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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Risk-Based Breast Cancer Screening versus Population-Based Breast Cancer Screening: A Review of the Comparative Clinical and Cost-Effectiveness

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Authors: Chuong Ho, Sarah Visintini

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Context and Policy Issues

Breast cancer was the most common cancer in Canadian women in 2016, with one in four cancer diagnoses being breast cancer.[1] The risk of getting this condition increases with age; it was estimated in 2016 that 83% of new breast cancer cases would occur in Canadian women over the age of 50, and 51% of breast cancers will be diagnosed in women 50-69 years of age (17% in women less than 50 years of age, and 32% in women over 69).[1] Despite being the second leading cause of cancer deaths in Canadian women (after lung cancer) leading to 4,900 deaths in 2016, breast cancer mortality rates in Canada have decreased by 44% since their highest in 1986, as a result of better screening technologies, increased screening rates, and improved treatments.[1] All women are at some risk of developing breast cancer. The majority (around 80%) of Canadian women have a risk of 11% of developing breast cancer in their lifetime due to gender and aging, while 1 to 2% of Canadian women have high risk of developing breast cancer (>25% lifetime risk) due to risk factors such as genetic mutation (e.g., BRCA1 or BRCA2), or family history (first degree relative of a carrier of a genetic mutation), personal history of breast cancer before the age of 35, or high radiation exposure to the chest before the age of 30. Women are considered at intermediate, or medium risk of developing breast cancer (11% to 25% risk) when they have biological risk factors such as high breast density, or personal history of breast cancer without genetic mutation, or a prior high risk lesion.[2] Some other risk factors including hormones and menstrual history, increased body weight, physical inactivity and alcohol use may also increase the risk of breast cancer.[2,3]

Currently in Canada, with the exception for women with high risk, an age-based (or universal) strategy is used, with biennial mammography breast cancer screening recommended for all women between the age of 50 and 69 even though programs and guidelines may vary between provinces.[4-6] Despite the significant benefit of universal screening in reducing breast cancer mortality compared to no screening,[7] this strategy is associated with harms such as the potential for over-diagnosis (when screening leads to identification of breast cancer that would not have caused clinical consequences in a woman's lifetime had it not been detected), false-positive findings, patient anxiety, and unnecessary treatment and its associated risks, together with economic burden.[8] On the other hand, since many screen-detected breast cancers occurred in women without dense tissue or a family history of breast cancer,[9] the risk of missing breast cancer cases (increase of false-negative cases) that may happen with risk-based screening strategies is a concern. Shortcomings of both universal and risk-based screening strategies have raised questions about the best strategy to detect breast cancer.

This Rapid Response report aims to review the clinical and cost-effectiveness of the risk-based screening approach for women with medium risk compared to the current age-based approach.

Research Questions

1. What is the comparative clinical effectiveness of risk-based breast cancer screening versus age-related population-based breast cancer screening?

2. What is the comparative cost effectiveness of risk-based breast cancer screening versus age-related population-based breast cancer screening?

Key Findings

Data from one clinical study showed that population-based universal screening (biennial mammography on women 50 to 69 years of age) led to a higher breast cancer detection rate and lower mortality rate than risk-based screening did, when both strategies were compared to an annual clinical breast exam screening strategy. However, risk-based screening slightly reduced the over-diagnosis rate while universal screening significantly increased over-diagnosis rate compared to an annual clinical breast exam. One cost-effectiveness analysis from Spain showed that compared to the universal population-based strategies, risk-based screening resulted in a higher benefit for a specific cost, with reductions in costs, false-positive results and over-diagnosed cases, while it increased false-negative results. Findings were from a clinical trial with a short follow-up period for the outcome of mortality (10 years), and a single cost-effectiveness study from Spain, which may limit generalizability to the Canadian context.

