Cost Effectiveness Analysis of a Polygenic Risk Tailored Breast Cancer Screening Programme in Singapore

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Abstract

Background

This study aimed to evaluate the cost effectiveness of a breast cancer screening programme that incorporates genetic testing using breast cancer associated single nucleotide polymorphisms (SNPs) in Singapore, against the current biennial mammogram only screening programme.

Methods

A Markov model was used to compare the costs and health outcomes of the current screening programme, against a polygenic risk tailored screening programme that advises long term screening depending polygenic risk. The model took the perspective of the healthcare system, with a time horizon of 40 years, following women from the age of 35 to 74. Epidemiological and cost data was taken from Asian studies. An annual discount rate of 3% was used. The model outcome was the incremental cost-effectiveness ratio (ICER), calculated from the difference in costs per quality adjusted life year (QALY). Scenarios with varying risk thresholds for each polygenic risk group were examined. One-way and probabilistic sensitivity analyses were performed to assess parameter uncertainty.

Results

The ICER for a polygenic risk tailored breast cancer screening programme, compared to the current biennial mammogram only screening programme, was -3,713.80, with incremental costs <0 and incremental effects >0. Scenario analysis of different polygenic risk cutoffs showed that the ICERs remain negative, with all ICERs falling within the south east quadrant of the cost effectiveness plane, indicating that tailored screening dominates mammogram only screening with lower costs and higher QALYs. This suggests that a polygenic risk tailored breast cancer screening programme is cost effective, being cheaper than the current mammogram only programme while bringing no additional harm to women.

Conclusion

Results from this cost effectiveness analysis show that polygenic risk tailored screening is cost effective with an ICER of –3,713.80 SGD/QALY. Tailored screening remains cost effective even when varying percentile cutoffs for each risk group. While the results look promising for incorporating polygenic risk into the current breast cancer screening programme, further studies should be conducted due to various limitations.

Background

Breast cancer is the most prevalent cancer among women globally. In 2018 alone, approximately two million new cases of breast cancer were diagnosed, accounting for 11.6% of all cancers, while also resulting in more than 626,000 deaths [1]. In Singapore, breast cancer is also the most common cancer among women, accounting for 29.1% of all cancer diagnoses. The incidence rate of breast cancer has been steadily increasing and has almost tripled from 24.6 per 100,000 person-years in 1976 to 65.3 per 100,000 person-years in 2011–2015 [2]. In the 5-year period of 2011–2015, a total of 9,634 new cases of breast cancer were diagnosed. In comparison, there were 3,136 new cases of breast cancer in 2018 alone [3]. Furthermore, breast cancer is consistently the cancer type with the highest number of fatalities, accounting for 2,105 women in the period of 2011–2015 [2]. The survival rates of women diagnosed with stage IV breast cancer are also much lower compared to the survival rates of those diagnosed at the earlier stages. Hence, it is imperative that a screening programme takes into account all these factors and screens for breast cancer promptly and effectively.

Early detection is vital in improving breast cancer mortality and outcomes in patients. In Singapore, the BreastScreen Singapore programme was established in 2002 by the Health Promotion Board and has promoted the early detection of breast cancer to improve mortality rates [4–5]. Singapore adopts an age-based screening approach, where women aged 50 years or older are advised to go for a mammogram once every two years. If below the age of 50, women should seek advice from their doctor. While national mammography screening programmes have been widely implemented and shown to be cost effective in countries including the US [6], Australia [7], and South Korea [8], their respective guidelines for screening still differ. The American Cancer Society advises annual mammography screening beginning from the age of 45 [9], while South Korea recommends mammography screening every two years from the age of 40 [10]. The current strategy in Singapore has its limitations, such as poor attendance, with only 66% of women aged 50 to 69 ever getting a mammogram in 2018 [11]. It was observed that half of these women do not come back for regular screening at two-year intervals. This lukewarm response to mammogram screening may be due to the high potential for false-positive results and unnecessary biopsies [11]. Furthermore, the recommended screening commencement age of 50 may be inadequate as breast cancer can develop before that. These cases would be clinically diagnosed at later stages that exhibit worse survival rates, as breast cancer may not show symptoms in the early stages [12].

Hence, improvements can be made to the Singaporean age-based mammogram screening programme. Polygenic risk scores (PRS) have been shown to predict an individual's risk to diseases [13–15]. Using breast cancer associated SNPs, an individual's PRS can be calculated to stratify their risk of developing breast cancer [16–17]. Here, we introduce a polygenic risk tailored screening programme which aims to facilitate early detection by providing tailored screening recommendations based on an individual's risk group. This may reduce unnecessary testing and false positives that are common in a one size fits all mammogram screening programme. The PRSs would also act as an educational platform, increasing awareness in women for their breast cancer risk, while encouraging compliance to a screening programme. Therefore, the aim of our project is to compare the current age-based biennial mammogram screening programme, with a strategy that incorporates genetic testing using breast cancer associated SNPs, thus evaluating the cost effectiveness of a breast cancer genetic risk prediction approach in Singapore.

Methods

The target population of this cost effectiveness analysis is Singaporean women aged 35 to 74, a time horizon of 40 years. The two strategies being compared are – the proposed tailored screening strategy, which advises a screening programme based on an individual's PRS, and the current mammogram screening only strategy, where mammogram screening is done every two years. A Markov model (Fig. 1) for breast cancer screening in Singaporean women was developed in Microsoft Excel to model the differences between the two strategies. This study takes the perspective of the healthcare system in Singapore.

