RICE UNIVERSITY

Statistical Modeling in the Optimization of Breast Cancer Screening Schedules

by

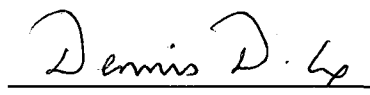
Charlotte Hsieh Ahern

A Thesis Submitted
in Partial Fulfillment of the
Requirements for the Degree

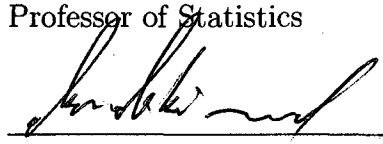
Doctor of Philosophy

Approved, Thesis Committee:

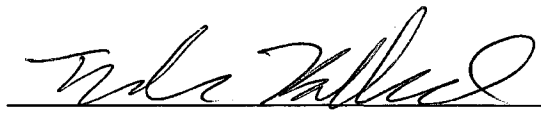
Yu Shen, Director
Professor of Biostatistics
UT-MD Anderson Cancer Center



Dennis D. Cox, Chair
Professor of Statistics



Marek Kimmel
Professor of Statistics



J. Nathaniel Holland
Assistant Professor of Ecology and
Evolutionary Biology

Houston, Texas
September 2008

Abstract

Statistical Modeling in the Optimization of Breast Cancer Screening Schedules

by

Charlotte Hsieh Ahern

Although screening for breast cancer is broadly utilized in the United States, the optimal approach in terms of examination modality, frequency, and starting age is unclear. Furthermore, there is no consensus on the benefit from earlier, more frequent, or additional modes of screening for women with high-risk for breast cancer. This thesis explores methods for finding optimal screening strategies by modeling the costs and benefits of breast cancer screening programs through a simulation-based and a theoretical approach, which incorporate some ignored or unexplored components. For the general population, cost-effectiveness studies evaluating breast cancer screening have focused on mammography alone, and have not assessed the impact of its combination with clinical breast exam, a cheaper and more practical exam. Costs incurred beyond screening including costs for work-up, biopsy, and treatment have often been ignored. We account for these factors in a comprehensive microsimulation analysis by modeling the natural history of the disease including age-specific incidence, sojourn time, and exam sensitivity and specificity, and evaluate

the cost-effectiveness of a set of screening programs on a simulated cohort of women. Similarly, we focus on a special case of high-risk women where we include screening programs that begin at an earlier age, have more frequent examinations, and include combinations of magnetic-resonance imaging, which has recently been recommended for women at high-risk for breast cancer. The most cost-effective approach depends on how much society is willing to pay to save a year of life. Finally, we take a theoretical approach which is motivated by the idea that other optimal screening programs may exist outside a set of predetermined strategies used in a simulation-based approach. While empirical studies give a better idea of which screening schedules are useful, a theoretical approach may uncover a true optimal schedule. We assume a nonstable disease model and account for costs of screening and dollar value of benefit in a utility function under two different frameworks to estimate the optimal number or ages of examinations given certain general assumptions. We show that a solution exists for these models and demonstrate in numerical studies that they will give reasonable results.

Acknowledgements

I have found the journey as a graduate student to be long and challenging, but it has been a worthwhile and rewarding experience. There are many people who have contributed to my progress and success, and I'd like to recognize them here.

First and foremost, I praise God for His good gifts, for this opportunity, for surrounding me with the support I need, and for providing me with this work by which to glorify Him.

I would not have reached this point without the education I have received or the mentors I have had. I thank my advisor, Professor Yu Shen, for guiding me through this research with her constant encouragement and support, our weekly meetings, and her unfailing optimistic attitude. Special thanks also go to the Statistics faculty at Rice, and the Biostatistics faculty at MD Anderson Cancer Center who have contributed to my learning experience, and have provided me with a strong statistical foundation. I would also like to thank Professor Giovanni Parmigiani for providing us with some computer code for our reference, Professor Tina Shih for her helpful comments related to health economics, and Professor Yi Cheng for her mathematical insight and assistance.

The constant support of my family and friends has been an integral part of this entire journey. Nate, thank you for loving me even in my busiest and most stressful days, and for always encouraging me through thick and thin. Mom and Dad, thank

you for always being proud of me regardless of my achievements. To my most recent officemates, Jamie, Talithia, and Garrett, thank you for being an ever-present encouragement in the daily grind. And to my countless friends, thank you for reminding me to focus on the big picture in life and for keeping a smile on my face.

Contents

Figures

Tables

Chapter 1

Introduction

Breast cancer is the leading cancer for women in the United States. Screening for breast cancer is important in the early detection of the disease, which may lead to longer survival when combined with effective treatments. While screening is broadly utilized in the United States, the optimal approach in terms of examination modality, frequency, and starting age of screening for women of average-risk and high-risk remains unclear. This thesis intends to explore statistical methods for finding optimal screening strategies by modeling the costs and benefits of various breast cancer screening programs through a simulation-based approach and a theoretical approach, which incorporate some ignored or unexplored components.

1.1 Simulation-Based Approach

Mammography and clinical breast exam are common examples of screening for the presence of breast cancer. However, cost-effectiveness studies evaluating breast cancer screening in an average-risk cohort have focused on mammography alone, and have not assessed the impact of the combination of the modalities of mammography and clinical breast exam. In addition, most analyses have been limited to screening exam costs and have not accounted for subsequent costs for work-up examinations, biopsies, or treatment and maintenance costs, and do not directly account for false-positive

examinations. We incorporate these overlooked components into a simulation model.

It is also important to distinguish between average-risk and high-risk cohorts, as the optimal screening strategy may not be the same for both groups due to differences in incidence rate, tumor characteristics, screening modalities, and so forth. No official guidelines currently exist for screening among high-risk women, however, screening with magnetic resonance imaging (MRI) has recently been discussed as a requisite mode of screening for women with high-risk for breast cancer.

We conduct separate cost-effectiveness analyses for average-risk and high-risk cohorts of women by simulating their natural histories of disease and then assessing the impact of screening on their survival and accrual of costs. Investigated screening strategies included the modalities of mammography and clinical breast exam, with the addition of MRI for the high-risk cohort.

1.2 Theoretical Approach

In contrast to the broad attention to modeling the general screening process in a simulation-based approach, less attention has been paid to the optimization of examination schedules for screening examinations using mathematical models. Although a simulation approach allows for the exploration of multiple specific screening programs, none of them are necessarily optimal for any given utility function. This theoretical approach is motivated by the idea that other optimal but unexplored screening programs may exist. Under a theoretical framework, a mathematical model of the costs

and benefits of a screening program may be used to determine the optimal ages and spacing of examinations, or the optimal number of examinations within a specified screening horizon.

A utility function has previously been proposed under the assumption that preclinical disease incidence is independent of age under the stable disease model (Zelen 1993). We generalize this approach by Zelen and propose a model which reflects an age-dependency in the transition into the preclinical state and also incorporates a cost component. We show that under two separate frameworks, an optimal solution exists, and give some numerical results as examples.