Methods

A limited literature search, with main concepts appearing in the title or major subject heading, was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to the main search to limit the retrieval by study type. A second broader search with main concepts appearing in the title, abstract or subject heading was also included. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, and meta-analyses. For both searches, retrieval was limited to the human population where possible and English-language documents published between January 1, 2012 and November 21, 2017.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Women who are at medium risk for breast cancer (risk based on biologic risk factors or patient history [e.g. history of breast cancer without genetic mutation, smoking, obesity, breast density, hormonal factors, reproductive history, use of oral contraceptives, previous exposure to radiation, use of hormone replacement therapy, alcohol consumption, physical inactivity])
Intervention	Risk-based breast cancer screening
Comparator	Age-related population based breast cancer screening

Outcomes	Clinical benefit (e.g., survival, mortality rate) and harms (e.g., quality of life, screening-related harms, other harms); clinical effectiveness (e.g., number of cancers detected) Cost-effectiveness outcomes
Study Designs	Heath technology assessments, systematic reviews, meta-analyses, RCTs, non-RCTs, cost effectiveness evaluation studies

RCT = randomized controlled trial.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications were already reported in the included SRs, or were published prior to 2012. Studies on patients with a high-risk of breast cancer (due to genetic mutation [e.g., BRCA1 or BRCA2] or first-degree relative of a carrier of a genetic mutation, personal history of breast cancer before the age of 35, or high radiation exposure to the chest before the age of 30) were also excluded.

Critical Appraisal of Individual Studies

The included clinical studies and cost studies were assessed using the Downs & Black[10] and Drummond[11] checklists, respectively. Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 527 citations were identified in the literature search. Following screening of titles and abstracts, 516 citations were excluded and 11 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search. Of these potentially relevant articles, ten publications were excluded for various reasons, while two publications (one clinical study, one cost study) met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

The literature search identified two relevant studies, one clinical study[12] and one cost analysis study.[13]

The clinical study is a prospective cohort study that compared the benefits and harms of risk-based screening, universal screening and clinical breast exam.[12] Risk-based screening was performed by biennial mammography on 298,345 women 50 to 69 years of age with medium risk; universal screening was performed by biennial mammography on 594,345 women 50 to 69 years of age; clinical breast exam was done annually on 896,596 women 35 years or older. Risk factors were not assessed in the universal screening group, and all study groups were mutually exclusive. Follow-up time was from 1999 to 2009. Outcomes reported were breast cancer detection rate, incidence of breast cancer stage II+, over-diagnosis detection rate (not otherwise defined in the study) and mortality reduction rate. The study was conducted in Taiwan.

The second study is a cost study that assessed the gain in terms of cost and harm reductions using risk-based screening compared to the usual practice in Spain.[13] Usual breast cancer screening was performed by biennial (B) mammography for women 50 to 69 years of age (B5069), or 45 to 74 years of age (B4574). Risk-based strategies were performed by annual (A), biennial (B), triennial (T), and quinquennial (Q) mammography, for women starting at ages 40, 45 and 50 years and ending ages 69 and 74 years in the four risk groups, low, medium low, medium high and high (risks in all four groups were based on the degree of breast density, and belonged to medium breast cancer risk as defined for the purposes of this report, detailed in Appendix 2). The study used a probabilistic model that allows to estimate the cumulative probability of death for a particular cohort exposed to a specific screening scenario after certain years of follow up.[14] Data sources were based on Catalan or Spanish data from population based registries for breast cancer screening programs. When the input data were not available, data from the Cancer Intervention and Surveillance Modeling Network (CISNET) or from the Breast Cancer Surveillance Consortium groups in the USA were used. The study assumed that there are no changes in the risk factors after the age at which screening exams start (i.e., the proportion of women in the risk groups remained constant over time). Outcomes reported were the number of lives extended (LE) quality-adjusted life years (QALYs), cost, false positives (FP), false negatives (FN), and over-diagnosis. The study was conducted in Spain.

Characteristics of the included studies are detailed in Appendix 2.

