Economics of Breast Cancer Screening, Genetic Testing, and Treatment

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Declaration

I, Li Sun, confirm that the work presented in the thesis is my own.

When information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Publications, presentations and posters

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Abstract

Breast cancer is the most common female cancer worldwide. This thesis aims to evaluate the cost-effectiveness of breast cancer control across different healthcare contexts and estimate the costs of breast cancer treatment. Four case studies are presented providing detailed estimates of the cost-effectiveness of risk-based breast screening in urban China, the cost-effectiveness of population-based breast screening in rural China, the cost-effectiveness of panel genetic testing among unselected breast cancer patients in the UK and US, and cost of breast cancer treatment by stage at diagnosis in England.

The economic evaluation studies on breast cancer screening show that in urban China, high-risk population-based screening for breast cancer is very likely to be cost-effective. But in rural China, breast screening among the general population reports uncertain cost-effectiveness and could potentially harm women's health due to false positives with the current screening tools. In a rural setting with such low breast cancer incidence, 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.

The economic evaluation on genetic testing based on a microsimulation model showed that unselected panel genetic-testing for all breast cancer patients is extremely cost-effective compared to the current practice of family-history/clinical-criteria based genetic (BRCA)-testing for both UK and US health systems. This supports changing the current policy to expand genetic-testing to all women with breast cancer.

Costs of breast cancer care increased with increasing stage of the disease at diagnosis in England. Considerable cost savings could be made if breast cancer was detected and treated earlier. Variations in breast cancer costs by age and region raise questions about the efficiency and consistency of breast cancer treatment patterns. Future research could be conducted by undertaking multiple imputation for missing data and censored-adjusted analysis.

Content Page

List of Tables

List of Figures

Abbreviations

CBE	Clinical breast examination
CEAC	Cost-effectiveness acceptability curve
CPM	Contralateral prophylactic mastectomy
DALY	Disability-adjusted life year
DSA	Deterministic sensitivity analysis
GDP	Gross domestic product
GLM	Generalised linear model
HIC	High-income countries
ICER	Incremental cost-effectiveness ratio
INMB	Incremental net monetary benefit
LMICs	Low- and middle-income countries
LYG	Life years gained
NICE	National Institute for Health and Care Excellence
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RRM	Risk-reducing mastectomy
RRSO	Risk-reducing salpingo-oophorectomy
WHO	World Health Organisation
WTP	Willingness to pay

Chapter 1 Introduction

1.1 Introduction to this thesis

Breast cancer is the most common cancer among women worldwide. The aim of this thesis is to evaluate the cost-effectiveness of breast cancer control across different healthcare contexts and estimate the costs of breast cancer treatments. I present four empirical case studies in this thesis, including the cost-effectiveness of risk-based breast screening in urban China, the cost-effectiveness of population-based breast screening in rural China, the cost-effectiveness of panel genetic testing among unselected breast cancer patients in the UK and US, and cost of breast cancer treatment by stage at diagnosis in England.

Breast cancer screening is the key to breast cancer control. Numerous economic evaluations have been published that explore the cost-effectiveness of breast cancer screening in low- and middle-income countries (LMICs) (1-15), but the evidence on the breast cancer screening programme in China is insufficient. In China, two pilot breast cancer screening programmes have been conducted in urban and rural areas respectively. Chinese urban women at high risk aged 40-69 years were screened by ultrasound and/followed by mammography (16), and rural women at average risk aged 35-64 years were screened by clinical breast examination coupled with ultrasound as the primary tool (17). However, the relevant economic evidence on the two pilot breast cancer screening programmes in China is still lacking. In this thesis, two of the case studies are presented on the economic evaluation of breast cancer screening in the pilot programmes in urban and rural China respectively.

Breast cancer genetic testing has been increasingly conducted in high-income countries (HIC) over the past few years (18-21). Current national and international guidelines recommend genetic testing in breast cancer patients only if they have a $\geqslant$10% risk of being a BRCA carrier based on family history and clinical criteria (22, 23). However, breast cancer patients with gene mutations do not always have a positive family history and these criteria can miss a large proportion (~50%) of mutation carriers (21, 24, 25). For breast cancer patients, mutation identification enables primary prevention of contralateral breast cancer and ovarian cancer. For the relatives of breast cancer mutation carriers, mutation identification provides the opportunity for early diagnosis and prevention of breast cancer and ovarian cancer. In the third case study, I used data from four large clinical trials/research cohorts to evaluate the cost-effectiveness of offering unselected panel genetic testing to all breast cancer patients compared to the current

practice of restricting genetic testing for breast cancer patients based on family history and clinical criteria in the UK and US settings.

In addition to economic evaluations of breast cancer control based on modelling, I analysed the treatment costs of breast cancer care based on patient-level data. UK data on the costs of breast cancer treatment by stage at diagnosis are out-of-date and were published over 20 years ago (26). Recent NICE appraisals on the cost-effectiveness of breast cancer treatments have instead relied on modelled assumptions (27). Up-to-date estimates of the costs of breast cancer treatments by stage are thus required. In the fourth case study, I used patient-level data from women aged 50 years and over diagnosed with early invasive breast cancer in England to estimate the costs of breast cancer care by stage at diagnosis, and explore to what extent the breast cancer costs vary across different patient groups and regions.

1.2 Research aim and objectives

1.2.1 Aim

To evaluate the cost-effectiveness of breast cancer control across different healthcare contexts and estimate the costs of breast cancer treatment.

1.2.2 Research objectives

- To review the literature on economic evaluations of breast cancer screening in LMICs and breast cancer genetic testing in HICs
- To evaluate the cost-effectiveness of breast cancer screening in the pilot programmes in urban and rural China compared to no screening
- To evaluate the cost-effectiveness of offering multi-gene testing to all breast cancer patients compared to the current practice of family-history/clinical-criteria based genetic testing in the UK and the US
- To review the literature on treatment costs of breast cancer by stage across all countries and identify the methodological differences in costing approaches
- To analyse the treatment costs of breast cancer by stage at diagnosis using patient-level data in England

1.3 Thesis structure

This thesis is structured as follows.

- *Chapter 2* provides an overview of economic evaluation methods, an overview of costing analysis methods, and background information on breast cancer screening, genetic testing, and treatment.
- *Chapter 3* reviews the literature on breast cancer control modelling, including economic evaluation of breast cancer screening in low- and middle-income countries, and economic evaluation of breast cancer genetic testing in high-income countries.
- *Chapter 4* evaluates the cost-effectiveness of risk-based breast cancer screening programmes in urban China based on a Markov model.
- *Chapter 5* evaluates the cost-effectiveness of population-based breast cancer screening programmes in rural China based on a Markov model.
- *Chapter 6* evaluates the cost-effectiveness of offering panel genetic testing to all breast cancer patients compared to the current practice of genetic testing for breast cancer patients based on family history/clinical-criteria using a microsimulation model.
- *Chapter 7* reviews the literature on treatment costs of breast cancer globally and compare the methodological differences in costing approaches.
- *Chapter 8* analyses the costs of care among women aged 50 years and over with a histological diagnosis of early invasive breast cancer in England.
- *Chapter 9* reviews the key findings, discusses the policy and practice implications, reflects on the methodology for modelling, and discusses the limitations. The areas of future research are also discussed.

Chapter 2 Background

The aims of this Chapter are: (i) to give an overview of economic evaluation methods; (ii) to give an overview of costing analysis methods; (iii) to provide a background to breast cancer screening, genetic testing, and treatment.

2.1 Overview of Economic Evaluation

The objective of this section is to provide an overview of economic evaluation methods including the rationale, approaches, and uncertainty.

2.1.1 Economic evaluation rationale

Economic evaluation of health interventions is defined as "the comparative analysis of alternative courses of action in terms of their costs and consequences" (28). The main types of economic evaluation include cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis, and cost-minimisation analysis. Cost-benefit analysis is very rarely conducted in the context of health care as all health benefits are measured in monetary terms. Cost-minimisation analysis should only be used where there is strong evidence that health outcomes are equivalent.

Cost-effectiveness analysis

In cost-effectiveness analysis, effects are measured in natural units which can be either intermediate outcomes (e.g. cases detected, change in mortality) or final outcomes (e.g. life years gained). Cost-effectiveness analysis can be easily performed but it has very limited scope of comparability because it is difficult to compare alternatives with different outcome measures (29).

Cost-utility analysis

Cost-utility analysis uses quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs) to measure health consequences (29). QALY and DALY are generic health outcomes and therefore can be compared across disease areas and interventions. QALYs are estimated by weighting time spent in the relevant health states by the health-related quality of life, with both morbidity and mortality taken into account. DALYs are used to calculate the years of life lost from illness and years lived with a disability. The advantage of cost-utility analysis is that the health outcomes are measured with the same units. Therefore, it can be used to compare results in different health areas. Sometimes the term 'cost-utility analysis' can be used interchangeably with the term 'cost-effectiveness analysis'. In the UK, US, and China settings, cost-utility analysis is primarily recommended with QALYs considered to be the most appropriate generic measure of health outcomes (30-32).

Decision rules in economic evaluation

Economic evaluation is the comparative analysis of alternative interventions in terms of costs and health effects. When comparing a new intervention to a current comparator, four scenarios could arise which can be represented on a cost-effectiveness plane in Figure 2-1 (33).

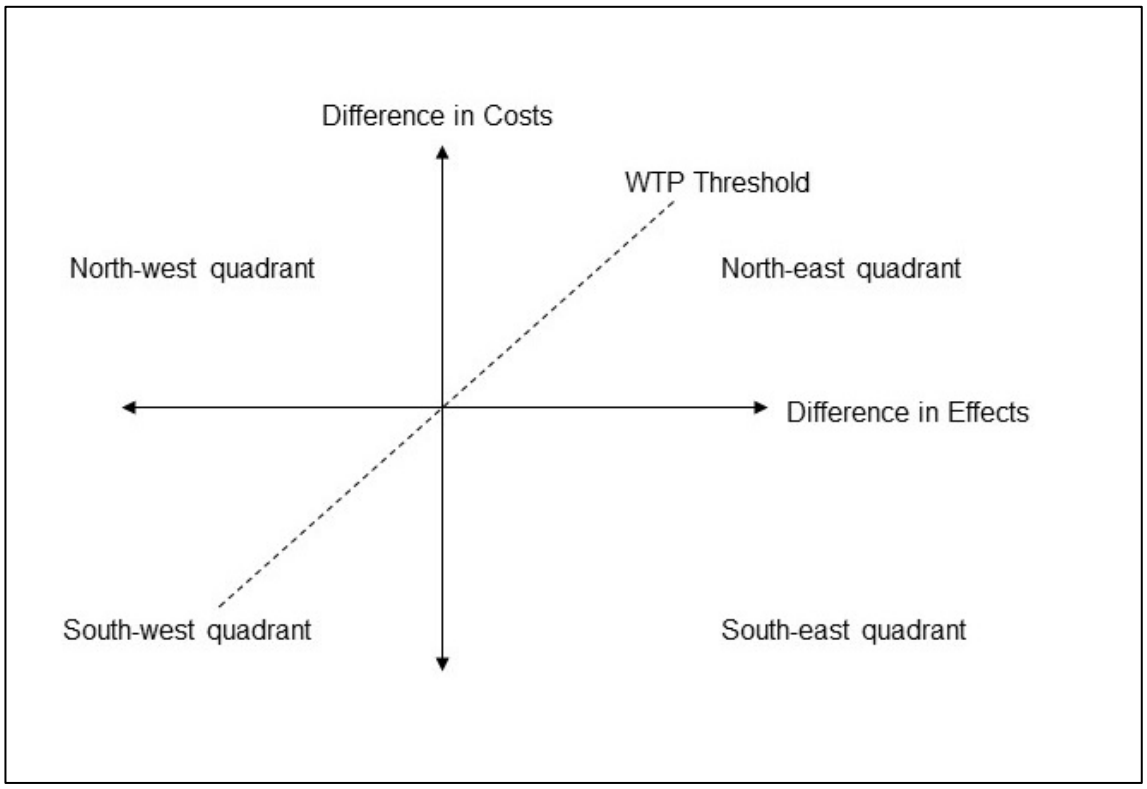

Figure 2-1 Cost-effectiveness plane

The horizontal axis reflects the difference in effects between the new intervention and the comparator, and the vertical axis the difference between costs of the new intervention relative to the comparator. In the north-west quadrant, the new intervention is more costly and less effective, so the comparator dominates the intervention. In the south-east quadrant, the new intervention is cheaper and more effective, so the intervention dominates the comparator. In the north-east quadrant, the new intervention is more effective but also costlier. This scenario is the most commonly encountered in economic evaluation. Also in the south-west quadrant, the new intervention is cheaper but less effective so there is no clear dominating intervention.

The traditional statistic of interest from an economic evaluation is the incremental cost-effectiveness ratio (ICER), which is derived by dividing the difference in intervention and comparator costs by the corresponding difference in effects between the comparators, as below:

$$ICER = (Cost^{Strategy\text{-}A} - Cost^{Strategy\text{-}B}) / (Effect^{Strategy\text{-}A} - Effect^{Strategy\text{-}B})$$

To understand whether the resultant ICER represents good value for money, it needs to be compared with the willingness to pay (WTP) threshold, which indicates the amount that the decision makers are willing to pay for an additional unit of health benefit. If the ICER is lower than WTP threshold (intervention falling below the threshold), the intervention is cost-effective and could be adopted. This is because the net gain in health from the allocation of resources is said to be positive.

In the UK, the National Institute for Health and Care Excellence (NICE) provides the current threshold guideline (30). Broadly speaking, it suggests that interventions with good evidence that an ICER is lower than £20,000/QALY should be accepted. Between £20,000/QALY and £30,000/QALY, other reasons than cost-effectiveness are required, for example equity considerations, and above £30,000/QALY interventions should not be adopted (30). In the US, the $50,000/QALY to $100,000/QALY amount is often cited in the literature as the cost-effectiveness threshold: interventions that produce a QALY for $50,000 or less are good value for money, where those that require $100,000 or more are not (34). Whilst there is no recommended threshold in China, the World Health Organisation suggested that three times Gross Domestic Product (GDP) per capita as the threshold of being cost-effective and one time GDP per-capita as the threshold of being highly cost-effective (35). Therefore, in this thesis I used the thresholds of £20,000/QALY-£30,000/QALY (UK analysis), $50,000/QALY-$100,000/QALY (US analysis), and $23,050/QALY (36) (China analysis, three times GDP per capita). The choice of cost-effectiveness thresholds is discussed in Chapter 9.

2.1.2 Economic evaluation approaches

Clinical trials/cohort studies and decision models are two dominant approaches to conducting economic evaluations.

Clinical trials/cohort studies occupy an important role in evaluating health interventions (37). Economic evaluations conducted alongside pragmatic trials or cohorts provide an opportunity to collect costs and health effects prospectively. Also, this provides access to data on individual patients so sampling uncertainty can be captured (38). In addition, costs and outcomes are correlated because data are collected from the same settings.

A key concern about clinical trials and cohort studies is the limited follow-up periods where events can happen beyond follow-up periods, while decision models are potentially able to predict both short-time and lifetime cost-effectiveness. However, these predictions are conditional on the models being correct. Secondly, few clinical trials or cohort studies will include more than two options and therefore it is hard to compare multiple comparators. Thirdly, single studies often fail to collect all the data necessary

for economic evaluation, such as resource use and health-related quality of life. Some evidence needs to be obtained from other studies to help inform decision-making (37).

A decision model is a mathematical structure that represents a disease process with probabilities of health events occurring. Decision models for economic evaluations are subject to some limitations such as combining heterogeneous pieces of information and adopting modelling assumptions. Different types of decision models and methods by which they are run, exist, such as decision trees, Markov models, and microsimulation models.

Decision trees

Decision trees are the simplest form of decision model where health events are modelled by a series of nodes and branches. Decision trees are only used to solve simple problems because it assumes events occur instantaneously and is not efficient for events that occur repeatedly such as cancer screening.

Markov models

Markov models currently dominate the healthcare economic evaluation literature (39). It is an analytical structure characterised by the Markov assumption of memorylessness, whereby the transition probabilities are independent of the nature or timing of earlier transitions (39). Discrete-time Markov model has an explicit time horizon which is separated into fixed time cycles. Individuals in the cohort are in one of the finite set of health states that reflect the disease progression, and they transition between states according to the transition probabilities over the time horizon.

Microsimulation models

Microsimulation is an individual-based model that follows the progress of individuals with specific attributes over time (40). It permits individual heterogeneity when patient characteristics impact the pathways through the model. Also, it could track individual patient history if the memory of events impacts future cycles. Individual-based models are more flexible and adopt less stringent assumptions compared to cohort models, but require more data and are typically more computationally expensive. For example, in Chapter 6 the microsimulation model required data on characteristics relating to each genetic mutation type.

In this thesis I used Markov models in Chapter 4 and Chapter 5 to estimate the lifetime costs and health effects of breast cancer screening. Also the individuals in the cohorts had the same start age and were screened with the same tools. Therefore, Markov models were the most appropriate in these analyses. In Chapter 6, individuals were different in age and gene types. The individual history of undertaking different risk-

reducing options needs to be tracked as this would impact their disease transition probabilities in future cycles. So microsimulation modelling was used in Chapter 6.

2.1.3 Uncertainty in economic evaluation

In addition to the point estimate of ICER, uncertainty information is required to inform decision-making.

Parameter uncertainty

The uncertainty of model parameter exists due to the sampling errors and the synthesis of data from different sources (41).

Parameter sensitivity analysis includes deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA). DSA varies individual parameters (one-way sensitivity analysis) or a few parameters individually (multi-way sensitivity analysis) to observe their effect on the ICERs. PSA could interpret the joint effect of uncertainty across multiple variables simultaneously. In PSA, the input variables are defined as random variables. Costs are normally specified as having a Gamma distribution, quality of life as having a Log-normal distribution, and probability as having a Beta distribution, as suggested in the literature (42). The incremental net monetary benefit (INMB) is a summary statistic that represents the value of an intervention in monetary terms when a WTP threshold is known. The use of INMB scales both health outcomes and resource use to costs, which allows the comparison of results without using the traditional ICER thus avoiding the problems of interpreting a negative ICER (43). INMB is defined as (44):

$$INMB = \lambda * (Effect^{Strategy\text{-}A} - Effect^{Strategy\text{-}B}) - (Cost^{Strategy\text{-}A} - Cost^{Strategy\text{-}B})$$

Where λ is the WTP threshold. If INMB>0, the new intervention is cost-effective because the cost to derive the health benefit is less than the maximum amount that the decision-maker would be willing to pay for this benefit. For PSA, a large number of estimates of incremental costs and effects can be obtained by sampling from the distributions and the widespread convention in current practice is to conduct between 1,000 and 10,000 simulations (45). Then a cost-effectiveness acceptability curve (CEACs) could be plotted to show the probability of the intervention being cost-effective at different levels of WTP thresholds.

Other forms of uncertainty

There are other forms of uncertainty in economic evaluation, including model structure uncertainty (uncertainty about assumptions that underlie decision models), methodological uncertainty (uncertainty regarding the scope of analysis), heterogeneity uncertainty (variation between patients with particular characteristics), and generalisability uncertainty (uncertainty about whether the results apply in different

contexts). The uncertainty can be reduced by improved analysis (e.g. scenario analysis) with more information or clarity regarding decision-makers objective function.

2.2 Overview of costing analysis

The objective of this section is to provide an overview of cost data collection, perspective, and statistical analysis.

2.2.1 Cost data collection

There are two main approaches to collecting cost data. One approach is micro-costing, also called the bottom-up method, which entails the direct measurement of resource use and the associated unit costs at the micro-level. The other approach is gross costing or top-down method. In gross costing, health services or healthcare interventions are broken down into large components and these large cost items have to be identified (46, 47). Gross costing is faster and cheaper but may lead to low accuracy because of the relatively large measurement units. Micro-costing is more reliable but may be expensive and not always practical (47). Costing data collection methods should depend on the aim of the study and the availability of data (47).

2.2.2 Perspective

The main perspectives for economic evaluations and costing studies are societal perspective and payer perspective. From a societal perspective, all costs (direct medical costs, direct non-medical costs, and indirect costs) are taken into account. Direct medical costs are the expenditures on direct purchasing of inpatient and outpatient medical services, such as diagnostic fees, drug fees, etc. Direct non-medical costs are expenditures as the result of an illness but not involved in the direct purchasing of medical services, such as travel and lodging. Indirect costs are the lost earnings due to the productivity loss related to the morbidity and mortality of illness (48), including temporary disability due to short-term work absences following diagnosis, permanent disability due to reduced working hours following a return to work or workforce departure, and premature mortality due to death before retirement (49).

From a healthcare system/payer perspective, health care providers are only concerned about the direct medical costs falling on their institutions irrespective of any wider implication (50). A payer perspective may provide evidence to allocate resources within the limited budget, but not necessarily maximize the welfare of the whole society (51).

The UK recommends a payer perspective for the primary analysis (30), while in China a societal perspective is primarily recommended (32). In the US, all cost-effectiveness analyses should report two reference case analyses: one based on a payer perspective and the other based on a societal perspective (52). In this thesis, I adopt a societal perspective in the two case studies of economic evaluation in China, both payer and

societal perspectives in the case study of economic evaluation in the UK and US, and a payer perspective in the case study of costing analysis in England.

2.2.3 Statistical analysis

Cost data have some statistical issues, including skewness, zero costs, and censoring.

Skewness

Skewness is a measure of the asymmetry of the distribution of a variable, which can be positive or negative or zero. Positive skewness indicates that the tail on the right side of the distribution is longer than the left side and the main part of the values (including the median) lie to the left of the mean (53). The distribution of cost data is almost always right-skewed due to a minority of patients with very high medical costs (47). In this case, some argued that median can be an alternative to mean as the response to the violation of normality, representing the measure of central tendency better (54, 55). However, costs are usually added together to build up the total expenditure, thus mean is a more meaningful measure than median for decision makers (56).

Zero values

Zero-costs indicate that according to the definition of cost adopted in the study (for example hospitalization costs), no actual costs have been recorded for that patient (e.g. because no hospitalizations occurred) and thus to the cost variable is given a value of zero. A possible large mass of zero observations (true zeroes, not censored values) can cause problems to the application of standard methods. It could also be highly questionable that the two populations, one with zero and the other with positive costs, have the same behaviour with respect to the covariates (53).

Censoring

Censoring occurs when the value of an observation is only partially known which can be caused by loss to follow up or administrative censoring (53). Censoring should be considered to make sure the individuals still under observation are representative of the study population. Otherwise the results may be biased (57).

Different regression models have been developed for cost modelling to address the issues of cost data. In general, in cases of no censoring and no zero-costs, the log-gamma generalised linear model (GLM) is favoured, which deals with non-normality and avoids back-transformation issues (58). Back-transformation issues indicate that if geometric means (means on log scale rather than the logged means) were obtained, it would be difficult to interpret the coefficient results (59, 60). Regarding the zero-cost issues, the two-part mixed model is the most informative by showing the possibility of any expenditure first. For the censoring issues, a regression model can be used which is weighted by the probability of not being censored. There is no unique model that can

deal with all the problems, and the final choice depends on the type and design of the study. In the case study of costing analysis, I have checked different regression models comparing different distribution assumptions. The model that best fit the data based on model selection criteria was selected for further analysis.

2.3 Background to breast cancer

The objective of this section is to provide a background to breast cancer, including screening, genetic testing, and treatment.

Breast cancer is the most common cancer among women worldwide. Globally, 2.1 million new cases of breast cancer were diagnosed in 2018, contributing to more than 24% of female cancer incident cases (61). The incidence rates of breast cancer vary between world regions (62). In more developed regions, the incidence rates are more than twice higher compared to less developed regions (93.6 per 100,000 person-years in the UK, 84.9 per 100,000 person-years in the US, and 36.1 per 100,000 person-years in China in 2018) (63). Breast cancer risk is associated with lifestyle and environmental factors (64). In HICs, the most important contributor is being overweight and obese, whereas in LMICs the lack of physical activity is the most important determinant (65).

Within China, the breast cancer incidence rate in rural areas is lower than the rate in urban areas. However, the mortality from the disease among women residing in rural areas is higher due to poorer survival (66). Marked urban-rural differences in breast cancer stage at diagnosis (67) and survival have been reported (68), 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%) (68).

Breast cancer is potentially a curable disease if diagnosed and treated at an early stage. The Surveillance, Epidemiology, and End Results Programme reported that breast cancer 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% (69). Early detection in order to improve breast cancer outcome and survival remains the cornerstone of breast cancer control (70).

The breast cancer TNM staging system is commonly used to stage breast cancer, while the current practice is to use the International Federation of Gynaecology and Obstetrics (FIGO) classification system by assigning the number of 0, I, II, III, and IV to group these TNM combinations. The relationship between FIGO and TNM classification is detailed in Appendix-1.

2.3.1 Breast cancer screening

Clinical downstaging and screening are two different but complementary approaches to achieving early detection of breast cancer (71). Clinical downstaging is the early diagnosis in the symptomatic population, aiming to ensure that symptomatic women are diagnosed with early (Stage I/II) and curable breast cancer rather than advanced (Stage

III/IV), mainly incurable disease (72). Downstaging could reduce breast cancer mortality, primarily through the initiation of effective treatments earlier. The other method is breast cancer screening in the asymptomatic population with screening technologies such as mammography, ultrasound, and clinical breast examination (CBE, also used in clinical downstaging).

Mammographic screening (using X-rays to examine breasts) has been widely adopted in HICs for over 30 years. It is capable of detecting some tumours several years before they would be palpable (73). The primary determinant of mammographic screening accuracy is breast density. Compared to fatty breasts, mammographic screening is more likely to miss breast cancers in radiographically dense breasts (74). Since an inverse relationship has been found between patient age and breast density, women at younger ages have denser breast and therefore they are more likely to have false-negative results (73). Chinese women's peak age of breast cancer diagnosis is between 45 and 55, which is about ten years younger than that of Caucasian women (75, 76). Chinese women tend to have dense breasts (77, 78), leading to mammography having lower accuracy and being less effective (79-81). Many studies have shown that breast ultrasound has the potential of detecting small invasive breast cancers in women with dense breasts not detected by mammography, thus improving the effectiveness of screening (82-86).

In LMICs mammographic breast cancer screening is prohibitively expensive and a cheaper alternative option is to use ultrasound as the primary screening test. China recommends ultrasound, as opposed to mammography, 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. 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 (17). The screening flow is presented in Figure 2-2.

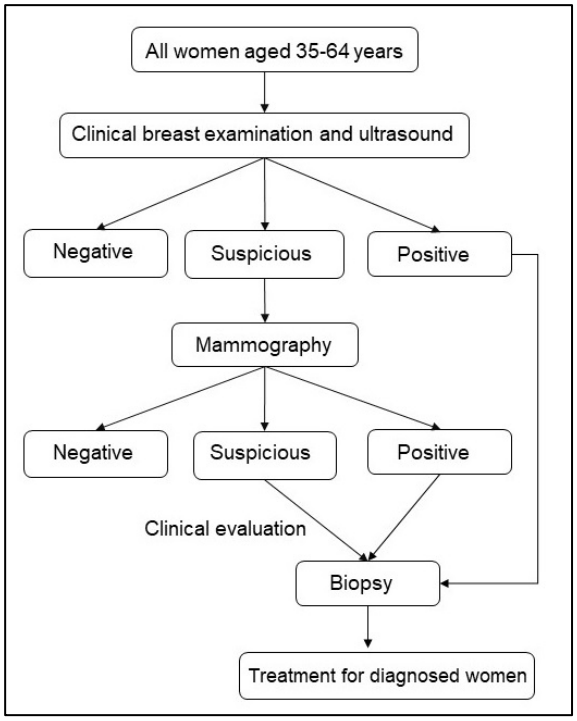

Figure 2-2 Breast cancer screening flow in rural China

In 2012, China launched a risk-based cancer screening programme for urban women aged 40-69 years to screen common cancers including breast cancer. To measure the individual risk of breast cancer, health professionals invited women to health facilities and used paper-based questionnaires to collect information on individual breast cancer exposure (16). The health professionals then used the Harvard Cancer Index online tool, now called Your Disease Risk, to process the collected information and identify women at high risk of developing breast cancer. High-risk women aged 40-44 years are screened by ultrasound and the women with suspected results are further examined by mammography. Women with a suspicious mammography result are tested by biopsy for diagnostic confirmation. High-risk women aged 45-69 years are screened by both mammography and ultrasound, and suspected results from either method are confirmed with biopsy (16). The screening flow is presented in Figure 2-3.

These two pilot programmes of breast cancer screening are still ongoing in China.

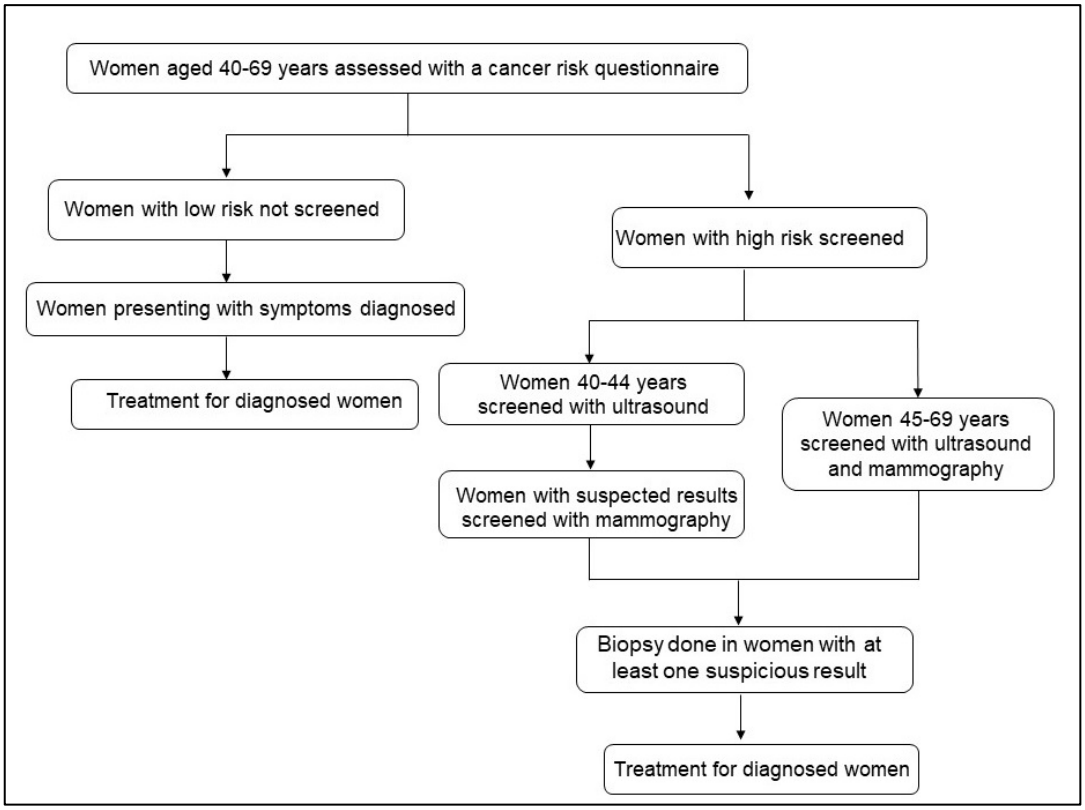

Figure 2-3 Breast cancer screening flow in urban China

In Chapter 3 (first part 3.1), I reviewed the literature on economics of breast cancer screening in LMICs. Since there was no economic evidence of the two pilot breast cancer screening programmes in China, I evaluated the cost-effectiveness of the risk-based breast cancer screening programme in urban China (Chapter 4) and the population-based breast cancer screening programme in rural China (Chapter 5).

2.3.2 Breast cancer genetic testing

BRCA1, BRCA2, and PALB2 are the three most common genes that can mutate and increase the risk of breast cancer. A harmful mutation could be inherited from either parent, and each child of a parent who carries a mutation in these genes has a 50% chance of inheriting the mutation. BRCA1/BRCA2 carriers have a 17-44% risk of developing ovarian cancer and 69-72% risk of developing breast cancer up to age 80 years (87). PALB2 is a more recently established moderate penetrance breast cancer gene, testing for which is now advocated. PALB2 carriers have a 44% risk of breast cancer up to age 80 years (88).

Identifying mutation carriers provides the opportunity for early diagnosis and prevention of breast cancer. There are a number of risk management options for unaffected women with known mutations. To reduce breast cancer risk, BRCA1/BRCA2/PALB2 mutation carriers can be offered enhanced MRI/mammography screening (89), risk-reducing

mastectomy (RRM) (90), or chemoprevention with selective estrogen-receptor-modulators (91). To reduce ovarian cancer risk, BRCA1/BRCA2 mutation carriers can opt for risk-reducing salpingo-oophorectomy (RRSO) (92, 93). For patients that have already been diagnosed with unilateral breast cancer (cancer in one breast), mutation carriers can choose contralateral prophylactic mastectomy (CPM) (preventative mastectomy on the other breast) to reduce their risk of developing contralateral breast cancer as well as surgical prevention for ovarian cancer. Cancer-affected carriers may become eligible for treatment with novel drugs (like poly ADP ribose polymerase (PARP) inhibitors, a group of oral pharmacological inhibitors for targeted therapy) and newer precision medicine based therapeutics through clinical trials. Therefore, knowing genetic mutation status is important for breast cancer clinical management and overall prognosis.

Current national and international guidelines recommend genetic testing in individuals who fulfill recognised/established family-history or clinical-criteria. These criteria are surrogates for BRCA probability with testing offered at around a ≥10% probability of being a BRCA-carrier (22). However, people with genetic mutations do not always have a positive family history and these criteria can miss a large proportion (~50%) of mutation carriers (21, 24, 25). Also, family history/criteria-based strategy is dependent on patient and their doctor's awareness of and understanding the importance of their family history, the accuracy of family history, communication within/between families and timely referrals to clinical genetics. Limited health professional/public awareness and complexity of the current structure and testing pathway has fostered restricted access and massive under-utilisation of genetic testing services (94-96). Unfortunately, this gate-keeper approach has resulted in only 20%-30% of patients eligible for testing being referred for this, missing huge opportunities for precision prevention (94).

An alternative option is to offer panel BRCA1/BRCA2/PALB2 genetic testing for all breast cancer cases instead of the current practice of family-history/clinical-criteria based genetic (BRCA)-testing. A further advantage is the opportunity to test relatives of breast cancer patients. This offers the potential to identify relatives carrying mutations and the opportunity for early diagnosis and prevention of cancer as they are at higher risk.

In Chapter 3 (second part 3.2) I reviewed the literature on economics of genetic testing for breast cancer patients in HICs. In Chapter 6, I compared the downstream health impacts, costs, and cost-effectiveness of panel BRCA1/BRCA2/PALB2 genetic testing for all breast cancer cases with the current practice of BRCA testing based on family history/clinical criteria in the US and UK settings. I have obtained data from four large breast cancer clinical trials/research cohorts and used a microsimulation model to conduct the cost-effectiveness analysis. The microsimulation model permits individual heterogeneity in gene types and ages, and can track individual patient history if the

memory of events (e.g. risk-reducing options for breast cancer and ovarian cancer) impacts future cycles.

2.3.3 Breast cancer treatment

Treatment options for breast cancer consist of surgery, radiotherapy, chemotherapy, endocrine therapy, and targeted therapy. There are three important receptors for breast cancer: estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2).

Surgery

Breast resection surgeries include breast-conserving surgery, mastectomy, and mastectomy with reconstruction. Breast-conserving surgery is the removal of the cancerous lump. Studies have shown that breast-conserving surgery followed by radiotherapy is as successful as mastectomy at treating early-stage breast cancer (97). Mastectomy is the removal of all the breast tissue. Reconstruction can be carried out at the same time as a mastectomy (immediate reconstruction) or later (delayed reconstruction) (97).

The types of lymph node involvement procedures are directed by axillary ultrasound (+/- axillary biopsy) findings. If the ultrasound assessment and histological assessment of the axilla show that cancer has spread to the axillary lymph node, a patient will typically have axillary lymph node dissection (ALND) which removes all the axillary lymph nodes. If the ultrasound shows no evidence of cancer spread, patients undergo sentinel node biopsy (SNB) which involves the removal and examination of the first few lymph node/s (sentinel node/s) to which a tumour is likely to spread. If the sentinel node contains macrometastatic (a tumour deposit in a lymph node with a diameter>2mm) involvement with cancer, a patient may go on to have an ALND (98) or in some circumstances may have axillary radiotherapy as an alternative axillary treatment.

Radiotherapy and chemotherapy

Radiotherapy uses controlled doses of radiation to kill remaining cancer cells usually after surgery or chemotherapy. Chemotherapy involves using cytotoxic medication to kill cancer cells, including both neoadjuvant chemotherapy before surgery to shrink a large tumour and adjuvant chemotherapy after surgery to destroy remaining cancer cells. For patients with early breast cancer, preoperative chemotherapy is proved to be equally effective as postoperative chemotherapy regarding survival (99).

Endocrine therapy

Endocrine therapy is given to hormone receptor-positive breast cancer. ER+ cancer cells depend on estrogen for growth, so drugs blocking the estrogen effects can be used for

treatment (e.g. tamoxifen) (100). In most cases, endocrine therapy lasts a total of five years (97).

Targeted therapy

Targeted therapy is given to patients with HER2+ breast cancer. HER2+ breast cancers are generally more aggressive than HER2- breast cancers (101), but HER2+ cancer cells respond to drugs such as the monoclonal antibody trastuzumab (102).

The general therapy strategies are summarised for patients with early breast cancer (Figure 2-4) (100) and metastatic breast cancer (Figure 2-5) (103), which can be individualised based on disease characteristics and patient characteristics (104).

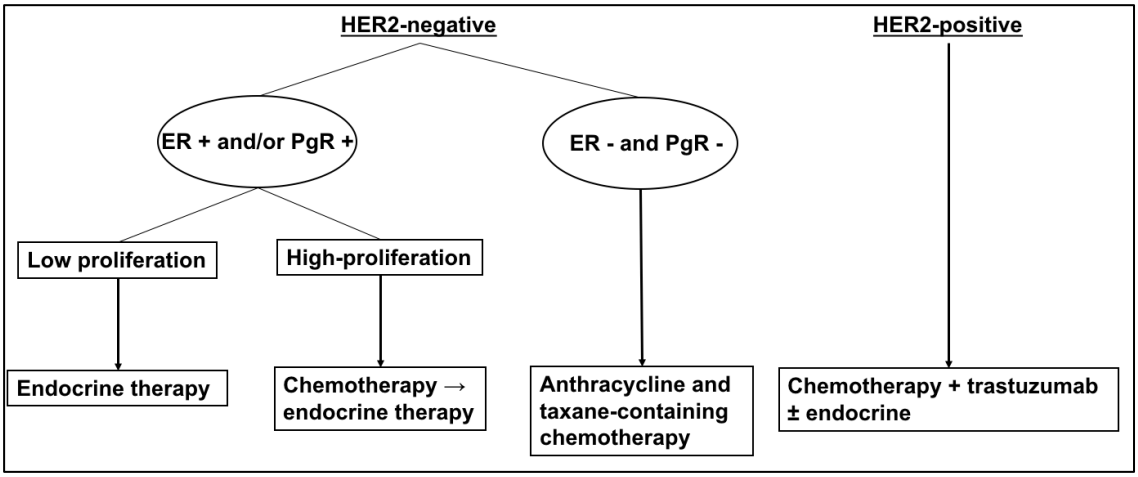

Figure 2-4 Systematic therapy strategies in early breast cancer

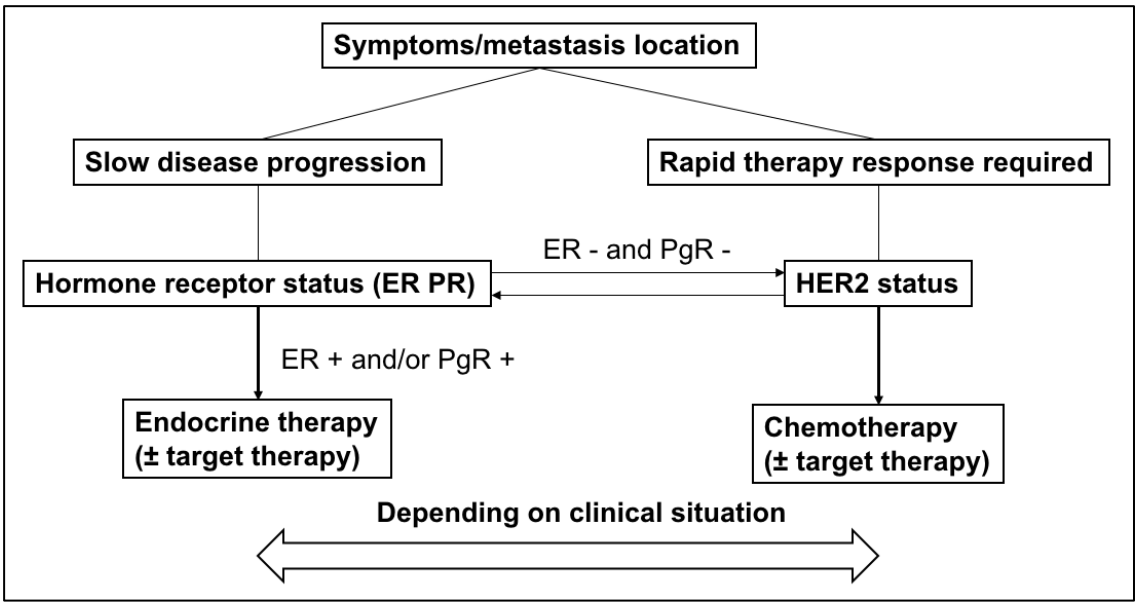

Figure 2-5 Systematic therapy strategies in metastatic breast cancer

Although the case for earlier diagnosis with respect to survival has been well made, the financial implications are not well understood (105, 106). Stage of disease at diagnosis is an important predictor of treatment costs. Treatment for more advanced disease is often more intensive or invasive than treatment for the earlier stages (105). As a result, a more advanced stage tends to be associated with more resource utilisation in addition to poorer health outcomes (107).

Treatment costs by stage at diagnosis are important in quantifying the gains from early detection. If early treatment lowers costs, this will help offset some cost of interventions for earlier diagnosis and treatment. In addition, treatment costs by stage would be valuable to inform the cost-effectiveness studies for treatment or preventative interventions of breast cancer. However, the mean costs by stage do not reveal the heterogeneity across patients. Patient-level data can contain information such as socioeconomic group, medical history, and treatment options, thus allowing the comparison of costs across patient subgroups and identification of cost predictors. Therefore, it is important to analyse the costs of breast cancer treatment by stage at diagnosis using patient-level data.

In Chapter 7, I conducted a systematic review to compare treatment costs of breast cancer by stage at diagnosis across countries. UK data on the costs of breast cancer treatment by stage at diagnosis are out-of-date and were published over 20 years ago (26). Recent NICE appraisals on the cost-effectiveness of breast cancer treatments have instead relied on modelled assumptions (27). Up-to-date estimates of the costs of breast cancer treatments by stage are thus required. In Chapter 8, I used patient-level data from women aged 50 years and over diagnosed with early invasive breast cancer in England to estimate the costs of breast cancer care by stage at diagnosis, and explore to what extent the breast cancer costs vary across different patient groups and regions.

Chapter 3 Literature review on modelling

The aims of this Chapter are: (i) to review the literature on economic evaluation of breast cancer screening in low- and middle-income countries (LIMCs); and (ii) to review the literature on economic evaluation of breast cancer genetic testing in high-income countries (HICs).

3.1 Economic evaluation of breast cancer screening in LMICs

3.1.1 Introduction

Breast cancer incidence rates in LMICs are lower but survival rates are poorer than the rates in HICs (62). The poor prognosis of breast cancer in LMICs is mainly related to the disadvantage in access to breast cancer screening and treatment (108, 109). Breast cancer screening programs in LMICs are often hampered by limited health resources (110). Also, LMICs often lack evidence-based information on breast cancer screening strategies in contrast to the established strategies in HICs (111-115). Due to the differences in population characteristics and the functioning of health systems, LMICs cannot adopt the results in HICs and need to develop their own breast cancer screening strategies.