1.3 Outline

The content of this work is organized as follows. We introduce and review cost-effectiveness analysis and previous works for women at average risk for breast cancer (referred to as the average-risk cohort) in Chapter 2, with a description of the present work's model, data inputs, and results. In Chapter 3, we extend the analysis to women with high risk for breast cancer (referred to as the high-risk cohort) and describe changes to the original model and present the results. Next, in Chapter 4, we review other works in the mathematical modeling of optimal screening strategies and present two proposed frameworks with proofs and results. Finally, we conclude this work with a summary of findings and a discussion of possible future work.

Chapter 2

Microsimulation Model: Average Risk Cohort

2.1 Background

Breast cancer remains the most common malignancy affecting women in North America. Early detection and effective treatment of the disease may significantly reduce mortality rates. In fact, the rate of death from breast cancer in U.S. women decreased between 1990 and 2000, while the incidence of the disease increased[1]. It has been shown that early detection and effective treatments for the disease have contributed to the observed decline in the rate of death from breast cancer[2].

Screening examinations such as mammography and clinical breast exam are common examples of screening for the presence of preclinical breast cancer. Despite broad utilization, there is no consensus on the approach to screening, including frequency, starting age, and examination modality. For example, the American Cancer Society (ACS) recommends annual mammography screening for women ages 40 and older, clinical breast exam triennially beginning at age 20, and annually beginning at age 40[3]. The National Cancer Institute (NCI) recommends screening mammography every 1-2 years[4], and the U.S. Preventive Services Task Force (USPSTF) recommends screening mammography, with or without clinical breast examination, every 1-2 years for women aged 40 and older[5]. Because of the existing controversy over

the most appropriate screening strategy, it is important to evaluate various screening strategies to determine the optimal strategies in terms of costs and benefits.

It is difficult to evaluate screening strategies since many factors related to screening exist, such as the relative advantage of early detection compared to waiting for symptoms to manifest without screening, the preclinical sojourn time distribution, and competing causes of mortality. Also, it is clear that early detection trials are very difficult to carry out in terms of size of the trial, length of follow-up, and compliance issues. Conducting future breast cancer early detection trials to evaluate various screening strategies among different age cohorts is difficult and unlikely, for ethical and economic reasons. On the other hand, data collected from completed large randomized early detection trials and other observational studies present a unique opportunity to evaluate and compare different screening strategies in order to find the optimal ones, by using microsimulation methods.

Computer based simulation models are useful and popular tools in the systematic evaluation of the effectiveness of various cancer screening programs, including breast, cervical, and lung cancers[6, 7, 8, 9, 10, 11]. Microsimulation models use Monte Carlo methods to model the cost and effectiveness of screening in a screening cohort. The life history of each subject is simulated, and disease progression can be modeled according to previously published natural history models[12, 13, 14], based on the probability distribution of each event. Such simulations are performed for a large number of subjects producing outputs of interest such as life expectancy and

costs. The natural histories of each woman in a birth cohort may be generated by utilizing evidence from available sources such as completed clinical trials and previously published mathematical models and analyses.

Eight major randomized early detection trials have been carried out in North America and Europe evaluating the early detection of breast cancer using mammography with or without clinical breast exam, beginning with the Health Insurance Plan (HIP) of New York in 1963. The trials that followed were the Edinburgh study, the Swedish Two-County studies, Malmo, Stockholm, Gothenburg, and the Canadian National Breast Screening Studies (CNBSS). The HIP, Edinburgh, and CNBSS trials offered both modalities of screening: mammography and clinical breast exam, while the remaining trials focused on mammography alone. Overall, evidence of benefit from screening varied across these randomized clinical trials[15], and findings led to controversy regarding the relevance of the suggested benefits for individual women[16, 17, 18, 19]. The discrepancies in the evidence may be explained by differences in trial design, screening schedules, and age cohorts. Rather than directly drawing inferences based on these trials alone, we use data obtained from these trials as data inputs in a microsimulation model to evaluate various screening programs by adding uncertainties.

Optimal screening strategies must balance the tradeoff between mortality reduction and the associated costs and burdens to society. Although two of the major guidelines suggest clinical breast exam in combination with mammography, almost

all literature in breast cancer screening addressing the balance between mortality reduction and costs have focused on mammography only[20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31], and have paid less attention to the combined use of mammography with clinical breast examination.

However, recent studies have shown that periodic clinical breast exam combined with mammography improves the overall sensitivity compared with mammography alone[32, 33, 34, 35]. As a routine part of a woman's recommended annual well-woman physical examination, clinical breast examinations are easy to administer and generally cheaper than mammography, making them a sensible complement to mammography. Shen and Parmigiani[7] found that biennial mammography coupled with an annual clinical breast examination can be a cost-effective strategy compared to forty-seven alternative screening strategies. However, only the cost of screening examinations was used in their cost-effectiveness analysis.

To date there is little research evaluating the cost-effectiveness of breast cancer screening programs combining both mammography and clinical breast exam while incorporating costs other than screening examinations, including costs of diagnostic follow-up due to abnormal examinations, treatment, and maintenance costs after diagnosis. While some studies of breast cancer screening have included treatment costs subsequent to diagnosis[26, 27, 28, 20, 25, 30, 36, 37], they have often been limited to specific age cohorts or subgroups, such as women older than 65, or African American women. For example, Mandelblatt *et al.*[28] investigated optimal screening strategies

using mammography for older women including costs of screening, treatment, and care. While these studies incorporate costs beyond screening, only one accounts for a general added cost due to false-positive mammography, and none of them consider the combination of screening modalities of mammography and clinical breast exam, or the direct cost of biopsy.

Because these components may play important roles in the cost-effectiveness of a screening program, they should not be neglected. Therefore, it is of interest to account for the above components in a comprehensive microsimulation analysis to determine which strategies are cost-effective. For each investigated screening strategy, the direct medical costs include the cost of screening examinations, the cost of work-up examinations for positive or abnormal exams, the cost of necessary and unnecessary biopsies due to true and false positive examinations, and the costs incurred from treatments after diagnosis. The measure of benefits used are the expected quality-adjusted life years (QALYs).

