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Cost-effectiveness analysis of breast cancer screening using mammography in Singapore: a modelling study

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Abstract

Background—Limited research is available on the cost-effectiveness of breast cancer screening programs in Asian countries. We evaluated the cost-effectiveness of Singapore's national mammography screening program, implemented in 2002, recommending annual screening between ages 40–49 and biennial screening between ages 50–69, and alternative screening scenarios taking into account important country-specific factors.

Methods—We used national data from Singapore in the MISCAN-Fadia model to simulate 302 screening scenarios for 10 million women born between 1910–1969. Screening scenarios varied by starting and ending age, screening interval and attendance. Outcome measures included: life-years gained (LYG), breast cancer deaths averted, false positives, overdiagnosis, Quality-Adjusted-Life-Years (QALYs), costs (in 2002 Singapore dollars; S\$), and incremental cost-effectiveness ratios (ICERs). Costs and effects were calculated and discounted with 3% using a health-care provider's perspective.

Results—Singapore's current screening program at observed attendance levels required 54,158 mammograms per 100,000 women, yielded 1,054 LYG and averted 57 breast-cancer deaths. At

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CONFLICT OF INTEREST

The authors declare no potential conflicts of interest.

attendance rates 50%, the current program was near the efficiency frontier. Most scenarios on the efficiency frontier started screening at age 40. The ICERs of the scenarios on the efficiency frontiers ranged between S\$10,186–S\$56,306/QALY, which is considered cost-effective at a willingness-to-pay threshold of S\$70,000/QALY gained.

Conclusion—Singapore's current screening program lies near the efficiency frontier and starting screening at age 40 or 45 is cost-effective. Furthermore, enhancing screening attendance rates would increase benefits while maintaining cost-effectiveness.

Impact—Screening all women at age 40 or 45 is cost-efficient in Singapore and a policy change may be considered.

Keywords

Singapore; Mammography; Breast Neoplasms; Early Detection of Cancer; Mass Screening

Introduction

Breast cancer is the most common cancer and among the leading causes of deaths in women worldwide¹. In Singapore, the age-standardized incidence rate of female breast cancer has risen steeply from 24.6 per 100,000 person-years in 1976–1980 to 65.3 in 2011–2015². Despite the rising incidence, the mortality rate has remained relatively stable since 1991 to 2015 as reported by the cancer registry annual report². Early detection by mammographic screening and advances in treatment are most likely causes of the stable mortality rate³.

The national breast cancer screening program BreastScreen Singapore (BSS) was launched in 2002, aiming to reduce breast cancer mortality in Singapore. Female Singaporeans and Permanent Residents between 50–69 years, are invited through personalized letters for biennial screening⁴. Women aged 40–49 may attend annual screening but are recommended to consult their physician regarding the benefits and harms of screening. Physicians can discuss benefits of screening for eligible women such as better survival when finding an early stage of breast cancer, and harms such as the possibility of false positive test results, overdiagnosis and anxiety. Eligible women receive subsidized screening mammography at government-funded polyclinics or approved private centres⁵.

An essential factor to reduce breast cancer mortality through mammography screening is high attendance rates⁶. In addition, attendance at the first screening round is important, because it is a predictor for attending subsequent screening rounds⁷. An effective screening program relies largely on the adherence of the target population, which includes two components: the proportion of the target women that undergo screening and the regularity with which they attend the program⁸.

Despite its relative affordability with Singaporean women paying only S\$50 (45% of total mammogram cost) out-of-pocket, only 11% of the target population aged 50–69 attended screening under BSS in 2008–2009⁹. In a 2010 national health survey, 40.4% of women aged 50–59 and 38.1% of women aged 60–69 reported attending mammogram screening in the past two years, which include screening outside the BSS screening program¹⁰. To

increase screening uptake, the Singapore Government extended Medisave, a compulsory medical savings scheme, in 2011 to offset the cost of screening mammograms⁹.

Currently, the breast cancer screening recommendations are predominantly based on research from Western countries, but these may be less appropriate in Asian settings due to cultural and biological differences. For instance, well-established risk factors for breast cancer such as alcohol, smoking, low intake of fresh fruit and vegetables are in general less prevalent among Asian women than among Western women^{11–13}. Biological differences between Asian and Western women such as density of the breast could influence the detection of breast cancer when using mammography^{14, 15}. Furthermore, other potential differences between Western and Asian women could be their perception on breast cancer screening in terms of quality of life as well as the differences in health care context in terms of available monetary resources and human resources¹⁶.