Summary of Critical Appraisal

The included study[12] was a population-based cohort study, had clearly described hypotheses, method of selection from source population and representation of the study population, main outcomes, interventions, patient characteristics, and main findings. Estimates of random variability and actual probability values were provided with appropriate methods. The study quality was limited with short follow-up time (1999 to 2009) which may cause underestimation of outcomes such as death. The study had enough power to detect clinically important effects.

The included cost study[13] had an economic evaluation that is likely to be usable (see Appendix 3 for more detail), and outcomes and costs were assessed and compared appropriately. The presentation and discussion of study results include issues of concern to users. The analysis was based on a variety of data sources (Spanish and American), and screening sensitivity was based on film mammography (the sensitivity, specificity and cost may be different from digital mammography). The assumption that there are no changes in the risk factors after the age at which screening exams may not be correct (personal and family history tend to change with time). The generalizability of the results is therefore limited to film mammography and the above assumptions.

Details of the critical appraisal of the included studies are presented in Appendix 3.

Summary of Findings

What is the comparative clinical effectiveness of risk-based breast cancer screening versus age-related population-based breast cancer screening?

The clinical study compared the benefits and harms of risk-based screening (biennial mammography on women 50-69 years of age with medium risk), universal screening (biennial mammography on women 50-69 years of age) and annual clinical breast exam on

women 35 years or older.[12] Detection rates (per 1000 women) were 2.80, 4.86 and 0.97 for risk-based mammography, universal biennial mammography, and annual clinical breast exam screenings, respectively, with a similar trend for women who got repeated screening for the confirmation of diagnosis. Mortality reduction, compared to annual clinical breast exam was 14% with risk-based (difference not statistically significant), and 41% with universal screening (statistically significant difference). Stage II+ breast cancer incidence reduction (compared with annual clinical breast exam) was 8% with risk-based and 30% with universal screening (all differences were statistically significant). Compared to annual clinical breast exam, the over-diagnosis rate was reduced by 3% with risk-based screening (difference not statistically significant) and increased by 13% with universal screening (statistically significant difference).

The authors concluded that compared with annual clinical breast exam , "universal biennial mammography resulted in a substantial reduction in breast cancer deaths, whereas risk-based biennial mammography resulted in only a modest benefit. Compared with annual clinical breast exam, risk-based and universal mammography screening did not result in significant over-diagnosis of breast cancer."[12] Given the finding of a statistically significant increase in over-diagnosis with universal screening, it is possible that this concluding statement refers to clinical significance. No results or conclusions were provided directly comparing risk-based with universal breast cancer screening.

What is the comparative cost effectiveness of risk-based breast cancer screening versus age-related population-based breast cancer screening?

The cost study assessed the gain in terms of cost and harm reductions using risk-based screening compared to the usual practice universal (or uniform) screening strategies) in Spain (biennial mammography for women 50 to 69 years of age).[13] In this study, universal screening was analyzed using two strategies, biennial mammography on women 50 to 69 years of age (B5069) or 45 to 74 years of age (B4574). Risk-based strategies were performed by annual (A), biennial (B), triennial (T),and quinquennial (Q) mammography, for women starting ages 40, 45 and 50 years and ending ages 69 and 74 years in the four risk groups, low (L), medium low (ML), medium high (MH) and high (H) (the risk for all four groups depends on breast density and belongs to medium breast cancer risk as defined for the purposes of this report).

As biennial mammography on women 50 to 69 years of age is the current universal screening strategy in Canada, the following summary of findings is focused on the comparison of risk-based strategies with the uniform strategy B5069. When effectiveness was measured as LE, if risk-based strategies were used instead of usual practice B5069, with Q, T and A exam periodicities for women at L/ML, MH, and H risk, respectively, reductions of costs, FP results and over-diagnosis would be achieved. Namely, the optimal risk-based strategies were Q5074-Q5074-T5074-A5074 for the L, ML, MH and H risk groups, respectively. In other words, the optimal screening strategy is quinquennial periodicity for the L and ML risk groups, triennial periodicity of the MH risk group, and annual periodicity for the H risk group for women 50 to 74 years of age. This strategy yielded 3.8% higher benefits in terms of LE and reductions of 8.9% in costs, 25.1% in FPs, and 20.6% in over-diagnosed cases; however, FNs were increased by 22.7%. In absolute numbers, with an annual discount rate of 3% for every 2,000 women screened, that risk-based strategy would extend about the same number of lives as the usual practice B5069 strategy but would avoid 1.5 over-diagnosed cases, 97 FP mammograms (six of them

ending with a biopsy) and would save 250,000 Euros, with one additional FN as the drawback.