In the polygenic risk tailored screening strategy, individuals aged 35 to 74 will be genotyped by buccal swab and asked to complete a breast cancer risk factor questionnaire, before being stratified into three risk groups based on their initial PRS – low, intermediate, and high. The PRSs are stratified by setting cut offs at below 60th percentile for the low risk group, 60th to 95th percentile for intermediate risk group and above 95th percentile for the high risk group. In the Asian population, these cutoffs correspond to expected proportions of 51%, 41% and 8% for low, intermediate and high risk groups respectively [18]. The starting age for this strategy was chosen based on findings that women with a high genetic risk for developing breast cancer may reach the equivalent 10-year risk to an average 50-year old woman at 35 years of age [18]. There is no clear guideline on the ending age for mammogram. The U.S. Preventive Services Task Force (USPSTF) recommends screening up to the age of 74 [19]. The American Cancer Society recommends that mammogram may be performed as long as an individual is in good health and expected to live for another 10 years

[20]. Hence, we have chosen an ending age of 74 for the tailored screening arm, to compare against the current Singapore mammogram only strategy that screens every two years from the age of 50 to 69.

Individuals in each risk group will receive their initial PRSs within three to six months. Depending on their age group, these individuals will be required to undergo a subsequent follow up screening test comprising of self-examination, ultrasound or mammogram (Fig. 1). Results from the follow up screening tests will used to give a holistic genetic score. Individuals will then be advised with a long term screening plan tailored to their updated risk group from this genetic score. For the high risk group, annual ultrasound will be done for individuals aged 35 to 39, followed by annual mammogram for those aged 40 to 74. For the intermediate and low risk groups, self-examination is done for ages 35 to 39. For individuals aged 40 to 74 in intermediate and low risk groups, biennial and triennial mammograms will be carried out respectively. In contrast, all women in the current mammogram screening only strategy undergo biennial mammogram screening from age 50 to 69, with no screening done before the age of 50. In terms of last screens, for the mammogram arm it is at age 68, with no screening after the age of 69. In the proposed tailored screening strategy, the last screen is at age 73 for the low risk group and 74 for intermediate and high risk groups.

Direct medical costs by breast cancer stage and genotyping buccal swab cost were obtained from Wong [21]. The costs of mammogram and ultrasound tests were adapted from local public and private hospitals. All costs were expressed in Singapore Dollars (SGD). The discount rate used for the costs and health outcomes is 3% [22].

Parameters were extracted from Singaporean studies or closely related Asian studies if Singaporean equivalents were not available. Age specific incidence rates (ASIR) for breast cancer were provided by the Demographic Epidemiological Model of Singapore (DEMOS), a published local micro-simulation disease model that synthesizes evidence from multiple data sources [23]. Screened and unscreened breast cancer stage distributions were taken from a previous study by Wong [21], where the MISCAN-Fadia model [24] was calibrated to Singaporean breast cancer incidence data. Mammography sensitivity was incorporated to account for any missed cases. To illustrate the differences between breast cancer incidence in each polygenic risk group, multipliers of 2x, 1x, and 0.5x were used for high, intermediate, and low risk groups respectively. Transition probabilities between healthy and each disease state were then calculated using these parameters (ASIR x Stage Specific Proportion x Mammography Sensitivity x Risk Multiplier (if applicable)). Mortality rates were derived from the Singapore Cancer Registry Annual Registry Report 2015 [2].

The health outcomes used were Life Years (LYs) gained and Quality Adjusted Life Years (QALYs) gained. QALYs are calculated by multiplying time spent in a health state with an appropriate utility score. We used stage specific health utility scores from Wong [21], that were adapted from a Korean study [25].

100% attendance from all women was assumed. The model also assumes that all women can die from natural causes in between screening cycles. Those who are diagnosed with breast cancer do not go into remission and instead remain in the diseased states. Risk group multipliers were selected based on the assumption that high risk women for instance, are approximately twice as likely as the average population to develop breast cancer. Low risk women, conversely, would be half as likely as the average population to develop breast cancer [16, 26]. These assumptions were based on various PRS studies, for example Mavaddat *et al.* [16], who found that compared with women in the middle quintile of breast cancer PRSs, those in the top 1% had 4.37- and 2.78-fold risks of developing ER (Estrogen Receptor)-positive and ER-negative disease, respectively.

Probabilistic sensitivity analysis (PSA) and one-way sensitivity analysis (OSA) were carried out to assess parameter uncertainty. For OSA, the lower and upper limits of each parameter were calculated using 80% and 120% respectively of the original value. PSA was conducted on the cost parameters (+/- 30%, Gamma distribution) and utilities (+/-0.1, Beta distribution). 10,000 runs of Monte Carlo simulations were carried out for the PSA.

Different cutoffs for the risk groups were explored in a scenario analysis. For cutoffs for the high-risk group, a range of 5th to 10th percentile was explored, while for the low risk group, a range of 40th to 60th percentile was explored. These ranges were covered by three separate scenarios – 1) 60th percentile low-30th percentile intermediate-10th percentile high (60L-30I-10H), 2) 40th percentile low-55th percentile intermediate-5th percentile high (40L-55I-5H), and 3) 40th percentile low-50th percentile intermediate-10th percentile high (40L-50I-10H), all in comparison with the base case scenario of 60th percentile low-35th percentile intermediate-5th percentile high (60L-35I-5H).

