] from the corresponding age-specific all-cause mortality rates [22].

Breast cancer incidence among Chinese women is increasing twice as fast as the global (worldwide) rate [23] but the most recent year for which data for rural areas are available is 2012. However, the incidence of this cancer in Hong Kong, and its time trends, have been shown to be similar to those for the whole of China [23]. Therefore, we took the breast cancer incidence rates in Hong Kong for the year 2015 [24] as a proxy for the future incidence of this cancer in rural China, and used these rates to assess the likely impact of foreseeable trends in breast cancer incidence on the robustness of the conclusions.

Effectiveness of screening

At baseline we used the sensitivity (probability of positive diagnosis if diseased) and specificity (probability of negative diagnosis if not disease) values from 26,224 Chinese women participating in the rural breast cancer screening programme [25]. The screening modality in this study was the same as the measure required for the input to our model. The biopsy test was performed for diagnostic confirmation of breast cancer. Due to limited evidence on the performance of the screening programme in rural China, we explored a 30% reduction in the screening sensitivity and specificity as the lower values in the one-way sensitivity analysis.

Quality-adjusted life years (QALYs)

QALYs are recommended by China Guidelines for Pharmacoeconomic Evaluations [26] as the most suitable summary measure for economic evaluation of health outcomes. They adjust changes in length of life by potential alterations in quality of life, and thus reflect both mortality and health-related quality-of-life effects. QALYs equal time spent in the relevant health states multiplied by an appropriate utility score. We identified the utility scores for patients at stage I, II, III, and IV from a cross-sectional survey in which EuroQol five-dimension (EQ5D) questionnaires were used to evaluate the quality of life of breast cancer patients in 13 Chinese provinces [27]. In addition, women with false-positive results experience important psychological distress [28]. We estimated 25% disutility from false positives at baseline [29, 30] and explored the uncertainty by varying the utility decrement from 11% to 34% in the sensitivity analyses [29]. A scenario analysis of no utility loss from false positives was also considered.

Costs

We obtained the screening costs from the cost accounting of the rural breast cancer screening programme, including the costs of clinical breast examination ($1.4), ultrasound ($19.9), mammography ($57.0) and biopsy ($45.6) [9]. The average screening cost in the rural breast cancer screening programme is reported to be $22.7 per capita [9].

We derived the direct medical costs and non-medical costs by stage from a study which enrolled 2,746 patients with invasive breast cancer from 37 hospitals across 13 provinces in China [5]. We used the productivity loss days and the net income per capita of Chinese rural residents ($7.7 per day) to calculate the indirect costs. As the

treatment costs of DCIS patients were not reported in the nationwide study [5], we estimated the DCIS costs from a study of 211 patients treated in the Sichuan Cancer Hospital [31]. We used purchasing power parity (PPP) to convert cost values to US dollars [32]. All costs in this analysis are presented at 2014 values.

Analysis

In line with China Guidelines for Pharmacoeconomic Evaluations [26], we conducted the analysis from a societal perspective (2011), and discounted future costs and future benefits at 3%. We calculated the incremental cost-effectiveness ratios (ICER) by dividing the difference in lifetime costs by the difference in lifetime effects. The willingness-to-pay threshold was estimated to be three times the gross domestic product (GDP) per capita in China in 2014 (US$ 7683) [33]. An incremental cost-effectiveness ratio of less than US$ 23 050/QALY is therefore an indication that the breast cancer screening for rural Chinese women aged 35-64 years, compared with no screening, is cost–effective.

We carried out one-way and probabilistic sensitivity analyses to explore parameter uncertainty. In the one-way sensitivity analysis, we varied the effectiveness of screening, utility parameters and cost values between the minimum and maximum estimates to assess the impact on overall results. In the probabilistic sensitivity analysis, costs were specified as having a Gamma distribution, quality of life as having a Log-normal distribution, and sensitivity and specificity of screening as having a Beta distribution – as suggested in the literature [34]. All the input variables were varied simultaneously and we could obtain 1,000 estimates of incremental costs and effects by sampling from the distributions. Then a cost-effectiveness acceptability curve was plotted to show the probability of breast cancer screening being cost-effective at different willingness to pay thresholds.

Other scenarios explored included: (i) the impact of screening every year or every five years compared with no screening; (ii) screening every three years, but only 70% compliance rate of screening; (iii) age-specific breast cancer incidence in 2015 from Hong Kong; and (iv) no utility loss from false positives.