When effectiveness was measured in QALYs, compared to the usual practice strategy B5069, the optimal risk-based strategy was Q5069-Q4574-Q4574-A4074. In other words, the optimal screening strategy was quinquennial periodicity for the L risk group (for women aged 50 to 69 years) as well as ML and MH risk groups (women aged 45 to 74 years), and annual periodicity for the H risk group (for women 40 to 74 years of age). This strategy yielded reductions of 8% in costs, 17.2% in FPs, 25% in over-diagnosed cases, and a 26.2% increase in FN. The same trend of benefit was found for all risk-based strategies compared to uniform (or universal) strategy.

The authors concluded that compared to uniform screening strategies, risk-based strategies can reduce harm and costs, and the optimal screening strategy is characterized by quinquennial or triennial periodicities for the low or moderate risk groups and annual periodicity for the high-risk group.

The main findings of the included studies are presented in Appendix 4.

Limitations

The literature search found a limited number of relevant studies: one clinical and one cost study. The clinical study is a population-based cohort study with short follow-up time for outcomes such as death. The cost effectiveness analysis was based on a variety of data sources, and screening sensitivity was based on film mammography (not digital mammography). The assumption that there are no changes in the risk factors after the age at which screening exams may not be correct (personal and family history tend to change with time), limiting the accuracy and generalizability of the findings.

Conclusions and Implications for Decision or Policy Making

A limited quantity of evidence showed that, compared to an annual clinical breast exam screening strategy, population-based universal screening (biennial mammography on women from 50 to 69 years of age) led to a higher breast cancer detection rate and lower mortality rate than risk-based screening did. However, risk-based screening slightly reduced the over-diagnosis rate while universal screening significantly increased the over-diagnosis rate compared to annual clinical breast exams. There were no direct comparisons between risk-based and universal screening strategies. Cost-effectiveness analysis showed that, compared to the universal population-based strategies, risk-based screening resulted in a higher benefit for a specific cost, with reductions in costs, false-positive results and over-diagnosed cases, while increased false-negative results.

In 2016, the Canadian Clinical Advisory Committee on Breast Cancer Screening and Prevention supported the integration of a risk stratification screening approach into clinical practice, and recommended collection of breast density data as an important factor for determining disease risk, and that for women with medium risk, annual or biennial mammography is recommended starting at age 40.[15] The evidence upon which this recommendation was based was not clearly described in this publication.

Clinical and cost-effectiveness studies with long follow-up times comparing current practice to risk-based strategies in a Canadian context using both film and digital mammography is needed to confirm the optimal breast cancer strategies in Canada.