Table 1: Input parameters for the cost effectiveness model.

Variables	Baseline	Minimum	Maximum	Distribution	Reference
Age Specific Incidence Rates		-	-	-	Demographic Epidemiological Model of Singapore, DEMOS [23]
35 – 39	0.000617				
40 – 44	0.001114				
45 – 49	0.001733				
50 – 54	0.001775				
55 – 59	0.002073				
60 – 64	0.002119				
65 – 69	0.002056				
70 – 74	0.002063				
75 – 79	0.001974				
80 – 84	0.001710				
>=85	0.001530				
Annual discount rate for costs and benefits	0.03	-	-	-	Haacker*et al.* (2020) [22]
Stage Specific Mortality Rates		-	-	-	Singapore Cancer Registry Annual Registry Report 2015 [2]
Stage I	0.020				
Stage II	0.044				
Stage III					
Stage IV	0.083				
	0.268				
All Cause Mortality Rate	0.002896	-	-	-	Singstat Life Tables [27]
Polygenic Risk Distribution		-	-	-	Study team's unpublished data
Low	0.51				
Intermediate	0.41				
High	0.08				
Breast Cancer Stage Distribution (Screened/Unscreened)		-	-	-	Wong (2019) [21]
Stage I					
Stage II	0.53/0.22				
Stage III	0.43/0.57				

Stage IV	0.03/0.12 0.01/0.09				
Stage Specific Utility Values				Beta	Wong (2019) [21]
Healthy *Stage I* *Stage II* *Stage III* *Stage IV*	1.000 0.731 0.731 0.599 0.352	1.000 0.63 0.63 0.499 0.252	1.000 0.83 0.63 0.599 0.452		
Risk Group Multiplier		-	-	-	-
High	2				
Intermediate	1				
Low	0.5				
Mammogram & Ultrasound Sensitivity	0.8	-	-	-	[27–30]
Stage Specific Direct Medical Costs (SGD)				Gamma	Wong (2019) [21]
Stage I *Stage II* *Stage III* *Stage IV*	63,983.00 78,226.00 91,129.00 110,136.00	44,788.10 54,758.20 63,790.30 77,095.20	83,177.90 101,693.80 118,467.70 143,175.80		
Cost of Buccal Swab (SGD)	210.00	122.50	227.50	Gamma	Local Singapore Hospitals, Wong (2019) [21]
Cost of Mammogram (SGD)	110.00	87.50	162.50	Gamma	Local Singapore Hospitals, Wong (2018) [32], Wong (2019) [21]
Cost of Ultrasound (SGD)	230.00	161.00	299.00	Gamma	Local Singapore hospitals, Wong (2019) [21]
Cost of Questionnaire (SGD)	2.00	1.40	2.60	Gamma	Sun et al. (2018) [33]

Results

Table 2
Costs and health outcomes of the cost effectiveness model for two screening strategies.

Strategy	Lifetime costs per case (SGD)	Life Years	Quality Adjusted Life Years (QALYs)	Incremental Calculations (Tailored – Current)			
				Costs	Life Years	QALYs	ICER (SGD/QALY)
Current mammogram only screening	23,729.57	21.89	21.80	-	-	-	-
Polygenic Risk Tailored Screening (60th low, 35th int, 5th high)	20,058.74	22.86	22.79	-3,670.83	0.9720	0.9884	-3,713.80
Scenario Analysis							
60th low, 30th int, 10th high	21,474.94	22.86	22.78	-2,254.63	0.9686	0.9800	-2,300.45
40th low, 55th int, 5th high	22,242.34	22.85	22.77	-1,487.23	0.9599	0.9681	-1,536.20
40th low, 50th int, 10th high	23,658.54	22.85	22.76	-71.02	0.9566	0.9598	-74.00

Table 2 Legend: The strategies being compared are the current mammogram only screening strategy and a proposed polygenic risk tailored screening strategy. Scenario analysis compared three scenarios (60L-30I-10H, 40L-55I-05H, 40L-50I-10H) with different polygenic risk cutoffs in percentiles for polygenic risk tailored screening.

The cost effectiveness model estimated 25.5 cases of breast cancer per 1,000 women over the time horizon of ages 35–74 years old in the tailored screening arm, compared to 31.2 cases in the mammogram screening arm. Overall, the life year and quality adjusted life year gain per woman in the tailored screening programme is approximately 0.9720 and 0.9884, respectively. The tailored screening programme is cheaper by SGD3,670.83, resulting in an ICER of -3,713.80 SGD/QALY (Table 2).

Three scenarios with different percentile cutoffs were explored with splits of 60L-30I-10H, 40L-55I-5H, 40L-50I-10H, giving ICERs of -2,300, -1,536, -74 SGD/QALY, respectively. The ICERs for all three scenarios were negative, and remained in the south east quadrant of the cost effectiveness plane, that is with a negative incremental cost and positive incremental QALYs.