An earlier study reviewed economic studies about breast cancer control (screening, diagnostic, and therapeutic interventions) in LMICs published until January 2013 (111). Studies in Mexico, Poland, Turkey identified mammography screening as a cost-effective intervention (1-4), whereas studies in India, Ghana, and Egypt found other strategies (such as clinical breast examination screening or mass-media awareness raising) to be more economically attractive (5-7). The systematic review argued that more economic analyses of better quality should be conducted to give more clear recommendations (111). Updated evidence is required on economic analyses of breast cancer screening in LMICs after 2013. In this section, I undertook a systematic review to update the economic evidence on breast cancer screening in LMICs.

3.1.2 Method

Eligibility criteria

The inclusion criteria were based on the PICOS framework: (i) population: asymptomatic women in LMICs; (ii) intervention: any form of breast cancer screening; (iii) comparator: not restricted; (iv) outcome: incremental cost-effectiveness ratio; and (v) study design: modelling studies or trial-based economic evaluations.

I excluded studies with the following characteristics: (i) only costs or clinical efficacy reported; (ii) cost minimisation analysis; (ii) budget impact analysis alone but without cost-effectiveness or cost-utility analysis; (iv) review articles.

Eligibility criteria

I searched MEDLINE(R) (2013 to Week 2 March 2019) and EMBASE Classic + EMBASE (2013 to 15 March 2019) with search terms presented in Appendix-2. I employed Cochrane LMIC Filters to limit the studies to low- and middle-income countries (116). Also, reference lists from relevant primary studies and review articles were used to identify other relevant publications. My search was limited to publications in English. Titles and abstracts were first reviewed, and full-texts of the studies that potentially met the eligibility criteria were retrieved and full-text reviewed.

Data extraction

I extracted the study characteristics including settings, population, interventions, comparators, and conclusions. Also, I documented the following methodological characteristics: economic evaluation types, perspectives of analysis, study designs, time horizons, sources for costs, sources for clinical effectiveness, outcome measures, discount rates, incremental analyses, and sensitivity analyses.

Economic evaluation types are categorised as cost-effectiveness, cost-utility analysis cost-benefit analysis, and cost-minimisation analysis. Study designs include experimental, observational (cohort, case-control, or cross-sectional), Markov model-based, and decision tree model-based. I classified the sources for estimation of effectiveness and resource utilization by primary data collection (e.g. questionnaires, patients), secondary data collection (e.g. unit cost lists), literature, and expert opinion. Also I documented whether future costs and health effects were discounted to reflect the positive time preference. I also summarised whether incremental analyses and sensitivity analyses were conducted.

Critical appraisal

The established Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (117) was employed to assess the reporting quality of the reviewed studies. A three-point response scale was used to grade the quality of each item on the checklist, ranging from 0 (not considered), through 1 (partially considered), to 2 (fully considered) (118). I summed up all scores and compared this with the maximum attainable score to calculate the percentage of the maximum attainable score.

3.1.3 Results

Search results

The search took place in March 2019 and the stepwise selection flow of articles is presented in Figure 3-1. The MEDLINE and the EMBASE search yielded 52 and 176 possible studies respectively. The collective searches yielded 193 unique studies after removing duplicates. Based on the eligibility criteria, I excluded 185 studies and included eight studies in this review.

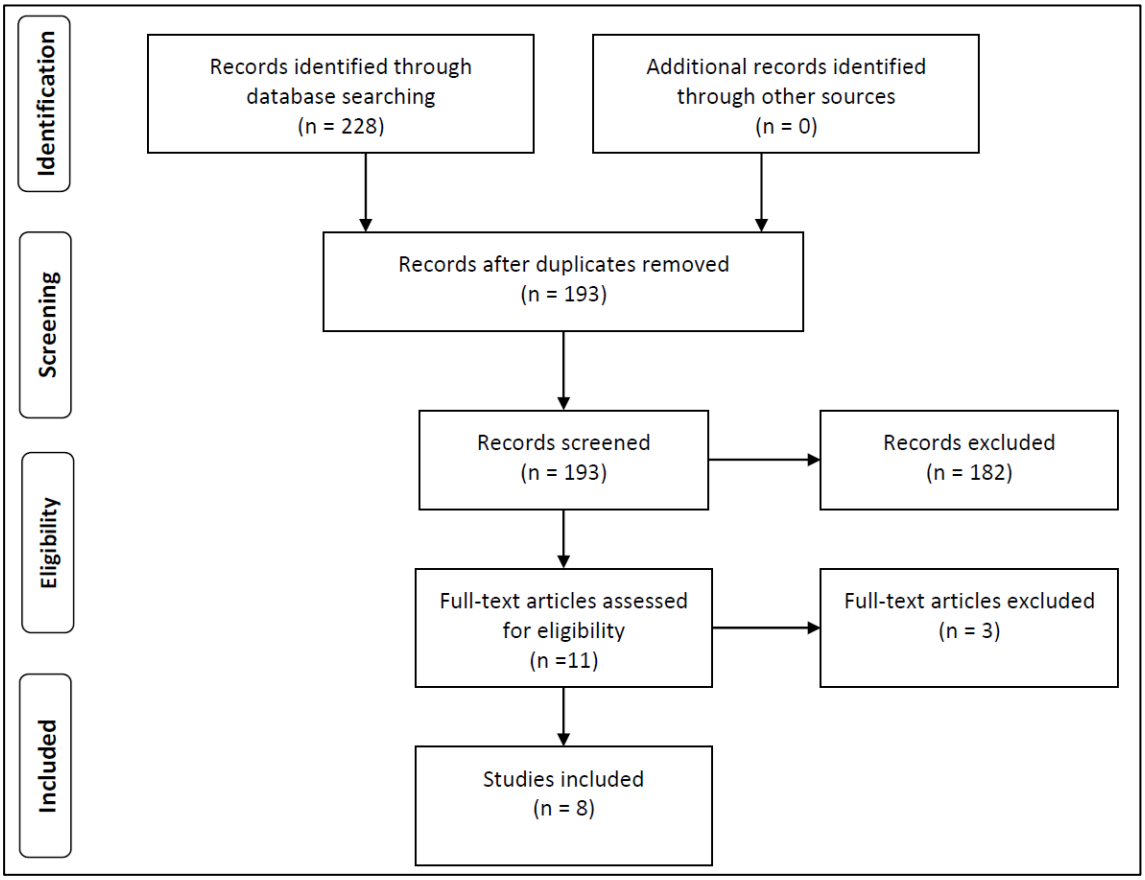

Figure 3-1 Breast cancer screening – study flow diagram

Study characteristics

Table 3-1 describes the baseline characteristics of the eight included studies. I found five studies from Asia including Iran (n=2), Vietnam (n=2), China (n=1), two from Latin America including Peru (n=1), Costa Rica and Mexico (n=1), and one on a sub-regional level from Southeast Asia and eastern sub-Saharan Africa (n=1).

Five studies evaluated breast cancer screening interventions alone (8-12). The other three studies compared a variety of breast cancer-related intervention scenarios, including screening, early detection, palliative, or treatment interventions (13-15). These three studies allowed a situation that no interventions were implemented, where the counterfactual acted as a reference to compare all possible interventions (119).

The studies in Vietnam and Peru identified mammography screening as cost-effective (11, 13), whereas studies in Iran provided evidence that mammography screening was not cost-effective mainly due to screening harms (9, 10). Some other screening strategies have been shown to be economically attractive, such as clinical breast examination (CBE) in Vietnam and Costa Rica (8, 14), mass-media awareness in Mexico (14), and CBE followed by mammography and ultrasound in China (12).

The study for Southeast Asia and eastern sub-Saharan Africa compared three breast cancer interventions, including: (1) screening with mammography every two years for 50-59 years linked with timely diagnosis and treatment; (2) treatment of breast cancer stages I and II with surgery and/or systematic therapy; (3) basic palliative care for breast cancer. The study showed that the treatment of breast cancer (Stage I and II) with surgery and/or systematic therapy at 95% coverage was the most cost-effective intervention in both regions (15).

Methodological characteristics

Table 3-2 presents the methodological characteristics of the reviewed articles. The majority of studies combined both costs and effects in a single cost-effectiveness estimate (n=7). One experimental study reported costs and effects separately (9). The majority of these conducted cost-utility analysis based on Markov models, measuring health outcomes in QALYs (10, 12, 15) or DALYs (13, 14). Other outcome measures were also used such as life years gained (8, 11) and the number of cases detected (9). Most studies used the payer perspective (n=6), one used the social perspective (12), and one did not present the perspective (15). The time horizons among the reviewed studies varied between one year and a lifetime horizon. One-way sensitivity analyses (8, 10-12, 14), probabilistic sensitivity analyses (8, 10, 12, 15) and scenario analyse (9, 13) were conducted to explore the uncertainty.

Study quality

The quality of the reviewed studies is presented in Table 3-3, as indicated by the percentage score ranging from 72.7% to 97.7%. Studies by Nguyen et al. (8) had the highest total scores among the reviewed papers. The average score for titles and abstracts was 84.4%, measuring whether the studies reported all the elements in titles and abstracts so they could be identified as economic evaluation studies. On the methodological domain, studies scored 89.7% of the maximum obtainable score across all studies. The average scores for results and discussion were 62.5% and 87.5% respectively.

3.1.4 Discussion

This study supplemented the economic evidence from eight studies after 2013 to the existing studies about breast cancer screening in LMICs identified in the earlier systematic review (111).

Although mammography-based screening strategies have been widely adopted in developed countries for over 30 years, this study suggests that there is mixed evidence on the cost-effectiveness of mammography screening in LMICs. Mammography was shown to be not economically attractive in Iran (9, 10), but it was good value for money in Vietnam and Peru (11, 13). My results are consistent with the inconclusive economic evidence on mammography screening from the previous literature review in 2013 (111).

The inconsistent results of the reviewed cost-effectiveness studies on mammography screening for breast cancer are partly due to the debatable effectiveness of mammography. Although mammographic screening has been shown to reduce breast cancer mortality by 20%, it is associated with considerable harm in terms of overdiagnosis (120). Carcinoma in situ is much more likely to be detected by mammography screening, but more than half of the cases will not progress to be invasive cancer (121). Also, some identified tumours may be slow-growing that would never have been clinically apparent before a woman dies from another cause (73). Overdiagnosis could undermine the quality of life because women would experience important psychological distress (122). In addition, mammography for breast cancer screening is prohibitively expensive in LMICs. This also makes mammography as the primary screening tool less cost-effective in LMICs. More economic evidence on mammography screening is required to determine its economic attractiveness in LMICs.

It was emphasised in 2013 that there was very little economic evidence on the less established interventions such as tactile imaging, awareness raising, clinical breast examination screening, or palliative interventions in LMICs (111). Over the past years, some screening methods have been shown to be cost-effective such as CBE in Vietnam and Costa Rica (8, 14), CBE followed by mammography and ultrasound in China (12), and mass-media awareness raising in Mexico (14). However, the evidence is still insufficient and economic studies should aim to evaluate these interventions more often.

The quality of the reviewed articles over the past five years has improved compared to those published before 2013, of which the majority failed to score at least 50% on every domain (111). Among the five reviewed studies in our analysis, the studies on average scored 84.7% of the maximum obtainable score. However, we used the latest version of Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (2013) (117) in our review, rather than the Guidelines for Authors and Peer Reviewers

of Economic Submissions to the British Medical Journals in 1996 (123). Therefore, the different assessment domains deserve careful consideration.

The most adopted study design was modelling-based study. Compared to trial-based studies, decision models could include multiple relevant comparators and allow sufficient time horizon to reflect the changes in costs and health outcomes. Also, modelling-based studies could incorporate data from different sources and play an important role in extrapolating results to a wider population or a broader setting (37). Markov model is an analytical structure with explicit consideration of time and individuals transition between health states according to the transition probabilities over stated time cycles. Markov model is a good choice for repeat events such as breast cancer screening (124). Therefore, we advocate the use of Markov modelling in the economic studies of breast cancer control in LMICs.

This study may be limited by the publication bias, indicating that studies with negative outcomes are less likely to be published. Also, as with the previous systematic review of economic analyses on breast cancer control, I only searched for articles published in English. Ideally, two investigators should independently extract the data and assess the study quality. As this systematic review was undertaken by only one investigator, potential bias deserves careful considerations.

In conclusion, our findings indicate that although some more studies have been performed, the economic evidence on breast cancer screening interventions in LMICs is still insufficient. There is one study providing economic evidence of breast cancer screening in China. However, it was a community-level screening programme in one city, in which the age group of the target population and screening method were different from those in China's rural or urban breast cancer screening pilot programmes. In Chapter 4, I evaluated the cost-effectiveness of risk-based breast cancer screening programmes in urban China. In Chapter 5, I analysed the cost-effectiveness of population-based breast cancer screening programmes in rural China.

3.1.5 Tables

Table 3-1 Study characteristics of reviewed papers

Study	Setting	Population	Intervention	Comparator	Conclusion
Screening interventions					
Nguyen et al., 2013 (8)	Vietnam	Asymptomatic women aged 40 years	An annual CBE screening program for 15 years	No Screening	Annual CBE screening is cost-effective at 3*GDP per capita.
Barfar et al., 2014 (9)	Iran	Asymptomatic women aged 35 years and over	Mammography screening	No Screening	Mammography screening is not cost-effective.
Haghighat et al., 2016 (10)	Iran	Asymptomatic women aged 40-70 years	Three rounds of organised triennial mammography screening	No Screening	The first round of screening is cost-effective but the second and third rounds are not cost-effective at 3*GDP per capita.
Nguyen et al., 2018 (11)	Vietnam	Asymptomatic women aged 45-64 years	One round of mammography screening	No screening	One round of mammography screening to women aged 50–59 years is cost-effective at 3*GDP per capita.
Yang et al., 2018 (12)	China	Asymptomatic women aged 35-69 years	BCE and mammography followed by ultrasound	No screening	Annual community-based screening is cost-effective at 3*GDP per capita.
Multiple interventions					
Zelle et al., 2013 (13)	Peru	Depends on the interventions	94 breast cancer-related interventions	No intervention (WHO-CHOICE)	A combined mobile and fixed mammography screening triennially is the most cost-

					effective. Triennial CBE, and CBE combined with fixed mammography screening, are more feasible and also cost-effective.
Niens et al., 2014 (14)	Costa Rica, Mexico	Depends on the interventions	19 breast cancer-related interventions	No intervention (WHO-CHOICE)	In Costa Rica, the current strategy of treating breast cancer in stages I to IV at an 80% coverage level is the most cost-effective. At a coverage level of 95%, biennial CBE screening could be very cost-effective. In Mexico, a mass-media awareness raising program at 95% coverage could be the most cost-effective with the threshold of GDP and 3*GDP per capita.
Ralaidovy et al., 2018 (15)	Southeast Asia, Eastern Sub-Saharan African	Depends on the interventions	Three breast cancer-related interventions	No intervention (WHO-CHOICE)	The treatment of breast cancer (Stage I and II) with surgery and/or systematic therapy at 95% coverage is the most cost-effective intervention in both regions.

Table 3-2 Methodological characteristics of reviewed papers

Study	Type	Perspective	Study design	Time horizon	Sources for costs	Sources for effectiveness	Outcome measure	Discount	Incremental analysis	Sensitivity analysis
Nguyen et al., 2013 (8)	CEA	Payer	Markov	Lifetime	Secondary/ Literature	Literature	LYG	Yes	Yes	One-way and PSA
Barfar et al., 2014 (9)	Costs and effects separately	Payer	Experimental	1 year	Primary	Primary data	Cases detected	No	No	Scenario analysis
Haghighat et al., 2016 (10)	CUA	Payer	Decision tree and Markov	50 years	Literature	Literature	QALY	Yes	Yes	One-way and PSA
Nguyen et al., 2018 (11)	CEA	Payer	Markov	Lifetime	Secondary/ Literature	Literature	LYG	Yes	Yes	One-way and PSA
Yang et al., 2018 (12)	CUA	Societal	Markov	Lifetime	Literature	Literature	QALY	Yes	Yes	One-way and PSA
Zelle et al., 2013 (13)	CUA	Payer	Markov	Lifetime	Secondary/ Literature	Literature	DALY	Yes	No	Scenario analysis
Niens et al., 2014 (14)	CUA	Payer	Markov	100 years	Secondary/ Expert opinion	Literature	DALY	Yes	No	One way
Ralaidovy et al., 2018 (15)	CUA	NA	Markov	NA	Secondary	Literature	QALY	Yes	Yes	NA

*LYG: life year gained; QALY: quality-adjusted life year; DALY: disability-adjusted life year; PSA: probabilistic sensitivity analysis; CEA: cost-effectiveness analysis; CUA: cost-utility analysis

Table 3-3 Quality assessment of reviewed studies using CHEERS checklist

Study	Title and abstract	Introduction	Methods	Results	Discussion	Sum of scores
Nguyen et al., 2013 (8)	4 (100%)	2 (100%)	27 (96.4%)	8 (100%)	2 (100%)	43 (97.7%)
Barfar et al., 2014 (9)	4 (100%)	2 (100%)	27 (96.4%)	4 (50%)	0 (0%)	37 (84.1%)
Haghighat et al., 2016 (10)	3 (75%)	2 (100%)	23 (82.1%)	5 (62.5%)	2 (100%)	35 (79.5%)
Nguyen et al., 2018 (11)	4 (100%)	2 (100%)	26 (92.9%)	8 (100%)	2 (100%)	42 (95.5%)
Yang et al., 2018 (12)	2 (50%)	2 (100%)	25 (89.3%)	6 (75%)	2 (100%)	37 (84.1%)
Zelle et al., 2013 (13)	3 (75%)	2 (100%)	26 (92.9%)	3 (37.5%)	2 (100%)	36 (81.8%)
Niens et al., 2014 (14)	3 (75%)	2 (100%)	26 (92.9%)	3 (37.5%)	2 (100%)	36 (81.8%)
Ralaidovy et al., 2018 (15)	4 (100%)	2 (100%)	21 (75%)	3 (37.5%)	2 (100%)	32 (72.7%)
Average	3.4 (84.4%)	2 (100%)	25.1 (89.7%)	5 (62.5%)	1.8 (87.5%)	37.3 (84.7%)

3.2 Economic evaluation of genetic testing in HICs

3.2.1 Introduction

A systematic review has been performed on economic evaluations of healthcare programmes involving BRCA testing, searching studies until December 2014 (125). Nine economic evaluations were included and four categories of BRCA testing programmes were identified, including (i) testing population-based individuals without cancer (126-129), (ii) testing individuals without cancer but with family history-suggestive of BRCA mutation (129, 130), (iii) testing patients with BRCA-related cancers (131), and (iv) testing patients with BRCA-related cancers and their cancer-free relatives sequentially if a mutation was identified (18-20).

Specifically for economic evaluations on testing women with BRCA-related cancers and cascade testing of relatives of the index cases, all the three studies showed some evidence for cost-effectiveness (18-20). In the two studies in Spain and the US (19, 20), genetic tests were offered to affected women at risk for inherited breast/ovarian cancer according to personal and familial criteria. Another Norwegian study compared genetic testing of all incident breast and ovarian cancers with family history-based testing (18). However, this study is outdated, published 20 years ago, and only took BRCA1 mutation into consideration.

In this section, I reviewed relevant papers published after December 2014 to find out whether there is any updated economic evidence on unselected testing of breast cancer patients and cascade testing of relatives of index cases.

3.2.2 Method

The inclusion criteria were based on the PICOS framework: (i) population: breast cancer patients; (ii) intervention: genetic testing to breast cancer patients and cascade testing of relatives; (iii) comparator: not restricted; (iv) outcome: incremental cost-effectiveness ratio; and (v) study design: modelling studies or trial-based economic evaluations. The exclusion criteria were: (i) only costs or clinical efficacy reported; (ii) cost minimisation analysis; (ii) budget impact analysis alone but without cost-effectiveness or cost-utility analysis; (iv) review articles.

I searched MEDLINE(R) (2015 to Week 2 March 2019) and EMBASE Classic + EMBASE (2015 to 15 March 2019) to search papers published after 2015 (search terms in Appendix-3). Titles and abstracts were first reviewed, and full-texts of the studies that potentially met the eligibility criteria were retrieved and full-text reviewed.

3.2.3 Results

The study flow diagram is presented in Figure 3-2. The MEDLINE, the EMBASE, and other sources yielded 27 possible studies. Based on the eligibility criteria, only one study about cost-effectiveness of unselected genetic testing in breast cancer patients was identified in Norway.

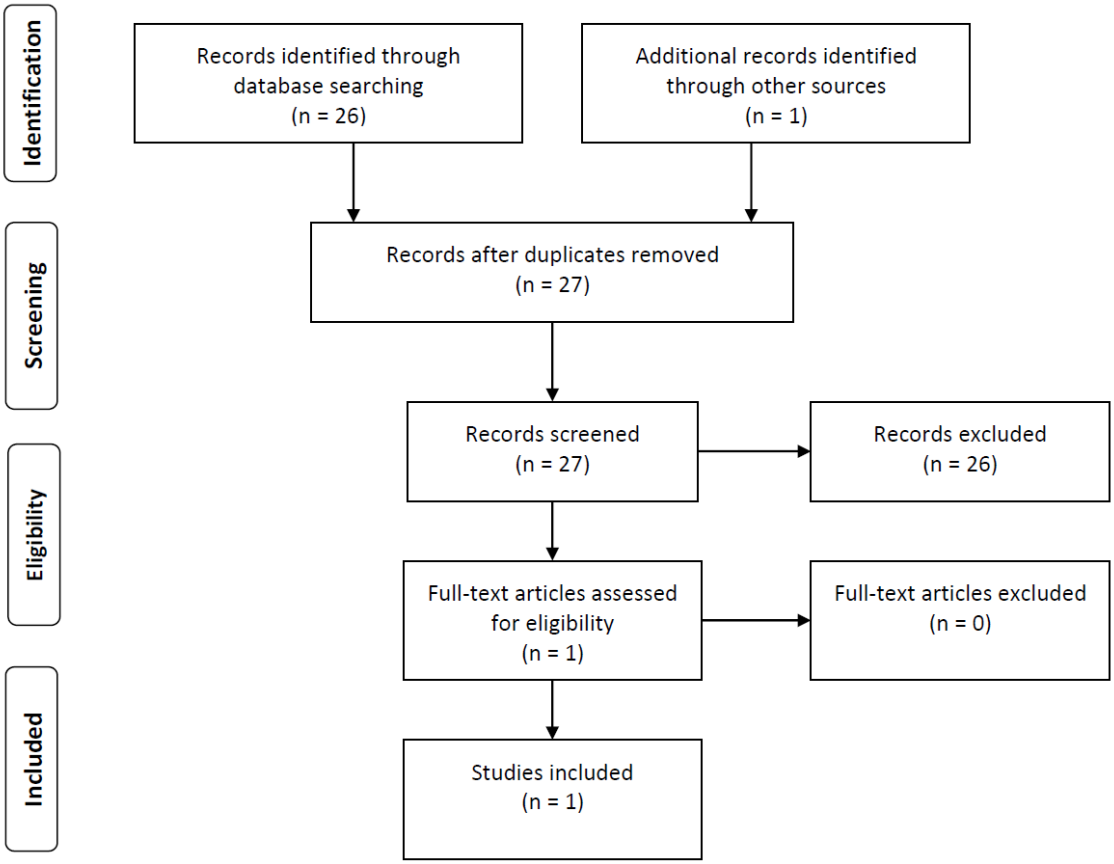

Figure 3-2 Breast cancer genetic testing – study flow diagram

The Norwegian study used a decision tree-based model to evaluate the lifetime cost-effectiveness of genetic testing all patients with breast cancer and their unaffected relatives compared to testing based on family history. Breast cancer patients with BRCA1/BRCA2 mutations can choose risk-reducing salpingo-oophorectomy (RRSO) to reduce ovarian cancer. Unaffected BRCA1/BRCA2 mutation carriers can choose risk-reducing mastectomy (RRM) to reduce breast cancer risk and RRSO to reduce ovarian cancer risk. The analysis was conducted from the payer and the societal perspectives, with data employed from 535 breast cancer patients (21). Life years gained were used to measure health outcomes. It was reported that the ICER was lower than the frequently used WTP thresholds, and thus BRCA testing of all breast patients was economically superior to family-history approach. The sensitivity analysis documented that the cost of genetic test was the prominent parameter affecting the results.

3.2.4 Discussion

In conclusion, there is only a recent small Norwegian study (535 patients) showing the cost-effectiveness of BRCA-testing all breast cancer patients. In Chapter 6, I obtained data from 11,836 population-based breast cancer patients regardless of family history from four large research studies to estimate the lifetime cost-effectiveness of multigene-testing (BRCA1/BRCA2/PALB2) all breast patients in the UK and US, which is both broader in scope and draws on a much larger sample-size of population-based breast cancer patients.

Chapter 4

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed <u>for each</u> research paper included within a thesis.

SECTION A – Student Details

Student ID Number	15115005	**Title**	Miss
First Name(s)	Li		
Surname/Family Name	Sun		
Thesis Title	Economics of breast cancer screening, genetic testing, and treatment		
Primary Supervisor	Rosa Legood		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

<u>SECTION B – Paper already published</u>

Where was the work published?	Bulletin of the World Health Organisation		
When was the work published?	2018		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Please refer to details on the following page

SECTION E

Student Signature	
Date	

Supervisor Signature	
Date	

Chapter 4

Cost-effectiveness of risk-based breast cancer screening programme in urban China

Chapter 4 evaluates the cost-effectiveness of breast cancer screening programmes in urban China. I conceived the research question, developed the Markov model, collected the data, discussed the results and wrote the manuscript. Professor Isabel dos Santos Silva helped revise the Markov model to simulate the disease progression better. Dr Rosa Legood, Dr Zia Sadique, and Dr Li Yang gave comments and suggestions on findings and interpretations. All authors approved the final draft prior to journal submission and inclusion in the thesis. This paper has been published by Bulletin of the World Health Organisation.

Research

Cost–effectiveness of risk-based breast cancer screening programme, China

Li Sun,[a] Rosa Legood,[a] Zia Sadique,[a] Isabel dos-Santos-Silva[b] & Li Yang[c]

Objective To model the cost–effectiveness of a risk-based breast cancer screening programme in urban China, launched in 2012, compared with no screening.

Methods We developed a Markov model to estimate the lifetime costs and effects, in terms of quality-adjusted life years (QALYs), of a breast cancer screening programme for high-risk women aged 40–69 years. We derived or adopted age-specific incidence and transition probability data, assuming a natural history progression between the stages of cancer, from other studies. We obtained lifetime direct and indirect treatment costs in 2014 United States dollars (US$) from surveys of breast cancer patients in 37 Chinese hospitals. To calculate QALYs, we derived utility scores from cross-sectional patient surveys. We evaluated incremental cost–effectiveness ratios for various scenarios for comparison with a willingness-to-pay threshold.

Findings Our baseline model of annual screening yielded an incremental cost–effectiveness ratio of US$ 8253/QALY, lower than the willingness-to-pay threshold of US$ 23 050/QALY. One-way and probabilistic sensitivity analyses demonstrated that the results are robust. In the exploration of various scenarios, screening every 3 years is the most cost–effective with an incremental cost–effectiveness ratio of US$ 6671/QALY. The cost–effectiveness of the screening is reduced if not all diagnosed women seek treatment. Finally, the economic benefit of screening women aged 45–69 years with both ultrasound and mammography, compared with mammography alone, is uncertain.

Conclusion High-risk population-based breast cancer screening is cost–effective compared with no screening.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

Breast cancer is the most common cancer among women. Globally, 1.67 million women were diagnosed with breast cancer in 2012, contributing to more than 25% of female cancer incident cases.[1] The incidence of breast cancer among Chinese women is increasing twice as fast as the global rate.[2] In China, breast cancer is the most frequently diagnosed cancer and the fifth leading cause of cancer-related deaths.[3]

Breast cancer is a potentially curable disease if diagnosed and treated at an early stage. The Surveillance, Epidemiology, and End Results Programme reported that women diagnosed with breast cancer at an early stage (Stage I or II) have a better prognosis (5-year survival rate, 85–98%) than for advanced breast cancer (5-year survival rate for Stage III or IV, 30–70%).[4] The strong argument for earlier diagnosis with respect to patient outcome has resulted in the initiation of breast cancer screening programmes in many countries. The aims of such programmes are the early diagnosis and treatment of cancer patients to improve disease outcomes and to reduce mortality.[5]

Although population-based mammography has been widely adopted in high-income countries for more than 30 years,[6] it is less cost–effective in low- and middle-income countries.[7] Studies in China,[8–10] Ghana[11] and the Islamic Republic of Iran[12,13] have revealed that population-based mammography is not economically attractive. However, a high-risk population-based breast cancer screening programme could contribute to a much higher detection rate[14–16] and could therefore be good value for money in low- and middle-income countries.

Experts have recommended ultrasound as an adjunct to mammography among high-risk women.[17–20] For patients with dense breasts, non-calcified breast cancers are more likely to be missed by mammography;[21] ultrasound permits the detection of small, otherwise occult, breast cancer.[22]

In 2012, the Government of China launched a cancer screening programme in 14 cities to screen common cancers, including breast cancer. Our objective was to provide policy-makers with economic information regarding the cost–effectiveness of breast cancer screening for high-risk women. In this paper, we used a Markov model to compare the lifetime effects, costs and cost–effectiveness of breast cancer screening, versus no screening, using published data from this programme (Fig. 1).

Methods

Screening strategy

To measure the individual risk of breast cancer, health professionals invited women aged 40–69 years to health facilities and used paper-based questionnaires to collect information on individual breast cancer exposure. The health professionals then used the Harvard Cancer Index online tool, now called Your Disease Risk, to process the collected information.[23,24] The tool calculates individual cancer scores, by giving risk scores to exposures, including family history, height, age of first period, age of first birth, number of births, age at menopause, use of oral contraceptives, estrogen replacement, Jewish heritage (i.e. higher prevalence of *BRAC1/2* gene mutations) and exposure to ionizing radiation. A total of 198 097 women completed a

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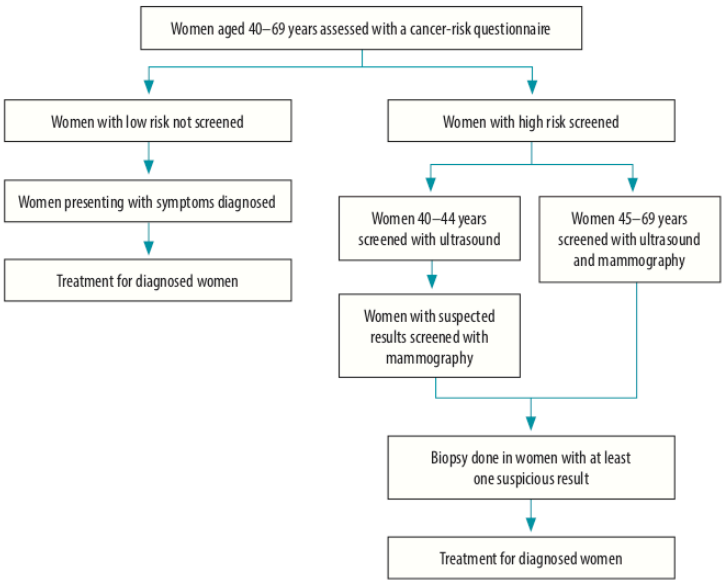
Fig. 1. **Current risk-based breast cancer screening programme in urban China, launched in 2012**



Box 1. **Model assumptions for estimating cost–effectiveness ratios of risk-based breast cancer screening programme in urban China**

Parameters

- For progression rates between disease stages and relative risk of invasive cancer in ductal carcinoma in situ, we obtained data from other countries and assumed the parameters were applicable to China. We also used disutility score of screening from United Kingdom of Great Britain and Northern Ireland in the baseline analysis. However, we explored the uncertainty in the sensitivity analyses.
- We assumed the risk of developing breast cancer among high-risk women was twice as much as the general population, based on the minimum threshold in Harvard Cancer Index (now called Your Disease Risk).

Model structure

- We assumed patients at stage I can progress to stage II, stage III and stage IV. All women can die from non-breast cancer causes during disease progression, but only patients at stage IV can die from breast cancer.
- We assumed all women with suspicious screening findings either with mammography or ultrasound proceeded to diagnostic biopsy. This follows the protocol of the Cancer Screening Programme in Urban China.
- In the base-case analysis, we assumed all breast cancer patients diagnosed by biopsy received treatment. However, because uptake of treatment is uncertain, we explored the scenario where only 70% of detected breast cancers received treatment.

risk assessment questionnaire during 2012–2013; 17 104 were identified as being at high risk of developing breast cancer.[14]

The programme working group estimated the population average score based on the prevalence of risk factors among the Chinese population, and adjusted according to China's cancer epidemiology data over 20 years.[14] The relative risk was obtained by comparing the individual risk score with the population average. Women with a relative risk of > 2 are defined as being at high risk. The programme screens high-risk women aged 40–44 years by ultrasound and the women with suspected results are further examined by mammography. Women with a suspicious mammography result are tested by biopsy for diagnostic confirmation. The programme screens high-risk women aged 45–69 years by both mammography and ultrasound, and suspected results from either method are confirmed with biopsy.

For low-risk women, breast cancer is only diagnosed on presentation of symptoms. Breast cancer patients in the screening arm can be diagnosed while still asymptomatic, that is, at an earlier stage of the disease when prognosis is better.

Modelling strategy

Box 1 presents our model assumptions. We adapted a prior natural history Markov model[8] 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 urban women with no previous history of breast cancer, from age 40 years to death. We used an annual screening frequency as the baseline, and we explored the scenarios of screening every 3 and 5 years.

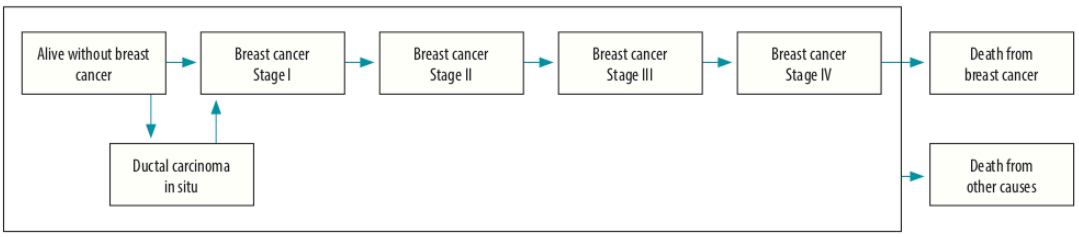
Natural history

Fig. 2 illustrates the various health states and the potential transitions between them.[8] Healthy women can transition to ductal carcinoma in situ or stage I cancer, or remain free of cancer. Women with ductal carcinoma in situ are at a higher risk of developing invasive breast cancer (relative risk: 2.02).[4] Patients at stage I can progress to stage II, stage III and stage IV in turn. All women can die from causes other than breast cancer 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.[8,25]

We estimated the probability of symptoms in an unscreened population by calibrating the model as follows. In the non-screening arm, incident cases are only detected on presentation with symptoms; the distribution of incidence cases by stage is therefore a function of the probability of transitions and the probability of symptoms.[26] We adjusted the probability of symptoms until the distribution of cases presented at each stage was similar to the distribution of reported incidence cases.[3,27] Our estimates of transition probabilities are provided in Table 1.

We assumed that all suspected cases proceeded to biopsy and that all diagnosed cases received treatment at

Fig. 2. **Natural history model for breast cancer progression, China**



Notes: The box represents the process of disease progression. We adapted the model from Wong et al.[8,25] and Tsokos & Oğuztöreli.[25]

baseline. We also explored a scenario of only 70% treatment uptake.

Epidemiological and clinical data

We obtained the age-specific invasive breast cancer incidences from the 2012 Chinese Cancer Registry Annual Report.[3] Since ductal carcinoma in situ incidence is not recorded locally, we estimated the proportion of ductal carcinoma in situ among all breast cancer incidence cases from a Chinese study of 3838 patients.[28] We calculated age-specific mortalities from other causes by subtracting age-specific breast cancer mortality rates[35] from the corresponding age-specific all-cause mortality rates.[36]

Costs

Data describing the costs of questionnaire, screening (whether ultrasound followed by mammography if required or ultrasound plus mammography, depending on age) and biopsy were available from the screening programme.[32] We also obtained the treatment costs by stage from the study by the programme working group;[34] such treatment cost data were estimated from 2746 invasive breast cancer patients from 37 hospitals across 13 provinces in China, comprising direct medical costs, direct non-medical costs and indirect costs. We used the disposable income per capita of Chinese urban residents (22.5 United States dollars (US$) per day)[37] and productivity loss days to calculate the indirect costs. The Chinese screening programme did not report treatment costs for women with ductal carcinoma in situ, so we estimated these costs from a study of 211 Sichuan Cancer Hospital patients.[33] All costs are presented at 2014 values. We used the purchasing power parity conversion factor to convert cost values to US$, with US$ 1 equal to 3.51 Chinese yuan.[38]

Effectiveness of screening

We used the sensitivity (probability of positive diagnosis if diseased) and specificity (probability of negative diagnosis if not diseased) values from an earlier study[29] that enrolled 3062 Chinese women (average age, 45 years) at risk of breast cancer. 11 screening modalities were compared, which are different combinations of clinical breast examination, mammography and ultrasound. We varied the estimates in the sensitivity analyses in case of any variation in diagnostic performance due to the age of the screened population.

QALYs

QALY is a measurement that reflects both length of life and health-related quality of life. It is calculated as the product of the utility score of a particular state of health, defined as a dimensionless number between 1 (perfect health) and 0 (death), and the number of years lived. We identified the utility scores for patients at stage I, II, III and IV from a cross-sectional survey conducted as part of the screening programme,[30] in which breast cancer patients across 13 Chinese provinces completed EuroQol five-dimensional questionnaires.

False-positive results could be argued to undermine quality of life due to psychological distress incurred;[39] a systematic review estimated a utility decrement (disutility) of 11–34% for false-positive results.[31] We estimated a loss of 25% at baseline[40] and explored the uncertainty in the sensitivity analysis.

Analysis

In agreement with the China Guidelines for Pharmacoeconomic Evaluations,[41] we conducted the analysis from a societal perspective. In agreement with these guidelines,[41] we discounted future costs and future benefits at 3%. We estimated the lifetime costs of screening and its effects in terms of QALY. We calculated the incremental cost–effectiveness ratios, defined as the difference in cost divided by the change in QALY. The willingness-to-pay threshold was estimated to be three times the gross domestic product (GDP) per capita in China in 2014 (US$ 7683).[42] An incremental cost–effectiveness ratio of less than US$ 23 050/QALY[41] is therefore an indication that the risk-based breast cancer screening for urban Chinese women aged 40–69 years, compared with no screening, is cost–effective.

To explore the effect of parameter uncertainty, we conducted one-way and probabilistic sensitivity analyses. In the one-way sensitivity analysis, we used the minimum and maximum estimates for effectiveness of screening, utility scores and costs. We varied each parameter individually to assess its impact on overall results. In the probabilistic sensitivity analysis, we varied all variables simultaneously to further explore model uncertainty. The input variables were specified as distributions: costs have a gamma distribution; QALY values follow a log-normal distribution; and sensitivity and specificity of screening follow a beta distribution as suggested in the literature.[43] By varying input parameters over their respective distributions, we obtained 1000 estimates of incremental costs and incremental effects. We then plotted the cost–effectiveness acceptability curves to show the proportion of simulations for which the intervention was cost–effective at different willingness-to-pay thresholds.

Other scenarios explored included: (i) the impact of screening every 3 years or every 5 years, compared with no screening; (ii) screening every year, but only 70% of the detected cases having

Table 1. **Parameter values for modelling cost–effectiveness of risk-based breast cancer screening programme launched in 2012 in urban China**

Variables	Baseline	Minimum	Maximum	Distribution	Reference/source
Disease state progression transition probabilities					
Age-specific incidence, years					
40–44	0.0006100	–	–	–	Chinese Cancer Registry Annual Report[3]
45–49	0.0010056	–	–	–	Chinese Cancer Registry Annual Report[3]
50–54	0.0011650	–	–	–	Chinese Cancer Registry Annual Report[3]
55–59	0.0011179	–	–	–	Chinese Cancer Registry Annual Report[3]
60–64	0.0010458	–	–	–	Chinese Cancer Registry Annual Report[3]
65–69	0.0009782	–	–	–	Chinese Cancer Registry Annual Report[3]
70–74	0.0009912	–	–	–	Chinese Cancer Registry Annual Report[3]
75–79	0.0009067	–	–	–	Chinese Cancer Registry Annual Report[3]
80–84	0.0007803	–	–	–	Chinese Cancer Registry Annual Report[3]
≥ 85	0.0006430	–	–	–	Chinese Cancer Registry Annual Report[3]
Ratio of DCIS incidence to invasive breast cancer incidence	0.12	–	–	–	Lu et al.[28]
RR of invasive cancer from DICS	2.02	–	–	–	SEER Program[4]
Progression rate					
Stage I–Stage II	0.06	–	–	–	Tsokos & Oğuztöreli[25]
Stage II–Stage III	0.11	–	–	–	Tsokos & Oğuztöreli[25]
Stage III–Stage IV	0.15	–	–	–	Tsokos & Oğuztöreli[25]
Stage IV–death	0.23	–	–	–	Wong et al.[8]
Stage-specific probability of symptoms					
Stage I	0.004	–	–	–	Model calibration
Stage II	0.014	–	–	–	Model calibration
Stage III	0.380	–	–	–	Model calibration
Stage IV	0.980	–	–	–	Model calibration
Annual fatality rate after treatment					
Stage I	0.006	–	–	–	Ginsberg et al.[27]
Stage II	0.042	–	–	–	Ginsberg et al.[27]
Stage III	0.093	–	–	–	Ginsberg et al.[27]
Stage IV	0.275	–	–	–	Ginsberg et al.[27]
Effectiveness of screening					
Ultrasound followed by mammography if required[a]					
Sensitivity	0.848	0.681	0.949	Beta	Huang et al.[29]
Specificity	0.994	0.990	0.996	Beta	Huang et al.[29]
Ultrasound and mammography					
Sensitivity	0.939	0.798	0.993	Beta	Huang et al.[29]
Specificity	0.980	0.975	0.985	Beta	Huang et al.[29]
Utility scores					
Stage I	0.79	0.77	0.80	Log-normal	Shi et al.[30]
Stage II	0.79	0.78	0.80	Log-normal	Shi et al.[30]
Stage III	0.77	0.76	0.79	Log-normal	Shi et al.[30]
Stage IV	0.69	0.65	0.72	Log-normal	Shi et al.[30]
Disutility from false-positive	0.25	0.11	0.34	Log-normal	Peasgood et al.[31]

(*continues. . .*)

(. . .*continued*)

Variables	Baseline	Minimum	Maximum	Distribution	Reference/source
Costs, US$					
Questionnaire	1.6	1.1	2.1	Gamma	Cancer Screening Programme in Urban China[32]
Screening	85.5	59.8	111.1	Gamma	Cancer Screening Programme in Urban China[32]
Biopsy	45.6	31.0	59.3	Gamma	Cancer Screening Programme in Urban China[32]
Treatment costs					
DCIS	2435	1705	3166	Gamma	Li et al.[33]
Stage I	10067	7047	13087	Gamma	Liao et al.[34]
Stage II	11068	7748	14388	Gamma	Liao et al.[34]
Stage III	12867	9007	16727	Gamma	Liao et al.[34]
Stage IV	17766	12436	23096	Gamma	Liao et al.[34]

DCIS: ductal carcinoma in situ; US$: United States dollars.
[a] For women aged 40–44 years.
[b] For women aged 45–69 years.

access to breast cancer treatment; and (iii) screening women aged 45–69 years every 1, 3 and 5 years via mammography and ultrasound, compared with mammography alone (maintaining the original screening strategy for women aged 40–44 years).

Results

Our model estimated 43 incident cases of breast cancer per 1000 women over a lifetime; 21 were detected via screening and 22 on presentation with symptoms. Table 2 reports the discounted lifetime costs, QALYs and incremental cost–effectiveness ratios. Overall, the risk-based breast cancer screening yielded higher QALYs compared with no screening (23.0129 QALYs versus 22.9843 QALYs), but was more expensive than no screening (US$ 335.43 versus US$ 99.68). The baseline discounted incremental cost–effectiveness ratio was US$ 8253/QALY, well below the threshold of US$ 23 050/QALY, indicating that the risk-based breast cancer screening programme is cost–effective.

