國立臺灣大學公共衛生學院流行病學與預防醫學研究所

碩士論文

Graduate Institute of Epidemiology and Preventive Medicine

College of Public Health

National Taiwan University

Master Thesis

危險導向為主乳癌篩檢之成本效益分析

Cost-effectiveness Analysis of Risk-guided Screening of Breast Cancer

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中華民國 106 年 7 月

July, 2017

doi:10.6342/NTU201702793

誌謝

在流預所的兩年，除了學習到學術研究的相關知識外，更多的是從「陳秀熙教授」學習到怎麼將所學習到的知識運用在生活當中，以及如何有效的學習新的事物，除此之外陳教授也用身教告訴每一個學生，比起學術研究更重要的是需懂得為人處世的道理，取之社會用之社會，這也是身為一個公衛人需謹記在心的。

感謝口試委員陳祈玲老師、范靜媛老師，許辰陽老師在口試過程當中給予關於論文的寶貴建議，使學生的論文可以更加完善。在碩士班的兩年，感謝一路上有許多同學的陪伴與加油，像是瑞珊、淑儀、立旻、珮樺，尤其在最後論文衝刺的一個月，因為有大家的陪伴，論文也才能如期地完成。在寫論文的過程中也感謝許多老師、學長姊、同學們的解惑幫忙，讓做論文當中遇到的問題能順利解決。

最後要感謝我的家人，做我最佳的後盾，讓我能無後顧之憂地努力學習，以及感謝我碩士班最好的兩位朋友，佩臻跟亭方，因為有妳們的支持及鼓勵，我才能順利完成碩士班的學習，也期望自己在未來的人生道路上能一步一腳印穩定的前進。

周佑霖 謹致於國立臺灣大學

doi:10.6342/NTU201702793

中文摘要

前言

運用乳房攝影術以及其他工具進行乳癌檢在過去三十年間已發展得相當成熟並且廣泛運用於乳癌防治。雖然以族群方式運用乳房攝影作為篩檢工具可有效進行乳癌防治，對於運用個人化風險評估進行個人化的乳癌防治策略以在效率以及效用雙方面達成乳癌防治的目的近年來益發受到重視。對於 BRCA 第一型與第二型帶因者與非帶因者之乳癌防治措施有相當大的差異，如何區分族群中 BRCA 第一型與第二型帶因者與非帶因者並分別提供適切的個人化乳癌防治策略做系統性的完整經濟評估在先前的研究中卻甚少被提及。

研究目標

本研究的主要目標在於

(1) 發展部分潛藏馬可夫模型在描述乳癌進展的同時將包含基因因子、傳統風險因子以及乳癌表現型等風險因子對於 BRCA 第一型與第二型帶因者與非帶因者在不同階段乳癌進程的影響納入模型考量中;

(2) 運用(1)之參數發展對於發生乳癌臨床症前期(preclinical detectable phase(PCDP)，即無症狀期)以及由臨床症前期進展成為臨床期(clinical phase, CP)之危險分數，藉以對目標族群進行危險分層；

(3) 架構於(1)與(2)之乳癌多階段疾病進程發展運用不同乳癌防治策略之馬可夫決策模型，藉以對各種防治策略進行評估；

(4) 對個人化乳癌防策略以及一致性乳癌防治策略分別以整體族群觀點以及 BRCA 第一型與第二型帶因者與非帶因者之觀點進行經濟評估。

材料與方法

本研究依 BRCA 第一型與第二型帶因者與非帶因者模擬一百萬名婦女，並發展三階段潛藏馬可夫模型描述無症狀乳癌存留於乳癌臨床症前期並成為篩檢偵測

doi:10.6342/NTU201702793

個案，以及其後續發展為具有症狀之臨床期乳癌成為篩檢間隔個案或拒絕個案之疾病進展過程。對於影響乳癌多階段進程之風險因子及其造成之疾病進展危險程度則由系統性文獻回顧獲得乳癌發生危險因子 (promotor) 以及乳癌進展危險因子(initiator)之影響。藉由不同危險因子的參數估計以及組合，可進一步得到乳癌由發生階段到進展階段之危險分數並據以對族群進行危險分層。對於不同乳癌疾病階段之防治策略，例如以預防性手術或以泰莫西芬(Tamoxifen)進行預防性投藥防止乳癌發生；或以不同篩檢間隔或篩檢工具進行乳癌篩檢偵測早期乳癌則以降低晚期乳癌以及乳癌死亡做為不同策略之效益評估指標。

本研究以所發展之部分潛藏馬可夫模型結合由實證資料中獲取之各乳癌疾病階段進程的危險因子模擬族群之乳癌進展過程。族群中之 BRCA 帶因狀態亦納入影響疾病演進之考量。 其他包含於模型之個人危險因子包含傳統風險因子(如身體質量指數、第一次足產年齡、使用荷爾蒙療法之病史)、基因因子如 P53 及單核苷酸多型性變異(SNPs)及乳癌病灶之免疫化學表徵(如 ER、PR 及 Ki67)等不同類型之風險因子以建構多階段乳癌進展風險模型。這些個人化因子與對於不同階段之乳癌風險影響則進一步用以形成個人化危險分數據以進行族群危險分層。

基於上述之架構，本研究以馬可夫決策分析方法對個人化乳癌防策略以及一致性乳癌防治策略分別以整體族群觀點以及 BRCA 第一型與第二型帶因者與非帶因者之觀點進行經濟評估。

結果

對 20 到 60 歲為起始年齡之 BRCA 帶因者估算之十年及終生乳癌發生危險分別介於 6.5 到 22% (十年乳癌危險)以及 58 到 39% (終身罹癌危險)。對非 BRCA 帶因的 50 歲婦女，其十年及終生乳癌發生危險性在前 10%高危險族群分別為 3.36%及 14.56% ，對最低 10%危險性的婦女則分別為 0.24%及 1.1%。從無症狀至有症狀時期的時間間隔則隨著危險性增加而變短，介於 3.74 年至 1.45 年之間。

doi:10.6342/NTU201702793

就均一乳癌防治策略而言，同樣利用乳房攝影術進行篩檢，族群採用的篩檢間隔愈短其效益愈大。一年一次的乳房攝影術篩檢相對於不篩檢在晚期乳癌及乳癌死亡的降低分別為 13.9% (95% CI: 13.8-14.0%)及 31% (95% CI: 30.9-31.1%)。若採風險分層建議篩檢間隔的個人化策略，則其效益介於統一每年篩檢與兩年一次篩檢之間，在晚期乳癌及乳癌死亡的降低分別為 12.5% (95% CI: 12.4-12.6%)及 28.4% (95% CI: 28.4-28.5%)，相似的結果可見於非 BRCA 帶因者之效益分析。對非 BRCA 帶因者而言，個人化篩檢間隔策略在風險較高者的效益較顯著，對具最高風險 30%的婦女其晚期乳癌及乳癌死亡的降低分別為 14.9% (95% CI: 14.8-15.1%) 及 30.4 (95% CI: 30.3-30.5%)。針對個人化篩檢工具策略，其利用不同工具對於中度危險層(40-70 百分位婦女)採乳房攝影術及乳房超音波之效益最大。

對 BRCA 帶因者結合初段與次段預防策略的效益整體說來不若非帶因者佳，主要是因為其疾病負擔較大。每年一次之篩檢所帶來之晚期乳癌風險降低介於 16-18%之間，乳癌死亡降低則介於 22-38%之間，此一效益之結果在合併預防性手術或預防性投藥作為介入策略之結果皆相近。若合併對以兩年於非 BRCA 帶因族群進行篩檢以及不同之 BRCA 帶因者介入策略以全族群角度進行效益評估結果顯示，對非 BRCA 帶因族群提供兩年一次乳房攝影以及對 BRCA 帶因族群中最高之 20%婦女提供預防性手術結合對其餘 80%風險之婦女進行每年乳房攝影可達成之效益最佳 (晚期乳癌風險降低：13.3%, 95 信賴區間: 12.6-13.9%, 乳癌死亡風險降低：36.2%, 95CI: 25.3-26.6%)。

運用所發展之部分潛藏多階段馬可夫模型對以風險分層進行個人化篩檢間隔之乳癌防治策略進行經濟評估之結果顯示，此一篩檢策略之增量成本效益比 (incremental cost-effectiveness ratio, ICER)為每人年美金 34,585 元 (95%信賴區間: 34,464-34,707 元)，低於提供均一性每年乳房攝影篩檢(47,096 元，95%信賴區間 46946-47247 元)以及每兩年乳房攝影篩檢(36,691 元，95%信賴區間 36,550-36,831

doi:10.6342/NTU201702793

元)。增量成本效益比在以風險分層提供個人化影像篩檢工具之策略則增為每人年 115,838 元(95%信賴區間: 115,396-116,281)，此一結果主要是由於使用磁振掃描作為篩檢工具所需要之昂貴成本。對於非 BRCA 第一型與第二型帶因之族群進行個策略之經濟評估結果與此相似。綜合上述效益分析與經濟評估之結果顯示以風險分層為基礎之個人化篩檢間隔策略對於乳癌防治可用低於每兩年一次族群乳房攝影篩檢之增量成本效益比達到與對全族群提供每年一次乳房攝影篩檢相近之效益。此個人化篩檢間隔策略在付費意願(Willing-to-Pay, WTP)為 2 個平均國民所得標準下為一可接受之策略，而個人化篩檢工具策略即使在付費意願達 3 個平均國民所得標準仍未能達接受標準。

對於 BRCA 第一型與第二型帶因族群結合初段與次段預防策略之經濟評結果估計顯示，預防性手術結合乳房攝影之增量成本效益比為每人年 2,722 元，此一結果在增加磁振造影為篩檢工具之策略則增為 49,884 元。但若將對全族群進行基因檢測以獲取其 BRCA 帶因資訊所需花費之成本納入考量時，這些策略之增量成本效益比將大幅增加。對於 BRCA 帶因族群進行之策略在以 2 個平均國民所得作為付費意願標準多為可接受之策略。

結論

本研究為第一個運用系統化方式針對乳癌個人化防治策略進行經濟評估，並分別從 BRCA 帶因與非帶因者的角度進行詮釋。利用多階段個人風險預測模式的建構進行乳癌個人化防治不僅能有效降低乳癌的嚴重事件，且具成本效益。在個人化防治策略中，依個人危險提供不同篩檢間隔建議的策略最具成本效益，而個人化篩檢工具的使用能否具成本效益則被高危險族群所使用的影像工具之成本所決定。

關鍵字：多階段馬可夫模式、個人化篩檢、乳癌、成本效益分析

doi:10.6342/NTU201702793

Abstract

Introduction

In spite of the advent of widely used mammography and other alternative imaging techniques for breast cancer screening over the past three decades, risk-guided preventive strategies have increasingly gained attention as individually-tailored strategies guided by the risk of breast cancer may render prevention of breast cancer death not only effective but also efficient. However, a systematic economic evaluation of risk-guided personalized preventive strategies, particularly separating the entire cohort into the carrier and non-carrier of BRCA1/2, has been never addressed before as preventive strategies for the carriers of BRCA 1/2 would be different from those for the non-carrier of BRCA 1/2.

Aims The goals of this thesis are to

(1) Develop a partially-hidden three-state Markov model to incorporate state-specific covariates including genetic variants, conventional risk factors, clinical attributes, and tumour phenotypes by the stratification of the status of BRCA1/2;

(2) Develop the risk score for onset of pre-clinical detectable phase (PCDP) (e.g. asymptomatic) and that for the transition from PCDP to clinical phase (CP)

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based on the parameters abstracted from (1) so as to stratify the risk of underlying population;

(3) Develop Markov analytical decision model by the assignment of different preventive strategies to different risk groups as opposed to the disease natural history based on information gleaned from (1) and (2) in order to evaluate the efficacy and effectiveness of these preventive strategies;

(4) Do economic appraisal of universal and personal preventive strategies for the overall group, the carrier of BRCA 1/2, and the non-carrier of BRCA 1/2.

Material and Methods

The entire population around one million women were simulated by the stratification of the status of BRCA 1/2. A three-stage partially-hidden Markov model was developed to identify asymptomatic BC staying in the PCDP detected and symptomatic BC such as interval cancer and cancers from non-participants. Systematic literature review has been done to estimate the effect sizes of state-specific factors accounting for each transition, mainly including initiators and promoters after systematic literature review. State-specific risk scores based on these estimated parameters were formed for the classification of the entire population into ten risk groups. Various preventive and strategies for reducing the following outcomes,

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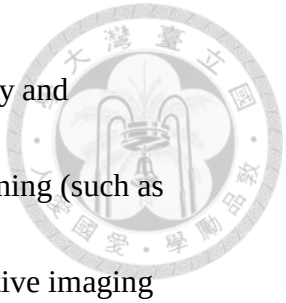

including incidence of asymptomatic BC through prophylactic surgery and chemoprevention with tamoxifen and symptomatic BC through screening (such as different inter-screening interval and various combinations of alternative imaging techniques), leading to the reduction in death from and advanced BC and were deployed.

Using the proposed partially-hidden Markov model in conjunction with the state-specific effect on the occurrence and progression of breast cancer, we simulated the path of breast cancer evolution. The effect of BRCA carrier status was included in the derivation of risk of breast cancer for simulated subjects. The covariates included in the model including conventional risk factor such as BMI, age at first pregnancy and hormone therapy history, genetic factor such as P53 and multiple mutations of SNPs, immunochemical characteristics of breast lesion such as ER, PR, and Ki67. The risk scores derived from these covariates enable us to stratify the population into a series of gradient of breast cancer risk.

Analytical Markov health economic decision model was proposed to do economic appraisal for universal screening and personalized preventive strategies.

Results

Considering the BRCA carriers, the 10-year and lifetime risk of breast cancer for

doi:10.6342/NTU201702793

women aged at 20 to 70 years ranged from 6.5 to 22% and 58 to 39%, respectively. For women of non-BRCA carrier at their 50 years, the 10 year and lifetime risks were 0.24% and 1.1% for first decile and 3.36% and 14.56% for the tenth decile, respectively. The time of breast cancer progression from asymptomatic to symptomatic one ranged from 3.74 to 1.45 year from the first decile to the tenth decile with an increasing trend.

For the universal screening strategies, the shorter the screening interval, the higher the efficacy is. For the annual mammographic screening, the efficacies were 13.9% (95% CI: 13.8-14.0%) and 31% (95% CI: 30.9-31.1%) in terms of advanced cancer reduction and breast cancer death reduction. The efficacy of risk based screening interval was between that of universal biennial and annual strategy with 12.5% (95% CI: 12.4-12.6%) and 28.4% (95% CI: 28.4-28.5%) in reducing advanced breast cancer and breast cancer death, respectively. Similar results were observed for non-BRCA carrier women. The benefit of risk based screening interval bring down the risk of advanced breast cancer and breast cancer death mainly for the high risk group (8^{th} to 10^{th} decile) with risk reduction of 14.9% (95% CI: 14.8-15.1%) and 30.4 (95% CI: 30.3-30.5%), respectively. Similar was observed for risk-based screening modality with larger extent for middle risk group (4^{th} to 7^{th} decile) for whom mammography and ultrasound was applied.

doi:10.6342/NTU201702793

Considering the efficacy of primary and secondary prevention for BRCA carriers, the efficacy was generally lower compared with non-BRCA carrier women due to the elevated risk for breast cancer. The efficacy for annual screening with and without combined with preventive mastectomy or tamoxifen were around 16-18% and 22-38% for advanced cancer reduction and death reduction, respectively. Taking into account for the risk reduction attributable to the intervention for BRCA carrier and non-BRCA carrier, the strategy of biennial mammography for the non-carrier and preventive mastectomy for the 9^{th} and 10^{th} decile and annual mammographic screening for BRCA carriers demonstrated the one with highest efficacy (13.3%, 95CI: 12.6-13.9% for advanced cancer reduction and 36.2%, 95CI: 25.3-26.6% for death reduction).

The economical appraisal for personal strategy with risk-based inter-screening interval found the incremental cost-effectiveness ration (ICER) of 34,585 (95% CI: 34464-34707) which was lower than that of universal annual (47,096, 95% CI: 46946-47247) and biennial (36691, 95% CI: 36550-36831) but the ICER of personal strategy with risk-based alternative imaging technique was elevated to 115,838 ((95% CI: 115,396-116,281)) due to the administration of costly MRI. This results were similar when considering only non-BRCA carrier population. These result show that personalized screening strategy with risk-based screening interval has the efficacy close

doi:10.6342/NTU201702793

to annual screening and the ICER lower than universal biennial screening strategy. Personalized strategy with various inter-screening was acceptable when 2GDP is taken as the threshold of WTP whereas personalized strategy with multimodality was not acceptable even 3GDP is taken as the threshold of WTP

Regarding the ICER for primary and secondary prevention strategies for BRCA carrier, the ICER values ranged from 2,722 for mammography with surgery to 49,884 when MRI was added. It is not surprising that when all women had the uptake of genetic testing to get information on BRCA carrier the ICER increased substantially. Most of preventive strategies for women with BRCA carrier were acceptable within the range of 2 GDP of willingness to pay (WTP).

Conclusion

This is the first study to provide a systematic economic appraisal of breast cancer screening with personalized preventive strategies by separating the entire cohort carrier and non-carrier of BRCA. Such personalized preventive strategies in the light of risk-based strategies is not only efficacious but also cost-effective, particularly considering risk-adjusted inter-screening interval. However, risk-adjusted multimodality is highly dependent on the cost involved in the high-risk group.

KEYWORDS: Multistate Markov Model, Individually Tailored Screening, Breast Cancer, Cost-effectiveness analysis

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Chapter 1 Introduction

Among the neoplastic diseases of women, breast cancer is the most common one regardless of race or country with the mortality rate at second place word-widely. Around half of breast cancer cases and nearly 60 percent of breast cancer deaths occur in women in less-developed countries (Ferlay, Shin et al. 2010, WHO 2014). In 2013, there were about 1.8 million new breast cancer cases and 464,000 breast cancer deaths in women worldwide (Jemal, Bray et al. 2011, Fitzmaurice, Dicker et al. 2015).

There are many factors identified as the risk for development of breast cancer including the demographic factors such as age, family history of breast cancer, traditional hormonal exposures including early menarche, late menopause, nulliparity /first pregnancy after 30, postmenopausal hormone therapy, behavior factors such as postmenopausal obesity, alcohol use, absence of physical activity, and gene mutations such as BRCA1, BRCA2, CHEK2, ATM, FGFR2, MAP3KI (Wu, Chen et al. 2006, Chen, Wu et al. 2016, Yen, Wu et al. 2016). In addition to genome influence, epigenetic mechanism, like DNA methylation, is an alternative genetic mechanism which may lead to heterogeneous genotype expression in the absence of DNA mutation. It was well known that c-erbB2 is one of epigenetic factors responsible for breast cancer (Yen, Wu et al. 2016). Although the prediction for the occurrence, even the progression, of breast cancer using these identified risk factors were fruitful, most of them were not modifiable and can hardly been using as the target for primary prevention. The mass screening program, mainly using mammography as the tool, thus plays a pivotal role for the goal of early detection and mortality reduction of breast cancer (Tabar, Vitak et al. 2011, Yen, Tsau et al. 2016, Chen, Yen et al. 2017).

Since 1980, population-based screening using mammography has been used as a

doi:10.6342/NTU201702793

major strategy for secondary prevention of breast cancer (Shapiro 1997). The efficacy in bringing down the breast cancer mortality by the implementation of population-based mass screening program have been demonstrated with the ground of evidence (Tabar, Vitak et al. 2011, Marmot MG 2012, Yen, Tsau et al. 2016, Chen, Yen et al. 2017). However, the implementation of a screening program at the scale of population is often faced with the confrontation of the organization of resources to achieve the goal of mortality reduction (Chen, Yen et al. 2017). Furthermore, there is raising concerns in the benefits and harms, such as false negative, false positive cases and over-diagnosis brought by the implementation of such a unifying strategy for all of the target population (Marmot MG 2012, Chen, Yen et al. 2017). Stemming from the identified risk factors responsible for the occurrence and progression of breast cancer, a personalized screening strategy for subjects at different level of risk in terms of both the occurrence and progression of neoplastic lesion may be a solution to optimize the benefit of breast cancer screening (Esserman, Shieh et al. 2009, Wu, Yen et al. 2013, Wu, Yen et al. 2014).

The risk factors in association with breast cancer include genetic and environmental factors. There are a number of predicted models for estimating the risk of breast cancer. The drawback is that they are all classified as two-state models rather than multi-state models which can delineate multi-states disease progression in related to genetic and environmental factors. The multi-state risk stratification by using state-of-the-art evidence derived from molecular, clinical, and epidemiological studies on the occurrence and progression of breast neoplasm was first been proposed by Wu et al. in 2013(Wu, Yen et al. 2013). Following the framework of multi-state risk stratification, a three-state Markov model was constructed to depict breast cancer nature

doi:10.6342/NTU201702793

history from normal, preclinical, and to clinical phases. Genetic, epigenetic, and personal attributes obtained from literature are incorporated into model to assess their influences on disease progression in current study.

In spite of the advent of widely used mammography and other alternative imaging techniques for breast cancer screening over the past three decades, risk-guided preventive strategies based in personalized multi-state risk model indicated above have increasingly gained attention as individually-tailored strategies guided by the risk of breast cancer may render prevention of breast cancer death not only effective but also efficient. However, a systematic economic evaluation of risk-guided personalized preventive strategies, particularly separating the entire cohort into the carrier and non-carrier of BRCA1/2, has been never addressed before as preventive strategies for the carriers of BRCA 1/2 would be different from those for the non-carrier of BRCA 1/2.

The aims of this thesis are to

(1) Develop a partially-hidden three-state Markov model to incorporate state-specific covariates including genetic variants, conventional risk factors, clinical attributes, and tumour phenotypes by the stratification of the status of BRCA1/2;

doi:10.6342/NTU201702793

(2) Develop the risk score for onset of pre-clinical detectable phase (PCDP) (e.g. asymptomatic) and that for the transition from PCDP to clinical phase (CP) based on the parameters abstracted from (1) so as to stratify the risk of underlying population;

(3) Develop Markov analytical decision model by the assignment of different preventive strategies to different risk groups as opposed to the disease natural history based on information gleaned from (1) and (2) in order to evaluate the efficacy and effectiveness of these preventive strategies;

(4) Do economic appraisal of universal and personal preventive strategies for the overall group, the carrier of BRCA 1/2, and the non-carrier of BRCA 1/2.

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Chapter 2 Literature review

2.1 Literature review on breast cancer risk prediction

In the past, there have been many mathematical models for the risk prediction of breast cancer, which can be broadly divided into three sections:

(1) Only use conventional risk factors or genetic risk factors to predict breast cancer risk

(2) Estimate risk of carrying an inherited genetic mutation (BRCA 1 and BRCA 2)

(3) Use conventional risk factors or genetic risk factors to predict breast cancer risk and risk of carrying an inherited genetic mutation (BRCA 1 and BRCA 2)

In Table 2.1.1 and 2.1.2, we arrange the information of past breast cancer risk prediction models and cancer mutation models including those risk factors they incorporated in models.

2.1.1 Risk prediction models for breast cancer using conventional factors

A. Gail model (Gail, Brinton et al. 1989)

The Gail model is the most widely used and earliest model, developed using case-control study (Breast Cancer Detection Demonstration Project (BCDDP)). It used multivariate logistic regression based on hormonal factors (age at menarche, age at first live birth), personal history factors (number of prior breast biopsies, personal history of atypical hyperplasia) and family history (the number of first-degree female relatives

doi:10.6342/NTU201702793

with breast cancer) to calculate a woman's absolute risk of developing invasive breast cancer over the next five years and lifetime risk (until age 90).

Model formulation

The risk prediction model proposed Gail et al was expressed as follows

OR= exp[-0.075+ 0.09×(age at menarche)+ 0.53×(number of breast biopsies)+ 0.22×(age at first live birth)+ 0.96×(number mother/sisters with breast cancer)+ 0.01×(age >= 50)-0.29×(age×number of biopsies)-0.19×(age at first live birth×number of mother/sisters with breast cancer)].

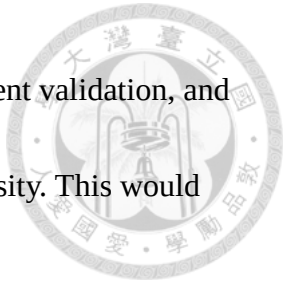
The performance of Gail model is acceptable for average risk women aged 35 and order. For high risk women such as those with family history or individualized risk prediction, the application of Gail model was suboptimal. Efforts for the improvement of the precision in breast cancer risk prediction were achieved by including factors such as breast density and BMI demonstrated in the Chen model and Barlow model.

B. Chen model (Chen et al. , 2006)

The Chen model is an extension to the Gail model that incorporates breast density as a risk factor, and is intended for white women 35 years or older.

Chen model incorporated risk factors included age of first live birth, number of benign breast biopsies, and number of first-degree relatives with breast cancer, weight, and

doi:10.6342/NTU201702793



breast density (based on percent density). This model lacks independent validation, and while weight is a factor in this model, BMI is not used to modify density. This would likely be a more accurate way of modifying this risk factor.

C. Barlow model (Barlow, White et al. 2006)

The Barlow model was developed by using retrospective reviewed data (Breast Cancer Surveillance Consortium (BCSC)). The Barlow model could be divided in two parts: premenopausal model/ postmenopausal. The risk factor incorporated: age, breast density (by BIRADS category), number of first-degree relatives with breast cancer, and previous breast procedures were selected among premenopausal women. For postmenopausal women, risk factors included age, ethnicity (Hispanic or non-Hispanic), race, BMI, hormonal factors (age of birth of first child, use of hormonal therapy, type of menopause), hereditary factors (number of first degree relatives with breast cancer), mammographic findings (breast density, prior mammographic findings), and prior breast procedures. It had more ability to identify women at high risk for breast cancer for preventive interventions or more intensive surveillance.

D. Colditz model (Colditz and Rosner 2000)

The Colditz model was developed by using Nurses' Health Study data and applied Poisson regression model incorporated benign breast disease, first-degree family history

doi:10.6342/NTU201702793

of breast cancer, postmenopausal hormone use, BMI, height, and alcohol consumption to predicts the risk of developing invasive breast cancer (until age 70) in women.

E. Claus model (Claus, Risch et al. 1991)

The Claus model was first described by Claus et al. in 1991 by using a large population-based, case–control study conducted by the Centers for Disease Control, prior to the discovery of the BRCA1 and BRCA2 gene loci. The model uses more complex family history (at least one female first- or second-degree relative with breast cancer) on women and uses hereditary variables to predict the lifetime risk of breast cancer without any conventional risk factors.

Above the model were introduced, just used conventional risk factors or hereditary variables to predict breast cancer risk (regardless absolute risk or relative risk). However, it is not sufficient to just know simple relationship between particular risk factors and the occurrence of breast cancer in the era of preventive medicine. Therefore, it is essential to develop a model incorporated the natural history of the breast cancer. We can estimate the sojourn time (the duration of the preclinical screen-detectable period) considering more and more risk factors (regardless conventional risk factor or new finding of medicine). Furthermore, we can also estimate different screening tools' sensitivity which is crucial for deciding effective screening programmes.

doi:10.6342/NTU201702793

2.1.2 Risk prediction models for BRCA carrier status

A. Myriad I model (Shattuck-Eidens, Oliphant et al. 1997)

The Myriad I model (Shattuck-Eidens model) is an early model for determining the risk of the BRCA1 mutation for women with a personal or family history of breast cancer utilizing hereditary variables. The Myriad I model cannot be applied to women without a personal or family history of breast or ovarian cancer. The Myriad I model incorporated risk factors included: age of first diagnosis of breast or ovarian cancer, Ashkenazi Jewish ethnicity, bilateral breast cancers, number of relatives (any degree) affected by breast cancer, number of relatives (any degree) affected by ovarian cancer, number of relatives (any degree) affected by both breast and ovarian cancer.

B. Penn and Penn II models (Couch, DeShano et al. 1997)

The Couch model (UPenn or Penn Model) was develop in 1997, and is intended for patients with a family history of breast cancer. The model estimates the probability of a BRCA1 mutation in both individuals and in family members based on their relation to an affected family member. The Couch (Penn) model was subsequently updated to the Penn II model, which predicts the pretest probability of identifying a BRCA1 or BRCA2 mutation in an individual or family member.

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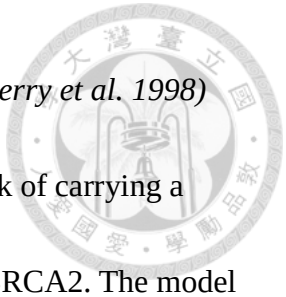

C. BRCAPRO model (Berry, Parmigiani et al. 1997, Parmigiani, Berry et al. 1998)

BRCAPRO was developed in 1997 as a model predicting the risk of carrying a deleterious BRCA1 mutation and subsequently extended to include BRCA2. The model is targeted to individuals, males and females, both with and without a family history of breast or ovarian cancer (or both), and it is usable to assess either personalized or family risk. BRCAPRO predicts the probability of carrying BRCA1 or BRCA2 germline mutation, the probability of developing invasive breast cancer or ovarian cancer (for undiagnosed individuals), and the probability of developing a contralateral breast cancer (for already diagnosed individuals). Predictions of mutation carrier status are calculated based on one's family history and published estimates of the prevalence and penetrance of BRCA1 and BRCA2, baseline rates of breast cancer in the population, and applying Bayes' theorem. BRCAPRO is continuously updated as information on these rates is refined.

D. Tyrer-Cuzick model (Tyrer, Duffy et al. 2004)

The Tyrer-Cuzick was originally developed in 2004; it estimates a woman's risk for carrying a BRCA1 or BRCA2 mutation and the risk of breast cancer (invasive or in situ) over time, accounting for hereditary, hormonal, and pathological risk factors. Risk factors used include: age, BMI; age at menarche, age at first live birth, parity, age at

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menopause, use of hormone replacement therapy; breast biopsies, presence of hyperplasia, atypical hyperplasia (ductal or lobular), or LCIS; and hereditary information including first- and second-degree relatives with breast cancer and/or ovarian cancer, incorporating age of onset, and the presence of bilateral breast cancers The model is a two-locus genetic model, accounting for (1) a locus containing information on BRCA genes (containing either a “normal” allele, a BRCA1 or a BRCA2 allele); (2) a locus for an hypothetical low-penetrant susceptibility gene, accounting for an increase of relative hazard of breast cancer.

2.1.3 Risk prediction models associated with SNPs

The variation in lower-impact, common susceptibly loci or SNPs can be responsible for a larger percentage of cancers in the population. For example, over 75 single-nucleotide polymorphisms (SNPs), conferring an odds ratio for breast cancer of 0.72 to 1.97, have been identified and contribute to approximately 14 percent of occurrence of breast cancer.(Couch, Nathanson et al. 2014) There are some large-scale studies to provide evidence that each SNP is associated with a small increase or decrease in risk. Based on the few SNPs identified, studies were performed to determine how they might add to the Gail model. (Gail 2008, Gail 2009) A first study used receiver operating characteristic (ROC) curves to predict that the area under the curve (AUC) would improve from 0.607

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for the Gail model alone, as implemented in the National Cancer Institute's Breast Cancer Risk Assessment Tool (BCRAT), to 0.632 when risk information from the seven SNPs was combined with the Gail model (BCRAT plus seven SNP).(Mealiffe, Stokowski et al. 2010) A second analysis showed that it could be achieved in re-classification of risk, under the assumption that the model combining information from the seven SNPs with the Gail model was well calibrated. (Mealiffe, Stokowski et al. 2010)

2.2 Literature review on multistate disease progression of breast cancer

Three-state progression of breast cancer can consist of three parts, free-of-breast-cancer(FBC), through the pre-clinical detectable phase (PCDP) and finally to clinical phase (CP), three of which have been well defined by using various detection methods and broadly used (Shapiro, Goldberg et al. 1974, Prorok 1976, Day and Walter 1984, van Oortmarssen, Habbema et al. 1990, Chen, Kuo et al. 2000) In this process, there are many risk factors such as genetic and environmental that can speed up the progression of breast cancer.

2.2.1 Risk factors for the occurrence of breast cancer

(1) BRCA1 and BRCA2

Two major susceptibility genes, BRCA1 and BRCA2, were identified. We assumed that subjects would not carry BRCA1 and BRCA2 mutations together, although this occurs with very low probability.(Hall, Reid et al. 2009) The population mutation frequencies of the BRCA1 and BRCA2 carriers (0.11% and

doi:10.6342/NTU201702793

0.12% or 0.7% and 1.3%) used for generating simulated data(Peto, Collins et al. 1999, Anglian Breast Cancer Study 2000) The incidence rate of breast cancer among carriers was estimated from the results of a meta-analysis.(Land, Tokunaga et al. 2003)

(2) Single-nucleotide polymorphisms (SNPs)

Based on genome research, we also consider seven established single-nucleotide polymorphisms (SNPs), including rs2981582, rs3803662, rs889312, rs3817198, rs13281615, rs13387042, rs1045485, rs9485372, rs9383951, rs7107217, rs12118297 and rs16992204 from population-based genetic epidemiological study,(Cox, Dunning et al. 2007, Easton, Pooley et al. 2007, Stacey, Manolescu et al. 2007, Long, Cai et al. 2012, Han, Long et al. 2016) the risk-allele frequencies for rs2981582, rs3803662, rs889312, rs3817198, rs13281615, rs13387042, rs1045485, rs9485372, rs9383951, rs7107217, rs12118297 and rs16992204 are 0.38, 0.25, 0.28, 0.30, 0.40, 0.50, 0.86, 0.454, 0.1,0.358, 0.38 and 0.12 ,and the relevant relative risks per allele were 1.26, 1.20, 1.13, 1.07, 1.08, 1.20, 1.13, 0.9, 0.88 ,1.08, 0.91 and 1.13.

(3) Breast density

It is well known that breast density is strongly associated with the risk of being susceptible to breast cancer. A meta-analysis of breast density data was used to derive the distribution of breast density in an Asian population. There are 0.92%, 15.86%, 56.09%, and 27.13% women with almost entirely fat, scattered fibroglandular densities, heterogeneously dense, and extremely dense breast. Using the entirely fat group as the reference group, the corresponding relative risks for three other BI-RADS categories in Taiwan were 1, 2.03, 2.95, and

doi:10.6342/NTU201702793

4.03.(Cummings, Tice et al. 2009)

(4) Conventional risk factors

In the past, there are many conventional risk factors well recognized, such as pregnancy and hormonal-related factors. In our study, we obtained the distributions of the body mass index (BMI) and age at first pregnancy (AP) from the Keelung Community-Based Integrated Screening in Taiwan. BMI and AP also play important roles in the onset of breast cancer and subsequent progression. There are 62.89% women with BMI greater than 23 kg/m^2 and 33.47% women with AP greater than 25 years. The corresponding relative risks of BMI and AP for occurrence of breast cancer were 2.59 and 1.99.(Hsieh, Chen et al. 2002) In addition, we also obtained the distribution of age at menarche and age at menopause. There are 67.85% women with menarche age greater than 13 years and 55.11% women with menopause age greater than 50 years. The corresponding relative risks of menarche age and menopause age for occurrence of breast cancer were 1.05 and 1.03.(Cancer 2012)

2.2.2 Risk factors for the progression of breast cancer

(1) Conventional risk factors

The role of promoter from both BMI and AP was also obtained from the Hsieh three-state model that identified that the roles of promoter and the corresponding relative risks for progression were 2.00 and 1.56.(Hsieh, Chen et al. 2002)

(2) Tumor attributes

In addition to conventional risk factors, some tumor phenotypes also act as promoters. Based on Dong's study, it identified the relationship between tumor

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biomarkers and detection methods.(Dong, Berry et al. 2008) From this study, the proportion of negative ER expression was 19% and the corresponding odds ratio (OR) was 1.35 and the proportion of negative PR expression was 34% and the corresponding odds ratio (OR) was 1.08. For Ki-67 expression, the proportions of moderate and high proliferation (10-30% and >30% expression) were 50.7% and 19.2% (OR, 1.40 and 2.11). For HER-2/ neu expression, the proportions of 2+ and 3+ were 11.9% and 12.5%, respectively (OR, 1.28 and 1.07).

2.3 Literature review on guidelines of breast cancer screening and diagnosis based on risk levels

In general, the risk categories are classified three parts: average (less than 15 percent), moderate (approximately 15 to 20 percent), or high (greater than 20 percent) risk. As shown in Table 2.3.1, our study reviewed the strategies of different countries among average risk group (approximately less than 15 percent lifetime risk of breast cancer). In general, the interval of screening often was decided about two years in most countries because of breast cancer's natural history. The 40 to 49 age group, it does not suggest screening because of higher false-positive mammogram rates in women under age 50. The USA and Canada's guideline suggest that it needs individualized screening less than 50 years of age.