RESULTS

Our model estimated 20 incident breast cancer cases per 1,000 women over a lifetime, with 13 detected via screening and the remaining seven on presentation with symptoms. Table 2 reports the discounted lifetime costs, QALYs and ICERs. Overall, breast cancer screening gained 0.04 life years for women attending the screening programme in the lifetime horizon, but it was more expensive ($186.7) and yielded lower QALYs (-0.20) than no screening. Breast cancer screening with clinical breast examination and ultrasound combined as the primary screening tool lowers breast cancer mortality but does harm to health among Chinese rural women and is dominated by no screening.

The one-way sensitivity analysis results (Figure 3) indicates that the most influential factor on the results was the reduction in quality of life from false positives; however, its variability did not change the conclusion that breast cancer screening is not cost-effective. The ICERs are negative (incremental costs>0; incremental effects<0) at both upper and lower limits of these variables. Probabilistic sensitivity analysis (Figure 4) shows that all simulation points fall within the north-west quadrant, indicating breast cancer screening led to higher costs and

lower QALYs. The cost-effectiveness acceptability curve shows that at the threshold of US$ 23 050/QALY, the probability of breast screening doing more harm than good for Chinese rural women is 100% (Appendix 1).

In the scenario analysis (Table 2), screening every year and every 5 years achieves an ICER of US$ -704/QALY and US$ -996/QALY. A scenario of annual screening but only 70% compliance rate yields an ICER of US$ -956/QALY. If we parameterise the model using the 2015 Hong Kong data, breast screening still costs more ($257.8) and yields lower QALYs (-0.12) than no screening. In these scenarios, breast cancer screening does harm to health of Chinese rural women participating in the programme. If we were to assume no disutility from false-positive screening results, breast cancer screening in rural China would achieve an ICER of US$5,078/QALY.

DISCUSSION

Our baseline results indicate that rural breast cancer screening in China, which is based on clinical breast examination and ultrasound as the primary tool, leads to higher costs and poorer health with a discounted ICER of $-916/QALY, thus dominated by no screening. Comparing these results to those from earlier studies, we found that whilst the economic evidence on ultrasound screening is lacking in low and middle-income countries, some studies evaluating clinical breast examination as the primary screening tool showed that it was cost-effective relative to mammographic screening in India [35] and Ghana [36], or to no screening in Vietnam [37] and Costa Rica [38]. The apparent discrepancies in the conclusions between our study and the earlier studies are mainly due to the differences in quality of life decrements from false positives. If we were to assume that false-positive screening results do not affect a woman's quality of life then breast cancer screening in rural China would achieve an ICER of US$5,078/QALY, well below the threshold of $23,050/QALY – consistent with previous cost-effectiveness studies. None of the earlier cost-effectiveness studies considered disutility from false-positives, but we used a loss of 11%-34% in health-related quality of life at baseline based on a systematic review [29]. With reduction in quality of life associated with a diagnosis of breast cancer considered, even in the UK there is uncertainty about cost-effectiveness of breast cancer screening [39].

Our finding is consistent with a recent review which shows that even in a high incidence country mammographic screening is associated with considerable harm [40]. Carcinoma in situ is very likely to be detected by mammographic screening, but more than half of the cases will not progress to be invasive cancer [41]. Also, some tumours identified by mammography may be slow-growing that would never have been clinically apparent before a woman dies from another cause [42]. Some have argued that the harm may be even higher with ultrasound screening as this modality is associated with higher false-positive rates and hence higher levels of unnecessary anxiety, biopsy tests and treatments [43]. Furthermore, the accuracy of ultrasound screening may be compromised by the fact that it is labour-intensive and very operator-dependent. Health care workers report a lack of confidence in their clinical breast examination skills highlighting the need for proper training and practical recommendations to ensure screening performance is optimised [44].