The one-way sensitivity analysis (Fig. 3) indicates that the costs, utility scores and effectiveness of screening have little individual influence on the cost–effectiveness of the programme. We found the incremental cost–effectiveness ratios to be lower than the threshold at both the upper and lower limits of these variables. The results of the probabilistic sensitivity analysis (Fig. 4) show that, at the threshold of US$ 23 050/QALY, nearly 100% of the simulations indicate that the risk-based breast cancer screening programme is cost–effective compared with no screening.

In the scenario analysis (Table 2), screening every 3 years and every 5 years achieves an incremental cost–effectiveness ratio of US$ 6671/QALY and US$ 6917/QALY, respectively. A scenario of annual screening, but where only 70% of detected cases are treated, yields a higher incremental cost–effectiveness ratio of US$ 11 223/QALY, which is still lower than the threshold. We also found the scenario of both mammography and ultrasound for women aged 45–69 years, compared with mammography alone, to be cost–effective. However, in the probabilistic sensitivity analysis, the confidence intervals of the incremental cost–effectiveness ratios are very wide: an indication of considerable uncertainty.

Discussion

The results indicate that compared with no screening, the risk-based breast cancer screening programme is cost–effective. The results prove to be robust in the sensitivity analyses when we varied the estimates for effectiveness of screening, utility scores and costs.

Our finding that high-risk population-based breast screening is cost–effective has implications for breast cancer control in other low- and middle-income countries. Previous studies have reported that population-based mammography screening is not economically attractive in countries, such as the Islamic Republic of Iran and Ghana, with incremental cost–effectiveness ratios of US$ 389 184/QALY[12] and US$ 12 908/QALY,[11] respectively. The Chinese screening programme is more likely to be cost–effective than other general population-based screening programmes, since the detection rate in the Chinese programme is higher (16%)[14] than in general screening programmes (e.g. 3% in the United States of America and 6% in New Zealand).[15,16] This finding is consistent with the study comparing risk-based breast cancer screening strategies with general programmes, reporting that risk-based strategies result in greater health benefits for a given cost.[44]

For high-risk women aged 45–69 years, our scenario analysis shows that the benefits of ultrasound in addition to mammography are considerably uncertain. The wide confidence intervals, indicating uncertainty in the incremental cost–effectiveness ratios, do not appear to justify the increased costs. A potential alternative to the current screening strategy could therefore be mammography screening alone for high-risk women aged 45–69 years, instead of both ultrasound and mammography.

Screening every 3 years is the most cost–effective frequency among alternatives. Compared with screening every year, screening every 3 years decreases the total costs significantly, but does not change the effects significantly. The results vindicate the 3-year screening interval for breast cancer in some countries, such as the United Kingdom of Great Britain and Northern Ireland.[5]

Our study explored the impact of access to treatment on the overall results, suggesting that the screening

programme is less cost–effective if not all detected cases go on to receive treatment. In China, patients need to pay on average 34% of total medical costs;[45] this can limit access to medical treatment for some women who have been diagnosed with breast cancer. Some women may also decide not to seek medical treatment if they are not experiencing any pain or do not feel ill;[46] such delays in the onset of treatment can however lead to a poorer prognosis,[46] reducing the cost–effectiveness of a screening programme.

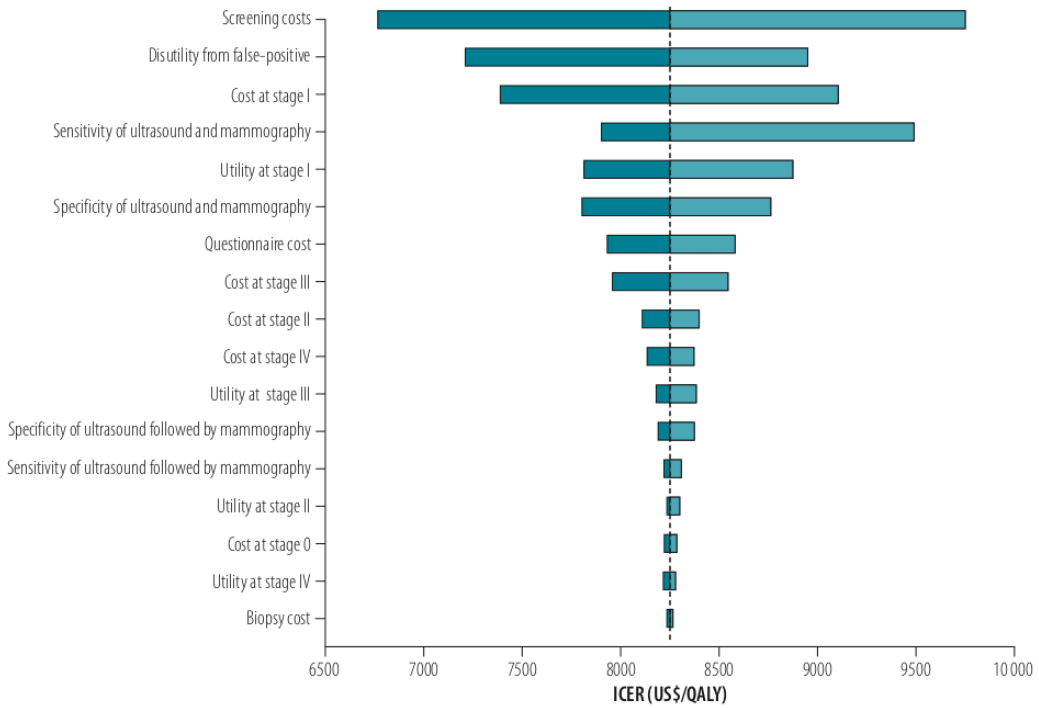
As with the previous models,[8] we adopted the Markov approach in our

Table 2. **Modelled cost–effectiveness ratios of risk-based breast cancer screening programme in urban China, 2014**

Comparators	Lifetime costs per case (US$)	QALY	Incremental costs (US$)	Difference in QALY	ICER (95% CI)[a]
Baseline analysis					
No screening	99.68	22.9843	–	–	–
Annual screening	335.43	23.0129	235.76	0.0286	8 253 (6 170 to 11 483)
Screening programme variations versus no screening					
Screening every 3 years	184.67	22.9971	84.99	0.0127	6 671 (5 019 to 9048)
Screening every 5 years	152.09	22.9919	52.41	0.0076	6 917 (5 157 to 9416)
Annual screening, but only 70% of detected cases treated	324.17	23.0043	224.49	0.0200	11 223 (8 137 to 17 127)
Mammography only versus mammography and ultrasound[b]					
Annual screening	306.41	23.0115	−29.02	−0.0014	21 246 (−172 049 to 168 866)
Screening every 3 years	172.94	22.9960	−11.73	−0.0011	11 000 (−73 330 to 99 983)
Screening every 5 years	145.37	22.9912	−6.72	−0.0007	9 366 (−114 804 to 98 149)

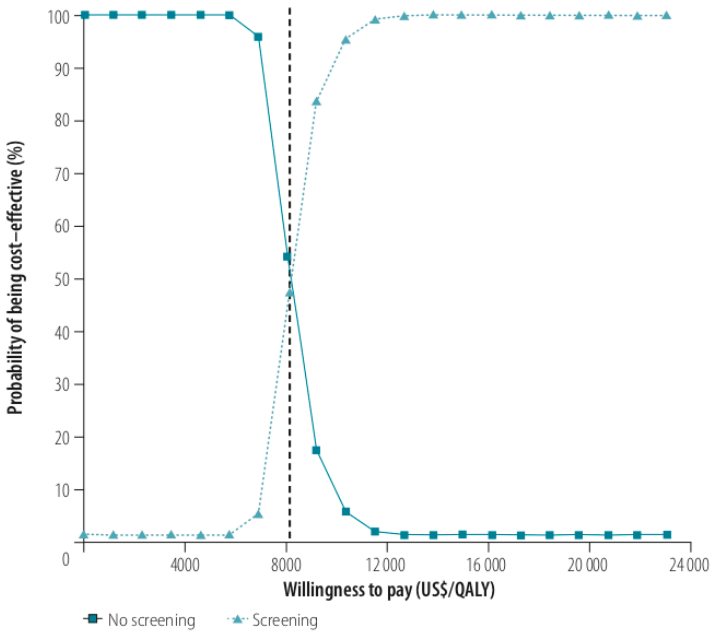
CI: confidence interval; ICER: incremental cost–effectiveness ratio; RR: relative risk; QALY: quality-adjusted life year; US$ United States dollars.
[a] Discounted at 3%.
[b] For women aged 45–69 years. Screening regime for women aged 40–44 years remains unchanged.
Note: Some inconsistency arise in some value due to rounding.

Fig. 3. **One-way sensitivity analysis of modelled cost–effectiveness of risk-based breast cancer screening programme, urban China, 2014**



ICER: incremental cost–effectiveness ratio; QALY: quality-adjusted life year; US$: United States dollars.
Notes: The width of the bars represents the range of ICER when each parameter was varied individually. The vertical dashed line represents incremental cost–effectiveness ratio of US$ 8253/QALY.

Fig. 4. **Probabilistic sensitivity analysis of modelled cost–effectiveness of risk-based breast cancer screening programme, urban China, 2014**



QALY: quality-adjusted life year; US$: United States dollars.
Note: The vertical dashed line represents incremental cost–effectiveness ratio of US$ 8253/QALY.

modelling. While costs and quality of life are provided in the publications by the Chinese screening programme,[30,32,34] no long-term follow-up data are available. We therefore used a mathematical model from age 40 years to death to reflect the differences in costs and effects. We also adopted a prior natural history model, meaning that women free of breast cancer first transition to ductal carcinoma in situ or stage I, followed by the remaining stages in sequence; in contrast, another study[47] used a model in which it is possible to progress from being free of breast cancer to stage IV. In addition, we calibrated our model to estimate the probability of symptoms by cancer stage, using the distribution of incidence cases reported in the Chinese Cancer Registry Annual Report 2012[3] in an unscreened population.

Further, we incorporated the decrements in health-related quality of life from false-positive screening results into our model. In this analysis, we used a loss of 25% at baseline and explored the uncertainty (11–34%). However, the utility loss from false–positive results[39] remains controversial. Although some argue that pathologically elevated levels of distress and anxiety are not apparent,[48] the relatively small number of studies means that the long-term effects of false-positive breast cancer screening are still unknown.[48] In this analysis we used estimates from studies based in the United Kingdom of Great Britain and Northern Ireland,[31,40] which might bias the cost–effectiveness results of the Chinese screening programme. However, we explored the uncertainty and the results proved to be robust through the sensitivity analyses.

Limitations of our study also include the assumption of high-risk women having a cancer risk index twice that of other women;[23] the real relative risk among high-risk women in urban China is still unknown. Further, the costs of questionnaires and clinical screening in this study are derived from the cost accounting of the screening programme; other implementation costs such as the identification of eligible women, the administration of risk questionnaires and other ancillary costs were not included. This may lead to an underestimation of costs and subsequently the cost–effectiveness. For progression rates between stages and the relative risk of invasive cancer from ductal carcinoma in situ, we used data from other countries and assumed the parameters were applicable to China. These factors require careful consideration and further research is required to reduce uncertainty.

We used three times the Chinese gross domestic product (GDP) per capita as the willingness-to-pay threshold in our cost–effectiveness analysis. Although GDP-based thresholds are commonly cited,[41] they have been critized.[49] Even if estimated accurately, GDP-based cost–effectiveness ratios, or other estimates of willingness to pay, do not provide information on affordability, budget impact or the feasibly of implementation. Although cost–effectiveness ratios are informative in assessing value for money, willingness-to-pay thresholds should therefore not be used alone as a decisions rule for priority setting. Local policy context must also be considered.[49]

In conclusion, our analysis provides economic evidence for the cost–effectiveness of risk-based breast cancer screening in urban China. ■

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Competing interests: None declared.

ملخص

فعالية التكلفة لبرنامج فحص سرطان الثدي القائم على المخاطر، الصين

الغرض وضع نموذج لفعالية التكلفة لبرنامج فحص سرطان الثدي القائم على المخاطر في الصين الحضرية، والذي تم إطلاقه في عام 2012، مقارنة بعدم إجراء فحص.

الطريقة لقد قمنا بتطوير نموذج ماركوف لتقدير التكاليف والآثار مدى الحياة، بالنسبة سنوات العمر معدلة الجودة (QALYs)، لبرنامج فحص سرطانٍ الثدي للنساء المعرضات لخطر كبير في سن من 40 إلى 69 عاماً. لقد استنبطنا أو انتهجنا بيانات –تعتمد على السن– لاحتمالية الانتقال والحدوث، بافتراض تقدم التاريخ الطبيعي بين مراحل السرطان، من دراسات أخرى. لقد حصلنا على تكاليف العلاج المباشر وغير المباشر طوال العام 2014 بالدولار الأمريكي من مسوحات لمريضات سرطان الثدي في 37 مستشفى صينيًا. لحساب QALY، قمنا باستنتاج تقييمات للمرافق من خلال مسوحات متعددة القطاعات للمرضى. قمنا بتقييم نسب متزايدة لفعالية التكاليف لمختلف السيناريوهات، وذلك للمقارنة مع عتبة الاستعداد للدفع.

النتائج أسفر نموذجنا الأساسي للفحص السنوي عن نسبة متزايدة لفعالية التكلفة قدرها 8253 دولار أمريكي/ QALY، وهي أقل من عتبة الاستعداد للدفع البالغة قيمتها 23050 دولار أمريكي/ QALY. أظهرت تحليلات الحساسية أحادية الاتجاه والاحتمالية أن النتائج قوية. ومع استكشاف السيناريوهات المختلفة، فإن الفحص كل 3 سنوات يكون هو الأكثر فعالية من حيث التكلفة، مع نسبة متزايدة لفعالية التكلفة تبلغ 6671 دولارًا أمريكيًا/ QALY. تقل فعالية تكلفة الفحص إذا لم تقم كل النساء اللواتي يتم تشخيصهن بالسعي للعلاج. وأخيرًا، فإن الفائدة الاقتصادية لفحص النساء اللواتي تتراوح أعمارهن بين 45 و69 عامًا باستخدام كلٍ من الموجات فوق الصوتية والتصوير الشعاعي للثدي، مقارنة بالفحص الشعاعي للثدي وحده، غير مؤكدة.

الاستنتاج إن فحص سرطان الثدي في التجمعات السكانية عالية الخطورة، يعد فعالا من حيث التكلفة مقارنة بعدم إجراء أي فحص.

摘要

中国基于风险的乳腺癌筛查项目的成本效果分析

目的 为 2012 年启动的中国城市基于风险的乳腺癌筛查项目建模进行成本效果分析，与不筛查的情况进行比较。

方法 我们运用马尔可夫模型来估计 40-69 岁高危妇女乳腺癌筛查的终身成本和根据质量调整生命年 (QALYs) 的终身效应。我们从其他研究中推导出或采用了各年龄组发病率和转移概率数据，并假设癌症不同分期间为自然发展病程。我们从中国 37 家医院的乳腺癌患者调查中获得了 2014 年美元 (US$) 的终身直接和间接治疗费用。为了计算 QALYs，我们从横断面患者调查中得出效用分数。我们评估了不同情景下的增量成本效果比，与意愿支付最低阈值进行比较。

结果 我们每年筛查一次的基线模型得到的增量成本效益比为 8253 美元 /QALY，低于 23050 美元 /QALY 的意愿支付最低阈值。单因素和概率敏感性分析表明结果可靠。在探索不同情景时，每三年进行一次筛查最具成本效果，增量成本效果比为 6671 美元 /QALY。如果并非所有被诊断的女性都寻求治疗，筛查的成本效果会降低。最后，与单独使用乳腺钼靶 X 线摄像比较，同时采用超声和乳腺钼靶 X 线检查筛查 45-69 岁女性的经济效益尚不确定。

结论 与不筛查情况相比，高风险人群的乳腺癌筛查具有成本效果。

Résumé

Rapport coût-efficacité du programme de dépistage du cancer du sein fondé sur les risques en Chine

Objectif Modéliser le rapport coût-efficacité d'un programme de dépistage du cancer du sein fondé sur les risques en Chine urbaine, lancé en 2012, comparé à l'absence de dépistage.

Méthodes Nous avons élaboré un modèle de Markov pour estimer le coût et les effets portant sur la vie entière, au regard des années de vie pondérées par la qualité (QALY), d'un programme de dépistage du cancer du sein chez les femmes à haut risque âgées de 40 à 69 ans. Nous avons tiré ou adopté des données sur l'incidence selon l'âge et la probabilité de transition, dans l'hypothèse d'une évolution naturelle entre les phases du cancer, à partir d'autres études. Nous avons obtenu les coûts directs et indirects de traitement au cours d'une vie en dollars des États-Unis de 2014 ($US) à partir d'enquêtes menées auprès de patientes atteintes du cancer du sein dans 37 hôpitaux chinois. Pour calculer les QALY, nous avons déduit des scores d'utilité à partir d'enquêtes transversales auprès de patientes. Nous avons évalué le rapport coût-efficacité différentiel selon différents scénarios pour établir une comparaison avec un seuil de consentement à payer.

Résultats Notre modèle de référence de dépistage annuel a donné un rapport coût-efficacité différentiel de 8253 $US/QALY, soit moins que le seuil de consentement à payer de 23 050 $US/QALY. Les analyses à un seul critère de classification et de sensibilité probabiliste ont démontré que les résultats sont fiables. L'examen de différents scénarios a révélé que le dépistage tous les 3 ans présente le meilleur rapport coût-efficacité, avec un rapport coût-efficacité différentiel de 6671 $US/QALY. Le rapport coût-efficacité du dépistage est réduit si toutes les femmes diagnostiquées ne se font pas soigner. Enfin, l'avantage économique lié au dépistage des femmes âgées de 45 à 69 ans par échographie et mammographie, comparé à un dépistage par mammographie uniquement, est incertain.

Conclusion Le dépistage du cancer du sein dans les populations à haut risque présente un bon rapport coût-efficacité par rapport à l'absence de dépistage.

Резюме

Экономическая эффективность программы скринингового обследования рака молочной железы на основе оценки риска, Китай

Цель Смоделировать экономическую эффективность программы скринингового обследования рака молочной железы на основе оценки риска в городах Китая, которая была запущена в 2012 году, при сравнении с отсутствием скрининга.

Методы Авторы разработали марковскую модель для оценки затрат на медицинское обслуживание в течение жизни и результатов (с точки зрения количества лет жизни с поправкой на ее качество (QALY)) внедрения программы скринингового обследования рака молочной железы для женщин с высоким риском в возрасте 40–69 лет. Авторы вывели самостоятельно или позаимствовали данные о зависимости частоты возникновения рака от возраста и о вероятности перехода, основываясь на естественной истории прогрессирования между стадиями рака по данным других исследований. В ходе обследований пациентов с раком молочной железы в 37 китайских больницах были получены данные о прямых и косвенных затратах на медицинское обслуживание в течение жизни в долларах США (долл. США) по курсу 2014 года. Чтобы вычислить показатель QALY, авторы получили индексы оценки общего состояния здоровья из перекрестного обследования пациентов. Была проведена оценка инкрементных коэффициентов эффективности затрат для различных сценариев для сравнения с порогом платежеспособности.

Результаты Созданная авторами базовая модель ежегодного скрининга привела к увеличению коэффициента эффективности затрат в размере 8253 долл. США/QALY, что ниже порога платежеспособности в размере 23 050 долл. США/QALY. Односторонний и вероятностный анализ чувствительности показал, что результаты являются надежными. Исходя из результатов исследования различных сценариев, проведение скринингового обследования через каждые 3 года является наиболее рентабельным с инкрементным коэффициентом эффективности затрат в размере 6671 долл. США/QALY. Экономическая эффективность скринингового обследования снижается, если не все прошедшие диагностику женщины обращаются за лечением. Наконец, экономическая выгодность скринингового обследования женщин в возрасте 45–69 лет с использованием и ультразвука и маммографии по сравнению с результатами при использовании только маммографии является неопределенной.

Вывод Скрининговое обследование рака молочной железы среди женщин с высоким уровнем риска является экономически эффективным по сравнению с результатами при отсутствии скрининга.

Resumen

Rentabilidad del programa de detección del cáncer de mama basado en el riesgo en China

Objetivo Demostrar la rentabilidad de un programa de detección del cáncer de mama basado en el riesgo en las zonas urbanas de China, iniciado en 2012, en comparación con la ausencia de detección.

Métodos Se desarrolló un modelo Markov para estimar los costes y efectos durante el ciclo vital, en términos de años de vida ajustados por calidad de vida (AVAC), de un programa de detección del cáncer de mama para mujeres con alto riesgo de entre 40 y 69 años de edad. Se obtuvieron o adoptaron datos de la probabilidad de incidencia y transición específicos por edad, sobre la hipótesis de una progresión de la historia natural entre los estadios del cáncer, a partir de otros estudios. Se obtuvieron los costes directos e indirectos del tratamiento vitalicio en dólares estadounidenses (USD) en 2014 a partir de encuestas a pacientes con cáncer de mama en 37 hospitales de China. Para calcular los AVAC, se derivaron las puntuaciones de los servicios públicos de las encuestas transversales a los pacientes. Se evaluaron las relaciones de rentabilidad incrementales para diversos escenarios en comparación con un umbral de la disposición a pagar.

Conclusión La detección del cáncer de mama basada en la población de alto riesgo es rentable en comparación con la ausencia de detección.

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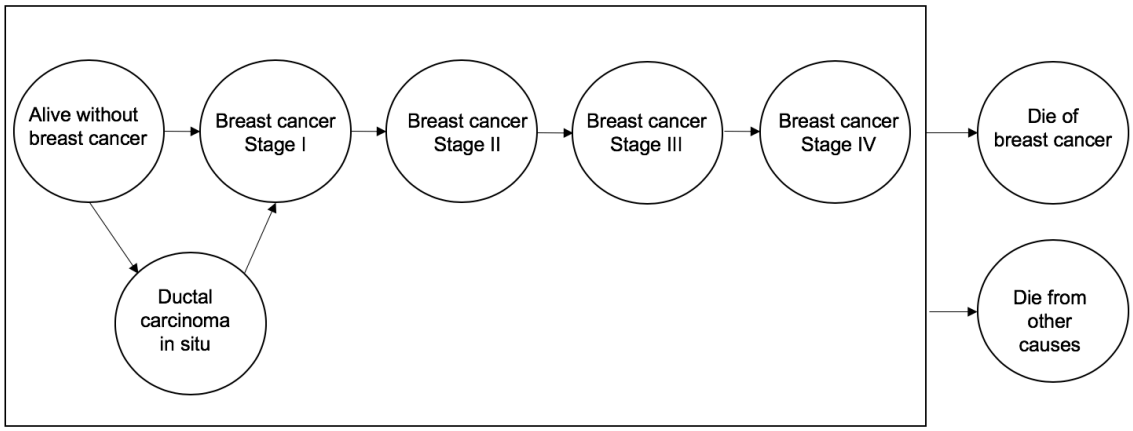
Commentary

The treatment costs of breast cancer by stage obtained from the literature were lifetime costs. In the model, the costs were one-off costs and the utilities were on an annual basis according to the health states.

Based on a systematic review supplemented by relevant randomised trials and values in previous models (132-136), the loss of quality of life from false positive results is 5% and the duration of loss is 0.2 years, which corresponds to 0.01 QALYs decrement in the year of screening. With the 0.01 QALYs loss from false positives in the screening year incorporated in the model, the baseline model of annual risk-based screening would yield an ICER of US$ 6,645/QALY, suggesting the urban breast cancer screening programme to be cost-effective. In the one-way sensitivity analysis, the loss of quality of life from false positive results over the 0.2 years was varied from 5% to 34% (137), leading to the QALYs decrement from 0.01 to 0.068 in the screening year. This results in the ICERs of US $6,645/QALY – US$ 6,960/QALY, which does not change the conclusion that the risk-based screening for the asymptomatic disease was economically attractive in urban China in the one-way sensitivity analysis.

This study is subject to some limitations. Firstly, a systematic literature review of the evidence for the parameter inputs was not conducted to inform the model. This might potentially lead to biased inputs based on single study estimates. Secondly, the uncertainty ranges of some parameters such as progression rates were not available. The uncertainty of the resulting incremental cost-effectiveness ratios could therefore be underestimated. Thirdly, another limitation of the model is the annual cycle length, assuming the transitions between health states are unable to occur within one year. Fourthly, the analysis is limited by parameter correlations not accounted for in the probabilistic sensitivity analysis. In future research, input correlations could be included to reduce decision uncertainty.

In Table-1, the minimum and maximum values of effectiveness of screening and utility scores should have been labelled as lower and upper limits of 95% confidence intervals. The confidence intervals of costs were not available from the literature and therefore costs were varied by ±30% as the minimum and maximum values in the one-way sensitivity analysis. In Table-2, the baseline analysis corresponds to a screened woman (annual screening arm) and a non-screened woman (no screening arm) respectively. The scenario analyses correspond to a screened woman. In Figure-2, patients at different stages can die from breast cancer with different fatality rates. This diagram should be updated as below.



Updated Fig 2. Natural history model for breast cancer progression, China

Chapter 5

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed <u>for each</u> research paper included within a thesis.

SECTION A – Student Details

Student ID Number	15115005	**Title**	Miss
First Name(s)	Li		
Surname/Family Name	Sun		
Thesis Title	Economics of breast cancer screening, genetic testing, and treatment		
Primary Supervisor	Rosa Legood		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

<u>SECTION B – Paper already published</u>

Where was the work published?	International Journal of Cancer		
When was the work published?	2018		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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SECTION E

Student Signature	
Date	

Supervisor Signature	
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Chapter 5

Cost-effectiveness of population-based breast cancer screening programme in rural China

Chapter 5 evaluates the cost-effectiveness of breast cancer screening programmes in rural China. I conceived the research question, developed the Markov model, collected the data, discussed the results and wrote the manuscript. Professor Isabel dos Santos Silva helped revise the Markov model. Dr Rosa Legood, Dr Zia Sadique, and Dr Li Yang gave comments and suggestions on findings and interpretations. All authors approved the final draft prior to journal submission and inclusion in the thesis. This paper has been published by the International Journal of Cancer.

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Cost-effectiveness of breast cancer screening programme for women in rural China

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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. Our study aimed to analyse the cost-effectiveness of breast screening compared to 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 3 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 breast cancer 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

Key words: cost-effectiveness, breast cancer, screening, rural, China
Abbreviations: DCIS: ductal carcinoma *in situ*; GDP: gross domestic product; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year
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What's new?

Whilst breast cancer incidence is lower among women in rural areas, mortality is higher due to lower access to screening, diagnosis, and treatment. China thus 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 cancer screening compared with no screening. The findings reveal overall reduction in health-related quality of life due to false-positives, with breast cancer screening doing more harm than good. Priority should be given to offering symptomatic women proper access to early diagnosis and treatment.

with ultrasound as the primary screening tool for rural women aged 35–64 years in 31 provinces.[9] However, the impact of this programme remains 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 our 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 to 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 judgement 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 3 years) in the baseline analysis, and we explored the scenarios of screening every year and every 5 years.

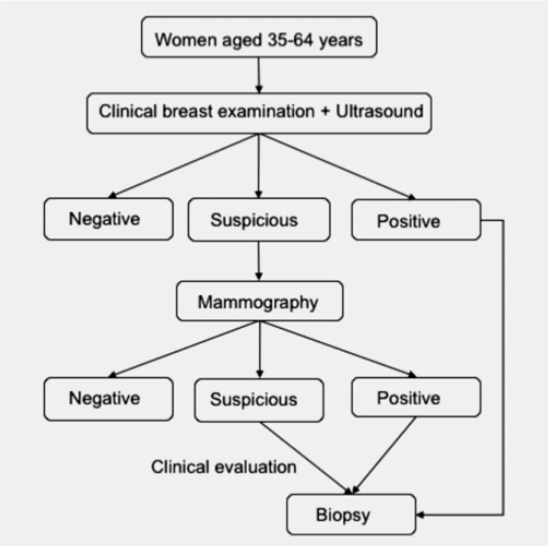

Figure 1. Screening flow in the breast cancer programme in rural China.

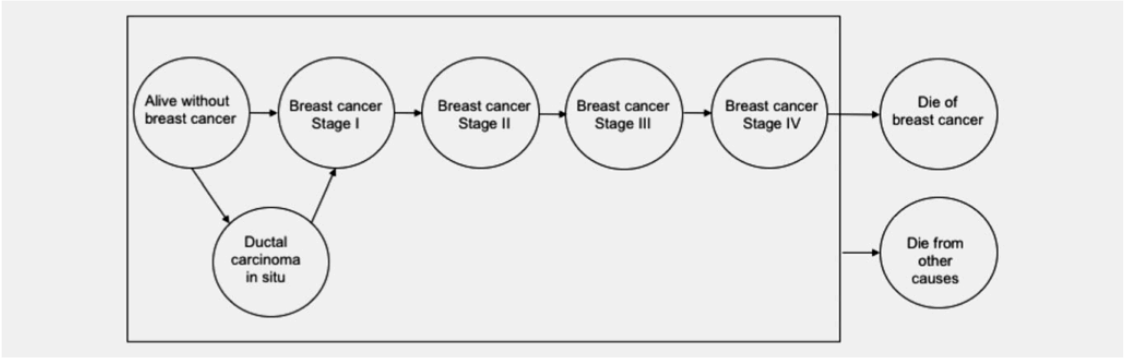

Figure 2. The Markov model for breast cancer progression.

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 for these participants 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

Quality-adjusted life years (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.

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[19]
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[17]
Stage II–Stage III	0.11	–	–	–	
Stage III–Stage IV	0.15	–	–	–	
Stage IV–death	0.23	–	–	–	Wong *et al.*, 2007[15]
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[16]
Stage II	0.042	–	–	–	
Stage III	0.093	–	–	–	
Stage IV	0.275	–	–	–	
Effectiveness of screening					
Sensitivity	0.833	0.731	0.936	β	Chu, 2014[22]
Specificity	0.857	0.801	0.913	β	
Utility scores					
Stage I	0.79	0.77	0.80	Log-normal	Shi *et al.*, 2016[24]
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[26]
Costs					
Screening costs	22.7	15.9	29.5	γ	Cost accounting[9]
Treatment costs					
DCIS	2,189	1,532	2,845	γ	Li *et al.*, 2013[28]
Stage I	9,219	6,453	11,984	γ	Liao *et al.*, 2017[5]
Stage II	10,118	7,083	13,153	γ	
Stage III	11,895	8,326	15,463	γ	
Stage IV	16,156	11,309	21,003	γ	

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$ 7,683).[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 to 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 5 years compared to no screening; (ii) screening every 3 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 (Fig. 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 (Fig. 4) shows that all simulation points fall within the north-west

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

				Incremental comparisons			
	Lifetime costs per case (US$)	Life years	QALY	Costs	Life years	QALY	ICER ($/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 (−1,651, −562)
Scenario analysis							
Screening every year	525.7	23.80	23.03	482.4	0.05	−0.68	−704 (−1,644, −345)
Screening every 5 years	167.1	23.78	23.59	123.8	0.03	−0.12	−996 (−2,950, −461)
Screening every 3 years but 70% compliance rate	180.4	23.78	23.57	137.1	0.03	−0.14	−956 (−2,783, −435)

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.

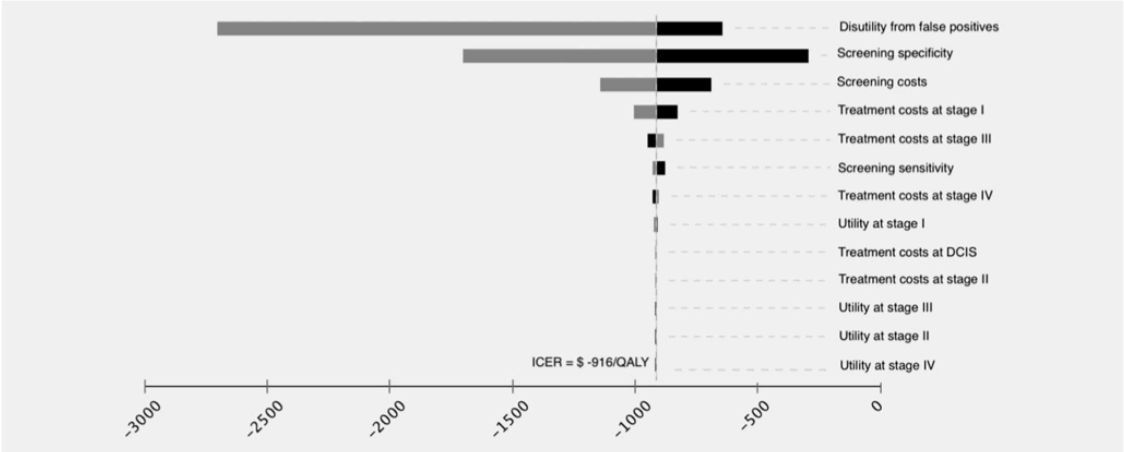

Figure 3. Tornado diagram.

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 S1, Supporting Information).

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

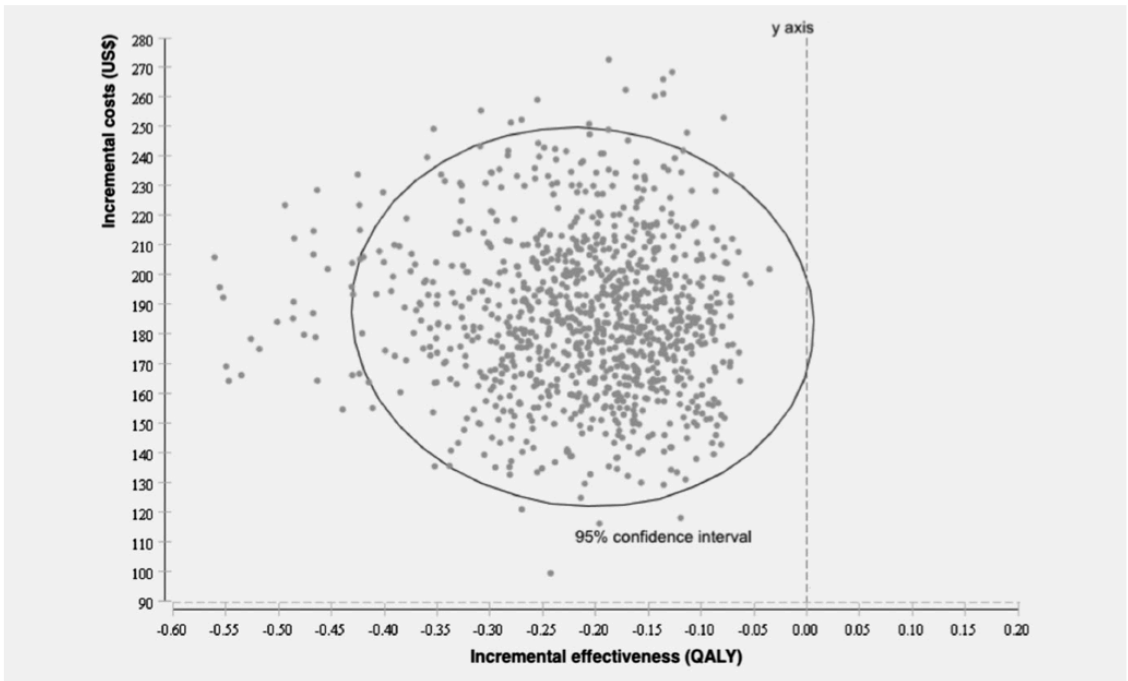

Figure 4. Incremental discounted lifetime costs and effects of rural screening compared to no screening.

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 harmful.[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-organised 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 our 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 remains 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 personalised. 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 ongoing in rural China. Therefore, in the absence of evidence from RCTs, we have adopted a Markov natural history model in our 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.

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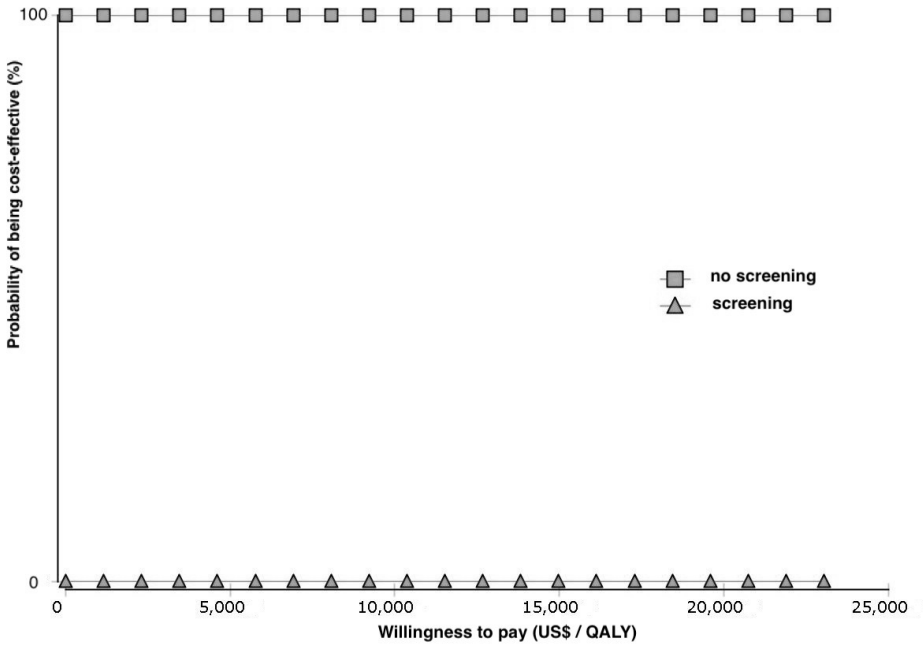
Appendix-S1

Cost-effectiveness acceptability curve



Commentary

Based on a systematic review supplemented by relevant randomised trials and values in previous models (132-136), the loss of quality of life from false positive results is 5% and the duration of loss is 0.2 years, which corresponds to 0.01 QALYs decrement in the year of screening. With the 0.01 QALYs loss from false positives in the screening year incorporated in the model, the baseline model of annual population-based screening would yield an ICER of US$ 6,879/QALY, suggesting the rural breast cancer screening programme to be cost-effective. In the one-way sensitivity analysis, the loss of quality of life from false positive results over the 0.2 years was varied from 5% to 34% (137), resulting in the ICERs of US $6,879/QALY – US$ -6,511/QALY. With the maximum 34% quality of life decrement of full health over 0.2 years (0.068 QALYs decrement), breast cancer screening cost $186.7 more and led to a loss of 0.03 QALYs. Compared to no screening, annual screening would lead to an extra cost of $6,511 per QALY lost in rural China. Therefore, the cost-effectiveness of the rural breast cancer screening programme is very uncertain in the one-way sensitivity analysis and breast screening among the general population in rural China could potentially harm women's health due to false positives with the current screening tool. A threshold analysis was conducted to explore the minimum disutility from false positives at which the ICER reached the willingness-to-pay threshold of US$ 23,050/QALY to maintain the cost-effectiveness of breast cancer screening in the rural programme. The lower limit of disutility from false positives at which rural breast cancer screening programme would remain cost-effective at the threshold was 0.029 QALYs in the screening year, corresponding to 14.5% quality of life decrement of full health over 0.2 years.

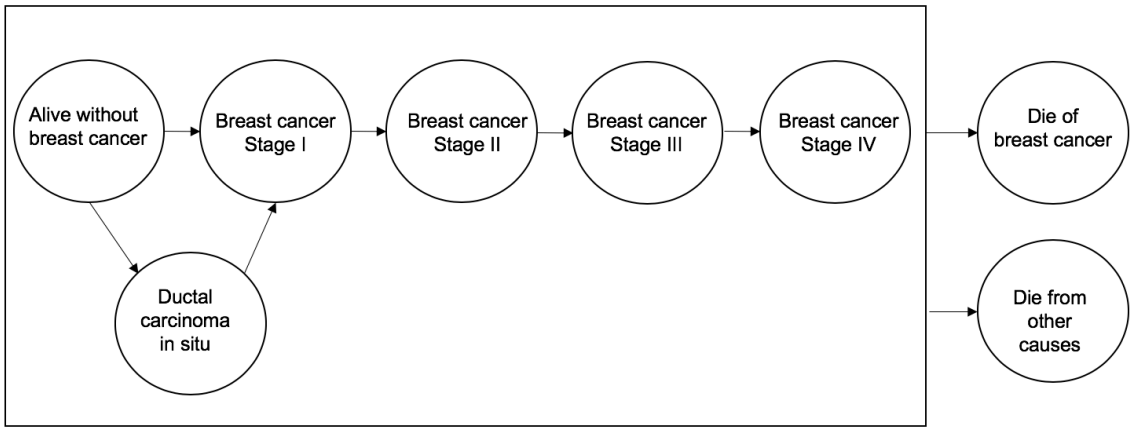
The effectiveness of screening is obtained from a study of 26,224 Chinese women participating in the rural breast cancer screening programme (Chu 2014). The screening modality for these participants was the same as the measure required for the input to our model. The biopsy test was performed for diagnostic confirmation of breast cancer. Due to limited evidence on the performance of the screening programme in rural China, I explored a 30% reduction in the screening sensitivity and specificity as the lower values in the one-way sensitivity analysis. Unfortunately, the length of follow-up was not reported in this study.

One potential limitation is that I assumed the same transition probabilities, treatment costs of breast cancer, and utility scores in the rural screening model as those used in the urban model due to lack of data, which deserves careful considerations. However, some inputs in the rural model were different from those used in the urban model, including age-specific invasive breast cancer incidence, effectiveness of screening, and screening costs. The urban programme screens high-risk women aged 40–69 years by

ultrasound and/or followed by mammography, while the rural programme screens women aged 35-64 years with clinical breast examination coupled with ultrasound as the primary tool. Therefore, the effectiveness of screening (sensitivity and specificity) and the screening costs were different in urban and rural China. In addition, 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) (138).

In Table-1, the transition probabilities correspond to one year. The treatment costs of breast cancer by stage were lifetime costs. In the model, the costs were one-off costs and the utilities were on an annual basis according to the health states. The row titles for effectiveness of screening and utility scores should have been labelled as lower and upper limits of 95% confidence intervals. The confidence intervals of costs were not available from the literature and therefore costs were varied by ±30% as the minimum and maximum values in the one-way sensitivity analysis.

In Figure-2, patients at different stages can die from breast cancer with different fatality rates. This diagram should be updated as below.



Updated Figure 2. The Markov model for breast cancer progression

Chapter 6

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	15115005	**Title**	Miss
First Name(s)	Li		
Surname/Family Name	Sun		
Thesis Title	Economics of breast cancer screening, genetic testing, and treatment		
Primary Supervisor	Rosa Legood		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	JAMA Oncology		
When was the work published?	Oct 2019		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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SECTION D – Multi-authored work

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SECTION E

Student Signature	
Date	

Supervisor Signature	
Date	

Chapter 6

Cost-effectiveness of multi-gene testing to all patients with breast cancer

This chapter presents analyses estimating the incremental lifetime effects, costs, and cost-effectiveness of offering panel genetic testing to all breast cancer (BC) patients compared to current practice of genetic (BRCA) testing for BC patients based on family history/clinical-criteria.

Data were collected from 11,836 population-based BC patients with family history information from four large research studies based in the UK, US and Australia. Our collaborators are from Wolfson Institute of Preventive Medicine, Manchester University, Southampton University, Melbourne University, and Kaiser Permanente Washington Health Research Institute. I developed the micro-simulation model from scratch with support from Dr Ranjit Manchanda, Dr Rosa Legood, Dr Zia Sadique and Shreeya Patel. All authors approved the final draft prior to journal submission and inclusion in the thesis. This paper has been published by JAMA Oncology.

JAMA Oncology | Original Investigation

A Cost-effectiveness Analysis of Multigene Testing for All Patients With Breast Cancer

Li Sun, MSc; Adam Brentnall, PhD; Shreeya Patel, MSc; Diana S. M. Buist, PhD; Erin J. A. Bowles, PhD; D. Gareth R. Evans, PhD; Diana Eccles, PhD; John Hopper, PhD; Shuai Li, PhD; Melissa Southey, PhD ; Stephen Duffy, PhD; Jack Cuzick, PhD; Isabel dos Santos Silva, PhD; Alec Miners, PhD; Zia Sadique, PhD; Li Yang, PhD; Rosa Legood, PhD; Ranjit Manchanda, MD, PhD

IMPORTANCE Moving to multigene testing for all women with breast cancer (BC) could identify many more mutation carriers who can benefit from precision prevention. However, the cost-effectiveness of this approach remains unaddressed.