To assess the impact of the parameters on the health outcomes and ICERs, both one-way and probabilistic sensitivity analysis were conducted. Figure 3 shows the tornado diagram for the OSA. Low and high risk multipliers, direct medical costs for Stage II breast cancer, and sensitivity of mammogram and ultrasound tests were the top four parameters that most affect the ICER. However, the ICERs remain negative, with incremental costs < 0 and incremental effects > 0. Figure 4(a) shows the cost effectiveness plane from the PSA on the baseline scenario, where all ICER points fall within the south east quadrant, indicating that tailored screening dominates mammogram only screening with lower costs and higher QALYs. After 10,000 runs of Monte Carlo simulations, the probability of tailored screening being cost effective compared to the mammogram screening arm is 100%, with the ICER remaining negative with incremental costs of < 0 and incremental effects of > 0. The willingness-to-pay (WTP) threshold represents an estimate of what an individual is willing to pay for a health benefit, in this case 1 QALY. For PSA done on the three additional

scenarios with different risk group cutoffs, to note is the 40L-50I-10H scenario where the ICER crosses into the positive. Approximately 57% of the ICERs for tailored screening will be cost-effective when WTP is at 1SGD /QALY, compared to the mammogram arm (Fig. 3). At maximum WTP of 1,820 SGD/QALY, tailored screening is 100% cost effective. In other scenarios, tailored screening dominates mammogram only screening.

Discussion

A breast cancer screening programme incorporating polygenic risk scores could be implemented in Singapore to improve the current age-based mammogram screening programme. The cost effectiveness of genetic risk tailored screening policies have been studied in the United Kingdom [17], Canada [34], and the United States [35]. However, little is known of the cost effectiveness of such policies in Asia. Hence, we developed a cost effectiveness model to examine the feasibility of a genetic risk, tailored screening approach in Singapore, where individuals are advised on a screening strategy based on their predicted risk.

The cost effectiveness model estimated approximately 25.5 cases of breast cancer per 1,000 women, over the 35–74 years old time horizon in the tailored screening arm. In the mammogram only screening arm, the model estimated 31.2 cases per 1,000 women. Based on 2018 statistics from Globocan, women in Singapore have a cumulative risk of 6.39% of developing breast cancer, which equates to 60.9 cases per 1,000 women. While this shows that the model may underestimate the number of breast cancer cases, it has to be noted that the model considers women aged 35–74, a subset of all women in Singapore.

Results from the cost effectiveness analysis suggest that a polygenic risk-based tailored screening approach may offer improvements in detecting breast cancer cases promptly over the current age-based mammogram only screening programme in Singapore. An ICER of − 3,713.80 SGD/QALY not only makes polygenic risk-based tailored screening more cost effective than the current mammogram screening programme, but the incremental cost of -SGD3,709 shows that tailored screening may be cheaper. This is supported by a number of Western studies that indicate that a polygenic risk-stratification component may improve cost effectiveness of a breast cancer screening programme [17, 34, 35]. In terms of ending age, we opted for the age of 74 based on American recommendations, over mirroring the current strategy's ending age of 69, which in comparison would give an ICER of -3,717.72 SGD/QALY.

The observed small difference in QALYs of 0.9853 suggests that tailored screening does not differ considerably from mammogram only screening in terms of QALYs gained, with almost one QALY gained per individual. This implies that tailored screening does not result in a significant stage shift in terms of stage distribution of breast cancer cases. We believe that this is a positive finding, as it ensures that there will be no harm inflicted onto individuals in transitioning from mammogram only screening to polygenic risk tailored screening. These findings indicate that there is no significant difference in cancer survival, as quality of life is tied to cancer staging and survival time. It was also observed that the probability of death over lifetime per individual also does not differ significantly between the two arms, 13.0% in the tailored screening arm and 13.4% in the mammogram screening arm. This further demonstrates that there are no adverse outcomes to the patient when switching to the tailored screening programme.

We compared outcomes using different percentile cutoffs for the low, intermediate, and high risk groups to examine their influence on model outcomes. We examined cutoffs that range from 5th to 10th percentile for the high risk group, and 40th to 60th percentile for the low risk group, assigning any remainder into the intermediate risk group. Among the three additional scenarios (60L-30I-10H, 40L-55I-5H, 40L-50I-10H, with base case 60L-35I-5H), all had an ICER value in the south east quadrant of the cost effectiveness plane, indicating lower costs and higher QALYs. Notably, the 40L-55I-

10H scenario has an ICER of -74.00 SGD/QALY. Results from PSA on this scenario indicate approximately 57% probability that tailored screening dominates mammogram only screening when WTP is 1 SGD/QALY. This is due to a shift in screening frequencies, with more screening done in the high risk groups due to the higher proportions, resulting in higher costs, which drives the ICER up. Nonetheless, at the approximate maximum WTP of 1,820 SGD/QALY, tailored screening is 100% cost effective.

Both one-way and probabilistic sensitivity analysis were carried out to assess parameter uncertainty. The results of the one-way sensitivity analysis indicate that risk multipliers for low and high risk groups, breast cancer stage II costs and mammography sensitivity had substantially higher impact on the ICER compared to the other parameters. These findings for the risk multipliers are to be expected, as they are the main drivers for influencing proportions of cases in each risk group. Mammography sensitivity was a limitation on this study, as scarcity and age of the data may impact the final results. The Singapore MOH Clinical Practice Guidelines 2010 estimated the sensitivity of mammography to range from “68% to over 90%” [31]. As such, we set our mammography sensitivity parameter to a base case value of 80%, while studying the possible effects of mammogram sensitivity in which we varied from 64–96% in the one-way sensitivity analysis. The effects of breast cancer stage II costs may be due to the breast cancer stage specific proportions of 43% in a screened group and 57% in an unscreened group. This means that in our model, an individual is most likely to be diagnosed with stage II breast cancer compared to other stages. Hence, stage II cancer cost featured more prominently.