2.2 Model and Data Inputs

The continuous time simulation model follows the general structure of Shen and Parmigiani[8] with modifications to incorporate false-positive examinations and subsequent interventions following screening. The general model structure may be visualized in Figure 2.1. Data inputs for each component of the simulation model are estimated from existing data from published studies or randomized breast cancer

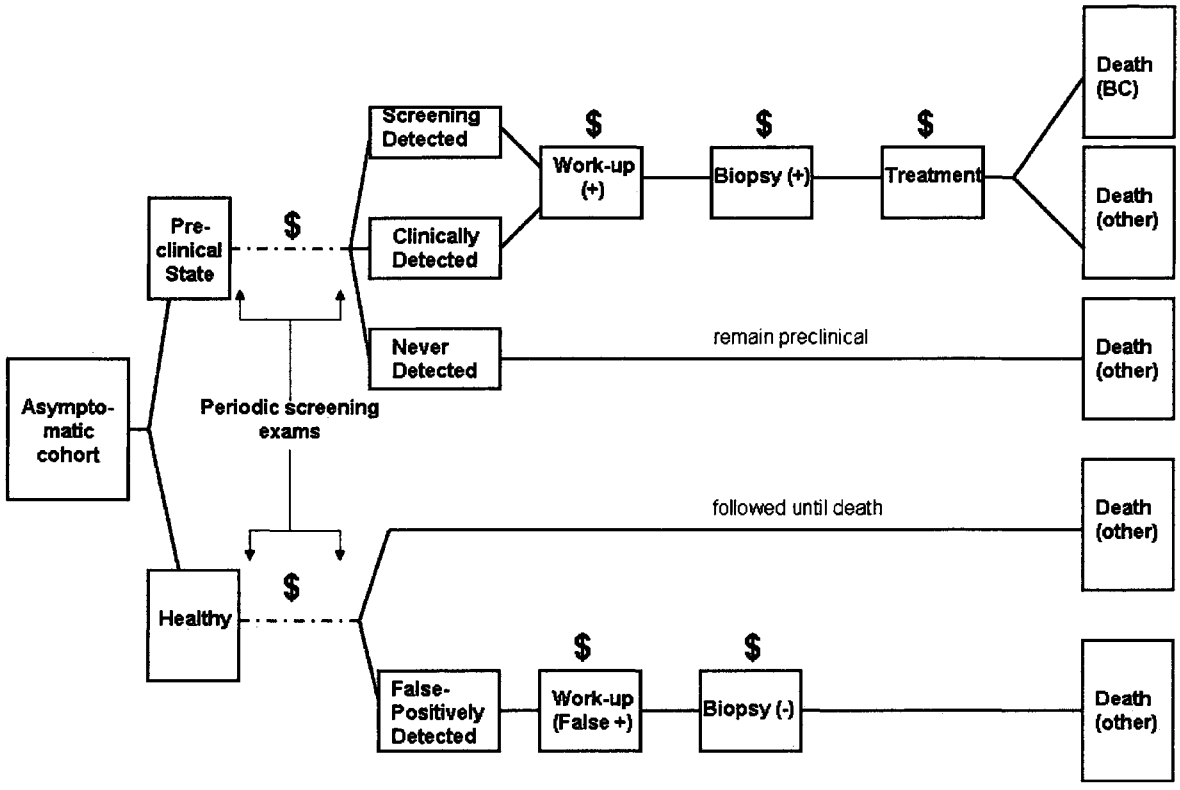


Figure 2.1 : Model structure for evaluating costs of screening, work-up, biopsy, and treatment for breast cancer.

screening trials. We discuss each component of the model below. See Table 2.1 for a list of references for each model component.

We considered ten screening strategies, plus a strategy of no screening, listed in Table 2.2. The selected strategies focus on realistic screening intervals, and include the recommended strategies from the ACS, NCI, and USPSTF. We varied time intervals between exams in different age cohorts in some strategies to accommodate the age-dependency of incidence, sensitivity, and sojourn time.

Model Components	**Data Inputs**	**References**
Natural History	Age-Specific Incidence	[38]
	Age-Specific Pre-clinical Transition	[6, 39]
	Sojourn Time Distributions	[32, 40]
	Tumor Growth Distributions	[41]
Screening Impacts	Mammography Sensitivity (by age and tumor size)	[42]
	Mammography Specificity (by age)	[43]
	Clinical Breast Exam Sensitivity, Specificity	[44]
	Diagnostic Mammography Sensitivity, Specificity	[45]
Costs Related to Screening, Workup, and Treatment	Mammography and Clinical Breast Exam	[46, 47]
	Diagnostic Mammography	[46]
	Breast Biopsy	[46]
	Treatment by Stage	[27]
Indirect Costs	Lost Productive Time (lost wages)	[48]
Survival Models	By Age, Tumor Size, Nodal Status at Diagnosis, ER status, and Treatment	[6, 49, 50, 51] [52]
	Competing Risks by Age	[53]
	Quality of Life Adjustments by Treatment	[6, 54]

Table 2.1 : Model components and data inputs for average-risk analysis.

	MM intv(age)	CBE intv(age)
1	1(40-79)	
2	2(40-79)	2(40-79)
3	2(40-79)	2(41-79)
4	2(40-79)	1(40-79)
5	1(40-79)	1(40-79)
6	1(40-49),2(50-79)	1(40-79)
7	1(40-59),2(60-79)	1(40-79)
8	1(40-69),2(70-79)	1(40-79)
9	2(40-49),1(50-79)	1(40-79)
10	1(40-79)	3(20-39),1(40-79)

MM=Mammography; CBE=Clinical Breast Exam;
intv=interval between exams; age=age range

Table 2.2 : Screening strategies investigated for the average-risk cohort.

The outcomes were the expected QALYs and expected total medical costs per woman, each discounted at 3% annually beginning at age 20. We compared screening strategies using incremental cost-effectiveness ratios in an incremental analysis[55, 56].

2.2.1 Natural History Model

We generate a birth cohort of 500,000 women by Monte Carlo simulation, where the cohort size is chosen so that the standard errors of the gain in QALYs compared to no screening is less than 0.2 daysn for all ten strategies. Each woman's natural history is simulated independently. Prevalent cases are simulated according to age-specific incidences of breast cancer. Among women who develop breast cancer, we generate their natural histories of the disease over time. In the natural history model, we assume four relevant states of the progressive disease, as described by Zelen and Feinleib[12]: disease-free or asymptomatic state (H); detectable pre-clinical state (P); clinical state (C); and death state (D). For women who have the disease, we simulate their preclinical duration and ages at onset of clinical disease based on an assumed distribution and published data, respectively; and survival time, based on simulated age and tumor characteristics at detection.

The latent ages at onset of preclinical disease must be derived given age-specific incidence of clinical disease and preclinical sojourn time. We may easily obtain the age-specific incidences of breast cancer which are observable and well-documented, and we use age-specific estimates from an analysis by Moolgavkar *et al.*[38]. On the

other hand, transition into the preclinical state is an unobservable event. We must therefore numerically derive the age-specific incidences of preclinical disease through a deconvolution approach described in Parmigiani[6] given the age-specific incidence of clinical disease at age y ($I_c(y)$) and the sojourn time distribution ($w_{pc}(y-t|t)$), where t is the age of transition from H to P, and $y-t$ is the time spent in P. The instantaneous probability of transition from P to C at age y is:

$$I_c(y) = \int_0^y w_{hp}(t) w_{pc}(y-t|t) dt,$$

where $w_{hp}(t)$ is the instantaneous probability of transitioning from H to P at time t. Using a method by Parmigiani and Skates[39], the age-specific transition rate w_{hp} may be estimated from the convolution relationship above.