For women with moderate risk (approximately 15 to 20 percent lifetime risk of breast cancer), including most women who have a family history of breast cancer

doi:10.6342/NTU201702793

in a first-degree relative but do not have a known genetic syndrome, some guideline suggest that the age to begin mammography screening and the Inter-screening interval of screening be the same as for women at average risk. Many experts suggest that in women at moderate risk, the decision to apply supplemental screening (with either MRI or ultrasound in addition to mammography) should be determined after a discussion with the patient regarding personal preferences for known risks versus possible benefits, availability, and insurance coverage. Additionally, the American Cancer Society (ACS) suggests that there is no enough evidence to recommend for or against supplemental screening MRI as an adjunct to mammography in moderate-risk women. (Saslow, Boetes et al. 2007)

Among high risk group (eg, those who have BRCA or other susceptibility genes, or a history of chest radiation, or a calculated lifetime risk of developing breast cancer of greater than 20 percent), it usually include both annual screening mammogram and annual supplemental screening breast MRI scheduled six months apart, so effectively the woman is having one screening test every six months. (Saslow, Boetes et al. 2007)

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2.4 Literature review on the cost-effectiveness analysis of breast cancer screening based on risk levels

Women who test positive for BRCA1 or BRCA2 mutations are at increased risk of both breast and ovarian cancer. Women with a mutation in the BRCA1 or BRCA2 gene are at an increased lifetime breast cancer risk and they have a younger mean age at breast cancer diagnosis than that in the general population (mean age of onset: BRCA1, 53.9 years; BRCA2, 58.5 years; general population, 69.5 years). (Easton, Ford et al. 1995, Ford, Easton et al. 1998, Chen and Parmigiani 2007) In general population, mammography screening is the main and extensive screening test associated with reduced breast cancer mortality even though it has some controversy (over-diagnosis, false positive). However, mammography has reduced screening sensitivity in younger age groups and in gene mutation carriers. It has an increased risk of false-positive results at young age and also gives an additional risk of radiation-induced tumors, which is particularly relevant in younger women and in those with cancer susceptibility genes.(Armstrong, Moye et al. 2007, Warner, Messersmith et al. 2008, Yankaskas, Haneuse et al. 2010) In the past decision analysis of preventive strategies, prophylactic surgery(such as Mastectomy) or chemoprevention could lead to better survival and quality-adjusted survival than surveillance alone for women with a positive test result

doi:10.6342/NTU201702793

for BRCA1 or BRCA2 mutations.(Grann, Jacobson et al. 2002) However, risk-reducing surgery (such as prophylactic surgery) does not completely eliminate the risk of developing cancer as residual risks remain after mastectomy. Although prophylactic surgery is effective to reduce breast cancer risk, women should consider for the potential morbidity and the possibility that surgery may affect libido, sexual functioning, and body image. Management guidelines have been developed for BRCA1/2 mutation carriers to reduce the risk of being diagnosed with advanced stage breast cancer; options include surveillance with breast MRI and mammography, pharmacologic risk reduction with tamoxifen or aromatase inhibitors, or procedures such as prophylactic mastectomies.(Daly, Pilarski et al. 2017)

Risk factors of breast cancer can be classified into two groups: initiators (related to the onset of the breast cancer) and promoters (accelerate to the progression of breast cancer).(Hsieh, Chen et al. 2002) The different risk factors play different roles of preventive approaches. For example, the initiators can be used to identify high-risk groups for incidence of breast cancer in order to set up the priority of invitation to screen. The estimates of mean sojourn time (MST; the average duration between the PCDP and CP) by different promoters also give a key to clinical surveillance of these SD cancers, such as chemoprevention.(William, Heymach et al. 2009) When using these factors into multi-state model, we can classify population into different risk group and develop an individualized screening program based on different screening interval and modalities.(Wu, Yen et al. 2013) Furthermore, we can also make a comprehensive

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economic appraisal to decision makers.

doi:10.6342/NTU201702793

Chapter 3 Risk-guided personalized preventive strategies for breast cancer

3.1 Systematic framework of risk-guided prevention of breast cancer

Doing economic appraisal of risk-guided personalized preventive strategies has many steps. First, as there are two major types of BC, hereditary and non-hereditary types, we first divide the entire population into BRCA carrier, including BRCA1 and BRCA2, and non-carrier. Second, since the aim of this thesis is to identify asymptomatic BC, staying in the PCDP, through early detection such as genetic testing for BRCA carrier and screening for both types we have to develop a predictive multi-state model for the identification of asymptomatic BC staying the PCDP detected by screening and confirmatory diagnosis and symptomatic BC such as interval cancer and cancers from non-participants. The third step is to identify state-specific factors accounting for each transition, mainly including initiators and promoters. The fourth is to develop state-specific risk score for the classification of risk groups for the corresponding step of transition. The six step is related to the deployment of various preventive and strategies for reducing the following outcomes, including incidence of asymptomatic BC through prophylactic surgery and chemoprevention with tamoxifen, symptomatic BC through screening, recurrence of early-detected BC through scheduled

doi:10.6342/NTU201702793

surveillance after treatment (surgery and adjuvant therapy), advanced BC like metastases through targeted therapy.

We then develop a multi-state model for state-specific covariates in the light of Figure 3.2 to develop state-specific risk scores.

3.2 Personalized strategies for risk-score-based breast cancer screening

We proposed an individual-risk-score-based approach that translates state-of-the-art scientific evidence into the initiators and promoters affecting onset and subsequent progression of breast cancer underpinning the novel multi-variable multi-state temporal natural history models. The application of multi-state model in genetic counseling enables one to estimate the probability of carrying BRCA1 or BRCA2 given information on pedigree information and the cumulative risk of breast cancer. Following the framework of assessing the decision on a series of strategies of breast cancer screening proposed by Chang et al(Chang et al. , 2010), there are seven steps for assessing the cost-effectiveness of different strategies based on the proposed method (Figure 3.1). The flowchart start from the construction of the three-state Markov model for breast cancer progression of free-of-breast cancer, preclinical detectable phase, and clinical detectable phase using observed data on breast cancer progression considering the Taiwan population during the year 2004 through 2012. This is followed

doi:10.6342/NTU201702793

by the inclusion of the effects including traditional risk factors and genetic and epigenetic factors based their roles as initiator or promotor or both, on the constructed three state breast cancer progression model using proportional hazard form. Based on the three-state Markov model constructed as above, data on breast cancer progression for the population can be simulated with the consideration of the effect of risk factors on disease initiation and progression. By the comparison between the disease status of simulated cohort and that of observed one, the constructed model can be validated with risk of breast cancer progression verified. The proposed cohort can then be used for evaluation a series of strategies including the one with unified criteria for all of the target population and that with different inter-screening intervals provided by using the risk score for stratifying the population.

doi:10.6342/NTU201702793

Chapter 4 Methodology of personalized partially-hidden multistate prediction model for breast cancer

4.1 Multi-state prediction model for asymptomatic and symptomatic BCs

In contrast to previous prediction models that are often specified for symptomatic BC, the development of prediction model here illustrated by Figure 4.1 is to identify potential of being susceptible to symptomatic BC but still staying in the PCDP without being diagnosed earlier. In reality, the transition from pre-symptomatic phase to symptomatic phase is unobservable as indicated by broken arrow as shown in Figure 4.1. The major aim of developing multistate prediction model is to identify these asymptomatic BCs with the incorporation of hidden state named as PCDP indicated above to accommodate this unobservable phenomenon. Basically, the hidden state can be extended from a simple PCDP to the complex one classified by conventional tumour attributes such as tumour size or the spread of regional lymph node (Int J Cancer 1998; Biometrics 2000). In my thesis, only the hidden state of PCDP is considered and a three-state model is therefore constructed. More importantly, as the PCDP can be observed by defining a detection mode such as screen-detected mode but its subsequent transition cannot be observed such a kind of hidden state is therefore partially observed.

doi:10.6342/NTU201702793

Therefore, Figure 4.1 sketches a three-state partially-hidden continuous-time Markov model, which is the core model used for constructing state-specific risk scores

4.2 Quantifying individual risk for the progression of breast cancer

The risk of developing asymptomatic BC during time from t_1 to t_2 expressed as following Markov property

$$P_\alpha(t_1 - t_2; X_\alpha(t_1)$$

$$= \int_{t_1}^{t_2} \lambda_\alpha(S; X_\alpha(s))\exp\left\{-\left[H_\alpha\left(S; X_\alpha(s)\right) + H_\beta\left(S; X_\beta(s)\right)\right]\right\} ds \qquad \text{— (4-1)}$$

$H(\cdot)$ is the cumulative hazard of $\lambda(\cdot)$, which is expressed as

$$\mathrm{H(s)} = \int_0^t \lambda\,(s)ds$$

The risk of developing symptomatic BC during time from t_1 to t_2 is written as follows

$$P_\beta\left(t_1 - t_2; X_\alpha(t_1); X_\beta(t_1)\right)$$

$$= \int_{t_1}^{t_2} \lambda_\alpha(S; X_\alpha(s))\exp\left\{-\left[H_\alpha\left(S; X_\alpha(s)\right) + H_\beta\left(S; X_\beta(s)\right)\right]\right\} ds \int_{t_1}^{t_2} \lambda_\beta(\mu; X_\beta(u) exp - H(\mu; X_\beta(u)) du ds \quad \text{–(4-2)}$$

The risk of transition from PCDP to CP is written as follows

$$P_{\alpha\beta}\left(t_1 - t_2; X_\beta(t_1)\right)$$

$$= \int_{t_1}^{t_2} S; X_\beta(s)\; exp - \left[H\left(S; X_p(s)\right)\right] ds \qquad \text{–(4-3)}$$

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4.3 Efficacy of intervention program

We evaluated the efficacy of different preventive strategies by comparing the probability of the outcome (advanced BC and death from BC) for the intervention (Po) with the probability of the outcome in the absence of intervention (natural history) (Pe) using the following formula: [(1-Po/Pe)*100%].

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4.4 Cost-effectiveness analysis of personalized strategies for prevention of breast cancer

Personalized strategies for prevention of breast cancer are classified by the status of BRCA carrier. Table 4.4.1 shows all the possible preventive strategies for the carrier of BRCA and the non-carrier of BRCA guided by decile risk stratification. The former consists of prophylactic surgery (including mastectomy and oophorectomy), annual MRI in combination with mammography, and chemoprevention. The latter are mainly related to the administration of alternative imaging technique and inter-screening interval or age to begin with screen. The method including seven steps have been delineated in Figure 3.3. The parameters of cost are listed in Table 4.4.2.

4.5 Markov decision framework for prevention of breast cancer

The strategies considering the prevention of breast cancer embedded within the natural history of breast cancer progression for generation population and women with and without BRCA carrier status are depicted through Figure 4.5.1 to Figure 4.5.6. The screening activities were incorporated with the multistate disease progression from free-of-breast cancer to PCDP and to CP. The probability of death due to breast cancer were determine by whether the lesion is advanced or early one, which is in turn resulted from the immunochemical characteristics and also the mode (screening detected or

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clinical detected) of being detected. The efficacy of screening activity is thus determined by the ability of the screening tool to discover PCDP from women attended the screening program. On the other hand, for a screening tool with decreased specificity, additional cost will be incurred by confirmation fee due to classifying women at the state of free-of-breast cancer as positive (specificity).

In addition to the diagnostic characteristics of the screening tool, the rate of disease progression depicted by the three state Markov model is another crucial factor. For women at higher risk of developing breast cancer, an universal two or three year interval may be insufficient to identify such a subject before the lesion progress and turning into clinical detected case. Under such circumstance, an advanced lesion resulted and thus the efficacy was decreased. The details on the path history of breast cancer depicted by the partial-hidden multistate model was provide as follows.

4.5.1 Markov decision model for the disease natural history of breast cancer

The history path for normal subject and those with PCDP are described by Figure 4.5.1 to Figure 4.5.3. Subject start with the state of free of breast cancer (Normal, Figure 4.5.1), and may or may not attend the provided screen strategy determined by attendance rate. The results of screening activity may turn out to be positive or negative given the underlying disease status of free-of-breast cancer and in the state of PCDP

doi:10.6342/NTU201702793

determined by sensitivity and specificity, respectively, of the screening tool. For women with positive results, confirmatory workup was performed to determine the disease status of having breast cancer or not. Given a subject in the status of PCDP and with positive screening result, she will turn out to be screening detected case with decreased risk of progress to advanced cancer and an improved survival as depicted by Figure 4.5.2 (Early PCDP).

For women in the status of PCDP but missed by the screening, the lesion may progress with the probability of being advanced lesion and thus at increased risk of dying from breast cancer (negative results and progress to advanced PCDP, Figure 4.5.1). The lesion may also progression from PCDP to CP and follow the path demonstrated in Figure 4.5.4. The screening activity embedded with the progression following early PCDP is demonstrated in Figure 4.5.2 and that for advanced PCDP is demonstrated in Figure 4.5.3. Women with early or advanced PCDP have the chance to attend screening program and being identified as breast cancer caser to have an improved survival before the lesion progress and surfacing to clinical phase.

Figure 4.5.4 depicted the curse of clinical detected breast cancer cases. Given the mode of clinical detection, she had a higher chance of turning out to be advanced lesion and thus an poorer survival. The efficacy of a strategies is thus reflected by the

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distribution of advanced and early lesion and also the death rate of breast cancer.

Both screening detected (PCDP and recognized by screening activity) and clinical detected cases will receive treatment following the identification of breast cancer and treatment cost incurred. At each year through the history path of breast cancer evolution, the competing risk of other cause of death was considered by comparing with the age-specific death rate derived from the 2009-2011 population of Taiwan.

4.5.2 Markov decision model for the carrier of BRCA

Two types of preventive strategies were assessed for women with BRCA carrier, universal annual screening strategies and personalized strategies combing primary and secondary prevention. For the universal annual screening, two modalities were adopted, mammography and MRI combined with mammography. For personalized intervention strategies, there were also two type of interventions, preventive mastectomy and chemoprophylaxis with tamoxifen. For the personalized intervention using preventive mastectomy as primary prevention strategy, BRCA carrier women with 9^{th} and 10^{th} decile of risk and mammography or MRI combined mammography for the rest of the population. For the strategy using chemoprophylaxis with tamoxifen, the subject at 9^{th} and 10^{th} decile receiving tamoxifen and also biennial screening using mammography or MRI combined with mammography as screening tool. Table 4.5.3 summarizes these

doi:10.6342/NTU201702793

personalized strategies.

4.5.3 Markov decision model for the non-BRCA carrier

We performed the cost-effectiveness analysis with risk-based screening interval for non-carrier. The Markov decision model was depicted in Figure 4.5.6. The non-carrier women were categorized into different risk groups by deciles. Screening interval was suggested according to the risk level (Table 4.5.2). Women in the top 10% risk are advised to take mammography every 6 months. For those in 70-90th percentiles, they are advised to screen annually. The lower risk level, the longer screening interval. For the lower 20% risk women, the suggested interscreening interval was 6 years.

4.6 Computer code for the cost-effectiveness analysis

4.6.1 Incorporating conventional risk factors and genetic factors in the progression of breast cancer

We first generate a cohort characterized by a two-stage evolution of breast cancer from the development of incipient status (preclinical detectable phase, PCDP) to overt clinical disease (clinical phase, CP) based on a nested Poisson process (Casaller and Berger). The simulation on both the generation of a cohort with a specified distribution of relevant covariates along with their state-specific effect on the occurrence and progression of breast cancer were accomplished under the environment of SAS IML

doi:10.6342/NTU201702793

language (SAS).

In addition to the two-stage evolution of breast cancer, the distribution of relevant covariates including the category of BMI, age at first pregnancy, and breast density (using BIRAD classification), the status of immunohistochemical (IHC) markers (ER (estrogen receptor), PR (progesterone receptor) and HER2 (human epidermal growth factor receptor 2)), the SNPs status, and the carrier status of two major gene, BRCA1 and BRCA2 were incorporated in the simulated cohort with their effect on the rates of occurrence or progression of breast cancer specified according to the results of literature review.

%macro m(n, xn, xseed, v_int,v_sen,v_spe,v_patt);

A macro language was applied to reach the goal of microsimulation under the framework of probabilistic cost-effectiveness analysis. The simulation was designed for the scenario of breast cancer screening program such that 100000 (denoted by macro variable *n*) subjects attend a screening program with a predetermined inter-screening interval (denoted by macro variable *v_int*) using a screening tool with the diagnostic characteristics represented by sensitivity (denoted by macro variable *v_sen*) and

doi:10.6342/NTU201702793

specificity (denoted by macro variable v_spe). The attendance rate (denoted by macro variable v_patt) was also included as a parameter to assessing its effect on outcomes of interest.

```
proc iml;
/*lamda weight age distribution*/
l11=2.1355e-5/53.26;
l12=2.71e-4/53.26;
l13=3.3e-4/53.26      ;
l2=0.160803425;
gamma=1.9368;
```

The baseline rate of the occurrence and progression of breast cancer was specified by parameters l1 and l2. For the rate of breast cancer occurrence (incidence rate), a Weibull distribution with the shape parameter of 1.94 was applied according to the estimated results using Taiwan population reported by Hsish et al. (). An exponential distribution was assigned for depicting the progression rate of breast cancer from incipient disease (PCDP) to that with overt clinical symptom (CP). The scale parameters

doi:10.6342/NTU201702793

of incidence rate and progression rate were tuned using the detonators (in this case, 20.64 for the incidence rate and 2.63 for the progression rate) to guarantee the incidence rate and progress rate of simulated population were consistent with the underlying population after the incorporation of relevant covariates such as SNPs, BRCA carrier status, and conventional risk factors such as BMI, age at first pregnancy.

---

subject=&xn;

x=J(subject,5,.);tm=J(subject,5,.); diag=J(subject,1,.);

cov=J(subject,39,.);

score=J(subject,2,.);

y=J(subject,50,.);

eta=J(subject,1,.);

st1=50;

A cohort consisted with 15000 (*&n*1.5*) women were simulated to have their path through the two-stage process of the development of breast cancer. Matrix of covariate (cov), summation of risk scores (score) were declared in advance under the IML environment. The screening program were eligible if a woman is aged 50 years or older

doi:10.6342/NTU201702793

and without clinical breast cancer. The starting point of 50 (st1) is thus specified.

```
obs=0;
do i=1 to subject until (obs=&xn);
*bmi;
cov[i,1]=(rantbl(0,0.6289)=1);
*ap;
cov[i,2]=(rantbl(0,0.3347)=1);
*birads;
cov[i,3]=rantbl(0,0.0092,0.1586,0.5609);
if cov[i,3]=1 then do; cov[i,4]=0; cov[i,5]=0; cov[i,6]=0; end;
if cov[i,3]=2 then do; cov[i,4]=1; cov[i,5]=0; cov[i,6]=0; end;
if cov[i,3]=3 then do; cov[i,4]=0; cov[i,5]=1; cov[i,6]=0; end;
if cov[i,3]=4 then do; cov[i,4]=0; cov[i,5]=0; cov[i,6]=1; end;
```

The proportion of subjects with BMI>25, age at first pregnancy later than 23 years old, and breast density using BIRADS category were simulated according to the results of literature review. Taking the status of BMI>25 as example, 62.9% of the simulated

doi:10.6342/NTU201702793

subjects were generated with this condition using a binomial distribution random generator, rantbl(0,0.6289)=1. The status of BMI was then recored into the covariate matrix (cov[i,1]) declared in the previous step . The three categories were further turning into three dummy variables (cov[i,4], cov[i,4], and cov[i,4]).

---

*brca1, brca2;

cov[i,7]=-1+rantbl(0,1-0.0011-0.0012,0.0011);

The proportion of BRCA carrier status was also simulated based on that reported in literature, 1.1 and 1.2 % for BRCA1 and BRCA2, respectively. Note that there are three carrier status, non-carrier, BRCA1 carrier, and BRCA2 carrier.

/*Poly genes*/

pg1=1-0.38; pg2=1-0.25; pg3=1-0.28; pg4=1-0.30; pg5=1-0.40; pg6=1-0.50;

pg7=1-0.86;

pg8=0.454; pg9=0.10; pg10=1-0.358; pg11=0.38; pg12=1-0.122;

cov[i,8]=-1+rantbl(0,pg1*pg1,2*pg1*(1-pg1)); /*rs2981582*/

cov[i,9]=-1+rantbl(0,pg2*pg2,2*pg2*(1-pg2)); /*rs3803662*/

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```
cov[i,10]=-1+rantbl(0,pg3*pg3,2*pg3*(1-pg3));      /*rs889312*/

cov[i,11]=-1+rantbl(0,pg4*pg4,2*pg4*(1-pg4));      /*rs3817198*/

cov[i,12]=-1+rantbl(0,pg5*pg5,2*pg5*(1-pg5));      /*rs13281615*/

cov[i,13]=-1+rantbl(0,pg6*pg6,2*pg6*(1-pg6));      /*rs13387042*/

cov[i,14]=-1+rantbl(0,pg7*pg7,2*pg7*(1-pg7));      /*rs1053485*/

cov[i,30]=-1+rantbl(0,pg8*pg8,2*pg8*(1-pg8));      /*rs9485372*/

cov[i,31]=-1+rantbl(0,pg9*pg9,2*pg9*(1-pg9));      /*rs9383951*/

cov[i,32]=-1+rantbl(0,pg10*pg10,2*pg10*(1-pg10));      /*rs7107217*/

cov[i,33]=-1+rantbl(0,pg11*pg11,2*pg11*(1-pg11));      /*rs12118297*/

cov[i,34]=-1+rantbl(0,pg12*pg12,2*pg12*(1-pg12));      /*rs16992204*/
```

The proportions of the SNPs of the simulated cohort were generated following similar rationale. For the SNPs, the status can be non-carrier, single SNP carrier, and two SNP carrier. The probability was simulated following Mendelian rule as demonstrated in the assignment of the multinomial parameters, rantbl(0,pg1*pg1,2*pg1*(1-pg1)). Subjects with homozygous recessive status of the SNP was used as reference group with a contrast array of (0, 1, 2), representing the highest risk for subjects with homozygous dominant carrier.

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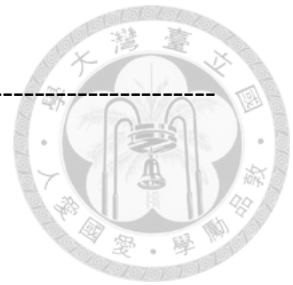

---

*PR;

cov[i,28]=(rantbl(0, 0.66)=1);

*basal;

cov[i,29]=(rantbl(0, 0.1075)=1);

/*P53*/

cov[i,35]=(rantbl(0, 0.22)=1);

/*HRT use*/

cov[i,36]=rantbl(0, 0.3945, 0.1865, 0.1427, 0.2763);

if cov[i,36]=1 then do; cov[i,37]=1; cov[i,38]=0; cov[i,39]=0; end; *never;

if cov[i,36]=2 then do; cov[i,37]=0; cov[i,38]=1; cov[i,39]=0; end; *current oral estrogen;

if cov[i,36]=3 then do; cov[i,37]=0; cov[i,38]=0; cov[i,39]=1; end; *Current combination therapy;

if cov[i,36]=4 then do; cov[i,37]=0; cov[i,38]=0; cov[i,39]=0; end; *past user;

The proportions of the immunohistochemical characteristics of the breast neoplastic lesion including ER, HER2, and Ki67 for the simulated cohort were also

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generated based on the report abstracted from literatures. The mechanism of generating the covariate status and dummy variable were consistent with that mentioned above.

/* true bmi ap b1 b2 b3 snp1-snp7 */

b1={0.9517 0.6875 0.693147181 1.205970807 1.368639426

0.231111721 0.182321557 0.122217633 0.067658648 0.076961041 0.182321557

0.122217633

0.105 0.128 0.077 0.094 0.122 0.78 0.083381609 0.240385358

0.482157729};

b2={0.6918 0.4468 0.300104592 0.246860078 0.067658648 0.336472237 0.104360015

0.077 0.536493371};

Arrays of the effect of covariates for the incidence rate (b1) and progression rate (b2) were assigned by using the effect size abstracted from literatures. Taking BMI for example, the effect on breast cancer incidence rate and progression rate were assigned as 0.9517 and 0.6918, respectively. This assignment corresponding to the hazard ratio of 2.59 and 2.00 for the occurrence and progression of breast cancer for subjects with BMI >= 25 compared with those <25 (cite).

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```
-----------------------------------------------------------------------------------------------

score[i,1]=b1[1]*cov[i,1]+b1[2]*cov[i,2]+b1[3]*cov[i,4]+b1[4]*cov[i,5]+b1[5]*cov[i,6
]+b1[6]*cov[i,8]+b1[7]*cov[i,9]+b1[8]*cov[i,10]+b1[9]*cov[i,11]+b1[10]*cov[i,12]+
b1[11]*cov[i,13]+b1[12]*cov[i,14];
score[i,2]=b2[1]*cov[i,1]+b2[2]*cov[i,2]+b2[3]*cov[i,15]+b2[4]*cov[i,17]+b2[5]*cov[
i,18]+b2[6]*cov[i,20]+b2[7]*cov[i,21];
score1=score[i,1]; score2=score[i,2]; expscore1=exp(score1);expscore2=exp(score2);
expscore1=exp(score1); expscore2=exp(score2);
-----------------------------------------------------------------------------------------------
```

By using the product of the effect size array and the status of covariates, the risk scores can be derived, both for the incidence and progression of breast cancer which was then written into the matrix, score1 and score2, respectively. An exponential form was then applied to these two scores and written into the matrix, expscore1 and expscore2, respectively.

```
-----------------------------------------------------------------------------------------------

q1=l1*exp(score1);
q2=l2*exp(score2);
taup=ranexp(&xseed)/q1;
```


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```
tau1=20+taup**(1/gamma);

tau2=ranexp(&xseed)/q2;

t=tau1+tau2;
```

The breast cancer incidence rate and progression rate can thus be derive by using the baseline rates, l1 and l2, and the exponential form of two scores, score1 and score2, based on the proportional hazard form

$$\lambda_1 = \lambda_{10} \exp\{score_1\}$$
$$\lambda_2 = \lambda_{20} \exp\{score_2\}$$

The times to the occurrence of the events of PCDP and CP were then generated using the random number generator function ranexp of the IML language with the random seed specified. The incorporation of the effects of covariates on the occurrence and progression of breast cancer was performed through the risk scores, score1 and score2. Taking the progress rate for example, the time evaded from the occurrence of PCDP to CP (*tau2*) were generated by using exponential distribution which was then scaled by *q2* which is in turn expressed as the product of baseline progress rate and the exponent of socre2, *l2*exp(score2)*.

For the time of breast cancer occurrence, Weibull distribution was applied. An scaled exponential time was generated by using the expression *taup=l2*exp(score2).* To

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accommodate the Weibull distribution for time to occurrence of breast cancer, the expression *tau1=20+taup**(1/gamma)* was applied to taking into account the influence of shape parameter, gamma. Considering the scenario of breast cancer occurrence among generation population, the starting point for the occurrence of breast cancer was set at 20 years old. Total time, *t*, is thus the summation of that to the occurrence of PCDP (*tau1*) and then progress to CP (*tau2*).

---

interval=2; st1=50;

if t>=st1 then obs=obs+1;

An inter-screening interval of 2 years (*interval=2*) was applied according to the predetermined strategy. The age at starting screening was 50 years old (*st1=50*). As a screening programme for breast cancer, only those with the onset of CP later then 50 years old were eligible for attending the screening program.

---

do k=1 to 21;

y[i,k]=cov[i,k];

end;

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```
y[i,22]=q1; y[i,23]=q2; y[i,24]=tau1; y[i,25]=tau2;

y[i,26]=score1; y[i,27]=score2;

end;

create    stateinfo09 from y [colname={c1 c2 c3 c4 c5 c6

c7 c8 c9 c10 c11 c12 c13 c14 c15 c16 c17 c18 c19 c20 c21 q12 q23

tau1 tau2 score1 score2}];

append from y;

run;

quit;

data stateinfo092;

set stateinfo09;

if tau1+tau2>50;

run;
```

The generated covariates for the simulated population alone with the underlying time to the occurrence of PCDP, CP, and total time were stored in the dataset named *stateinfo09* by using the create statement in IML environment. Only those with eligible for attending screening at predefined age of attendance were enrolled for the following

doi:10.6342/NTU201702793

simulation.

```
---------------------------------------------------------------------------------------------------

proc iml;

use stateinfo092;

read all var{c1 c2 c3 c4 c5 c6 c7 c8 c9 c10 c11 c12 c13 c14 c15 c16 c17 c18 c19 c20

c21} into cov;

read all var{tau1 tau2} into tt;

read all var{score1 score2} into score;

subject=nrow(cov);

w=j(subject,6,.);

p=j(subject,5,.);

w[,5]=rank(score[,1]);

l1=2.13769e-5/20.6409; l2=0.42307/2.63067; gamma=1.9368;

---------------------------------------------------------------------------------------------------
```

We then simulate the history of screening activities for each enrolled subjects by using the dataset *stateinfo092*. The same condition for simulation considering the baseline rates of breast cancer occurrence (*l1*) and progression (*l2*) was applied. The risk scores were read from the simulated dataset, *stateinfo092*.

doi:10.6342/NTU201702793

4.6.2 Define risk levels of breast cancer according the individualized risk score

---

```
do i=1 to subject;
score1=score[i,1];
lamda1=l1*exp(score1);
mp11_10=1-exp(-lamda1*((60-20)**gamma-(50-20)**gamma));
mp11_50=1-exp(-lamda1*((85-20)**gamma-(50-20)**gamma));
p[i,1]=log(lamda1);
p[i,2]=mp11_10;
p[i,3]=mp11_50;
w[i,1]=tt[i,1]; w[i,2]=tt[i,2];
w[i,3]=tt[i,1]+tt[i,2];
w[i,4]=log(lamda1);
```

The cumulative risk of the occurrence of breast cancer since eligible fro attending breast cancer screening program for each subject can be derived from the Weibull distribution indicated by the scale and shape parameters in conjunction with her covariate values. For example, the 10 year (till 60 years old) cumulative risk (*mp11_10*)

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is expressed as *1-exp(-lamda1*((60-20)**gamma-(50-20)**gamma))*, where the scale parameter is in turn the function of subject-specific covariates (*l1*exp(score1)*).

The matrix p and w stored the risk levels in terms of the cumulative probability and times to the occurrence and progression of breast cancer and total time, which can be used to determine the history path of screening activities.

```
if 0*subject<=w[i,5] & w[i,5]<(0.1)*subject          then group=1;
else if (0.1)*subject<=w[i,5] & w[i,5]<(0.2)*subject then group=2;
else if (0.2)*subject<=w[i,5] & w[i,5]<(0.3)*subject then group=3;
else if (0.3)*subject<=w[i,5] & w[i,5]<(0.4)*subject then group=4;
else if (0.4)*subject<=w[i,5] & w[i,5]<(0.5)*subject then group=5;
else if (0.5)*subject<=w[i,5] & w[i,5]<(0.6)*subject then group=6;
else if (0.6)*subject<=w[i,5] & w[i,5]<(0.7)*subject then group=7;
else if (0.7)*subject<=w[i,5] & w[i,5]<(0.8)*subject then group=8;
else if (0.8)*subject<=w[i,5] & w[i,5]<(0.9)*subject then group=9;
else    if (0.9)*subject<=w[i,5] & w[i,5]<=1*subject        then group=10;
w[i,6]=group;
end;
```


doi:10.6342/NTU201702793

```
print w;
create pwopt from w[colname={tau1 tau2 t rscore1 rank group}];
append from w;
run;
quit;
```

By using the rank of the risk score for the occurrence of breast cancer, the simulated cohort was categorized into 10 risk groups, from low to high risk levels. This can further be used to determine the individual tailored strategies according to the risk level one belongs to. The matrix of risk levels, cumulative probabilities of occurring breast cancer were then write to data named *pwopt*.

4.6.3 Simulate the process of breast cancer evolution embedded in screening activity

---

```
data t;
if _n_=1 then set life1;      *Prepare file;
set pwopt;
run;
data a0;
```


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```
set t;

array dpo{26} deathpo45-deathpo70;

death_bcp=0.030485;     dpbcx=0.009498;

t=tau1+tau2;

seed=&xseed;*seed=79031425;
```

The history path of the occurrence and progression breast cancer embedded in screening activities with the consideration of other cause of death was then generated by using the data set *t*.

```
e0=0;

do sf1=1 to 25 until (e0=1);

dro=ranuni(seed);    st=sf1+44;

if 0<dro<dpo[sf1] then do; odeathage=sf1+44; death=5; e0=1;end;

*death=5: other cause of death;

if tau1<st and st<t then do;

if ranuni(seed)<=dpbcx then do; bcdeathage=sf1+44; death=3; e0=1; end;

end;
```


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```
else if t<st then do;
if ranuni(seed)<=death_bcp then do; bcdeathage=sf1+44; death=4; e0=1; end;
end;
end;`
deathage=min(odeathage,bcdeathage);
id+1;
drop sf1 deathpo45-deathpo70;
run;
```

We first determine whether an attendee is subject to other cause of death by comparing a random number draw from uniform with the age-specific probability of other cause of death along the screening history from the age of 45 to 69 years. For those censored due to other cause of death, a code, *death=5*, and an indicator, *e0=1*, were add the the subject at the specified round of screening period. For the subjects after the occurrence of breast cancer and before she surfacing to clinical phase (*tau1<st and st<t*), the cause of death could be dual, namely breast cancer associated and other cause of death. These subjects escaping from other cause of death were thus faced with the probability of breast cancer death simulated by comparing the uniform random number

doi:10.6342/NTU201702793

with the probability of breast cancer death (*if ranuni(seed)<=dpbcx*). A corresponding code, death=3, and an indicator, e0=1, were also assigned for such subjects dying from breast cancer. The situation for subjects surfacing to clinical phase (*t<st*) was similar. Whether a subject was dying from clinical breast cancer was determined by the comparison between a uniform random number and the probability of breast-cancer death (*ranuni(seed)<=death_bcp*) and marked by a code, death=4, and an the same indicator, e0=1.

The observed age of death occurrence (*deathage*), due to other cause or breast cancer, was then derived by taking the minimum of the two,

deathage=min(odeathage,bcdeathage).

```
data a1;
set a0;
interval=&v_int;
t=tau1+tau2;
seed=0;
start=45; end=69;
tsfreq=int((end-start)/interval)+1;
```


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```
if mod((end-start),interval)^=0 then follow=1;
```

The screening path was then generated under the scenario of using the age of 45 to 69 years as the age of start and end of screening programme. For programme with uniform screening interval, the inter-screening interval was expressed by using macro variable *&v_int*, which can be extended by using a series of intervals according to the risk levels for each subjects in the scenario of individual-tailored screening programme. Total number of possible screening rounds (*tsfreq*) is thus *int((end-start)/interval)+1*.

```
array o{49} o1-o49;
array s{49} s1-s49;
array sto{49} sto1-sto49;
   sen=&v_sen;
   spe=&v_spe;
   att=1;
   enddeath=0;
   st1=45;
   nsd=0;
```


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```
nin=0;
patt=&v_patt;
sto1=start;
```

The parameters of characteristics of screening tool including sensitivity (*&v_sen*) and specificity (*&v_spe*) and attendance rate of screening programme were declared using macro variables. The status of screening activities were recorded in three array of variables, o, s, and sto, representing, observed status, underlying true status, and time of observation in terms of age, respectively. The age of first enrollment (*sto1*) was the age of attending screening progamme, *start*.

```
elig=1;
if elig=1 then do sfreq=1 to tsfreq until (enddeath=1);
st=sto1+interval*(sfreq-1); sto[sfreq]=st;
if 0<deathage<st then do;
elig=0; enddeath=1;
s[sfreq]=death; o[sfreq]=death;
end;
```


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The screening history through the attendance to the possible number of screening rounds attended (*tsfreq*) for each attendee were generated till the occurrence of death using the statement *do sfreq=1 to tsfreq until (enddeath=1)*. An update time of observation in terms of age was recorded by variable *st* with incremental increase of each screening round using *sto1+interval*(sfreq-1)* and then written into the array of *sto* at each attendance of screening round. For each simulated subject, an indicator, *elig*, was used to identify whether she was eligible for attending screening porgramme. The indicator was switch off (*elig=0*) after the occurrence of death (*0<deathage<st*). Meanwhile, both the underlying true status and observed status were recorded according to the cause of death (*s[sfreq]=death; o[sfreq]=death;*). The final destiny of the subject was recorded by the variable *enddeath*.

```
if elig=1 then do;
if st<tau1
then do;
    s[sfreq]=0;
end;
```


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```
if tau1<=st & st<t then do;
                    s[sfreq]=1;
                end;
if t<=st then do;
                    s[sfreq]=2;
                end;
```

The subsequent underlying disease status of each screening round for attendee of the simulated cohort was determined by the relationship between the time (age) of attending screening and that of the occurrence of breast cancer (*tau1*) and turning into clinical breast cancer case (*t*). For example, for an attendee who have entered the state of PCDP without turning into clinical breast cancer case (*tau1<=st & st<t*) the underlying disease status was recorded as PCDP (*s[sfreq]=1*) at the time she attend screening (*sfreq*).