OBJECTIVE To estimate incremental lifetime effects, costs, and cost-effectiveness of multigene testing of all patients with BC compared with the current practice of genetic testing (*BRCA*) based on family history (FH) or clinical criteria.

DESIGN, SETTING, AND PARTICIPANTS This cost-effectiveness microsimulation modeling study compared lifetime costs and effects of high-risk *BRCA1/BRCA2/PALB2* (multigene) testing of all unselected patients with BC (strategy A) with *BRCA1/BRCA2* testing based on FH or clinical criteria (strategy B) in United Kingdom (UK) and US populations. Data were obtained from 11 836 patients in population-based BC cohorts (regardless of FH) recruited to 4 large research studies. Data were collected and analyzed from January 1, 2018, through June 8, 2019. The time horizon is lifetime. Payer and societal perspectives are presented. Probabilistic and 1-way sensitivity analyses evaluate model uncertainty.

INTERVENTIONS In strategy A, all women with BC underwent *BRCA1/BRCA2/PALB2* testing. In strategy B, only women with BC fulfilling FH or clinical criteria underwent *BRCA* testing. Affected *BRCA/PALB2* carriers could undertake contralateral preventive mastectomy; *BRCA* carriers could choose risk-reducing salpingo-oophorectomy (RRSO). Relatives of mutation carriers underwent cascade testing. Unaffected relative carriers could undergo magnetic resonance imaging or mammography screening, chemoprevention, or risk-reducing mastectomy for BC risk and RRSO for ovarian cancer (OC) risk.

MAIN OUTCOMES AND MEASURES Incremental cost-effectiveness ratio (ICER) was calculated as incremental cost per quality-adjusted life-year (QALY) gained and compared with standard £30 000/QALY and $100 000/QALY UK and US thresholds, respectively. Incidence of OC, BC, excess deaths due to heart disease, and the overall population effects were estimated.

RESULTS *BRCA1/BRCA2/PALB2* multigene testing for all patients detected with BC annually would cost £10 464/QALY (payer perspective) or £7216/QALY (societal perspective) in the United Kingdom or $65 661/QALY (payer perspective) or $61 618/QALY (societal perspective) in the United States compared with current *BRCA* testing based on clinical criteria or FH. This is well below UK and US cost-effectiveness thresholds. In probabilistic sensitivity analysis, unselected multigene testing remained cost-effective for 98% to 99% of UK and 64% to 68% of US health system simulations. One year's unselected multigene testing could prevent 2101 cases of BC and OC and 633 deaths in the United Kingdom and 9733 cases of BC and OC and 2406 deaths in the United States. Correspondingly, 8 excess deaths due to heart disease occurred in the United Kingdom and 35 in the United States annually.

CONCLUSIONS AND RELEVANCE This study found unselected, high-risk multigene testing for all patients with BC to be extremely cost-effective compared with testing based on FH or clinical criteria for UK and US health systems. These findings support changing current policy to expand genetic testing to all women with BC.

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Author Audio Interview

Supplemental content

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Current national and international guidelines recommend genetic testing in women with breast cancer (BC) who fulfill recognized or established family history (FH) or clinical criteria. These criteria are surrogates for *BRCA* (*BRCA1* [OMIM 113705] and *BRCA2* [OMIM 600185]) probability, with genetic testing usually offered at approximately a 10% probability threshold of being a *BRCA* carrier.[1,2] Being a *BRCA* (mutation) carrier refers to carrying an inheritable genetic pathogenic variant that predisposes to development of *BRCA*-associated cancers. However, patients with BC and genetic pathogenic variants do not always have a positive FH, and these criteria miss a large proportion (approximately 50%) of pathogenic variant carriers.[3-5] A genetic testing strategy based on clinical criteria or FH depends on the patient and their physician's awareness and understanding of the importance of FH, FH accuracy, communication within or between families, and timely referrals to clinical genetics departments. Limited awareness by health care professionals and the public, complexity of the current structure, restricted genetic counseling services, and current testing pathways have fostered restricted access and massive underuse of genetic testing services.[6-8] Only 20% to 30% of eligible patients are referred and access testing, and 97% of estimated carriers in the population remain unidentified,[7] missing substantial opportunities for precision prevention.[6] Testing all patients with BC at diagnosis can increase testing access and uptake and identify many more pathogenic variant carriers for screening and prevention. We herein evaluate the cost-effectiveness of this alternative approach of providing genetic testing to all patients with BC regardless of FH.

Knowing a patient's genetic pathogenic variant status is important for the management and prognosis of BC. After unilateral BC, pathogenic variant carriers can choose contralateral prophylactic mastectomy (CPM) to reduce their risk of developing contralateral BC and opt for surgical prevention of ovarian cancer (OC). Cancer-affected carriers may become eligible for novel drugs (eg, poly [adenosine diphosphate ribose] polymerase [PARP] inhibitors) and other precision medicine-based therapeutics through clinical trials.[9] A major advantage of genetic testing is enabling testing among relatives of BC pathogenic variant carriers in order to identify unaffected relatives carrying pathogenic variants for early diagnosis and cancer prevention. *BRCA1/BRCA2* carriers have a 17% to 44% risk of developing OC and 69% to 72% risk of BC to 80 years of age.[10] *PALB2* (OMIM 610355) is a recently established high-penetrance BC gene associated with a 44% BC risk.[11] A number of risk management options are available for unaffected relatives with pathogenic variants. To reduce OC risk, *BRCA1/BRCA2* pathogenic variant carriers can undergo risk-reducing salpingo-oophorectomy (RRSO).[12,13] To reduce BC risk, *BRCA1/BRCA2/PALB2* pathogenic variant carriers can be offered enhanced magnetic resonance imaging and mammography screening,[14,15] risk-reducing mastectomy (RRM),[16] or chemoprevention with selective estrogen receptor modulators.[17]

Current restricting of testing to FH- or clinical criteria-based selection misses important opportunities to prevent BC and OC in unaffected individuals. In this study, we obtained data from 4 large BC clinical trials and/or research cohorts in the United States, United Kingdom, and Australia. We used modeling to estimate downstream health effects and costs and explore the cost-effectiveness of multigene *BRCA1/BRCA2/PALB2* testing for all cases with BC compared with current *BRCA* testing based on clinical criteria or FH alone. We restrict this analysis to *BRCA1/BRCA2/PALB2*, keeping in mind the principles of the ACCE framework (analytic validity, clinical validity, clinical utility and associated ethical/legal/social implications)[18] advocated for clinical applicability of genetic testing.[18,19]

Key Points

Question Is unselected genetic testing of all women with breast cancer cost-effective compared with testing based on clinical criteria or family history?

Findings In this cost-effectiveness microsimulation modeling study incorporating data from 11 836 women, unselected *BRCA1/BRCA2/PALB2* testing at breast cancer diagnosis was extremely cost-effective compared with *BRCA1/BRCA2* testing based on clinical criteria or family history for UK and US health systems, with incremental cost-effectiveness ratios of £10 464 or £7216 and $65 661 or $61 618 per quality-adjusted life-year, respectively. One year's unselected panel genetic testing could prevent 2101 cases of breast or ovarian cancer and 633 deaths in the United Kingdom and 9733 cases and 2406 deaths in the United States.

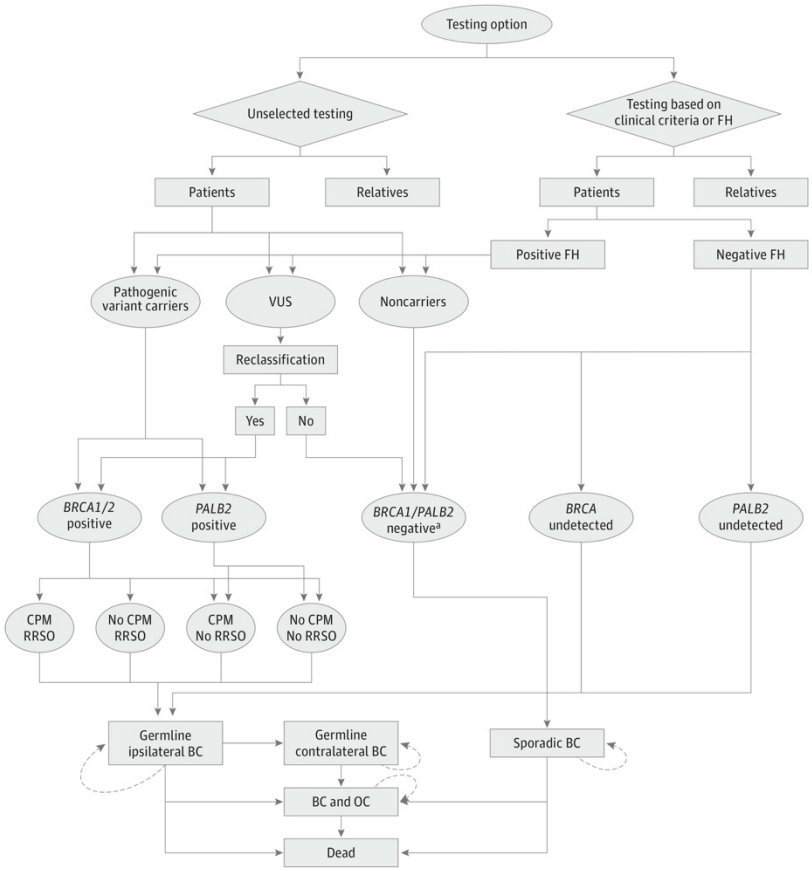
Meaning These findings support changing current policy to expand genetic testing to all women with breast cancer.

Methods

This analysis received full ethics approval from the Institute of Child Health/Great Ormond Street Hospital Research Ethics Committee as well as the London School of Hygiene and Tropical Medicine Ethics Committee, waiving informed consent for the use of anonymized data. A patient and public involvement statement is found in eMethods 4 in the Supplement.

Data were collected and analyzed from January 1, 2018, through June 8, 2019. We obtained data on FH by age from 11 836 women diagnosed with invasive BC, including (1) 1389 unselected patients with BC older than 45 years who were identified among 57 902 women in the Predicting Risk of Breast Cancer Screening study, a large-scale study within the Greater Manchester UK National Health Service Breast Screening Programme[20]; (2) 2885 patients with BC younger than 40 years from 127 UK hospitals in the Prospective Outcomes in Sporadic vs Hereditary Breast Cancer study[21]; (3) 5892 unselected patients with BC older than 40 years among 132 139 women enrolled in the Kaiser Permanente Washington Breast Cancer Surveillance Consortium registry who underwent mammography screening from 1996 to 2014[22]; and (4) 1670 patients with BC younger and older than 40 years who were randomly selected from the unselected population-based BC cases

Figure 1. Model Structure



Schematic diagram shows the microsimulation model structure for unselected and clinical criteria–or family history (FH)–based panel genetic testing for patients with breast cancer (BC). CPM indicates contralateral prophylactic mastectomy; OC, ovarian cancer; RRSO, risk-reducing salpingo-oophorectomy; and VUS, variant of uncertain significance.

[a] Includes individuals testing negative for *BRCA1/BRCA2/PALB2* mutations and VUS not reclassified as pathologic variants.

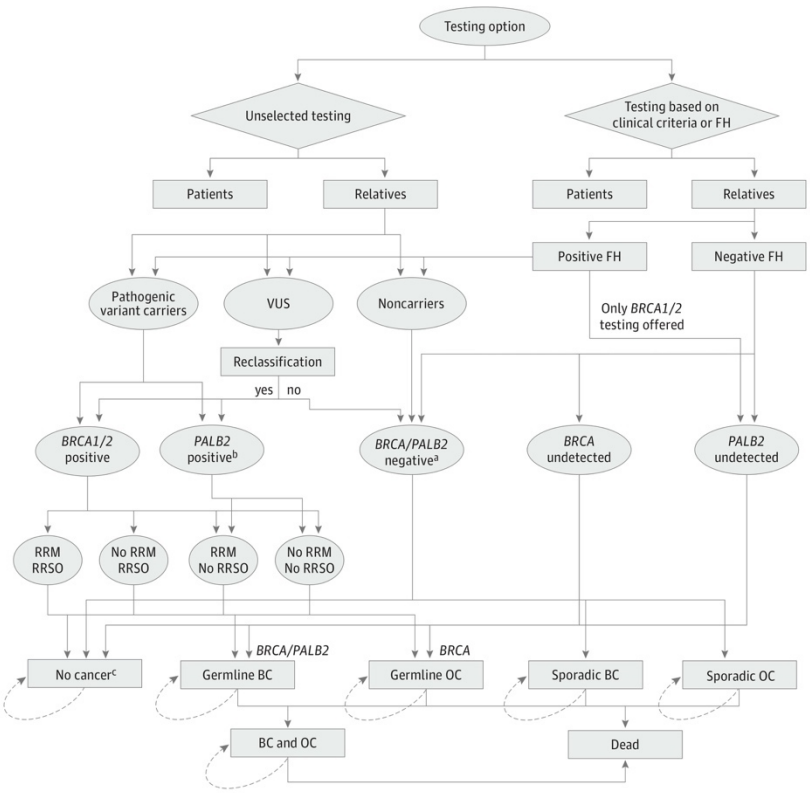
from the Australian Breast Cancer Family Study.[23] The proportion of cases fulfilling FH or clinical criteria for testing based on at least a 10% *BRCA1/BRCA2* probability threshold was estimated using standard risk models (eg, BOADICEA [UK and Australian data] and BRCAPRO [US data]).[24,25] We thus obtained the proportion fulfilling FH or clinical criteria (hereinafter referred to as FH positive) for *BRCA* testing by age group among unselected BC cases in each setting (eTable 1 in the Supplement). The women in these cohorts are predominantly white and representative of a Western population ethnicity (details in eTable 1 in the Supplement). We obtained population-based BC incidence data by age from Cancer Research UK 2015[26] for the UK analysis and from US Cancer Statistics 2015[27] for the US analysis. Then we estimated the total number of FH-positive BC cases based on the number of new invasive BC cases by age group in the UK and US populations.

Model and Genetic Testing Strategy

We developed an individual-level microsimulation model (illustrated and described in **Figure 1** and **Figure 2**) (TreeAge Pro 2018; TreeAge Software) to analyze costs and effects of *BRCA1/BRCA2/PALB2* testing for all patients with BC (strategy A) compared with the current practice of *BRCA* testing using clinical- or FH-based criteria (≥10% pathogenic variant risk) (strategy B). Microsimulation permits individual heterogeneity in gene types and ages and can track individual patient history if the memory of events (eg, risk-reducing options) affects future cycles. The model assumes all patients in the unselected testing arm (strategy A) and only those fulfilling clinical or FH criteria in strategy B are offered genetic counseling and testing. We assume all eligible patients undergo genetic testing in our base-case analysis. If patients had a *BRCA1/BRCA2/PALB2* pathogenic variant, their first-degree relatives undergo testing for the familial pathogenic variant. If the first-degree relative had a *BRCA1/BRCA2/PALB2* pathogenic variant, second-degree relatives undergo testing. We incorporate a 6.4% variant of uncertain significance (VUS) rate (*BRCA1*, 1.23%; *BRCA2*, 3.29%; and *PALB2*, 1.86%)[28] and 8.7% pathogenic or likely pathogenic reclassification rate for VUS.[29]

Figure 1 provides a schema of the model with respect to patients with BC. In the unselected testing arm, all patients with BC are offered genetic testing and are classified as pathogenic

Figure 2. Model Structure



Schematic diagram shows the microsimulation model structure for unselected and clinical criteria–or family history (FH)–based panel genetic testing for relatives of patients with breast cancer (BC). CPM indicates contralateral prophylactic mastectomy; OC, ovarian cancer; RRM, risk-reducing mastectomy; RRSO, risk-reducing salpingo-oophorectomy; and VUS, variant of uncertain significance.

[a] Includes individuals testing negative for *BRCA1/BRCA2/PALB2* mutations and VUS not reclassified as pathologic variants.

[b] In the model structure for relatives, *PALB2*-positive individuals are identified only through the unselected testing arm. Relatives in the clinical criteria/FH testing arm only undergo *BRCA1/BRCA2* testing.

[c] Unaffected relatives can progress from no cancer to germline BC (*BRCA1/BRCA2/PALB2*), germline OC (*BRCA1/BRCA2*), sporadic BC, or sporadic OC (or remain in that health state).

variant carriers, VUS carriers, or noncarriers. A proportion (8.7%) of patients with VUS results will subsequently get reclassified as pathogenic variant carriers. Identified *BRCA1/BRCA2* pathogenic variant carriers are offered options of CPM and RRSO, and identified *PALB2* pathogenic variant carriers are offered CPM. Depending on the probability of patients undertaking a CPM and/or RRSO, they may progress to germline contralateral BC or both BC and OC. They also have a probability of dying due to germline BC. Patients who do not progress or die would stay in the state of germline ipsilateral BC and undertake the next cycle. Patients with negative findings for *BRCA1/BRCA2/PALB2* have sporadic BC. Age-dependent probabilities allow them to develop sporadic OC and progress to the health state of BC and OC. They also have a probability of dying due to sporadic BC. Women who do not progress to BC and OC or die would stay in the health state of sporadic BC to undertake the next cycle.

In the clinical criteria/FH testing arm, patients with positive FH (fulfilling clinical criteria) undergo genetic testing and are classified as pathogenic variant carriers, VUS carriers, or noncarriers. A proportion of patients with VUS results will subsequently be reclassified as pathogenic variant carriers. Patients with negative FH do not undertake genetic testing. They can be undetected *BRCA1/BRCA2* pathogenic variant carriers, undetected *PALB2* pathogenic variant carriers, or negative for *BRCA1/BRCA2/PALB2*. Options of CPM and/or RRSO and disease progression for identified *BRCA1/BRCA2/PALB2* pathogenic variant carriers and disease progression for patients who are BC negative for *BRCA1/BRCA2/PALB2* is the same as those in the unselected testing arm described above. Undetected *BRCA1/BRCA2* pathogenic variant carriers are not offered CPM or RRSO, and undetected *PALB2* pathogenic variant carriers are not offered CPM. Depending on the baseline risk (no risk-reducing options), they progress to germline contralateral BC or both BC and OC. They also have a probability of dying due to germline BC. Patients who do not progress or die would stay in the state of germline ipsilateral BC and undertake the next cycle.

Figure 2 provides a schema of the model with respect to unaffected relatives identified through cascade testing. Progression through the model depends on the probabilities provided in eTable 2 in the Supplement. In the unselected testing arm, relatives of pathogenic variant carriers with BC are offered *BRCA1/BRCA2/PALB2* genetic testing and classified as pathogenic variant carriers or noncarriers. Relatives of patients with BC and VUS (8.7%) who are reclassified as pathogenic variant carriers are also offered predictive *BRCA1/BRCA2/PALB2* testing. Relatives identified with *BRCA1/BRCA2*

pathogenic variants are offered options of RRM and RRSO, and those identified with *PALB2* pathogenic variants are offered RRM. Unaffected relatives can also opt for chemoprevention for BC. Depending on the probability of pathogenic variant carriers undertaking an RRM and/or RRSO (with or without chemoprevention), they progress to germline BC (*BRCA1/BRCA2/PALB2*) or germline OC (*BRCA1/BRCA2*) or stay in the health state of no cancer. They have a probability of background all-cause mortality. Women who are negative for *BRCA1/BRCA2/PALB2* progress to sporadic BC or sporadic OC or stay in the health state of no cancer. They have a probability of background all-cause mortality.

In the clinical criteria/FH testing arm, relatives of identified patients with *BRCA1/BRCA2* mutation undergo predictive *BRCA1/BRCA2* genetic testing. They are classified as pathogenic variant carriers or noncarriers. Relatives of patients with BC and VUS who are reclassified as pathogenic variant carriers also undergo predictive *BRCA1/BRCA2* testing. *PALB2* pathogenic variant carriers cannot be detected when only FH-based *BRCA1/BRCA2* genetic testing is offered. Relatives of patients with negative FH may be undetected *BRCA1/BRCA2* pathogenic variant carriers, undetected *PALB2* pathogenic variant carriers, or negative for *BRCA1/BRCA2/PALB2*. The options of RRM and RRSO for identified carriers are the same as in the unselected testing arm. For identified *BRCA1/BRCA2/PALB2* pathogenic variant carriers and noncarriers (*BRCA1/BRCA2/PALB2* negative), the disease progression is the same as in relatives in the unselected testing arm. Undetected *BRCA1/BRCA2* pathogenic variant carriers are not offered RRM or RRSO, and undetected *PALB2* pathogenic variant carriers are not offered RRM. Depending on the baseline risk, they progress to germline BC or germline OC or stay in a no cancer health state. They also have a probability of background all-cause mortality.

As shown in the model, unaffected *BRCA1/BRCA2/PALB2* pathogenic variant carriers can choose RRM and/or chemoprevention to reduce BC risk and RRSO (*BRCA1/BRCA2* only) to reduce OC risk in addition to undertaking enhanced BC screening. Patients with BC found to have pathogenic variants can opt for CPM. Although initial studies suggested that premenopausal RRSO is associated with reduced BC risk,[13,30,31] more recent data contradict this observation, especially in *BRCA1*,[32] raising uncertainty around this issue. We explored no reduction in BC risk in our scenario analysis. We incorporated the excess risk and mortality due to coronary heart disease (CHD) after premenopausal oophorectomy (after RRSO) for premenopausal women who do not take hormone replacement therapy (HRT) (absolute mortality increase, 3.03%).[33,34] In our model, a hypothetical cohort of patients with BC and their cancer-free relatives can transition to different health states, including no cancer, germline ipsilateral BC, germline contralateral BC, sporadic BC, germline OC, sporadic OC, and both BC and OC. Cancer incidence was estimated by summing the probabilities of pathways ending in OC or BC. The potential population effect was calculated by estimating additional reduction in BC and OC incidence obtained through testing the entire population of BC cases occurring annually in UK and US women. In line with the National Institute of Health and Clinical Excellence (NICE) economic evaluation guidelines, costs and outcomes are discounted at 3.5%.[35]

Probabilities

Model probabilities for the different pathways are shown in eTable 2 in the Supplement. The age-specific incidences of BC and OC among the general population are obtained from Cancer Research UK 2015[26,36] and US Cancer statistics 2015.[27] The age-specific incidence of BC and OC for *BRCA1/BRCA2*[10] carriers and of BC for *PALB2* carriers,[11] along with the incidence of contralateral BC after first BC diagnosis,[10] are obtained from the literature.

Number and Age Distribution of Relatives

We used the number of new BC cases by age groups in the United Kingdom and United States to calibrate the age distribution of patients in the model.[26,27] The mean number of first- or second-degree relatives and their ages relative to index cases are derived from data from the Office for National Statistics (in the United Kingdom)[37] and the National Center for Health Statistics (in the United States)[38] (details in eTable 3 in the Supplement). We used life tables based on age and sex to estimate the probability of being alive for relatives at different ages and to calculate the number and age distribution of relatives who need to undergo testing.

Costs

All costs are reported at 2016 prices. The analysis was conducted from payer and societal perspectives. Costs included genetic testing, pretest and posttest genetic counseling,[39,40] BC, OC, excess CHD, and productivity loss. In line with NICE recommendations, future health care costs not associated with BC, OC, or CHD were not considered.[35] A summary of costs and detailed explanation are given in eTable 4 in the Supplement (medical costs) and eMethods 1 in the Supplement (costs from productivity loss).

Life-Years

Our analysis incorporates lifetime risks and long-term consequences to provide a lifetime horizon. Female life tables from the Office of National Statistics (UK women)[41] and the National Center for Health Statistics (US women)[42] were used to estimate life expectancy by 80 years for women who did not develop OC or BC. We assumed the median age for undergoing RRM and RRSO in unaffected pathogenic variant carriers was 37 and 40 years, respectively.[43] We also explored older age at RRM (42 years) and RRSO (46 years) reported in a scenario analysis.[44] Survival after BC and OC (from diagnosis to death) was modeled using 10-year survival data. Details of survival estimates used are given in eMethods 2 in the Supplement.

Quality-Adjusted Life-Years

A quality-adjusted life-year (QALY) is a measurement of health outcomes in economic evaluations recommended by NICE. An explanation of QALY and utility scores in the model is given in eMethods 3 in the Supplement.

Statistical Analysis

In the microsimulation model, we used the number of annual new BC cases (United Kingdom, 54 483; United States, 242 463) and corresponding female relatives (United Kingdom, 215 401; United States, 993 757) by age for running simulations. Internal validation of the model was undertaken through a process of descriptive, technical, and face validity.[45] We calculated the incremental cost-effectiveness ratio (ICER) by dividing the difference in lifetime costs by the difference in lifetime effects (QALYs) between the 2 strategies as follows: (Cost of Strategy A − Cost of Strategy B)/(Effect of Strategy A − Effect of Strategy B). By comparing the ICER with the willingness-to-pay (WTP) threshold of £30 000/QALY (UK analysis)[46] and $100 000/QALY (US analysis),[47,48] we determined whether genetically testing all patients with BC is cost-effective compared with testing based on clinical criteria or FH alone. We undertook a number of scenario analyses, including (1) no reduction in BC risk due to RRSO; (2) nil HRT adherence; (3) lower genetic testing uptake rate (70%) in patients with BC and relatives; (4) 15% *BRCA1/2* pathogenic variant prevalence in patients with BC fulfilling clinical criteria or FH; (5) double cost of genetic counseling (United Kingdom, £40; United States, $80); (6) higher median age for RRM (42 years) and RRSO (46 years) in unaffected pathogenic variant carriers; and (7) the maximum values of cost(s) of genetic testing at which the ICERs reach the WTP thresholds to maintain cost-effectiveness of unselected multigene testing (strategy A).

We performed extensive 1-way and probabilistic sensitivity analyses to explore model parameter uncertainty. In the 1-way sensitivity analysis, each variable or parameter was varied individually to assess the effect on results. Probabilities and utility scores were varied by their 95% CIs or range where available or by ±10%, and costs were varied by ±30%. In the probabilistic sensitivity analysis, all of the input variables were varied simultaneously (as recommended by NICE).[49] As suggested in the literature,[50] costs were given a γ distribution; quality of life, a log-normal distribution; and probability, a β distribution. For probabilistic sensitivity analysis, we obtained 1000 estimates of incremental costs and effects by sampling from the distributions of each variable. A cost-effectiveness acceptability curve was then plotted to show the probability of genetically testing all patients, with BC (strategy A) being cost-effective at different WTP thresholds.

Results

Compared with the current practice of genetic testing based on clinical criteria or FH, offering unselected multigene testing for all patients diagnosed annually with BC (54 483 in the United Kingdom and 242 463 in the United States) and subsequent predictive/cascade testing of relatives (strategy A) was highly cost-effective. The ICER for the UK payer perspective was £10 464/QALY (credible interval, £8347/QALY to £28 965/QALY) and for the societal perspective, £7216/QALY (credible interval, £6194/QALY to £23 575/QALY). The ICER for the US payer perspective was $65 661 per QALY (credible interval, $46 613/QALY to $248 185/QALY) and for the societal perspective, $61 618/QALY (credible interval, $42 927/QALY to $221 781/QALY). The lifetime costs, QALYs, and population effects (reduced cancer incidence and deaths) for UK and US women are shown in **Table 1** and **Table 2**. Strategy A was associated with an additional 419-day increase in life expectancy for UK and 298 days for US *BRCA1/BRCA2/PALB2* pathogenic variant carriers. One year's unselected genetic testing of all patients with BC could prevent an additional 1142 BC cases and 959 OC cases in the United Kingdom and 5478 BC cases and 4255 OC cases in the United States (Table 2). This finding corresponds to averting 633 deaths due to cancer in UK populations and 2406 deaths due to cancer in US populations during a lifetime horizon (Table 2). The corresponding excess deaths due to heart disease were 8 in UK and 35 in US women annually.

The 1-way sensitivity analysis (eFigure 1A-D in the Supplement) indicates that pathogenic variant prevalence, costs, utility scores, and transition probabilities had little individual influence on the cost-effectiveness of unselected genetic testing (strategy A) from a payer or a societal perspective. Scatterplots for the UK and US analyses are given in eFigure 2 in the Supplement and show that all simulations and iterations lie in the northeast quadrant, indicating unselected testing was always more effective. The ICERs are lower than the UK and US WTP thresholds at the upper and lower limits of these variables. Probabilistic sensitivity analysis (**Figure 3**) shows that at the £30 000/QALY or $100 000/QALY thresholds, 98% (UK payer perspective), 99% (UK societal perspective), 64% (US payer perspective), or 68% (US societal perspective) of simulations indicate that unselected genetic testing is cost-effective compared with testing based on FH or clinical criteria.

The number of pathogenic variant carriers among unaffected female relatives identified through cascade testing was 1.41 in the United Kingdom and 1.46 in the United States per index pathogenic variant carrier with BC (details in eTable 4 in the Supplement). Scenario analyses are presented in Table 1. Unselected testing was cost-effective from payer and societal perspectives, even with alternative scenarios of no reduction in BC risk due to RRSO (ICER payer perspective, £10 532/QALY or $66 136/QALY; ICER societal perspective, £7291/QALY or $62 102/QALY); nil HRT adherence (ICER payer perspective, £11 303/QALY or $89 705/QALY; ICER societal perspective, £7870/QALY or $85 337/QALY); and lower (70%) genetic testing uptake rate in patients with BC and relatives (ICER payer perspective, £10 991/QALY or $71 006/QALY; ICER societal perspective, £8046/QALY or $67 285/QALY). Although the probability of being a *BRCA1/BRCA2* carrier in those fulfilling FH or clinical genetic testing criteria was reported at approximately 10%,[51,52] we also explored a scenario of overall 15% *BRCA1/BRCA2* carrier probability. This variable had only a minimal effect on ICERs from the payer (£10 585/QALY) and societal (£7332/QALY) perspectives among UK women and from the payer ($66 694/QALY) and societal ($62 646/QALY) perspectives among US women. The upper limit of genetic testing costs at which unselected genetic testing for all patients with BC would still remain cost-effective at the established WTP thresholds was approximately £1626 from the payer perspective and £1868 from the societal perspective for the UK health

Table 1. Lifetime Discounted Costs and Effects per Woman and ICER After Genetic Testing for All Patients With BC[a]

	Testing All Patients With BC				Testing Based on Family History				ICER			
	Health Effects		Costs[b]		Health Effects		Costs[b]		Cost/LYG[b]		Cost/QALY[b]	
Country	LYGs	QALYs	Payer	Societal	LYGs	QALYs	Payer	Societal	Payer	Societal	Payer	Societal
Baseline												
United Kingdom	18.772	17.941	7213	11 147	18.755	17.922	7016	11 011	11 817	8149	10 464	7216
United States	18.652	17.813	32 721	36 561	18.639	17.798	31 724	35 625	82 789	77 691	65 661	61 618
No Reduction in BC Risk Due to RRSO[c]												
United Kingdom	18.772	17.941	7214	11 148	18.755	17.922	7016	11 011	11 846	8201	10 532	7291
United States	18.652	17.813	32 724	36 564	18.639	17.798	31 724	35 625	82 902	77 844	66 136	62 102
No HRT Adherence[d]												
United Kingdom	18.771	17.940	7218	11 152	18.755	17.922	7016	11 011	12 706	8846	11 303	7870
United States	18.651	17.812	33 013	36 852	18.639	17.798	31 751	35 652	113 342	107 823	89 705	85 337
Lower Uptake Rate of Genetic Testing in Patients and Relatives[e]												
United Kingdom	18.766	17.934	7132	11 096	18.755	17.922	7009	11 007	11 363	8319	10 991	8046
United States	18.644	17.804	32 299	36 170	18.637	17.796	31 691	35 595	80 043	75 849	71 006	67 285
15% Probability of Being a *BRCA* Carrier in Patients With Positive FH[f]												
United Kingdom	18.771	17.941	7213	11 147	18.755	17.923	7022	11 015	11 973	8293	10 585	7332
United States	18.653	17.814	32 723	36 563	18.641	17.800	31 759	35 657	84 453	79 326	66 694	62 646
Double Cost of Counseling[g]												
United Kingdom	18.772	17.941	7220	11 154	18.755	17.922	7016	11 011	12 189	8521	10 794	7546
United States	18.652	17.813	32 734	36 574	18.639	17.798	31 725	35 625	83 798	78 701	66 462	62 419
Older Ages for RRM and RRSO in Unaffected Pathogenic Variant Carriers[h]												
United Kingdom	18.770	17.938	7216	11 165	18.755	17.922	7016	11 013	13 181	10 043	12 214	9306
United States	18.650	17.811	32 722	36 578	18.639	17.798	31 720	35 622	92 304	88 063	77 715	74 144

Abbreviations: BC, breast cancer; FH, family history; HRT, hormone replacement therapy; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year; RRM, risk-reducing mastectomy; RRSO, risk-reducing salpingo-oophorectomy.

[a] Costs and outcomes are discounted at 3.5%. Data are given at baseline (for the base case) and for separate scenarios.

[b] Costs are given in dollars for the United States and pounds sterling for the United Kingdom.

[c] Probability P 15 = 1 (eTable 2 in the Supplement).

[d] Probability P 21 = 0 (eTable 2 in the Supplement).

[e] Indicates a genetic testing uptake rate of 70%.

[f] Probability P 4 = 0.15 (eTable 2 in the Supplement).

[g] Indicates £40 in the United Kingdom and $80 in the United States.

[h] Indicates ages 42 and 46 years for RRM and RRSO, respectively.

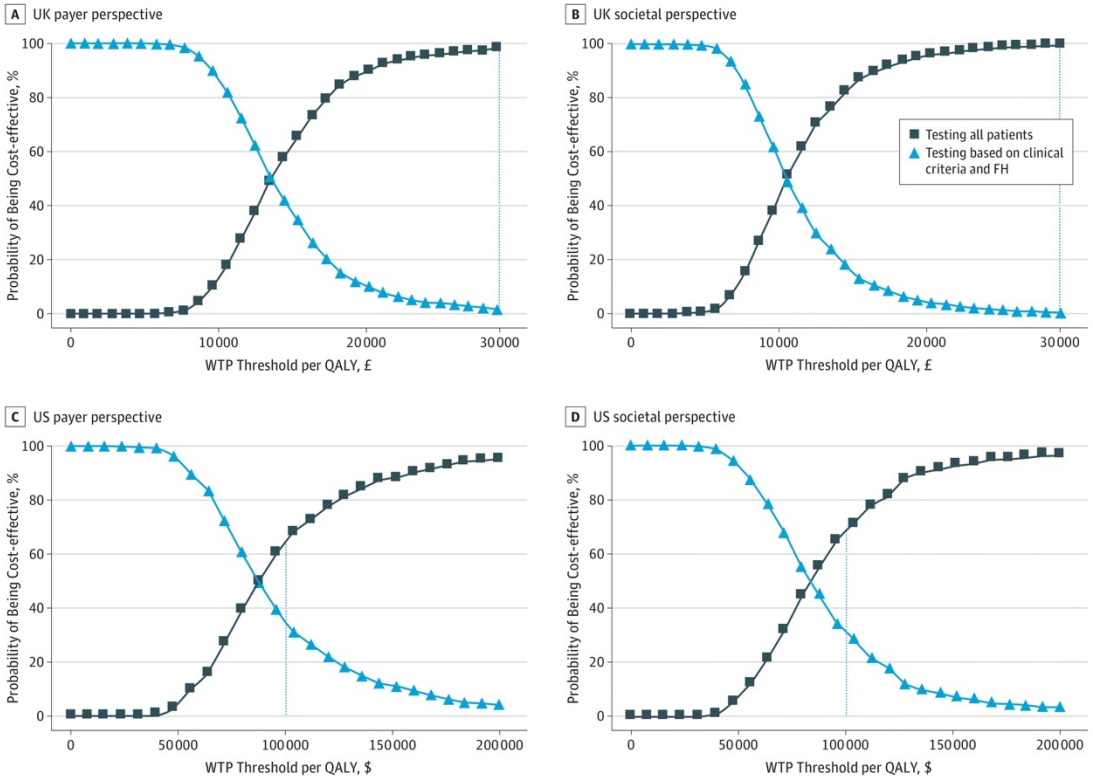
Table 2. Population Effect of Genetic Testing for Patients With BC

	Testing in All Patients With BC		Testing Based on FH		Differences		
Estimated Effect	Patients	Relatives	Patients	Relatives	Patients	Relatives	Total
UK germline cancer							
No. of BC cases	364[a]	1965	684[a]	2787	320[a]	822	1142
No. of OC cases	447	1882	871	2417	424	535	959
No. of BC and OC deaths	451	988	748	1325	296	337	633
US germline cancer							
No. of BC cases	1639[a]	8727	3230[a]	12 614	1591[a]	3887	5478
No. of OC cases	2087	8655	3916	11 081	1829	2426	4255
No. of BC and OC deaths	1555	4168	2621	5508	1066	1340	2406

Abbreviations: BC, breast cancer; FH, family history; OC, ovarian cancer.

[a] Indicates contralateral BC cases in patients with unilateral BC.

Figure 3. Cost-effectiveness Acceptability Curves (Probabilistic Sensitivity Analyses)



Probabilistic sensitivity analysis in which all model parameters/variables are varied simultaneously across their distributions to further explore model uncertainty. The results of 1000 simulations were plotted on a cost-effectiveness acceptability curve showing the proportion of simulations that indicated that the intervention was cost-effective at different willingness-to-pay (WTP) thresholds. A and B, The dotted line marks the proportion of simulations found to be cost-effective at the WTP threshold of £30 000 per quality-adjusted life-year (QALY) in the UK analysis. At the £30 000/QALY WTP threshold from the payer perspective, 2% simulations are cost-effective for testing based on clinical criteria or family history (FH) and 98% simulations are cost-effective for unselected genetic testing; from the societal perspective, 1% simulations are cost-effective for testing based on clinical criteria or FH and 99% simulations are cost-effective for unselected genetic testing. C and D, The dotted line marks the proportion of simulations found to be cost-effective at the WTP threshold of $100 000/QALY in the US analysis. At the $100 000/QALY WTP threshold from the payer perspective, 36% simulations are cost-effective for testing based on clinical criteria or FH and 64% simulations are cost-effective for unselected genetic testing; from the societal perspective, 32% simulations are cost-effective for testing based on clinical criteria or FH and 68% simulations are cost-effective for unselected genetic testing.

system and $2432 from the payer perspective and $2679 from the societal perspective for the US health system.

Lower RRSO and RRM rates are reported in some populations.[53] The minimum RRSO uptake rate to maintain cost-effectiveness was 29% from the payer perspective or 28% from the societal perspective for the United States (ICER, $100 000/QALY), but unselected BC genetic testing was cost-effective in the United Kingdom even if the RRSO rate was nil (ICER from the payer perspective, £26 392/QALY; ICER from the societal perspective, £23 802/QALY). The strategy was cost-effective even if RRM rates in unaffected relatives approached 0 (UK ICER from the payer perspective, £9969/QALY; UK ICER from the societal perspective, £7041/QALY; US ICER from the payer perspective, $67 235/QALY; US ICER from the societal perspective, $63 643/QALY). However, if RRM uptake was 0, then the minimum RRSO uptake rate to maintain cost-effectiveness at the WTP thresholds (United States, $100 000/QALY; United Kingdom, £30 000/QALY) was 33% (payer perspective) or 32% (societal perspective) in the US health system and 5% (payer perspective) or 4% (societal perspective) in the UK health system.

Discussion

Our analysis addresses a topical and important issue of unselected multigene testing for all patients with BC. We show for the first time, to our knowledge, that multigene testing for high-penetrance BC pathogenic variants of well-established clinical utility is more cost-effective and outperforms standard

BRCA testing driven by clinical criteria or FH alone. Moving toward such a program could lead to 1142 fewer BC cases, 959 fewer OC cases, and 663 fewer deaths due to BC or OC in UK women and 5478 fewer BC cases, 4255 fewer OC cases, and 2406 fewer deaths due to BC or OC in US women annually. Our study provides QALY-based health outcomes that justify the cost differences between the 2 strategies that are needed for health care professionals, providers, and policy makers to guide or direct resource allocation. The ICERs (£10 464/QALY and £7216/QALY in the United Kingdom and $65 661/QALY and $61 618/QALY in the United States) lie well below the established cost-effectiveness thresholds for the UK (£20 000/QALY to £30 000/QALY) and the US ($100 000/QALY) health systems. Continuing with the current FH- or clinical criteria-based policy reflects important opportunities missed for BC and OC prevention.

Comparison With Other Studies

Although earlier studies have reported cost-effectiveness of *BRCA* testing at the 10% pretest probability threshold,[54] we report cost-effectiveness of unselected *BRCA/PALB2* testing irrespective of a priori mutation probability. Our findings are in line with a recent, small Norwegian study (535 patients) showing cost-effectiveness of *BRCA* testing for all patients with BC.[5] Our study is broader in scope and draws on a much larger sample size of population-based UK, US, and Australian patients with BC. Testing at cancer diagnosis has now moved toward multigene testing. *PALB2* is associated with nonsyndromic, quasi-mendelian BC susceptibility (BC risk, 44%), and magnetic resonance imaging screening and RRM are now offered for pathogenic variants. Other high-risk genes are identifiable as pleiotropic syndromic (*STK11, PTEN, or p53*) or associated with only a small subset (lobular), and all are very rare.[19] In addition, reliable risk estimates corrected for ascertainment bias are lacking.[19] Although *ATM* and *CHEK2* are included in some commercial panels, clinical testing for these genes is not routine in most centers. Risks conferred by these pathogenic variants are lower (relative risk, approximately 1.5-2.0), and although National Comprehensive Cancer Network guidelines support breast screening, RRM is not routinely offered, FH needs incorporation into risk assessment and management, and many health care professionals believe that they fall below the clinical intervention threshold.[19] Hence, we incorporated *PALB2* along with *BRCA* but excluded other genes.

Implications

The current health care model of testing based on clinical criteria or FH has numerous limitations. It misses a large proportion of pathogenic variant carriers who fall below the current clinical threshold.[3,5] The current system is plagued by massive underuse of genetic testing and missed opportunities for BC and OC screening and prevention.[6,7] Moving toward unselected BC testing may give an impetus for prevention in unaffected family members along with clinical implications for the patient with BC. Pathogenic variant carriers with newly diagnosed BC can opt for bilateral mastectomy rather than breast conservation at initial BC surgery. Bilateral mastectomy reduces contralateral BC risk, may provide better options for breast reconstruction, and may obviate the need for adjuvant radiotherapy.[55] The patients also become eligible for therapeutic options, such as PARP inhibitors. Addressing the increasing burden of long-term and chronic disease, including cancer, is one of the world's greatest public health challenges and is important for future viability of health systems across the world.[56] The Milken Institute estimates that improving prevention can cut millions of cases of chronic disease and reduce treatment costs by billions.[57] The applicability of genomics to medicine is growing and expanding. Moving toward unselected multigene testing for patients with BC can provide a huge stimulus for precision prevention.

Existing genetic counseling services operating through high-risk cancer genetics clinics do not have the resources or manpower to deliver unselected genetic testing for all patients with BC given the large numbers of patients who receive a diagnosis annually. Hence, newer context-specific delivery models will be needed for implementing this approach. These models may require pretest counseling to be undertaken by nongenetic health care professionals who will need to be trained for this. This approach of mainstreaming genetic counseling and testing has recently been successfully implemented in OC treatment pathways.[58,59] Oncologists, surgeons, and clinical nurse specialists have provided pretest counseling and genetic testing,[58,59] with genetic services focusing on posttest counseling and support for women carrying pathogenic variants. A similar approach could work for patients with BC. Examples of other delivery options include a genetics service–coordinated nurse-led model,[60] a genetics-embedded model (genetics health care professional or counselor embedded in the cancer clinic),[61,62] and telephone counseling[40,63,64] or telegenetics services[65] for genetic counseling and testing.