Our choice for the sojourn time distribution is based on the commonly used exponential distribution[57, 58, 59], which was shown to be a satisfactory fit in an analysis of the HIP database[40]. In our simulations, we assume an exponential sojourn time distribution with an age-dependent component where the mean sojourn time, $\mu(t)$, depends on age at onset of preclinical disease. Uncertainty is incorporated through an inverse gamma prior for μ with scale and shape parameters that match the estimated mean and standard deviation from the CNBSS trials, where the mean sojourn time (and standard deviations) for ages ≤ 50 was 1.9 (1.2) years, and 3.1 (0.94) years for ages > 50 [32]. Thus, a random sojourn time is simulated for each subject depending

on her age at onset of preclinical disease.

We modeled tumor growth by tumor volume-doubling time under the exponential growth model[41]. We assume that the threshold diameter for a tumor to be detectable by screening is 0.5cm[60], and that the diameter at which breast cancer becomes clinically manifested is 2cm or more, based on data from the CNBSS trials[61]. Depending on the number of tumor volume doublings between the minimum detectable tumor volume and the clinically symptomatic tumor volume, we calculate the doubling time (DT) for each woman as a quotient of the woman's sojourn time and the number of doublings. We then obtain each woman's tumor volume at diagnosis (TV), a random quantity which depends on the woman's individual time spent in the preclinical state at the time of detection ($time\ in\ P$):

$$\begin{aligned} TV &= (minVol) * 2^{\#doublings} \\ &= (minVol) * 2^{\frac{time\ in\ P}{DT}}, \end{aligned}$$

where $minVol$ is the minimum detectable tumor volume.

2.2.2 Screening Impacts and Diagnostic Procedures

Because there is evidence that the sensitivity of mammography depends on tumor size and age at screening[32, 62, 63, 60, 42, 35], we model such a dependency using a

logit model:

$$\beta(t,d) = \frac{\exp(\alpha_0 + \alpha_1(t-40) + \alpha_2(d-1))}{1+\exp(\alpha_0 + \alpha_1(t-40) + \alpha_2(d-1))},$$

where t is age at diagnosis, and d is tumor diameter in cm. The coefficients of the logit model for mammography are determined based on sensitivity estimates from an analysis by Kolb *et al.* (2002)[42]. For example, we let a sensitivity for mammography of 0.58 correspond to a woman at age 40 with a tumor diameter of 1cm; a sensitivity of 0.1 correspond to a woman of the same age but with a tumor diameter of 0.05cm; and a sensitivity of 0.83 correspond to a woman age 65 with a tumor diameter of 1cm. Then $\beta_{MM}(40,1) = 0.58, \beta_{MM}(40,0.05) = 0.1, \beta_{MM}(65,1) = 0.83$ and the coefficients of the logit model are $\alpha_0 = 0.323, \alpha_1 = 0.051$, and $\alpha_2 = 2.653$ for mammography. Because insufficient evidence indicates that clinical breast exam sensitivity depends on age or tumor size, we used a constant value for clinical breast exam sensitivity ($\beta_{CBE} = 0.541$) taken from Elmore *et al.* (2005)[44]. To account for random variation in sensitivity within the cohort we used a beta prior distribution for each sensitivity so that each woman receives a random sensitivity depending on her age or tumor size at time of examination. Using an effective sample size (s) of $s_{MM} = 30$ for mammography and $s_{CBE} = 40$ for clinical breast exam, the parameters a and b of the $Beta(a,b)$ distribution for mammography are $a = \beta_{MM} * s_{MM}$ and $b = (1-\beta_{MM}) * s_{MM}$, and $a = \beta_{CBE} * s_{CBE}$ and $b = (1-\beta_{CBE}) * s_{CBE}$ for clinical brast exam, so that

the variance of the distribution is larger for mammography, consistent with previous screening trials[32, 44].

We similarly model age-dependent false-positive rates (γ) for mammography and clinical breast exam at screening using false-positive rate estimates reported in the literature[43, 44], with $\gamma_{MM}(50) = 0.076$ and $\gamma_{MM}(70) = 0.048$, and $\gamma_{CBE} = 0.10$. Again, we use a logit function for mammography as above, using these reported estimates but depending on age only. Random variation within the cohort is again accounted for using a beta prior distribution on the false-positive rate of each screening modality, where $s_{MM} = 30$ and $s_{CBE} = 40$.

According to the National Comprehensive Cancer Network Breast Cancer Screening and Diagnosis Guidelines, women with positive or abnormal screening examinations are recalled for further work-up[64]. A recalled woman receives a diagnostic mammography or ultrasound, then biopsy (the gold standard) if the diagnostic test is positive[64]. The recall rate after a positive or abnormal initial screening examination ranges from 1-17%[65, 66]. We used diagnostic mammography as the form of work-up, with sensitivity ($\beta_{dMM} = 0.80$) and specificity ($\delta_{dMM} = 0.90$) estimates from the Breast Cancer Surveillance Consortium[45]. For a woman whose tumor is detected symptomatically, a diagnostic mammography and breast biopsy are also given to confirm the disease status. Women in the preclinical state who are never diagnosed are assumed to have died of other causes.

The overall sensitivity and false-positive rate using both mammography and clini-

cal breast exam were calculated assuming the independence of the two modalities. It has been shown from analyses of data from the HIP and CNBSS trials that mammography and clinical breast exam contribute independently to the detection of breast cancer[67]. Then the overall sensitivity of a screening program using both mammography and clinical breast exam is calculated:

$$\beta(t,d) = \beta_{MM}(t,d) + \beta_{CBE}(t,d) - \beta_{MM}(t,d)\beta_{CBE}(t,d),$$

A similar model is assumed for false-positive rates of the two screening modalities.

Table 2.3 : Mean values of observed sensitivity (Sens.), specificity (Spec.), and recall rate (RR) for various age groups.

	Mammography			Clinical Breast Exam			Mammography & Clinical Breast Exam		
Age	Sens.	Spec.	RR	Sens.	Spec.	RR	Sens.	Spec.	RR
40-49	0.6603	0.9141	0.0860	0.5385	0.9400	0.0601	0.8419	0.8593	0.1408
50-59	0.7460	0.9311	0.0690	0.5391	0.9400	0.0602	0.8836	0.8754	0.1247
60-69	0.8278	0.9452	0.0550	0.5420	0.9402	0.0600	0.9211	0.8878	0.1124

2.2.3 Treatment and Prediction of Survival

Because treatment options vary with a patient's tumor characteristics at diagnosis, the cost of treatment is different according to disease stage at diagnosis. For patients diagnosed with breast cancer, we record their simulated tumor size and age at time of

diagnosis. A predictive Poisson linear model based on tumor size and age at diagnosis was developed using SEER registry data[53] to predict the number of nodes involved at diagnosis. A truncated Poisson distribution was then used to constrain the number of nodes involved in a screen-detected case to be less than or equal to that of the same case at the expected time of clinical manifestation.

Given tumor size and number of nodes, stage of disease was determined using the tumor-node-metastasis staging system[68]. Patients with positive nodal involvement were considered to have metastatic disease (stage III/IV) if their tumor had a diameter greater than 5 cm at diagnosis; otherwise they were considered to have stage IIB cancer if their tumor diameter was less than 5 cm. Patients with node-negative tumors were considered to have stage I or IIA disease if the tumor diameter was less than or equal to 2 cm, or greater than 2 cm, respectively.