```
senr=ranuni(seed);
if ranuni(seed)<patt then att=1; else att=0;
if att=1 then do;
```


doi:10.6342/NTU201702793

```
if s[sfreq]=0 and senr<=spe then o[sfreq]=0;
if s[sfreq]=0 and senr>spe then o[sfreq]=1;
if s[sfreq]=1 and senr<=sen then o[sfreq]=1;
if s[sfreq]=1 and senr>sen then o[sfreq]=0;
end;
if s[sfreq]=2 then o[sfreq]=2;
end;
```

After the underlying disease status been determined, the observed disease status at each screening round can be projected by comparing a random number draw from *uniform*(0,1) to the specificity and sensitivity specified above. For example, for a subject with the underlying disease status of PCDP (state 1), she can be identified as in PCDP by using the statement *if s[sfreq]=1 and senr<=sen then o[sfreq]=1*, where senr is the uniform random number. We also allow for the the incorporation of attendance rate and make it possible for the simulated subjects to attend the screening programme following the specified attendance rate by using the statement *ranuni(seed)<patt then att=1; else att=0.*

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4.6.4 Assessing efficacy of intervention

```
---------------------------------------------------------------------------------------------------

endfreq1=0;

do sf1=1 to tsfreq until (endfreq1=1);

if ( s[sf1]=2 and o[sf1]=2 ) or (s[sf1]=1 and o[sf1]=1) or s[sf1] in ( 3 4 5) then

endfreq1=1;

endfreq=sf1;

end;

end;

if o[endfreq]=1 and s[endfreq]=1 then nsd=1;

if o[endfreq]=2 and s[endfreq]=2 then nin=1;

---------------------------------------------------------------------------------------------------
```

For each simulated subject, the end of screening round was recorded in the variable *endfreq*. For subject who end up with the states of screen-detected cancer (state 1), clinical breast cancer (state 2), and death of other cause (state 3) and breast cancer (state 4 and 5), the round of the occurrence of these status was recorded as the termination of screening activity. This variable was used later for the calculation of cost incurred by screening activities. For breast cancer cases detected during screening rounds (screening

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detected cases) or surfacing to clinical face after then (interval cancers), their status were also recorded with the indicator variables of nsd and nin, respectively.

```
if s[endfreq]=2    or (o[endfreq]=1 & s[endfreq]=1) then tx_year=sto[endfreq];
if o[endfreq]=1 & s[endfreq]=1 then do;
surstart=INT((endfreq-1)*interval)+1;
do sf2=surstart to 25 until (sd=9);
if ranuni(seed)<=dpbcx then do; txbcdeathage=sf2+44; sd=9; end;      /*dpbcx:
probability of BC Death in PCDP*/
end;
if    txbcdeathage=. then bcdeath=0;
end;
if tx_year^=. and bcdeath=0 then do;
fdeathage=odeathage;
if fdeathage=. then death=.; if fdeathage^=. then death=5;
end;
if tx_year^=. and txbcdeathage^=. then do;
fdeathage=min(odeathage, txbcdeathage);
```


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```
if fdeathage=txbcdeathage then death=3;

if fdeathage=odeathage then death=5;

end;

if nin=1 then    fdeathage=min(odeathage, bcdeathage);

if tx_year=. then fdeathage=deathage;

drop    sfreq sf1    ;

run;
```

Following the identification of breast cancer cancers, through screening or clinical symptoms, she is not eligible for attending screening and receives treatment for breast cancer. For subjects with screening detected and interval cancers, the time at which the lesion was identified was also recored as the year of receiving treatment (*tx_year=sto[endfreq]*). The subjects with breast cancer were then followed until the occurrence of terminal event including death, either from breast cancer or other causes, or upper limit of study period, 70 years old (*do sf2=surstart to 25 until (sd=9)*). Whether an attendee diagnosed as breast cancer case died from the disease was identified and recorded in variable *death* (code 3 for breast cancer death and 5 for death from other cause).

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4.6.5 Assessing cost of interventions

```
Data. a2;

set a1;

array o{49} o1-o49;

array s{49} s1-s49;

array cso{49} cso1-cso49;

array sto{49} sto1-sto49;

array cs{25} cs1-cs25;

array stm{26} st1-st26;

array csc{25} csc1-csc25;
```

We the incorporate cost based on the simulated

```
array sm{26} sm1-sm26;

do w=1 to 49;

cso[w]=0;

end;

do w2=1 to 25;
```


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```
cs[w2]=0; csc[w2]=0;

end;

do sf2=1 to endfreq;

if o[sf2]=0 then cso[sf2]=1;

if o[sf2]=1 then cso[sf2]=1;

end;

st1=45;

do sf1=2 to 26;

stm[sf1]=44+sf1; ss=0; ss_confirm=0;

do sf2=1 to tsfreq;

if stm[sf1-1]<=sto[sf2]<stm[sf1] then

do;

ss+cso[sf2];

if o[sf2]=1 then    ss_confirm+cso[sf2];

state=s[sf2];

if endfreq=sf2 and (o[sf2]=2 or o[sf2]=3) then ss_confirm+1;

end;

cs[sf1-1]=ss;
```


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```
csc[sf1-1]=ss_confirm;

end;

end;

drop sf1 sf2 w w2;

run;

/*Cost & effectiveness*/

data a3;

set a2;

array o{49} o1-o49;

array s{49} s1-s49;

array sto{49} sto1-sto49;

array cs{25} cs1-cs25;

array stm{25} st1-st25;

array csc{25} csc1-csc25;

array sm{26} sm1-sm26;

discount=0.05;

c_mammo=41.03; c_sono=30;c_sa1=0.24; c_sa2=0.29; c_sa3=4.41;

c_sother=c_sa1+c_sa2+c_sa3; ic_s=6.09*1.2*7.5;
```


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```
/*confirm fee*/

c_con_biopsy=86.79; c_con_under=47.06; ic_con=6.09*1.2*7.5*2;

/*tx fee*/

c_tx1=6661.76; c_tx2=666.18;

ic_tx1=5917.11; ic_tx2=1570.40; ic_tx3=1168.94; ic_tx4=1972.44; ic_tx5=1369.85;

c_te1=23529.41; c_te2=254.41; ic_te1=2094.35;

ic_txf1=359.45;

if sen=0.8 and spe=0.9879 then c_stool=c_mammo;

if sen=0.915 and spe=0.9670 then c_stool=c_sono;

cumcost_s=0; cumcost_con=0;

do sf1=1 to 25;

cost_s=cs[sf1]*(c_stool+c_sother+ic_s)/((1+discount)**(sf1-1));

cumcost_s+cost_s;

cost_confirm=csc[sf1]*(c_con_biopsy+ c_con_under+ic_con)/((1+discount)**(sf1-1));

cumcost_con+cost_confirm;

end;

cost_tx=(c_tx1+c_tx2+ic_tx1+ic_tx2+ic_tx3+ic_tx4+ic_tx5)/((1+discount)**(tx_year-4

4-1));
```


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```
if death in (3 4) then

cost_death=(c_te1+c_te2+ic_te1)/((1+discount)**(fdeathage-44-1));

cost_txf=0;

end_year=min(fdeathage, 69);

if tx_year^=. and end_year>tx_year then do txf=tx_year-44+1 to end_year-44 by 1;

*follow到死亡為止;

cost_txf=cost_txf+(ic_txf1)/((1+discount)**(txf-1));

end;

cumdpy=0; endst3=0;

do st3=1 to 25 until (endst3=1);

st=st3+44;

if st<tau1                    then do; sm[st3]=0;

cumdpy=cumdpy+1/((1+discount)**(st3-1));      end;

if tau1<=st & st<t then do; sm[st3]=1; cumdpy=cumdpy+0.85/((1+discount)**(st3-1));

end;

if t<=st and tx_year<t then do;    sm[st3]=3;

cumdpy=cumdpy+0.85/((1+discount)**(st3-1));    end;

if t<=st and tx_year>=t then do; sm[st3]=2;
```


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```
cumdpy=cumdpy+0.75/((1+discount)**(st3-1));    end;

if 0<fdeathage<=st then do; sm[st3]=4;    endst3=1; end;

end;

run;

data a4;

set a3 (keep=cumcost_s cumcost_con cost_tx cost_txf cost_death cumdpy nsd nin)

end=fz;

if cumcost_s=. then cumcost_s=0;

if cumcost_con=. then cumcost_con=0;

if cost_tx=. then cost_tx=0;

if cost_txf=. then cost_txf=0;

accost_s+cumcost_s;

accost_con+cumcost_con;

acost_tx+cost_tx;

acost_txf+cost_txf;

acdpy+cumdpy;

last=fz;

if cost_death=. then cost_death=0;
```


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```
acost_death+cost_death;

allcost=sum(of accost_s, accost_con, acost_tx, acost_txf,acost_death);

run;

ods output OneWayFreqs=d1;        *Note! different SAS version has different name.;

proc freq data=a1;

tables nsd nin    death;

run;

ods output close;

data oo;

set d1 end=fz;

retain onin onsd pcdpdeath cpdeath odeath;

if table='Table nin' & nin=1 then onin=Frequency;

if table='Table nsd' & nsd=1 then onsd=Frequency;

if table='Table death' & death=3 then pcdpdeath=Frequency;

if table='Table death' & death=4 then cpdeath=Frequency;

if table='Table death' & death=5 then odeath=Frequency;

if fz=1;

keep onin onsd pcdpdeath cpdeath odeath;
```


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```
run;

title "Interval=&v_int          Sen=&v_sen Spe=&v_spe    attendence rate=&v_patt ";

data a5;

set a4;

if _n_=1 then set oo;

if last=1;

keep acdpy accost_s accost_con acost_tx acost_txf acost_death allcost onin onsd

pcdpdeath cpdeath odeath;

run;

proc print;

var acdpy accost_s accost_con acost_tx acost_txf acost_death allcost onin onsd

pcdpdeath cpdeath odeath;

run;