Going forward, most health care professionals who practice medicine will need an increased understanding of genetics and ability to counsel patients about this topic.[8,66] As the volume of testing rises, the number of mutations and VUS being diagnosed along with the need for correct interpretation and management will increase. Implementation will need to be accompanied by a process of training and education for relevant physicians and other health care professionals involved in the care pathway so that they can understand the implications for management, including that of VUS. This process is critical to ensure best evidence-based care[67] and to avoid unintended or inappropriate management, such as downstream predictive testing, screening, or prevention in VUS cases.[68] Updated guidelines need to reflect the importance of appropriate management. Appropriate clinical decision support tools can facilitate this transformation. Another potential bottleneck to address is laboratory infrastructure to manage increased sample throughput. Although some health systems have adequate capacity, others may lack this infrastructure. Future research needs to evaluate the effects and downstream outcomes of various context-specific genetic testing implementation and management pathways for patients with BC.

Strengths and Limitations

Our study has several strengths. The model incorporates unselected BC data from large population-based studies, up-to-date information from the Genetics Cancer Prediction Through Population Screening study,[69] published literature, and public databases such as those of the Office for National Statistics (United Kingdom),[37,41] National Center for Health Statistics (United States),[38,42] and Cancer Research UK.[26,36] We use the current standard of clinical care (approach based on clinical criteria or FH) as the comparator and present analyses from the payer and societal perspectives. Our analysis follows NICE recommendations: QALYs to measure health outcomes; cost-effectiveness analysis for health economic evaluation,[49] integration of utility scores, discounting costs and outcomes (rate, 3.5%), sufficiently long horizon (lifetime) to uncover important differences in costs and outcomes, and extensive and thorough 1-way and probabilistic sensitivity analyses that support robustness and accuracy of results (eFigure 1 in the Supplement and Figure 2). We include a detriment for CHD mortality.[33] Our costs include genetic testing, VUS management, pretest and posttest genetic counseling, HRT use, and protection from osteoporosis.

Our study has limitations related to modeling assumptions. Our baseline model assumes that all women with BC and their unaffected relatives undergo genetic testing. Although very high (≤98%), genetic testing rates are reported in unselected genetic testing at OC diagnosis, and corresponding genetic testing uptake data in unselected patients with BC are not well established. Our scenario analysis reconfirms cost-effectiveness at lower (70%) uptake rates. Although our base model incorporates reduction in BC risk with premenopausal oophorectomy in keeping with many initial analyses,[13,30,31,70] recent uncertainty surrounds this.[32] Our scenario analysis reconfirms cost-effectiveness even without this benefit. Although genetic testing costs have fallen drastically, some health care providers charge higher prices than our base-case assumption. Nevertheless, unselected BC testing would remain cost-effective even at £1626 to £1868 in the United Kingdom or $2432 to $2679 in the United States, which is many times greater than costs charged by most health care providers today. Another limitation is that our model incorporates data predominantly from white women, which can limit interpretation of generalizability to nonwhite populations.

Although we have incorporated disutility for RRSO and RRM, surgical prevention might have associated complications (RRSO, approximately 3%-4%[71]; RRM, approximately 21%)[72,73] that need to be factored into the informed consent and decision-making process. Although premenopausal RRSO is not associated with worsening general quality of life, poorer sexual function is reported (despite HRT).[74,75] This outcome is compensated by extremely high satisfaction rates and reduction in perceived cancer risk and/or worry with RRSO.[74,76] Risk-reducing mastectomy is negatively associated with sexual pleasure and body image. These disadvantages may be offset by reduced anxiety, improved social activity,[77] good cosmetic satisfaction rates,[78,79] and lack of negative impact on sexual activity/habit/discomfort,[77] anxiety/depression, or generic quality of life.[77,80,81] We confirmed that unselected multigene testing remains cost-effective at recently reported older ages of RRM and RRSO.[44] The surgical prevention (RRM and RRSO) rates used are based on established UK and US data.[43,82] However, these rates can vary, with lower rates reported in some populations.[53] Those ascertained from population testing may have lower BC risks and result in lower uptake, particularly in the absence of death due to BC and heavy cancer burden in the family. Our scenario analyses show that unselected testing remains cost-effective at lower RRSO and RRM rates.

Conclusions

This study's findings suggest that unselected multigene testing for BC susceptibility genes *BRCA1/BRCA2/PALB2* can substantially reduce future BC and OC cases and related deaths compared with the current clinical strategy. Our analysis suggests that an unselected testing strategy is extremely cost-effective for UK and US health systems and provides a basis for change in current guidelines and policy to implement this strategy.

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Supplementary Online Content

Sun L, Brentnall A, Patel S, et al. A cost-effectiveness analysis of multigene testing for all patients with breast cancer. *JAMA Oncol.* Published online October 3, 2019. doi:10.1001/jamaoncol.2019.3323

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Family History Information in Breast Cancer Cases

	POSH		BCSC		PROCAS		ABCFS		Overall			BC cases in population		FH+ BC cases in population	
Age	Total BC cases	FH+ BC cases	Total BC cases	FH+ BC cases	Total BC cases	FH+ BC cases	Total BC cases	FH+ BC cases	Total BC cases	FH+ BC cases	Proportion of FH+ in BC cases	UK	USA	UK	USA
<40	2885	548	0	0	0	0	890	44	3775	592	15.7%	2194	10679	344	1675
40-44	0	0	262	40	0	0	198	5	460	45	9.8%	2754	12818	269	1254
45-49	0	0	578	58	59	3	202	7	839	68	8.1%	5228	19949	424	1617
50-54	0	0	874	71	289	10	191	2	1354	83	6.1%	6391	25506	392	1564
55-59	0	0	978	49	241	9	156	0	1375	58	4.2%	5410	29388	228	1240
60-64	0	0	1036	42	290	3	17	0	1343	45	3.4%	6276	33231	210	1113
65-70	0	0	909	33	323	5	16	0	1248	38	3.0%	7672	35651	234	1086
70-74	0	0	698	22	156	5	0	0	854	27	3.2%	5127	28571	162	903
75+	0	0	557	17	31	2	0	0	588	19	3.2%	13431	46670	434	1508
Total	2885	548	5892	332	1389	37	1670	58	11836	975	8.2%	54483	242463	2697	11959

ABCFS - Australian Breast Cancer Family Study, BC – breast cancer, FH+ – family history positive, POSH – Prospective Outcomes in Sporadic versus Hereditary breast cancer study, PROCAS - Predicting Risk of Breast Cancer Screening study

The numbers of breast cancer cases by age group in the population are obtained from Cancer Research UK 2015[1] and US Cancer Statistics 2015[2]. The probability of having a positive FH among unselected patients is 2697/54483 in the UK and 11959/242463 in the USA.

Ethnicity Distribution:

PROCAS study: 91% White, 1.54% Asian, 1.16% Black, 0.9% Jewish, 0.5% Mixed, 1.68% other and 3.23% Unknown.[3]

POSH study: 92.7% White, 3.7% Black, 3% Asian, 0.7% from 'other' ethnic groups, and 0.5% Mixed.[4]

BSCS registry: 85% White, 7% Asian, 3% Black, 3% Mixed, 1% Native American Indian/Alaskan, 1% Other and <1% Unknown.[5]

ABCFS: 92% White, 5.9% Asian, 1% Maori/Aboriginal/Pacific, 1.3% Other

eTable 2. Probabilities of Different Pathways in the Model and Explanations

Probability	Value	(95% CI) [Range]	Description	Source
P1	0.0464	(0.044,0.049)	*BRCA1/BRCA2* mutation prevalence in unselected breast cancer patients	[6]
P2	0.0089	(0.008,0.010)	*PALB2* mutation prevalence in unselected breast cancer patients	[6]
P3	0.0495	(0.048,0.051)	Probability of having a positive FH among unselected patients	[7-9]
P4	0.1	--	*BRCA1/BRCA2* mutation prevalence in FH-positive patients	[10]
P5	0.008	(0.005,0.013)	*PALB2* mutation prevalence in FH-positive patients	[11]
P6	0.0453	(0.0350, 0.0585)	*BRCA1/BRCA2* VUS prevalence in breast cancer patients	[12]
P7	0.0186	(0.0130, 0.0264)	*PALB2* VUS prevalence in breast cancer patients	[12]
P8	0.0869	(0.0755, 0.0999)	Reclassification rate of VUS	[13]
P9	0.47	(0.34,0.56)	Uptake of RRM in unaffected mutation carriers	[14]
P10	0.539	(0.442,0.636)	Uptake of CPM in carriers with breast cancer	[15]
P11	0.55	(0.45,0.64)	Uptake of RRSO in unaffected carriers	[16]
P12	0.567	(0.506,0.629)	Uptake of RRSO in carriers with breast cancer	[17]
P13	0.911	(0.62,0.98)	Reduction in breast cancer risk from RRM without RRSO in unaffected mutation carriers	[18]
P14	0.95	(0.78,0.99)	Reduction in breast cancer risk from RRM with RRSO in unaffected mutation carriers	[18]
P15	0.49	(0.37,0.65)	HR for breast cancer from RRSO alone in unaffected mutation carriers	[19]
P16	0.18	(0.07,0.45)	HR for contralateral breast cancer risk from CPM after breast cancer diagnosis	[15]
P17	0.35	(0.20,0.61)	HR for contralateral breast cancer risk from RRSO after breast cancer diagnosis	[20]
P18	0.96	[0.8,0.96]	Reduction in ovarian cancer risk from RRSO	[19,21]
P19	0.46	(0.27,0.79)	HR for breast cancer survival from RRSO	[22]
P20	0.37	(0.17,0.80)	HR for breast cancer survival from CPM	[15]
P21	0.8	(0.76,0.83)	Compliance of HRT	[23]
P22	0.71	(0.60,0.83)	HR of breast cancer risk from chemoprevention	[24]
P23	0.163	(0.136,0.19)	Uptake of breast cancer chemoprevention	[25]
P24	0.0072	(0.0068,0.0076)	Annual excess risk of developing CHD after RRSO	[26]
P25	0.0303	(0.011,0.043)	Cumulative mortality from CHD after RRSO without HRT	[26]

95%CI - 95% confidence interval, CHD - coronary heart disease, CPM – contralateral prophylactic mastectomy, FH - family history, HR - Hazard Ratio, HRT - hormone replacement therapy, RRSO – risk-reducing salpingo-oophorectomy, RRM – risk-reducing mastectomy, VUS – variant of uncertain significance.

Explanations:

P1-P2: The probabilities of carrying a *BRCA1/BRCA2/PALB2* mutation in unselected breast cancer patients are taken from a US analysis by Buys et al 2017 among 35,409 women with a single diagnosis of breast cancer undergoing clinical genetic testing [6].

P3: We obtained the proportion of having a positive family history (having ≥10% *BRCA1/BRCA2* mutation risk) among unselected breast cancer cases from Kaiser Permanente Washington breast imaging registry [7], POSH study [8], and PROCAS study [9] and unselected population based breast cancer cases from the ABFCS.[27] Then we used the number of breast cancer cases by age from Cancer Research UK[1] to calculate the overall proportion of having a positive family history among unselected breast cancer patients. Correspondingly the breast cancer cases by age for the US was obtained from the United States Cancer Statistics [2].

P4: The overall *BRCA1/BRCA2* mutation prevalence (10%) among FH positive breast cancer patients is based on the current testing guideline.

P5: The probability of carrying a *PALB2* mutation in breast cancer patients with a positive FH is taken from Slavin 2017.[11] The *BRCA1/BRCA2* mutation probability in FH positive individuals is 0.1, which is the threshold for genetic testing in the current guideline. Among *BRCA1/BRCA2* negative familial breast cancer patients (90% of patients), the *PALB2* prevalence is 0.89%. Therefore, the overall PALB2 prevalence in all FH positive breast cancer patients is 0.8% or 0.008.

P6-P7: We obtained the *BRCA1/BRA2/PALB2* VUS prevalence from a systematic review and meta-analysis by van Marcke et al 2018 including 1,870 breast cancer patients[12]. VUS rate to be 1.23% for *BRCA1*, 3.29% for *BRCA2* and 1.86% for *PALB2* in high-risk breast cancer patients.[12] This gives a total VUS rate of 6.4%.[12]

P8: The reclassification rate of VUS is taken from Mersch et al 2018[13]. 8.69% of VUS (178 of 2048) were upgraded to pathogenic or likely pathogenic variants.

P9: The probability that unaffected carriers will undergo RRM is taken from an analysis of UK *BRCA1/2* carriers by Evans et al 2009 [14]. A composite uptake rate for *BRCA1* (60% RRM rate) and *BRCA2* (43% RRM rate) carriers weighted for the relative prevalence of *BRCA1 and BRCA2* mutations was computed [14].

P10: The uptake of CPM in *BRCA1/BRCA2* women diagnosed with unilateral breast cancer is obtained from a cohort study by Evans et al 2013 in the UK [15].

P11: The uptake of RRSO in unaffected *BRCA1/BRCA2* carriers is taken from a study among high-risk UK women [16].

P12: The uptake of RRSO in women with *BRCA1/BRCA2* breast cancer is taken from Kauff et al 2008[17].

P13: The reduction in breast cancer risk from RRM in *BRCA1/BRCA2* mutation carriers not undergoing RRSO is taken from the PROSE study data by Rebbeck et al 2004 [18].

P14: The reduction in breast cancer risk in *BRCA1/BRCA2* mutation carriers undergoing RRM and RRSO is taken from the PROSE study data by Rebbeck et al 2004 [18].

P15: The Hazard Ratio for breast cancer in pre-menopausal unaffected *BRCA1/BRCA2* women undergoing RRSO alone is taken from a meta-analysis by Rebbeck et al 2009 [19].

P16: The Hazard Ratio for contralateral breast cancer risk from CPM in women with *BRCA1/BRCA2*-associated breast cancer is obtained from Evans 2013 [15].

P17: The Hazard Ratio for contralateral breast cancer risk from RRSO in *BRCA1/BRCA2* mutation carriers after breast cancer diagnosis is obtained from a UK study by Basu 2015 [20], using data from the regional genetics service and the family history clinic at the Genesis Breast Cancer Prevention Centre in Manchester.

P18: The reduction in ovarian cancer risk obtained from RRSO is taken from previous studies which report a 4% residual-risk of primary peritoneal cancer following RRSO [21].

P19: The Hazard Ratio for breast cancer survival from RRSO is obtained from Metcalfe 2015 [22].

P20: The Hazard Ratio for breast cancer survival from CPM is obtained from Evans 2013 [15].

P21: HRT compliance rate is obtained from a UK cohort (Read et al, 2010) [23].

P22: The Hazard Ratio for breast cancer risk from chemoprevention in high-risk women is obtained from the extended long-term follow-up of the IBIS-I breast cancer prevention trial (Cuzick et al 2015) [24].

P23: The uptake of breast cancer chemoprevention is obtained from a recent meta-analysis by Smith et al 2016 [25].

P24: Excess risk of CHD after RRSO is estimated using data from Parker 2013 [26]. The absolute excess CHD incidence is obtained by subtracting CHD incidence in women undergoing RRSO from those not.

P25: The risk of CHD mortality is obtained from the Nurses Health Study (Parker et al 2013) [26]. Death from CHD is reported in 1 in 33 pre-menopausal women undergoing RRSO and not taking HRT [26].

eTable 3. Generating Cohort of Relatives

Country	**UK**				**USA**			
First-degree relatives	Mother	Father	Siblings	Children	Mother	Father	Siblings	Children
Average number	1	1	0.91	1.91	1	1	0.99	1.99
Age relative to index case	30	32	0	-30	29	31	0	-29
Sex, probability female	100%	0%	50.78%	50.78%	100%	0%	50.76%	50.76%
Probability mutation	50%	50%	50%	50%	50%	50%	50%	50%
Second-degree relatives	Grandparents	Uncle/aunts	Nieces/nephews	Grandchildren	Grandparents	Uncle/aunts	Nieces/nephews	Grandchildren
Average number	4	1.82	1.74	3.65	4	1.98	1.97	3.96
Age relative to first-degree relatives	30	0	-30	-30	29	0	-29	-29
Sex, probability female	50%	50.76%	50.76%	50.76%	50%	50.76%	50.76%	50.76%
Probability mutation	25%	25%	25%	25%	25%	25%	25%	25%
Reference	Office for National Statistics [28]				National Centre for Health Statistics [29]			

The average number of first or second-degree relatives, ages relative to index cases, and the probability of being female are derived from data from the Office for National Statistics (UK) [28] and the National Centre for Health Statistics (USA).[29] The number of breast cancer cases by age group is reported by Cancer

Research UK 2015[1] and US Cancer Statistics 2015[2]. Based on the average number of relatives and the age relative to the index cases (see table above), we calculated the number of first-/second-degree relatives at different ages. Then we used the lifetables based on age and gender [30,31] to obtain the probability of being alive for relatives at different ages and to calculate the number of relatives that need to be tested. The probability of carrying a path-var/mutation in a first-degree relative of a known mutation carrier (following predictive testing) is 50%. The probability of carrying a path-var/mutation in a second-degree relative of a known mutation carrier (following predictive testing) is 25%. The number of unaffected female relative path var carriers identified through cascade testing is calculated to be 1.41 per index path var carrier with BC in the UK and 1.46 per index path var carrier with BC in the USA. Male first-degree relatives were tested to inform the need to test second-degree relatives but they were not followed in the model. Long-term outcomes-&-costs were only modelled for females.

eTable 4. Summary of Medical Costs Used in the Model (2016 Prices) and Explanation

Item	UK (£)	US ($)	Source
Cost of genetic testing	175	330	32,33
Cost of counselling (per session)	20	40	34-37
Cost of RRSO (and HRT and osteoporosis prevention)	3,618	8,476	38-41
Cost of ovarian cancer diagnosis and initial treatment	14,268	133,121	38,40,42
Yearly cost of ovarian cancer treatment and follow-up: years 1-2	5,433	14,635	38,40,42,43
Yearly cost of ovarian cancer treatment and follow-up: years 3-5	5,090	14,635	38,40,42,43
Terminal care cost with ovarian cancer	16,452	93,005	40,44
Cost of breast cancer screening general	417	1,596	38,45,46
Cost of breast cancer screening mutation carriers	5,094	34,896	38,40,46,47
Cost of RRM (and reconstruction and complications)	7,421	22,110	38,40,48-51
Cost of CPM (and reconstruction and complications)	5,545	20,426	38,40,51,52
Cost of chemoprevention	137	4,496	39,40
Cost of breast cancer diagnosis and initial treatment (Sporadic, *PALB2*)	19,663	90,040	38,40,53,54
Cost of breast cancer diagnosis and initial treatment (*BRCA1/BRCA2*)	17,920	83,633	38,40,53,54
Yearly cost of breast cancer follow-up and adjuvant treatment: years 1-5 (Sporadic)	1,436	8,048	38-40,45,53-55
Yearly cost of breast cancer follow-up and adjuvant treatment: years 1-5 (*BRCA1/BRCA2*)	1,458	8,048	38-40,45,53-55
Yearly cost of breast cancer follow-up and adjuvant treatment: years 1-5 (*PALB2*)	1,438	8,048	38-40,45,53-56
Terminal care cost with breast cancer	16,452	68,022	40,44
Cost of fatal CHD	3,387	23,934	38,44,57
Cost of excess CHD	3,425	196,477	26,58-62

BNF – British National Formulary, CPM – contralateral prophylactic mastectomy, GCaPPS – Genetics Cancer Prediction through Population Screening study, HRT – hormone replacement therapy, NHS – National Health Service, NICE – National Institute for Health and Clinical

Excellence, PSSRU – Personal Social Services Research Unit, RRSO – risk-reducing salpingo-oophorectomy, RRM – risk-reducing mastectomy. Model costs are estimated at 2016 prices

Explanations:

All costs are adjusted for 2016 price index. Costs were converted wherever needed using the Hospital and Community Health-Service-Index.[63] Costs of breast cancer (BC), ovarian cancer (OC) and excess coronary heart disease (CHD) are included. In line with NICE recommendations, future healthcare costs not associated with BC, OC, or CHD were not considered.[64]

Cost of genetic testing/counselling

The cost of *BRCA1/BRCA2/PALB2* testing is based on testing costs for these genes in the PROMISE research programme as well as confirmatory testing costs in an accredited national genetics laboratory for those testing positive. The UK national unit cost assumed for genetic counselling is £44 per hour of client contact from PSSRU Unit costs of Health and Social Care 2010.[34,35,65] The US cost estimates are obtained from Schwartz et al 2014[36]. All costs are adjusted for the 2016 price index. We assume/cost for 20 minutes of administrator time, 20 minutes of counsellor preparation and 20 min of counselling time (total 40 minutes of counsellor time)[36] for each counselling appointment. In the analysis we include costs for (a) pre-test counselling for all patients, (b) post-test counselling for path-vars and VUS, and (c) also for repeat counselling for VUS which get reclassified as pathogenic subsequently.

RRSO costs

The UK RRSO costs are obtained from NHS reference costs[38], and the US costs are from Grann 2011[40] inflated using the medical component of the US consumer price index to 2016 US$. Costs of HRT for the UK are taken from BNF [39] and for the US from William-Frame 2009.[41] Costs assume HRT is given from average age of RRSO to the average age of menopause (51 years). These costs are calculated for the 80% assumed to be compliant with HRT. Costs include the cost of three follow up DEXA scans for monitoring bone health and calcium and vitamin-D3 for additional osteo-protection.

RRM and CPM costs

The UK RRM and CPM costs are obtained from NHS reference costs [38], and the US costs are from Grann 2011[40] inflated using the medical component of the US consumer price index to 2016 US$.

Reconstruction rates of around 91% have been reported after RRM.[50] Costs for the UK are derived from NHS reference costs (code JA33Z).[38] Bilateral prophylactic mastectomy costs for the USA is $20, 827 (2016 price) to include reconstructive surgery.[51] For risk reducing bilateral prophylactic mastectomy (RRM) and reconstruction we assume a 26.2% minor complication rate and 5.6% major complication rate,[51] additional costs for which have been included for both minor and major complications.[51]

Reconstruction rate after contralateral prophylactic mastectomy (CPM) is 90%.[52] Complication rates for contralateral mastectomy are higher than unilateral mastectomy and the major complication rate with reconstruction is higher than without reconstruction. The complication rate for contralateral mastectomy without reconstruction is 42.9% (40.9% minor and 2% major)[52] and the complication rate for contralateral mastectomy and reconstruction is 41.6% (27.7% minor and 13.9% major).[52] Minor complications are costed at an additional cost of $822 (US) and £278 (UK) and major complications at $7492 (US) and £2535 (UK) (2016 prices).[51] All costs are adjusted for 2016 price index. UK costs were converted wherever needed using the Hospital and Community Health-Service-Index.[63]

Costs of ovarian cancer

We assume that the costs of ovarian cancer diagnosis include a pelvic examination, ultrasound scan, CA125 test, CT scan, percutaneous biopsy, and peritoneal cytology. The costs of ovarian cancer treatment include the reference cost for a lower and upper genital tract very complex major procedure and administration of chemotherapy based on 6 cycles of carboplatin and paclitaxel treatment. It is assumed that in the first and second years treated survivors would have a further three consultant visits, a CT scan and four CA125 tests each year. In the third to fifth years post-surgery it is assumed that survivors would have two consultant visits and two CA125 tests.

Costs for ovarian cancer diagnosis and treatment in the UK are derived from national reference costs and a recent ovarian cancer guideline developed by NICE[38,42]. Annual costs of ovarian cancer treatment in the US are taken from Grann et al 2011[40] and inflated using the medical component of the US consumer price index to 2016 US$. We include the costs of treatment of recurrence, taken from Cancer Research UK[43] and Grann 2011.[40]

The costs of ovarian cancer terminal care are derived from end-of-life costs for cancer patients based on a report from the National Audit office UK [44]. For the US the terminal care costs for ovarian cancer are obtained from Grann 2011 [40], inflated using the medical component of the US consumer price index to 2016 US$. In line with NICE recommendations future healthcare costs not associated with ovarian cancer are not considered [64].

Costs of breast cancer

In the general population, 10% breast cancer is non-invasive DCIS and 90% is invasive. 95% of invasive breast cancer is early and locally advanced (stage 1-3), and 5% of invasive breast cancer is advanced breast cancer (stage 4).[55] In *BRCA1/2* carriers, 20% of cancers are DCIS and 80% invasive.[66,67] Stage distribution in *PALB2* carriers is assumed to be the same as in the general population, owing to a lack of robust *PALB2* specific data.

Annual breast cancer treatment costs in the USA are obtained from Grann et al 2011,[40] and inflated using the medical component of the USA consumer price index to 2016 US$.
70% of invasive breast cancers are ER-positive,[54,68] among which 49% are premenopausal. 15% of early/locally advanced breast cancers and 25% of advanced breast cancers are HER2-positive. 27% *BRCA1* and 67% *BRCA2* breast cancers are ER-positive; 5% *BRCA1* and 14% *BRCA2* breast cancers are HER2-positive.[69-74] 74% of *PALB2* breast cancers are ER-positive.[56] All costs are adjusted for *BRCA1/BRCA2/PALB2* breast cancers for differences in stage at presentation, the proportion of being non-invasive, and the proportion of being ER-positive or HER2-positive.

Diagnosis costs: Whether suspected at breast screening or through presentation to the GP, diagnosis in the breast clinic is made by triple assessment (clinical assessment, mammography, and ultrasound imaging with core biopsy and/or fine needle aspiration cytology).[54] Clinical examination and mammography costs are from the paper by Robertson C et al.[45] Breast ultrasound and biopsy costs are obtained from NHS reference costs.[38] For all patients presented with suspected advanced breast cancer, MRI should be offered to assess for bone metastases.[68]

Sentinel lymph node biopsy (SLNB) costs: SLNB is used for staging axilla for early invasive breast cancer and no evidence of lymph node involvement on ultrasound or a negative ultrasound-guided needle biopsy (73% of early and locally advanced invasive cancers). The SLNB costs are obtained from NHS reference costs including sentinel lymph node scan and unilateral intermediate breast procedures.[38]

Pretreatment axilla ultrasound costs: Pretreatment ultrasound evaluation of the axilla should be performed for all patients being investigated for early invasive breast cancer and, if morphologically abnormal lymph nodes are identified, ultrasound-guided needle sampling should be offered.[54] The commissioning cost of pre-treatment ultrasound evaluation of the breast and axilla is the same as that of the breast only.[55] The costing model considers the cost of ultrasound-guided needle sampling only, obtained from NHS reference costs.[38]

Axillary lymph node dissection (ALND) costs: ALNB is undertaken for lymph node positive cancers (~31% early and locally advanced invasive cancers - NICE guideline and BCCOM project;[54,55,75] 30% node positive for BRCA1/2 breast cancer- familial breast cancer screening studies, breast cancer case series and Early Breast Cancer Trialists' Collaborative Group data).[66,69-71,76]Cost of ALND is assumed to be 25% of the cost of breast surgery as per NICE guideline development group recommendation.[55]

Breast surgery costs include costs of breast conserving surgery (assumed for all non-invasive cancers, and 75% of early/locally advanced invasive cancers) and costs of mastectomy (for 25% early/locally advanced and all advanced cancers). Reconstruction rates following mastectomy are reported to be 34% in the UK[77] and 55% in the US.[52] The complication rate following mastectomy alone is 21.5%

(19.5% minor and 2% major)[52] and complication rate following mastectomy and reconstruction is 28.6% (24.5% minor & 4.1% major).[52] Costs are obtained from the national NHS reference costs [38].

Chemotherapy and radiotherapy costs: Invasive breast cancers who are not at low risk [75,78,79] receive adjuvant treatment in line with NICE guidelines. Costs include radiotherapy costs for 60% of early invasive/locally advanced, radiotherapy and chemotherapy costs for 40% early invasive/locally advanced, and chemotherapy for all advanced cancers. Radiotherapy costs include planning and 40Gy in 15 fractions over 3 weeks [54] or palliative treatment, taken from national NHS reference costs [38]. Chemotherapy costs based on polychemotherapy [80], include administration costs, costs of 1st and 2nd line therapy and toxicity from NICE guidelines [55,68].

Endocrine therapy costs: As per NICE guidelines[54,55] , ER-positive invasive breast cancers receive Tamoxifen 20mg/day (premenopausal) or Anastrazole 1mg/day (postmenopausal). 70% of invasive breast cancers are ER-positive [54,68], among which 49% are premenopausal. We assume the length of endocrine therapy is 5 years. The drug costs are obtained from the BNF [39]. ER testing costs are obtained from a local NHS trust and included for all invasive breast cancers.

Target therapy costs: HER2-positive breast cancer patients can be given at 3-week intervals for 1 year or until disease recurrence as per NICE guidelines. Breast cancer patients with positive HER2 are eligible for treatment with trastuzumab [54,68]. 10% of the eligible patients are intolerant of trastuzumab. Among women suitable for this treatment, 80% receive trastuzumab [55]. HER2 testing costs are obtained from a local NHS trust and included for all invasive breast cancers. The trastuzumab cost per patient including administration of treatment and cardiac monitoring is £15080, obtained from NICE costing report [55].

Follow up costs: Breast cancer patients are offered mammographic surveillance and clinical follow-up, with the screening cost of £141.45 per women in 2011[45]. We assume patients are followed up

every four months in the first two years, every six months from the third to the fifth year, and every year from the sixth to the tenth year.

Bisphosphonate costs: Bisphosphonates is considered to be offered to patients newly diagnosed with bone metastases, to prevent skeletal-related events and reduce pain [68]. 74% patients with advanced breast cancer will develop bone metastases and 65% patients with bone metastases are offered bisphosphonates[55,81]. Bisphosphonates that are currently offered include oral sodium clodronate, ibandronic acid, zoledronic acid, and pamidronate. The proportions of patients receiving the four drugs are 20%, 30%, 25%, and 25% respectively. The annual costs including administration for the four drugs are £1971, £2541.96, £3208, and £3208 respectively, obtained from NICE costing report [55]. We assume the average length of bisphosphonates treatment is 2.7 years, which is the life expectancy of advanced breast cancers based on one-year survival rate (63.2%) [82].

Recurrence costs: For non-invasive breast cancers, the non-invasive and invasive relapse rates are both 12.5%. 35% of early and locally advanced invasive breast cancers progress to advanced disease [55]. The recurrence rates for early and locally advanced breast cancer are 15.9% for node-positive [83] and 11% for node-negative disease [84]. Weighted for 31% node positive and 69% node negative, the composite recurrence rate for early and locally advanced breast cancer is 12.5%. The recurrence rate for the advanced disease is 66% (34% relapse-free five-year survival) [85].

Terminal care costs: The costs of terminal care for breast cancer are derived from end-of-life costs for cancer patients based on a report from the National Audit office UK [44]. For the US the terminal care costs for breast cancer are obtained from Grann 2011 [40], inflated using the medical component of the US consumer price index to 2016 US$. In line with NICE recommendations future healthcare costs not associated with breast cancer ware not considered [64].

Cost of breast cancer screening

For non-carriers, we assume routine triennial mammography between 50-70 years as per UK NHS breast cancer screening programme[86] (seven mammograms on average). Breast screening in the US assumes mammography every two years starting at 50 years.[46]

For *BRCA1/BRCA2/PALB2* mutation carriers, we assume annual mammogram from 40-69 years and annual MRI from 30-49 years as per NICE guidelines for familial breast cancer[47] (30 mammograms and 20 MRIs on average). For the US, it is based on annual mammography and MRI starting at 30 years, and annual mammography only from age 50 years.[46]

Cost of chemoprevention

BRCA1/BRCA2/PALB2 mutation carriers are offered Tamoxifen (premenopausal) or Raloxifene (postmenopausal) for 5 years[47,87] to reduce breast cancer risk. The drug costs are obtained from BNF (UK)[39] and Grann 2011.[40] 16.3% uptake is assumed for chemoprevention.[25]

Cost of CHD

Cost of excess CHD: British Heart Foundation statistics reports costs per capita across four Commissioning Regions in England (London, Midlands and East, North and South) [59].

The costs of CHD and stroke are averaged across the four regions. The prevalence of CHD is estimated at 12.0% in the UK[59] and 11.7% in the USA[60] with the onset of CHD estimated at 55 years of age.[26,58]

The yearly cost of CHD in the UK is obtained by dividing the per capita cost by the population prevalence of CHD.[59] Using the report published by the American Heart Association,[61] the total cost of CHD, CHF and stroke were divided by the population with CHD[60,62] giving the yearly cost of CHD in the USA. This yearly cost is multiplied by the number of years between onset of CHD and average life expectancy to provide the cost attributed to excess CHD.

Cost of fatal CHD: This is costed on the basis of a fatal myocardial infarction using NHS reference costs.[38] USA costs are obtained from Afana et al 2015,[57] inflated using the medical component of the US consumer price index to 2016 US$.

In line with NICE recommendations, future healthcare costs not associated with BC, OC, or CHD were not considered.[64]

eMethods 1. Examination of Productivity Loss

The retirement ages for females are 65 in the UK and 62 in the USA. The female labour force participation rates are 56.77% in the UK and 55.99% in the USA, obtained from the World Bank [88]. The hourly wage rage are obtained from Office for National Statistics UK[89] and Bureau of Labour Statistics USA [90].

We categorised the productivity costs as three subcomponents: 1) temporary disability due to short-term work absences following diagnosis, 2) permanent disability due to reduced working hours following a return to work or workforce departure; and 3) premature mortality due to death before retirement [91], detailed below.

Descriptive statistics for productivity loss in breast and ovarian cancer patients

Variables	Breast cancer	Ovarian cancer
(1) Temporary disability		
Percentage of temporary disability cases	94.0%	98%[1]
Average time taken off work following diagnosis (weeks)	44.9	47.22[2]
(2) Permanent disability		
Percentage of permanent disability: reduced hours	26%	40%[3]
Reduced hours per week after returning to work (hours)	5.5	5.5
(3) Premature mortality (before retirement)		
Percentage of permanent disability: workforce departure	12.9%	30%[3]

The descriptive statistics for productivity loss in breast cancer patients are obtained from Hanly et al. 2012 [91].

[1] We assume 98% ovarian cancer patients have cancer-related short-term work absences after diagnosis.
[2] We assume ovarian cancer patients experience four weeks for surgery, 24 weeks for chemotherapy, and 24 weeks for recurrence treatment with the recurrence rate of 80% [92].
[3] We assume the percentages of permanent disability for ovarian cancer are 40% for reduced working hours and 30% for workforce departure.
We estimated temporary disability as time absent from work multiplied by age-specific gross earnings.

We calculated productivity costs due to permanent disability by applying age-specific gross earnings to the reduction in working hours, or the number of working hours if permanent workforce departure, until retirement age. Regarding productivity loss from premature mortality, we assumed that without cancer, the productive capacity of an individual would continue from the age of diagnosis until age of retirement. We multiplied the projected years of life lost by the age-specific gross earnings for the remainder of the working life to generate monetary estimates.

eMethods 2. Estimates for Age of Onset and Survival for Breast and Ovarian Cancers

Our analysis incorporates lifetime risks and long-term consequences providing a lifetime time-horizon. Female lifetables from the Office of National Statistics (UK women)[30] and National Centre for Health Statistics (USA women)[31] were used for life expectancy by 80-years for women not developing OC/BC.

We assumed that the median age for undergoing RRM and RRSO in unaffected path var carriers was 37 and 40 years respectively.[14] We explored 42 years for RRM and 46 years for RRSO in our scenario-analysis.[93] The uptake rates of RRSO and RRM are obtained from established literature.[14,16] OC/BC outcomes were modelled using 10-year survival data. No statistically significant survival difference between *BRCA1/BRCA2* and sporadic BC has been reported.[94,95] For BC, 10-year survival rates = 78.4% (CI: 78.3,78.4).[96] Long-term survival outcomes for *BRCA* and sporadic OC have also recently been reported to be similar.[97] For OC the 10 year survival rate is 34.5% (CI: 33.8,35.3).[98]

BC and OC survival (from diagnosis to death) were modelled using ten-year survival-data. After ten-years, we assumed the probability of death for all patients was same as the general-population. The excess risk of CHD following premenopausal oophorectomy is incorporated in the analysis.[26,99] We incorporated the fact that contralateral BC is associated with a higher risk of dying from BC.[100] We assume no significant long-term survival difference between germline and sporadic breast/ovarian cancers.[94,95,97]

eMethods 3. Quality-Adjusted Life-Years (QALYs) and Utility Scores

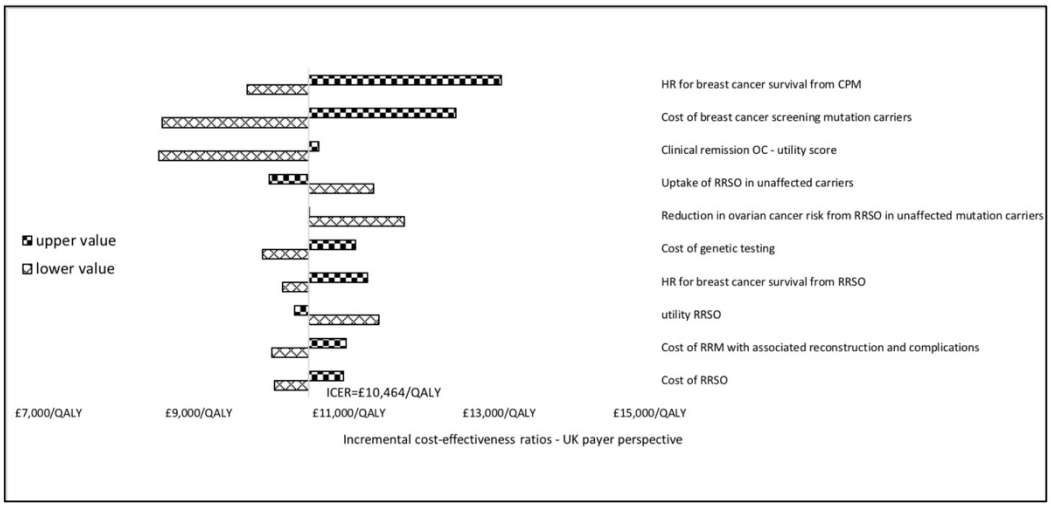
QALY is a measurement of health-outcomes in economic evaluations recommended by NICE. It equals time spent in the relevant health states multiplied by an appropriate utility-score. Utility-score is an indication of individual preferences for specific health-states where 1=perfect health and 0=death. Utility-score is an adjustment for quality-of-life and QALY adjusts changes in length-of-life by potential alterations in quality-of-life. The utility-scores for early, advanced, recurrent, remittent, and end-stage BC are 0.71, 0.65, 0.45, 0.81, and 0.16 respectively.[53] The utility-scores for early, advanced, recurrent, remittent, and end-stage OC are 0.81, 0.55, 0.50, 0.83, and 0.16 respectively[101]. In addition, women undergoing RRM or RRSO also experience negative health-effects.[102,103] We used utility-scores of 0.88 (SD=0.22) for RRM, 0.95 (SD=0.10) for RRSO, and 0.84 (SD=0.02) for CHD to account for the disutility.[40,104]

eMethods 4. Patient and Public Involvement Statement

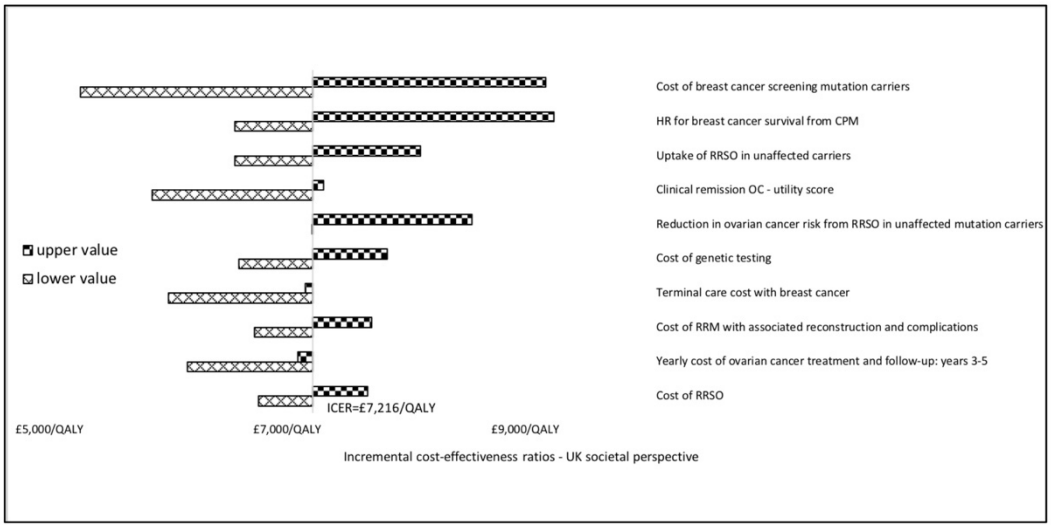
The study team has worked closely with patient support groups like *BRCA* Umbrella and Ask Eve. Increasing access to genetic-testing at cancer diagnosis has been highlighted to the team as an important issue affecting women with cancer and *BRCA*-carriers. Patients have indicated the need for access to unselected genetic-testing for BC. This has been highlighted at patient support days organised and attended by team members as well as in personal communication with leading patient stakeholders (e.g. Caroline Presho, *BRCA*-Umbrella). This work justifies relaxing testing guidelines, a key need highlighted by patients'. Patients did not directly input into the design and conduct of this analysis. Patient support groups and charities will be involved in dissemination of these research findings following acceptance for publication.

eFigure 1. Tornado Diagram of 1-Way Sensitivity Analysis

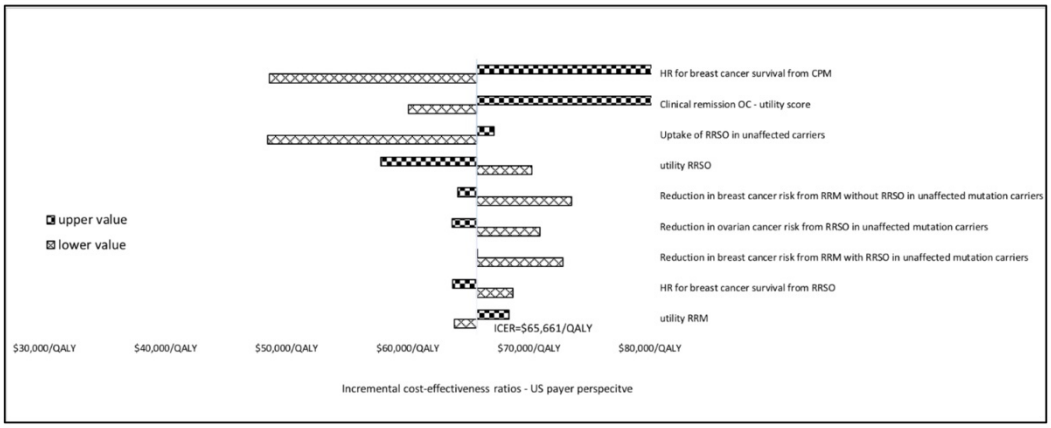
eFigure 1a. Tornado diagram – UK payer perspective



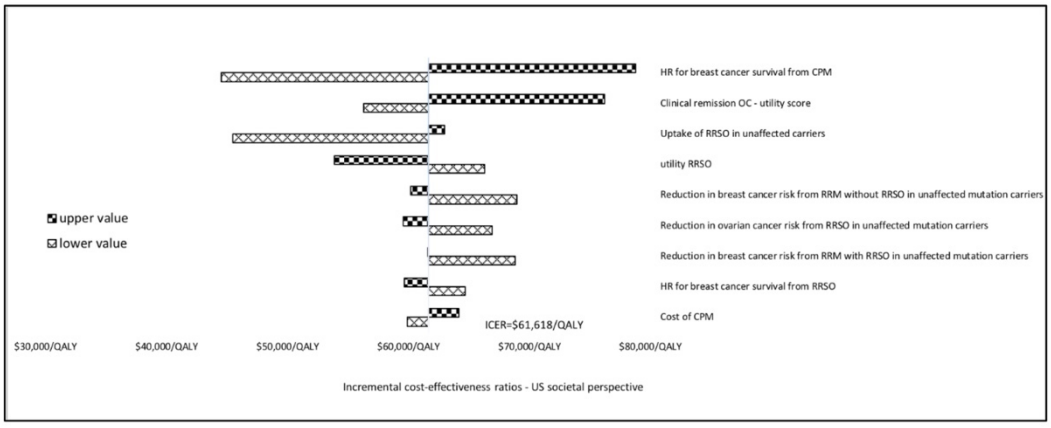
eFigure 1b. Tornado diagram – UK societal perspective



eFigure 1c. Tornado diagram – US payer perspective



e-Figure-1d. Tornado diagram – US societal perspective



BC – breast cancer, CPM – contralateral prophylactic mastectomy, HR – hazard ratio, ICER- incremental cost-effectiveness ration, OC – ovarian cancer, RRSO – risk-reducing salpingo-oophorectomy, RRM – risk-reducing mastectomy.