Although many cost-effectiveness analyses have been conducted for breast cancer screening¹⁷, no study has performed an extensive cost-effectiveness analysis of the Singaporean national breast cancer screening program. Therefore, the aim of this study was to assess the cost-effectiveness of the current screening policy and alternative breast cancer screening scenarios in Singapore with different attendance levels.

Materials and Methods

Microsimulation model MISCAN-Fadia

For this study, we used the Microsimulation SCreening ANalysis-Fatal diameter (MISCAN-Fadia) breast model. MISCAN-Fadia model has been used to inform policies and gain insights from clinical trials. For instance, in the US, a variety of screening strategies have been simulated and evaluated in order to determine the optimal screening strategy¹⁴. Another example is that MISCAN-Fadia has been used to simulate the UK Breast Screening Frequency trial in order to predict breast cancer mortality using a longer follow-up period, i.e. life time period^{18, 19}.

The MISCAN-Fadia model varies the breast tumor growth and fatal diameter among simulated women^{20, 21}. This unique biological component allows each simulated woman to have a different tumor size at which treatment is no longer effective (i.e. fatal). Furthermore, the model simulates two identical populations: one with and one without screening. By comparing the life-histories in the presence of screening with corresponding life-histories in the absence of screening, we can estimate harms and benefits of screening.

Simulated population

Women born between 1910–1969 were simulated by 5-year birth-cohorts (e.g. women born in 1910–1914 cohort were in the year 1971: age 57–61) which takes into account both the national screening program as well as the period prior the screening program. In total, 10 million women were simulated and followed until death. Age-specific all-cause mortalities by 5-year birth-cohort were derived by calibrating to observed mortality rates and birth-cohort specific expected life expectancies at age 65, obtained from the Singapore Department of Statistics (Supplementary Table S1).

Incidence, mortality, treatment and screening attendance data

Incidence data on invasive breast cancers (Figure 1) and breast cancer deaths from 1971–2014 were collected by 5- and 10-year age-groups, respectively from the National Registry of Diseases Office (NRDO). Mode of detection (screen- or clinically-detected), was included where possible. American Joint Committee on Cancer (AJCC) stage groupings were available from 2003 onwards, while screen detection information was available from 2008 onwards.

Additionally, treatment dissemination data were obtained from the NRDO. Percentage of breast cancer cases who received chemotherapy, endocrine therapy and both treatments combined were retrieved and categorized by year of diagnosis, 5- or 10-year age-groups and AJCC staging. Screening attendance data were derived from the NRDO and BSS by 5-year age-groups and calendar year. Singaporean data on attendance, specificity (Supplementary Table S1) and treatment were used to model the effect of screening on breast cancer survival. Estimated survival and mortality were compared to observed data.

Quality of life

As local data on phase- and stage-specific health state utilities for breast cancer were unavailable, we adapted values from a study conducted in the Korean general population²². We assume that the setting of Korea is more similar to Singapore in terms of economic wealth and culture than western countries. Utilities for screening and the diagnostic phase were obtained from de Haes²³. Utility values are shown in Table 1 (See Supplementary Table S1 for calculations).

Screening scenarios

Singapore's national breast cancer screening program recommends annual screening for women between ages 40–49 (upon doctor's advice) and biennial screening for women between ages 50–69. In total, 302 scenarios were simulated of which 1 scenario represented Singapore's current screening program at observed attendance levels varying between 3%–14% across different calendar years and age groups, 1 scenario assumed no screening and 300 scenarios varied by age ranges, screening interval, and attendance levels (Table 2). Starting ages for breast cancer screening were 40, 45, 50 or 55 and stopping ages were 64, 69, 74 or 79. Out of 300 scenarios, 240 scenarios included different screening frequencies: annually, biennially and triennially. The remaining 60 scenarios were hybrid scenarios which allowed women to be screened annually until the switching age, after which they were screened biennially. Switching ages considered in this study were ages 45 and 50. Furthermore, attendance levels of 10%, 30%, 50%, 70% and 100% were considered for each scenario.