%mend;
```


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Chapter 5 Results

5.1 Descriptive results of the simulated cohort

The characteristics of simulated data on one million women are listed in Table 5.1.1. The scenario of biennial screening with mammography targeted at one million women aged 45 to 69 years is adopted for simulating this cohort. The variables of interest included conventional risk factors (BMI, age at first full-term pregnancy, breast density, BRCA1/2, ER, Her-2, Ki-67, PR, basal phenotype, 12 alleles of SNP, P53, and life-time HRT use.

5.2 Estimated results of parameters on initiators and promoters

The effect size of the effects responsible for initiators and promoters of breast cancer in the simulated cohort along with the prevalence of the simulated cohort carrying the characteristics are listed in Table 5.2.1 and 5.2.2, respectively. All the figures are abstracted from literature view by using the principle of sufficient statistics.

5.3 Multistate risk scores for initiators and promoters

Following (4-1) to (4-3), we used the Weibull distribution to depict the occurrence and the progression of breast cancer. Factors associated with these two process are then incorporated using a proportional hazard form listed as follows

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$$\lambda_1 = \begin{cases} \lambda_{10} \exp(\boldsymbol{\beta}_1 \mathbf{X}_1), \text{ for non-BRCA carrier} \\ \lambda_{20} \exp(\boldsymbol{\beta}_1 \mathbf{X}_1), \quad \text{for BRCA}_1 \text{ carrier} \\ \lambda_{30} \exp(\boldsymbol{\beta}_1 \mathbf{X}_1), \quad \text{for BRCA}_2 \text{ carrier} \end{cases}$$

and .

$$\lambda_2 = \lambda_{20} \exp(\boldsymbol{\beta}_2 \mathbf{X}_2)$$

The relevant risk factors along with their effect size give a set of risk scores expressed by $score_1$ and $score_2$ which dominate the occurrence and progression of breast cancer. For the occurrence of breast cancer, the risk score is

$Score_1$= 0.952*(BMI>=23)+0.688*(Age at fist pregnancy>=25+0.693*(Breast density: scattered fibroglandular density)+1.206*(Breast density: heterogeneously dense)+1.369*(Breast density: extremely dense)+0.231(No. rs2981582)+ 0.182*(No. rs3803662)+ 0.122*(No. rs889312)+0.677(No. rs3817198)+ 0.077*(No. rs13281615)+0.182*(No. rs13387042)+ 0.122*(No. rs1045485)+ 0.105*(No. rs9485372)+ 0.128*(No. rs9383951)+ 0.077*(No. rs7107217)+ 0.094*(No. rs12118297)+ 0.122*(No. rs16992204)+ 0.78*P53+ 0.083*(HRT: Never use)+ 0.340*(HRT: Current oral estrogen use)+ 0.485*(HRT: current combination therapy).

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The risk score for breast cancer progression is thus

$Score_2$=0.692*(BMI>=23)+0.447*(Age at first pregnancy>25)+0.30*(ER negative)+0.247*(HER2 2+)+0.068*(HER2 3+)+0.336*(Ki67 10-30%)+0.104*(Ki67 >30%)+ 0.077(PR negative)+0.536*(Basal type)

Figure 5.3.1 (a) and (b) shows the distribution of two risk scores. It can be clearly seen that the risk score 1 behaves like a normal distribution as expected whereas the risk score 2 does not follow a normal distribution.

Table 5.3.1 and Figures presents 10-year breast cancer for BRCA carrier by age groups. The 10-year risk increased with age from 6.5% for women aged 20 years to 22% for women aged 70 years whereas the life-time risk of breast cancer decrease with age from 58% for women aged 20 years to 31% for women aged 70 years.

5.4 Decile risk stratification of asymptomatic and symptomatic breast cancer

Table 5.4.1 and Figure 5.4.1 show decile risk stratification of developing breast cancer, ranging from 1.10% in the lowest group to 14.56 in the highest risk group. Table 5.4.2 and Figure 5.4.2 show the corresponding 10-year and life-time risk of breast cancer by the status of BRCA carrier.

Table 5.4.3 gives the estimates of mean sojourn time (MST) by different risk

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groups, ranging from 1.45 years for the highest risk group to 3.74 for the lowest risk group.

5.5 Efficacy and effectiveness of intervention

5.5.1 Efficacy of universal breast cancer screening

Tables 5.5.1 (a) and (b) show the efficacy of reducing advanced BC and BC deaths by different inter-screening interval with the range from 13.85% for annual screening to 4.25% for triennial screening for the reduction of advanced BC and from 31% for annual screening to 20.77% for triennial screening for the reduction of breast cancer death.

Figure 5.4.3-5.4.8 gives dynamic curve of progression form free of breast cancer (FBC) through PCDP to CP by different levels of risk groups by the status of BRCA carrier with different levels of risk groups. These dynamic curved are very helpful for decide various screening strategies.

5.5.2 Efficacy of primary and secondary preventions for BRCA carriers

Tables 5.5.2 (a) and (b) show the efficacy of primary prevention with prophylactic mastectomy or chemoprevention and secondary prevention with annual mammography screening and annual mammography screening and annual MRI. The efficacy in the reduction of advanced BC was around 16%-18%. The efficacy in the reduction of breast

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cancer death was from 22% with Tamoxien to 38% with annual mammography and annual MRI.

5.5.3 Efficacy of screening with various inter-screening interval by risk groups

Tables 5.5.3 (a) and (b) show the efficacy of personalized strategy using various inter-screening interval was greater in the high risk group because short inter-screening interval is applied but lower in the low risk group. However, the opposite findings were noted for biennial universal screening.

5.5.4 Efficacy of multimodality approach

Tables 5.5.4 (a) and (b) show the efficacy of personalized strategy using various combination of screening tools was greater in the high risk group because costly screening is applied but lower in the low risk group because routine mammography with long inter-screening interval is applied. However, the opposite findings were noted for biennial universal screening.

5.6 Results on cost-effectiveness analysis

5.6.1 Universal strategies for the overall group

Table 5.6.1 and Figure 5.6.1 show the results of cost-effectiveness analysis of various inter-screening interval. The ICER values decreased from 47,079 for annual screening to 32,201 for triennial screening. Figure 5.6.1 shows if we take 2 GDP and

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willing to pay (WTP), only biennial screening and triennial screening was acceptable but annual screening was not acceptable.

5.6.2 Personalized strategies for the overall group

Table 5.6.2 (a) show the ICER values were 34,585 for various inter-screening interval guided by risk of breast cancer but increased to 115,838 for various alternative imagine techniques guided by risk of breast cancer (including >80% -MRI +sonography + mammography;60%-80% sonography+mammography; 40%-60% Biennial mammography;20%-40% Four-yearly mammography; < 20% Six-yearly mammography). Figure 5.6.2 shows personalized strategy with various inter-screening was acceptable when 2GDP is taken as the threshold of WTP whereas personalized strategy with multimodality was not acceptable even 3GDP is taken as the threshold of WTP (also see Figure 5.6.1). The similar findings were noted by using the results of acceptability curve (Figure 5.6.3). The similar findings were found when the baseline group is biennial screening as shown in Table 5.6.2 (b).

5.6.3 Screening strategies for non-BRCA carrier

The similar findings on the results of cost-effectiveness analysis were also found for non-carrier. For universal screening, the ICER values decreased from 48,026 for annual screening to 32,805 for triennial screening. Figure 5.6.3 (c) shows if we take 2

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GDP and willing to pay (WTP), only biennial screening and triennial screening was acceptable but annual screening was not acceptable. Regarding personal preventive strategy, the ICER values were 35,278 for various inter-screening interval guided by risk of breast cancer but increased to 119,315 for various alternative imagine techniques guided by risk of breast cancer (including >80% -MRI +sonography + mammography;60%-80% sonography+mammography; 40%-60% Biennial mammography;20%-40% Four-yearly mammography; < 20% Six-yearly mammography). The results of acceptability curve (Figure 5.6.3 (c) and (d)) show personalized strategy with various inter-screening was acceptable when 2GDP is taken as the threshold of WTP whereas personalized strategy with multimodality was not acceptable even 3GDP is taken as the threshold of WTP.

5.6.4 Preventive strategies for BRCA carrier

Table 5.6.4 and Figure 5.6.4 show the results of cost-effectiveness analysis of various inter-screening interval. The ICER values ranged from 2,722 for mammography with surgery to 49,884 when MRI was added. It is not surprising that when all women had the uptake of genetic testing to get information on BRCA carrier the ICER increased substantially. Figure 5.6.4 (a)-(h) shows most of preventive strategies for women with BRCA carrier were acceptable within the range of 2 GDP of willingness to

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pay (WTP).

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Chapter 6 Discussion

6.1 Era of tailored prevention of breast cancer

In spite of the advent of widely used mammography and other alternative imaging techniques for breast cancer screening over the past three decades, risk-guided preventive strategies have increasingly gained attention as individually-tailored strategies guided by the risk of breast cancer may render prevention of breast cancer death not only effective but also efficient. However, a systematic economic evaluation of risk-guided personalized preventive strategies has been never addressed before. To get a better understanding of personalized preventive strategies cannot be overemphasized particularly when a series of genetic and epigenetic markers and several new alternative imaging techniques have been proposed over the past two decades. It is therefore expected that the transition from the era of evidence-based prevention to the era of individually-tailored prevention. The shift is also driven by the urgent need of translational research that turns basic and molecular findings into clinical practice as these studies have got involved with enormous investment since 1990. The shift paradigm from evidence-based prevention to personalized prevention plays an important role in individual risk reduction of breast cancer because there are still 10-20% BCs still die from breast cancer even through diversified preventive approaches

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and also unknown but probable over-detection of breast cancer given the proposed state-of-the-art intervention technology. This is so called “a square peg in a round hole”. One of solution to this issue is the use personalized preventive strategies. To achieve this goal, personalized risk stratification of the underlying population and the corresponding economic appraisal are therefore required. This is one of the major contributions of this thesis.

6.2 Personalized risk stratification of the underlying population

This thesis developed a novel quantitative approach following the principle of translational research to provide a roadmap with state-of-the-art genomic discovery and clinical parameters to facilitate individually-tailored screening and also to personalized clinical surveillance of early breast cancer by the development of multiple risk score for different steps of progression of breast cancer with the incorporation of genetic variants, epigenetic markers, conventional risk factors, clinical attributes, and tumour phenotypes. The risk stratification using such comprehensive information renders information as precise as possible.

6.3 Risk-guided personalized prevention of breast cancer

This thesis here begins with the triage of women with the potential of having hereditary BC and without potential of the counterpart of non-hereditary BC by using