One-way sensitivity analysis for all probabilities, costs and utilities in terms of ICER of UK and USA Unselected testing for BRCA1, BRCA2 and PALB2 mutations, compared to a Clinical-criteria / FH-based approach for BRCA1 and BRCA2 testing.

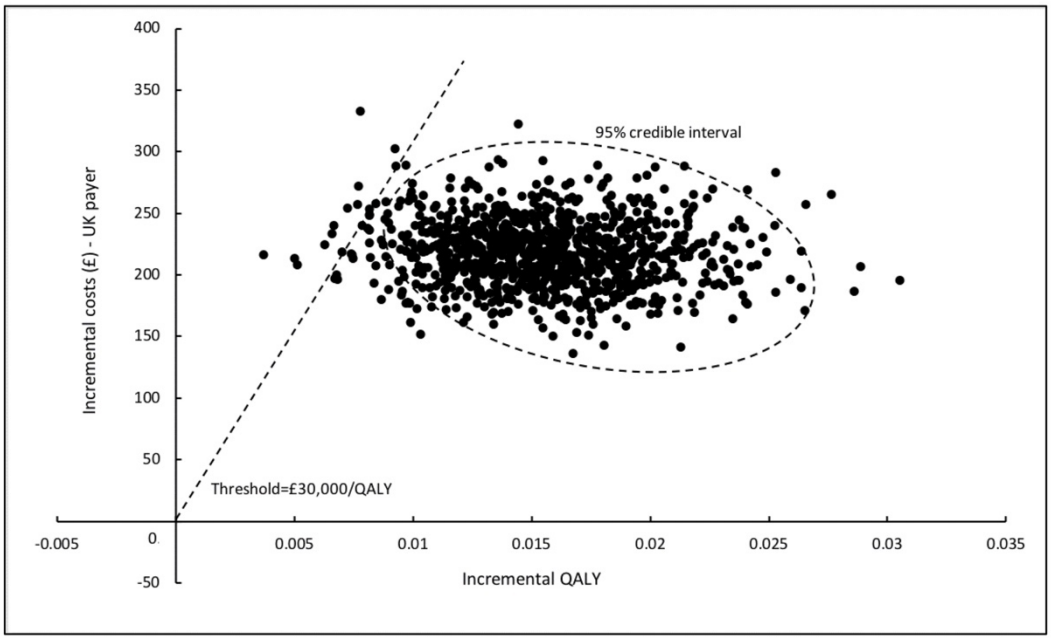
X-axis: Incremental cost-effectiveness ratio (ICER): Cost (£s or $s) per quality adjusted life year (QALY) (discounted).

Y-axis: Probability, cost and utility parameters in the model. The model is run at both lower and upper values/limits of the 95% confidence interval or range of all probability parameters described in Table-2; and both lower and upper values/limits of the cost and utility-score parameters given in methods and Appendix 3. Costs are varied by +/- 30%.

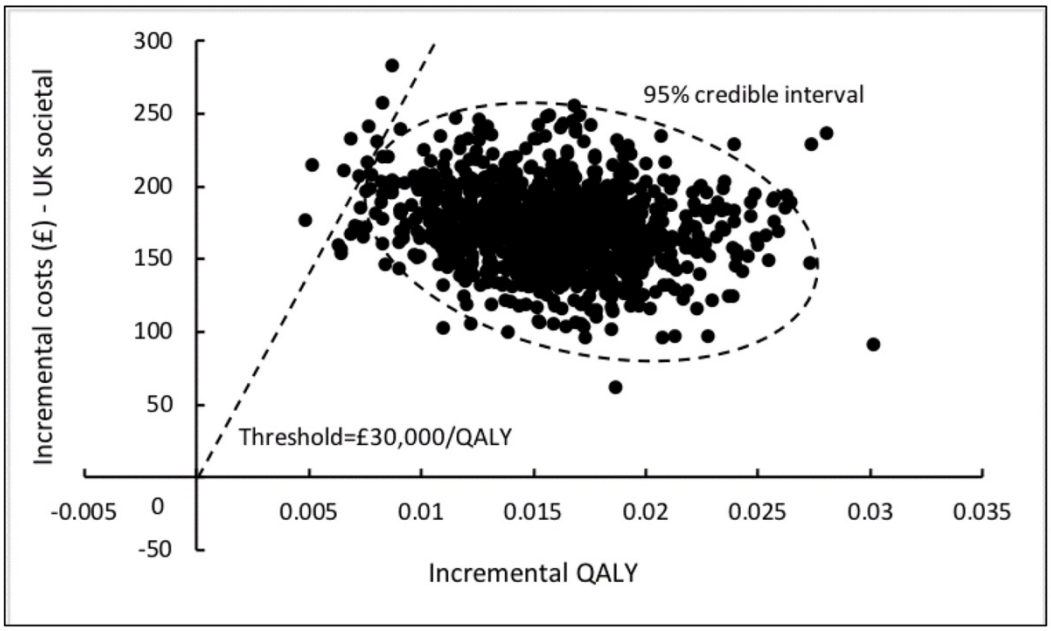
'Upper value' represents outcomes for upper limit and 'Lower value' represents outcomes for lower limit of the parameter.

eFigure 2. Scatterplots for Incremental Discounted Lifetime Costs and Effects of Unselected Multigene Testing Compared With *BRCA* Testing Based on Family History and Clinical Criteria

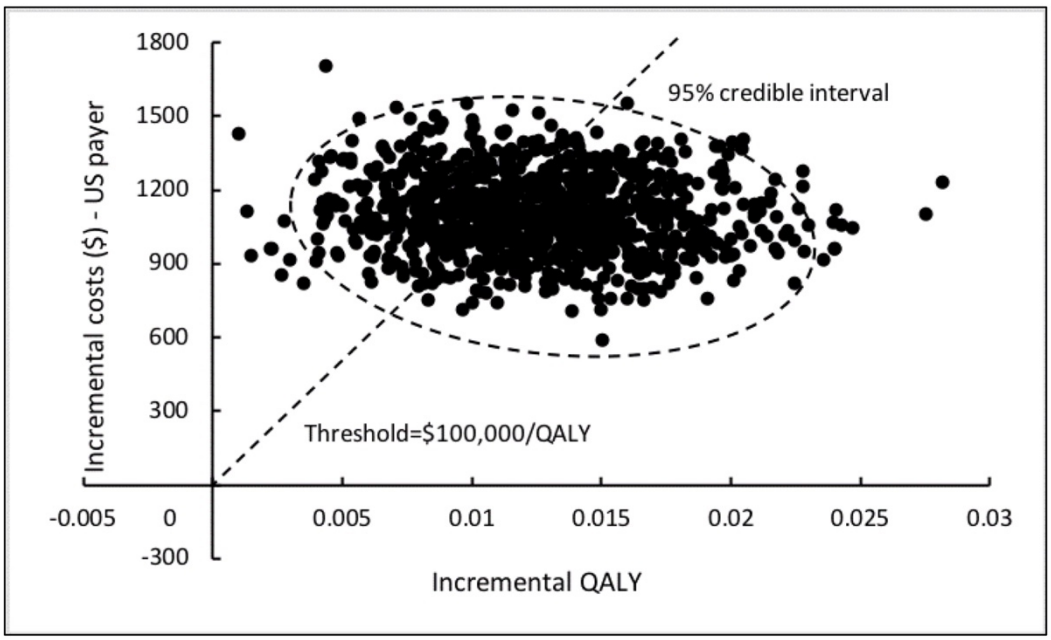
eFigure 2a. Incremental discounted costs and QALYs plots - UK payer perspective



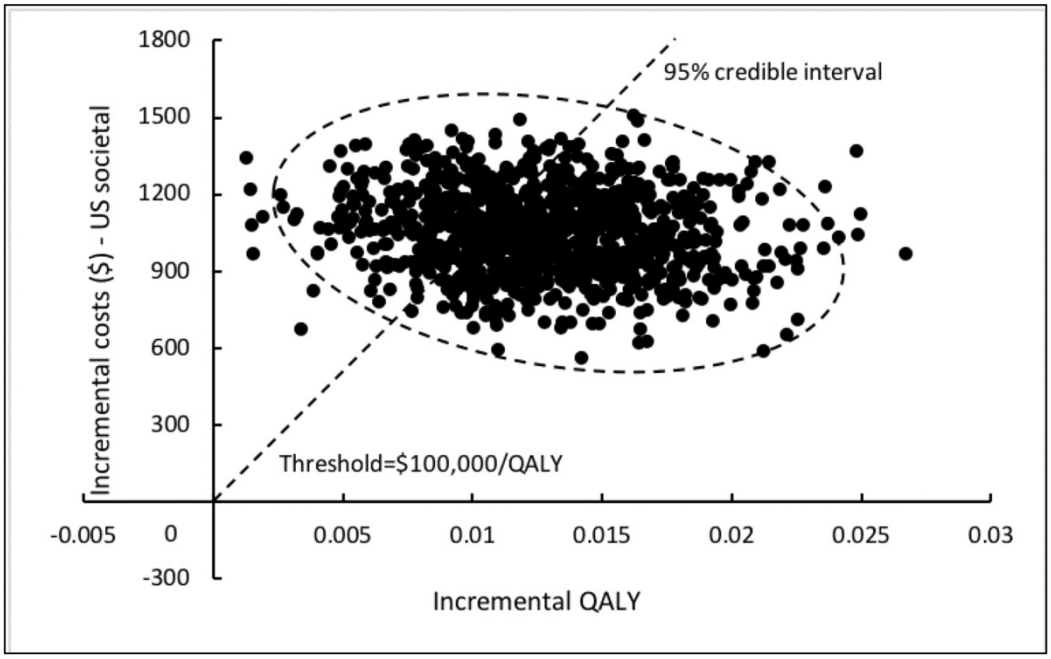
eFigure 2b. Incremental discounted costs and QALYs plots - UK societal perspective



eFigure 2c. Incremental discounted costs and QALYs plots – US payer perspective



eFigure 2d. Incremental discounted costs and QALYs plots – US societal perspective



The result of each iteration/simulation in the PSA is plotted on the CE plane, The results appear as a “cloud” of possible outcomes. Each point on the scatter plot represents one simulation/bootstrap iteration. All points lie in the North East quadrant of the CE plane, suggesting unselected testing is always more effective. The dotted line represents the willingness to pay threshold, thus enabling interpretation of number of simulations which lie above or below this threshold.

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Commentary

The willingness-to-pay (WTP) thresholds of £20,000/QALY-£30,000/QALY should have been adopted in the UK analysis and $50,000/QALY-$100,000/QALY adopted in the US analysis. Compared with the current BRCA testing based on clinical criteria/family history, unselected multigene testing for all breast cancer patients would cost £10,464/QALY (payer perspective) or £7,216/QALY (societal perspective) in the UK or $65,661/QALY (payer perspective) or $61,618/QALY (societal perspective) in the US. The incremental cost-effectiveness ratios (ICERs) in the UK are well below the WTP thresholds, while the ICERs in the US lie between the lower and upper limits of the thresholds. In the probabilistic sensitivity analysis, the cost-effectiveness acceptability curves were plotted to show the probability of unselected multigene testing for all breast cancer patients being cost-effective at different WTP thresholds in the UK and the US. From the payer perspective, unselected multigene testing remained cost-effective for 88% to 98% of UK and 5% to 64% of US health system simulations. From the societal perspective, unselected multigene testing remained cost-effective for 95% to 99% of UK and 8% to 68% of US health system simulations.

The utility score of incident breast cancer is weighted by the proportion of early (95%) and advanced (5%) breast cancer, and the utility score of prevalent breast cancer is weighted by the proportion of recurrent (8%) and remittent (92%) breast cancer. Similarly, the utility score of incident ovarian cancer is weighted by the proportion of early (30%) and advanced (70%) ovarian cancer, and the utility score of prevalent breast cancer is weighted by the proportion of recurrent (17.6%) and remittent (82.4%) ovarian cancer. In the model, the utilities were on an annual basis according to the health states. In the first year after diagnosis, patients were assigned the utility score of incident cancer and from the second year onwards, patients were assigned the utility score of prevalent cancer. In the last year before death, patients were assigned the utility score of end-stage cancer.

Potentially there are broader health and non-health benefits related to genetic testing for all breast cancer patients. A cost-benefit analysis could be conducted to capture all the benefits. However, it is difficult to measure all health and non-health benefits in monetary terms. Another limitation is that the disutility related to genetic testing is not considered in this study, which may lead to the overestimation of health outcomes in terms of QALYs. This deserves careful considerations. Also genetic testing could have important consequences beyond health with long-term implications. In this study, it was assumed that breast cancer patients and relatives of mutated patients at all ages in the unselected testing arm were offered genetic testing. Offering genetic testing to children may raise

ethical issues though they would not choose risk-reducing mastectomy until age 37 or risk-reducing salpingo-oophorectomy until age 40.

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Chapter 7

Global treatment costs of breast cancer by stage: a systematic review

In this chapter, I report on a review of the literature to compare treatment costs of breast cancer across countries at different levels of socio-economic development, and to identify methodological differences in costing approaches. I conducted the literature review design, methods, and analysis independently with supervision from Dr Rosa Legood and Dr Zia Sadique. Shivani Mathur Gaiha and I independently extracted the data and assessed the study quality. I have prepared the findings and results as a first draft of the manuscript, with comments on drafts from Dr Rosa Legood, Dr Zia Sadique, and Professor Isabel dos Santos Silva. All authors approved the final draft prior to journal submission and inclusion in the thesis. This paper has been published by PLOS One.

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RESEARCH ARTICLE

Global treatment costs of breast cancer by stage: A systematic review

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Abstract

Background

Published evidence on treatment costs of breast cancer varies widely in methodology and a global systematic review is lacking.

Objectives

This study aimed to conduct a systematic review to compare treatment costs of breast cancer by stage at diagnosis across countries at different levels of socio-economic development, and to identify key methodological differences in costing approaches.

Data sources

MEDLINE, EMBASE, and NHS Economic Evaluation Database (NHS EED) before April 2018.

Eligibility criteria

Studies were eligible if they reported treatment costs of breast cancer by stage at diagnosis using patient level data, in any language.

Study appraisal and synthesis methods

Study characteristics and treatment costs by stage were summarised. Study quality was assessed using the Drummond Checklist, and detailed methodological differences were further compared.

Results

Twenty studies were included, 15 from high-income countries and five from low- and middle-income countries. Eleven studies used the FIGO staging system, and the mean treatment costs of breast cancer at Stage II, III and IV were 32%, 95%, and 109% higher than Stage I. Five studies categorised stage as in situ, local, regional and distant. The mean treatment costs of regional and distant breast cancer were 41% and 165% higher than local

breast cancer. Overall, the quality of studies ranged from 50% (lowest quality) to 84% (highest). Most studies used regression frameworks but the choice of regression model was rarely justified. Few studies described key methodological issues including skewness, zero values, censored data, missing data, and the inclusion of control groups to estimate disease-attributable costs.

Conclusions

Treatment costs of breast cancer generally increased with the advancement of the disease stage at diagnosis. Methodological issues should be better handled and properly described in future costing studies.

Introduction

Breast cancer is the most common cancer among women worldwide, contributing more than 25% of the global new female cancer cases [1]. It is also the first leading cause of female cancer mortality, accounting for 14.7% of cancer deaths [1].

Breast cancer is a potentially curable disease if diagnosed and treated at an early stage. Surveillance, Epidemiology, and End Results (SEER) Program has reported that breast cancer cases diagnosed at an early stage (Stage I/II) have a better prognosis (5-year survival rate of 85%-98%). In contrast, patients diagnosed with advanced breast cancer (Stage III/IV) have a poor 5-year survival rate of 30%-70% [2]. Therefore, some intervention programmes have been initiated aiming for early diagnosis and treatment of breast cancer to reduce mortality and improve disease outcomes [3, 4].

Although the case for earlier diagnosis with respect to outcomes has been well made, the financial implications are less well understood [5, 6]. Stage of disease at diagnosis is an important predictor of treatment costs. Treatment for more advanced disease is often more intensive or invasive than treatment for the earlier stages [5]. As a result, a more advanced stage tends to be associated with more resource utilisation in addition to poorer health outcomes [7].

Treatment costs by stage at diagnosis are important in quantifying the gains from early detection. If early treatment lowers costs, this will help offset the cost of interventions for earlier diagnosis and treatment. In addition, treatment costs by stage would be valuable to inform the cost-effectiveness studies for treatment or preventative interventions of breast cancer. However, the mean costs by stage do not reveal the heterogeneity across patients. Patient level data can contain information such as socioeconomic group, medical history, and treatment options, thus allowing the comparison of costs across patient subgroups and identification of cost predictors. Therefore, availability of detailed patient level costing data by stage at diagnosis is important.

To date, no review has directly compared the methods used for collecting and analysing treatment costs of breast cancer across different settings. A systematic review, published in 2009, aimed to synthesize treatment costs of breast cancer per patient in the United States (US) [8]. However, this review did not assess between-study methodological differences, such as cost data collection methods, regression models, or whether breast cancer-attributable costs were estimated. Differences in methods should be examined, however, because they might have affected the cost estimates of breast cancer treatment.

In this paper, we undertook a systematic review of breast cancer treatment costs by stage at diagnosis based on patient level data to: (i) compare stage-specific treatment costs across

countries at different levels of socio-economic development; and (ii) identify key methodological differences in costing approaches.

Materials and methods

Eligibility criteria

This study has been registered in PROSPERO international prospective register of systematic review (CRD42018097473). The inclusion criteria were based on the PICOS framework: (i) population: female breast cancer patients; (ii) intervention: any form of clinical treatment interventions; (iii) comparator: not restricted; (iv) outcome: direct medical treatment costs (inpatient and outpatient) by stage incurred in hospital settings at the patient level; and (v) study design: costing studies with primary data.

We excluded studies with the following characteristics: (i) no treatment cost estimates by stage; (ii) treatment costs not incurred in hospital settings which cannot reflect direct medical costs (inpatient and outpatient); (iii) costs not estimated from actual patient level data, but calculated according to treatment pathways in clinical guidelines; (iv) disease stages categorised neither as 0, I, II, III and IV in the International Federation of Gynaecology and Obstetrics (FIGO) staging system, nor as in situ, local, regional and distant cancer; and (v) review articles. Only studies that had primary data on the breast cancer costs were selected to avoid repeating previously published information. There was no language limit for the eligibility criteria.

Search methods

We searched MEDLINE(R) (1946 to April Week 4 2018), EMBASE Classic + EMBASE (1947 to 30 April 2018), and NHS Economic Evaluation Database (NHS EED, 1960 to April 2018) with search terms in S1 Table. Also, reference lists from relevant primary studies and review articles were used to identify other relevant publications. Titles and abstracts were first reviewed, and full-texts of the studies that potentially met the eligibility criteria were retrieved and full-text reviewed.

Data extraction

Two investigators independently extracted the study characteristics and treatment costs of breast cancer by stage at diagnosis. Most studies conducted cost analyses up to a specified time rather than over a lifetime horizon. Although some studies reported the annual costs, we extracted the cumulative costs during the pre-specified time horizons for comparative purposes. We first summarised the cumulative treatment costs of breast cancer patients by stage in all reviewed studies. Then we compared the costs in studies with the same pre-specified time horizons.

We used US dollars with the base year of 2015 to facilitate the comparison of costs. In this study, we used purchasing power parity (PPP) conversion factor to convert cost estimates reported in different currencies to US dollars, and used the consumer price index (CPI) for health care to convert cost estimates reported at different time points to the same year. PPP is the rate of currency conversion at which a given amount of currency will purchase the same volume of goods and services in two countries. CPI is a measure that examines the changes in the price level of a basket of consumer goods and services.

Critical appraisal and methodological assessment

Two investigators used an established checklist by Drummond et al. [9] to assess the quality of reviewed studies independently. Items not applicable to costing studies were removed. A

three-point response scale was added to better grade the quality of each item on the checklist, ranging from 0 (not considered), through 1 (partially considered), to 2 (fully considered) [10]. We summed up all scores and compared this with the maximum attainable score to calculate the percentage of the maximum attainable score.

In addition, we conducted a more detailed analysis of the methods used, including whether costs were based on charges or claims, the data collection approaches, use of control groups, descriptive analysis of mean costs by stage, regression model choices, censored data analysis, missing data analysis, and timing issues.

We distinguished between whether charges or claims were used because charges are often higher than the insurer claim costs [8], though either of which does not necessarily reflect the true economic costs of providing the medical services.

Costing data collection methods should depend on the aim of the study and the availability of data [11]. One method is the ingredient approach, also called micro-costing, with resources and the associated unit costs directly measured. At the other end of the spectrum is the gross costing or top-down method. In this approach, the costs are usually estimated by reference costs from a non-patient-specific source [12]. Gross costing is faster and cheaper but may lead to low accuracy because of the relatively large measurement units. Micro-costing is more reliable but may be expensive and not always practical [11].

Non-breast cancer controls were included in some studies. The costs among patients often incorporate some costs incurred jointly with other diseases or interventions, leading to the overestimation of the disease-specific costs. By comparing costs of breast cancer cases to control groups without breast cancer, breast cancer-attributable treatment costs can be estimated.

Description of mean costs by stage was reported in all studies. Some presented only point estimates, while others also reported the uncertainty of mean values, such as standard errors and confidence intervals.

Different regression models have been developed for cost modelling to approach the issues of cost data, such as the skewness, zero-values, and censoring [13]. In general, in cases of no censoring and no zero-costs, the log-gamma generalised linear model (GLM) is favoured, which deals with non-normality and avoids back-transformation issues [14]. Regarding the zero-cost issues, the two-part mixed model is the most informative by showing the possibility of any expenditure first. For the censoring issues, a regression model can be used which is weighted by the probability of not being censored. There is no unique model that can deal with all the problems, and the final choice depends on the type and design of the study.

Missing data could reduce the representativeness of samples and therefore distort inferences about the population. So we summarised the methods of dealing with missing data in the reviewed studies. Also, we assessed whether cost calculations were adjusted for inflation or any other changes.

Results

Search results

The search took place in April 2018. MEDLINE search yielded 99 possible studies, EMBASE yielded 268, NHS EED yielded 32, and hand-searches produced seven from reference lists. The collective searches yielded 293 unique studies after removing duplicates. Based on the eligibility criteria, we excluded 273 studies and included 20 studies in this review (Fig 1). The two reviewers were in complete agreement for study eligibility. The identified studies were from ten countries: the US (n = 9), Canada (n = 2), China (n = 2), Italy (n = 1), Portugal (n = 1), the United Kingdom (UK) (n = 1), Vietnam (n = 1), France (n = 1), Iran (n = 1) and Mexico (n = 1).

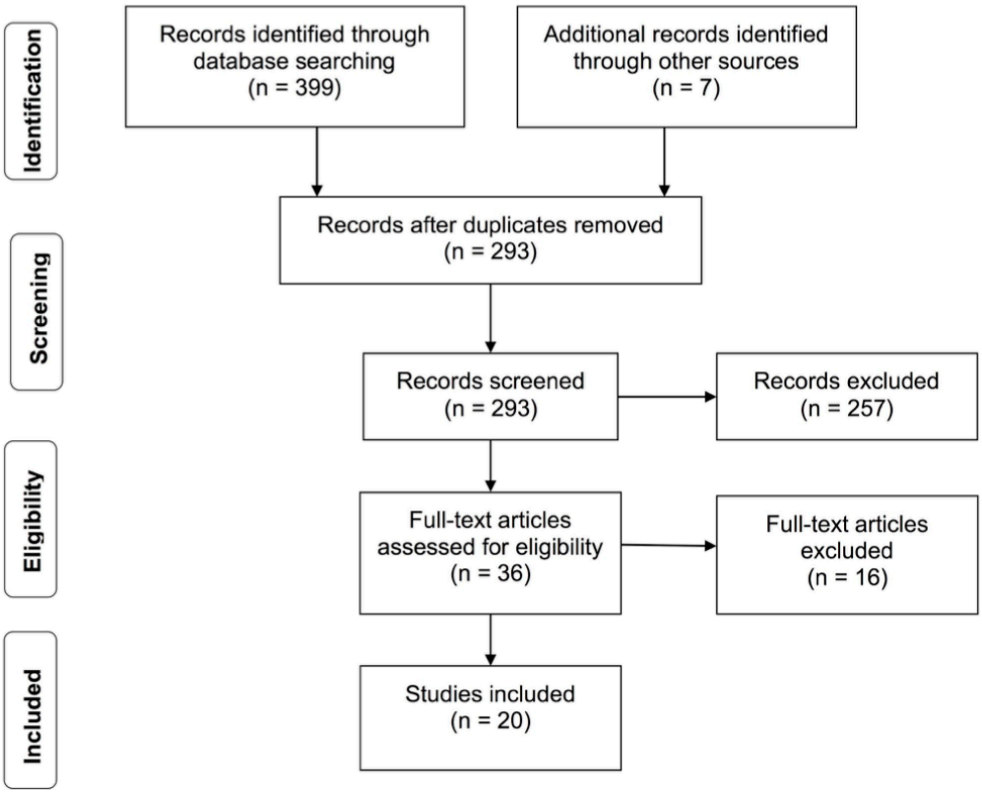

Fig 1. Study flow diagram.

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Treatment costs of breast cancer by stage

Table 1 summarises basic characteristics and cumulative treatment cost estimates by stage reported in the reviewed studies, with 85% agreement by two reviewers. Among the 15 studies using the FIGO staging system, the means of cumulative treatment costs weighted by sample sizes were $29,724 at stage I, $39,322 at stage II, $57,827 at stage III, and $62,108 at stage IV in 2015 US dollars. On average, costs at stage II, III and IV were 32%, 95%, and 109% higher than costs at stage I. In the other five studies where invasive breast cancer was categorised as local, regional and distant, the cost means weighted by sample sizes were $63,664, $89,898 and $168,906. Treatment costs of regional and distant breast cancer were 41% and 165% higher than local breast cancer on average. Figs 2 and 3 show that mean treatment costs generally increased with advanced stage at diagnosis.

The study by Riley et al. was not considered when we calculated the weighted mean values due to the unknown sample size [33]. This study reported that the lifetime payments between diagnosis and death were higher for patients diagnosed at an earlier stage, due to higher costs corresponded to longer survival time. However, they found that the annual average costs for

Table 1. Basic characteristics and cumulative breast cancer treatment costs by stage (US dollars in 2015).

Study	Setting	Sample	Year	Time horizon	Costs by stage				
					0	I	II	III	IV
Allaire et al, 2017 [15]	US	4,082	2003–2010	1y ad[1]	-	54,664	102,528	127,444	
Capri et al, 2017 [16]	Italy	12,580	2007–2011	2y ad[1]	-	12,187	14,541	15,108	17,339
Harfouche et al, 2017 [17]	Portugal	807	2014	2y ad[1]	6,564	10,380	16,667	20,257	24,758
Blumen el al, 2016 [18]	US	8,360	2010	2y ad[1]	81,181	109,582		180,001	206,207
Mittmann et al, 2014 [19]	Canada	39,655	2005–2009	2y ad[1]	-	25,969	40,676	56,703	57,794
Wolstenholme el al, 1998 [20]	UK	137	1991	4y ad[1]	-	8,638	9,652	9,459	15,918
Legorreta el al, 1996 [21]	US	200	1989–1993	4y ad[1]	41,546	50,998	63,308	-	-
Li el al, 2013 [22]	China	316	2009–2010	5y ad[1]	10,296	32,884	41,632	44,595	44,766
Hoang Lan el al, 2013 [23]	Vietnam	160	2001–2006	5y ad[1]	-	654	1,038	939	694
Laas E et al, 2012 [24]	France	62	2010	Ac[2]	-	14,817	13,553	-	-
Will el al, 2000 [25]	Canada	17,700	1995	lifetime	-	25,755	28,392	35,628	40,212
Farley el al, 2015 [26]	US	274	2008–2010	Unk[3]	-	27,288	49,680	78,670	-
Davari el al, 2013 [27]	Iran	467	2005–2010	Unk[3]	-	12,838	13,734	20,035	23,643
Meneses-Garcia el al, 2012 [28]	Mexico	633	2004	Unk[3]	-	8,146	9,819	12,586	12,988
Liao et al, 2017 [29]	China	2,746	2012–2014	Unk[3]	-	6,706	6,794	8,556	12,840
					In situ	Local	Regional	Distant	
Tollestrup el al, 2001 [30]	US	317	1990–1994	1y ad[1]	10,219	14,824	26,502		
Subramanian el al, 2011 [31]	US	848	2002–2004	2y ad[1]	31,033	83,455	154,145	320,655	
Fireman el al, 1997 [32]	US	886	1987–1991	15y ad[1]	-	67,778	87,921	74,616	
Riley el al, 1995 [33]	US	Unk[3]	1973–1989	lifetime	164,727	143,367	130,472	85,128	
Taplin el al, 1995 [34]	US	2,944	1990–1991	Unk[3]	47,783	61,985	78,814	-	

Ad[1] indicates after diagnosis, ac[2]: after chemotherapy, unk[3]: unknown.

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patients diagnosed at earlier stages were substantially lower than annual costs at advanced stages. This supported the finding that earlier diagnosis lowers treatment costs.

We should be cautious when synthesising these treatment costs because the time horizons in the reviewed studies are different. Therefore, we also compared the cumulative treatment costs during the same time horizons. Four studies reported two-year cumulative treatment costs after diagnosis by FIGO stages among breast cancer patients. After conversion to 2015 US dollars, the costs estimated by Blumen et al. in the US [18] are much higher than the costs estimated in Italy [16], Portugal [18], and Canada [19]. The participants in Blumen's study were commercially insured population, and they probably sought for more health services than populations with publically funded insurance.

Two other studies estimated five-year cumulative costs after diagnosis, with the study in China [22] reporting higher costs than the study in Vietnam [23]. The costs of breast cancer treatment in Vietnam were much lower than those reported in other countries, due to the limited use of new medications and advanced medical equipment during the study period [23]. The lack of affordable access to appropriate treatment of breast cancer also contributes to the low treatment costs. Some patients did not complete their treatment courses because they were not covered by insurance. In addition, the unit costs can be different across countries, such as the differences in remuneration of health staff and capital depreciation [23].

Two studies also reported the treatment costs at four years after diagnosis. The costs estimated by Legorreta et al. in the US [21] were higher than those estimated by Wolstenholme et al. in the UK [20]. However, both studies were conducted about thirty years ago and hence they were not very informative for the present comparison.

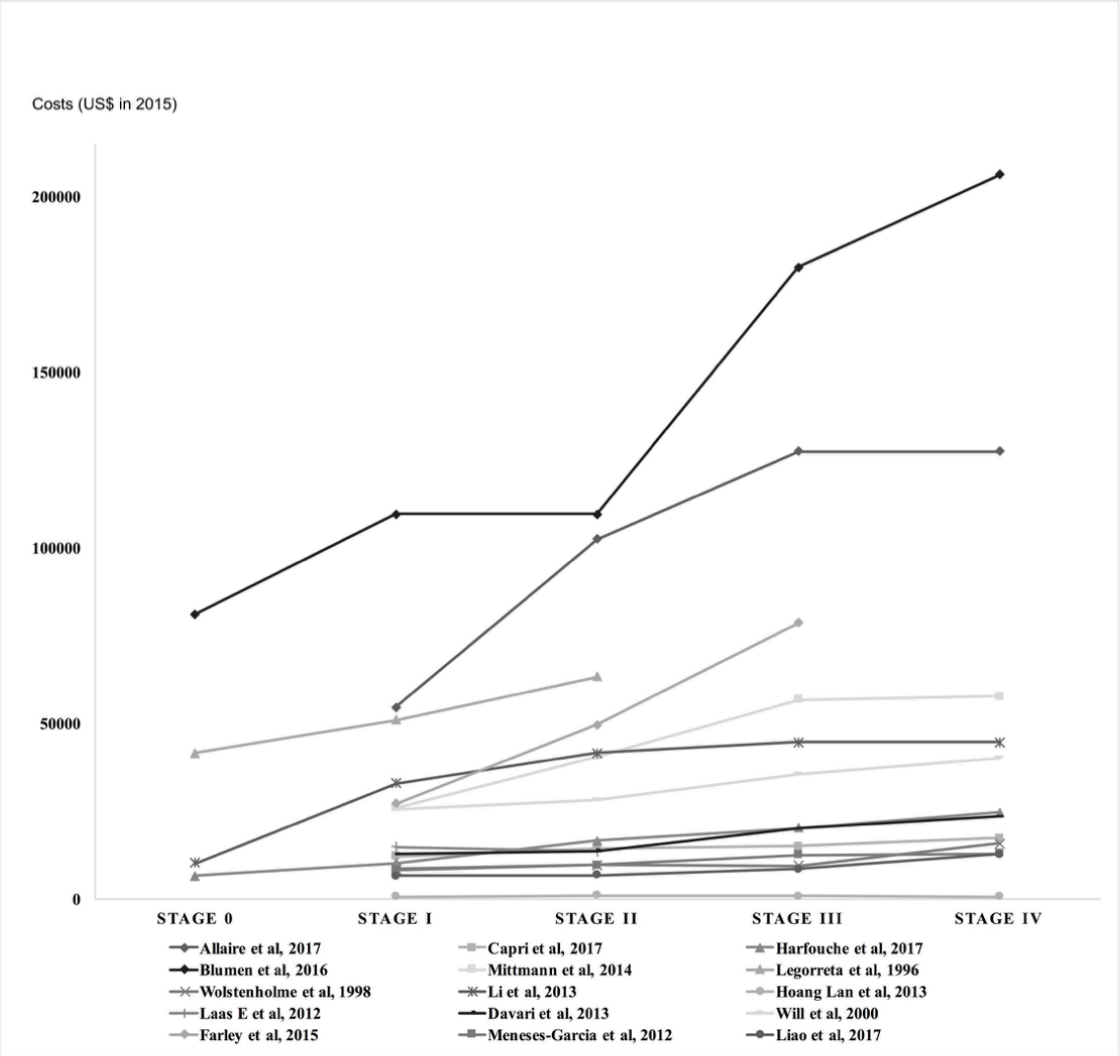

Fig 2. Cumulative breast cancer treatment costs by FIGO stages.

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Critical appraisal and methodological assessment

The quality of reviewed studies is presented in Table 2, as indicated by the percentage score ranging from 50% to 84%. Studies by Hoang Lan et al. [23] and Fireman et al. [32] had relatively high total scores among the reviewed papers. Studies scored relatively poorly on data collection items compared to other items. In addition, the choice of regression model was

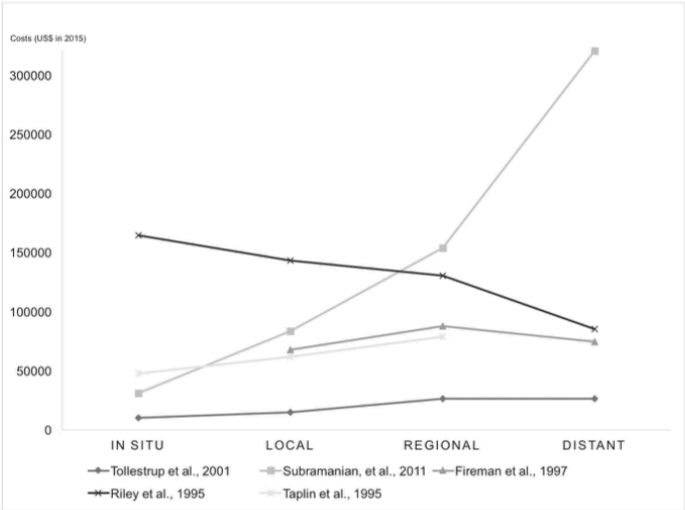

Fig 3. Cumulative breast cancer treatment costs by stages of in situ, local, regional and distant.

https://doi.org/10.1371/journal.pone.0207993.g003

Table 2. Critical appraisal scores (percentages of maximum attainable scores).

Studies	Scored domains			Summary scores
	Study design	Data collection	Analysis and interpretation	
Allaire et al, 2017 [15]	6 (100%)	6 (38%)	10 (63%)	22 (58%)
Capri et al, 2017 [16]	6 (100%)	9 (56%)	8 (50%)	23 (61%)
Harfouche et al, 2017 [17]	6 (100%)	8 (50%)	8 (50%)	22 (58%)
Blumen, et al., 2016 [18]	5 (83%)	7 (44%)	8 (50%)	20 (53%)
Mittmann, et al., 2014 [19]	6 (100%)	6 (38%)	16 (100%)	28 (74%)
Wolstenholme et al., 1998 [20]	4 (67%)	8 (50%)	16 (100%)	28 (74%)
Legorreta et al., 1996 [21]	4 (67%)	9 (56%)	16 (100%)	29 (76%)
Li, et al., 2013 [22]	6 (100%)	12 (75%)	10 (63%)	28 (74%)
Hoang Lan et al., 2013 [23]	6 (100%)	10 (63%)	16 (100%)	32 (84%)
Laas E et al, 2012 [24]	6 (100%)	14 (88%)	9 (56%)	29 (76%)
Will, et al., 2000 [25]	4 (67%)	6 (38%)	14 (88%)	24 (63%)
Farley, et al., 2015 [26]	6 (100%)	7 (44%)	6 (38%)	19 (50%)
Davari et al., 2013 [27]	6 (100%)	6 (38%)	15 (94%)	27 (71%)
Meneses-Garcia el al, 2012 [28]	5 (83%)	6 (38%)	14 (88%)	25 (66%)
Liao et al, 2017 [29]	6 (100%)	8 (50%)	7 (44%)	21 (55%)
Tollestrup et al, 2001 [30]	5 (83%)	10 (63%)	14 (88%)	29 (76%)
Subramanian et al, 2011 [31]	5 (83%)	10 (63%)	8 (50%)	23 (61%)
Fireman et al, 1997[32]	5 (83%)	9 (56%)	16 (100%)	30 (79%)
Riley et al, 1995 [33]	5 (83%)	6 (38%)	12 (75%)	23 (61%)
Taplin et al, 1995 [34]	5 (83%)	9 (56%)	12 (75%)	26 (68%)
Average (Kappa = 0.69)	5.4 (89.2%)	8.3 (51.9%)	11.8 (73.4%)	25.4 (66.8%)

https://doi.org/10.1371/journal.pone.0207993.t002

Table 3. Methodological assessment of the reviewed studies: frequency and percentage.

Charges/claim	Billed charges	Claim data	Unknown			
	9 (45%)	10 (50%)	1 (5%)			
Cost collection	Micro costing	Gross costing				
	15 (75%)	5 (25%)				
Control groups	Yes	No				
	6 (30%)	14 (70%)				
Descriptive analysis	Only mean	Mean and uncertainty				
	6 (30%)	14 (70%)				
Regression models	Parametric	Tobit	Two-part	GLM	Quantile	None
	6 (30%)	1 (5%)	1 (5%)	1 (5%)	1 (5%)	10 (50%)
Censored data	Described	Described				
	1 (5%)	19 (95%)				
Missing data	Imputation	CCA[1]	Assumption		Not mentioned	
	1 (5%)	9 (45%)	1 (5%)		9 (45%)	
Timing issues	Yes	No				
	16 (80%)	4 (20%)				

CCA[1] indicates complete case analysis.

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generally rarely justified. Table 3 summarises other aspects of the methodological assessment, with detailed study-specific results provided in S2 Table.

Charges/claims. Among the identified studies, nine studies used billed charges to measure costing data [20, 22, 23, 27–30, 32, 34], ten used claim datasets[15–19, 21, 24, 26, 31, 33], and one study did not provide information about this [25].

Cost collection and control groups. Fifteen studies used the micro-costing approach to measure and value cost [15–20, 23–25, 27, 28, 30–33]. However, they did not report the quantities of resource use separately from the unit costs. Five studies used the gross-costing approach to collect data [21, 22, 26, 29, 34]. Six studies included control groups to estimate the breast cancer-attributable treatment costs [15, 19, 30–32, 34].

Descriptive analysis. All of the reviewed studies estimated the means of breast cancer treatment costs in descriptive analyses. Fourteen studies among these also reported the uncertainty of estimated means [15, 19, 20, 22–24, 27–34], such as standard errors, 95% confidence intervals, or ranges between the minimum and maximum values.

Regression models. Ten studies used regression models to analyse the breast cancer treatment costs [16, 20–24, 30–32, 34]. Common parametric tests were conducted in six studies. Fireman et al. [32] used ordinary least squares (OLS) to analyse the relationship between patient characteristics and treatment costs. Three studies by Legorreta et al. [21], Wolstenholme et al. [20], and Li et al. [22] used analysis of variance (ANOVA) to examine differences in estimated costs across stages at diagnosis. Legorreta et al. [21] also used Chi-square test to evaluate the association between disease stage at diagnosis and other covariate variables. Taplin et al. [34] conducted multivariable regression for analysis, but the details of the models used were not explained.

Parametric approaches may sacrifice robustness when the assumptions of normality or homoscedasticity are violated. To deal with the large mass of observations with zero costs, Subramanian et al. [31] used the two-part model. In the first part, a logistic regression was conducted to predict the possibility of any expenditure. In the second part, the generalised linear model with a gamma distribution and a log link was used conditional on having positive

expenditures. Tollestrup et al. [30] considered a Tobit regression model which allowed a point mass at zero but assumed an underlying normal distribution [35]. Also, Capri et al. [16] used a generalised linear model to identify predictors of log-transformed costs. In addition to the estimation of mean costs, Hoang Lan et al. [23] used the quantile regression aiming at estimating the conditional medians of costs.

Censored data. Meneses-Garcia el al. performed analysis of censored-data costs though no details were described [28]. In the other 19 studies, there was no mention to the approaches used to deal with censored observations.

Missing data. Only one study dealt with missing data by multiple imputation [20]. Nine studies conducted complete-case analysis [16, 17, 19, 23, 26–29, 34] and another made assumptions about the incomplete information [24]. In the remaining studies, there was no mention to the issue of missing data.

Timing issues. Sixteen studies considered timing issues such as using consumer price index (CPI) for inflation or discounting the cost values to reflect time preferences. In the other four studies [18, 22, 26, 28], timing issues were not described.

Discussion

This study systematically reviewed published studies on breast cancer treatment costs by stage at diagnosis using patient level data from countries at different levels of socio-economic development. The review highlighted the fact that published data on this topic are rather limited and predominantly from high-income countries, and among the latter predominantly from the US. Of the 20 eligible studies identified, nine were from the US and only five from low- and middle-income countries. In addition, many of the studies were very dated. The paucity of the published evidence reflects in part the limited availability of staging information. The WHO International Classification of Diseases (ICD), which is the international standard used for reporting diseases and health conditions in routinely collected data, does not include codes for the stage at cancer diagnosis. Therefore, acquisition of stage information usually requires the collection of additional data from other (non-routine) sources or needs to be inferred from recommended stage-specific treatment protocols, neither of which is always feasible. It is worthwhile noting that the present review excluded studies that used a combination of clinical guidelines and unit costs, instead of patient level data, to estimate treatment costs as such cost estimates cannot reveal between-patient heterogeneity [36]. The review also excluded any data published in the grey literature by design, e.g. governmental reports, as its search was restricted to the scientific peer-reviewed literature. As studies with unfavourable results are less likely to be published, publication bias can be a potential concern for this review.

Nevertheless, the review's findings are consistent with treatment costs increasing with the advancement of the disease stage at diagnosis. The mean treatment costs of stages II, III and IV breast cancer were 32%, 95%, and 109% higher than those of stage I disease, and the mean treatment costs of regional and distant breast cancer were 41% and 165% higher than those of local disease. It has been shown that patients with more advanced disease receive more treatments than early-stage patients, such as chemotherapy and targeted therapy [37]. Also, medication therapy is usually a costly part of treatment for patients at stages III and IV because of the prescription of more expensive drugs [27, 38, 39].

The review revealed between-country differences in treatment costs, with these likely to be partly due to the variation in treatment patterns. For example, the UK used human epidermal growth factor receptor 2 (HER2)-targeted medicine the least frequently among five European Union countries [40]. The US uses three times as many mammograms compared to other developed countries [41]. Also, the high administrative costs and drug costs in the US make

the breast cancer treatment costs higher there than in many other high-income countries. Between-country differences in treatment costs might have also arisen because breast cancer survival rates vary widely across countries, overall ranging from 80% or over in North America to around 60% in middle-income countries and below 40% in low-income countries [42]. This reflects partly differences in stage at diagnosis as well as variations in the availability and access to appropriate treatments.