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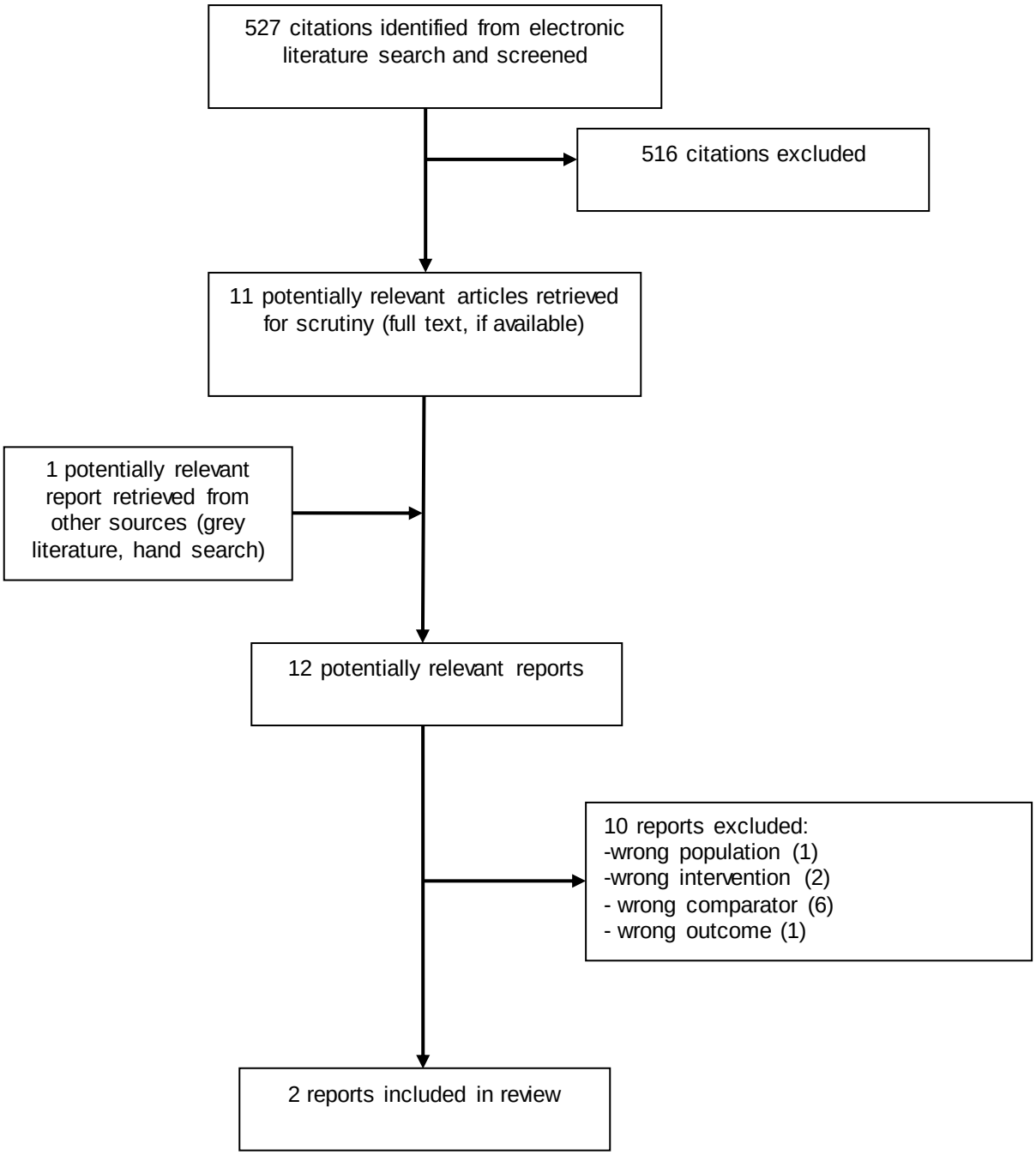
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Publications