According to treatment guidelines, patients with stage I to IIIA breast cancer should receive breast conserving surgery (BCS) or mastectomy with or without radiation. We simulated surgery and radiation procedures according to recent studies, given disease stage at diagnosis [69, 70]. Administration of tamoxifen, chemotherapy, or a combination of the two was simulated in accordance with observed U.S. dissemination patterns based on age, stage of disease, and ER status at diagnosis[52]. Due to limited knowledge of the connection of ER status with other risk factors, ER status is simulated independently, allowing about 70% of the tumors to be ER positive, according to the general population[71].

Treatment	Age < 50	Age 50-59	Age ≥ 60
Tamoxifen			
ER pos	0.28	0.28	0.28
ER neg	0	0	0
Chemotherapy	0.27	0.14	0.08
Tamoxifen+Chemo			
ER pos	0.47	0.38	0.34
ER neg	0.27	0.14	0.08

Table 2.4 : Reduction in mortality hazard ratio due to treatment effects.

Treatment type	Months 1-6	Months 7-12	Year 2	Years 3-5	Remainder
No treatment	1	1	1	1	1
Tamoxifen	0.99	0.99	0.99	0.99	1
Chemotherapy	0.60	0.90	0.99	0.99	0.99
Tamoxifen+Chemo	0.99*0.60	0.99*0.90	0.99*0.99	0.99*0.99	0.99

Table 2.5 : Quality-of-life adjustment factors used in analysis based on treatment.

To estimate survival, measured from the time of diagnosis, we used a Cox regression model on age, ER status, primary tumor size, and number of nodes at diagnosis. We estimated covariate coefficients ($\exp(\beta_{age}) = 1.008$, $\exp(\beta_{ER}) = 0.669$, $\exp(\beta_{tvol}) = 1.063$, $\exp(\beta_{nodes}) = 1.038$) in the predictive survival model based on a combined analysis of four Cancer and Leukemia Group B trials[6, 49, 51, 50]. We used hazard reduction estimates due to treatment effects[52] and quality of life adjustments according to the type of adjuvant treatment[72, 54], listed in Tables 2.4 and 2.5.

The woman may die from breast cancer or from other competing causes, where death from other causes is based on actuarial tables using a 1960 birth cohort from the census database[53]. If her estimated breast cancer survival time is shorter than her simulated natural lifetime, then she is assumed to die from breast cancer. Otherwise, she dies from other competing risks. In addition, any woman who never enters the clinical stage is assumed to die from other causes.

2.2.4 Costs

Total medical costs (Table 2.6) included costs of mammography and clinical breast exam, diagnostic mammography, biopsy, and treatments. The cost of biopsy was a weighted average of costs of common biopsy procedures[46]. We included costs of primary surgery (BCS or mastectomy with or without radiation), and adjuvant chemotherapy and/or tamoxifen as part of the initial phase of care, followed by con-

Table 2.6 : Direct costs due to breast cancer screening, diagnosis (work-up and biopsy), and treatment according to stage and type of surgery (year 2004 dollars). The initial phase of care includes any adjuvant chemotherapy.

Cost Components		**Cost ($)**			**Ref.**
Screening-related Costs					
Mammography (bilateral)		83			[46]
Clinical Breast Exam		47			[47]
Diagnostic Mammography (Unilateral)		78			[46]
Breast Biopsy		832			[46]
Treatment-related Costs					
Tamoxifen/5yr.		7,553			[27]
Adjuvant Chemotherapy/1yr. (initial phase)		5,618			[27]
Monthly Costs by Phase and Stage					[27]
Treatment Phase	BCS	BCS +rad.	Mast.	Mast. +rad.	
Initial Phase					
I	1,611	2,688	2,228	3,228	
II	2,636	3,088	2,895	3,895	
III/IV	-	3,391	3,119	4,119	
Continuing-Care Phase					
I	287	185	250	250	
II	344	197	252	252	
III/IV	-	681	233	233	
Terminal Phase (BC death)					
I	3,904	3,071	3,945	3,945	
II	2,936	3,810	3,247	3,247	
III/IV	-	3,773	3,315	3,315	
Monthly Terminal Phase Costs (non-BC)		2,775			[73]

Ref = reference number corresponding to cost estimate;BCS = breast conserving surgery; Mast. = mastectomy; +rad. = (a primary treatment) plus radiation therapy; BC = breast cancer

tinuing care, and terminal phase care[27]. The initial phase included the first twelve months after diagnosis, and the terminal phase covered the last twelve months before death. The continuing-care phase included the duration between the end of the initial phase and beginning of the terminal phase, or a maximum of 25 years if the woman dies from competing risks. We included indirect costs from lost productive time through lost wages by age[48] for women who die prematurely from breast cancer. We converted all costs to year 2004 U.S. dollars using the medical care component of the Consumer Price Index[74].

2.2.5 Incremental Cost-Effectiveness Analysis

We used an incremental analysis to reflect the relative cost-effectiveness of the screening strategies among one another. This method allows us to assess the cost of using one strategy in preference to another. Screening strategies were rank-ordered by increasing cost, and we used simple dominance to rule out strategies that are more costly but less effective than an alternative. The incremental cost-effectiveness ratio (ICER) was calculated for each strategy by dividing the difference in cost by the difference in benefit compared with the next least-expensive strategy. Strategies with lower effectiveness and higher ICER were ruled out by extended dominance and the ICER was recalculated after their elimination[56]. ICERs for the strategies not ruled out by dominance (efficient or cost-effective strategies) are interpreted as the ratio of additional cost per QALY saved compared to the next least-expensive alternative.

2.2.6 Sensitivity Analysis

We conducted two 1-way sensitivity analyses. Because average sensitivity and specificity values for community-based clinical breast exam may be different from estimates obtained in randomized clinical trials, we used a lower sensitivity of 0.276 and a higher specificity of 0.994, according to community-based estimates[44]. In a separate sensitivity analysis, we predicted survival using age- and stage-specific estimates calculated from the SEER database, which have been used in the Cancer Intervention and Surveillance Modeling Network models[75]. In contrast to the original model, detailed tumor characteristics do not individually contribute to the survival estimate.

2.3 Results

The results (Table 2.7) showed that although every screening strategy extended life expectancy compared to no screening, some were more efficient with a lower cost per QALY saved than the alternatives: strategies B, D, G, I, and J, in order of increasing expense. Among them, biennial mammography and clinical breast exam in alternating years from ages 40-79 (B) saved about 13 days of life for an additional $1,200, equivalent to $32,700 to save a year of life compared to no screening. The next cost-effective alternative was strategy D, with biennial mammography and annual clinical breast exam from ages 40-79, which saved 1.5 additional days of life for $500, compared to strategy B. By replacing biennial with annual clinical breast exam in strategy B, it costs $99,500 to save an additional year of life compared to strategy

B. The most expensive strategy J saved only a half day for an additional $5,500 compared to strategy I, with a very high ICER of over $3.8 million per QALY saved. Other strategies were eliminated by simple or extended dominance because of their inefficiency.