In addition to the loss in quality of life from false-positive results, the low incidence in rural China may also decrease the utility and cost-effectiveness of the breast cancer screening programme. The incidence rate of breast cancer in China's rural areas is significantly lower than that in urban areas (17.0 vs 34.3 per 100,000 person-years in 2009) [6], thus leading to a lower detection rate of screening. We investigated the impact of future increases in

breast cancer incidence in rural China in the scenario analysis, but this did not affect the conclusion that the breast cancer screening programme in rural China was more expensive and less effective. Furthermore, the strategy of screening with clinical breast examination and ultrasound at the first stage may not be suitable for Chinese women residing in rural areas. Although clinical breast examination has been used in low resource settings, there is no evidence so far that it will lead to reductions in breast cancer mortality [45]. Also, whilst ultrasound may be better at detecting small invasive breast cancers in women with dense breasts [12], it is usually recommended as an adjunct to mammography screening among women at higher risk for breast cancer rather than as a primary screening method for women at average risk [46-49].

In rural China, priority should be given to downstaging by ensuring symptomatic women have proper access to diagnosis and treatment at an early stage, as this will lead to reductions in mortality from the disease without the usual harms associated with screening. In China, breast cancer has become one of the leading causes of catastrophic medical expenses and can rapidly impoverish families [23]. This is of particular relevance in rural areas where the disease is diagnosed at a later stage [7] and thus survival is poorer (5-year survival rates: 55.9 (51.9–60.3) in rural areas versus 77.8 (75.7–79.9) in urban areas [8]). More cost-effective approaches should be implemented to reduce delays in diagnosis and treatment and thus improve the prognosis of breast cancer among rural Chinese women. Downstaging is likely to be more cost-effective than screening in rural China because the resources will be concentrated on women with breast symptoms instead of the general population. Also, in order to cope with a large number of screen-detected suspicious lesions, a cancer care system must be well-organized enough and able to deal appropriately with symptomatic disease [50]. Hence, developing culturally-sensitive and cost-effective strategies to promote early diagnosis and treatment of clinically detectable women, rather than screening asymptomatic women, should be regarded as a priority.

Our study is limited by the lack of data on treatment costs for rural patients with breast cancer. The rural residents in China with severe diseases tend to seek the secondary or tertiary level of medical treatment in urban hospitals [51]. Since they usually need to travel further to reach the hospitals, the direct non-medical costs including transport costs might be underestimated in the study. In addition, the rural-urban differences have been observed in the choice of neo-adjuvant chemotherapy and surgical procedures [52]. Rural patients with breast cancer also tend to have worse adherence to adjuvant treatment, which is strongly associated with recurrence [53]. These factors could result in differences in the direct medical costs between urban and rural patients. Although our sensitivity analysis proves that the results are quite robust when the costs are varied up and down by 30%, the impact of cost variations on the overall results could be further explored if more evidence on the treatment costs of rural patients is available. Another limitation of this study is the assumption of progression rates between stages and the relative risk of invasive cancer from ductal carcinoma in situ. We used the estimated data from other countries and assumed the parameters were applicable to China. These factors require careful consideration. In addition, due to a limited number of studies on false-positives, there is still uncertainty about the utility loss from false-positive screening results. In this analysis, we used the estimate from the UK studies at baseline which might bias the cost-effectiveness results of the screening programme in China. Ideally, individual women should be allowed to specify their own utility loss associated with a false-positive screening result as risk averseness would conceivably be highly personalized. Further research is required to reduce uncertainty.

This is a modelling study based on the natural history of breast cancer. However, the biology of breast cancer may be heterogeneous. Some tumours are detected late because they are aggressive and fast-growing. Others may spread before screen-detection is possible, in which case early detection may not improve disease prognosis. There is so far no evidence on the benefits of breast ultrasound screening [13]. Similarly, data from two large randomised clinical trials (RCTs) do not suggest a beneficial effect of screening by breast examination [45]. Ideally, RCTs should be conducted to evaluate the benefits and harms of the breast cancer screening programme in rural China, and their time horizon should be long enough to capture differences in long-term health outcomes including breast cancer mortality - the ultimate outcome of interest. To our knowledge no such RCTs have been conducted or are on-going in rural China. Therefore, in the absence of evidence from RCTs, we have adopted a Markov natural history model in this study to evaluate the cost-effectiveness of the breast cancer screening programme in rural China.

In conclusion, our finding shows that in a rural setting with such low breast cancer incidence, screening for asymptomatic disease is not cost-effective with the current screening tools. Instead, priority should be given to ensure that symptomatic women are diagnosed and treated appropriately at an early stage as this will lead to reductions in mortality from the disease without the usual harms associated with screening.