First Author, Year, Country	Study Design Study Objectives	Interventions and Comparators	Patients	Main Outcomes
Clinical studies				
Yen,[12] 2016, Taiwan	Population-based cohort study *"To assess the benefits and the harms of risk-based and universal mammography screening in comparison with annual clinical breast examination (CBE)"* (p 915) Follow-up times from 1999 to 2009	Universal screening (biennial mammography for women 50-69 years of age) Risk-based screening (biennial mammography for women 50-69 years of age) Clinical breast exam (annual exam for women 35 years and older)	Universal screening: 594,345 women Risk-based screening: 298,345 women with medium risk (conventional risk factors, specifically reproductive and menstrual history, and family history of cancer) CBE: 896,596 women	Breast cancer detection rate (or incidence) Stage II+ breast cancer incidence Over-diagnosis detection rate Mortality reduction rate
Cost studies				
Vilaprinyo,[13] 2014, Spain	Cost-effectiveness study *"1) To perform an economic evaluation and to assess the harm-benefit ratios of screening strategies that vary in their intensity and interval ages based on breast cancer risk; and 2) To estimate the gain in terms of cost and harm reductions using risk-based screening with respect to the usual practice"* (p 1)	Usual practice screening [biennial mammography for women 50-69 years of age (B5069), or 45-74 years of age (B4574)] Risk-based strategies (annual, biennial, triennial, and quinquennial mammography, for women starting ages 40, 45 and 50 years and ending ages 69 and 74 years in the four risk groups, L, ML, MH and H. Risk-based strategies are abbreviated with four strings, e.g. Q5069-Q4574-T4574-A4074, that correspond to the L, ML, MH and H risk groups, respectively	1) Low (L) risk: Category 1 breast density with at most one risk factor - family history or breast biopsy - and Category 2 breast density with no risk factors 2) Medium-Low (ML) risk: Category 1 breast density with two risk factors, Category 2 breast density with one risk factor, and Categories 3 or 4 breast density with no risk factors 3) Medium-High (MH) risk: Category 2 breast density with two risk factors, Categories 3 or 4 breast density with one risk factor 4) High (H) risk: Categories 3 or 4 breast density with two risk factors.	Effects measured in lives extended (cost, false positive, false negative, over-diagnosis) Effects measured in QALY (cost, false positive, false negative, over-diagnosis)

QALY = quality adjusted life year

Appendix 3: Critical Appraisal of Included Publications

Table 3: Summary of Critical Appraisal of Included Studies

First Author, Publication Year	Strengths	Limitations
Critical appraisal of included clinical trial (evaluated with the Downs & Black Checklist[10])		
Yen[12]	• hypothesis clearly described • method of selection from source population and representation described • loss to follow-up reported • main outcomes, interventions, patient characteristics, and main findings clearly described • estimates of random variability and actual probability values provided • study had sufficient power to detect a clinically important effect	• limitations inherent to population-based cohort studies (such as necessary information may be unavailable, data collection is not done by the researcher, confounder information is lacking, missing information on data quality) • short follow-up time
Critical appraisal of included cost study (evaluated with the Drummond Checklist[11])		
Vilaprinyo[13]	• the economic evaluation is likely to be usable (a well-defined question posed in an answerable form; a comprehensive description of the competing alternatives given; evidence for the programme's effectiveness established) • outcomes and costs assessed and compared appropriately (all the important and relevant outcomes and costs for each alternative identified; outcomes and costs measured accurately in appropriate units prior to evaluation; outcomes and costs valued credibly; outcomes and costs adjusted for different times at which they occurred) • a sensitivity analysis performed (modifying risk group distributions, over-diagnosis of invasive tumours, and excess of DCIS, costs of cancer treatment, and disutility of false-positive results) • an incremental analysis of the outcomes and costs of alternatives performed • the presentation and discussion of study results include all issues of concern to users	• variety of data source (RCTs and observational studies; Spanish and US data) • assumption that there are no changes in the risk factors after the age at which screening exams start • the generalizability of the results is limited to the Spanish National Health System

DCIS = ductal carcinoma in situ; RCT = randomized controlled trial.

Appendix 4: Main Study Findings and Author's Conclusions

Table 5: Main Study Findings and Authors' Conclusions

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusions</th></tr>
<tr><td colspan="2">Yen[12] (Clinical Trial)</td></tr>
<tr><td>Breast cancer detection rates (per 1000 women)
Universal biennial mammography screening: 4.86 (2.98 for women with repeated screening)
Risk-based mammography screening: 2.80 (2.77 for women with repeated screening)
Annual CBE screening: 0.97 (0.70 for women with repeated screening)

Mortality reduction (compared with annual CBE)
Universal biennial mammography screening: 41% (RR 0.59; 95%CI, 0.48-0.73)
Risk-based mammography screening: 14% (RR 0.86; 95%CI, 0.73-1.02).