The tradeoff between total costs and expected QALYs for each screening strategy is visualized in a tradeoff plot (Figure 2.2), corresponding to the results in Table 2.7. Dominated strategies fall below the line connecting the non-dominated alternatives, representing the efficiency frontier. The most expensive (and effective) strategy J, on the upper right corner of the efficiency frontier, is the current recommendation from the ACS. Compared to the alternatives, the gain in QALYs is small considering the large cost difference.

In a separate plot (Figure 2.3), we show the standard errors of the mean gain in QALY and mean total cost difference compared to no screening. Although strategies F and H do not directly fall on the line of efficiency, their standard errors indicate that they may still be cost-effective in spite of the small absolute deviation from the efficiency frontier.

Sensitivity Analysis

When alternative sensitivity and specificity values were used for clinical breast exam, the results showed lower overall gains in QALYs and costs compared to the original analysis (Table 2.8). These changes may be explained by a delay in disease detection

Table 2.7 : Results of cost-effectiveness analysis including screening, biopsy, and treatment costs. Costs and QALYs are discounted at 3%. Strategies that are dominated or eliminated through extended dominance are indicated with '—'.

Strat	MM intv(age)	CBE intv(age)	Total Cost ($)	QALYs (years)	Incremental QALYs gained	ICER
X	—	—	13,100	27.3936		
A	**2(40-79)**	**2(40-79)**	14,300	27.4254	—	—
B	2(40-79)	2(41-79)	14,300	27.4306	0.0370	32,700
C	**1(40-79)**		14,600	27.4316	—	—
D	2(40-79)	1(40-79)	14,700	27.4346	0.0040	99,500
E	1(40-49), 2(50-79)	1(40-79)	15,000	27.4350	—	—
F	1(40-59), 2(60-79)	1(40-79)	15,200	27.4364	—	—
G	2(40-49), 1(50-79)	1(40-79)	15,200	27.4368	0.0022	197,900
H	1(40-69), 2(70-79)	1(40-79)	15,300	27.4371	—	—
I	**1(40-79)**	**1(40-79)**	15,400	27.4376	0.0007	330,000
J	**1(40-79)**	**3(20-39)** **1(40-79)**	20,900	27.4390	0.0014	3,839,800

MM=Mammography; CBE=Clinical breast exam; intv=interval between examinations (years)

Total Cost: Mean total cost per woman in the complete cohort, rounded to the nearest $100

QALYs: Mean total expected quality-adjusted life years per woman from age 20

ICER: Incremental cost-effectiveness ratio (incremental cost/incremental QALYs gained compared to next least-expensive strategy)

Current recommended strategies are shown in boldface: A=NCI/USPSTF; C=NCI; I=NCI/USPSTF; J=ACS

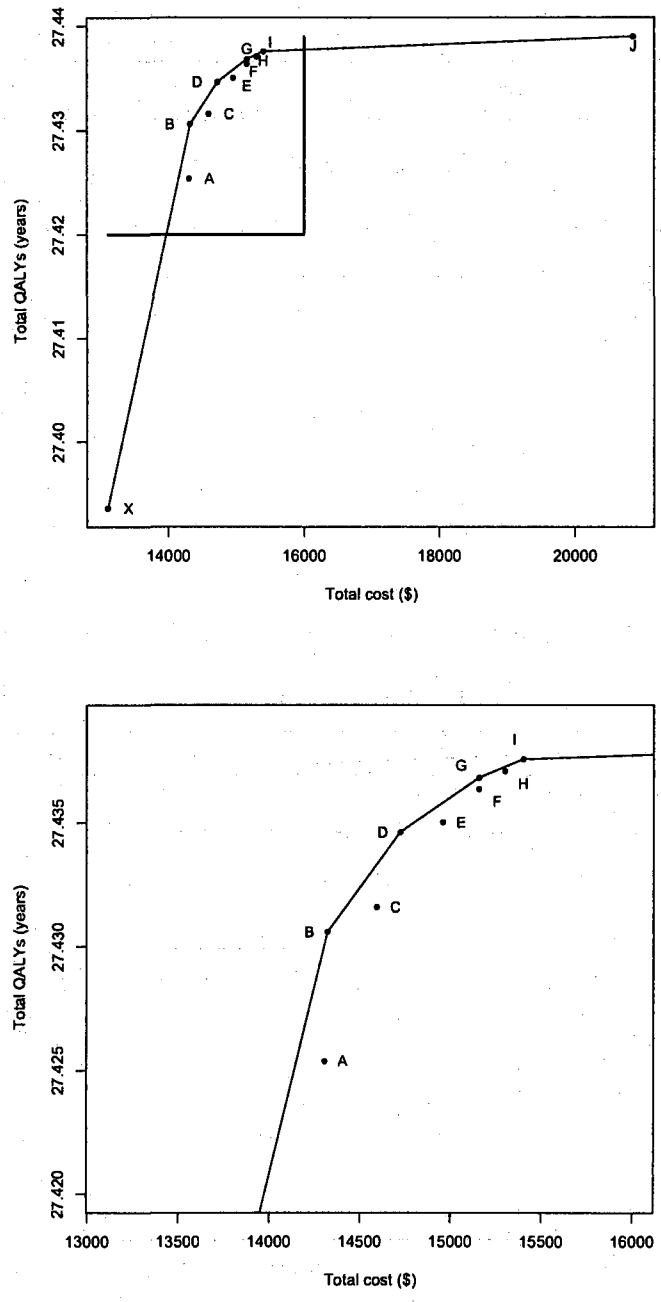


Figure 2.2 : Tradeoff plot for strategies A-J (left) and excluding strategy J (right). X-axis is mean total cost in U.S. dollars. Y-axis is mean quality-adjusted life-years. Dominated strategies (A, C, E, F, H) fall below the line of efficiency connecting the non-dominated alternatives (B, D, G, I, J). The plot on the bottom allows better visualization of strategies A-I.