Costs

This analysis considered the health care provider perspective. Screening program costs such as screening invitations and mammograms were obtained from BSS. Diagnostic work-up costs (imaging, laboratory investigations and biopsies) were obtained from the National University Hospital Patient Affordability Simulation System (NUH PASS). Treatment costs were provided by the Ministry of Health and were aggregated by AJCC stages 1–4 and

phases of care. The phases of care include initial care: the first 12 months after diagnosis of breast cancer, terminal care: the last 6 months prior to death, and continuing care: the period between initial and terminal care²⁴ (Table 1). Costs were expressed in Singapore dollars using 2010 as a base year, when consumer price index (CPI) =100²⁵. All costs were converted to the year 2002 using the CPI for health care²⁵, as the breast screening program started in 2002. Both costs and health outcomes were discounted with 3%, in line with recommendations by the Agency for Care Effectiveness Singapore²⁶. The willingness-to-pay (WTP) threshold was set at one gross domestic product (GDP) per capita of approximately S \$70,000/QALY (US\$50,000) gained for the purpose of our study. It should be noted that Singapore does not have an explicit WTP threshold.

Benefits, harms and cost-effectiveness of screening scenarios

For each scenario, we calculated the discounted costs and Quality-Adjusted-Life-Years (QALYs), average cost-effectiveness ratio (ACER; ratio of differences in costs to differences in QALYs compared to no screening), incremental cost-effectiveness ratio (ICER) and number of mammograms. Furthermore, benefits of screening (e.g. number of breast cancer deaths averted, reduction in breast cancer mortality and number of life-years gained) were compared against the situation without screening. The harms of screening include number of false positive, overdiagnosis for ductal carcinoma in situ (DCIS) and invasive breast cancers (IBC) combined. The latter was calculated by dividing the number of screen-detected overdiagnosed cases by the total number of screen-detected DCIS and IBC.

We constructed 5 cost-effectiveness planes by attendance level, with efficiency frontiers. The efficiency frontier plot depicts scenarios based on the additional costs and QALYs gained which can be found on the x-axis and y-axis, respectively. When establishing the efficiency frontier for each attendance level, Singapore's current program at its observed attendance level was excluded. Scenarios on the efficiency frontiers were cost-efficient while those below the efficiency frontier were dominated. ICERs were computed for each scenario on the efficiency frontier as the incremental net costs per incremental QALY gained compared to the previous efficient scenario. Lifetime time horizons for costs and effects of screening were considered for each simulated person. A sub-analysis assessed whether the current screening program would be on a frontier across all attendance levels. All outcomes were reported per 100,000 women alive in 2002.

Sensitivity analyses

One-way sensitivity analyses were performed to estimate the impact of a lower/higher work up costs (Table 1) as well as the effect of a continuous care of five years on the efficiency frontier.

Results

Current screening program with assumed and observed attendance levels

At observed attendance levels of 3%–14% which vary by age groups and calendar year, Singapore's current screening program yielded 1,054 life-years gained and averted 57 breast cancer deaths, while requiring 54,158 mammograms and resulting in 2,101 false positives

findings (Table 3). Further, we estimated an increase of 312 QALYs at an additional cost of S\$ 3,799,641 (both discounted) compared to no screening. When assuming attendance levels 50% for the current screening program, it was near the efficiency frontier (Figure 2C–E). Increasing the current screening program's attendance level to 50% resulted in an addition of 659,934 mammograms; 10,030 LYG; 479 breast cancer deaths averted and 25,962 false positives when compared to observed attendance level (Table 3). Compared to no screening, the current screening program reduced breast cancer mortality by 3%, 11% and 19% at attendance levels of 10%, 50% and 100%, respectively.

Efficiency frontier by attendance level

Regardless of attendance level (Figure 2A–E), the majority of screening scenarios on the cost-efficiency frontiers start at ages 40 and 45. At attendance levels <70%, few scenarios on the cost-efficiency frontiers had stopping ages >69.

Few hybrid scenarios were on the cost-efficiency frontiers (Figure 2A, 2B, and 2E). Annual screening scenarios were most common on the cost-efficiency frontier at attendance level 70%, while more biennial screening scenarios tend to be on the efficiency frontier when attendance levels increased (Figure 2D–E). Triennial screening was generally inefficient, with 1–2 screening scenarios on each cost-efficiency frontier (Figure 2A–E).