This study used model-based estimates based on assumptions. The model assumes 100% attendance and compliance to breast cancer screening and follow ups. This would not be representative of real-world situations. A 2010 national health survey showed that only 39.6% of women aged 50–69 years old have attended screening in the previous two years [38]. In comparison, screening attendance according to national guidelines was 61.1% in South Korea in 2010 [39]. In the United Kingdom, 73.4% of women aged 45 to 74 years old have attended a mammogram screen from 2010–2011 [40]. At lower attendance rates, there is expected to be higher rates of clinically detected breast cancer cases compared screen detected cases. Consequently, there will be a stage shift to later, symptomatic breast cancer stages, resulting in lower quality of life and higher mortality. To improve screening attendance, the Singapore Government extended the use of the national health savings scheme, Medisave, as well as subsidies to pay for screening procedures since July 2011. A 2017 focus group study examining Singaporean women’s views towards breast cancer screening concluded that there were numerous barriers to consistent mammogram attendance, such as laziness and pain [30, 31]. Interestingly, Singaporean women were found to be generally receptive to SNP testing, citing only a need for additional information, such as test accuracy and cost, before getting tested, which may indicate the public’s favour for a screening programme incorporating genetic testing. Further studies and pilot testing will be carried out to validate the findings from the study.

Another limitation of this cost effectiveness study is that the natural history of breast cancer is not fully modeled. Progression between stages of breast cancer is not modeled due to the lack of local data on transition probabilities between stages, alongside ethical issues in collecting such data. While this may be problematic, it is consistent between both arms and any significant effect may be minimized. Treatment, remission and follow ups after diagnosis are also not modeled. This means that individuals diagnosed with breast cancer simply remain in the diseased state until the age of 75 or eventually progress to the death state. Due to a lack of Singaporean data on ductal carcinoma in situ (DCIS), a non-invasive form of breast cancer, DCIS was not also modeled. Nonetheless, for a cost effectiveness study examining the incorporation of genetic testing and risk stratification to an age-based mammography screening programme, these limitations may not have too adverse an impact on the final model outcomes.

Conclusions

We have carried out a cost effectiveness analysis comparing Singapore's current age-based mammogram breast cancer screening programme against a screening programme that tailors screening advice based on an individual's risk group. Our results show that polygenic risk tailored screening, is cost effective with an ICER of − 3,713.80 SGD/QALY. It is cheaper than the current mammogram only programme, and brings no additional harm to women. Tailored screening is flexible where it remains cost effective even when varying percentile cutoffs for each risk group. Low and high risk multipliers, breast cancer stage II costs and mammography sensitivity have a big impact on the ICER, although the ICER remains in the south east quadrant of the cost effectiveness plane. While the results look promising, further studies should be conducted due to limitations related to data availability and breast cancer natural history modeling.

Abbreviations

SNPs
Single Nucleotide Polymorphisms
ICER
Incremental Cost-Effectiveness Ratio
LY
Life Year
QALY
Quality Adjusted Life Year
PRS
Polygenic risk score
SGD
Singaporean Dollars
ASIR
Age specific incidence rates
MISCAN-Fadia
MIcrosimulation SCreening Analysis (MISCAN) Fatal Diameter
ER
Estrogen receptor
PSA
Probabilistic sensitivity analysis
OSA
One-way sensitivity analysis
H
High risk
I
Intermediate risk
L
Low risk
WTP
Willingness-to-pay
MOH
Ministry of Health
DCIS

Ductal carcinoma in situ

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Author Contributions:

MH and YYT conceived and designed the study. Data collection and analysis were performed by JZYW, with support from JHC and HLW. Epidemiological data and screening strategy was provided by YSH, NKMR, JL, and MH. The first draft of the manuscript was written by JZYW and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conceptualization: MH, YYT; Methodology: YYT, MH, HLW; Formal analysis and investigation: JZYW; Model replication: JHC; Writing - original draft preparation: JZYW; Writing - review and editing: JHC, HLW; Resources: YSY, NKMR, JL, MH; Supervision: YYT, HLW.