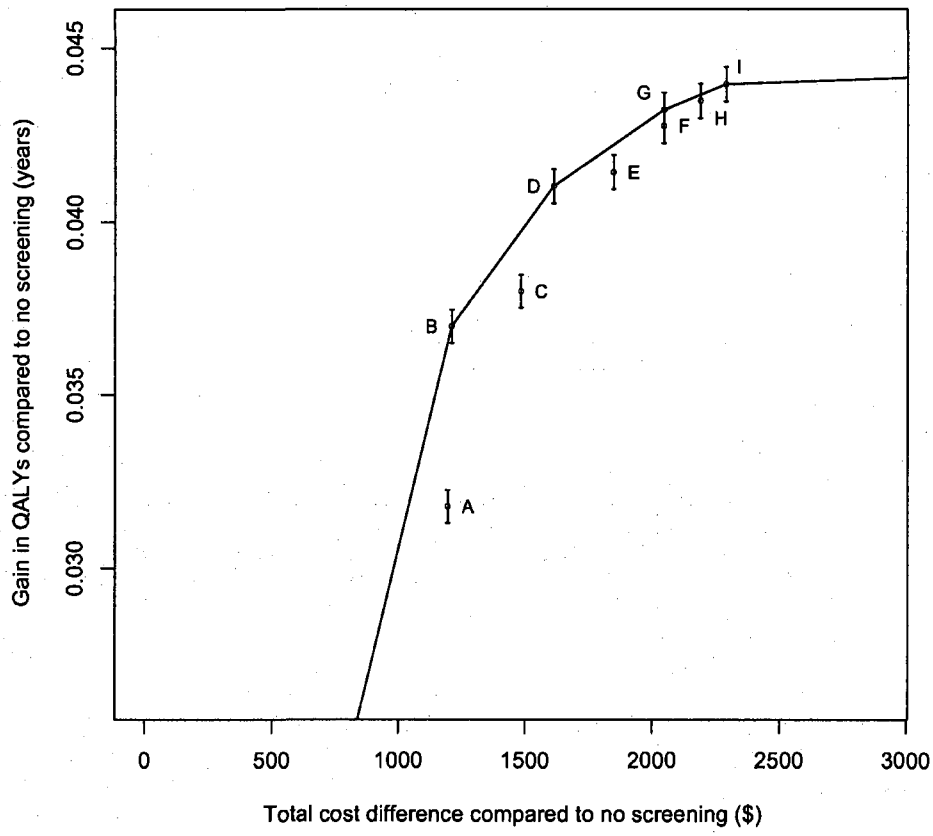


Figure 2.3 : Tradeoff plot for strategies A-I, including standard error bars for the mean gain in QALYs (vertical) and mean total cost difference (horizontal endpoints) compared to no screening. X-axis is mean total cost difference in U.S. dollars. Y-axis is mean gain in quality-adjusted life-years compared to no screening.

caused by the lower exam sensitivity, which leads to shorter survival. The reduction in medical costs is a result of fewer unnecessary work-ups and biopsy procedures due to the higher specificity. It is not surprising that strategy C, which does not use clinical breast exam and was not cost-effective before, became more cost-effective, since using clinical breast exam as a complement to mammography is less effective when the sensitivity of clinical breast exam is low. The higher frequency of mammography becomes more important in strategies complemented by clinical breast exam, which explains why strategies D and G, which were cost-effective in the original analysis, become dominated.

Under the alternative survival model, the gain in QALYs compared to no screening appears smaller than that in the original analysis. Because disease stages do not capture detailed tumor characteristics, this model may not predict survival as accurately as the original model, which may explain the observed difference in survival. It is likely for a woman to be defined in the same disease stage at screening and clinical detection, despite any progression in tumor size or nodal status, making the survival estimates in both cases more similar. Compared to the original analysis, strategies C and H shifted and became cost-effective, while strategies G and I were not. This may be explained by the underestimation of survival which may cause those strategies giving mammography alone (C) or with less frequent screening (H) to become more comparable to strategies using both mammography and clinical breast exam (G) or that have more frequent screening (I).

Table 2.8 : Results of sensitivity analyses assuming lower sensitivity and higher specificity for clinical breast exam, and assuming an alternative treatment distribution. Costs and QALYs are discounted at 3%. Strategies that are dominated or eliminated through extended dominance are indicated with '—'.

			Assuming lower sensitivity and higher specificity for CBE				Assuming alternative survival model			
Strat	MM intv (age)	CBE intv (age)	Total Cost ($)	QALYs (years)	Incremental QALYs gained	ICER	Total Cost ($)	QALYs (years)	Incremental QALYs gained	ICER
X	—	—	13,100	27.3931			13,000	27.4140		
A	**2(40-79)**	**2(40-79)**	14,300	27.4234	—	—	14,200	27.4378	—	—
B	2(40-79)	2(41-79)	14,300	27.4253	0.0322	35,400	14,200	27.4401	0.0261	47,000
C	**1(40-79)**		14,600	27.4315	0.0062	54,100	14,500	27.4426	0.0025	110,900
D	2(40-79)	1(40-79)	14,600	27.4272	—	—	14,600	27.4425	—	—
E	1(40-49), 2(50-79)	1(40-79)	14,800	27.4300	—	—	14,800	27.4425	—	—
F	1(40-59), 2(60-79)	1(40-79)	15,000	27.4324	—	—	15,000	27.4432	—	—
G	2(40-49), 1(50-79)	1(40-79)	15,000	27.4327	—	—	15,000	27.4440	—	—
H	1(40-69), 2(70-79)	1(40-79)	15,200	27.4341	—	—	15,200	27.4448	0.0022	321,700
I	**1(40-79)**	**1(40-79)**	15,300	27.4346	0.0031	219,700	15,300	27.4444	—	—
J	**1(40-79)**	**3(20-39) 1(40-79)**	20,700	27.4359	0.0013	4,234,900	20,700	27.4454	0.0007	8,531,100

MM=Mammography; CBE=Clinical breast exam; intv=time interval between examinations (in years)
Total Cost: Mean total cost per woman in the complete cohort, rounded to the nearest $100
QALYs: Mean total expected quality-adjusted life years per woman from age 20 in the complete cohort
ICER: Incremental cost-effectiveness ratio (incremental cost/incremental QALYs gained compared to next least-expensive strategy)
Current recommended strategies are shown in boldface: A=NCI/USPSTF; C=NCI; I=NCI/USPSTF; J=ACS

2.4 Discussion

This study is the first to comprehensively evaluate the cost-effectiveness of the combined use of mammography with clinical breast exam in breast cancer early detection while accounting for costs of screening, work-up, biopsies due to true or false-positive examinations, and treatments. We assessed current recommended guidelines from three major cancer organizations and compared them with other realistic strategies that combine mammography and clinical breast exam with different starting ages and intervals.

Compared to the alternatives, two of the recommended strategies are cost-effective in general: the NCI/USPSTF recommendation of annual mammography and clinical breast exam from ages 40-79, and the most effective but expensive recommendation from the ACS that begins clinical breast exam at age 20, followed by mammography and clinical breast exam from ages 40-79. The NCI/USPSTF recommendation of annual mammography alone from ages 40 to 79 is cost-effective when the sensitivity of clinical breast exam is low, according to community-based settings. The NCI/USPSTF guideline of mammography with clinical breast exam every two years was not an efficient strategy. A more cost-effective alternative is to provide mammography and clinical breast exam in alternating years, which leads to more savings in QALYs with similar costs. Alternating exam years allows for annual examinations with one of the two screening modalities.

The strategy recommended by the ACS was the most expensive and effective. If

society is willing to pay the required costs to save an additional QALY, this strategy is favorable. Alternatively, the cheapest but also effective alternative would be to offer biennial mammography and clinical breast exam alternatively from ages 40-79 (strategy B).

Among all the strategies, only strategy B fell under the commonly accepted cost-effectiveness threshold of $50,000/QALY[76, 36]. Although this strategy is not as life saving as some other alternatives, the gains in QALYs for the other efficient strategies D, G, I, and J, are not very large in comparison (1.5, 2.3, 2.5, or 3.1 days compared to strategy B), with extra costs of $400, $900, $1,100, or $6,600 compared to strategy B. Compared to B, strategy J costs over $778,000 for an added QALY. The large cost difference is explained by the early accumulation of costs and discounting beginning at age 20. Under realistic monetary constraints, we must consider this large added expense when cheaper but still effective strategies exist. This issue is debatable for ethical reasons and depends on how much society is willing to pay to save an additional year of quality-adjusted life.