Scenarios with lowest costs were biennial and triennial screening intervals while scenarios with annual screening interval generally incurred higher costs. More intense screening resulted in higher mortality reductions and more life-years gained. However, it also increased false positives and overdiagnosis rates, which becomes more pronounced at higher attendance rates (more details in Supplementary Table S2).

Assuming a threshold of S\$70,000/QALY gained, all scenarios on the frontier were cost-effective for all attendance levels (Table 4). The highest ICER was S\$56,306/QALY gained for screening annually from ages 40–79, while the lowest ICER was S\$10,186/QALY gained for screening triennially from ages 50–64, both assuming 10% attendance. The latter is also the least intensive screening scenario with 44,075 mammograms. Compared to no screening, this screening scenario averted 46 breast-cancer deaths, reducing breast cancer mortality by 1% and yielded 944 LYG; 1,716 false positives, 39 and 3 overdiagnosis for DCIS and IBC, respectively (Supplementary Table S2).

Sensitivity analyses

Varying the work-up costs did not show any major differences in the efficiency frontiers by attendance level (see Supplementary Figure S1–S2 and Supplementary Table S3–S4). When reducing the continuous care period to five years, more scenarios appear near the efficiency frontier compared to the conservative approach in which the continuous care phase includes the period between the initial care and terminal care (Supplementary Figure S3 and Supplementary Table S5).

Discussion

Our study showed that breast cancer screening in Singapore is cost-efficient when starting screening at ages 40 or 45 for all women. Singapore's current breast cancer screening policy recommends annual screening between ages 40–49 and biennial screening between ages 50–69⁴. Women age 40–49 are recommended to first consult their physician in order to assess the necessity of screening at these ages. We found that Singapore's current screening recommendation was near the efficiency frontier at attendance levels 50%. The current screening policy appears to strike a good balance among cost, benefits (mortality reduction and life-years gained) and harms (false positives and overdiagnosis) given an attendance level 50%. Policy makers should therefore focus their efforts on increasing the participation rates of breast cancer screening up to at least 50%²⁷.

Surprisingly, screening biennially from 50–69, was not on the efficiency frontiers. This was striking as this has been recommended by many countries, especially in Europe²⁸. In Singapore, almost a third of breast cancers were found in women aged 45–54². Therefore, starting screening from age 50 may be less effective in Asian countries as a significant number of women with breast cancer are not picked up in a timely manner. This was also observed in our study, as several screening scenarios that involved screening starting age 40 were on the efficiency frontier. However, given the adoption of western life-style patterns in different Asian countries, a shift in incidence could occur over time. This implies that a breast cancer screening program should be periodically re-evaluated in order to optimize the screening ages for future cohorts. Furthermore, some consideration should be made on lowering the screening age²⁹.

Our study suggests that starting at age 40 will be cost-efficient as several of these scenarios were on the efficiency frontier. However, important to note is that results in this study are conservative estimates as the continuous phase of care includes the entire period between the initial phase of care and terminal phase of care. Our sensitivity analysis results show that when the continuous phase of care is set on five years, more scenarios approach the efficiency frontier.

Our analyses are useful to non-Singaporean readers. For example, governments with limited budgets may opt for triennial screening as it has the lowest financial impact. Our study found that triennial screening between ages 50–64 has the lowest ICERs varying between S \$10,186–S\$10,713. Although ICERs varied little across attendance levels, at 100% attendance, 426 deaths could be averted compared to 46 at a 10% attendance level. Nonetheless, it is important to note that a higher attendance level also increases false positives and overdiagnosis rates. It is therefore essential to find the optimal balance between benefits and harms.

The major strengths of this study were the inclusion of country specific model inputs, such as incidence data, official statistics of the breast cancer screening program, and the extensive range of screening scenarios. This allowed the model to estimate the effects of introducing breast cancer screening in Singapore. However, our research had some limitations. First, a distinguishing characteristic of Singapore is that it has 3 major ethnicities. Yet, we were