DECLARATION OF INTERESTS

The authors declare that there is no conflict of interest.

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FIGURE CAPTIONS

Fig.1 Screening flow in the breast cancer programme in rural China

Fig.2 The Markov model for breast cancer progression

Fig.3 Tornado diagram

Fig.4 Incremental discounted lifetime costs and effects of rural screening compared with no screening

Table 1: Parameter values in the Markov model

Variables	Baseline	Minimum	Maximum	Distribution	Reference
Transition probabilities					
Age-specific incidence in rural areas					
35-39	0.0002306	-	-	-	Chinese Cancer Registry
40-44	0.0003645	-	-	-	Annual Report [6]
45-49	0.0004659	-	-	-	
50-54	0.0006039	-	-	-	
55-59	0.0005969	-	-	-	
60-64	0.0005292	-	-	-	
65-69	0.0003608	-	-	-	
70-74	0.0003277	-	-	-	
75-79	0.0003248	-	-	-	
80-84	0.0002748	-	-	-	
85+	0.0001620	-	-	-	
Ratio of DCIS incidence compared to invasive breast cancer incidence					
	0.12	-	-	-	Lu et al., 2011 [20]
Relative risk of invasive cancer in DICS					
	2.02	-	-	-	SEER Program, 2002 [2]
Progression rate					
Stage I–Stage II	0.06	-	-	-	C.P.Tsokos, 1987 [18]
Stage II-Stage III	0.11	-	-	-	
Stage III-Stage IV	0.15	-	-	-	
Stage IV-death	0.23	-	-	-	Wong et al., 2007 [16]
Stage-specific probability of symptoms					
Stage I	0.004	-	-	-	Model Calibration
Stage II	0.014	-	-	-	
Stage III	0.380	-	-	-	
Stage IV	0.980	-	-	-	
Annual fatality rate after treatment					
Stage I	0.006	-	-	-	Ginsberg et al., 2012 [17]
Stage II	0.042	-	-	-	
Stage III	0.093	-	-	-	
Stage IV	0.275	-	-	-	
Effectiveness of screening					
Sensitivity	0.833	0.583	0.936	β	Chu, 2014 [25]
Specificity	0.857	0.600	0.913	β	
Utility scores					
Stage I	0.79	0.77	0.80	Log-normal	Shi et al., 2016 [27]
Stage II	0.79	0.78	0.80	Log-normal	
Stage III	0.77	0.76	0.79	Log-normal	
Stage IV	0.69	0.65	0.72	Log-normal	

Disutility – false positives	0.25	0.11	0.34	Log-normal	Peasgood et al., 2010 [29]
Costs					
Screening costs	22.7	15.9	29.5	γ	Cost accounting [9]
Treatment costs					
DCIS	2189	1532	2845	γ	Li et al., 2013 [31]
Stage I	9219	6453	11984	γ	Liao et al., 2017 [5]
Stage II	10118	7083	13153	γ	
Stage III	11895	8326	15463	γ	
Stage IV	16156	11309	21003	γ	

Table 2: Lifetime costs, QALYs, and incremental cost-effectiveness ratios

	Lifetime costs per case (US$)	Life years	QALY	Incremental comparisons			
				costs	Life years	QALY	ICER ($/QALY) (95% CI)
Baseline analysis							
No screening	43.3	23.75	23.71	-	-	-	-
Screening every 3 years	230.0	23.79	23.51	186.7	0.04	-0.20	-916 (-1651, -562)
Scenario analysis							
Screening every year	525.7	23.80	23.03	482.4	0.05	-0.68	-704 (-1644, -345)
Screening every 5 years	167.1	23.78	23.59	123.8	0.03	-0.12	-996 (-2950, -461)
Screening every 3 years, 70% compliance rate	180.4	23.78	23.57	137.1	0.03	-0.14	-956 (-2783, -435)
Breast cancer incidence in 2015 from Hong Kong	401.7	23.86	23.47	257.8	0.14	-0.12	- 2111 (-19020, -633)
No utility loss from false positives	230.0	23.79	23.75	186.7	0.05	0.04	5078 (3845, 6534)

CI: confidence interval; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; US$ United States dollars.

a Discounted at 3%.

Note: some inconsistency arose in some values due to rounding.

APPENDIX

Appendix 1 Cost-effectiveness acceptability curve