The review also revealed within-country variations in the treatment costs of breast cancer for the two countries with more than one study, i.e. the US, Canada, and China. Such differences may be partly due to differences in the years covered, i.e. the years of breast cancer diagnosis, as well as variations in time horizons. Advances in medicine have led to temporal changes in therapy strategies for breast cancer. Nowadays, breast conservation is the intended surgical standard approach for most women with early breast cancer [43]. Also, more systematic therapies have become available, such as endocrine therapy for hormone receptor positive breast cancer and target therapy for HER2-positive breast cancer [44].

The methodological assessment of the reviewed studies highlighted key methodological concerns. First, studies that used micro-costing approaches to collect cost data did not report the quantities of resources separately from the unit costs. Second, regression frameworks varied across studies. Some used common parametric tests such as ANOVA and OLS regression for cost estimations; however, these tests could be inappropriate due to the violation of their underlying assumptions. Two-part model and Tobit regression were conducted in some studies to deal with the impact of zero values, generalised linear model was applied to handle skewness, and quantile regression was used to estimate the median of costs. But the choice of these regression models was not fully justified. Third, only one study considered censored data though no details were described [28]. Censored data can be caused by death, loss to follow up, and administrative censoring [13]. If censoring is not accounted, the assessment of the importance of the disease severity on the cost of treatment may be biased [45]. Finally, the large majority of studies did not include a control group. Failure to do so might have resulted in an overestimation of cost values attributable to breast cancer treatment as some of the included costs might have been incurred by treatment of other co-existing diseases. All these methodological issues should be better dealt with in future costing studies.

Conclusions

This systematic review highlighted the paucity of published studies on breast cancer treatment costs by stage, based on patient-level data, from both high-income and low/middle-income countries. Nevertheless, the limited available data are consistent with earlier detection of breast cancer being associated with lower treatment costs. More up-to-date studies on treatment costs of breast cancer by stage are required from beyond the US including other developed and developing regions. Further costing studies should properly address and clearly describe key methodological issues (e.g. skewness, zero values, censored data, missing data).

Supporting information

S1 Checklist. PRISMA Checklist.
(DOC)

S1 Table. Search strategy.
(DOCX)

S2 Table. Detailed methodological assessment of the reviewed studies.
(DOCX)

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S1 Table

	Searches	MEDLINE	EMBASE	NHS EED
1	Breast cancer or breast tumor or breast tumour or breast neoplasm or mammon cancer or mammo tumor or mammo tumour or mammo neoplasm	208573	485451	2043
2	exp Breast Neoplasms/	262672	482860	1798
3	1 or 2	298094	529150	2339
4	Cost or treatment cost or health service cost or drug cost or surgery cost or mastectomy cost or breast-conserving cost or chemotherapy cost or radiotherapy cost or endocrine cost or targeted therapy cost	378394	762229	22534
5	exp Health Care Costs/	57935	263288	4990
6	exp Health Expenditures/	19239	263288	213
7	4 or 5 or 6	409040	776053	23053
8	3 and 7	6009	15490	793
9	Disease stage or cancer stage or by stage or stage-specific	23486	39578	318
10	Local and regional and remote	3781	6807	4
11	I and II and III and IV	63321	104261	255
12	9 or 10 or 11	89546	148561	549
13	8 and 12	99	268	36

S2 Table

Study	Type	Collection	Match	Description	Regression	Censoring	Missing data	Timing
Allaire et al, 2017 [15]	Claim	Micro	Yes	Mean, UNC[2]	--	No	NM	Yes
Capri et al, 2017 [16]	Claim	Mirco	No	Mean	GLM	No	CCA[3]	Yes
Harfouche et al, 2017 [17]	Claim	Mirco	No	Mean	--	No	CCA[3]	Yes
Blumen et al, 2016 [18]	Claim	Micro	No	Mean	--	No	NM	No
Mittmann, et al, 2014 [19]	Claim	Micro	Yes	Mean, UNC[2]	--	No	CCA[3]	Yes
Wolstenholme et al, 1998 [20]	Charge	Micro	No	Mean, UNC[2]	ANOVA	No	CCA[3], impute	Yes
Legorreta et al, 1996 [21]	Claim	Gross	No	Mean	χ2, ANOVA	No	NM[4]	Yes
Li et al, 2013 [22]	Charge	Gross	No	Mean, UNC[2]	ANOVA	No	NM[4]	No
Hoang Lan et al, 2013 [23]	Charge	Micro	No	Mean, UNC[2]	Quantile	No	CCA[3]	Yes
Laas E et al, 2012 [24]	Claim	Micro	No	Mean, UNC[2]	χ2, Fisher	No	Assumption	Yes
Will et al, 2000 [25]	UNK[1]	Micro	No	Mean	--	No	NM[4]	Yes
Farley et al, 2015 [26]	Claim	Gross	No	Mean	--	No	CCA[3]	No
Davari et al, 2013 [27]	Charge	Micro	No	Mean, UNC[2]	--	No	CCA[3]	Yes
Meneses-Garcia el al, 2012 [28]	Charge	Micro	No	Mean, UNC[2]	--	Yes	CCA[3]	Yes
Liao et al, 2017 [29]	Charge	Gross	No	Mean, UNC[2]	--	No	CCA[3]	Yes
Tollestrup et al, 2001 [30]	Charge	Micro	Yes	Mean, UNC[2]	Tobit	No	NM[4]	No

Subramanian et al, 2011 [31]	Claim	Micro	Yes	Mean, UNC[2]	Two-part	No	NM[4]	Yes
Fireman et al, 1997 [32]	Charge	Micro	Yes	Mean, UNC[2]	OLS	No	NM[4]	Yes
Riley et al, 1995 [33]	Claim	Micro	No	Mean, UNC[2]	--	No	NM[4]	Yes
Taplin et al, 1995 [34]	Charge	Gross	Yes	Mean, UNC[2]	Multivariate	No	CCA[3]	Yes

UNK[1] indicates unknown, UNC[2]: uncertainty, CCA[3] indicates complete case analysis, NM[4]: not mentioned.

Commentary

Two researchers independently extracted the study characteristics and assessed the study quality in this systematic review. If the extracted study characteristics or quality scores were different, the two investigators would discuss each item to reach consensus.

The Drummond checklist was employed to assess the reporting quality of the reviewed studies. In addition to employing the Drummond checklist to evaluate the study reporting quality, I have also summarised important dimensions of study quality in Table-3 and S2 Table, including whether costs were based on charges or claims, data collection approaches, use of control groups, descriptive analysis, regression model choices, censored data analysis, missing data analysis, and timing issues.

We should be cautious when synthesising the treatment costs in the reviewed studies because these costs incurred in different countries. However, this could provide evidence from the global perspective that treatment costs of breast cancer generally increased with the advancement of the disease stage at diagnosis.

Blumen et al and Subramanian et al reported that the first-year annual costs of breast cancer treatment were higher than the second-year costs. Riley et al divided the period from diagnosis to death into four phases and estimated average payments for each phase separately. The initial phase consists of the month prior to diagnosis and the ensuing six months. The final phase is the last six months of life. The pre-final phase is the 12 months immediately preceding the final phase. The time between initial and prefinal phases was designated the continuing care phase. The results showed that costs in the pre-final phases were more than double those in the continuing care phase for each stage. This reflects a period of rising costs before the last months of life.

Legorreta el al reported that annual costs drop for all clinical stages in the second year except stage III, which reflects the high early cost of the treatment of breast cancer diagnosed at stage III. Costs did not differ significantly by stage in years 3 and 4. However, the numbers were not given in Legorreta et al study and therefore not presented in the table below. Also another study by Capri et al reported breast cancer costs by time phases. However, the phases were overlapped so this study was not presented in the table below.

Breast cancer treatment costs by time phase and stage (US dollars in 2015)

Study	Time phase	Costs by stage			
		Stage 0	**Stage I/II**	**Stage III**	**Stage IV**
Blumen et al 2016 [18]	1st year	68,456	92,710	146,071	152,048
	2nd year	12,725	16,872	33,930	54,159
		In Situ	**Local**	**Regional**	**Distant**
Subramanian et al 2011 [31]	1st year	29,528	46,768	69,173	100,598
	2nd year	20,071	26,736	27,447	89,199
Riley et al 1995 [33]					
Less than 1 year survival	Total	Not available	47,544	48,093	45,347
Survived 1 year or more	Initial	18,733	22,679	26,432	32,156
	Continuing	7,907	8,003	8,731	12,444
	Pre-final	20,058	19,192	20,629	27,024
	Final	12,529	10,630	11,698	11,944

Chapter 8

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	15115005	**Title**	Miss
First Name(s)	Li		
Surname/Family Name	Sun		
Thesis Title	Economics of breast cancer screening, genetic testing, and treatment		
Primary Supervisor	Rosa Legood		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

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Where was the work published?			
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Where is the work intended to be published?	Value in Health
Please list the paper's authors in the intended authorship order:	Li Sun, David Cromwell, David Dodwell, Melissa Ruth Gannon, Jibby Medina, Mark Pennington, Rosa Legood, Isabel dos-Santos-Silva, Zia Sadique
Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Please refer to details on the following page

SECTION E

Student Signature	
Date	

Supervisor Signature	
Date	

Chapter 8

Costs of breast cancer care in England using national patient-level data

This chapter presents analyses estimating the costs of care among women aged 50 years and over with a histological diagnosis of early invasive breast cancer in England. The study is nested within the National Audit of Breast Cancer in Older Patients (NABCOP). I conducted statistical analysis, interpreted the findings, and written the manuscript with the supervision from Dr Zia Sadique and Dr Rosa Legood, and support from the members of the NABCOP project. All authors approved the final draft prior to journal submission and inclusion in the thesis. This paper has been submitted to Value in Health.

Costs of breast cancer care in England using national patient-level data

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ABSTRACT

Objectives: This study aimed to use patient-level data to provide up-to-date estimates of breast cancer care costs by stage in England, and explore to what extent these costs vary across patient age and geographic region.

Methods: This study identified women aged 50 years and over diagnosed with early invasive breast cancer between 01 January 2014 and 31 December 2015 from linked cancer registration and routine hospital datasets for England. Cost estimates were derived from hospital records in Hospital Episodes Statistics with additional chemotherapy and radiotherapy information from the national datasets. We fitted general linear regression models to analyse the cost data. The model that best fit the data was selected using the model selection criteria of Akaike information criterion.

Results: 55,662 women with early invasive breast cancer in England were included. The generalised linear model with log-gamma distribution fitted the data best. The costs of breast cancer care for one year following diagnosis were strongly dependent on stage at diagnosis adjusting for other covariates. The estimated average per-patient hospital-related costs were £5,224 at stage I, £7,617 at stage II, and £13,506 at stage IIIA. Costs decreased with increasing age and varied across region, deprivation level, referral source, presence of comorbidities, and tumour receptor (ER/PR/HER2) status.

Conclusions: In England, costs of breast cancer care increased with increasing stage of the disease at diagnosis. Variations in breast cancer costs by age and geographic region raise questions about the efficiency and consistency of breast cancer treatment patterns in England.

INTRODUCTION

Breast cancer is the most commonly diagnosed female cancer in the United Kingdom (UK) (62). As in other high-income countries, the number of women living with breast cancer in the UK is increasing due to rises in incidence rates (62), increases in the number of older women (139), and improved survival (140) as a result of earlier detection and treatment improvements. It has been clearly established that earlier diagnosis of breast cancer reduces mortality (69), but the cost implications of breast cancer care are not well understood (141).

Stage at diagnosis is an important factor shaping breast cancer treatment pathways. Treatment for more advanced breast cancer is more intensive and invasive (105), and tends to be associated with greater resource utilisation (107). Costs of breast cancer care by stage at diagnosis are important in quantifying the gains from early detection. If early treatment lowers costs, this will help offset some costs of interventions that aim to achieve earlier diagnosis. In addition, treatment costs by stage would be valuable to inform the cost-effectiveness of breast cancer therapies.

Existing UK data on the costs of breast cancer care by stage at diagnosis were published over 20 years ago and are out-of-date (26). Recent National Institute for Health and Care Excellence (NICE) appraisals on the cost-effectiveness of breast cancer treatment have relied on modelled assumptions (98). This may lead to biased estimates of the full cost as there are multi-modal treatments. The consequences of biased estimates are serious as, potentially, therapies may be incorrectly rejected or approved by NICE based on cost-effectiveness evidence. Up-to-date estimates of the costs of breast cancer care by stage are required.

In addition, recent evidence has revealed a differential approach to breast cancer management for the older patient in the UK (142), which may explain the poorer survival of older women in the UK compared to other European countries (143). Moreover, little is known about the geographic variation in costs of breast cancer care across England. For example, significant variations in rates and types of immediate breast reconstruction procedures were observed among National Health Service (NHS) hospitals in England (144). The differences in costs across patient age and region need to be determined.

In this study, we used patient-level data to estimate the costs of primary breast cancer care incurred in the first year after diagnosis, by stage among women aged 50 years and over diagnosed in England, and to explore to what extent breast cancer costs vary across different patient ages and regions.

METHODS

This study used data from the National Audit of Breast Cancer in Older Patients (NABCOP) project, a national clinical audit commissioned by the Healthcare Quality Improvement Partnership as part of its National Clinical Audit and Patient Outcomes Programme. The details of the national clinical audit were described elsewhere (145). In brief, the audit uses anonymised patient-level data from the English and Welsh Cancer Registration services, linked to other national datasets to provide information on hospital admissions and the use of chemotherapy and radiotherapy. The Office for National Statistics (ONS) Death Register provides information on date and cause of death.

Population and data

The study population was restricted to women aged 50 years and over with newly diagnosed early invasive breast cancer (stages I, II and IIIA) within England over the two years between 01 January 2014 and 31 December 2015 and who were treated within the NHS. The data was available up to 31 December 2016 so that no patients were censored. Patients with advanced (stage IIIb and IV) breast cancer were not included in this analysis because bone metastasises information was not available from the databases.

The cancer registration dataset contained patient demographics including age at diagnosis, ethnicity, date of diagnosis, and geographic region (cancer alliance). The 19 cancer alliances were established by NHS England to deliver the national recommendations within the NHS Cancer Strategy and to drive local quality improvements (146). Tumour characteristics included pathologic stage at diagnosis, oestrogen receptor (ER) status, progesterone receptor (PR) status, and human epidermal growth factor receptor 2 (HER2) status. ER, PR, and HER2 are breast cancer molecular markers that guide the selection of the most appropriate drug therapies and are individually recorded as positive, negative, or borderline.

Hospital admissions were identified from the Hospital Episode Statistics (HES) data. This contained date of admission, date of discharge, method of admission, method of discharge, date of spell (a continuous period of care in hospital) start, date of spell end, procedures undertaken (using the Office of Population Censuses and Surveys (OPCS) Classification of Surgical Operations version 4 codes) (147), and Healthcare Resource Group (HRG) (148). The HES data were also used as the data source for regional deprivation measured as the Index of Multiple Deprivation (IMD) (149) and comorbidity burden. Patient IMD scores were grouped into regional quintiles of deprivation, from most (=1) to least deprived (=5). Charlson Comorbidity Index was derived from the diagnosis fields within HES, which measures the presence of additional medical conditions co-occurring with breast cancer (150).

The use of chemotherapy and targeted therapy was identified from the Systematic Anti-Cancer Therapy (SACT) Dataset. The radiotherapy information was obtained from the National Radiotherapy Dataset (RTDS).

Resource use and measurement

We categorised resource use during the first year of breast cancer care into various aspects of the care pathway: 1) diagnosis (triple assessment in a single visit); 2) breast procedures (breast surgery (resection, reconstruction, and surgery for lymph node involvement), and hospital length of stay); 3) chemotherapy; 4) radiotherapy; 5) endocrine therapy; and 6) targeted therapy.

Patients with suspected breast cancer are recommended to undergo a triple diagnostic assessment in a single initial hospital visit, including clinical assessment, imaging (ultrasound and/or mammogram), and tissue biopsy (98, 151). We measured the use of these diagnostic interventions using dates of imaging and biopsy.

The types of breast resection surgeries include breast conserving surgery (BCS, removal of a part of the breast containing the cancer), mastectomy (removal of all breast), and mastectomy with reconstruction. Also, we measured whether or not the patients had lymph node involvement and axillary surgeries based on HES data. Axillary surgeries covered the activities of sentinel node biopsy and axillary lymph node dissection (98). A maximum length of stay is specified for each HRG code. Where the patient length of stay during a spell in hospital exceeded that point, we documented the excess hospital bed days recorded by the number of overnight admissions.

We assumed patients received chemotherapy, radiotherapy, or targeted therapy if these were reported in SACT and RTDS datasets. Information on endocrine therapy was not well captured in SACT so we assumed all ER positive (ER+) or PR positive (PR+) breast cancer patients were prescribed endocrine therapy.

Cost estimation

Healthcare Resource Groups (HRG) are groups of hospital admissions that have been judged to consume a similar level of resource (148). We used unit costs from NHS reference costs (152) to assign costs using breast procedure-driven and diagnosis-driven core HRGs for the continuous inpatient spell. Some patient care episodes may have associated high-cost care elements that will generate unbundled HRGs as additions to the core HRG, such as chemotherapy, radiotherapy, and other high-cost drugs. Only records clearly related to breast cancer care were retained.

Excess hospital bed days are reimbursed at a daily cost based on the core spell HRG code, which distinguishes between elective and non-elective admissions. With the information on admission method, we applied the elective or non-elective excess hospital bed day adjustment to the estimated cost where the patient length of stay exceeded the maximum specified for a given HRG code.

We used OPCS procedure codes from SACT and RTDS datasets to assign HRG codes to estimate the costs of chemotherapy and radiotherapy. All costs were converted to 2016 values using the Hospital and Community Health Service Index (153).

We assumed all ER+/PR+ patients aged over 50 years received an aromatase inhibitor (anastrozole) for postmenopausal endocrine therapy as per NICE guidelines (154, 155). We obtained the drug cost from the British National Formulary (BNF) (156) to estimate the endocrine therapy costs. In addition, we obtained the annual trastuzumab cost per patient including administration of treatment and cardiac monitoring from the NICE costing report to estimate the targeted therapy costs for HER2+ patients (155).

Cost analysis

We fitted generalised linear regression models to estimate the mean costs of primary breast cancer care up to one year after diagnosis for women in England. The model contained a number of explanatory variables to assess the relationship between cost and patient characteristics. Demographic variables included age at diagnosis, ethnicity, geographic regions, and IMD. Disease characteristics included disease stage, ER/PR/HER2 status, Charlson Comorbidity Index, and referral source (via screening or not). We predicted costs of primary breast cancer care by stage at diagnosis for the population average, as well as costs for patient subgroups including luminal A (ER+ and/or PR+, HER2-), luminal B (ER+ and/or PR+, HER2+), HER2-enriched (ER-, PR-, HER2+), and triple negative (ER-, PR-, HER2-) disease based on the St Gallen molecular subtype classification (157). As the disease stage may have different effects on costs across regions in England, we added the interaction term of stage and region in the regression models.

Using a generalised linear model (GLM) enabled the cost estimates to handle common features of health care cost data, such as the substantial skewness with long right-hand tails (158), heteroskedastic errors and non-linear responses to covariates (159). Typically, a log-link function with a Gamma distribution fitted health care costs well (158). However, there was no evidence that this was the dominant form of GLM in terms of model fit for cost data applications (160).

In this study, we compared the models checking distributions of normal, log-normal, and log-gamma respectively. Modified Park Test was conducted to guide the choice of distribution reflecting the relationship between variance and mean. The preferred model was selected as the one with the minimum Akaike information criterion (AIC) values. We reported the marginal effects of explanatory variables on the total costs for the models we compared. We conducted the complete case analysis using only data from patients for whom all variables involved in the analysis were observed. All statistical analyses were undertaken in STATA, version 15.1.

RESULTS

The study included 55,662 women aged 50 years and over diagnosed with early invasive breast cancer in England between January 2014 and December 2015. The characteristics of the women by stage at diagnosis are presented in Table 8-1. The mean age was 67 years. The percentages of breast cancer patients diagnosed at stage I, stage II, and stage IIIA were 51%, 44%, and 6% respectively. 40% of breast cancer patients were screen-detected (found on mammography undertaken by the NHS National Breast Cancer Screening Programme), while the other 60% were referred from GP or other specialities, or detected due to an emergency presentation (<1%).

The resource use of breast cancer care is shown in Table 8-2. Determining whether a woman had triple diagnostic assessment was not straightforward because many imaging and biopsy dates were incomplete in the datasets (145). Adopting a strict set of criteria for the analysis of English data suggested that among women diagnosed with early invasive breast cancer, and who were not referred from screening, 28% received triple assessment in a single visit. If the criteria were relaxed (assuming missing mammogram/biopsy dates were the same as the date of biopsy/mammogram respectively, incorporating the use of ultrasound where no mammogram was recorded, and allowing dates of biopsy and mammogram to differ by one day), the estimated proportion of women having a triple diagnostic assessment on the same day was 82%. The rates of mastectomy, mastectomy with reconstruction, and axillary lymph node dissection increased with more advanced cancer stage at diagnosis, while the rates of BCS and sentinel node biopsy decreased with advancing stage. The time spent in hospital was short for most breast cancer patients. Most women were typically admitted and discharged as day cases, and the excess hospital bed days per patient were 0.06 days showing increasing trend by advanced stage. In addition, the proportion of patients receiving chemotherapy or targeted therapy at stage IIIA was higher than stage I or II. The proportion receiving radiotherapy among patients having BCS was 88% compared to 41% for patients having mastectomy.

The crude costs of first-year breast cancer care among 55,662 patients increased with more advanced disease. The subcategories of diagnosis and procedure costs, chemotherapy costs, radiotherapy costs, and targeted therapy costs all rose with higher stage (Appendix 4). There was some variation in the crude costs of primary breast cancer care across cancer alliances, with overall costs typically falling between £5,500 and £7,000 (Figure 8-1).

The results of the compared regression models are shown in Table 8-3, using data from 22,537 patients for whom all variables involved in the analysis were observed. Missing data in HES was negligible with the exception of Charlson Comorbidity Index (3%) while the level of incompleteness in Cancer Registry was larger with PR status (51%), HER2 status (17%), ER status (14%), and ethnicity (6%). The Modified Park Test indicated the choice of a gamma distribution and the GLM with log-gamma distribution reported the minimum AIC. The regression model showed that the total cost of primary breast cancer care increased with advancing stage at diagnosis. Patients diagnosed at stage II incurred £2,031 (S.E. £71) more costs and patient at stage IIIA incurred £6,704 (S.E. £256) more costs compared to those diagnosed at stage I ($p<0.001$).

The regression model indicated that breast cancer costs decreased with increasing age ($p<0.001$), more comorbidities ($p<0.001$) and higher levels of deprivation ($p<0.001$). Patients with screen-detected cancers incurred lower costs than those diagnosed outside screening ($p<0.05$). There was strong evidence of lower costs in ER/PR+ patients and higher costs in HER2+ patients ($p<0.001$). There was also evidence that the costs of primary breast cancer care varied across regions in England ($p<0.001$). The coefficients are presented in Table 8-3 and Appendix 5.

We predicted the total costs of primary breast cancer care within one year after diagnosis using a GLM regression adjusting for patient demographics and tumour characteristics. For patient subgroups with different tumour receptor status, the predicted costs of primary breast cancer care were £5,082 (S.E. £18) for luminal A patients, £14,439 (S.E. £142) for luminal B patients, £18,949 (S.E. £238) for HER2-enriched patients, and £7,128 (S.E. £55) for triple-negative patients respectively, all decreasing by age with a linear trend (Figure 8-2). With regards to the population average, the adjusted costs of breast cancer care within one year after diagnosis in the base case was predicted to be £6,815 (S.E. £33) on average for all stages, with £5,224 (S.E. £29) at stage I, £7,617 (S.E. £49) at stage II, and £13,506 (S.E. £228) at stage IIIA (Figure 8-3).

DISCUSSION

The principle aim of this study was to generate up-to-date estimates of initial early invasive breast cancer care costs by stage at diagnosis in England, adjusting for patient demographics and tumour characteristics. Our results show that the costs of early breast cancer care for the first year after diagnosis increase with more advanced stage at diagnosis. The care costs of stage IIIA disease are more than double those of stage I disease. The finding is consistent with a global systematic review indicating increased breast cancer care costs with advanced stage, in which the treatment costs of breast cancer at stage II and stage III were reported to be 32% and 95% higher than stage I on average worldwide (141). Previous studies of the treatment costs of breast cancer by stage at diagnosis were rather limited due to the poor availability of staging information and were predominantly from the US (141). Before our analysis, there was only one very dated UK study estimating the costs of breast cancer care using patient-level data, reporting that the four-year costs of breast cancer were £6,039 at stage I, £6,749 at stage II, and £6,614 at stage III (converted to 2016 values) (26). Our study has therefore provided important updated evidence on primary treatment costs for breast cancer by stage in England. This is important for future comparative assessment of the cost-effectiveness of breast cancer screening and therapy interventions.

Compared to younger breast cancer patients, older patients were shown to incur lower costs. This is consistent with the studies that found older patients received fewer treatments in the UK. Clinical guidelines emphasise that breast cancer treatment should be based on clinical need and fitness for treatment rather than chronological age (98, 161, 162). Also, Breast Cancer Quality Standards [NICE 2013] explicitly state that women, “irrespective of age, are offered surgery, radiotherapy and appropriate systemic therapy, unless significant co-morbidity precludes it.” Chronological age should not be a dominant factor in the decision to offer a particular treatment. In this study, we attempted to control for comorbidity and so the differences across age groups raise questions about whether services in the UK have a non-standard approach to breast cancer management for older patients (142, 145). The different patterns of resource utilisation might be a reason why the survival of older breast cancer patients in the UK and Ireland has been reported to be lower compared to other European countries (143). Nonetheless, differences in the patterns of care among younger and older patients may arise for various reasons, including unmeasured differences in the disease, differences in the prevalence and severity of comorbidities and frailty that may contraindicate breast cancer treatments (e.g. surgery, chemotherapy or radiotherapy), differences in patient preferences and cultural attitudes, and less-involvement of older patients in the decision making process (145).

We further observed that the costs of breast cancer care varied across regions in England, after taking the differences in stage distributions across regions into consideration. This is of concern because it suggests different utilisation of breast cancer care across England. In the UK, hospitals receive payment based on the procedure types according to the NHS National Tariff Payment System (163). The tariffs are defined nationally and aligned to promote efficient and high-quality care but the actual cost of performing certain procedures can exceed the income that hospitals receive (144). The potential for a financial loss may impact on the consideration of the provision of different treatment options in hospitals and therefore be reflected by the total costs of breast cancer care across cancer alliances in England. An examination of costs could highlight areas for review locally and there would probably be a benefit in having benchmark costs for particular patient groups for regional audit. In addition to the financial consideration, future research could also examine whether the regional variation in costs of breast cancer care is related to service provision and/or capacity barriers.

The advantages of our study population are: (i) it includes all patients with a registered diagnosis of early invasive breast cancer in England, diagnosed and treated in an NHS trust, (ii) individual patient-based information is available on a large number of variables such as socio-demographic factors, comorbidities, and referral source; (iii) information on tumour characteristics and treatment received; (iv) linkage between multiple national databases.

Our study is subject to some limitations. We only included breast cancer patients aged 50 years and over, and limited the follow-up period to one year following diagnosis. Also, we excluded patients with metastatic breast cancer and did not consider the costs of recurrence. This deserves careful consideration and will underestimate the overall cost of care throughout the entire patient pathway. Costs of care in the context of higher stage disease are likely to be disproportionately underestimated given the higher risk of recurrence.

We have identified the key methodological differences in cost analysis in the previously published global systematic review comparing treatment costs of breast cancer by stage across countries (141). Our review showed that most studies used regression frameworks but the choice of regression models was rarely justified. Few studies described key methodological issues including skewness, zero values, censored data, missing data, and the inclusion of control groups to estimate disease-attributable costs (141). As no single regression model is dominant in costing analyses, we explored different regression models to deal with the skewness issue. In this study, we compared regression models with different distributions (normal, log-normal, and log-gamma).

Based on the model selection criteria, we evidenced that the GLM with a log-gamma distribution fit the data best.

In addition to skewness, there may also be censoring issues (164). The difference between the diagnosis date and the follow-up date is the maximum length of time the patients may be followed. If no death occurs in this period, a patient would potentially be censored. This type of censoring arising from the planned end of follow-up is known as administrative censoring (165). In this study, we used two years of diagnosis and included only patients with complete one-year follow up when the study ended on 31 December 2016. The study population in our analysis therefore includes women diagnosed between 01 January 2014 and 31 December 2015 because their follow-up information was complete. Future research could explore the impact of censored data, for which various methods have been developed (166-168). Moreover, there are many missing data in the imaging and biopsy dates due to the incomplete reporting of data. We adopted the relaxed criteria as described and assumed 82% of patients had a triple diagnostic assessment on the same day. To enable a better understanding of triple diagnostic assessment for breast cancer patients, the data completion on imaging and biopsy dates needs to be improved. In this study, we conducted complete case analysis using only data from 22,537 patients for whom all variables involved in the analysis were observed. Missing data in HES was negligible with the exception of Charlson Comorbidity Index (3%) while the level of incompleteness in Cancer Registry was larger with PR status (51%), HER2 status (17%), ER status (14%), and ethnicity (6%). In further research, one could use multiple imputation to impute the missing data (169). Ideally a matched control group could be included to estimate breast cancer-attributable costs. However, due to the data availability we only included breast cancer patients in this study. The inclusion of control groups to estimate disease attributable costs could be the direction of future research.

In conclusion, this study provides up-to-date estimates of breast cancer care costs by stage at diagnosis in England. Costs of early invasive (stage I, II and IIIA) breast cancer care up to one year after diagnosis increased with advancing stage of the disease at diagnosis in England. Variations in breast cancer costs by age and geographic region raise questions about the efficiency and consistency of breast cancer treatment patterns in England.

ETHICS APPROVAL

The study is exempt from UK National Research Ethics Committee approval as it involved secondary analysis of an existing dataset of anonymised data. The NABCOP has approval for processing health care information under Section 251 (reference number: 16/CAG/0079) for all NHS patients aged 50 years and over diagnosed with breast cancer in England and Wales. Also this analysis has received ethics approval from the London School of Hygiene & Tropical Medicine Ethics Committee (reference number 16184).

ROLE OF THE FUNDING SOURCE

This study was undertaken as part of the work by the National Audit of Breast Cancer in Older Patients (NABCOP). The Audit is commissioned by the Healthcare Quality Improvement Partnership (HQIP) as part of the National Clinical Audit and Patient Outcomes Programme, and funded by NHS England and the Welsh Government (www.hqip.org.uk/national-programmes). Neither the commissioner nor the funders had any involvement in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication. The authors had full independence from the HQIP. The aim of the NABCOP is to evaluate the care of older women with breast cancer in England and Wales, and support NHS providers to improve the quality of hospital care for these women.

Tables

Table 8-1 Cohort characteristics - n (%) unless otherwise stated

Variables		All (n=55,662)	Stage I (n=28,232)	Stage II (n=24,358)	Stage IIIA (n=3,072)
Age (years)	Mean (sd)	67 (11)	66 (10)	69 (12)	66 (11)
Ethnicity	White	49,175 (88%)	24877 (88%)	21559 (89%)	2739 (89%)
	Asian	1,364 (2%)	633 (2%)	633 (3%)	98 (3%)
	Black	766 (1%)	304 (1%)	398 (2%)	64 (2%)
	Other	862 (2%)	444 (2%)	367 (2%)	51 (2%)
	Unknown	3,495 (6%)	1974 (7%)	1401 (6%)	120 (4%)
Charlson Comorbidity Index	0	46,078 (83%)	23760 (84%)	19698 (81%)	2620 (85%)
	1	5,084 (9%)	2477 (9%)	2342 (10%)	265 (9%)
	2	1,764 (3%)	772 (3%)	889 (4%)	103 (3%)
	3+	914 (2%)	392 (1%)	492 (2%)	30 (1%)
	Unknown	1,822 (3%)	831 (3%)	937 (4%)	54 (2%)
Index of Multiple Deprivation	1 (most deprived)	7,608 (14%)	3674 (13%)	3468 (14%)	466 (15%)
	2	9,830 (18%)	4871 (17%)	4410 (18%)	549 (18%)
	3	11,585 (21%)	5945 (21%)	5011 (21%)	629 (20%)
	4	13,023 (23%)	6725 (24%)	5600 (23%)	698 (23%)
	5 (least deprived)	13,616 (24%)	7017 (25%)	5869 (24%)	730 (24%)
ER status	Positive	41,872 (75%)	22109 (78%)	17601 (72%)	2162 (70%)

	Negative	6,196 (11%)	2379 (8%)	3316 (14%)	501 (16%)
	Borderline	22 (<1%)	9 (<1%)	12 (<1%)	1 (<1%)
	Not performed/unknown	7,572 (14%)	3735 (13%)	3429 (14%)	408 (13%)
PR status	Positive	19,078 (34%)	10114 (36%)	7949 (33%)	1015 (33%)
	Negative	8,386 (15%)	3515 (12%)	4238 (17%)	633 (21%)
	Borderline	58 (<1%)	29 (<1%)	27 (<1%)	2 (<1%)
	Not performed/unknown	28,140 (51%)	14574 (52%)	12144 (50%)	1422 (46%)
HER2 status	Positive	5,494 (10%)	2144 (8%)	2900 (12%)	450 (15%)
	Negative	38,589 (69%)	20320 (72%)	16234 (67%)	2035 (66%)
	Borderline	2,296 (4%)	1165 (4%)	988 (4%)	143 (5%)
	Not performed/unknown	9,283 (17%)	4603 (16%)	4236 (17%)	444 (14%)
Referral source	Screen-detected	22,193 (40%)	15512 (55%)	6072 (25%)	609 (20%)
	Not screen-detected	33,469 (60%)	12720 (45%)	18286 (75%)	2463 (80%)

Sd: standard deviation

Table 8-2 Resource use – n (%) unless otherwise stated

Resource use	All (n=55,662)	Stage I (n=28,232)	Stage II (n=24,358)	Stage IIIA (n=3,072)
1. Diagnosis				
Breast ultrasound#	16,548 (30%)	7,394 (26%)	8,157 (33%)	997 (32%)
Mammography#	21,518 (39%)	10,012 (35%)	10,154 (42%)	1,352 (44%)
Biopsy#	43,523 (78%)	23,505 (83%)	17,998 (74%)	2,020 (66%)
2. Breast procedures				
Breast conserving surgery (BCS)	35,718 (64%)	21,962 (78%)	12,753 (52%)	1,003 (33%)
Mastectomy	12,585 (23%)	3,342 (12%)	7,411 (30%)	1,832 (60%)
Mastectomy and reconstruction	2,627 (5%)	1,131 (4%)	1,294 (5%)	202 (7%)
Axillary lymph node dissection	10,044 (18%)	835 (3%)	6,783 (28%)	2,426 (79%)
Sentinel node biopsy	42,091 (76%)	24,462 (87%)	16,469 (68%)	1,160 (38%)
Excess hospital bed days – mean (sd)	0.06 (1.24)	0.03 (0.77)	0.09 (1.55)	0.15 (1.81)
3. Chemotherapy				
Chemotherapy received	9,498 (17%)	2,404 (9%)	5,731 (24%)	1,363 (44%)
4. Radiotherapy				
Radiotherapy received	37,336 (67%)	19,895 (70%)	14,888 (61%)	2,553 (83%)
1) Radiotherapy received among patients having BCS	31,290 (88%)	19,181 (87%)	11,196 (88%)	913 (91%)
2) Radiotherapy received among patients having mastectomy	5,098 (41%)	348 (10%)	3,170 (43%)	1,580 (86%)
5. Endocrine therapy				
Endocrine therapy received†	42,080 (76%)	22,176 (79%)	17,711 (73%)	2,193 (71%)

6. Targeted therapy

Targeted therapy received	3,606 (6%)	1,250 (4%)	2,002 (8%)	354 (12%)

[#]Data on imaging and biopsy dates were incomplete in the datasets. Adopting a strict set of criteria, 28% received triple assessment in a single visit. If we assumed missing mammogram/biopsy dates were the same as the date of biopsy/mammogram respectively, incorporated the use of ultrasound where mammogram was not reported, and allowed dates of biopsy and mammogram to differ by one day, the estimated proportion of women having a triple diagnostic assessment on the same day was 82%.

[†]We assumed all ER+/PR+ breast cancer patients received endocrine therapy.

Table 8-3 Results for first-year total costs of breast cancer care comparing alternative models – coefficient (standard error)

Variables	**OLS**	**Log-Normal**	**Log-Gamma**
Stage II	2,002 (79)***	1,923 (70)***	2,031 (71)***
Stage IIIA	5,995 (159)***	4,683 (133)***	6,704 (256)***
Age	-160 (4)***	-145 (3)***	-192 (4)***
Region	***	***	***
Region × Stage	***	***	***
AIC	451,879	451,354	435,161
N		22,537	

The reference group is patients aged 50 years diagnosed at stage I from North East and Cumbria. We adjusted for ethnicity, Charlson Comorbidity Index, Index of Multiple Deprivation, ER/PR/HER2 status, and referral source (presented in Appendix 5).
We conducted the complete case analysis and the sample size was 22,537 patients for whom all variables involved in the analysis were observed. Missing data in HES was negligible with the exception of Charlson Comorbidity Index (3%) while the level of incompleteness in Cancer Registry was larger with PR status (51%), HER2 status (17%), ER status (14%), and ethnicity (6%).
***p<0.001

Figures

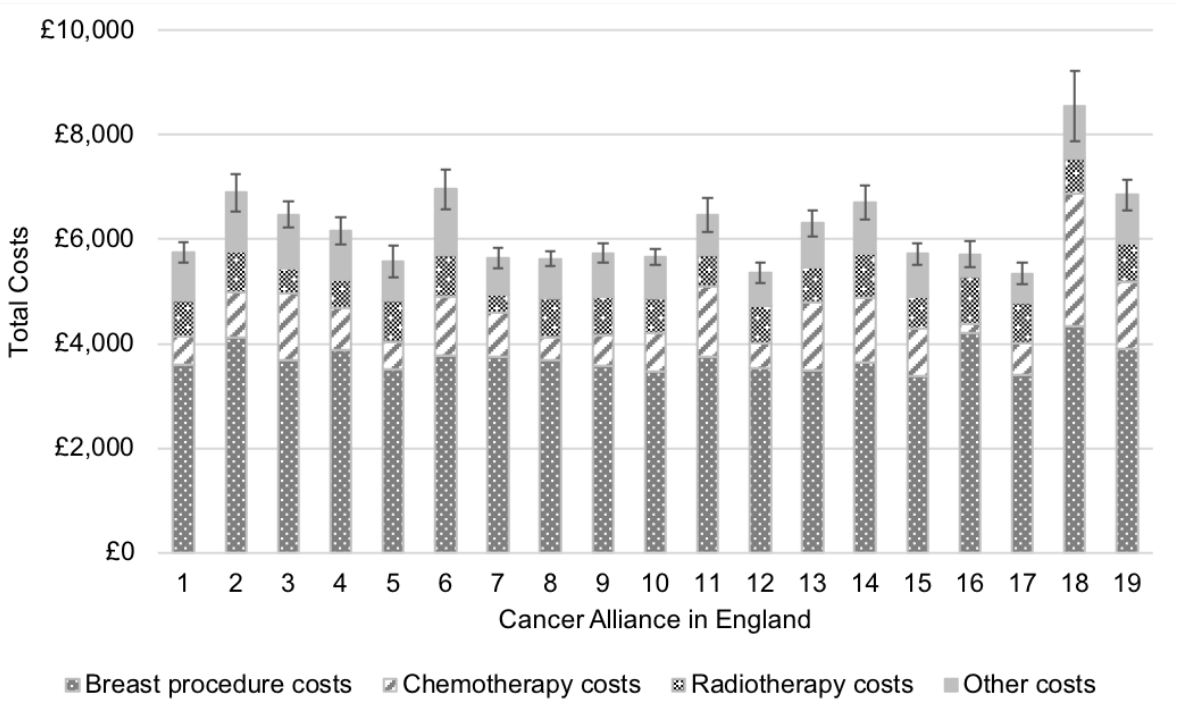

Figure 8-1 Crude costs of first-year primary breast cancer care by region

Regions are numbered from 1 to 19 for North East and Cumbria (6.2% of breast cancer patients diagnosed in this region), Lancashire and South Cumbria (2.8%), Greater Manchester (4.9%), West Yorkshire (4.3%), Humber, Coast and Vale (2.8%), South Yorkshire, Bassetlaw, North Derby (3.2%), Cheshire and Merseyside (5.1%), West Midlands (10.7%), East Midlands (7.2%), East of England (11.7%), Peninsula (3.9%), Somerset, Wiltshire, Avon & Gloucestershire (5.4%), Wessex (5.8%), Thames Valley (4%), Surrey and Sussex (6.3%), Kent and Medway (3.7%), West London (5.4%), South East London (2.2%), and North Central and East London (4.5%). The vertical lines at the top are 95% confidence intervals around the total costs. Alliance 18 is South East London. The variation in total costs of breast cancer care across cancer alliances was driven by all component costs according to one-way analysis of variance (ANOVA) results.

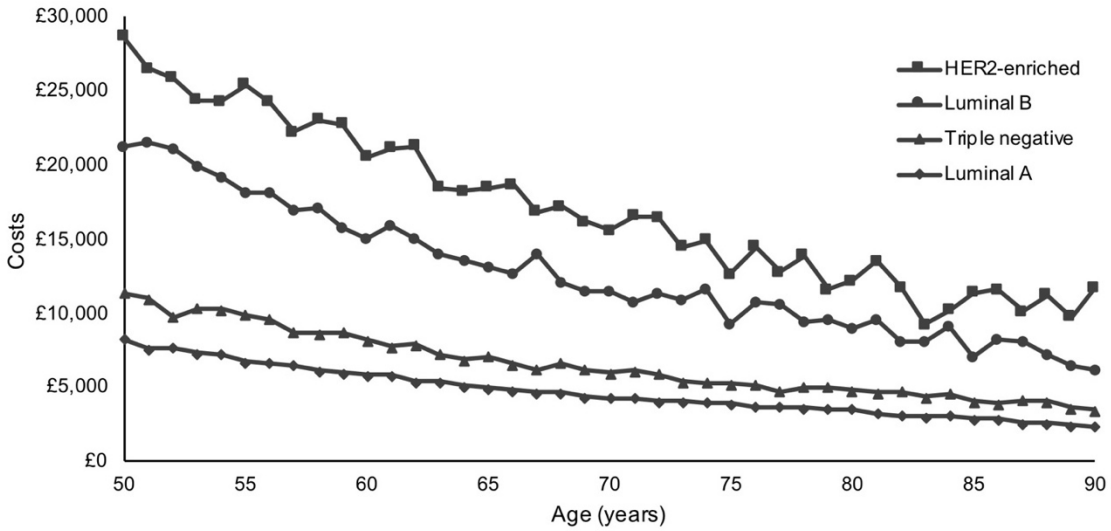

Figure 8-2 Predicted costs of first-year primary breast cancer care by patient subgroups

For patient subgroups with different tumour receptor status, the predicted average costs of primary breast cancer care were £5,082 (S.E. £18) for luminal A patients, £14,439 (S.E. £142) for luminal B patients, £18,949 (S.E. £238) for HER2-enriched patients, and £7,128 (S.E. £55) for triple-negative patients respectively, all decreasing by age with a linear trend.