unable to distinguish effects across different ethnic groups in Singapore as screening rates are very low among Malay women. Future research is required to investigate differences between ethnic groups. Second, registration of data has improved over time, resulting in good quality data after 1995 but less precise for earlier years. Hence, this has created some challenges when calibrating the model. Nonetheless, we were able to achieve a good model fit. Third, generalizations of results in this study to other settings should be done with caution as each country has its own characteristics. Fourth, we have assumed a WTP threshold of S\$70,000/QALY gained but there is no single official WTP threshold for Singapore. Furthermore, this WTP threshold is based on GDP, a demand side approach that has been suggested to be inadequate³⁰. An alternative approach based on the opportunity cost of health forgone has been proposed. However, such a supply side WTP threshold has not been estimated for Singapore. Hence, the conclusions of our paper may change, depending on the actual WTP threshold used by policy makers³¹. Fifth, we did not take into account the impact on financial and human resources that are needed to increase the screening attendance among eligible women. Although there are various interventions available to promote screening among women²⁷. It is important to take context specific factors into account such as cultural belief and attitudes towards screening^{32–34}. Future studies should focus on the required human resources and financial resources when using context specific interventions to increase the attendance levels in breast cancer screening. Last, we did not account for the impact of ageing on quality of life in the QALY estimations. However, for our analyses we have used utilities that were averages across all ages. Accounting for the impact of ageing, would have a stronger effect on the Quality Of Life (QOL) for higher age groups (>70 years) than younger age groups as the QOL would decrease relatively more among older ages than younger ages. In our study we found that the majority of the scenarios that were cost-effective included scenarios with relatively young stopping ages for screening. We would not expect a change in the ranking of the scenarios on the ICER but a slightly lower ICER. Therefore, adjusting for aging would have a relatively small effect on the results and conclusion. In conclusion, screening all women at age 40 or 45 is cost-efficient in Singapore and a policy change may be considered. At the current screening program attendance of 10%, annual screening will be more likely than biennial or triennial screening to be cost-efficient but with a tradeoff of higher false positives and overdiagnosis. It is thus important to increase the attendance level in order to gain more benefits in terms of life years and mortality reduction while retaining cost-effectiveness. In the future, focusing on risk stratification and tailoring breast cancer screening policies could enhance the benefits and limit the harms of screening.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Breast cancer incidence in 1971–2014 by 10-year age groups.
Data obtained from the National Registry of Diseases Office.

Figure 2. Efficiency frontier with 10%, 30%, 50%, 70% and 100% attendance level.

Each attendance level includes 60 scenarios plus 1 no screen scenario and 1 screening policy from Singapore with observed attendance level. Scenarios below the frontier are dominated. Both QALYs and costs are discounted with 3%. Scenarios on the frontier are abbreviated by screening interval, start age, stop age and attendance level. Screening interval abbreviation a = annual screening, b = biennial screening, t = triennial screening, hsw50 = hybrid screen with switching age at 50 from annual to biennial screening, hsw45 = hybrid screen with switching age at 45 from annual to biennial screening. Example of a scenario abbreviation:

t_50_64 refers to a triennial screening interval with a starting age at 50, a stopping age at 64 and a 10% attendance level. Singapore's current screening policy at observed attendance levels vary between 3%–14% across calendar years and age groups.

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Table 1

Costs and utilities for screening, diagnostics, and treatment by stage at diagnosis and phase of care

Screening mammography: costs and utilities						
	Costs (in S\$)	Utility	Duration			
Digital mammography	110	0.994	1 week			
Diagnostic work-up: costs and utilities						
	Costs (in S\$)	Utility	Duration			
Work-up cost for true positive and clinical detection	1018.50 – 1818.50	0.895	5 weeks			
Work-up cost for false positive	268.50 – 1018.50	0.895	5 weeks			
Treatment: costs and utilities by stage at diagnosis and phase of care						
	<i>Initial care^a</i>		<i>Continuous care^b</i>		<i>Terminal care^c</i>	
	Costs (in S\$)	Utility	Costs (in S\$)	Utility	Costs (in S\$)	Utility
DCIS	14,547	0.786	4,803	0.903	29,217	0.352
Stage 1	27,954	0.731	6,812	0.841	29,217	0.352
Stage 2	39,437	0.731	9,572	0.841	29,217	0.352
Stage 3	50,186	0.599	11,726	0.688	29,217	0.352
Stage 4	55,133	0.352	25,786	0.405	29,217	0.352

Abbreviations: DCIS = ductal carcinoma in situ, S\$ = Singapore dollar

^aInitial care phase is the first 12 months after breast cancer diagnosis^bContinuous care is the period between initial care and terminal care^cTerminal care is the last 6 months prior death

Table 2

Scenario features

Scenarios features	
Starting ages	40, 45, 50, 55
Stopping ages	64, 69, 74, 79
Screening interval	Annual, biennial, triennial, hybrid ^a
Attendance level	10%, 30%, 50%, 70% and 100%
Current screening policy in Singapore	
Hybrid screen	Annual from age 40–49 & Biennial from age 50–69
Overall attendance level	9% ^b

^a hybrid screen = annual screening and biennial screening with switching age at age 45 and 50.