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Figures

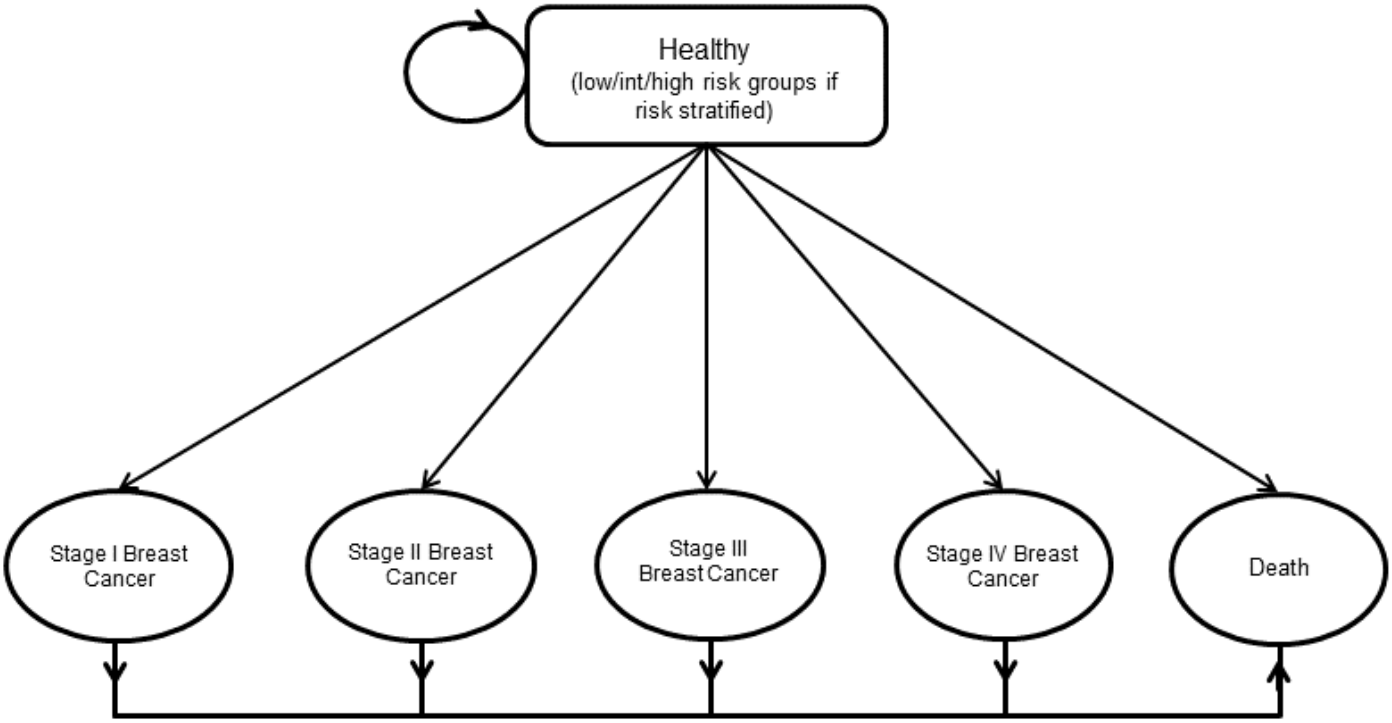

Figure 1

Markov Model of breast cancer progression. Patients diagnosed with breast cancer will transition into the stage specific diseased states and remain there, as remission and treatment is not modeled. Patients who are healthy remain in the healthy state until diagnosis or death.

Tailored Breast Cancer Screening procedure:

1. *Perform genotyping & complete risk factor questionnaire*
2. *Calculate initial polygenic risk score (PRS)*
3. *Stratify by polygenic risk (High – top 5%, intermediate – middle 35%, low – bottom 60%)*
4. *Within 3-6 months, carry out screening test to update PRS if required, based on table below:*

High	Intermediate	Low
35 to 39 yrs – ultrasound 40 to 74 yrs – mammogram	35 to 39 yrs – self examination 40 to 74 yrs – mammogram	35 to 39 yrs – self examination 40 to 74 yrs – mammogram

5. Advise long term screening plan based on table below:

High	Intermediate	Low
35 to 39 yrs – annual ultrasound 40 to 74 yrs – annual mammogram	35 to 39 yrs – self examination 40 to 74 yrs – biennial mammogram	35 to 39 yrs – self examination 40 to 74 yrs – triennial mammogram

Figure 2

Summary of proposed polygenic risk tailored screening programme.