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information on the carriers of BRCA 1/2. Preventive strategies offered for women with BRCA carrier are different from those for women without BRCA carriers. Within each groups, personalized preventive strategies can be tailored for individual women in the light of risk group. Doing so enables one to increase efficacy for high risk groups to reduce false negative cases and decrease false positive for low risk group. This can be seen in the results 5.3 section.

By using the proposed method of multi-state model on breast cancer progression in conjunction with the state-specific effect of risk factors on disease initiation and progression, data on cohort of breast cancer progression characterized by these risk factors can be projected. Based on the projected cohort on breast cancer progression, we demonstrated the results of cost-effectiveness analysis considering a series of strategies from annual to triennial screening and also the personalized screening strategy using the risk score developed from multi-state breast cancer progression as a stratification tool.

Compared with the current universal biennial screening strategy, personalized screening strategy had a lower ICER. However, it should be noted that whether personalized strategy is cost-effective is subject to enormous costs involved in the high risk group like the use of MRI in this thesis for non-carrier and also the carrier.

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6.4 Methodological Considerations

This thesis not only developed a personalized multistate risk prediction model with the incorporation of state-of-the-art genomic discovery and clinical parameters to facilitate individually-tailored screening and personalized clinical surveillance of early breast cancer but also developed the parallel of cost-effectiveness analysis on personalized preventive strategies. This is the principle of synthesis science for health decision making to achieve the optimal resource allocation at population level and also individual level.

6.5 Limitations

There are two major limitations of this thesis. The first is that the proposed multistate risk prediction model has not ye validated by external dataset. The model validation through external validation is necessary and should be conducted in the future. The second is that the costs for collecting information on state-specific covariates have not considered. This should be incorporated into economic appraisal and use the threshold analysis to assess the threshold they can afford to be cost-effective.

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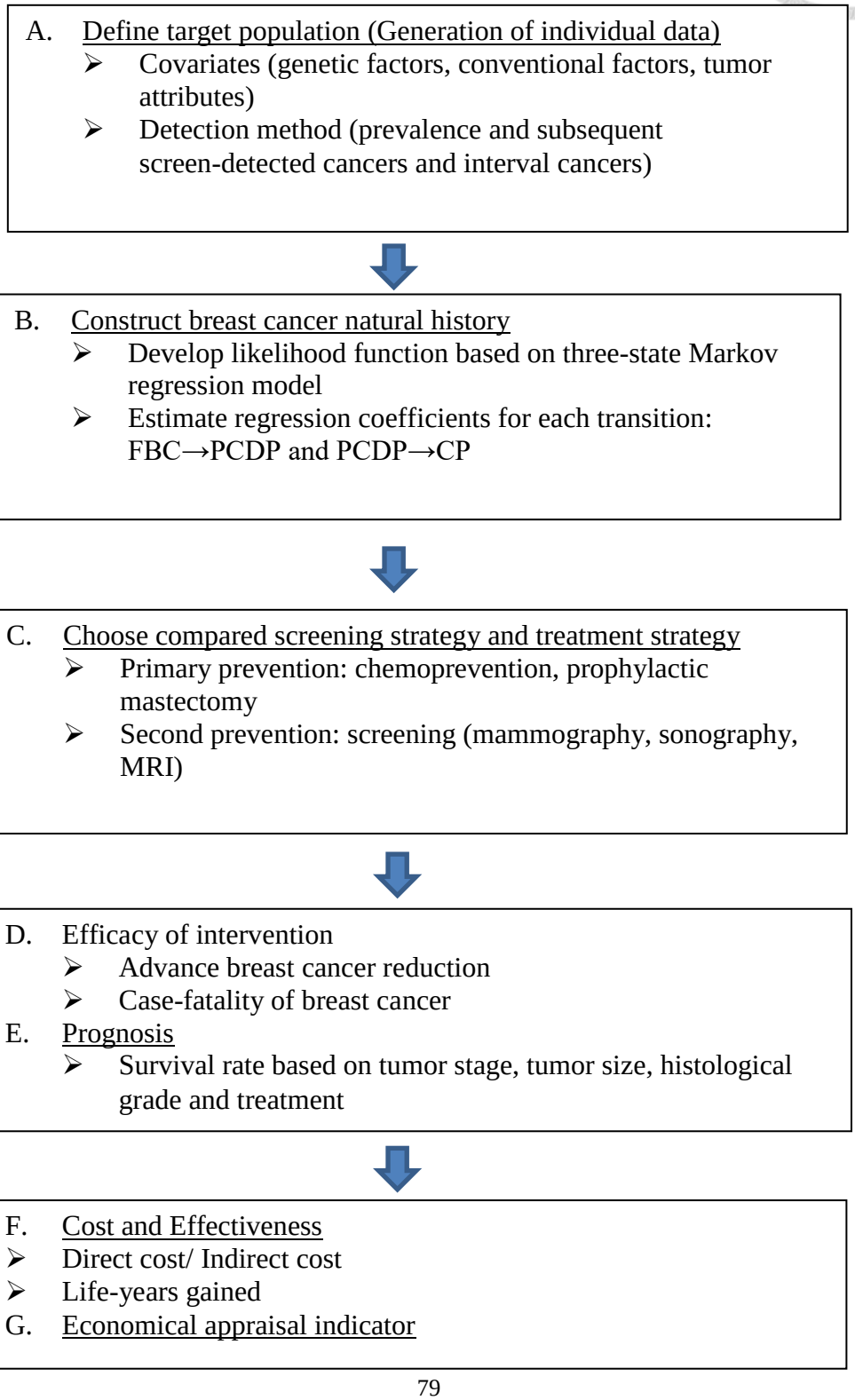
6.6 Conclusion

In conclusion, this is the first study to provide a systematic economic appraisal of breast cancer screening with personalized preventive strategies by separating the entire cohort carrier and non-carrier of BRCA. Such personalized preventive strategies in the light of risk-based strategies are not only efficacious but also cost-effective, particularly considering risk-adjusted inter-screening interval. However, risk-adjusted multimodality is highly dependent on the cost involved in the high-risk group. In addition, our thesis also gives a suggested when a person has BRCA 1/ 2 mutation. For example, BRCA mutation carrier may prevent breast cancer by doing the prophylactic bilateral mastectomy. However, it will influence BRCA carrier's future life. Based on our thesis result, annual MRI plus mammography will be better choose than prophylactic bilateral mastectomy and be cost-effectiveness.

doi:10.6342/NTU201702793

FIGURES

Figure 3.1 Seven steps of cost-effectiveness analysis for the risk-based screening of breast cancer



doi:10.6342/NTU201702793

Figure3.2 Conceptual multistate model incorporated with state-specific covariates on disease progression

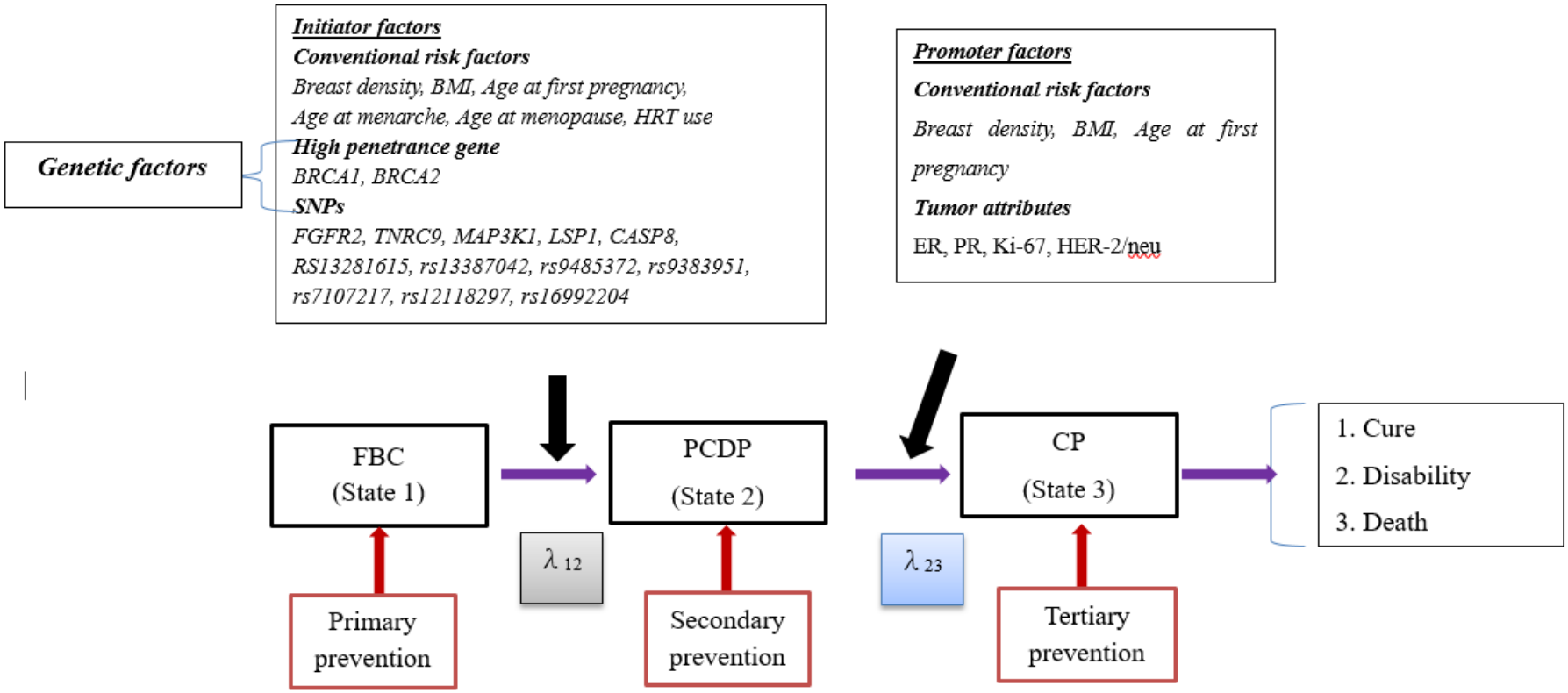


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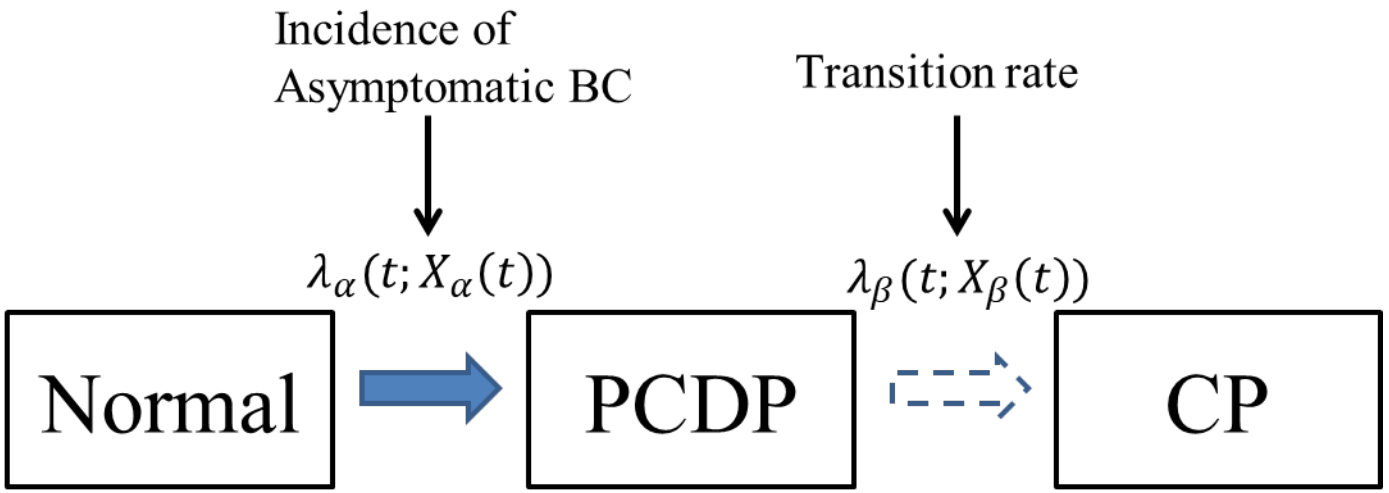
Figure 4.1 Three-state partially-hidden Markov model for the progression of breast cancer



$\lambda_\alpha(t; X_\alpha(t))$ is the function of time t(age) initiators denoted by $X_\alpha(t)$;
and $\lambda_\beta(t; X_\beta(t))$ is the function of time t and promoters denoted by $X_\beta(t)$

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Figure 4.5 1 Markov decision tree for multistate progression of breast cancer at normal status

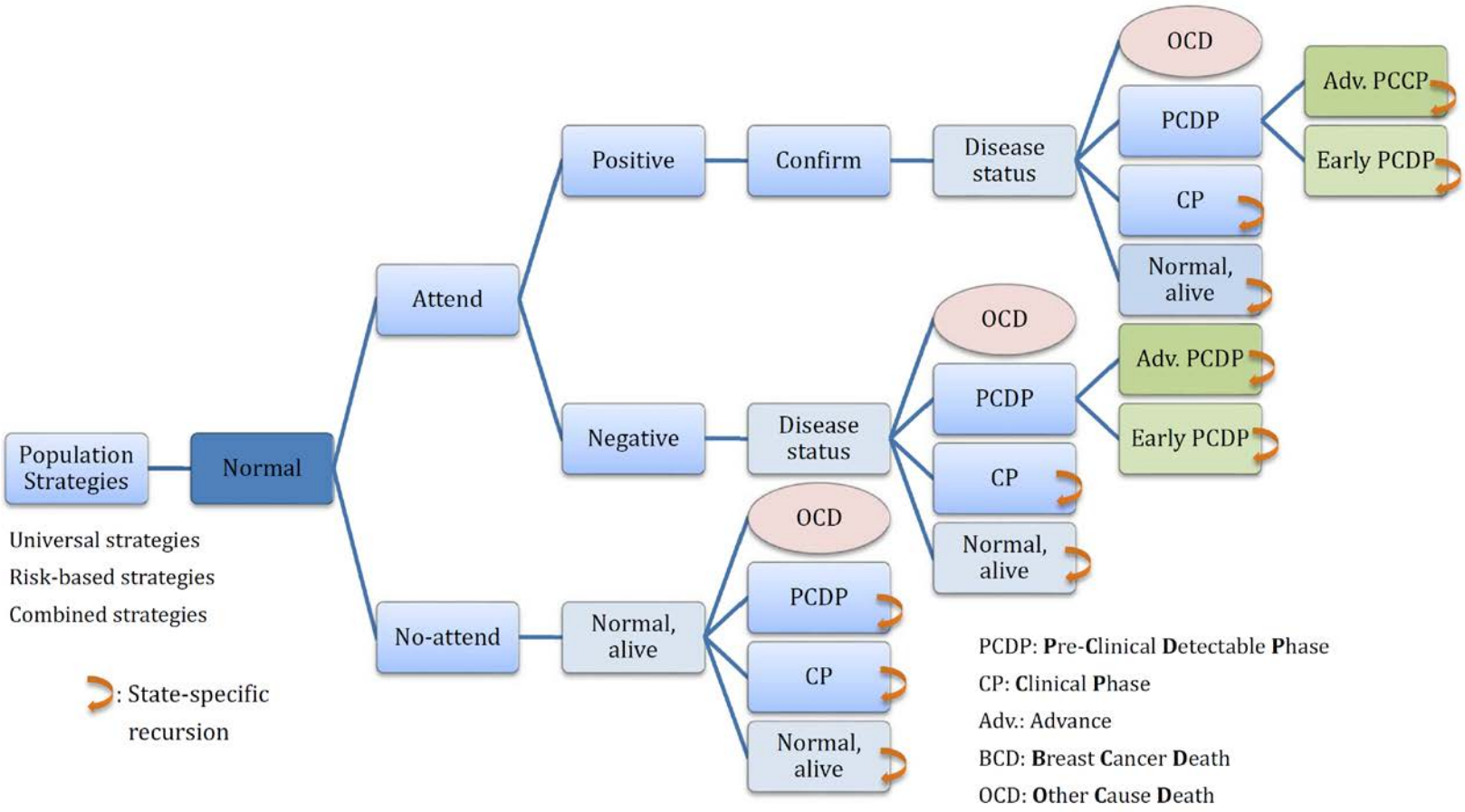

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Figure 4.5 2 Markov decision tree for subject start with the state of early PCDP

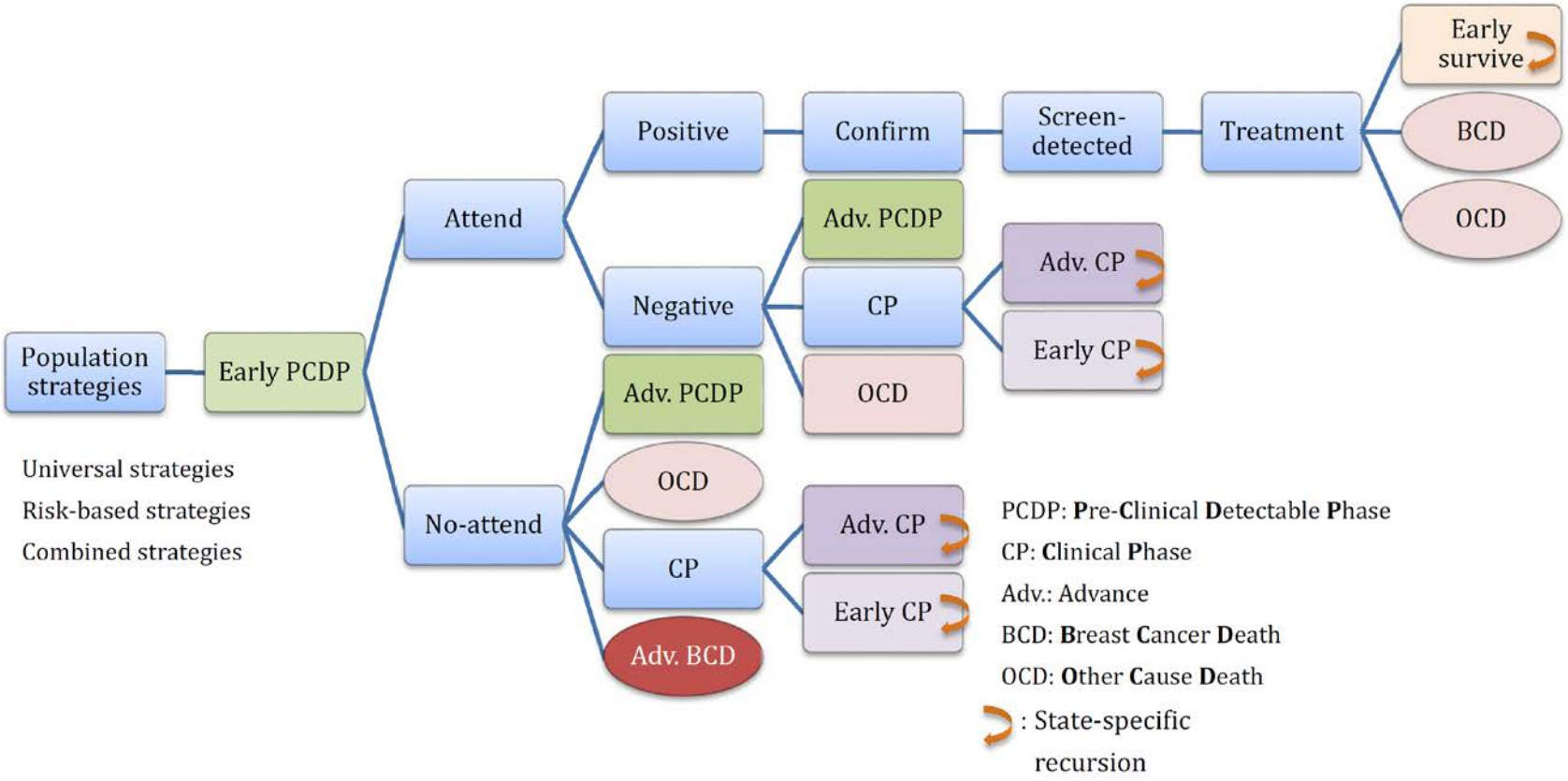

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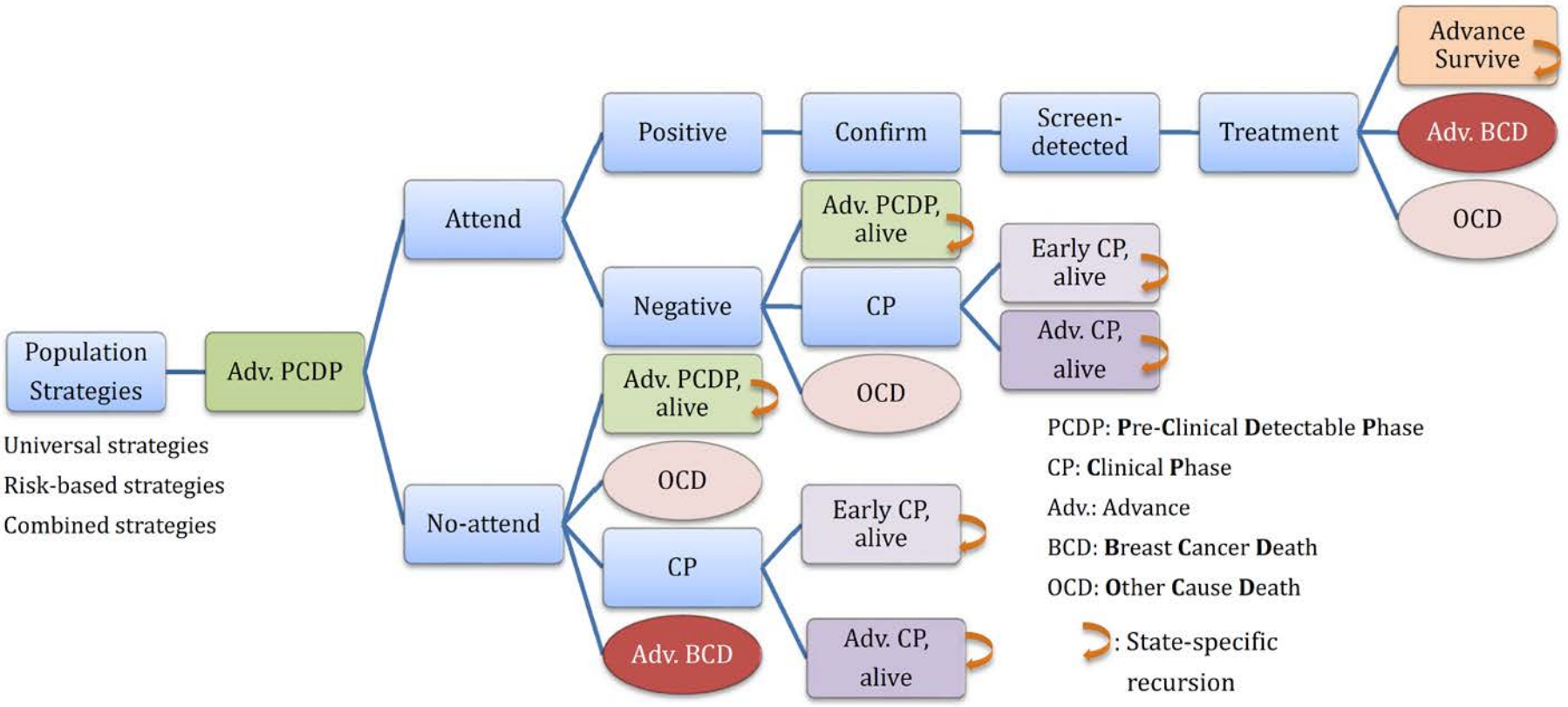
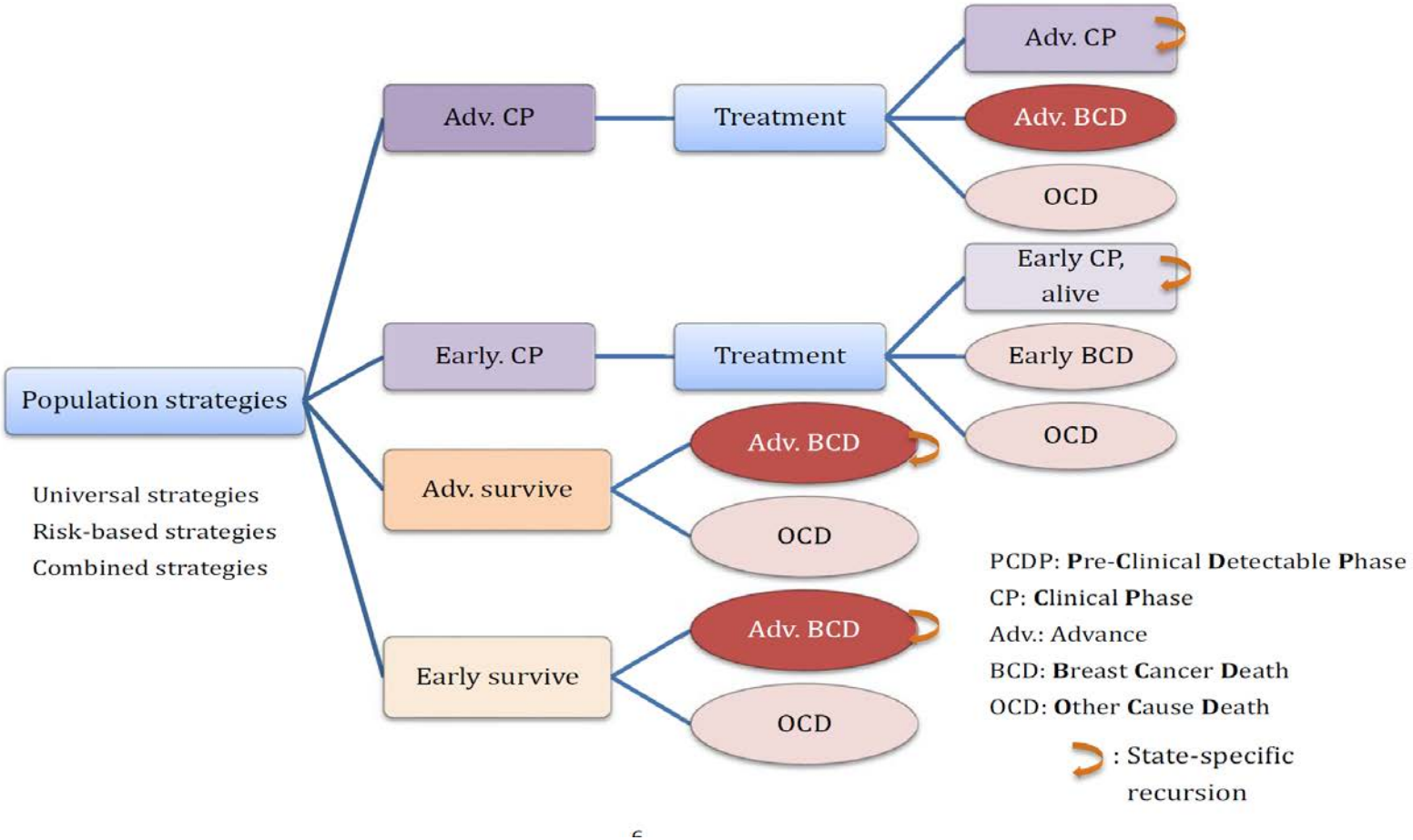
Figure 4.5 3 Markov decision tree for subject start with the state of advanced PCDP



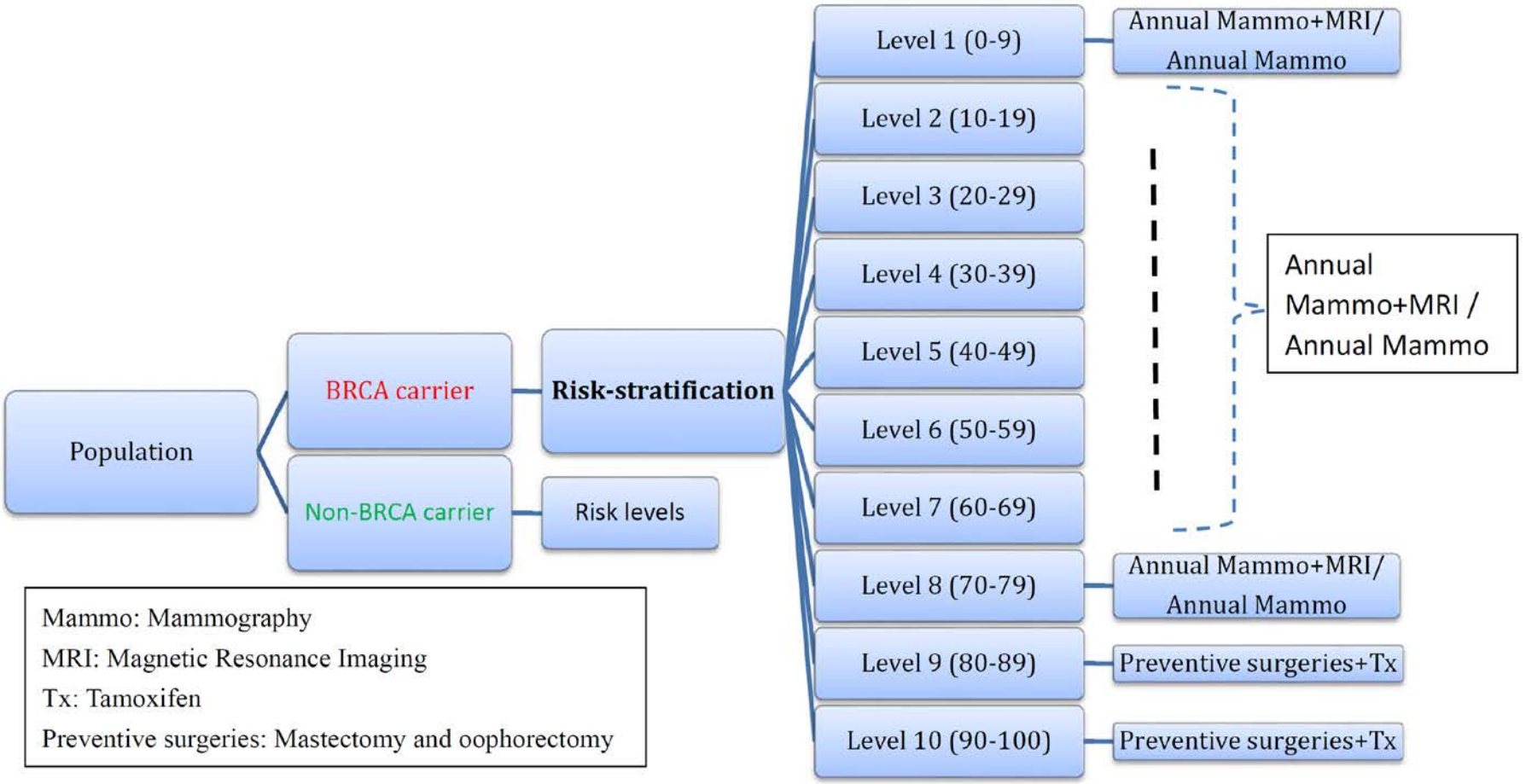
doi:10.6342/NTU201702793

Figure 4.5 4 Markov decision tree for multistate progression of breast cancer



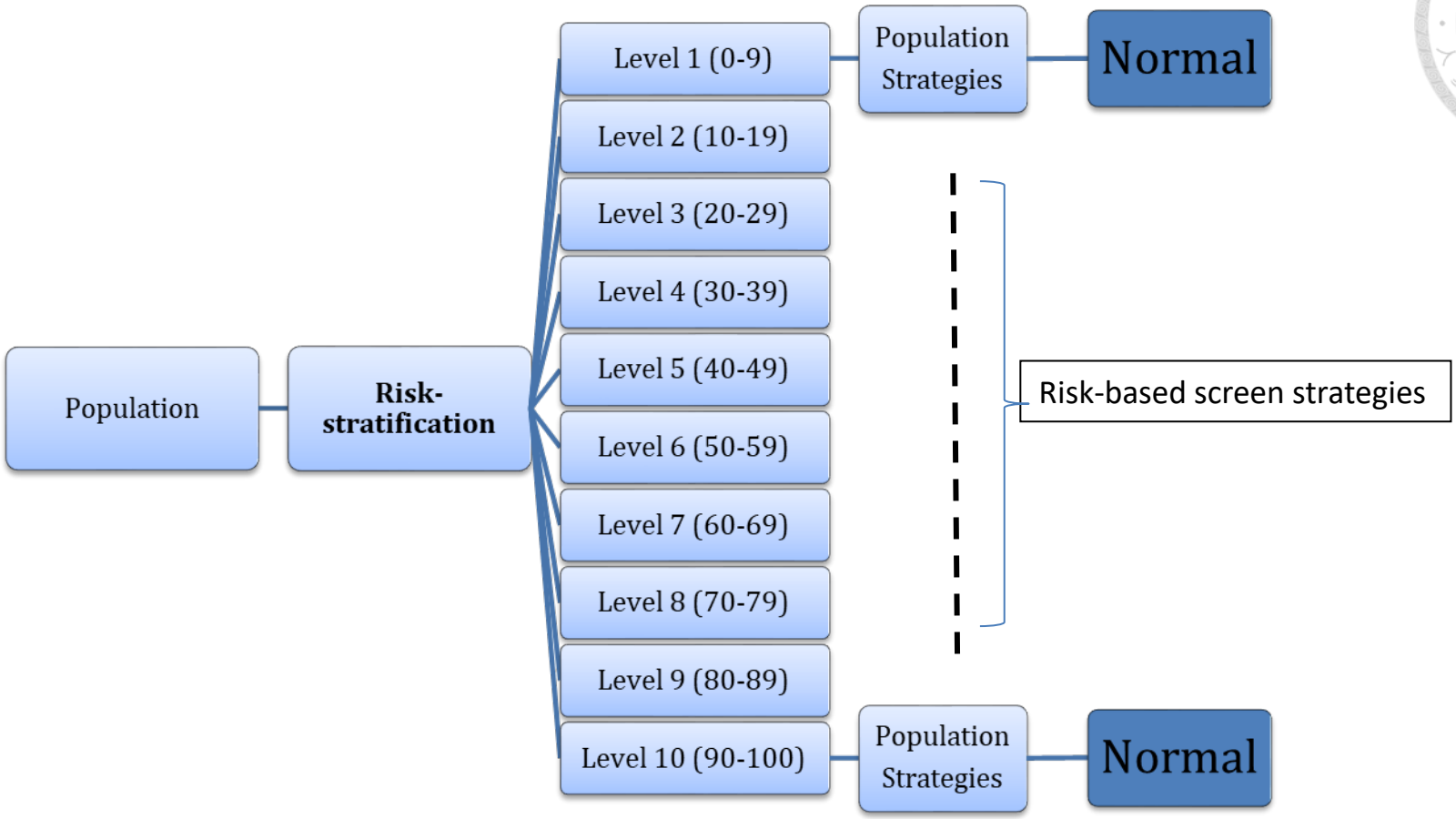
doi:10.6342/NTU201702793

Figure 4.5 5 Markov decision tree for BRCA-carriers



doi:10.6342/NTU201702793

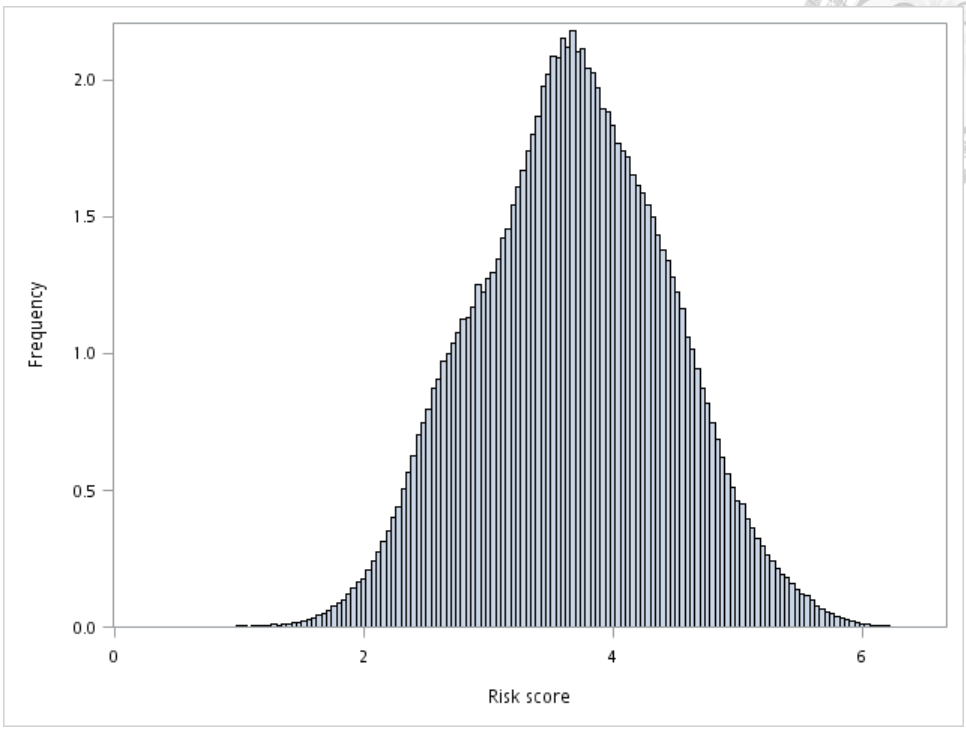
Figure 4.5 6 Markov decision tree for personalized screening intervals



doi:10.6342/NTU201702793

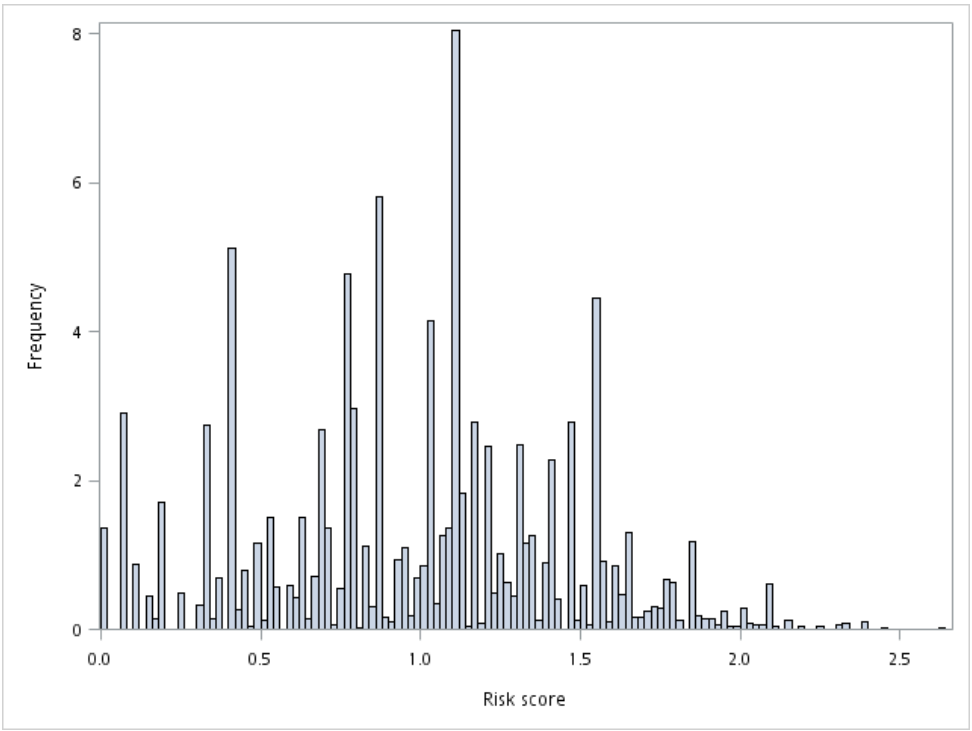
Figure 5.3 1 Distribution of risk scores

(a) Risk score distribution of FBC to PCDP



Mean: 3.68, Median: 3.68, SD: 0.770

(b) Risk score distribution of PCDP to CP

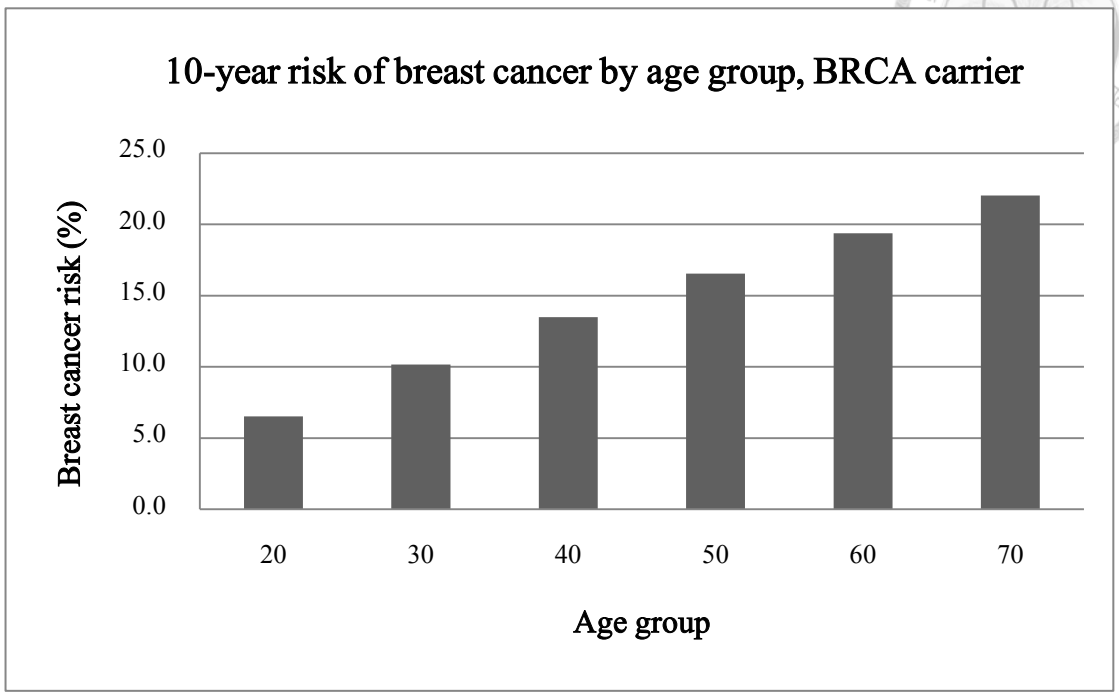


Mean: 0.98, Median: 1.03, SD: 0.48, IQR: 0.69-1.32

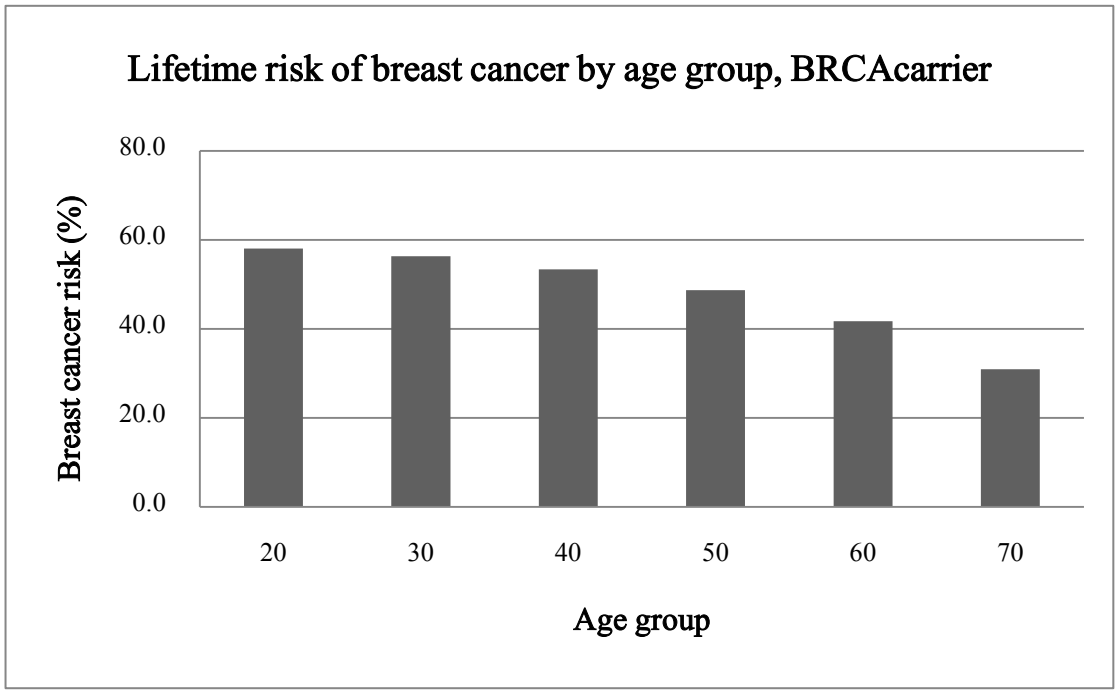
doi:10.6342/NTU201702793

Figure 5.3 2 Ten-year (a) and lifetime risk (b) of breast cancer for BRCA carrier women by age groups

(a) Ten-year risk of breast cancer for BRCA-carrier women by age groups



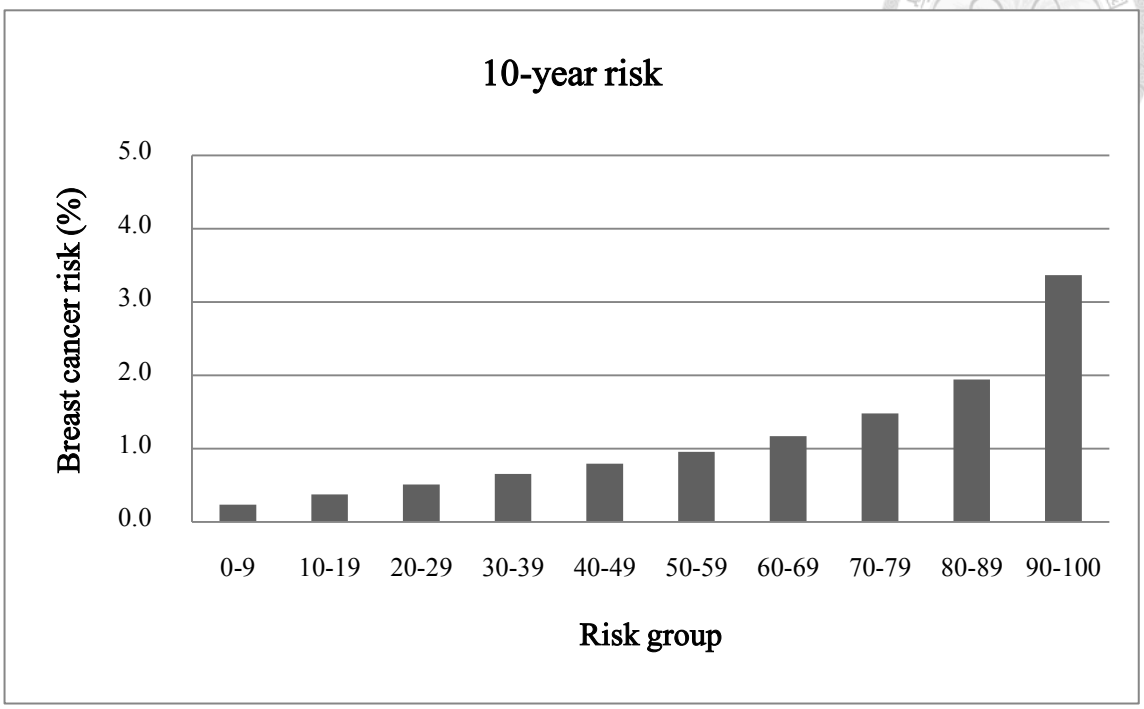
(b) Lifetime risk of breast cancer for BRCA-carrier women by age groups



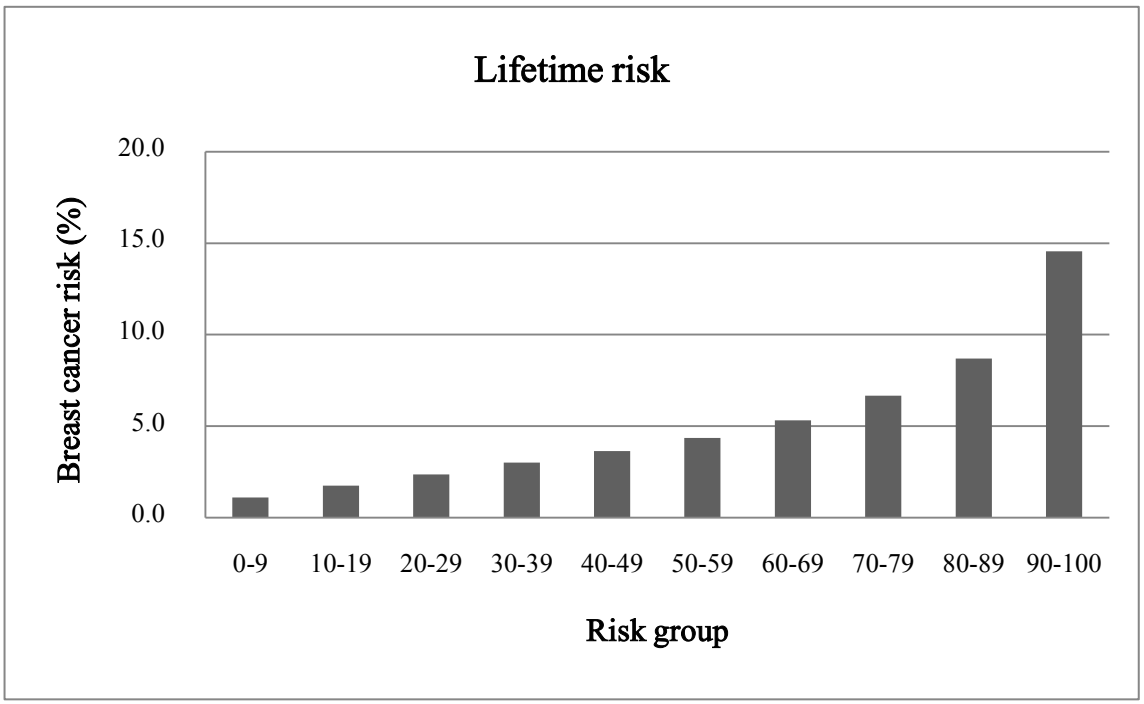
doi:10.6342/NTU201702793

Figure 5.4 1 Ten-year (a) and life-time risk (b) of breast cancer for women at 50 years by 10 risk categories

(a) Ten-year risk of breast cancer by 10 risk levels



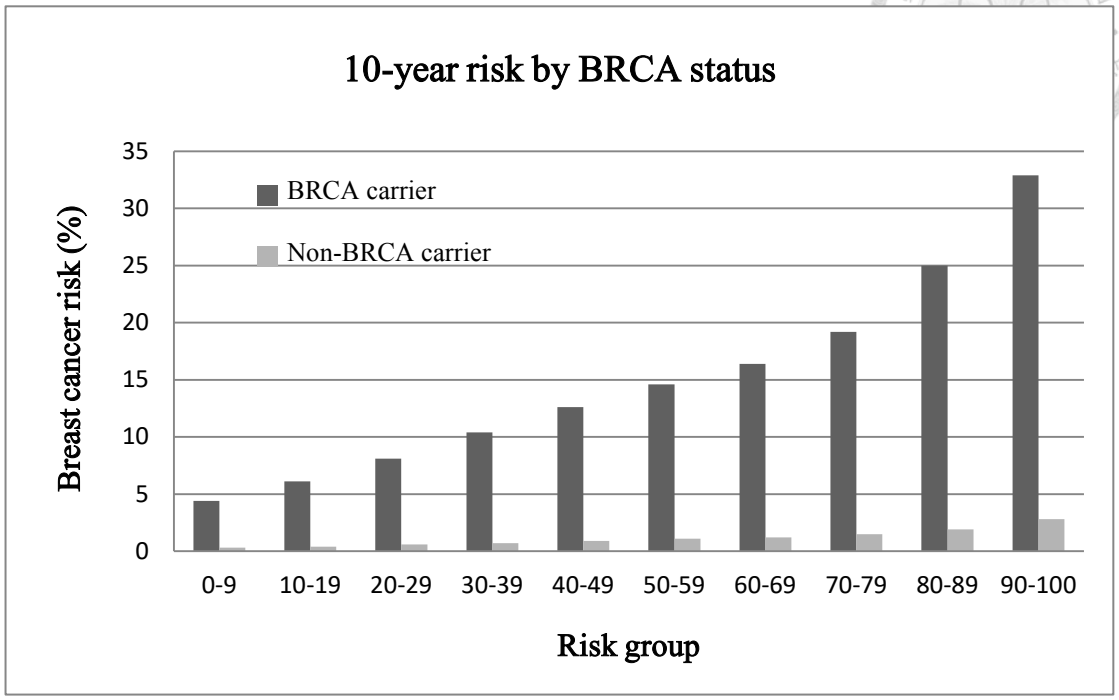
(b) Lifetime risk of breast cancer by 10 risk levels



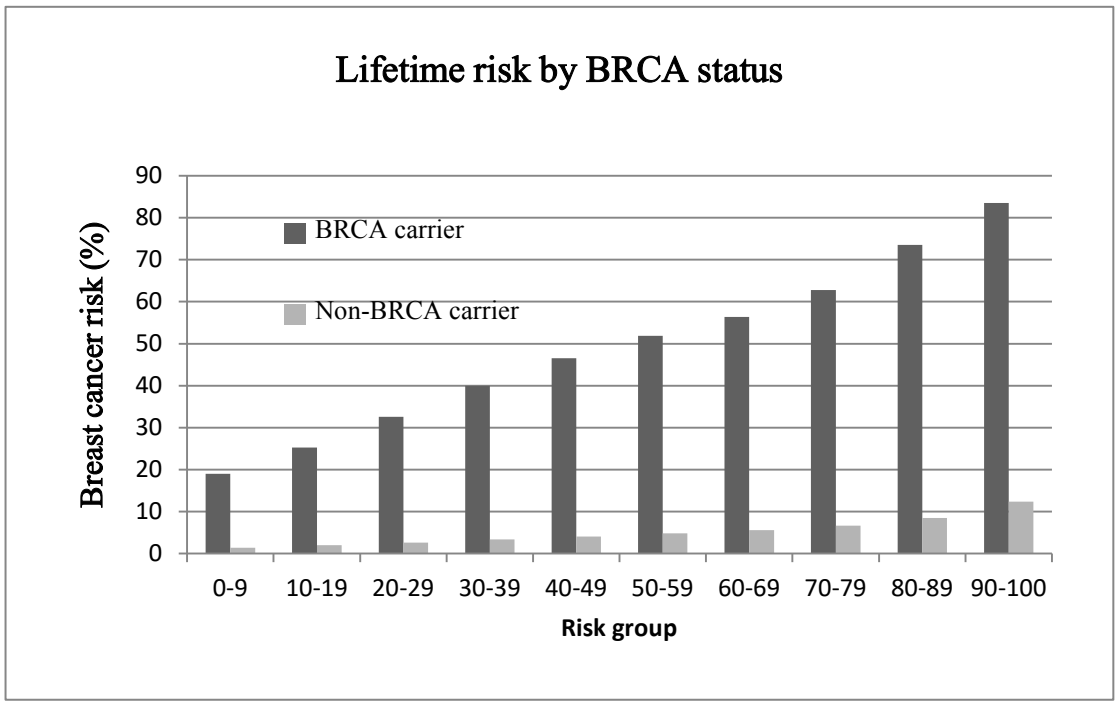
doi:10.6342/NTU201702793

Figure 5.4 2 Ten-year (a) and life-time (b) risk of breast cancer for women at 50 years by 10 risk categories

(a) Ten-year risk of breast cancer for women of BRCA carrier and non-BRCA carrier



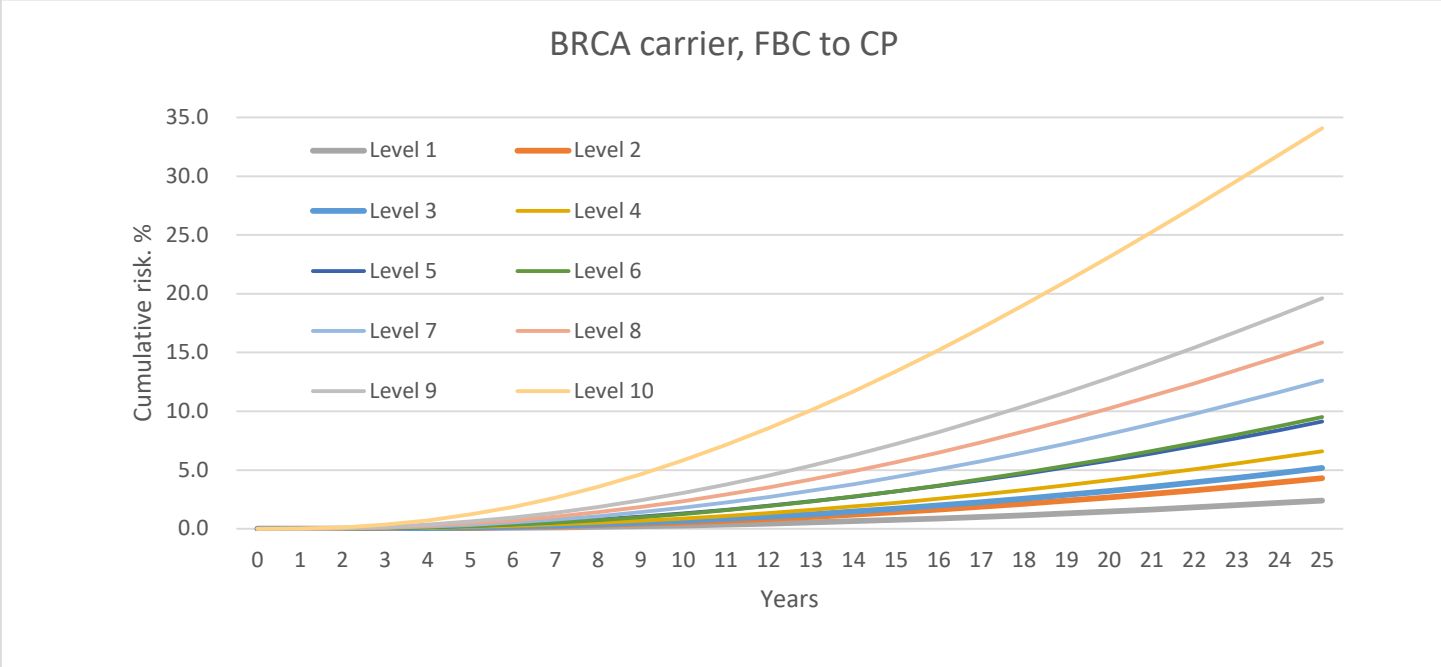
(b) Lifetime risk of breast cancer for women of BRCA carrier and non-BRCA carrier



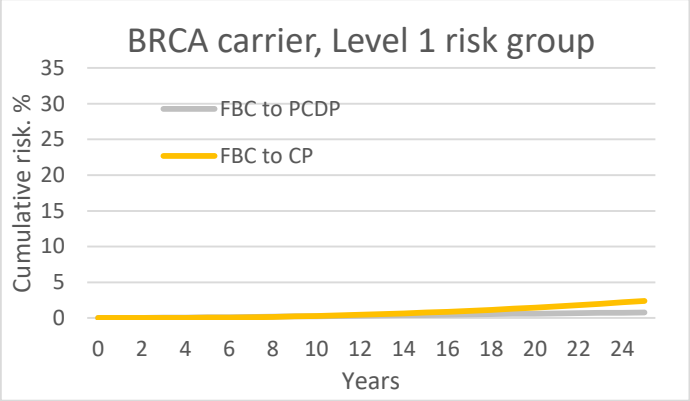
doi:10.6342/NTU201702793

Figure 5.4 3 Dynamic risk of breast cancer by ten-level categorization for women of BRCA carrier

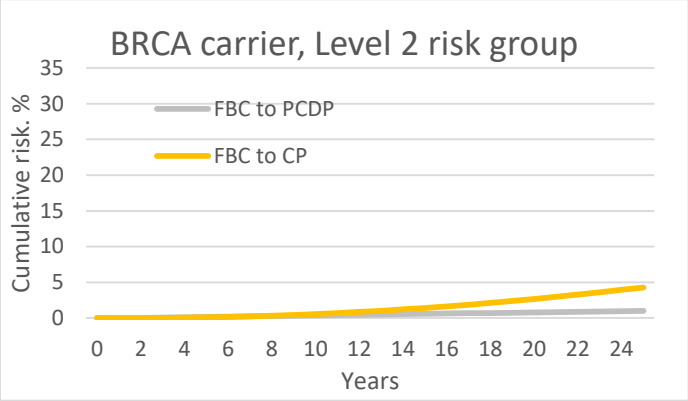
(a) The dynamic risk from free-of-breast-cancer (FBC) to clinical breast cancer (CP) by ten-level categorization



(b) Dynamic curve of breast cancer evolution to PCDP and CP for women at level 1 risk

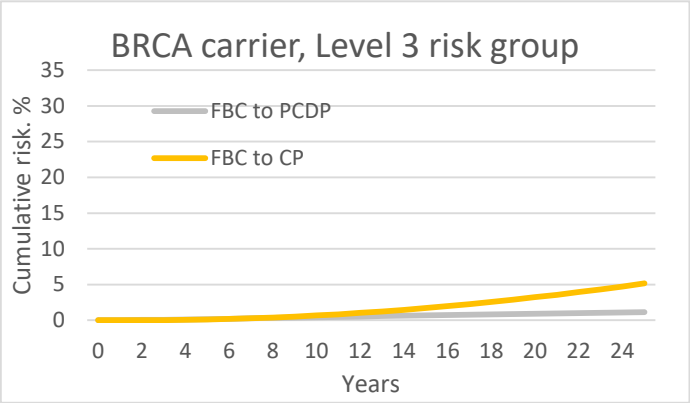


(c) Dynamic curve of breast cancer evolution to PCDP and CP for women at level 2 risk

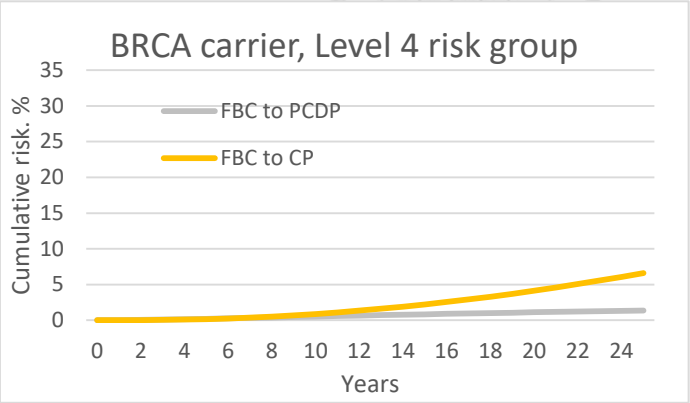


doi:10.6342/NTU201702793

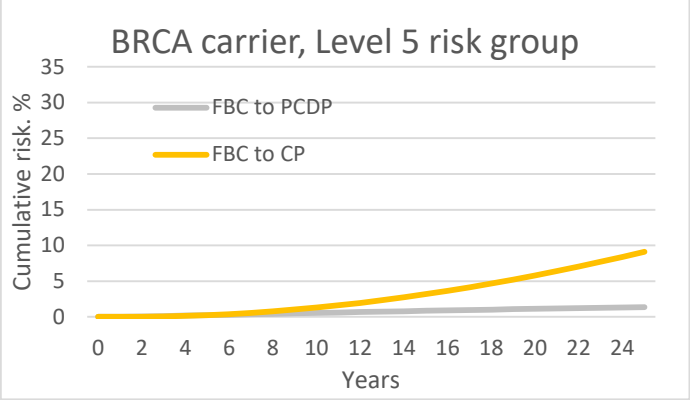
(d) Dynamic curve of breast cancer evolution to PCDP and CP for women at level 3 risk



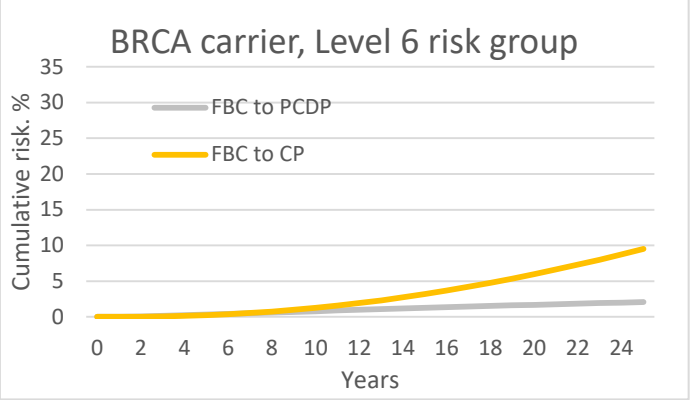
(e) Dynamic curve of breast cancer evolution to PCDP and CP for women at level 4 risk



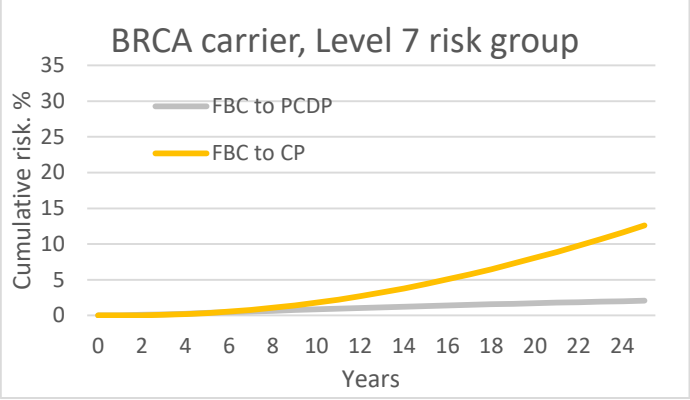
(f) Dynamic curve of breast cancer evolution to PCDP and CP for women at level 5 risk



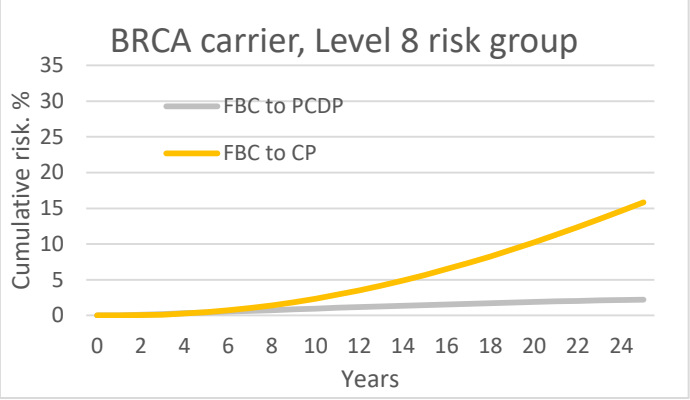
(g) Dynamic curve of breast cancer evolution to PCDP and CP for women at level 6 risk



(h) Dynamic curve of breast cancer evolution to PCDP and CP for women at level 7 risk

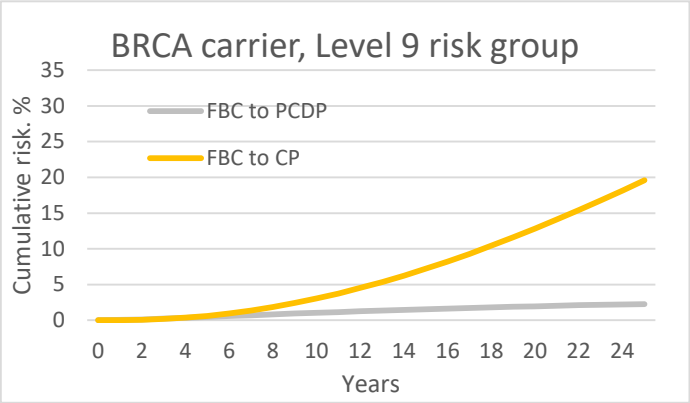


(i) Dynamic curve of breast cancer evolution to PCDP and CP for women at level 8 risk

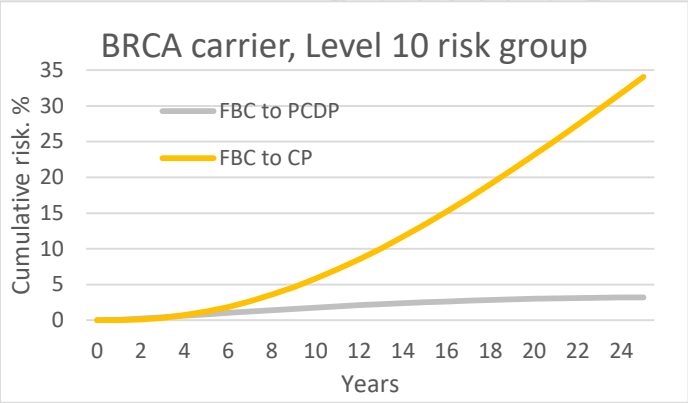


doi:10.6342/NTU201702793

(j) Dynamic curve of breast cancer evolution to PCDP and CP for women at level 9 risk



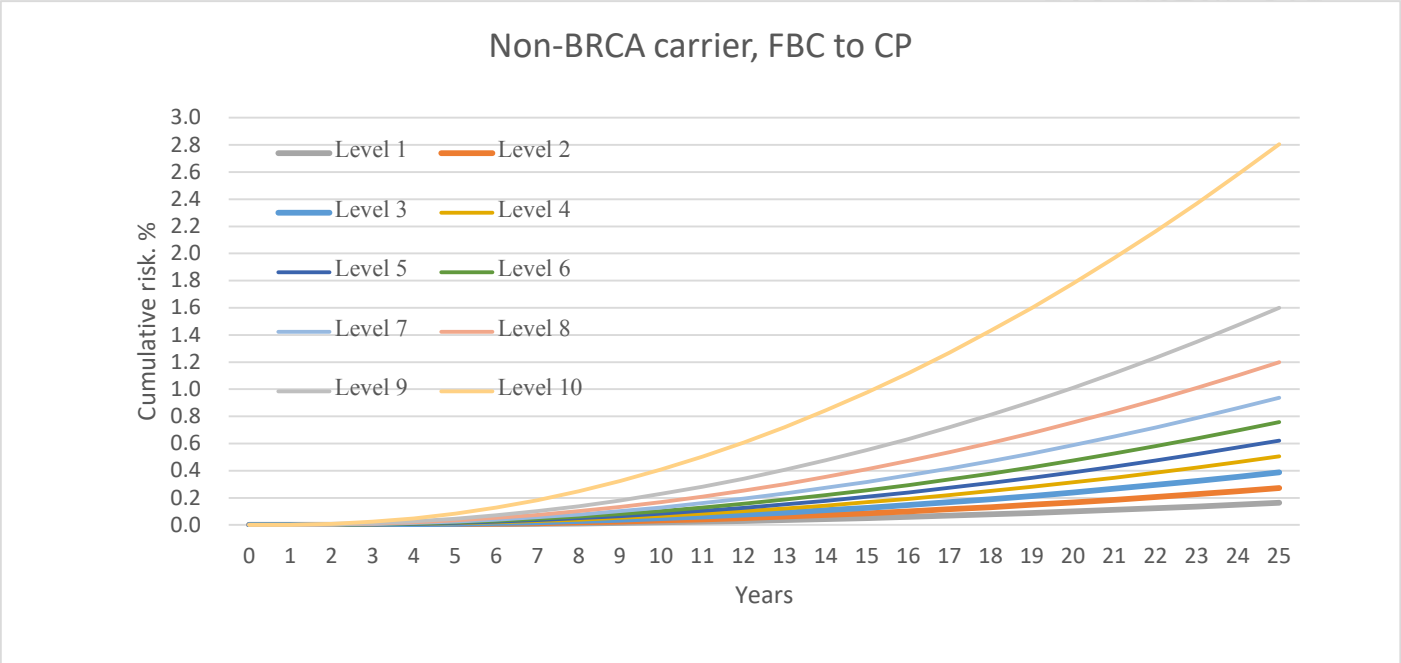
(k) Dynamic curve of breast cancer evolution to PCDP and CP for women at level 10 risk



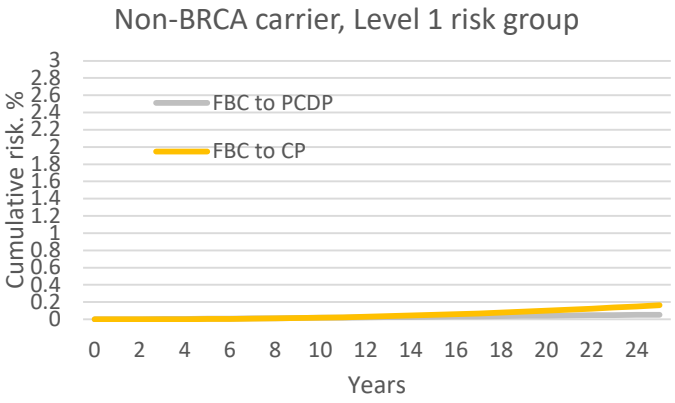
doi:10.6342/NTU201702793

Figure 5.4 4 Dynamic risk of breast cancer by ten-level categorization for women of non-BRCA carrier

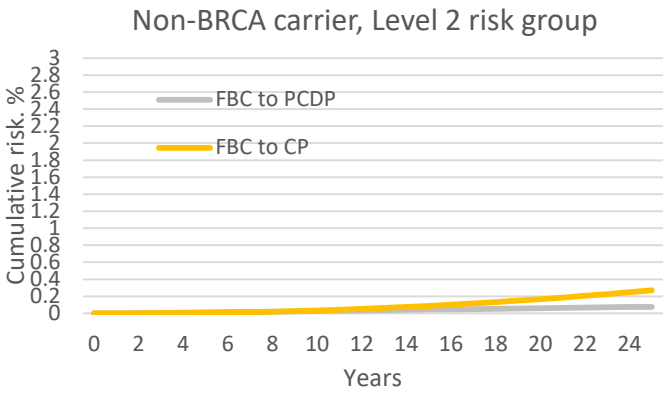
(a) The dynamic risk from free-of-breast-cancer (FBC) to clinical breast cancer (CP) by ten-level categorization



(b) Dynamic curve of breast cancer evolution to PCDP and CP for women at level 1 risk

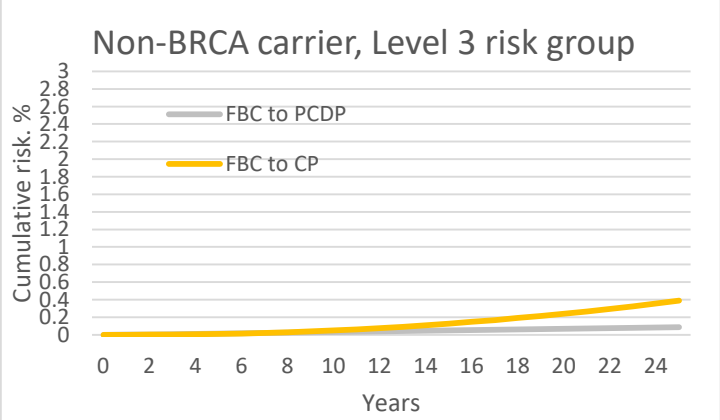


(c) Dynamic curve of breast cancer evolution to PCDP and CP for women at level 2 risk

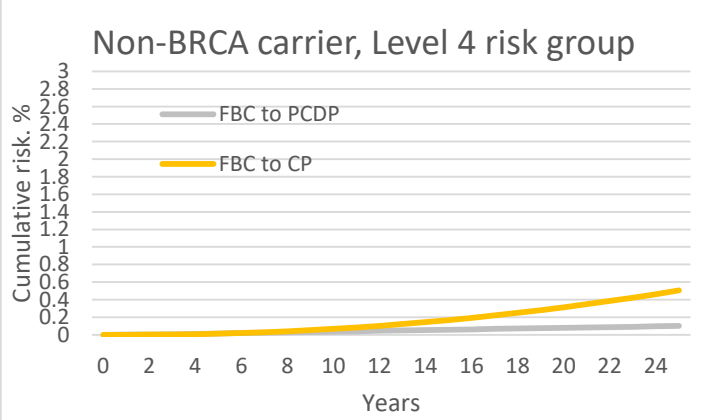


doi:10.6342/NTU201702793

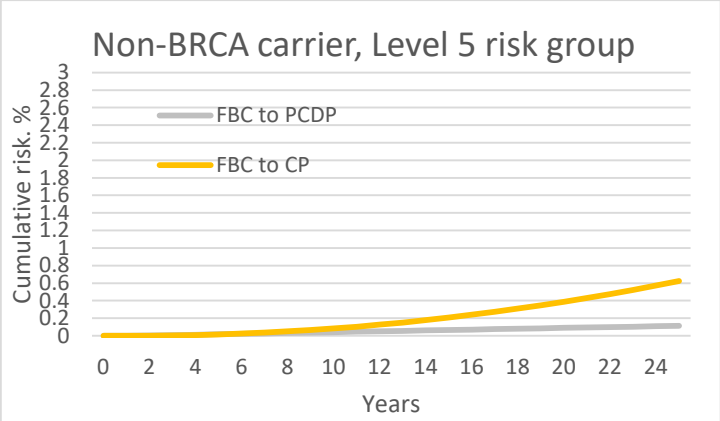
(d) Dynamic curve of breast cancer evolution to PCDP and CP for women at level 3 risk



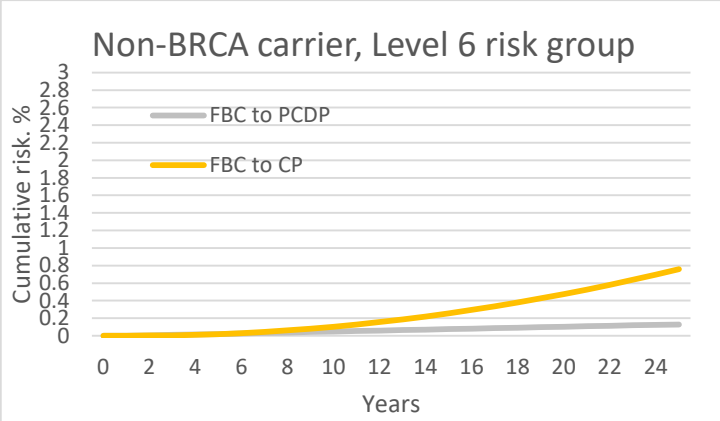
(e) Dynamic curve of breast cancer evolution to PCDP and CP for women at level 4 risk



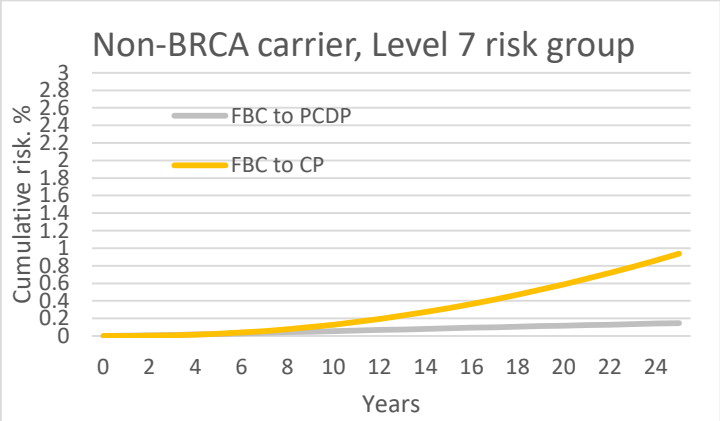
(f) Dynamic curve of breast cancer evolution to PCDP and CP for women at level 5 risk



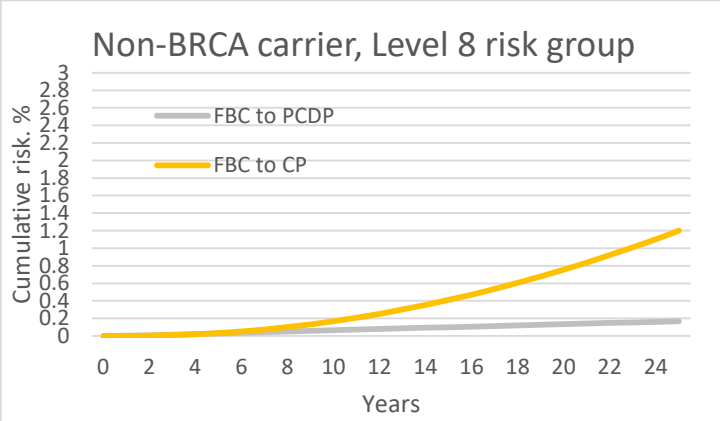
(g) Dynamic curve of breast cancer evolution to PCDP and CP for women at level 6 risk



(h) Dynamic curve of breast cancer evolution to PCDP and CP for women at level 7 risk

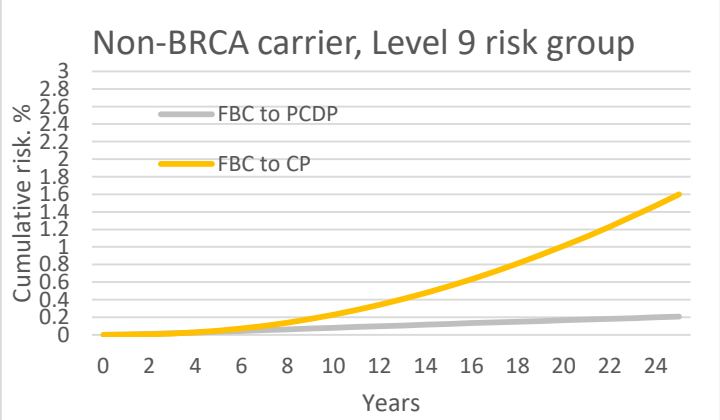


(i) Dynamic curve of breast cancer evolution to PCDP and CP for women at level 8 risk

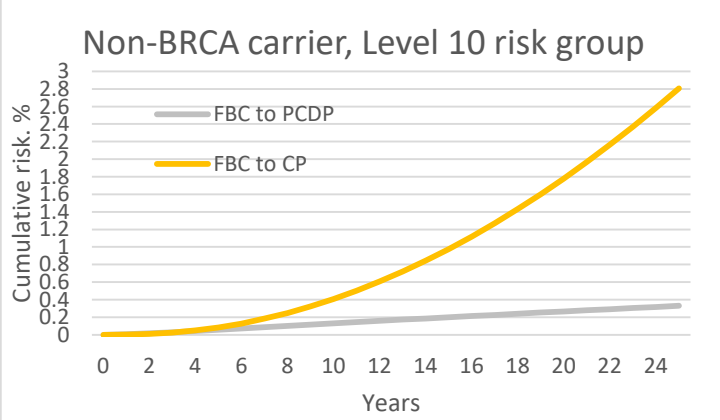


doi:10.6342/NTU201702793

(j) Dynamic curve of breast cancer evolution to PCDP and CP for women at level 9 risk



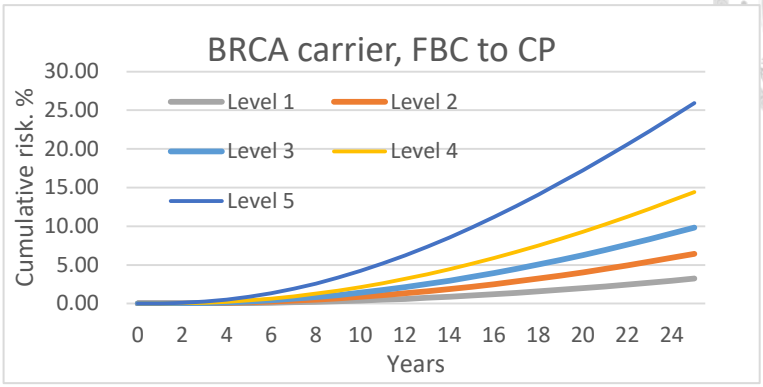
(k) Dynamic curve of breast cancer evolution to PCDP and CP for women at level 10 risk



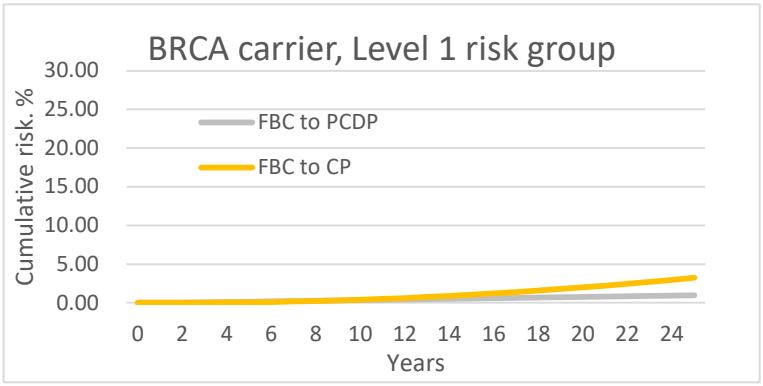
doi:10.6342/NTU201702793

Figure 5.4 5 Dynamic risk of breast cancer by five-level categorization for women of BRCA carrier

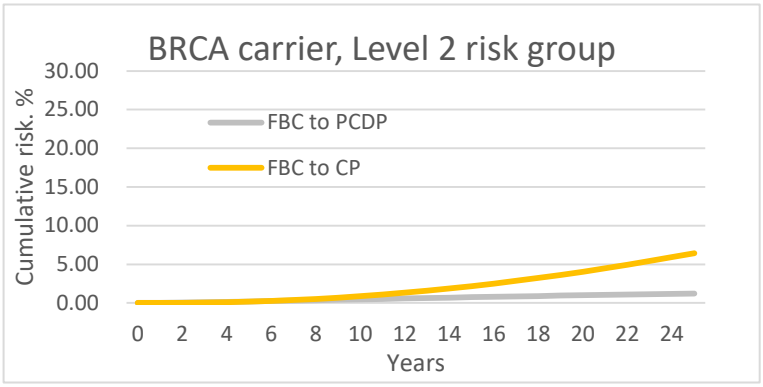
(a) The dynamic risk from free-of-breast-cancer (FBC) to clinical breast cancer (CP) by five-level categorization



(b) Dynamic curve of breast cancer evolution to PCDP and CP for women at level 1 risk

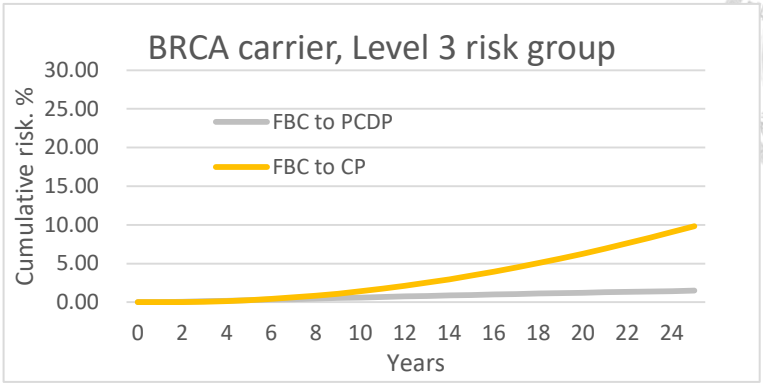


(c) Dynamic curve of breast cancer evolution to PCDP and CP for women at level 2 risk

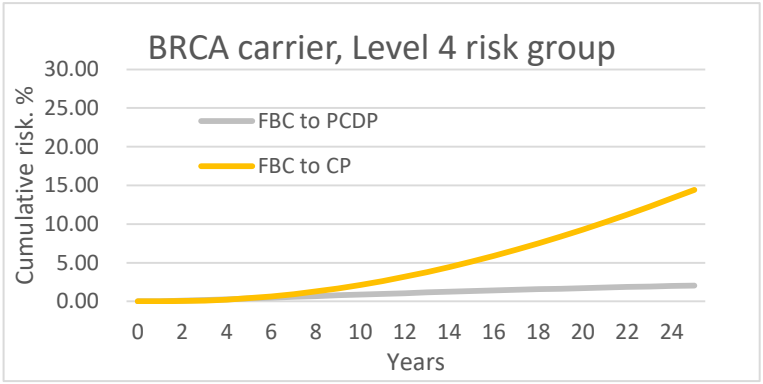


doi:10.6342/NTU201702793

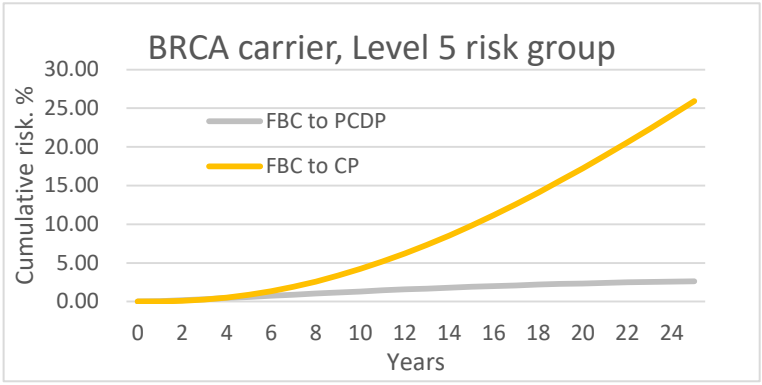
(d) Dynamic curve of breast cancer evolution to PCDP and CP for women at level 3 risk



(e) Dynamic curve of breast cancer evolution to PCDP and CP for women at level 4 risk



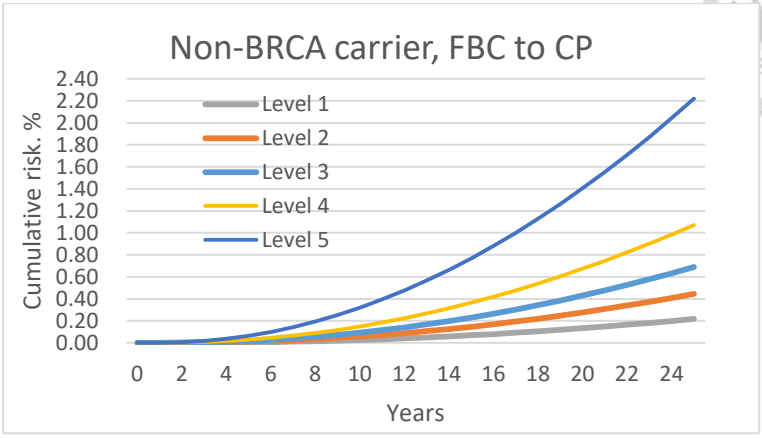
(f) Dynamic curve of breast cancer evolution to PCDP and CP for women at level 5 risk



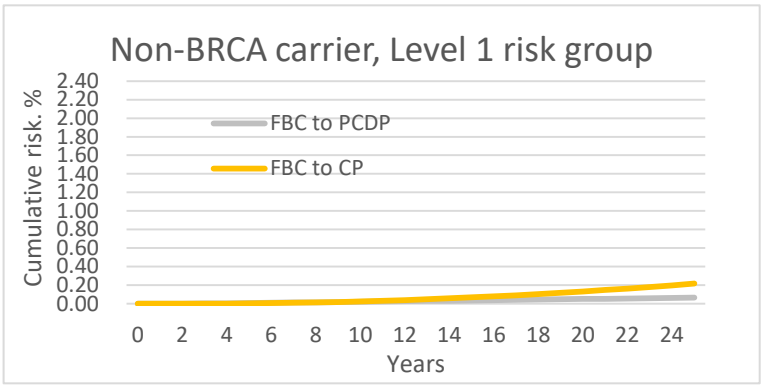
doi:10.6342/NTU201702793

Figure 5.4 6 Dynamic risk of breast cancer by five-level categorization for women of Non-BRCA carrier

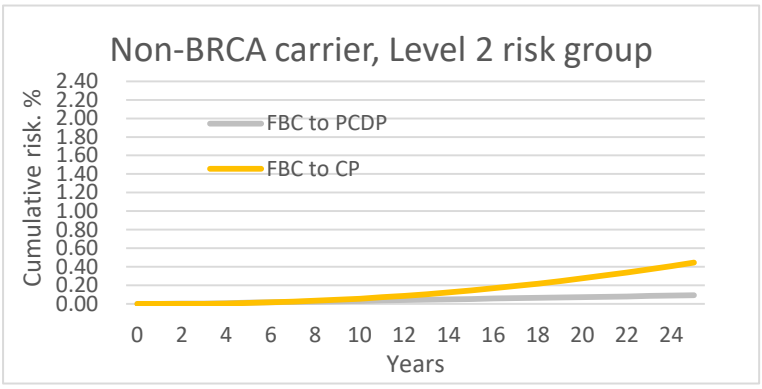
(a) The dynamic risk from free-of-breast-cancer (FBC) to clinical breast cancer (CP) by five-level categorization



(b) Dynamic curve of breast cancer evolution to PCDP and CP for women at level 1 risk

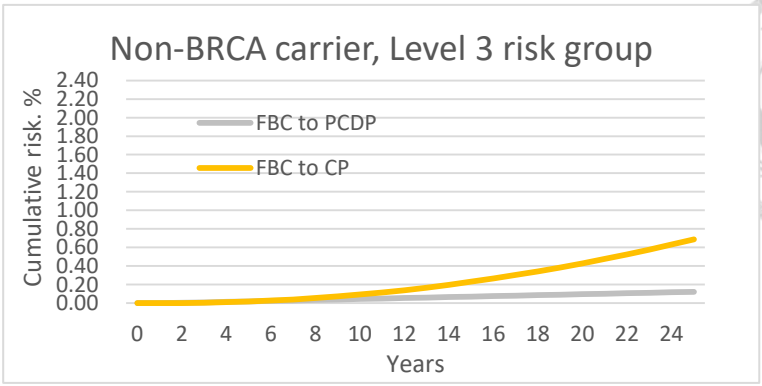


(c) Dynamic curve of breast cancer evolution to PCDP and CP for women at level 2 risk

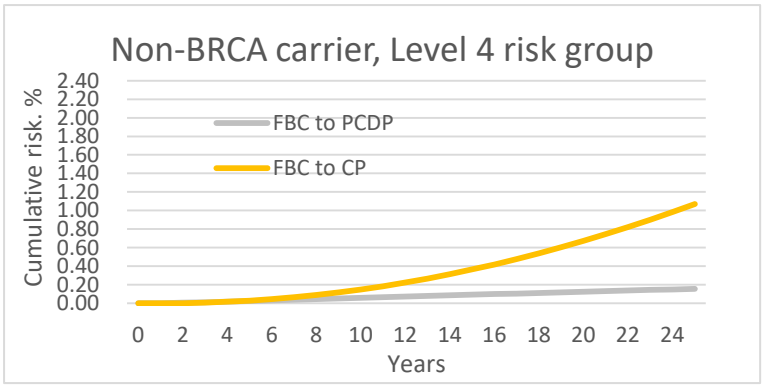


doi:10.6342/NTU201702793

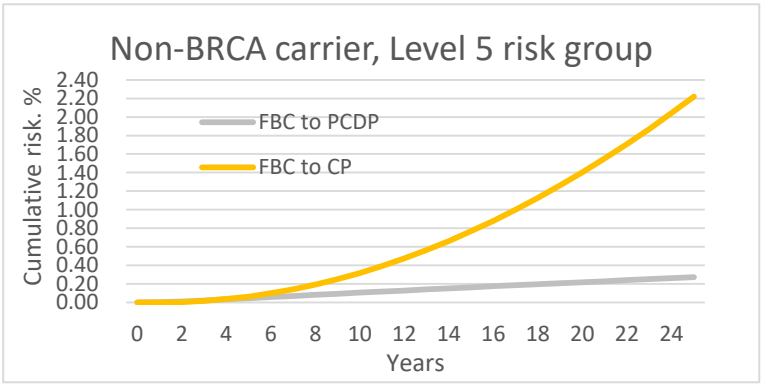
(d) Dynamic curve of breast cancer evolution to PCDP and CP for women at level 3 risk



(e) Dynamic curve of breast cancer evolution to PCDP and CP for women at level 4 risk



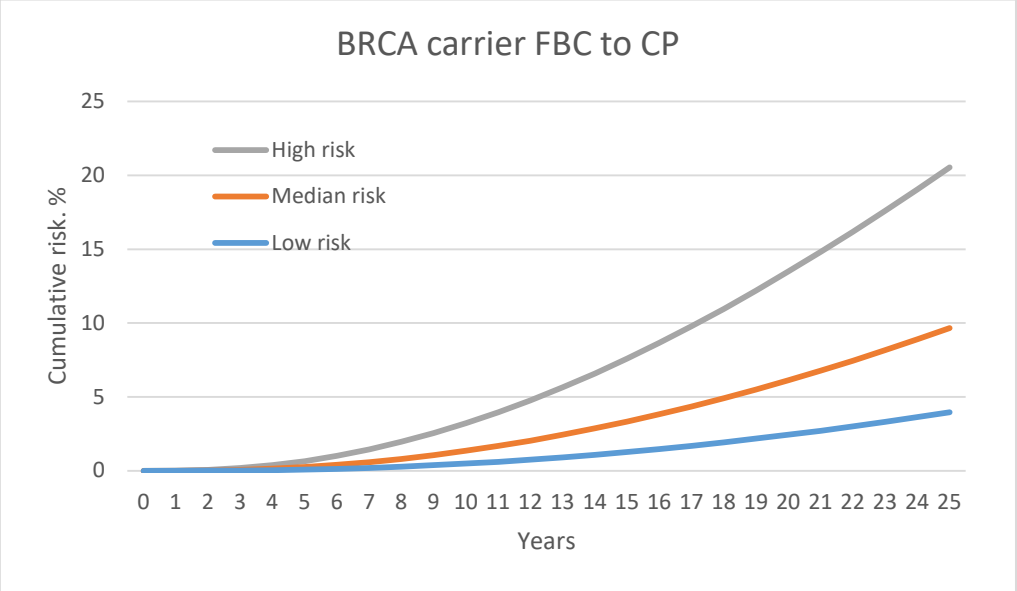
(f) Dynamic curve of breast cancer evolution to PCDP and CP for women at level 5 risk



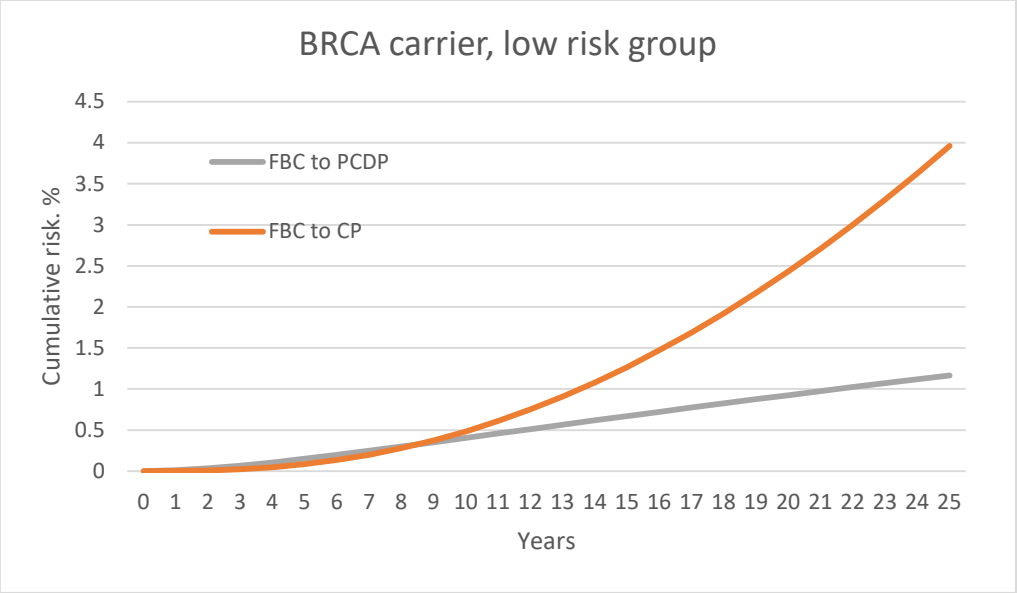
doi:10.6342/NTU201702793

Figure 5.4 7 Dynamic risk of breast cancer by three-level categorization for women of BRCA carrier

(a) The dynamic risk from free-of-breast-cancer (FBC) to clinical breast cancer (CP) by three-level categorization

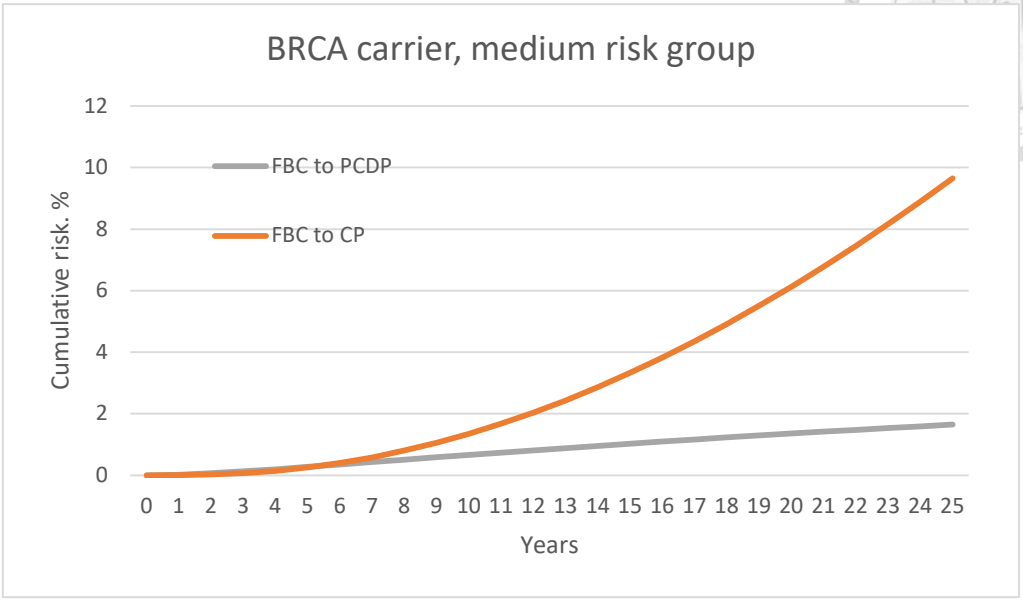


(b) Dynamic curve of breast cancer evolution to PCDP and CP for women at low-risk level

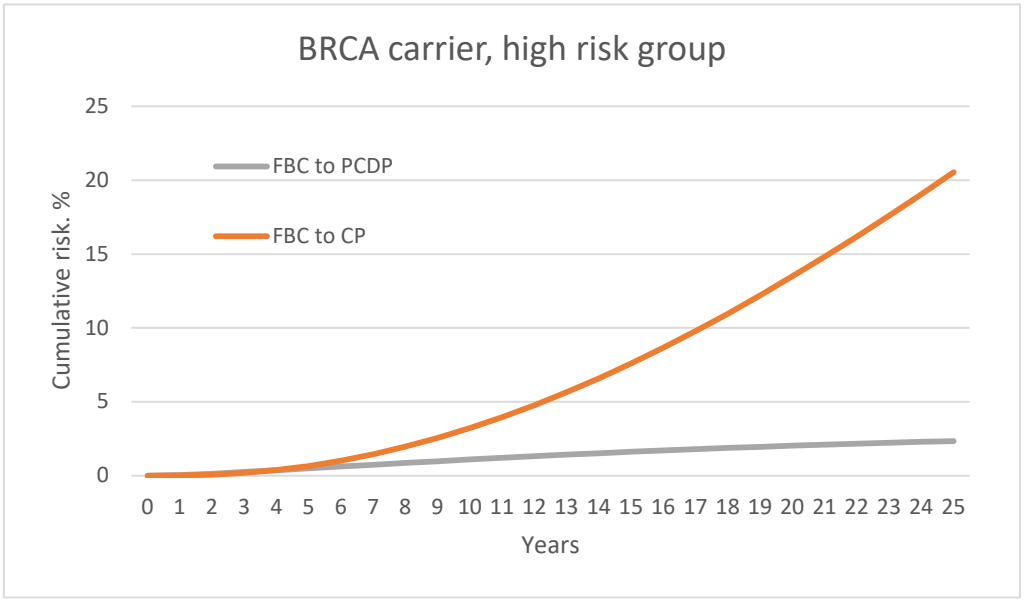


doi:10.6342/NTU201702793