^b Overall attendance was 9% for women age 40–69 in the period 2002–2014. Please note that in the model, observed attendance was specified by calendar year, birth cohort, and screening round.

Benefits, harms, costs and cost-effectiveness of the current screening policy by attendance level

Table 3

Attendance level	Scenario	Additional costs ^c	QALYs gained ^c	LYG	Mammo grams	Compared to no screening ^a					Total costs ^c	Total QALYs ^c	ICER ^d
						BC deaths averted	% BC mortality reduction	False positives	DCIS OD	IBC OD	% OD DCIS and IBC		
0	No screen	0	0	0	-			-	-	-	0	819,605,932	2,613,998
Observed attendance	Current Screening Policy ^b	3,799,641	312	1,054	54,158	57	1	2,101	53	6	14.3	823,405,573	2,614,311
	hsw50_40_69	9,961,074	820	2,584	143,248	125	3	5,611	123	12	15.5	829,567,005	2,614,818
	hsw50_40_69	29,059,517	2,236	7,078	429,095	343	7	16,836	352	32	16.5	848,665,449	2,616,235
	hsw50_40_69	47,400,848	3,512	11,084	714,092	536	11	28,063	564	46	17.3	867,006,780	2,617,511
	hsw50_40_69	65,135,303	4,593	14,491	998,381	699	15	39,289	757	59	18.2	884,741,235	2,618,592
100	hsw50_40_69	91,168,669	6,030	18,973	1,423,861	908	19	56,133	1,023	73	19.4	910,774,601	2,620,028
100	hsw50_40_69												18,117

Abbreviations: BC=breast cancer; DCIS=ductal carcinoma in situ; hsw50_40_69= hybrid screening scenario with annual screening at age 50 and switching to biennial screening from age 50–69; IBC=invasive breast cancer; ICER=incremental cost effectiveness ratio; LYG=life years gained; OD=overdiagnosis; QALY=quality adjusted life year

^a All results are per 100,000 women alive in 2002 and costs are expressed in 2002 Singaporean dollars

^b Annual screening age 40–49 & Biennial screening 50–69 with observed attendance of Singapore

^c Discount rate 3%

^d Current screening policy has been excluded in calculating the ICER

Table 4

Breast cancer screening scenarios on the efficiency frontier per attendance level

		ICER				
		100%	70%	50%	30%	10%
Scenario ^a	t_50_64	10,713	10,553	10,568	10,470	10,186
	t_45_64	13,043	13,263	NA	NA	NA
	b_45_64	15,654	13,615	12,596	12,007	NA
	b_40_64	15,770	15,023	13,818	NA	NA
	b_40_69	21,152	20,807	NA	NA	NA
	b_40_74	26,475	NA	NA	NA	NA
	hsw50_45_64	NA	NA	NA	13,793	11,241
	hsw50_40_74	31,136	NA	NA	NA	NA
	a_45_64	NA	NA	18,205	14,034	12,169
	a_40_64	NA	23,069	18,219	15,502	15,953
	a_40_69	NA	24,929	22,841	21,924	20,994
	a_40_74	36,670	30,370	29,373	29,216	29,918
	a_40_79	47,463	44,885	44,409	46,583	56,306
	Number of scenarios on the frontier/number of scenarios that were dominated	9/51	9/51	8/52	8/52	7/53

Abbreviations: ICER= incremental cost effectiveness ratio, NA = scenario is not on the frontier for that particular attendance level

^aScenarios are abbreviated by screening interval, start age and stop age. Screening interval abbreviation a=annual screen, b=biennial screen, t=triennial screen, hsw50=hybrid screen with switching age 50 from annual to biennial screening, hsw45=hybrid screen with switching age 45 from annual to biennial screening