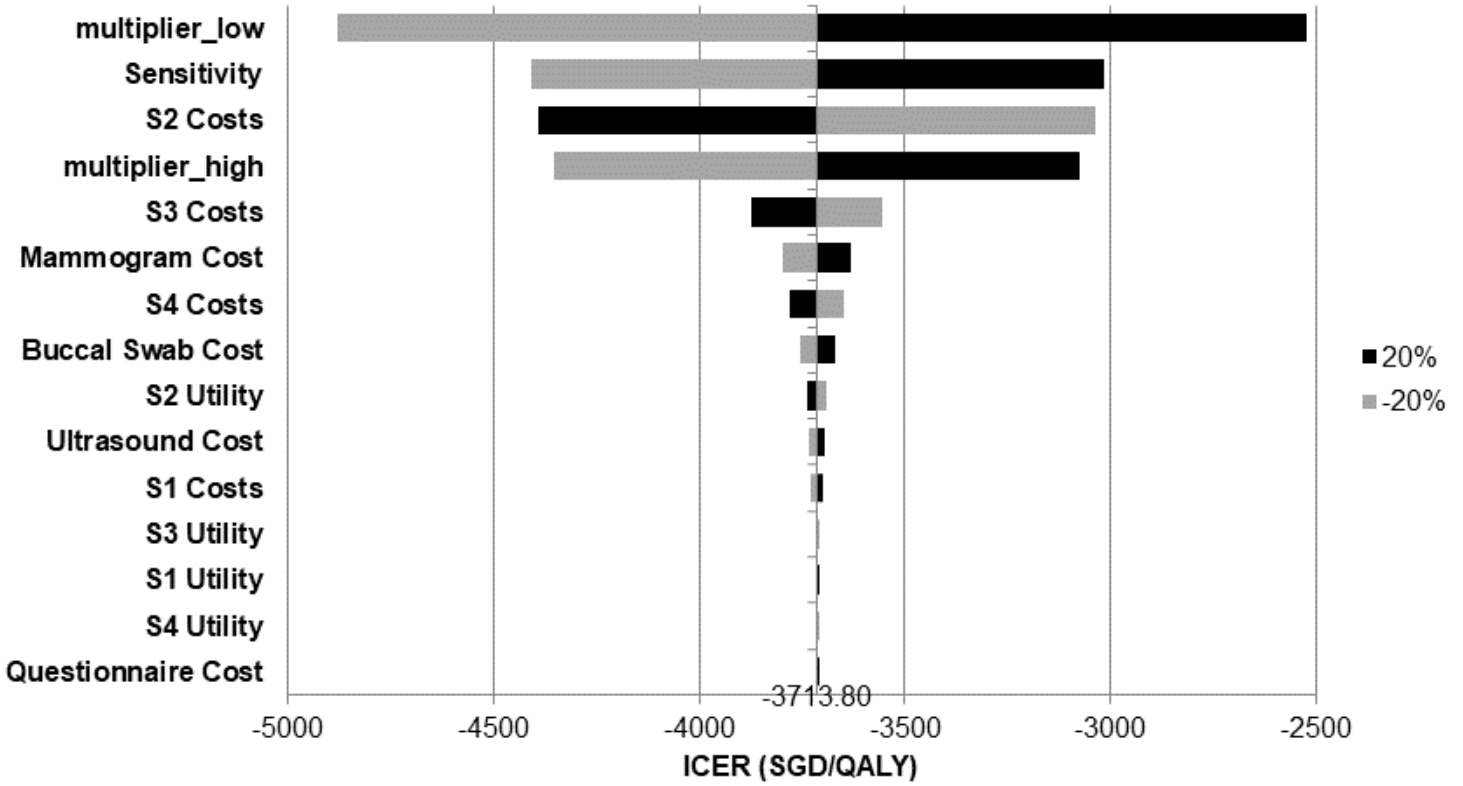

Figure 3

Tornado diagram of one-way sensitivity analysis. Low and high risk multipliers, direct medical costs for Stage II breast cancer, and sensitivity of mammogram and ultrasound tests were the top parameters that most affect the ICER. However, the ICERs remain negative with negative incremental cost and positive incremental QALYs.