(c) Dynamic curve of breast cancer evolution to PCDP and CP for women at median-risk level



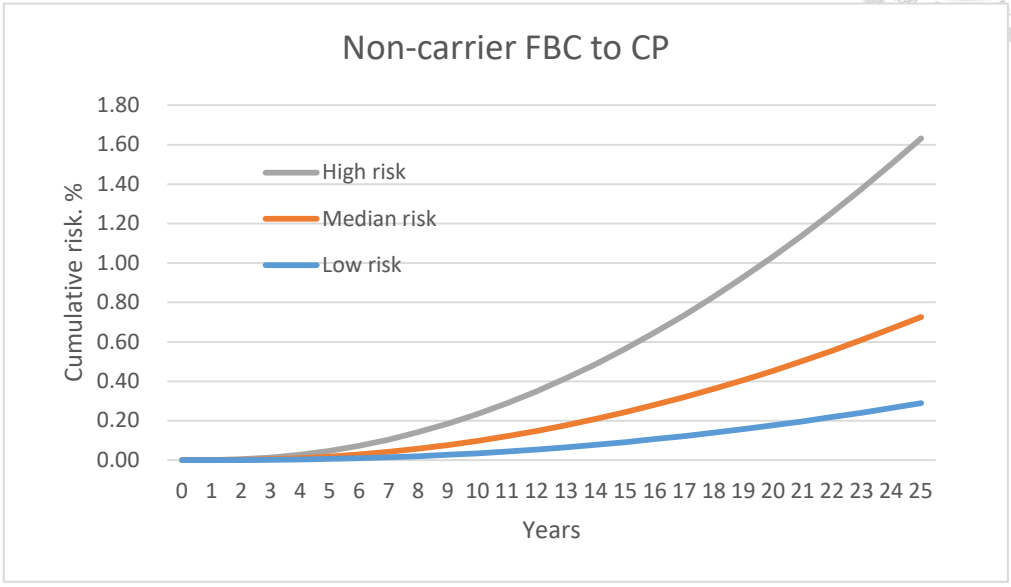
(d) Dynamic curve of breast cancer evolution to PCDP and CP for women at high-risk level



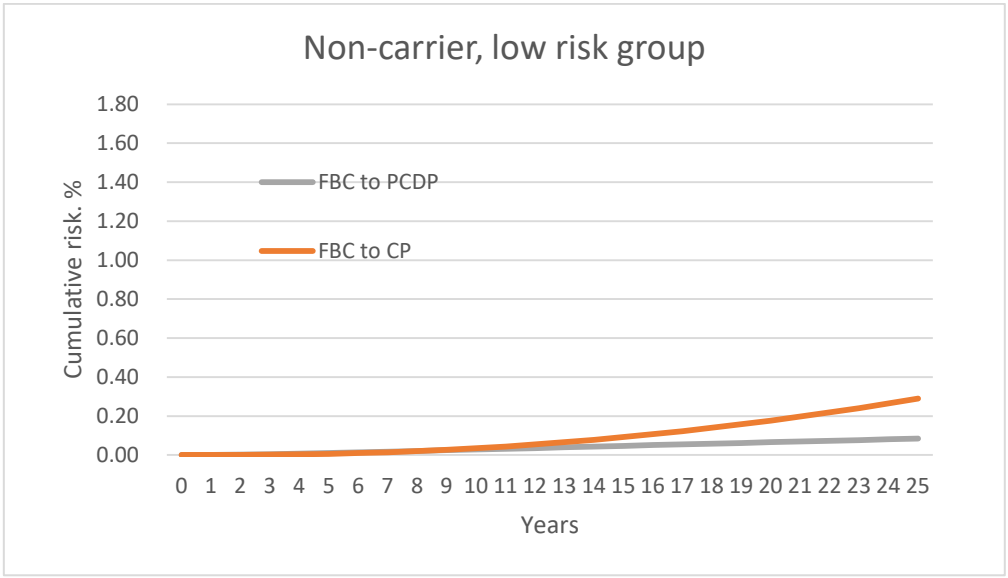
doi:10.6342/NTU201702793

Figure 5.4 8 Dynamic risk of breast cancer by three-level categorization for women of non-BRCA carrier

(a) The dynamic risk from free-of-breast-cancer (FBC) to clinical breast cancer (CP) by three-level categorization

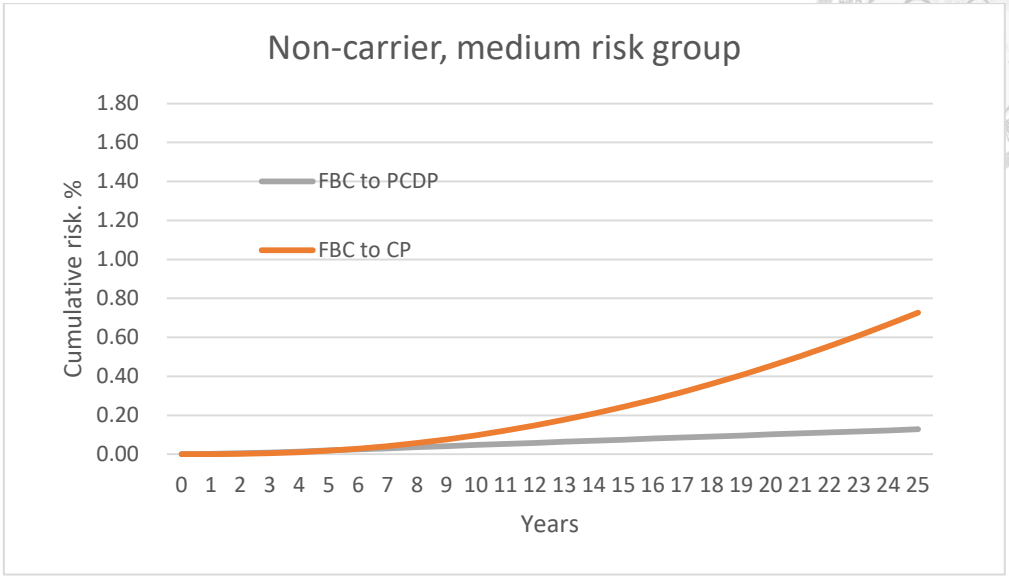


(b) Dynamic curve of breast cancer evolution to PCDP and CP for women at low-risk level

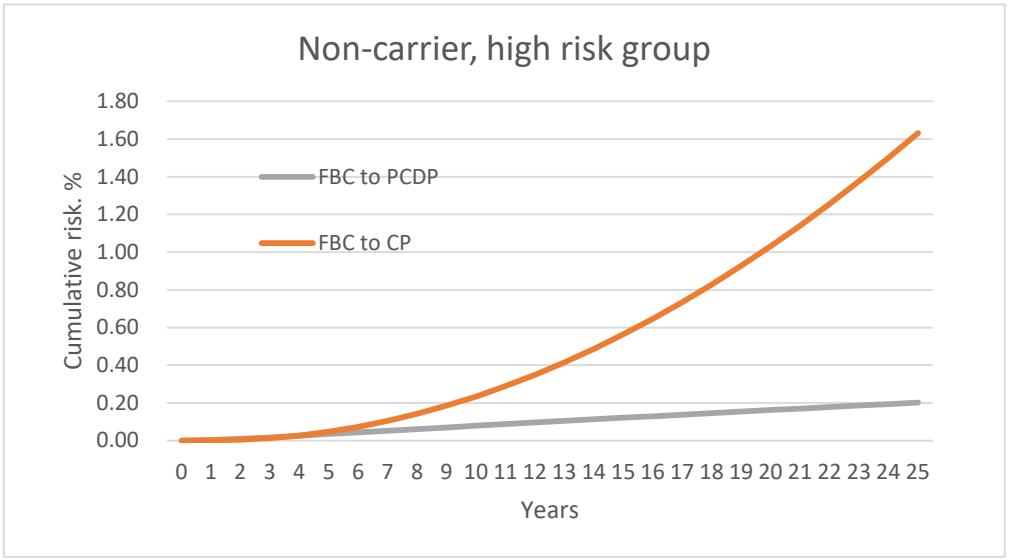


doi:10.6342/NTU201702793

(c) Dynamic curve of breast cancer evolution to PCDP and CP for women at median-risk level



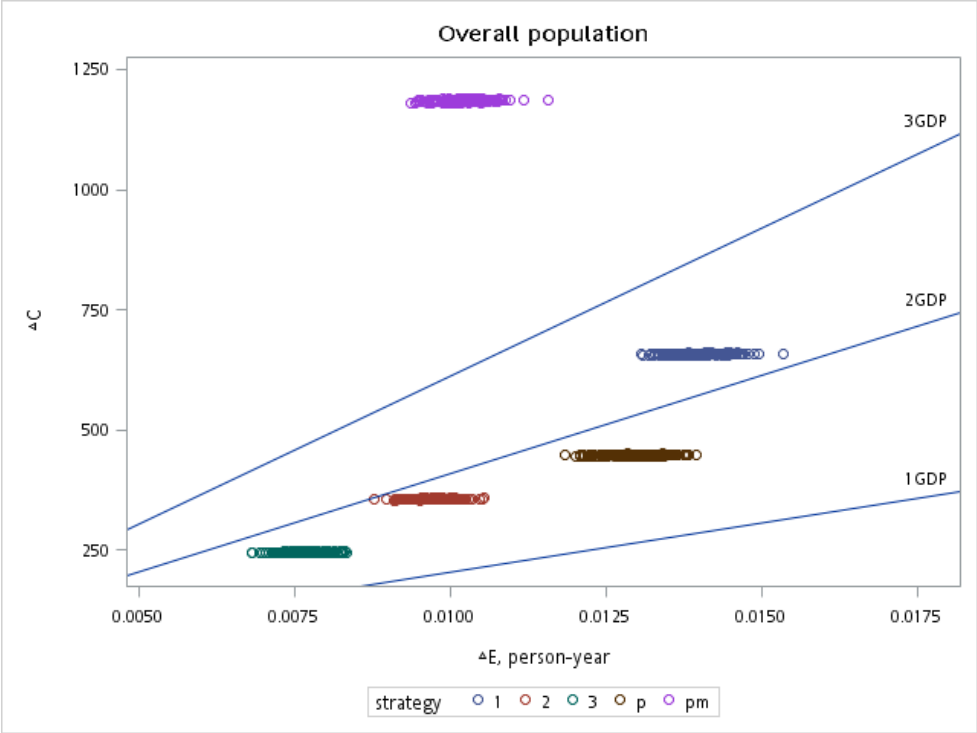
(d) Dynamic curve of breast cancer evolution to PCDP and CP for women at high-risk level



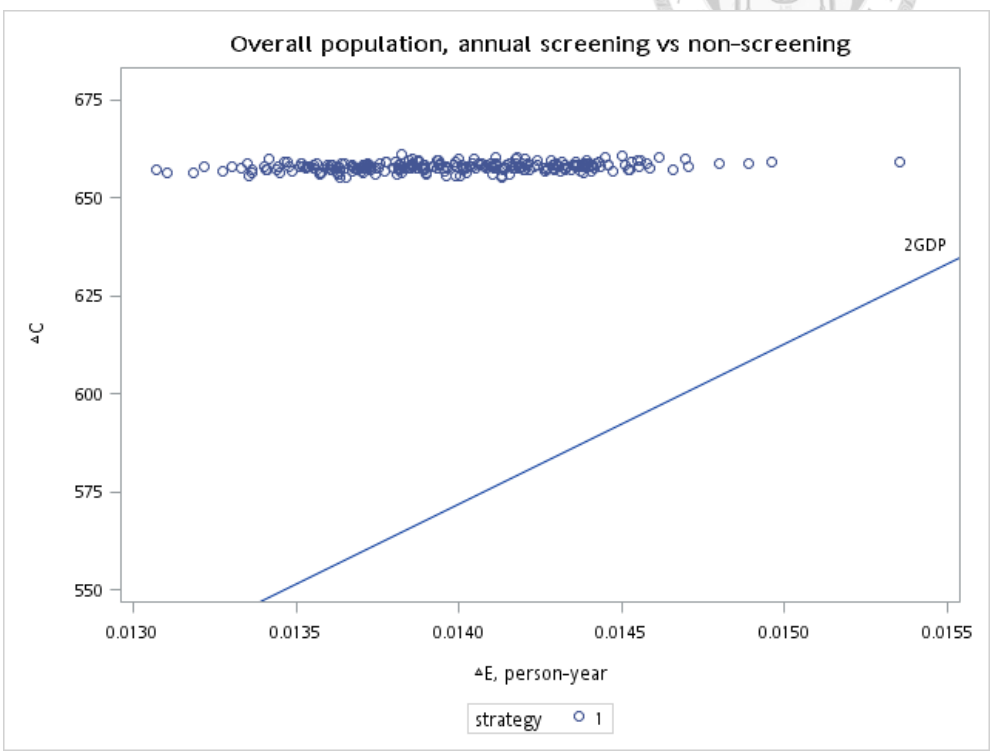
doi:10.6342/NTU201702793

Figure 5.6 1 Distributions of incremental cost and effectiveness of secondary prevention strategies compared with non-intervention group for breast cancer

(a) Comparison between secondary prevention strategies



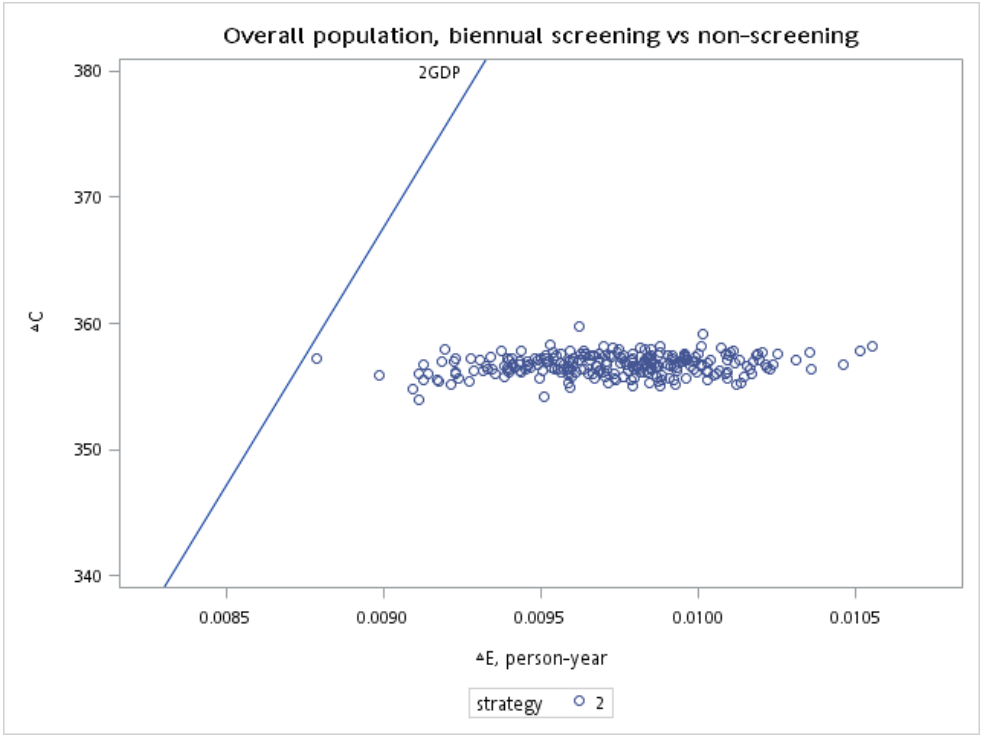
(b) Annual screening strategy



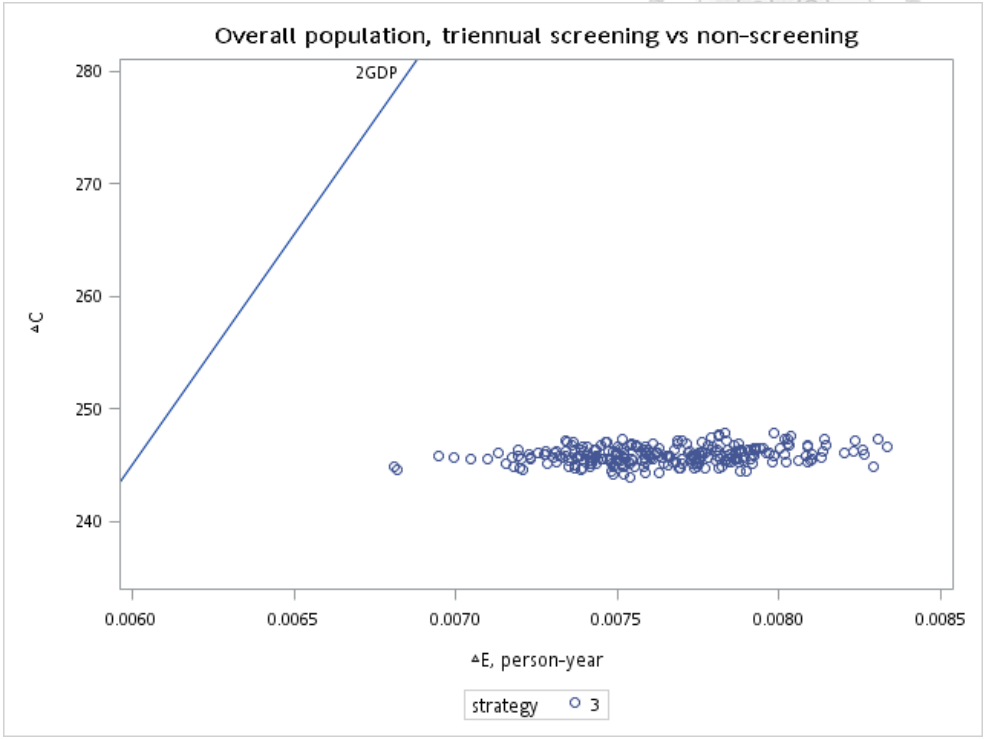
*p: personalized screening interval; pm: personalized screening modality

doi:10.6342/NTU201702793

(c) Biennial screening strategy



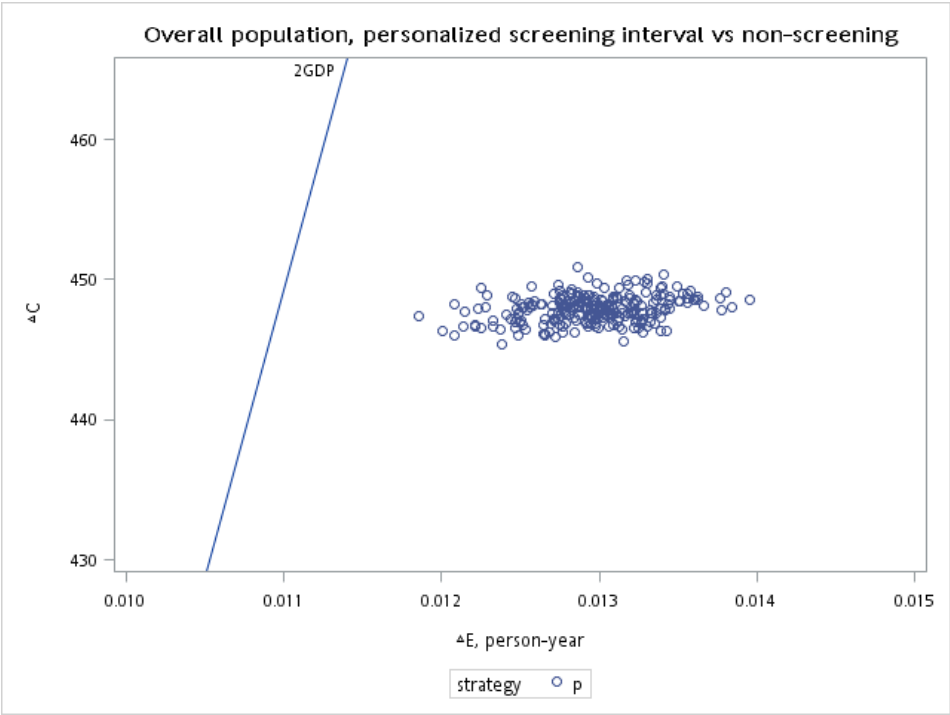
(d) Triennial screening



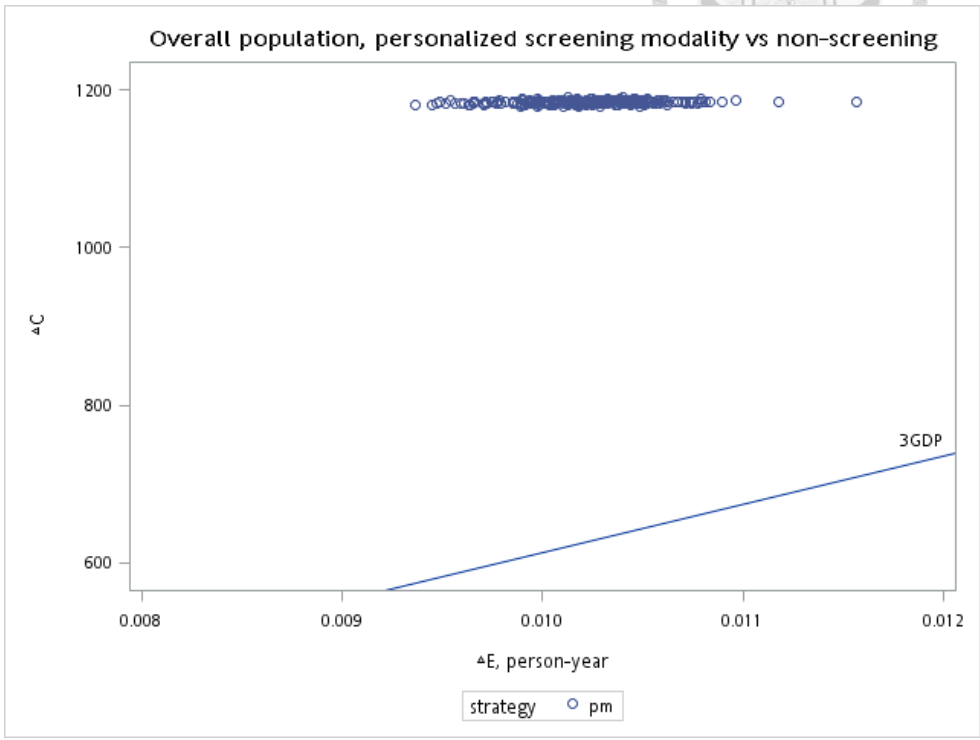
doi:10.6342/NTU201702793

Figure 5.6 2 Distribution of cost and effectiveness of personalized secondary prevention strategy for breast cancer

(a) Personalized screening interval



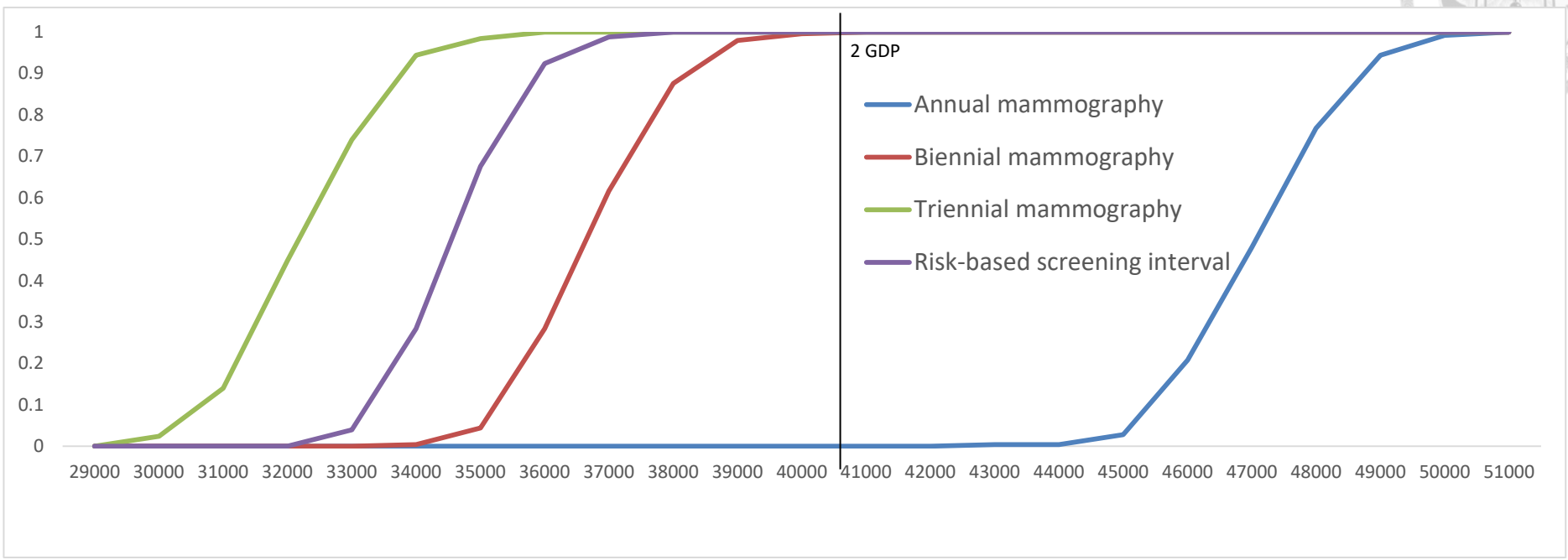
(b) Personalized screening modality



doi:10.6342/NTU201702793

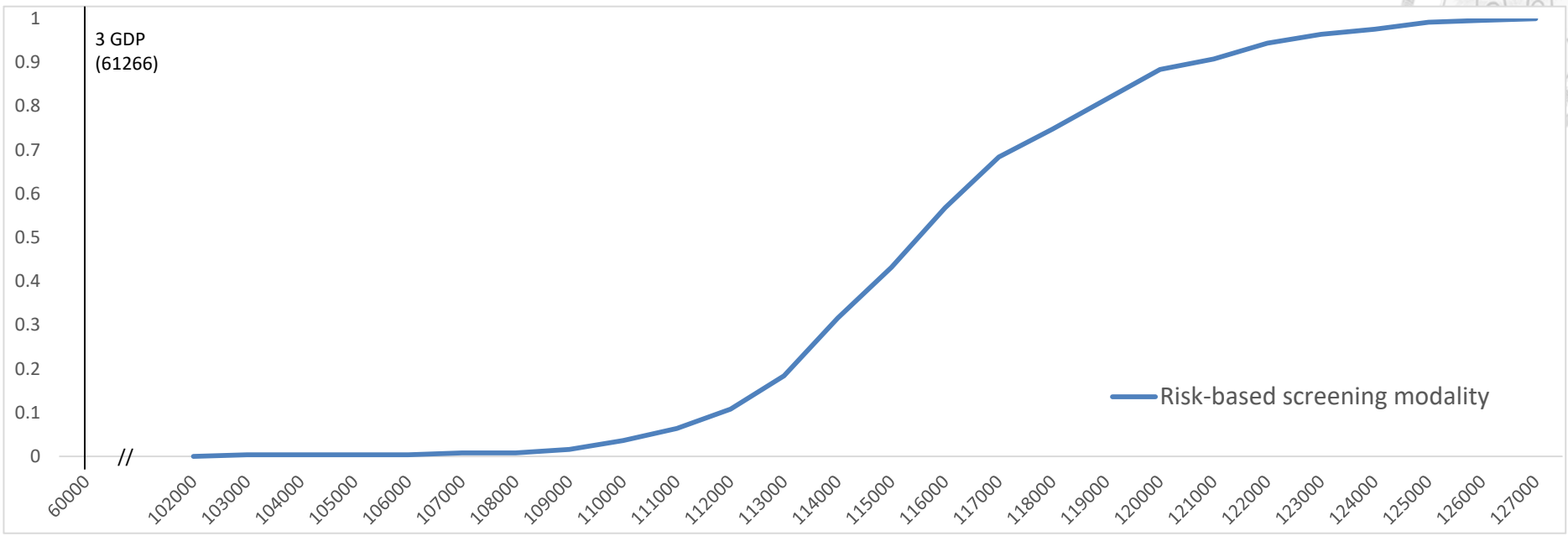
Figure 5.6 3 Acceptability curve of universal and personalized strategies of secondary prevention for breast cancer

(a) Acceptability curve of secondary preventive strategies (annual, biennial, triennial, and risk-based screening interval) for breast cancer prevention



doi:10.6342/NTU201702793

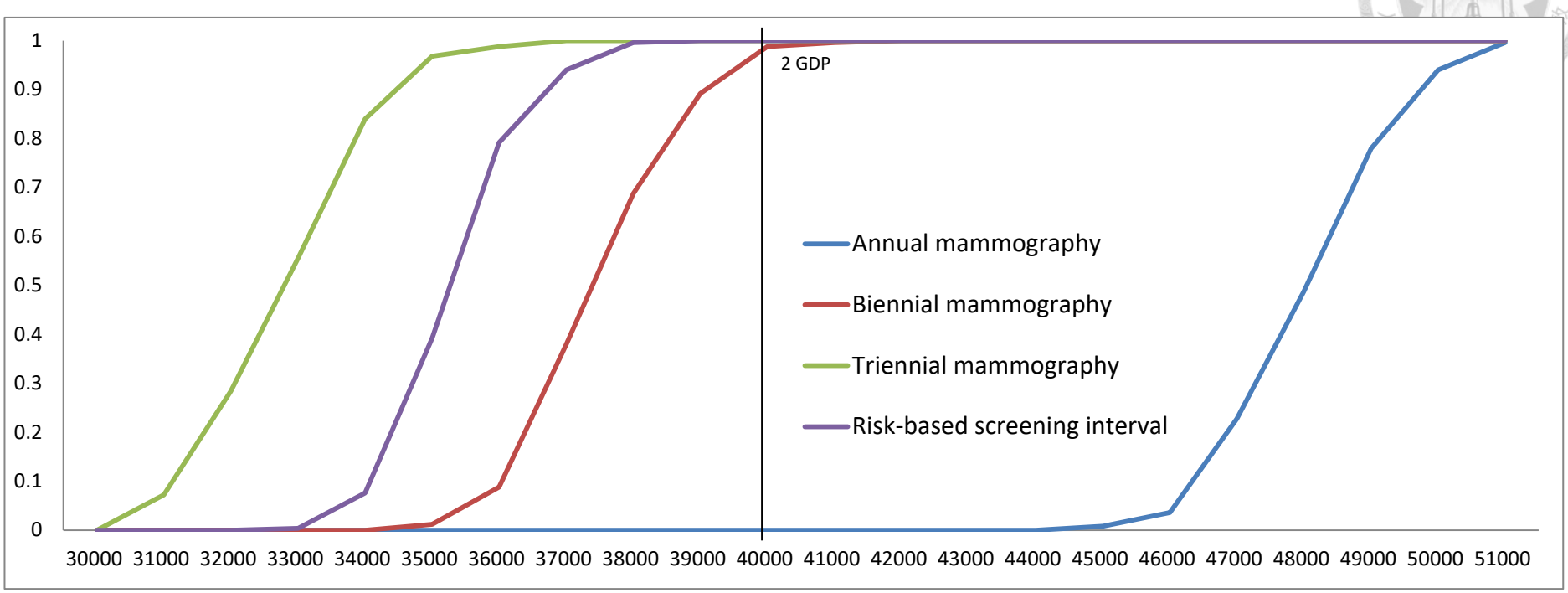
(b) Acceptability curve of personalized screening modality for breast cancer prevention



doi:10.6342/NTU201702793

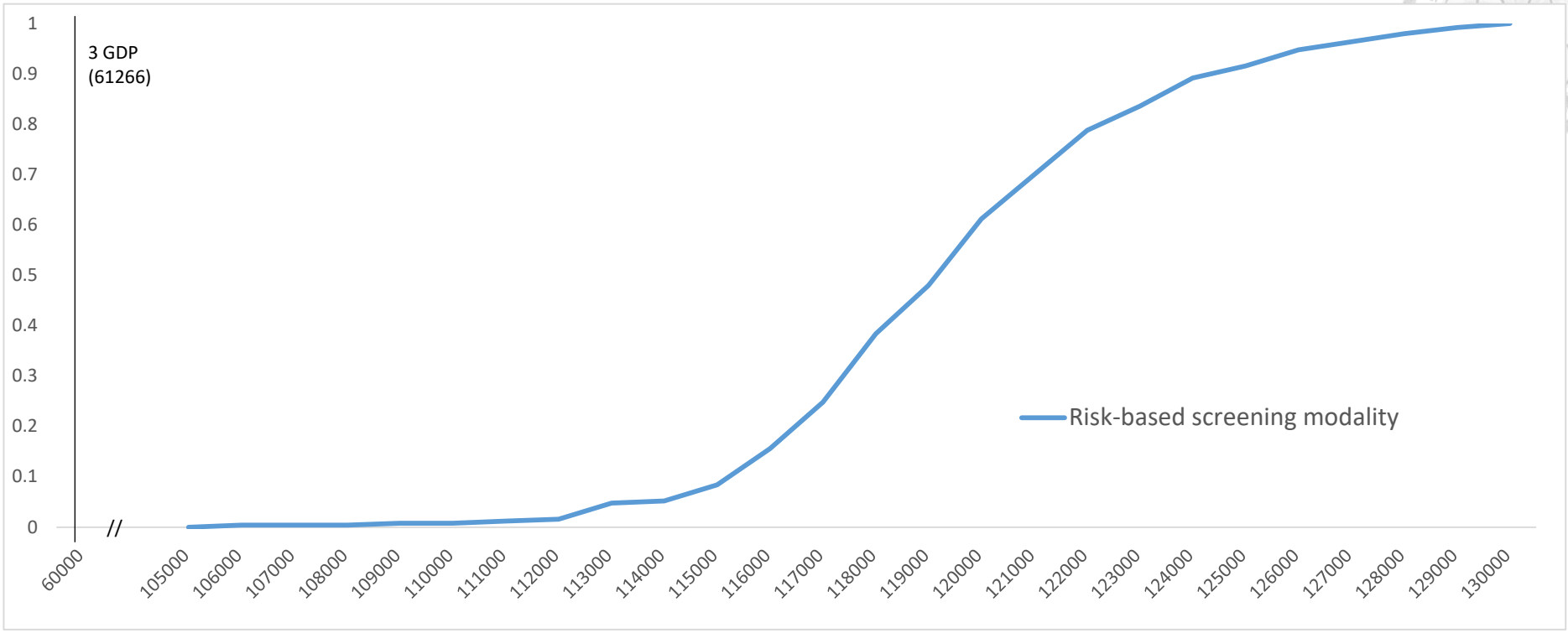
Figure 5.6 3 Acceptability curve of universal and personalized breast cancer prevention strategies for non-BRCA carrier women

(c) Acceptability curve of universal strategies and risk-based intervals for breast cancer screening for non-BRCA carrier women



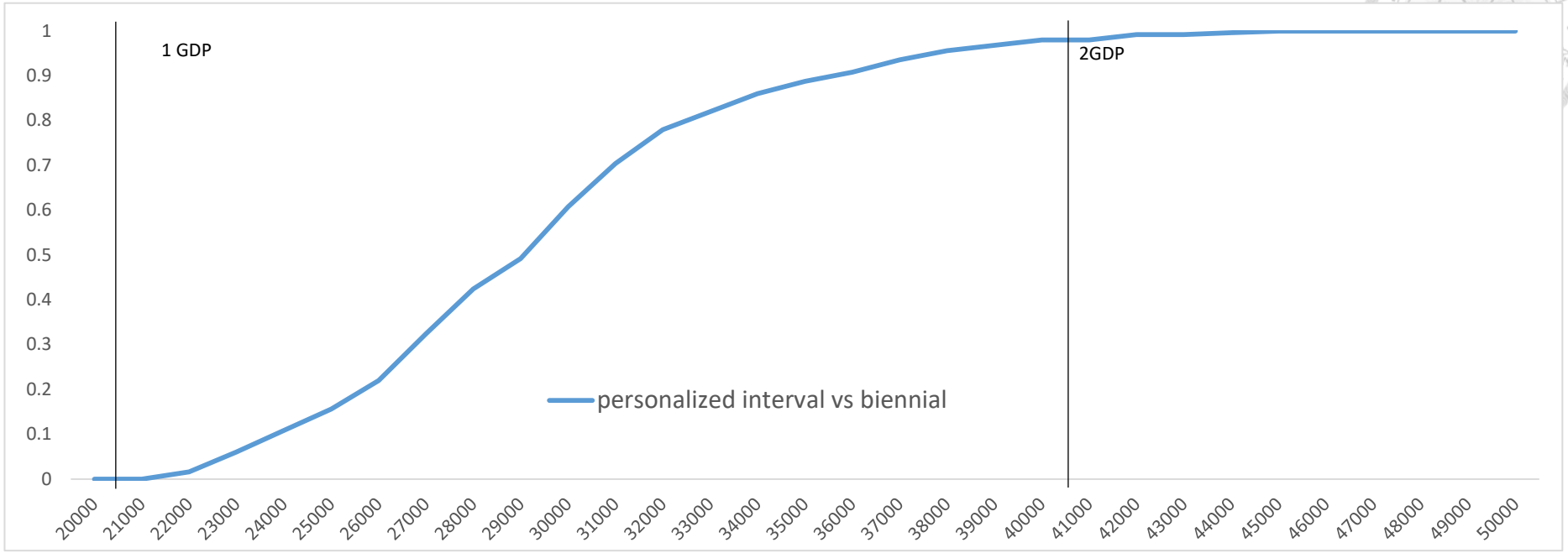
doi:10.6342/NTU201702793

(d) Acceptability curve of risk-based modality of breast cancer screening for non-BRCA carrier women



doi:10.6342/NTU201702793

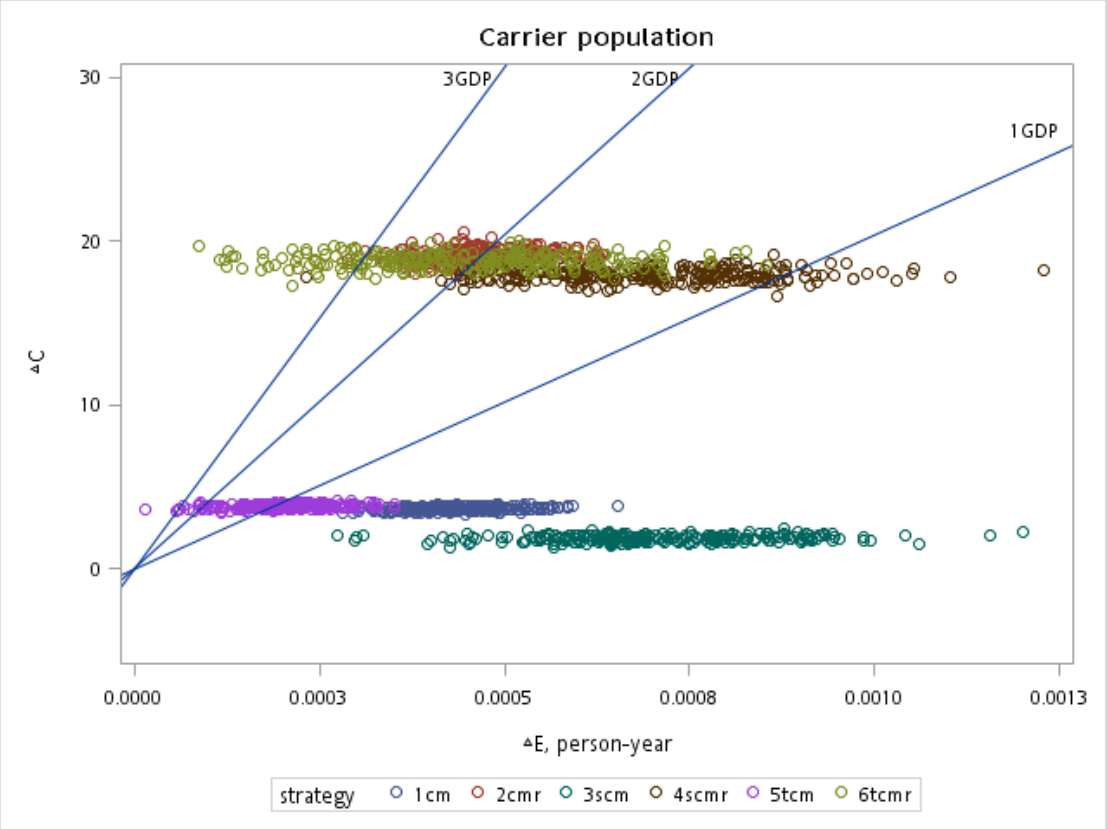
(e) Acceptability curve of risk-based interval compared with universal biennial screening for non-BRCA carrier



doi:10.6342/NTU201702793

Figure 5.6 4 Distributions of incremental cost and effectiveness of secondary prevention strategies compared with non-intervention group for breast cancer

(a) Comparison between strategies of primary prevention and secondary prevention for women of BRCA carrier



* cm: Annual mammographic screening;

cmr: Annual MRI and mammographic screening;

scm: Mastectomy for 20% high risk subjects and annual mammographic screening for the rest of population;

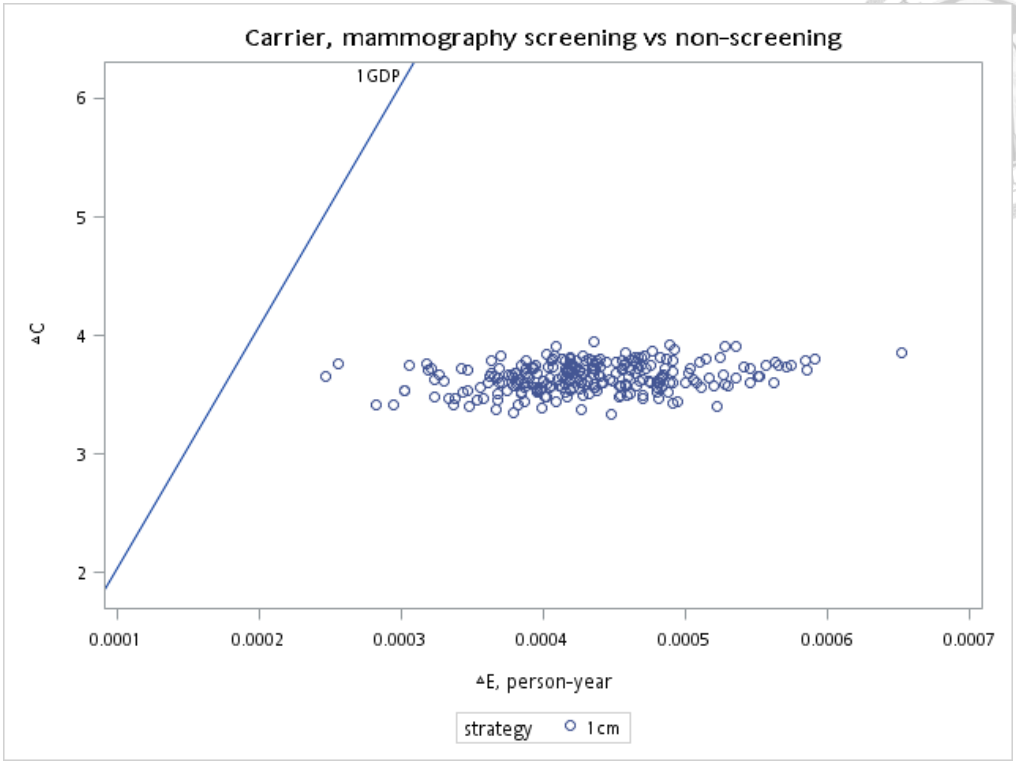
scmr: Mastectomy for 20% high risk subjects and annual MRI and mammographic screening for the rest of population;

tcm: Chemoprevention (tamoxifen) for 20% high risk subjects in conjunction with biennial mammographic screening and annual mammographic screening for the rest of population;

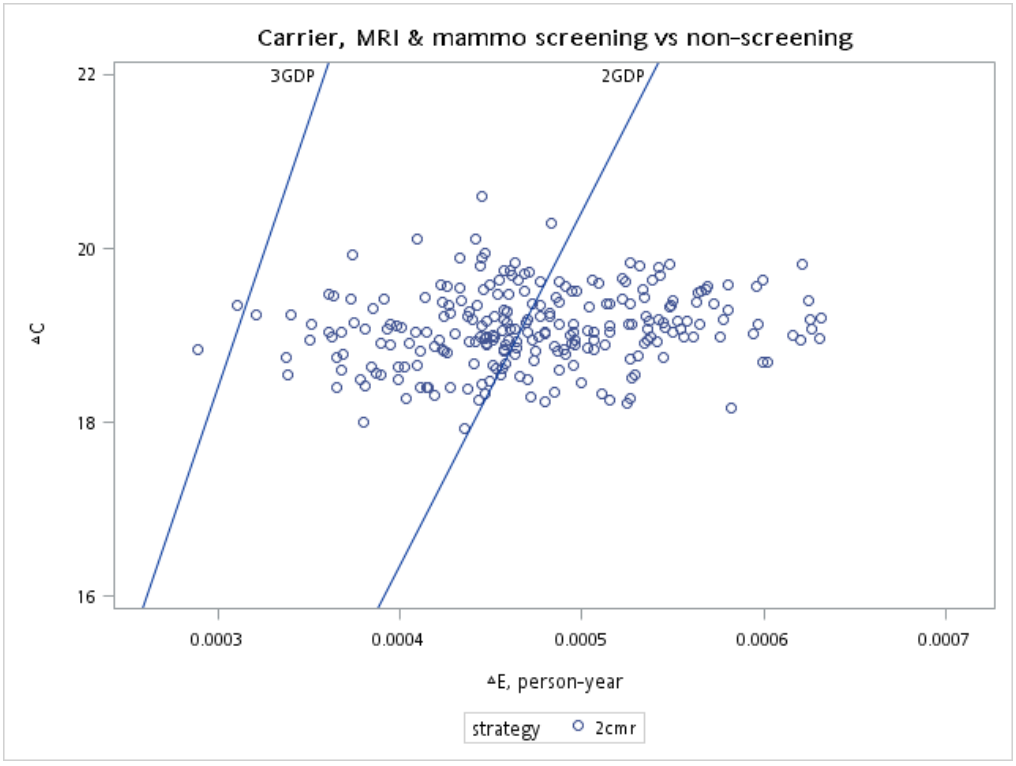
tcmr: Chemoprevention (tamoxifen) for 20% high risk subjects in conjunction with biennial MRI and mammographic screening and annual MRI and mammographic screening for the rest of population;

doi:10.6342/NTU201702793

(b) Annual Mammographic screening

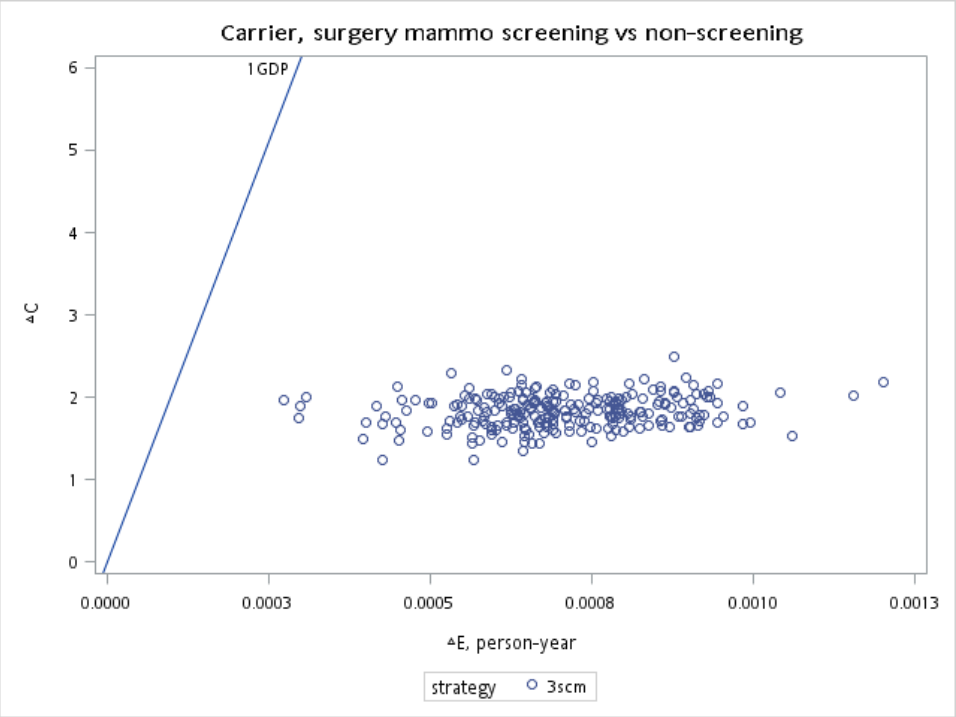


(c) Annual MRI and mammographic screening

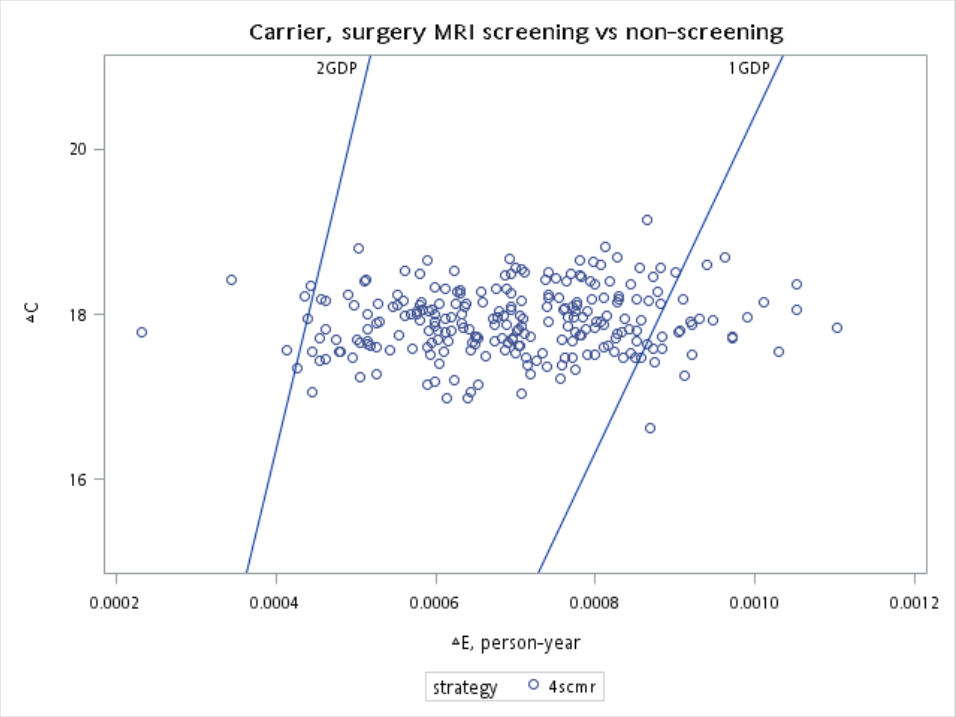


doi:10.6342/NTU201702793

(d) Preventive surgery for 20% high risk women and annual mammographic screening for the rest of population

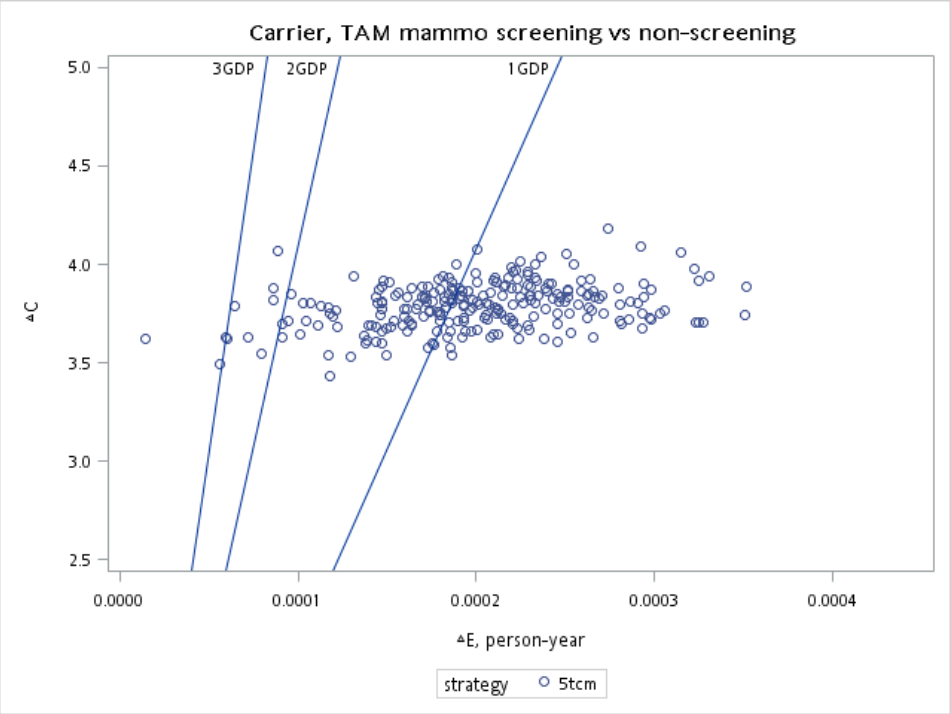


(e) Preventive mastectomy for 20% high risk women and annual MRI and mammographic for the rest of population

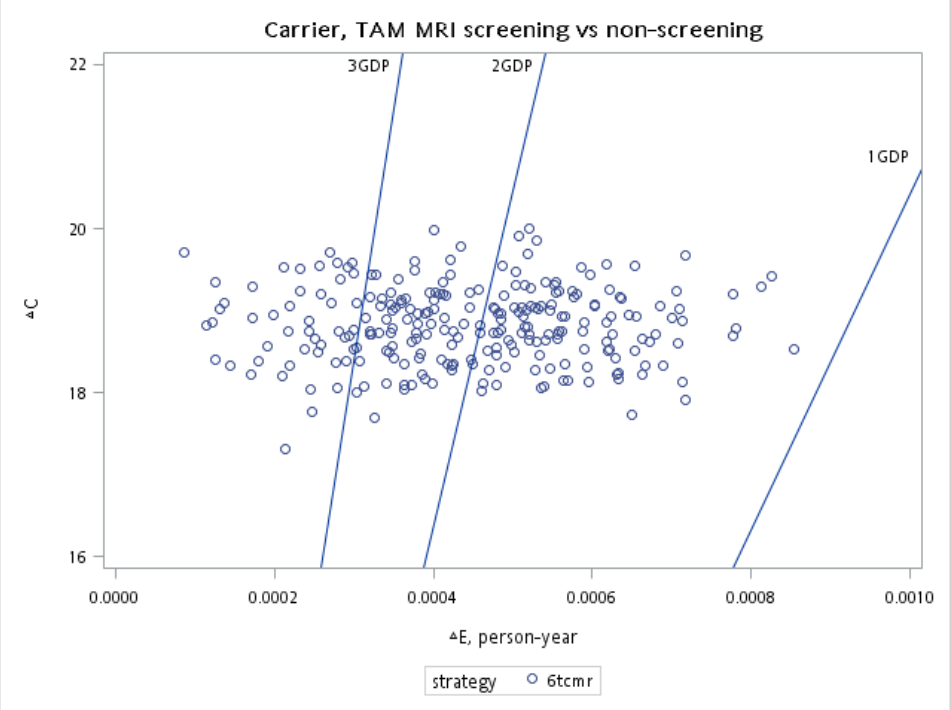


doi:10.6342/NTU201702793

(f) Preventive chemotherapy with tamoxifen for 20% high risk women and biennial mammographic screening and annual mammographic screening for the rest of population

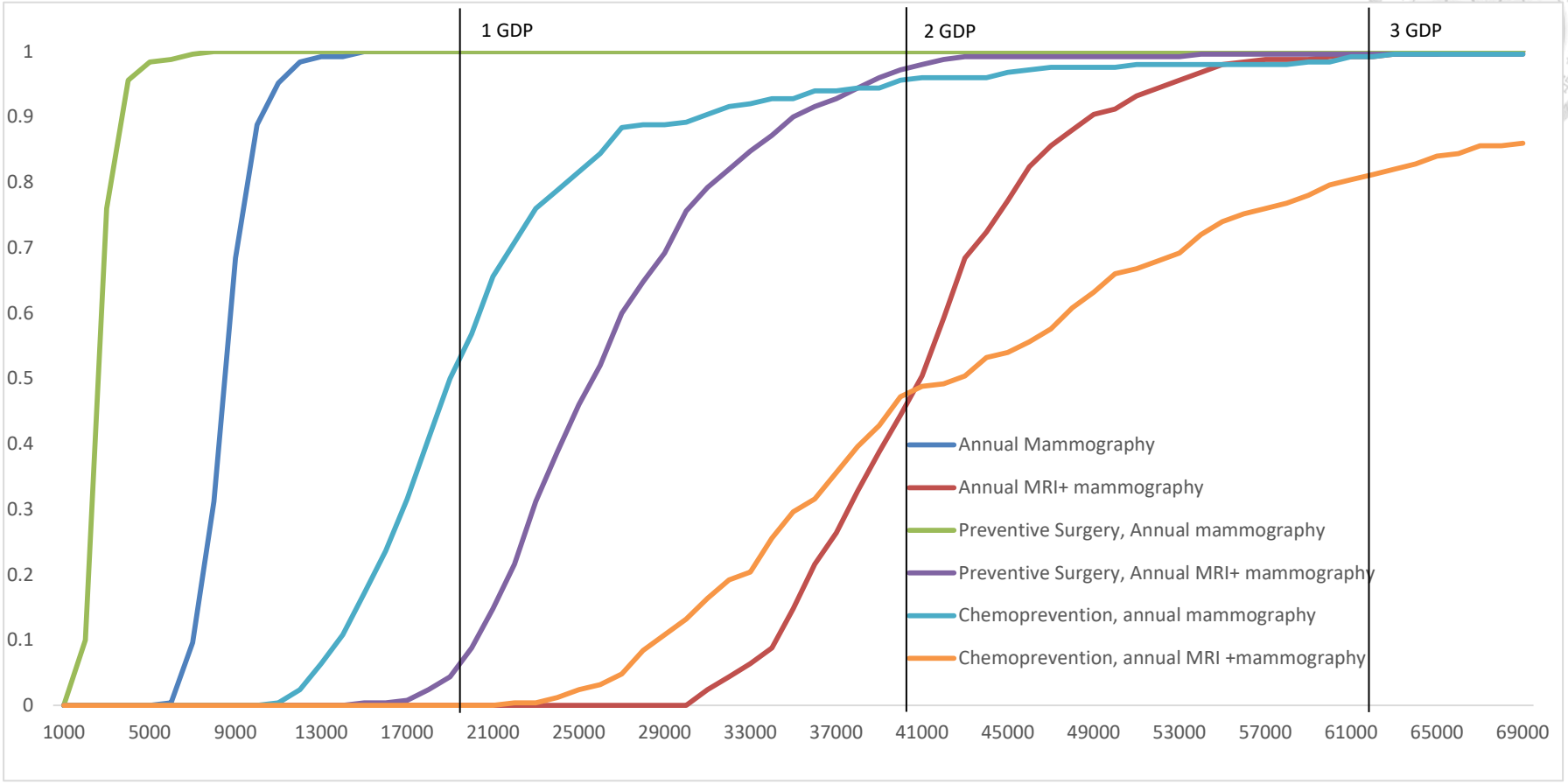


(g) Preventive chemotherapy with tamoxifen for 20% of high risk women and biennial MRI and mammographic screening and annual MRI and mammographic screening for the rest of population



doi:10.6342/NTU201702793

(h) Acceptability curve of primary and secondary prevention of breast cancer for BRCA-carrier women



doi:10.6342/NTU201702793

TABLES

Table 2.1 1 Summary of literature review on predicting breast cancer risk using conventional risk factors

Model	Conventional factor			Family history
Risk prediction model	Personal information	Hormonal and reproductive factors	Personal history of breast disease	Breast cancer or ovarian cancer
Gail/BCRAT/NCI	Age	Age at menarche/1st live birth	History of breast biopsies/ADH	First-degree female relatives with breast cancer
Chen	Age, weight	Age at 1st live birth, breast density	History of breast biopsies	First-degree female relatives with breast cancer
Barlow/BCSC-premenopausal	Age	Breast density (BI-RADS)	Prior breast procedures	First-degree relatives with breast cancer
Barlow/BCSC-postmenopausal	Age, BMI	Age at 1st live birth, Breast density	Use of HRT, Type of menopause, Prior mammographic findings/ breast procedures	First-degree relatives with breast cancer
Rosner–Colditz	BMI, height, alcohol use	Postmenopausal hormone use	Benign breast disease	First-degree relatives with breast cancer
Claus	No	No	No	First-second-degree relatives with breast or ovarian cancer

doi:10.6342/NTU201702793

Table 2.1 2 Summary of literature review on the prediction of breast cancer risk using conventional and genetic predictors

Risk prediction model for genetic mutation	Conventional factor	Genetic status	Family history	Other factors
Genetic mutation risk		BRCA gene mutation	Breast cancer or ovarian cancer	
MYRIAD I/ Shattuck-Eidens	Age of diagnosis of breast and/or ovarian cancer, bilateral breast cancer	No	Number of relatives (any degree) affected with breast cancer, ovarian cancer, or both	Ashkenazi Jewish ethnicity
MYRIAD II/ Frank	Breast cancer before or after age 50, ovarian cancer, male breast cancer	No	Breast cancer before or after age 50 and ovarian cancer in first or second-degree relatives	Ashkenazi Jewish ethnicity
Penn/ Couch	Age of diagnosis of breast and/or ovarian cancer	No	Limited breast cancer	Ashkenazi Jewish ethnicity
Penn II	Age of diagnosis of breast and/or ovarian cancer	No	Affected relatives with breast, bilateral breast, male breast, pancreas, and prostate cancers	Ashkenazi Jewish ethnicity
COS	No	BRCA1, BRCA2		Mastectomy/ oophorectomy
BRCAPRO	No	BRCA1, BRCA2	Affection status and age of breast or ovarian cancers for all relatives, current ages for unaffected individuals, twin status	Molecular markers, mastectomy/ oophorectomy, family, Race specification, Ethnicity.
BOADICEA	No	BRCA1, BRCA2, polygenetic component	Affection status and age of breast, ovarian, pancreatic, prostate cancers for all	Ashkenazi Jewish ancestry, pathology

doi:10.6342/NTU201702793

Risk prediction model for genetic mutation	Conventional factor	Genetic status	Family history	Other factors
Genetic mutation risk		BRCA gene mutation	Breast cancer or ovarian cancer	
			relatives, current ages for unaffected individuals, twins	markers
Jonker	No	BRCA1, BRCA2, BRCAu	Affection status and age of breast, ovarian, pancreatic, prostate cancers for all relatives, current ages for unaffected individuals, twins	
Tyrer-Cuzick/ IBIS	Age at menarche, age at first live birth, parity, age at menopause, use of hormone replacement therapy; breast biopsies, presence of hyperplasia, atypical hyperplasia (ductal or lobular), or LCIS	BRCA1, BRCA2, third gene hypothetical low penetrance	First- and second-degree relatives with breast cancer and/ or ovarian cancer, incorporating age of onset, and the presence of bilateral breast cancers	Ashkenazi Jewish

doi:10.6342/NTU201702793

Table 2.3 1 Review of breast screening guideline by different countries

Country (year)	Inter-screening interval (years)	Indication for age groups			Reference
		40 to 49 years of age	50 to 69 years of age	≥70 years of age	
Nationwide Programmes					
US Preventive Services Task Force (2016)	2	Individualize◆	Yes	Yes, to age 74	(Siu 2016)
Canadian Task Force on Preventive Health Care (2011)	2-3	Individualize◆	Yes	Yes, to age 74	(Care 2011)
National Health Service, United Kingdom (2013)	3	Yes, start age 47	Yes	Yes, to age 73	(Public Health Policy and Strategy Unit 2013)
Royal Australian College of General Practitioners (2012)	2	No (eligible but not targeted)	Yes	No (eligible but not targeted)	(Practitioners 2012)
Taiwan	2	Yes*	Yes#	No (eligible but not targeted)	

◆Women should consider the harms and benefits of mammography; individualized decision based on risks and patient preference.

*40-44 years, with breast cancer family history

45-69 years

doi:10.6342/NTU201702793

Table 4.4.1 Base-case estimate and distribution of efficacy parameters for interventions of breast cancer screening

Intervention	Effectiveness		*Reference*
	Breast cancer risk reduction		
Preventive Surgery			
Simple mastectomy- bilateral	0.9 (0.80-0.99)		(Anderson et al. , 2006)
Chemoprevention			
Tamoxifen	0.49 (0.42-0.56)		(Anderson et al. , 2006)
Secondary prevention			
Screening	Sensitivity	Specificity	
Mammography	79.5 (77-81.7)	0.9995 (0.9996,0.999)	Chen et al., 2017; Chen et al., 2013)
Mammography+ Sonography	91.5 (0.84,0.96)	96.7 (0.94-0.98)	(Berg et al. , 2008)
Mammography+ Sonography+ MRI	100 (79.4, 100)	65.4 (61.5,69.3)	(Berg et al. , 2012)
Mammography +MRI *	94 (0.90-0.97)	77 (0.75-0.80).	(Pataky et al., 2013)

*BRCA carrier

*Attendance rat: 0.7 (0.6-0.8)

doi:10.6342/NTU201702793

Table 4.4.2 Base-case estimate and distribution of parameters for breast cancer screening

Variable	Base case estimate	Distribution
Screening cost-Direct costs		
Mammography screening fee	41.03	Lognormal (3.71, 0.3)
Sonography screening fee	30	Lognormal (3.4, 0.3)
MRI screening fee	595.34	Lognormal (6.39, 0.201)
Administration per subject, local government (setting)	0.24	Lognormal(-1.43, 0.106)
Administration per subject, local government (telephone)	0.29	Lognormal(-1.24, 0.101)
Out of pocket: registration fee	4.41	Lognormal (1.48, 0.101)
Cost of the biopsy	86.79	Lognormal (4.46, 0.101)
Cost of pathology	47.06	Lognormal (3.85, 0.101)
Cost of BRCA testing	992.23	
Screening Indirect costs		
Production value per hour ($/hr)	6.09	
Number of company for screening	0.2	
Time Spent (hrs)	7.5	
Mean OPD visit frequency	1	
Production loss of screening	54.81=$6.09*1.2*7.5*1	
Biopsy Indirect costs		
Production value per hour ($/hr)	6.09	
Number of company for biopsy	0.2	
Time Spent (hrs)	7.5	
Mean OPD visit frequency	2	
Production loss of biopsy	109.62=$6.09*1.2*7.5*2	
Treatment Cost		
Treatment fee	6661.76	Lognormal (8.8, 0.101)
Out of pocket for treatment cost	666.18	

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Variable	Base case estimate	Distribution
Mean hospitalization day	14.33	
Number of company in hospital	1.25	
Production loss of inpatient	1570.4(=$6.09*8*14.33*2.25)	
Simple mastectomy - bilateral	278.82	Lognormal (5.6, 0.101)
Days of stay at home	20	
Number of company at home	0.2	
Production loss of outpatient	1168.94(=$6.09*8*20*1.2)	
Days for chemotherapy (day/frequency)	6	
Frequency of chemotherapy	6	
Number of company	0.2	
Time for Transportation (hrs)	7.5	
Production loss of chemotherapy	1973.16(=$6.09*1.2*7.5*6*6)	
Mean frequency	25	
Time for transportation	7.5	
Production loss of radiotherapy	1369.85(=$6.09*1.2*7.5* 25)	
	Follow-up cost	
Number of company	0.2	