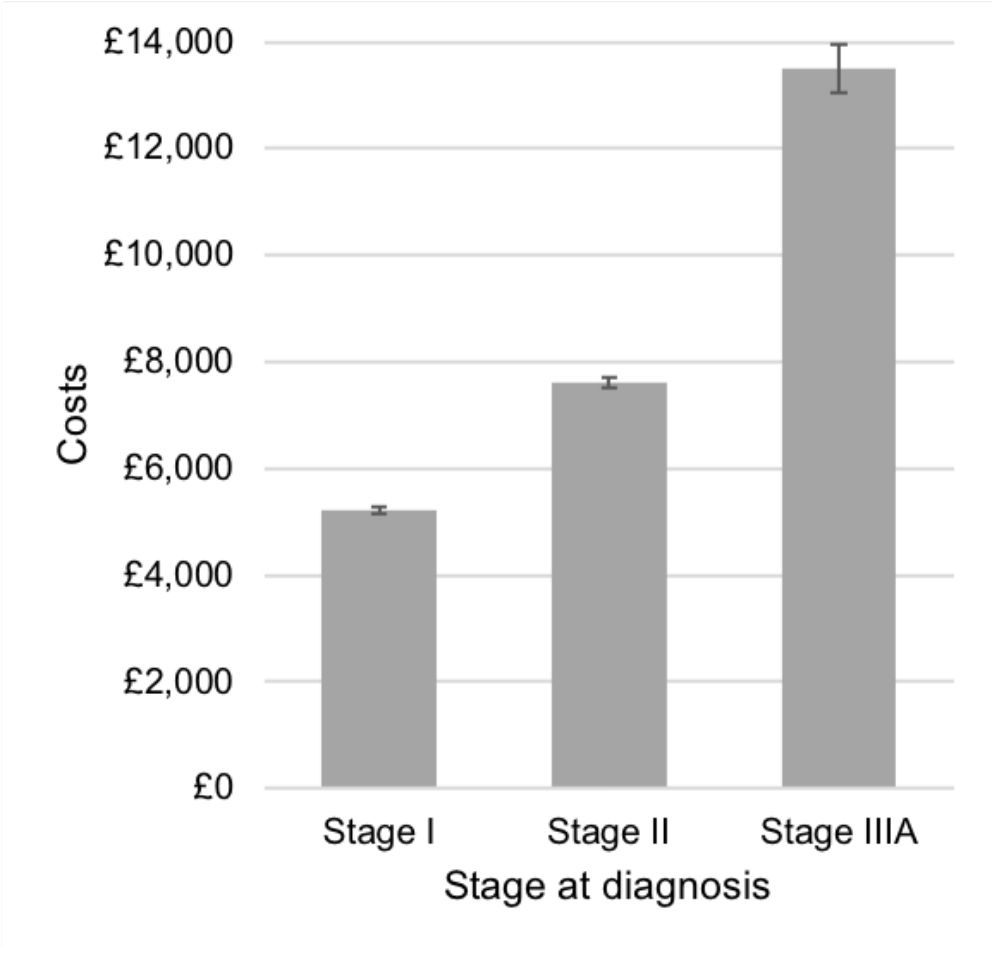

Figure 8-3 Predicted population average costs of first-year primary breast cancer care by stage at diagnosis

We predicted the first-year costs of breast cancer treatment by stage at diagnosis adjusting for age, ethnicity, Charlson Comorbidity Index, Index of Multiple Deprivation, tumour receptor (ER/PR/HER2) status, referral source, and regions. The predicted costs were £5,224 (S.E. £29) at stage I, £7,617 (S.E. £49) at stage II, and £13,506 (S.E. £228) at stage IIIA for the population average. The vertical lines at the top are 95% confidence intervals around the total costs.

F-test showed p-value <0.001.

Chapter 9 Discussion

In this discussion chapter, I first summarise the key findings of my thesis and the implications for policy and practice. Also I reflect on the methodology for breast cancer modelling and costing. Then I discuss the limitations of my thesis and identify the areas for future research. Finally, I draw a number of concluding comments.

9.1 Key findings

The first objective of my thesis was to review the literature and summarise the existing economic evidence on breast cancer screening in LMICs and breast cancer genetic testing in HICs (Chapter 3). Although some studies have been performed in recent years, the cost-effectiveness evidence on the ongoing breast cancer screening pilot programmes in urban and rural China is lacking. This led me to the second objective of this thesis, to conduct economic evaluations of breast cancer screening programmes in urban and rural China.

With regards to economic evidence on breast cancer genetic testing, there is only a recent small Norwegian study (535 patients) showing the cost-effectiveness of BRCA-testing in all breast cancer patients and cascade testing of relatives of index cases based on a decision tree model (21). This led me to the third objective of this thesis, to evaluate the cost-effectiveness of multigene testing all breast cancer patients and cascade testing the relatives of mutation carriers in the UK and US which is both broader in scope in terms of gene types and prevention options, as well as draws on a much larger sample-size of population-based breast cancer patients.

The second objective of the thesis was to evaluate the cost-effectiveness of Chinese urban and rural breast cancer screening pilot programmes compared to no screening. The urban programme screens high-risk women (with a questionnaire-generated risk score greater than the threshold risk) by ultrasound and/followed by mammography (16). I developed a Markov model to estimate the cost-effectiveness, showing that the risk-based screening in urban China was economically attractive with an ICER of US$ 6,645/QALY, well below the threshold of US$ 23,050/QALY (35, 36). One-way and probabilistic sensitivity analyses demonstrated that the results were robust. In the exploration of various scenarios, screening every 3 years was the most cost-effective strategy in urban China (Chapter 4).

The rural programme screened the general population with clinical breast examination coupled with ultrasound as the primary tool (17). The baseline results show that the rural population-based breast cancer screening is cost-effective with an ICER of $6,879/QALY.

However, the cost-effectiveness result is very uncertain in the sensitivity analysis and rural breast screening among the general population could potentially harm women's health due to false positives with the current screening tool. The sensitivity analysis identified utility loss from false positives as the factor that most influenced the results. The lower limit of disutility from false positives at which rural breast cancer screening programme would remain cost-effective at the willingness-to-pay threshold was 0.029 QALYs in the screening year, corresponding to 14.5% quality of life decrement of full health over 0.2 years (Chapter 5).

There are a few reasons that could explain the apparent discrepancies in conclusions between breast cancer screening programmes in urban and rural China. Firstly, the incidence rate of breast cancer in rural China is significantly lower than that in urban China (17.0 vs. 34.3 per 100,000 person-years in 2009) (138). The lower incidence rate results in fewer breast cancer patients detected, thus challenging the utility and cost-effectiveness of screening programmes in such settings. Secondly, screening by clinical breast examination and ultrasound as the primary tool may not be suitable in the rural breast cancer screening programme. Although clinical breast examination has been used in low resource settings, there are no randomised trials providing any evidence of whether clinical breast examination could lead to reductions in breast cancer mortality (170). Also, whilst ultrasound may be better at detecting small invasive breast cancers in women with dense breasts (82-86), 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 (171-174). This leads to lower screening sensitivity and specificity (175), thus against the cost-effectiveness of breast cancer screening among rural Chinese women. Thirdly, the urban programme deploys a risk-stratified screening strategy while the rural programme uses a 'one-size-fits-all' screening approach without individual variation in risk taken into consideration. Tailoring screening to an individual's risk level could improve the efficiency of the screening and reduce its adverse consequences (176-179). Whilst risk-based screening requires additional costs of assessing the risk of all women in the urban screening programme, these could be offset by avoiding some of the costs of biopsy confirmation and disutility from false-positives, thus maintaining the cost-effectiveness of the urban breast cancer screening program.

The third objective was to evaluate the cost-effectiveness of offering multi-gene testing to all breast cancer patients compared to the current practice of family-history/clinical-criteria based genetic (BRCA)-testing in the UK and US. I obtained data on family history from 11,836 population-based BC patients (regardless of family history) recruited to four large research studies in the UK, US, and Australia. I developed a microsimulation model

which could capture individual heterogeneity to estimate the lifetime cost, effects, and cost-effectiveness of unselected BRCA1/BRCA2/PALB2 testing for all breast cancer patients, compared with the current family-history/clinical-criteria based BRCA-testing. The ICERs from a payer perspective (UK £10,646/QALY or US $65,661/QALY) and societal perspective (UK £7,216/QALY or US $61,618 QALY) were well below the cost-effectiveness thresholds in the UK and US, and the results were robust to alternative assumptions considered in extensive sensitivity analyses. The scenario analysis reconfirms the cost-effectiveness of lower (70%) uptake rates of genetic testing by breast cancer patients and their relatives. One year's unselected multi-gene testing can prevent 2,101 breast cancer/ovarian cancer-cases and 633 deaths in the UK; and 9,733 breast cancer/ovarian cancer-cases and 2,406 deaths in the US. Correspondingly, 8 UK/35 US excess heart-disease deaths occur annually. Unselected multi-gene testing provides huge opportunities for preventing breast cancer/ovarian cancer cases and deaths. This conclusion can therefore provide a basis for changing the current guidelines and policy to expand genetic testing to all breast cancer patients (Chapter 6).

The fourth objective of the thesis was to review the literature on treatment costs of breast cancer by stage at diagnosis using patient-level data across countries at different levels of socio-economic development and to identify key methodological differences in costing approaches. Overall, the evidence suggested that the treatment costs of breast cancer generally increased with the advancement of the disease stage at diagnosis. Also, this published systematic review contributed to the scientific body of knowledge on the methodology of breast cancer cost analysis. Most existing studies on costs of breast cancer care used regression frameworks but the choice of regression models was rarely justified. Few studies described key methodological issues including skewness, zero values, censored data, missing data, and the inclusion of control groups to estimate disease-attributable costs (Chapter 7). From the literature, the evidence on breast cancer treatment costs by stage based on patient-level data in the UK is very limited and out-of-date, published 20 years ago (26). This leads me to the fifth objective to use patient-level data to estimate the costs of breast cancer treatment in the UK.

I obtained anonymised patient-level data of 55,662 breast cancer patients from the National Audit of Breast Cancer in Older Patients (NABCOP) project. Patient information is available on a large number of variables such as tumour characteristics, socio-demographic factors, and treatment regimens. I compared different data distributions in the regression model to deal with the cost data issues and the model that best fit the data was selected for the base case analysis based on the model selection criteria. The results show that the costs of breast cancer care increase with more advanced stage at diagnosis. The predicted costs were £5,224 at stage I, £7,617 at stage II, and £13,506

at stage IIIA. This has confirmed the findings in the literature about the significant cost savings if patients with breast cancer are detected earlier. Also breast cancer costs vary by age and region, raising questions about the efficiency and consistency of breast cancer treatment patterns in England. Due to the limited data availability, I only obtained the first-year treatment information of breast cancer patients and cannot estimate the total costs of breast cancer care from diagnosis to death. Therefore, the cost estimates of breast cancer care up to one year after diagnosis using patient-level data did not feed into the economic modelling of genetic testing (Chapter 6) in my thesis. I discussed this in the limitation section (section 9.4).

9.2 Implications for policy and practice

9.2.1 Discrepancy in breast cancer screening between urban and rural China

My studies on the cost-effectiveness of breast cancer screening in rural and urban China can inform whether we should continue the current breast screening policy in China. Risk-based breast cancer screening by ultrasound and/followed by mammography in urban China is economically attractive, while general population-based breast cancer screening with clinical breast examination coupled with ultrasound as the primary tool in rural China reports uncertain cost-effectiveness and could potentially do harm to women's health due to false positives.

In urban China, several challenges can be raised by the implementation of a risk-based screening programme, such as preparing and training the workforce, ensuring equitable access, and having regulatory approvals (180). In China, patients need to pay on average 34% of total medical costs (181); this can limit access to medical treatment for some women who have been diagnosed with breast cancer. Also, not offering screening to women at lower risk may not be acceptable (182) because women have been encouraged to see screening as universally beneficial and reduction in screening could be seen as service rationing (183). It is important to engage the public in decisions about screening programme modification and to communicate clearly the benefits and harms of screening.

In rural China with such low breast cancer incidence, risk-based breast screening could potentially be an option to screen high-risk women instead of the general population. In addition, 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 breast cancer without the usual harms associated with breast screening. In rural China, breast cancer is diagnosed at a later stage (67) and thus survival is poorer (68). 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-organised enough and able to deal appropriately with the symptomatic disease (184). 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 in rural China.

9.2.2 Expanding gene testing to all breast cancer patients

Unselected high-risk multigene-testing for all breast cancer patients is extremely cost-effective compared with the current family-history/clinical-criteria BRCA testing for UK and US health systems. Newly diagnosed breast cancer patients with identified mutations can opt for CPM to reduce the contralateral breast cancer risk. They may also become eligible for novel drugs like PARP-inhibitors and other precision-medicine based therapeutics through clinical trials (185). In addition, unaffected mutation carriers can choose different options to reduce their risks of developing breast cancer or ovarian cancer. We recommend changing the current policy to expand genetic testing to all breast cancer patients in the UK and US settings.

Existing genetic-counselling services running through high-risk cancer-genetics clinics do not have the resources or manpower to deliver unselected genetic-testing for all breast cancer patients due to the large numbers diagnosed annually. Hence, newer 'context-specific' delivery models will be needed for implementing this approach. This may require pre-test counselling to be undertaken by non-genetic clinicians who will need to be trained for this. This approach of 'mainstreaming' genetic-counselling and testing has recently been successfully implemented in ovarian cancer treatment pathways (186, 187). Oncologists, surgeons and clinical nurse-specialists have provided pre-test counselling and genetic-testing (186, 187), with genetic-services focusing on post-test counselling and support for women carrying pathogenic-variants. A similar approach could work for breast cancer patients too. Examples of other delivery options include a genetics-service coordinated nurse-led model (188), a Genetics-Embedded-Model (genetics clinician/counsellor embedded in the cancer clinic) (189, 190) and Telephone-counselling (191-193) or Tele-genetics services (194) for genetic-counselling and testing. Going forward, most clinicians practicing medicine will need an increased understanding of genetics and the ability to counsel patients about this (96, 195). Appropriate clinical decision-support tools can facilitate this transformation. Another potential bottleneck to address is laboratory infrastructure to manage increased sample throughput. The

outcomes of various genetic-testing implementation pathways for breast cancer patients could be evaluated.

9.2.3 Early diagnosis of breast cancer and different treatment patterns

In England, costs of early invasive breast cancer care increased with advancing stage of the disease at diagnosis. Considerable cost savings could be made if patients with breast cancer were detected and treated earlier. This also supports the future assessment of the cost-effectiveness of breast cancer screening interventions.

My study revealed a non-standard approach to breast cancer management for patients across age and regions. Clinical guidelines emphasise that breast cancer treatment should be based on clinical need and fitness for treatment rather than chronological age (98, 161, 162). Chronological age should not be a dominant factor in the decision to offer a particular treatment. In England, older patients were shown to incur lower costs of breast cancer care than younger patients. The different patterns of resource utilisation might be a reason why the survival of older breast cancer patients in the UK and Ireland was particularly low compared to other European countries (143). Also, costs of breast cancer care varied across regions within England, raising questions about the efficiency and consistency of breast cancer treatment patterns in England. Nonetheless, differences in the patterns of care among patients may arise for various reasons, including unmeasured differences in the disease nature, differences in the prevalence and severity of comorbidities and frailty that may contraindicate breast cancer treatments (e.g. surgery, chemotherapy or radiotherapy), differences in patient preferences and cultural attitudes, and different levels of involvement in the decision making process (145). These factors need to be taken into consideration when we explore unequal access to breast cancer care among patients in England.

9.3 Reflection on methodology for modelling and costing

9.3.1 Markov model of breast cancer screening

There was only one previously published Markov model of breast cancer screening specifically for Chinese women (196). This model assumed that breast cancer-related deaths only occurred among patients in stage IV, which may lead to biased transition probabilities. I adapted this model to make the model estimates more reliable in China. In my model, patients at different stages could die from breast cancer with different fatality rates. I modelled the cost-effectiveness of breast cancer screening compared with no screening, where breast cancer in the non-screening arm can only be diagnosed on presentation of symptoms. One issue is the lack of data on transition probabilities for China. Transition probabilities data are generally difficult to get and in this study I obtained the data from the literature and explored the uncertainty in the sensitivity

analyses. In addition, the probabilities of presenting symptoms by stage were not available from the literature. To help with this problem, I estimated the probability of presenting symptoms by stage via model calibration, using the distribution of incidence cases reported in an unscreened population based on the Chinese Cancer Registry Annual Report 2012 (138). The predicted breast cancer incidence by my Markov model fits with the real disease incidence in China. Therefore, the updated breast cancer screening model in my thesis reflects the disease natural history better and the transition probabilities are more applicable to the Chinese population (Chapter 4 & 5). However, I assumed the probabilities of presenting symptoms by stage in rural China were the same as the values in urban China, which may limit the accurate estimates of transition probabilities of disease progression in rural areas. Another limitation of my model is that transitions across more than one stage within one year were not allowed with an annual transition. Although breast tumours grow gradually, the progression could be sufficiently rapid so tumours progress through more than one stage within a year. Not allowing transitions across more than one stage in the presence of rapidly progressing tumours indicates the assumption of a slower progression rate in the model. This could lead to biased estimates of transition probabilities and deserves careful considerations.

9.3.2 Microsimulation model of breast cancer genetic testing

There was only one Norwegian study (535 patients) showing the cost-effectiveness of BRCA-testing all breast cancer patients and cascade testing of relatives of index cases (21). They used a decision tree to compare testing all breast cancer patients with the traditional family history-based approach, which was limited by not allowing the patient variability in age and prevention options. In my thesis I developed an individual-level microsimulation model of breast cancer genetic testing from scratch which has a few advantages over cohort-based models.

Microsimulation models permit individual differences in age and gene mutation type among breast cancer patients and relatives of index cases, which could impact the transition probabilities in the pathways through the model. I used the very large trial numbers in the microsimulation model to get robust and consistent results. In the microsimulation model, I ran 269,884 simulations (54,483 patients and 215,401 relatives) for the UK analysis and 1,236,220 simulations (242,463 patients and 993,757 relatives) for the US analysis. Gene types and age were assigned to breast cancer patients and relatives based on the corresponding distributions. In addition, the microsimulation model can track individual patient history if the memory of events impacts future cycles. In my model, breast cancer patients with BRCA/PALB2 mutations can choose CPM to reduce contralateral breast cancer risk and RRSO (BRCA only) to reduce ovarian cancer risk. Among relatives of index cases, unaffected BRCA/PALB2 mutation carriers can

choose RRM/chemoprevention to reduce breast cancer risk and RRSO (BRCA only) to reduce ovarian cancer risk. These risk-reducing options can be tracked in the microsimulation model, impacting their probability of developing breast cancer or ovarian cancer in future cycles.

9.3.3 Model validation

In Chapter 4 and Chapter 5, I adapted Markov models using data from the screening programmes that provided costs and quality of life of breast cancer patients by stage at diagnosis to inform the process of breast cancer screening. In Chapter 6, I established the microsimulation model using data from four large research studies that provided age and family history data of breast cancer patients to inform the process of unselected genetic testing and clinical-criteria/family history based testing. Internal Validation of the models was undertaken through a process of Descriptive Validity, Technical Validity and Face Validity (197).

Descriptive Validity- the models provide adequate pictures of clinical reality. The models cover all relevant aspects and do not miss any aspects that could alter its results and conclusions significantly. The data and the model structures were reviewed by national/international breast cancer clinical, epidemiological, and health economic experts to provide adequate pictures of models of breast cancer screening and genetic testing.

Technical Validity/Verification- I undertook a process of internal validation to ensure the model's proper functioning. This included debugging where needed and calibration to check the consistency of the model with observable data. Also in Chapter 6, I used the very large trial numbers in the microsimulation model to get robust and consistent results. In the microsimulation model, I run 269,884 simulations (54,483 patients and 215,401 relatives) for the UK analysis and 1,236,220 simulations (242,463 patients and 993,757 relatives) for the US analysis. Gene types and ages were assigned to breast cancer patients and relatives based on the corresponding distributions.

The model's technical functioning was also tested by extensive sensitivity analyses. Extreme values of the input variables were used, and the model's actual outputs were compared with expected outcomes. In Chapter 4 and Chapter 5, when assuming zero uptake rate of screening, the intervention arm and the comparator arm calculated the same outcomes. In Chapter 6, when assuming zero uptake rate of genetic testing, the unselecting testing arm and the clinical-criteria/family history based testing arm calculated the same outcomes. Moreover, I examined the individual impact on results of each parameter in the one-way sensitivity analysis and explored various scenarios such

as less frequent screening and lower uptake rate of treatment in the breast cancer screening models, and increased counselling costs, no HRT compliance after RRSO, increased age for RRM/RRSO in the genetic testing microsimulation model. The direction of changes in health effects and/or costs were all in line with expectations.

Face Validity was confirmed through the model producing outputs that were consistent with the theoretical basis of the disease and the medical interventions undertaken.

A limitation of model validation is that the predictive validity of breast cancer screening and genetic testing models was not able to be tested, which relates the modelling results to real-life outcomes. Up to now there have been no available outcomes reported from the urban or rural screening programme in China. Also the real-life outcomes of unselected multi-gene testing for all breast cancer patients in the UK and US are unknown. Tests of predictive validity are only possible if the modelled situation is observable and measurable.

9.3.4 Costing methodology

Health care cost data typically have some key statistical features. First, the distributions display substantial skewness usually with long right-hand tails. Second, their distributions may have a substantial point mass at zero (158). Moreover, there are issues of heteroskedastic errors and non-linear responses to covariates due to the implicit underlying data-generating process (159). Although ordinary least squares (OLS) has been widely used in regression models, it ignores the skewness and therefore is not appropriate in cost analysis. One classic econometric approach to deal with skewness is logarithmic transforming the data to an approximately normal distribution. However, transforming the data is not favoured due to back-transformation problems (60). The arithmetic mean cost is the parameter of interest, and retransforming costs to the natural scale requires difficult calculations, particularly when there is heteroskedasticity (198).

I used a generalised linear model (GLM) to analyse the cost data. This allowed me to model costs directly on the scale of interest and allowed for forms of heteroskedasticity (199). GLMs comprise a link function, which determines the relationship between a linear index of covariates and the mean, and a distribution function, which determines the relationship between the mean and the variance (198). Typically, a log-link function with a Gamma distribution fits the health care costs well (158). However, there is no evidence that this is the dominant form of GLM in terms of model fit for cost data applications (160). I compared the models checking distributions of normal, log-normal, and log-gamma respectively. The model that best fitted the data would be selected using the model selection criteria of Akaike information criterion (AIC). AIC estimates the relative amount

of information lost by a given model. The preferred model is the one with the minimum AIC values.

Based on the systematic review in Chapter 7 which identified the methodological differences in breast cancer costing approaches, most studies used regression frameworks but the choice of regression models was rarely justified. Few studies described key methodological issues including skewness, zero values, censored data, missing data, and the inclusion of control groups to estimate disease-attributable costs. This suggests that methodological issues should be better handled and properly described in future costing studies. My study has justified the choice of regression models and provided evidence to further understanding of cost analysis methodology to deal with data issues. In further research, I could use multiple imputation to impute the missing data.

9.4 Limitations

The first limitation is the uncertainty of disutility from false-positive breast cancer screening results among Chinese women. Although the concerns about false-positive breast cancer screening are justified, the decrements in health-related quality of life are still controversial (122). Some argue that pathologically elevate levels of distress and anxiety are not apparent (200), but the relatively small number of studies means that the long-term effects of false-positive breast cancer screening are still unknown (200). In this analysis, I used the estimate from the UK studies (132, 133) which might bias the cost-effectiveness results of breast cancer screening in China. If we were to assume the false-positive screening results do not affect a woman's quality of life, the results in urban China proved to be robust while breast cancer screening in rural China would achieve an ICER below the threshold. This deserves careful consideration and further research on disutility from false-positives in China is required to reduce uncertainty. In addition, duration between getting a positive screening result and undertaking a biopsy test for diagnostic confirmation is very likely to be much shorter than one year. As the relevant data is lacking in China, future research needs to be conducted to estimate the duration between false-positive screening results and biopsy tests, as well as to explore the fluctuations in the quality of life in terms of timing of assessment after false-positive results.

Second, there are different types of breast cancer and therefore the biology of breast cancer may be heterogeneous in the natural history Markov model. 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. In addition, some tumours may grow so slowly (or even not at all) that if they

went undetected they would never cause symptoms or people would die from another cause before breast cancer presented. The problem is that when these types of cancer are diagnosed early, it is very difficult to tell the potentially harmful ones from the harmless ones, and therefore everyone is then offered treatment. Ideally, RCTs should be conducted to evaluate the benefits and harms of the breast cancer screening programmes and the time horizon should be long enough to capture differences in long-term health outcomes including mortality. To our knowledge no such RCTs have been conducted or are ongoing in rural China. Therefore, in the absence of evidence from RCTs, I adopted a Markov natural history model to evaluate the cost-effectiveness of breast cancer screening in China. If more data on the biology of breast cancer and disease progression are available, model structure uncertainty could be explored in future studies with the heterogeneous breast cancer biology taken into consideration.

Third, the thesis is limited by the lack of data on the differences in the treatment costs of breast cancer between Chinese urban and rural patients. I obtained the costs of breast cancer treatment by stage at diagnosis from a study enrolling 2,746 patients from 37 hospitals across 13 provinces in China. However, the treatment costs incurred by rural and urban patients with breast cancer may be different. Rural residents in China with severe diseases tend to seek the secondary or tertiary level of medical treatment in urban hospitals (201). Since they usually need to travel further to reach the hospitals, the direct non-medical costs including transport costs might be underestimated in this study. In addition, the rural-urban differences have been observed in the choice of neo-adjuvant chemotherapy and surgical procedures (202). Rural patients with breast cancer also tend to have worse adherence to adjuvant treatment, which is strongly associated with recurrence (203). These factors could result in differences in the direct medical costs between urban and rural patients. The sensitivity analysis proves that the results are quite robust when the treatment costs are varied up and down by 30%, but the impact of cost variations on the overall results could be further explored if more detailed evidence is available on the treatment costs of urban and rural patients.

Fourth, the baseline microsimulation model of genetic testing assumes all breast cancer women and unaffected relatives undergo genetic-testing. While very-high (up-to 98%) genetic-testing rates are reported in unselected genetic-testing at ovarian cancer diagnosis, corresponding genetic-testing uptake data in unselected breast cancer patients are not well-established. To explore the model structure uncertainty, I conducted a scenario analysis at lower (70%) uptake rates and the results reconfirmed the cost-effectiveness of genetic testing in breast cancer patients and relatives of index cases.

Fifth, I used three times the Chinese GDP per capita ($23,050/QALY) as the China WTP threshold recommended by the WHO (35), £30,000/QALY as the UK WTP threshold recommended by the NICE guideline (30), and $100,000/QALY as the US WTP often cited in the literature (34). However, these thresholds have little theoretical justification. WTP thresholds should be based on estimates of the forgone benefit associated with alternative priorities which consequently cannot be implemented as a result of the commitment of resources to an alternative. Woods et al. estimated WTP thresholds for a number of countries based on recent empirical estimates of foregone benefits and internal income elasticities of the value of health (204). The WTP thresholds were reported to be $7,957/QALY in China, $18,607/QALY in the UK, and $40,112/QALY in the US respectively, which are much lower than those posited by WHO or NICE. Therefore, the cost-effectiveness of breast cancer screening and genetic testing strategies evaluated in my thesis may be overestimated and might be ruled out based on these thresholds. However, Woods suggested these WTP thresholds are not definitive; rather, further research needs to be provoked in the area of crucial policy importance and outlines how more robust estimates could be generated. In addition, even if estimated accurately, WTP thresholds do not provide information on affordability, budget impact or the feasibility of implementation. Although cost-effectiveness ratios are informative in assessing value for money, WTP thresholds should therefore not be used alone as a decisions rule for priority setting. Local policy context needs to be considered (205) and multiple-criteria decision analysis could be applied to inform decision-making (206).

Lastly, the cost estimates of breast cancer care using patient-level data in Chapter 8 did not feed into the economic modelling of genetic testing in Chapter 9. Ideally, the estimated breast cancer costs based on patient-level would inform the model inputs with sampling uncertainty captured. Unfortunately, due to limited data availability, I only obtained treatment information of breast cancer patients in the first year after diagnosis and therefore the full costs of breast cancer care cannot be estimated from diagnosis until death. Instead, I estimated the total costs of breast cancer care based on the clinical guidelines as the input to the economic model. Also I varied the cost estimates by +/-30% in the one-way sensitivity analysis and specified the costs as a Gamma distribution in the probabilistic sensitivity analysis to explore the uncertainty. If long-term treatment information was available among breast cancer patients, I would be able to compare estimating breast cancer care costs using patient-level routine data with using clinical guidelines. Also I would explore whether using cost estimates with patient-level routine data would change the cost-effectiveness results in the economic evaluation. In addition, treatment costs could ideally be split between initial treatment costs and recurrent costs.

However, in this analysis we were not able to distinguish recurrent costs from initial treatment costs. This could be a limitation of this study and deserves careful considerations.

9.5 Areas of further research

9.5.1 Disutility from false-positives to inform the economic evaluation of breast cancer screening

The current economic evaluation of breast cancer screening in China is limited by the lack of data on disutility from false-positive screening results among Chinese women. Although I explored the uncertainty in the one-way and probabilistic sensitivity analyses, the real effects of false-positive breast cancer screening on Chinese women's health are still unknown (122, 200). Further studies could be undertaken to explore the decrements in health-related quality of life due to false-positive breast cancer screening among Chinese women to reduce uncertainty. I would use EQ-5D questionnaires to measure the quality of life among Chinese women attending breast cancer screening with positive results and explore the durations between false-positive screening results and biopsy tests for diagnostic confirmation. As the timepoints of assessment are likely to influence the overall health-related quality of life decrements, I would be able to capture the fluctuation in the quality of life and the duration of disutility from false-positives to get more robust results.

9.5.2 Modelling on unselected gene testing to patients in China

Unselected multi-gene testing for all breast cancer patients can substantially reduce future breast cancer-&-ovarian cancer cases and deaths compared with the current clinical-strategy. My analysis suggests that an unselected-testing strategy is cost-effective for UK and US health-systems from both payer and societal perspectives. This provides a basis for expanding the study population to other countries. In China, the effectiveness and cost-effectiveness of unselected multi-gene testing for breast cancer patients have never been evaluated before. I could for the first time provide the economic evidence on unselected multigene testing among Chinese women diagnosed with breast cancer.

I have already developed a microsimulation model for the cost-effectiveness of multi-gene genetic testing in the UK/USA. The model would be adjusted/adapted for the Chinese evaluation by using Chinese data on parameter inputs supplemented with appropriate data from the international literature. As an example, Chinese family structures vary significantly from the UK especially reflecting the one-child policy in China (which has now been changed). I would utilise Chinese national statistics to explore the numbers of female relatives that would need to be tested as this would be very different

from the UK setting. Also we have got access to the Chinese Urban Basic Medical Insurance Database. I would use the 'big data' to analyse the treatment costs of breast cancer in China and explore the regional variations in costs.

Uncertainties would be explored through extensive one-way and probabilistic sensitivity analysis. I would also explore the cost-effectiveness at different genetic testing costs and the threshold to which the cost of genetic testing must fall in order for the policy to be cost-effective. As the willingness to pay (WTP) threshold is not clear in China, I would explore the probability of genetically testing all breast cancer patients being cost-effective across a range of different WTP thresholds. All these analyses would be conducted across regions to explore differences with regional variation. In addition, I would conduct the budget impact analysis to estimate the likely change in expenditures to the budget holder resulting from offering genetic testing to breast cancer patients. This modelling work would inform the potential cost-effectiveness of genetic testing for breast cancer in China and also provide much needed direction on further research that needs to be conducted in this field and the factors driving the uncertainty.

9.5.3 Further analysis of breast cancer costs

As I only obtained the first-year treatment information of breast cancer patients from the National Audit of Breast Cancer in Older Patients (NABCOP) project, the cost estimates of breast cancer care using patient-level data (Chapter 8) did not feed into the economic modelling of genetic testing (Chapter 6) in my thesis. If long-term treatment information is available in the future, I would be able to estimate the lifetime costs of breast cancer care and explore whether using cost estimates with patient-level routine data would change the cost-effectiveness results in the economic evaluation. Also, I conducted the complete case analysis using only data from patients for whom all variables involved in the analysis were observed. In future study, I could use multiple imputation to impute the missing data.

In addition, using the patient-level I would be able to match patients who were diagnosed with the same stage but had different treatment options. As the datasets have been linked to ONS Death Register, I could also conduct survival analyses and investigate the impact of patient characteristics on survival using regression modelling. This provides me an opportunity to compare both cost and survival among patients diagnosed at the same stage receiving different treatment, thus to inform the cost-effectiveness analysis of stage-specific breast cancer therapies. In Chapter 8, the study population was restricted to breast cancer patients diagnosed between 01 January 2014 and 31 December 2015 and the data was available up to 31 December 2016 so that no patients were censored in the current analysis of one-year breast cancer costs. Future research

could take censored data into consideration to predict two-year breast cancer costs, using principled methods for censored adjusted analysis (166-168).

9.6 Concluding comments

In urban China, risk-based screening for breast cancer is very likely to be cost-effective. But in rural China, breast screening among the general population reports uncertain cost-effectiveness and could potentially harm women's health due to false positives with the current screening tools. In a rural setting with such low breast cancer incidence, 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.

Unselected panel genetic-testing for all breast cancer patients is extremely cost-effective compared to the current practice of family-history/clinical-criteria based genetic (BRCA)-testing for both UK and US health systems. This supports changing the current policy to expand genetic-testing to all women with breast cancer.

Costs of breast cancer care increased with increasing stage of the disease at diagnosis in England. Considerable cost savings could be made if breast cancer was detected and treated earlier. Variations in breast cancer costs by age and region raise questions about the efficiency and consistency of breast cancer treatment patterns in England.

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Appendices

Appendix-1 Relationship between breast cancer FIGO staging and TNM classification

FIGO Stage	T	N	M
0	Tis	N0	M0
IA	T1	N0	M0
IB	T0	N1mi	M0
	T1	N1mi	M0
IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

In the TNM staging system for breast cancer, Tumour (T) describes the size of the tumour, Node (N) describes whether the cancer has spread to the lymph nodes, and Metastasis (M) describes whether the cancer has spread to a different part of the body.

Tis means ductal carcinoma in situ (DICS).

T1 means that the tumour is 2 centimetres (cm) across or less.

T2 means that the tumour is more than 2 centimetres but no more than 5 centimetres across.

T3 means the tumour is bigger than 5 centimetres across.

T4 is divided into four groups: T4a means the tumour has spread into the chest wall (the structures surrounding and protecting the lungs); T4b means the tumour has

spread into the skin and the breast might be swollen; T4c means the tumour has spread to both the skin and the chest wall; T4d means inflammatory carcinoma – this is a cancer in which the overlying skin is red, swollen and painful.

N0 means there are no cancer cells in any nearby nodes.

N1 means cancer cells are in the lymph nodes in the armpit but the nodes are not stuck to surrounding tissues.

N2 is divided into 2 groups: N2a means there are cancer cells in the lymph nodes in the armpit, which are stuck to each other and to other structures; N2b means there are cancer cells in the lymph nodes behind the breast bone (the internal mammary nodes), which have been seen on a scan or felt by the doctor. There is no evidence of cancer in lymph nodes in the armpit.

N3 is divided into 3 groups: N3a means there are cancer cells in lymph nodes below the collarbone; N3b means there are cancer cells in lymph nodes in the armpit and behind the breastbone; N3c means there are cancer cells in lymph nodes above the collarbone.

M0 means that there is no sign that the cancer has spread.

M1 means the cancer has spread to another part of the body.

Appendix-2 Search Strategy – MEDLINE and EMBASE (Ovid: Jan 2013 to Mar 2019)

	Searches	Results - MEDLINE	Results - EMBASE
1	Breast cancer or breast tumor or breast tumour or breast neoplasm or mammon cancer or mammo tumor or mammo tumour or mammo neoplasm	219218	510212
2	exp Breast Neoplasms/	273043	505250
3	1 or 2	310539	554987
4	exp Cost-Benefit Analysis/	75610	80246
5	econom* adj3 evaluation*	9869	23978
6	(cost* adj3 effective*) or (cost* adj3 benefit*) or (cost* adj3 utilit*) or willingness to pay or net benefit*	155879	312712
7	4 or 5 or 6	158866	322330
8	3 and 7	3334	8462
9	Developing Countries.sh,kf.	82257	21
10	(Africa or Asia or Caribbean or West Indies or South America or Latin America or Central America).hw,kf,ti,ab,cp.	225286	330203
11	(Afghanistan or Albania or Algeria or Angola or Antigua or Barbuda or Argentina or Armenia or Armenian or Aruba or Azerbaijan or Bahrain or Bangladesh or Barbados or Benin or Byelarus or Byelorussian or Belarus or Belorussian or Belorussia or Belize or Bhutan or Bolivia or Bosnia or Herzegovina or Hercegovina or Botswana or Brasil or Brazil or Bulgaria or Burkina Faso or Burkina Fasso or Upper Volta or Burundi or Urundi or Cambodia or Khmer Republic or Kampuchea or Cameroon or Cameroons or Cameron or Camerons or Cape Verde or Central African Republic or Chad or Chile or China or Colombia or Comoros or Comoro Islands or Comores or Mayotte or Congo or Zaire or Costa Rica or Cote d'Ivoire or Ivory Coast or Croatia or Cuba or Cyprus or Czechoslovakia or Czech Republic or Slovakia or Slovak Republic or Djibouti or French Somaliland or Dominica or Dominican Republic or East Timor or East Timur or Timor Leste or Ecuador or Egypt or United Arab Republic or El Salvador or Eritrea or Estonia or Ethiopia or Fiji or Gabon or Gabonese Republic or Gambia or Gaza or Georgia Republic or Georgian Republic or Ghana or Gold Coast or Greece or Grenada or Guatemala or Guinea or Guam or Guiana or Guyana or Haiti or Honduras or Hungary or India or Maldives or Indonesia or Iran or Iraq or Isle of Man or Jamaica or Jordan or Kazakhstan or Kazakh or Kenya or Kiribati or Korea or Kosovo or Kyrgyzstan or Kirghizia or Kyrgyz Republic or Kirghiz or Kirgizstan or	2977827	4106070

	Lao PDR or Laos or Latvia or Lebanon or Lesotho or Basutoland or Liberia or Libya or Lithuania or Macedonia or Madagascar or Malagasy Republic or Malaysia or Malaya or Malay or Sabah or Sarawak or Malawi or Nyasaland or Mali or Malta or Marshall Islands or Mauritania or Mauritius or Agalega Islands or Mexico or Micronesia or Middle East or Moldova or Moldovia or Moldovian or Mongolia or Montenegro or Morocco or Ifni or Mozambique or Myanmar or Myanma or Burma or Namibia or Nepal or Netherlands Antilles or New Caledonia or Nicaragua or Niger or Nigeria or Northern Mariana Islands or Oman or Muscat or Pakistan or Palau or Palestine or Panama or Paraguay or Peru or Philippines or Philipines or Phillipines or Phillippines or Poland or Portugal or Puerto Rico or Romania or Rumania or Roumania or Russia or Russian or Rwanda or Ruanda or Saint Kitts or St Kitts or Nevis or Saint Lucia or St Lucia or Saint Vincent or St Vincent or Grenadines or Samoa or Samoan Islands or Navigator Island or Navigator Islands or Sao Tome or Saudi Arabia or Senegal or Serbia or Montenegro or Seychelles or Sierra Leone or Slovenia or Sri Lanka or Ceylon or Solomon Islands or Somalia or South Africa or Sudan or Suriname or Surinam or Swaziland or Syria or Tajikistan or Tadzhikistan or Tadjikistan or Tadzhik or Tanzania or Thailand or Togo or Togolese Republic or Tonga or Trinidad or Tobago or Tunisia or Turkey or Turkmenistan or Turkmen or Uganda or Ukraine or Uruguay or USSR or Soviet Union or Union of Soviet Socialist Republics or Uzbekistan or Uzbek or Vanuatu or New Hebrides or Venezuela or Vietnam or Viet Nam or West Bank or Yemen or Yugoslavia or Zambia or Zimbabwe or Rhodesia).hw,kf,ti,ab,cp.		
12	((developing or less* developed or under developed or underdeveloped or middle income or low* income or underserved or under served or deprived or poor*) adj (countr* or nation? or population? or world)).ti,ab.	73390	112771
13	((developing or less* developed or under developed or underdeveloped or middle income or low* income) adj (economy or economies)).ti,ab.	368	621
14	(low* adj (gdp or gnp or gross domestic or gross national)).ti,ab.	208	329
15	(low adj3 middle adj3 countr*).ti,ab.	8800	14186
16	(lmic or lmics or third world or lami countr*).ti,ab.	4844	7444
17	transitional countr*.ti,ab.	131	217
18	or/9-17	3104135	4299459
19	8 and 18	308	989

20	Exp Mass Screening/	119703	224541
21	Screening.mp.	484160	975880
22	20 or 21	493005	976626
23	19 and 22	135	331
24	Limit 23 to yr="2013-2019"	52	176

Appendix-3 Search Strategy – MEDLINE and EMBASE (Ovid: Jan 2015 to Mar 2019)

	Searches	Results - MEDLINE	Results - EMBASE
1	Breast cancer or breast tumor or breast tumour or breast neoplasm or mammon cancer or mammo tumor or mammo tumour or mammo neoplasm	219218	510212
2	exp Breast Neoplasms/	273043	505250
3	310539	310539	554987
4	exp Cost-Benefit Analysis/	75610	80246
5	econom* adj3 evaluation*	9869	23978
6	(cost* adj3 effective*) or (cost* adj3 benefit*) or (cost* adj3 utilit*) or willingness to pay or net benefit*	155879	312712
7	4 or 5 or 6	158866	322330
8	3 and 7	3334	8462
9	Exp Genetic Testing/	42137	75324
10	Genetic testing.mp.	41928	29198
11	9 or 10	49397	84107
12	8 and 11	141	321
13	Exp patients/	59408	2643369
14	12 and 13	0	75
15	limit 12 to yr="2015-2019"	0	26

Appendix-4 Summary of crude costs of breast cancer care (GBP in 2016 values) – mean (standard error)

Cost categories	**All (n=55,662)**	**Stage I (n=28,232)**	**Stage II (n=24,358)**	**Stage IIIA (n=3,072)**
Diagnosis and procedure costs	3,659 (2,716)	3,366 (2,376)	3,831 (2,966)	4,998 (3,045)
Chemotherapy costs	837 (2,536)	437 (1,966)	1,141 (2,867)	2,097 (3,480)
Radiotherapy costs	689 (2,055)	341 (911)	815 (2,300)	2,892 (4,572)
Endocrine therapy costs	34 (19)	35 (18)	33 (20)	32 (20)
Targeted therapy costs	782 (2,973)	535 (2,484)	993 (3,317)	1,392 (3,857)
Total costs	6,002 (6,576)	4,714 (5,078)	6,812 (7,261)	11,412 (8,881)

Appendix-5 Results for first-year total costs of breast cancer care of alternative models – co-efficient (standard error)

Variables	OLS	Log-Normal	Log-Gamma
Stage II	2,002 (79)***	1,923 (70)***	2,031 (71)***
Stage IIIA	5,995 (159)***	4,683 (133)***	6,704 (256)***
Age	-160 (4)***	-145 (3)***	-192 (4)***
Ethnicity - Asian	-391 (227)	-319 (176)	-345 (201)
Ethnicity - Black	533 (305)	-432 (198)*	379 (300)
Ethnicity - other	307 (294)	120 (216)	50 (276)
Charlson score 1	-453 (126)***	-573 (119)***	-624 (110)***
Charlson score 2	-1,501 (208)***	-1,759 (213)***	-1,828 (147)***
Charlson score 3	-1,856 (288)***	-3,137 (328)***	-3,430 (142)***
IMD 2	305 (130)*	373 (108)**	204 (117)
IMD 3	374 (127)**	353 (106)**	368 (115)**
IMD 4	443 (125)***	398 (105)***	488 (114)***
IMD 5 – least deprived	599 (124)***	601 (104)***	572 (114)***
ER Negative	1,052 (126)***	543 (89)***	1,352 (129)***
ER Borderline	1,232 (1,519)	213 (835)	2,252 (1,818)
PR Negative	801 (106)***	871 (85)***	873 (102)***
PR Borderline	428 (801)	335 (624)	-41 (706)
HER2 Negative	-9,072 (112)***	-8,281 (107)***	-8,162 (195)***
HER2 Borderline	-7,645 (193)***	-6,716 (191)***	-6,927 (244)***
Screen-detected	-339 (84)***	-69 (71)	-155 (76)*
Region	***	***	***
Region × Stage	***	***	***

***p<0.001, **p<0.01, *p<0.05