Stage II+ breast cancer incidence reduction (compared with annual CBE)
Universal biennial mammography screening: 30% (RR 0.70; 95% CI, 0.66-0.74)
Risk-based mammography screening: 8% (RR 0.92; 95% CI, 0.86-0.99)

Over-diagnosis (compared with annual CBE)
Universal biennial mammography screening: 13% (RR 1.13; 95% CI, 1.08-1.18)
Risk-based mammography screening: -3% (RR 0.97; 95% CI, 0.92-1.03)</td><td>"Compared with population-based screening for breast cancer with annual CBE, universal biennial mammography resulted in a substantial reduction in breast cancer deaths, whereas risk-based biennial mammography resulted in only a modest benefit. Compared with annual CBE, risk-based and universal mammography screening did not result in significant overdiagnosis of breast cancer" (p 915)</td></tr>
<tr><td colspan="2">Vilaprinyo[13] (Cost study)</td></tr>
<tr><td>A) Effect measured in LE
<table>
<tr><th>Schedule</th><th>LE</th><th>Cost (x10^6€)</th><th>False positive</th><th>Over-diagnosis</th><th>False negative</th></tr>
<tr><td>Uniform B5069</td><td>201.9</td><td>139.6</td><td>19,256.3</td><td>347.6</td><td>223.9</td></tr>
<tr><td>Risk based strategies</td><td colspan="5">Percentage of change, compared to fixed B5069</td></tr>
<tr><td>Q5074-Q5074-Q4574-A4574</td><td>0.6</td><td>-9.3</td><td>-25.1</td><td>-25.9</td><td>22.7</td></tr>
<tr><td>Q5074-Q5074-T5074-A5074</td><td>3.8</td><td>-8.9</td><td>-25.1</td><td>-20.6</td><td>20.8</td></tr>
<tr><td>Uniform B4574</td><td>264.7</td><td>154.5</td><td>26,578.5</td><td>493.1</td><td>298.2</td></tr>
<tr><td>Risk based strategies</td><td colspan="5">Percentage of change, compared to fixed B4574</td></tr>
<tr><td>T5069-B5074-A5074-A5074</td><td>0.5</td><td>-7.7</td><td>-23.0</td><td>-12.4</td><td>-21.6</td></tr>
<tr><td>T5074-T5074-A4574-A4574</td><td>5.0</td><td>-6.8</td><td>-21.9</td><td>-10.1</td><td>-9.7</td></tr>
</table></td><td>"Compared to risk-based strategies, the uniform ones result in a much lower benefit for a specific cost. Reductions close to 10% in costs and higher than 20% in false-positive results and overdiagnosed cases were obtained for risk-based strategies. Optimal screening is characterized by quinquennial or triennial periodicities for the low or moderate risk-groups and annual periodicity for the high-risk group. Risk-based strategies can reduce harm and costs. It is necessary to develop accurate measures of individual risk and to work on how to implement risk-based screening strategies" (p 1)</td></tr>
</table>

Main Study Findings						Authors' Conclusions
B) **Effect measured in QALY**						
Uniform B5069	2,333.3	139.6	19,256.3	347.6	223.9	
Risk based strategies	Percentage of change, compared to fixed B5069					
Q5069-Q4574-Q4574-A4574	0.3	-8.3	-18.3	-25.9	24.9	
Q5069-Q4574-Q4574-A4074	1.5	-8.0	-17.2	-25.0	26.2	
Uniform B4574	2,848.8	154.5	26,578.5	493.1	298.2	
Risk based strategies	Percentage of change, compared to fixed B4574					
Q5074-Q5074-A4074-A4074	0.4	-9.2	-25.3	-23.4	-10.5	
Q4574-Q4574-A4574-A4074	4.0	-9.2	-20.4	-23.0	-7.2	

95% CI = 95% confidence interval; A = annual mammography; B = biennial mammography; CBE = clinical breast exam; LE = lives extended; Q = quinquennial mammography; QALY = quality-adjusted life years; RR = risk ratio; T = triennial mammography.