Times/ per year	6.56	
Time for Transportation (hrs)	7.5	
Production loss of follow-up	359.45 (=$6.09*1.2*7.5* 6.56)	Lognormal (5.88, 0.101)
Terminal care and death	23529.41	
Out of pocket co-payment	254.41	
Time spent (day)	43	
Production loss of terminal care and death	2094.35(=$6.09*43*8) (8 hours a day)	Lognormal (7.65, 0.101)

doi:10.6342/NTU201702793

Table 4.5 1 Personalized screening strategies with risk-based modality

Risk group	Screen interval (years)	Screening modality
90-100	2	MRI+Sono+Mammo
80-89	2	MRI+Sono+Mammo
70-79	2	Mammo+Sono
60-69	2	Mammo+Sono
50-59	2	Mammo
40-49	2	Mammo
30-39	4	Mammo
20-29	4	Mammo
10-19	6	Mammo
0-9	6	Mammo

Mammo: Mammography; Sono: Sonography; MRI: Magnetic Resonance Imaging

doi:10.6342/NTU201702793

Table 4.5 2 Personalized screening strategies with risk-based screening interval

Risk group	Screen interval (years)	Screening modality
90-100	0.5	Mammo
80-89	1	Mammo
70-79	1	Mammo
60-69	1.5	Mammo
50-59	2	Mammo
40-49	2	Mammo
30-39	4	Mammo
20-29	4	Mammo
10-19	6	Mammo
0-9	6	Mammo

Mammo: Mammography

doi:10.6342/NTU201702793

Table 4.5 3 Personalized breast cancer prevention for BRCA-carrier

Risk group	Screen interval (years)	Primary prevention	Screening Modality
90-100	- / 2	Prophylactic mastectomy/ Tamoxifen chemoprevention	Mammo/Mammo+MRI
80-89	- / 2	Prophylactic mastectomy/ Tamoxifen chemoprevention	Mammo/Mammo+MRI
70-79	1	-	Mammo/Mammo+MRI
60-69	1	-	Mammo/Mammo+MRI
50-59	1	-	Mammo/Mammo+MRI
40-49	1	-	Mammo/Mammo+MRI
30-39	1	-	Mammo/Mammo+MRI
20-29	1	-	Mammo/Mammo+MRI
10-19	1	-	Mammo/Mammo+MRI
0-9	1	-	Mammo/Mammo+MRI

Mammo: Mammography; Sono: Sonography; MRI: Magnetic Resonance Imaging

doi:10.6342/NTU201702793

Table 5.1.1 Characteristics of simulated cohort of one million women by detection mode and mortality rate of breast cancer

Variables		FBC		Screen-detected		Clinical detected		Person years	BC death	Mortality rate
		No.	%	No.	%	No.	%	Year	No.	(per 100,000)
BMI (kg/m^2)	<=23	364066	37.75	2610	26.48	1722	14.38	8265344.0	1346	16.28
	>23	600366	62.25	7248	73.52	10252	85.62	13776977.5	6238	45.28
AP	<=25	647832	67.17	5629	57.10	5525	46.14	14755557.0	3755	25.45
	>25	316600	32.83	4229	42.90	6449	53.86	7286764.5	3829	52.55
Breast density (BI-RADS)	Almost entirely fat	9103	0.94	26	0.26	41	0.34	207382.0	26	12.54
	Scattered fibroglandular densities	154763	16.05	982	9.96	1181	9.86	3513836.5	766	21.80
	Heterogeneously dense	540690	56.06	5691	57.73	6979	58.28	12365724.0	4418	35.73
	Extremely dense	259876	26.95	3159	32.05	3773	31.51	5955379.0	2374	39.86

doi:10.6342/NTU201702793

Variables		FBC		Screen-detected		Clinical detected		Person years	BC death	Mortality rate
		No.	%	No.	%	No.	%	Year	No.	(per 100,000)
BRCA	Non-carrier	963181	99.87	9655	97.94	11750	98.13	22008426.0	7460	33.90
	BRCA 1 carrier	461	0.05	74	0.75	72	0.60	12375.0	37	298.99
	BRCA 2 carrier	790	0.08	129	1.31	152	1.27	21520.5	87	404.27
ER	Negative	183147	18.99	1614	16.37	2466	20.59	4185538.5	1509	36.05
	Positive	781285	81.01	8244	83.63	9508	79.41	17856783.0	6075	34.02
HER-2	Negative	235721	24.44	2182	22.13	3104	25.92	5388224	1977	36.69
	Positive	728711	75.56	7676	77.87	8870	74.08	16654097.5	5607	33.67
KI67	Negative	185822	19.27	1958	19.86	2220	18.54	4246112.5	1621	38.18
	Positive	778610	80.73	7900	80.14	9754	81.46	17796209	5963	33.51
PR	Negative	327521	33.96	3501	35.51	4052	33.84	7488431.0	2733	36.50
	Positive	636911	66.04	6357	64.49	7922	66.16	14553890.5	4851	33.33
BASAL	Non-basal	861109	89.29	9102	92.33	10430	87.11	19678258.0	6652	33.80
	Basal	103323	10.71	756	7.67	1544	12.89	2364063.5	932	39.42

doi:10.6342/NTU201702793

Variables		FBC		Screen-detected		Clinical detected		Person years	BC death	Mortality rate
		No.	%	No.	%	No.	%	Year	No.	(per 100,000)
No. high-risk alleles on rs2981582	2	137477	14.25	1836	18.62	2244	18.74	3153319.5	1463	46.4
	1	454325	47.11	4894	49.64	5863	48.96	10391948	3671	35.33
	0	372630	38.64	3128	31.73	3867	32.29	8497054	2450	28.83
No. high-risk alleles on rs3803662	2	59831	6.2	768	7.79	996	8.32	1374193.5	618	44.97
	1	359780	37.3	4098	41.57	4883	40.78	8233788	3101	37.66
	0	544821	56.49	4992	50.64	6095	50.9	12434340	3865	31.08
No. high-risk alleles on rs889312	2	75175	7.79	860	8.72	1082	9.04	1722031	705	40.94
	1	387963	40.23	4196	42.56	5064	42.29	8873049.5	3215	36.23
	0	501294	51.98	4802	48.71	5828	48.67	11447241	3664	32.01
No. high-risk alleles on rs3817198	2	87040	9.03	988	10.02	1152	9.62	1990361.5	721	36.22
	1	404406	41.93	4233	42.94	5202	43.44	9245392	3201	34.62
	0	472986	49.04	4637	47.04	5620	46.94	10806568	3662	33.89
No. high-risk alleles on rs13281615	2	153969	15.96	1680	17.04	2097	17.51	3525035	1357	38.5
	1	462707	47.98	4797	48.66	5833	48.71	10578549	3693	34.91
	0	347756	36.06	3381	34.3	4044	33.77	7938737.5	2534	31.92

doi:10.6342/NTU201702793

Variables		FBC		Screen-detected		Clinical detected		Person years	BC death	Mortality rate
		No.	%	No.	%	No.	%	Year	No.	(per 100,000)
No. high-risk alleles on rs13387042	2	239820	24.87	2881	29.22	3512	29.33	5493847	2201	40.06
	1	482514	50.03	4909	49.8	5916	49.41	11024639.5	3792	34.4
	0	242098	25.1	2068	20.98	2546	21.26	5523835	1591	28.8
No. high-risk alleles on rs1045485	2	711457	73.77	7596	77.05	9139	76.32	16269205	5814	35.74
	1	233779	24.24	2109	21.39	2648	22.11	5335890	1658	31.07
	0	19196	1.99	153	1.55	187	1.56	437226.5	112	25.62
No. protective alleles on rs9485372	2	199608	20.7	1802	18.28	2219	18.53	4553931.5	1436	31.53
	1	478510	49.62	4908	49.79	5883	49.13	10935161.5	3621	33.11
	0	286314	29.69	3148	31.93	3872	32.34	6553228.5	2527	38.56
No. protective alleles on rs9383951	2	9568	0.99	83	0.84	92	0.77	217726.5	57	26.18
	1	173841	18.03	1672	16.96	1983	16.56	3971274.5	1265	31.85
	0	781023	80.98	8103	82.2	9899	82.67	17853320.5	6262	35.07
No. high-risk alleles on rs7107217	2	122892	12.74	1333	13.52	1735	14.49	2811741	1051	37.38
	1	443229	45.96	4627	46.94	5667	47.33	10131363.5	3594	35.47
	0	398311	41.3	3898	39.54	4572	38.18	9099217	2939	32.3

doi:10.6342/NTU201702793

Variables		FBC		Screen-detected		Clinical detected		Person years	BC death	Mortality rate
		No.	%	No.	%	No.	%	Year	No.	(per 100,000)
No. protective alleles on rs12118297	2	140495	14.57	1247	12.65	1549	12.94	3206525	970	30.25
	1	454870	47.16	4563	46.29	5628	47	10390389	3552	34.19
	0	369067	38.27	4048	41.06	4797	40.06	8445407.5	3062	36.26
No. high-risk alleles on rs16992204	2	14085	1.46	176	1.79	233	1.95	323503	144	44.51
	1	206065	21.37	2253	22.85	2806	23.43	4716248.5	1775	37.64
	0	744282	77.17	7429	75.36	8935	74.62	17002570	5665	33.32
P53	Non-carrier	758550	78.65	6159	62.48	7522	62.82	17291214.0	4775	27.62
	carrier	205882	21.35	3699	37.52	4452	37.18	4751107.5	2809	59.12
Lifetime HRT use	Never	268522	27.84	2352	23.86	2841	23.73	6124625.0	1807	29.50
	Current oral estrogen only	381250	39.53	3611	36.63	4394	36.70	8704104.0	2754	31.64
	Current combination therapy	179078	18.57	1993	20.22	2525	21.09	4097809.5	1584	38.65
	Past user	135582	14.06	1902	19.29	2214	18.49	3115783.0	1439	46.18
Overall		964432	100.00	9858	100.00	11974	100.00	22042321.5	7584	34.41

doi:10.6342/NTU201702793

Table 5.2 1 Factors and effect size associated with the occurrence of breast cancer included in the simulated cohort

Initiator	Parameter	Coefficient	Rate Ratio	Reference
		Genetic factors		
Gene mutation of major gene	BRCA 1 gene mutation	3.009	20.26	(Anglian Breast Cancer Study, 2000, Wu et al. , 2013b)
	BRCA 2 gene mutation	2.736	15.43	
	P53 gene mutation	22.8	0.788	(Elledge et al. , 1993, Lou et al. , 1997)
Polygenes (dbSNP no.) per allele	rs2981582	0.231	1.26	(Wu et al. , 2013b)
	rs3803662	0.182	1.20	
	rs889312	0.122	1.13	
	rs3817198	0.068	1.07	
	rs13281615	0.077	1.08	
	rs13387042	0.182	1.20	
	rs1045485	0.122	1.13	
	rs9485372	-0.105	0.9	(Han et al. , 2016, Long et al. , 2012)
	rs9383951	-0.128	0.88	
	rs7107217	0.077	1.08	
	rs12118297	-0.094	0.91	
	rs16992204	0.122	1.13	
		Conventional factors		
Breast density (BI-RADS)	Almost entirely fat Scattered	*reference*	1.00	(Wu et al. , 2013b)
	fibroglandular densities	0.708	2.03	
	Heterogeneously dense	1.082	2.95	
	Extremely dense	1.394	4.03	
BMI(kg/m^2)	<=23	*reference*	1.00	(Wu et al. , 2013b)

doi:10.6342/NTU201702793

Initiator	Parameter	Coefficient	Rate Ratio	Reference
Age at first pregnancy	>23	0.952	2.59	(Wu et al. , 2013b)
	<=25	*reference*	1.00	
	>25	0.688	1.99	
Lifetime HRT use	Never		1	(Chen et al. , 2002)
	Current oral estrogen only	0.157	1.17	
	Current combination therapy	0.399	1.49	
	Past users	-0.083	0.92	

doi:10.6342/NTU201702793

Table 5.2 2 Factors and effect size associated with the progression of breast cancer included in the simulated cohort

Promoter	Parameter	Coefficient	Rate Ratio	Reference
Conventional factors				
BMI(kg/m^2)	<=23		1.00	(Wu et al. , 2013b)
	>23	0.693	2.00	
Age at first pregnancy	<=25		1.00	(Wu et al. , 2013b)
	>25	0.445	1.56	
Immunochemical marker of breast cancer				
ER status	Positive		1.00	(Dong et al. , 2008)
	Negative	0.300	1.35	
PR status	Positive		1.00	(Dong et al. , 2008)
	Negative	0.077	1.08	
HER-2 status	0 or 1+		1.00	(Dong et al. , 2008)
	2+	0.122	1.13	
	3+	-0.128	0.88	
Ki-67 proliferation	<10%	0.000	1.00	(Dong et al. , 2008)
	10-30%	0.336	1.40	
	>30%	0.747	2.11	

doi:10.6342/NTU201702793

Table 5.3 1 Ten-year and lifetime risk of breast cancer for BRCA carrier women by age groups

BRCA carrier	10 year risk (%)		Lifetime risk (%)	
Age Group	Estimate	95% CI	Estimate	95% CI
20	6.5	(5.6, 7.4)	58.0	(54.0, 62.1)
30	10.2	(8.8, 11.5)	56.3	(52.3, 60.4)
40	13.5	(11.8, 15.2)	53.3	(49.3, 57.4)
50	16.5	(14.5, 18.6)	48.7	(44.7, 52.7)
60	19.4	(17.1, 21.7)	41.7	(37.9, 45.5)
70	22.0	(19.5, 24.6)	30.9	(27.7, 34.1)

doi:10.6342/NTU201702793

Table 5.4 1 Ten-year and life-time risk of breast cancer for women at 50 years by 10 risk categories

Risk Group (decil)	10 year risk (%)		Lifetime risk (%)	
	Estimate	95% CI	Estimate	95% CI
90-100	3.36	(3.35, 3.37)	14.56	(14.52, 14.59)
80-89	1.95	(1.94, 1.95)	8.69	(8.68, 8.71)
70-79	1.48	(1.47, 1.48)	6.66	(6.65, 6.68)
60-69	1.17	(1.17, 1.18)	5.32	(5.30, 5.33)
50-59	0.96	(0.96, 0.96)	4.37	(4.36, 4.38)
40-49	0.80	(0.79, 0.80)	3.64	(3.63, 3.65)
30-39	0.66	(0.65, 0.66)	3.01	(3.00, 3.02)
20-29	0.51	(0.51, 0.52)	2.36	(2.36, 2.37)
10-19	0.38	(0.38, 0.38)	1.75	(1.74, 1.75)
0-9	0.24	(0.24, 0.24)	1.10	(1.10, 1.10)

doi:10.6342/NTU201702793

Table 5.4 2 Ten-year and life-time risk of breast cancer by 10 risk categories for women with BRCA carrier (a) and non-BRCA carrier (b)

(a) Ten-year and life-time risk of breast cancer by 10 risk categories for women who are BRCA carrier

BRCA carrier	10 year risk (%)		Lifetime risk (%)	
Risk Group	Estimate	95% CI	Estimate	95% CI
90-100	33.6	(30.1, 37.1)	84.3	(81.0, 87.6)
80-89	23.2	(21.9, 24.5)	70.4	(68.1, 72.8)
70-79	19.2	(18.3, 20.0)	62.8	(60.9, 64.6)
60-69	15.0	(14.3, 15.7)	52.9	(51.2, 54.6)
50-59	13.3	(12.5, 14.0)	48.3	(46.2, 50.5)
40-49	11.8	(11.0, 12.6)	44.1	(41.7, 46.6)
30-39	9.4	(8.8, 10.1)	36.9	(34.9, 38.9)
20-29	7.5	(7.1, 7.8)	30.3	(29.0, 31.5)
10-19	5.9	(5.5, 6.2)	24.4	(23.1, 25.8)
0-9	3.8	(3.5, 4.1)	16.5	(15.3, 17.7)

(b) Ten-year and life-time risk of breast cancer by 10 risk categories for non-BRCA carrier women

Non-BRCA carrier	10 year risk (%)		Lifetime risk (%)	
Risk Group	Estimate	95% CI	Estimate	95% CI
90-100	2.69	(2.68, 2.70)	11.90	(11.85, 11.95)
80-89	1.78	(1.77, 1.78)	8.00	(7.99, 8.01)
70-79	1.38	(1.38, 1.38)	6.27	(6.26, 6.28)
60-69	1.15	(1.15, 1.15)	5.23	(5.22, 5.23)
50-59	0.98	(0.97, 0.98)	4.46	(4.45, 4.46)
40-49	0.83	(0.82, 0.83)	3.78	(3.78, 3.79)
30-39	0.68	(0.67, 0.68)	3.11	(3.10, 3.11)
20-29	0.53	(0.53, 0.53)	2.43	(2.42, 2.43)
10-19	0.40	(0.40, 0.40)	1.85	(1.85, 1.86)
0-9	0.27	(0.26, 0.27)	1.23	(1.22, 1.23)

doi:10.6342/NTU201702793

Table 5.4 3 Mean sojourn time by decile of breast cancer risk

Non-BRCA carrier	Mean sojourn time	
Risk Group	Estimate	95% CI
90-100	1.45	(1.45, 1.46)
80-89	1.58	(1.57, 1.58)
70-79	1.7	(1.70, 1.71)
60-69	1.88	(1.88, 1.89)
50-59	2.04	(2.04, 2.05)
40-49	2.18	(2.17, 2.18)
30-39	2.32	(2.32, 2.33)
20-29	2.64	(2.63, 2.65)
10-19	3.21	(3.20, 3.22)
0-9	3.74	(3.73, 3.75)

doi:10.6342/NTU201702793

Table 5.5 1 Results on the efficacy of universal breast cancer screening in terms of advanced cancer reduction (a) and the reduction of case-fatality of breast cancer (b)

(a) Results on the efficacy of universal breast cancer screening in terms of advanced cancer reduction