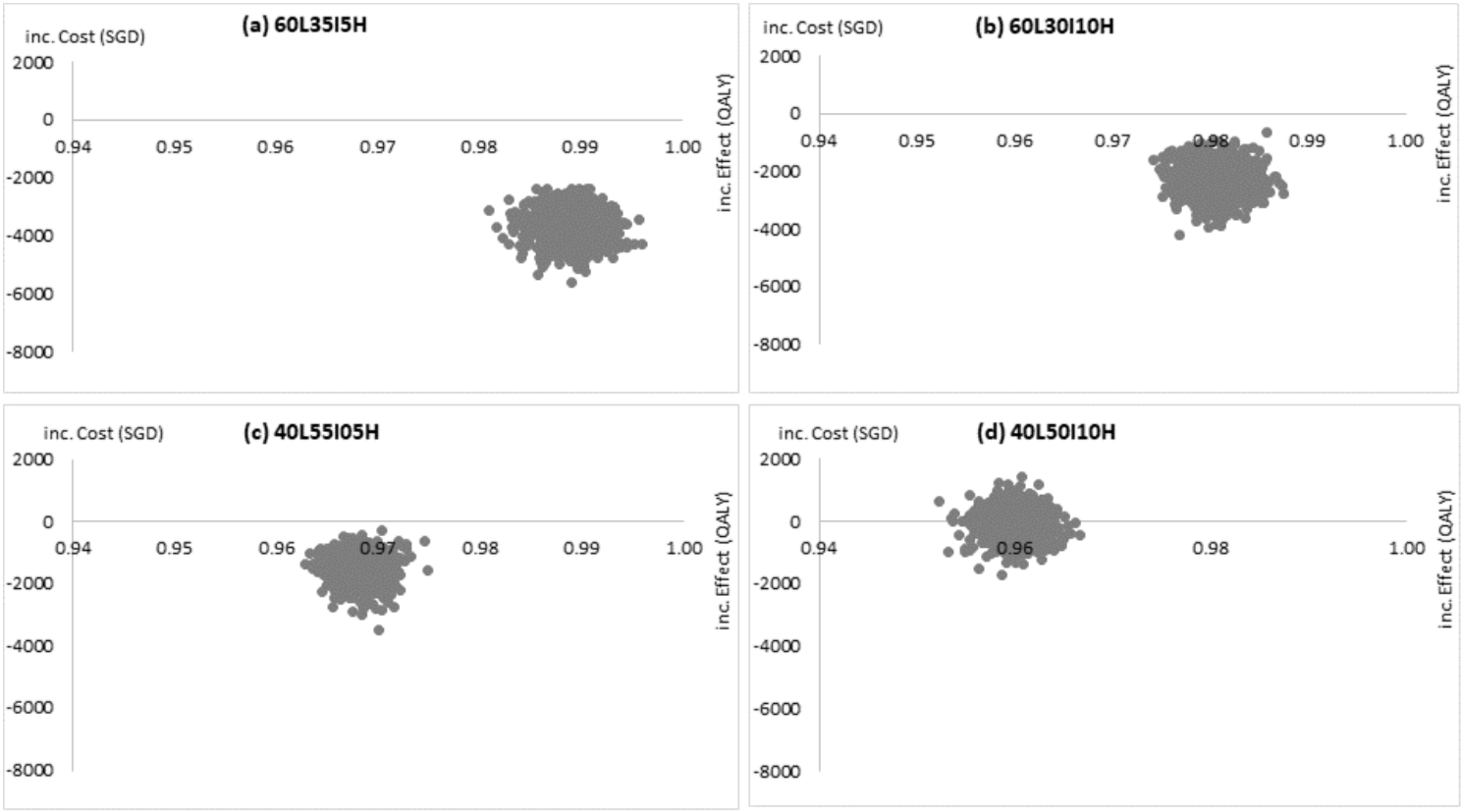

Figure 4

Cost effectiveness planes for probabilistic sensitivity analysis for all four scenarios in scenario analysis. The four scenarios examined were – (a) 60L-35I-5H (baseline), (b) 60L-30I-10H, (c) 40L-55I-05H, (d) 40L-50I-10H. In the 40L-50I-10H scenario (d), approximately 57% of the ICERs for tailored screening will be cost-effective when WTP is at 1SGD /QALY, compared to the mammogram arm. All ICER points for other scenarios remain in the south east quadrant.

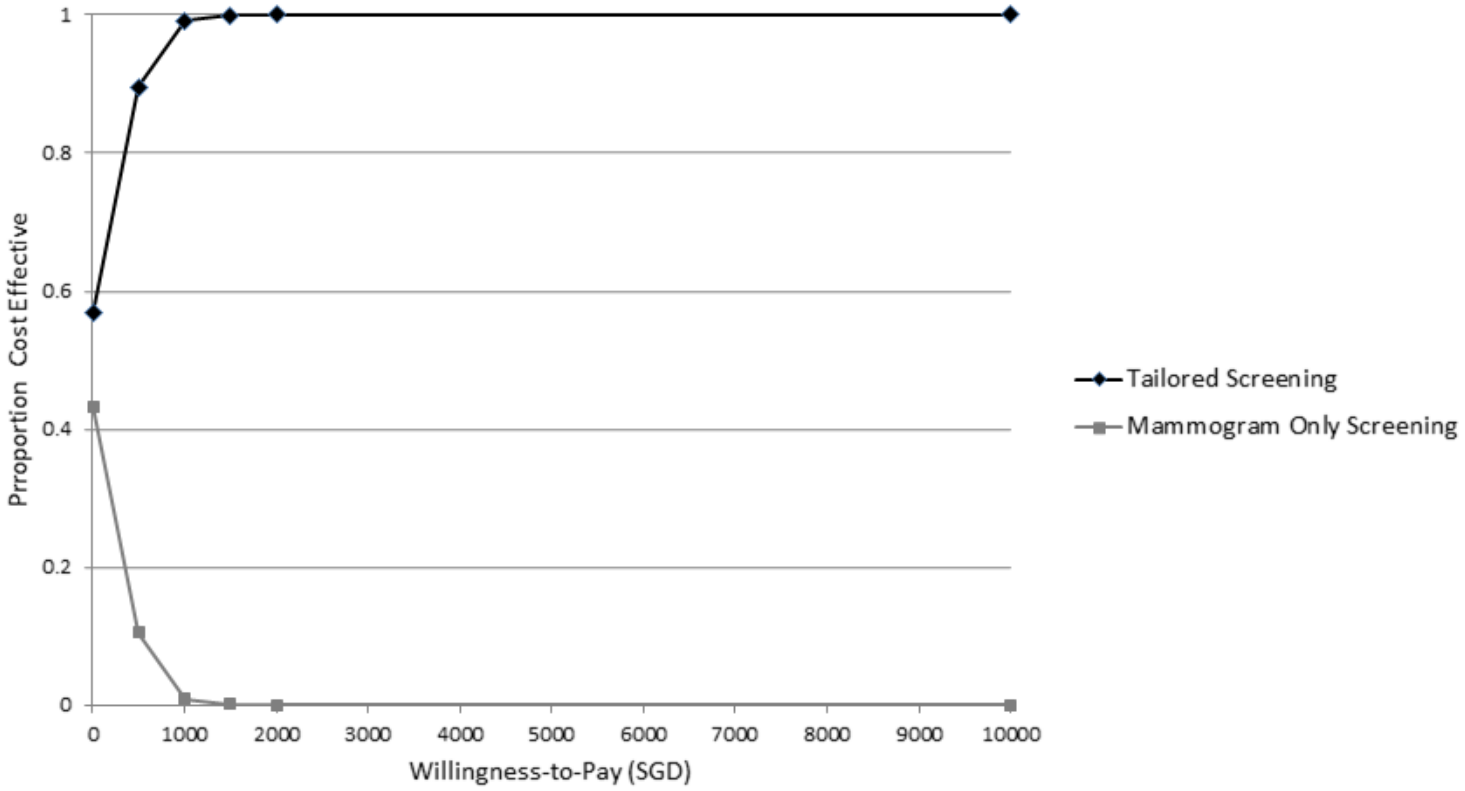

Figure 5

Cost effectiveness acceptability curve for the 40L-50I-10H scenario. There is an approximately 57% probability for tailored screening to be cost-effective when WTP is at 1 SGD/QALY, compared to the mammogram arm. At the approximate maximum WTP of 1,820 SGD/QALY, tailored screening is 100% cost effective.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFigure1.pptx
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- SupplementaryFigure3.pptx
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