Screening strategy	Observed probability (%)	95% CI		Expected probability (%)	95% CI		Efficacy (%)	95% CI	
Annual	55.98	55.92	56.03	64.98	64.94	65.02	13.85	13.76	13.95
Biennial	60.04	59.99	60.09	64.98	64.94	65.02	7.61	7.51	7.70
Triennial	62.19	62.14	62.23	64.95	64.91	64.99	4.25	4.16	4.35

(b) Results on the efficacy of universal screening strategies in terms of the reduction of case-fatality of breast cancer

Screening strategy	Observed probability (%)	95% CI		Expected probability (%)	95% CI		Efficacy (%)	95% CI	
Annual	57.82	57.76	57.87	83.79	83.72	83.86	31.00	30.93	31.06
Biennial	62.69	62.63	62.75	83.81	83.74	83.87	25.19	25.13	25.25
Triennial	66.41	66.35	66.47	83.81	83.75	83.87	20.77	20.71	20.82

doi:10.6342/NTU201702793

Table 5.5 2 Efficacy of primary and secondary prevention for BRCA carriers in terms of advance cancer reduction (a) and reduction of case-fatality for breast cancer (b)

(a) Efficacy of primary and secondary prevention for BRCA carriers in terms of advance cancer reduction

Screening strategy	Observed probability (%)	95% CI		Expected probability (%)	95% CI		Efficacy (%)	95% CI	
Mammo	56.47	56.18	56.76	67.43	67.22	67.65	16.21	15.72	16.70
MRI+ Mammo	55.13	54.84	55.42	67.58	67.36	67.79	18.37	17.88	18.86
Surgery+ Mammo	54.90	54.54	55.27	66.80	66.46	67.14	17.66	16.95	18.37
Surgery+ MRI	54.10	53.73	54.47	66.83	66.51	67.14	18.92	18.22	19.62
Tamoxifen+ Mammo	55.75	55.42	56.09	66.20	65.87	66.52	15.65	15.01	16.29
Tamoxifen+ MRI	54.74	54.41	55.06	66.64	66.32	66.96	17.74	17.13	18.36

*Mammo: annual mammographic screening

MRI+Mammo: annual MRI and mammographic screening

Surgery+Mammo: preventive mastectomy for 20% high risk women and annual mammographic screening for the rest of population

Surgery +MRI: preventive mastectomy for 20% high risk women and annual mammographic screening for the rest of population

Tamoxifen+Mammo: Tamoxifen chemoprevention for 20% high risk women and annual mammographic screening for the rest of population

Tamoxifen+MRI: Tamoxifen chemoprevention for 20% high risk women and annual mammographic and MRI screening for the rest of population

doi:10.6342/NTU201702793

(b) Efficacy of primary and secondary prevention for BRCA carriers in terms of reduction of case-fatality for breast cancer

Screening strategy	Observed probability (%)	95% CI		Expected probability (%)	95% CI		Efficacy (%)	95% CI	
Mammo	49.12	48.86	49.38	76.19	75.92	76.45	35.51	35.20	35.82
MRI+ Mammo	47.42	47.13	47.71	76.22	75.96	76.48	37.76	37.38	38.14
Surgery+ Mammo	34.84	34.46	35.21	47.30	46.93	47.68	26.09	25.14	27.04
Surgery+ MRI	34.37	34.03	34.70	47.20	46.82	47.58	26.91	26.01	27.80
Tamoxifen+ Mammo	35.63	35.30	35.95	46.06	45.66	46.47	22.45	21.71	23.19
Tamoxifen+ MRI	35.25	34.93	35.56	47.36	46.97	47.74	25.25	24.34	26.16

*Mammo: annual mammographic screening

MRI+Mammo: annual MRI and mammographic screening

Surgery+Mammo: preventive mastectomy for 20% high risk women and annual mammographic screening for the rest of population

Surgery +MRI: preventive mastectomy for 20% high risk women and annual mammographic screening for the rest of population

Tamoxifen+Mammo: Tamoxifen chemoprevention for 20% high risk women and annual mammographic screening for the rest of population

Tamoxifen+MRI: Tamoxifen chemoprevention for 20% high risk women and annual mammographic and MRI screening for the rest of population

doi:10.6342/NTU201702793

Table 5.5 3 Efficacy of risk-based screening interval in terms of advanced cancer reduction (a) and case-fatality of breast cancer (b)

(a) Efficacy of risk-based screening interval in terms of advanced cancer reduction

Screening strategy	Risk group	Observed probability (%)	95% CI		Expected probability (%)	95% CI		Efficacy (%)	95% CI	
Biennial	0-29	57.01	56.85	57.16	63.81	63.68	63.94	10.64	10.34	10.94
	30-69	59.03	58.93	59.12	65.72	65.64	65.79	10.17	10.00	10.34
	70-100	61.11	61.05	61.17	64.78	64.73	64.84	5.66	5.54	5.79
Personalized interval	0-29	61.23	61.06	61.40	63.90	63.77	64.03	4.16	3.83	4.48
	30-69	58.94	58.84	59.04	65.74	65.66	65.81	10.33	10.15	10.52
	70-100	55.13	55.06	55.20	64.81	64.76	64.87	14.93	14.80	15.06

(b) Efficacy of risk-based screening interval in terms of reduction in the case-fatality of breast cancer

Screening strategy	Risk group	Observed probability (%)	95% CI		Expected probability (%)	95% CI		Efficacy (%)	95% CI	
Biennial	0-29	61.13	60.94	61.32	90.72	90.50	90.95	32.61	32.40	32.81
	30-69	62.34	62.24	62.43	85.78	85.67	85.89	27.32	27.22	27.43
	70-100	63.16	63.08	63.24	81.71	81.63	81.80	22.71	22.63	22.78
Personalized interval	0-29	70.42	70.21	70.63	90.76	90.53	91.00	22.40	22.21	22.59
	30-69	63.01	62.91	63.12	85.84	85.73	85.96	26.59	26.48	26.70
	70-100	56.87	56.79	56.94	81.68	81.60	81.76	30.38	30.29	30.46

Various inter-screening interval guided by risk of breast cancer

doi:10.6342/NTU201702793

Table 5.5 4 Efficacy of risk-based screening modality in terms of advanced cancer reduction (a) and case-fatality of breast cancer (b)

(a) Efficacy of risk-based screening modality in terms of advanced cancer reduction

Screening strategy	Risk group	Observed probability (%)	95% CI		Expected probability (%)	95% CI		Efficacy (%)	95% CI	
Biennial	0-29	57.01	56.85	57.16	63.81	63.68	63.94	10.64	10.34	10.94
	30-69	59.03	58.93	59.12	65.72	65.64	65.79	10.17	10.00	10.34
	70-100	61.11	61.05	61.17	64.78	64.73	64.84	5.66	5.54	5.79
Personalized modality	0-29	61.40	61.21	61.58	63.56	63.41	63.70	3.37	3.01	3.73
	30-69	59.22	59.12	59.31	65.60	65.53	65.68	9.73	9.55	9.90
	70-100	59.46	59.39	59.53	64.76	64.71	64.82	8.18	8.05	8.31

Various alternative imagine techniques guided by risk of breast cancer

- >80% -MRI +sonography + mammography
- 60%-80% sonography+mammography
- 40%-60% Biennial mammography
- 20%-40% Four-yearly mammography
- < 20% Six-yearly mammography

doi:10.6342/NTU201702793

(b) Efficacy of risk-based screening modality in terms of reduction in the case-fatality of breast cancer

Screening strategy	Risk group	Observed probability (%)	95% CI		Expected probability (%)	95% CI		Efficacy (%)	95% CI	
Biennial	0-29	61.13	60.94	61.32	90.72	90.50	90.95	32.61	32.40	32.81
	30-69	62.34	62.24	62.43	85.78	85.67	85.89	27.32	27.22	27.43
	70-100	63.16	63.08	63.24	81.71	81.63	81.80	22.71	22.63	22.78
Personalized modality	0-29	70.39	70.16	70.62	90.26	90.02	90.50	22.01	21.80	22.22
	30-69	62.79	62.69	62.90	85.68	85.57	85.79	26.72	26.60	26.83
	70-100	60.80	60.72	60.88	81.39	81.31	81.47	25.30	25.22	25.39

Various alternative imagine techniques guided by risk of breast cancer

- >80% -MRI +sonography + mammography
- 60%-80% sonography+mammography
- 40%-60% Biennial mammography
- 20%-40% Four-yearly mammography
- < 20% Six-yearly mammography

doi:10.6342/NTU201702793

Table 5.6 1 Results of cost-effectiveness analysis of universal strategies of secondary prevention using mammography as screening tool

Strategy	Effectiveness			Cost			ΔE			ΔC			ICER		
	Estimate	95% C.I.		Estimate	95% C.I.		Estimate	95% C.I.		Estimate	95% C.I.		Estimate	95% C.I.	
Non-screen	6779327	6778549	6780105	145910543	145775290	146045796	-	-	-	-	-	-	-	-	-
Annual	6786316	6785535	6787097	474852188	474689128	475015247	6989	6966	7012	328941645	328876021	329007268	47096	46946	47247
Biennial	6784644	6783837	6785451	324086199	323946507	324225891	4866	4847	4884	178354000	178303027	178404972	36691	36550	36831
Triennial	6782484	6781626	6783342	268774840	268636119	268913562	3822	3805	3840	122920701	122873706	122967696	32201	32055	32347

doi:10.6342/NTU201702793

Table 5.6 2 (a) Results of cost-effectiveness analysis of personalized strategies of secondary prevention using mammography as screening tool

Strategy	Effectiveness			Cost			ΔE			ΔC			ICER		
	Estimate	95% C.I.		Estimate	95% C.I.		Estimate	95% C.I.		Estimate	95% C.I.		Estimate	95% C.I.	
Non-screen	6779327	6778549	6780105	145910543	145775290	146045796	-	-	-	-	-	-	-	-	-
Personalized interval	6787111	6786286	6787936	369759486	369615246	369903725	6480	6457	6503	223947096	223887315	224006877	34585	34464	34707
Personalized modality	6784112	6783239	6784986	737966171	737767520	738164823	5117	5098	5137	592240231	592106134	592374329	115838	115396	116281

doi:10.6342/NTU201702793

Table 5.6 2 (b) Results on cost-effectiveness analysis for personalized strategies compared with biennial screening strategy

	Effectiveness			Cost			ΔE			ΔC			ICER		
Screening strategy	Estimate	95% CI		Estimate	95% CI		Estimate	95% CI		Estimate	95% CI		Estimate	95% CI	
Biennial	6784644	6783837	6785451	324086199	323946507	324225891									
Personalized interval	6787111	6786286	6787936	369759486	369615246	369903725	1615	1585	1645	45593096	45512928	45673264	28883	28325	29440
Personalized modality	6784112	6783239	6784986	737966171	737767520	738164823	252	227	277	413886232	413739888	414032575	833147	-814282	2480576

doi:10.6342/NTU201702793

Table 5.6 3 (a) Results on cost-effectiveness analysis of universal screening strategies for non-BRCA carrier women

Strategy	Effectiveness			Cost			ΔE			ΔC			ICER		
	Estimate	95% C.I.		Estimate	95% C.I.		Estimate	95% C.I.		Estimate	95% C.I.		Estimate	95% C.I.	
Non-screen	6767053	6766275	6767832	140462037	140330566	140593507	-	-	-	-	-	-	-	-	-
Annual	6773882	6773101	6774664	468208405	468050647	468366163	6829	6806	6851	327746369	327681069	327811668	48026	47871	48181
Biennial	6772248	6771443	6773054	317841323	317701849	317980796	4743	4725	4761	177567104	177516405	177617803	37473	37331	37615
Triennial	6770135	6769276	6770993	262780991	262643476	262918507	3736	3718	3753	122375057	122328897	122421216	32805	32653	32958

doi:10.6342/NTU201702793

Table 5.6.3 (b) Results of cost-effectiveness analysis of personalized strategies for breast cancer prevention for non-BRCA carrier women

Strategy	Effectiveness			Cost			ΔE			ΔC			ICER		
	Estimate	95% C.I.		Estimate	95% C.I.		Estimate	95% C.I.		Estimate	95% C.I.		Estimate	95% C.I.	
Non-screen	6767053	6766275	6767832	140462037	140330566	140593507	-	-	-	-	-	-	-	-	-
Biennial	6772248	6771443	6773054	317841323	317701849	317980796	4743	4725	4761	177567104	177516405	177617803	37473	37331	37615
Personalized interval	6774677	6773856	6775497	363115579	362976503	363254656	6319	6297	6341	222751557	222692333	222810781	35278	35155	35401
Personalized modality	6771658	6770785	6772531	730112141	729917347	730306936	4948	4929	4968	589829215	589694158	589964272	119315	118850	119780

doi:10.6342/NTU201702793

Table 5.6 4 Results of cost-effectiveness analysis of Preventive strategies for BRCA carrier

Strategy	Effectiveness			Cost			ΔE			ΔC			ICER		
	Estimate	95% C.I.		Estimate	95% C.I.		Estimate	95% C.I.		Estimate	95% C.I.		Estimate	95% C.I.	
No invervention	17932	17883	17980	3029816	3013008	3046625									
Mammo	18156	18104	18207	4853854	4832694	4875013	216	212	220	1823361	1815800	1830922	8613	8451	8775
MRI+ Mammo	18168	18119	18218	12571706	12536119	12607293	237	232	241	9541889	9514597	9569182	41142	40389	41894
Surgery+ Mammo	18429	18377	18481	3461057	3446552	3475562	352	343	361	914088	901881	926295	2722	2630	2815
Surgery+ MRI	18421.63	18373	18470	11505841	11474406	11537276	354	345	364	8964063	8936849	8991278	26600	25790	27409
Tamoxifen+ Mammo	18251	18198	18304	4077816	4059623	4096008	100	96	104	1894696	1887353	1902038	21913	19839	23988
Tamoxifen+ MRI	18245	18194	18296	11955496	11921434	11989558	223	213	233	9409877	9380549	9439206	49884	46574	53193
*MAMMO	18107	18053	18161	487515560	486077367	488953753	212	208	216	484486761	483057475	485916046	2330690	2287927	2373454
*MRI+MAMMO	18169	18119	18220	496247858	494899043	497596673	237	233	241	493218648	491877401	494559896	2121640	2081593	2161687

Mammo: annual mammographic screening;

MRI+Mammo: annual MRI and mammographic screening

Surgery+Mammo: preventive mastectomy for 20% high risk women and annual mammographic screening for the rest of population

Surgery +MRI: preventive mastectomy for 20% high risk women and annual mammographic screening for the rest of population

Tamoxifen+Mammo: Tamoxifen chemoprevention for 20% high risk women and annual mammographic screening for the rest of population

Tamoxifen+MRI: Tamoxifen chemoprevention for 20% high risk women and annual mammographic and MRI screening for the rest of population

* Considering the cost of population-wide genetic test

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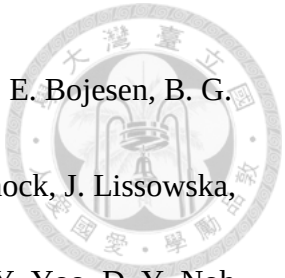

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