Our model does not make any assumptions on the efficacy of clinical breast exam on mortality reduction, but relies on estimates of its sensitivity and specificity. The role of clinical breast exam in combination with mammography depends on these estimates. The sensitivity analyses showed that higher specificity for clinical breast exam leads to lower patient recall rates, which decreases unnecessary work-ups and biopsies. However, the lower sensitivity of clinical breast exam increases the false-

negative rate and delays diagnosis. The performance of screening exams affects the timing of diagnosis, recall rate, and intensity of treatment, which all affect overall costs and survival. The choice of survival model also has significant impact on the results. In a survival model where small changes in tumor size or nodal status have little effect on survival, differences in years gained due to screening may be small. Regardless of these changes in model assumptions, only two strategies remained more effective for a lower cost per QALY saved compared to the alternatives: 1) B: biennial mammography and clinical breast exam in alternating years from ages 40-79, and 2) J: the most expensive strategy of screening beginning at age 20.

There are several limitations to our study. First, we considered average medical costs as constants and did not take into account the variation across institutions. However, we believe our cost inputs are sufficient for this comparative analysis. Second, the surgery pattern used may not represent the general population. However, it has been shown that long-term costs for mastectomy and BCS are not notably different[70]. Third, the treatment options do not include recent changes such as third-generation endocrine therapies and axillary or sentinel lymph node dissection, because these treatment patterns for the general population were not available in the literature. This study also excluded the detection of ductal carcinoma in-situ cases which may lead to overdiagnosis, and repeat mammography within six months after recall, the relevance of which has recently received attention. Other screening and treatment options may be included in a future analysis.

While we considered quality-of-life adjustments due to treatments, our analysis did not account for physical and emotional effects of screening, unnecessary work-ups, or biopsies. It is difficult to assign monetary values to such effects. Finally, our simulation model assumed full compliance of participants in a screening and treatment plan, which allowed us to evaluate the potential effectiveness of a screening program.

In summary, several alternative cost-effective strategies were found to be more efficient than the recommended guidelines, or to have lower costs with minimal loss of benefit. In place of current recommendations, biennial mammography and clinical breast exam in alternating years from ages 40-79 was the cheapest cost-effective alternative. If enough funds are available to add annual clinical breast exams to a screening program, the next cost-effective alternative is to offer biennial mammography and annual clinical breast exam from ages 40-79. Breast cancer screening strategies with lower costs and benefits comparable to those currently recommended should be considered for implementation in practice and for future guidelines.

Chapter 3

Microsimulation Model: High Risk Cohort

3.1 Background

The average lifetime risk of breast cancer for a woman in the United States is one in seven[77]. However, women who have a strong family history of breast or ovarian cancer, cancer-predisposing *BRCA* mutations, or other clinical indicators including Hodgkin disease may have an increased-risk. Some changes to normal screening guidelines that may benefit this subset of high-risk women are more frequent examinations, or earlier starting ages of examination such as age 30[78]. Due to the higher breast density of women at younger ages, mammography may not be as effective at an earlier age of screening. Recently the American Cancer Society developed recommendations for women at higher risk of breast cancer[79] to receive magnetic resonance imaging, or MRI, in addition to mammography. However, there is no consensus on the starting age or frequency of MRI.

While MRI has been found to have a higher sensitivity than mammography, reports of its specificity have been lower[80, 81, 82, 83] in high-risk women, resulting in more recalls and biopsies. In addition, MRI is expensive and its administration and interpretation requires more highly trained personnel. The potential survival benefit that the addition of MRI may provide must be weighed against its costs and higher

false-positive rate, which may lead to unnecessary procedures.

The literature for cost-effectiveness studies focusing on women of increased-risk for breast cancer is limited. In one simulation study, the cost-effectiveness of adding MRI to mammography screening for *BRCA1* or *BRCA2* carriers of different age groups was evaluated[46]. The authors found that the cost-effectiveness of adding MRI to mammography screening varied by age and was better in *BRCA1* carriers. Another observational study, conducted in the UK[84], also found that MRI might be cost-effective in high-risk women, especially in *BRCA1* and *BRCA2* carriers.

In the present study we conduct a cost-effectiveness analysis on a defined cohort of women with high-risk for breast cancer using simulation. We assess the cost-effectiveness of 28 screening strategies of different combinations of mammography and clinical breast exam, with or without MRI, with different starting ages and intervals between exams (Table 3.1). Included in these strategies are the current recommended guidelines for the general population and the cheapest cost-effective alternative for the general population. While many of the modeling assumptions in the microsimulation model are identical to those from Chapter 2, some changes were necessary in order to account for the differences in age-specific incidence, exam sensitivity and specificity, and tumor characteristics that are specific to women at higher risk for breast cancer. The details of the model are described below.

Table 3.1 : Screening strategies investigated for the high-risk cohort.

	MM intv(age)	CBE intv(age)	MRI intv(age)		MM intv(age)	CBE intv(age)	MRI intv(age)
1	2(40-79)			15	1(30-79)	1(30-79)	
2	1(40-79)			16	1(30-79)	1(30-79)	1(30-79)
3	2(40-79)	2(40-79)		17	1(30-79)	1(30-79)	2(30-79)
4	1(40-79)	1(40-79)		18	2(30-79)	0.5(30-79)	
5	2(40-79)	2(41-79)		19	2(30-79)	0.5(30-79)	1(30-79)
6	1(40-79)	3(20-39),1(40-79)		20	2(30-79)	0.5(30-79)	2(30-79)
7	0.5(40-79)			21	2(30-79)	1(30-79)	
8	0.5(40-79)	0.5(40-79)		22	2(30-79)	1(30-79)	1(30-79)
9	0.5(30-79)	0.5(30-79)		23	2(30-79)	1(30-79)	2(30-79)
10	0.5(30-79)	0.5(30-79)	1(30-79)	24	2(30-79)	2(30-79)	
11	0.5(30-79)	0.5(30-79)	2(30-79)	25	2(30-79)	2(30-79)	1(30-79)
12	1(30-79)	0.5(30-79)		26	2(30-79)	2(30-79)	2(30-79)
13	1(30-79)	0.5(30-79)	1(30-79)	27	1(30-79)	1(30-79)	1(30.5-79)
14	1(30-79)	0.5(30-79)	2(30-79)	28	2(30-79)	2(30-79)	2(31-79)

MM=Mammography; CBE=Clinical Breast Exam; MRI=Magnetic Resonance Imaging;intv=interval between exams; age=age range
Strategies 1-4, 6: Current recommended strategies for the general population; Strategy 5: most cost-effective strategy in the general population (see Chapter 2)

Model Components	Data Inputs	References
Natural History	Age-Specific Incidence*	[85]
	Age-Specific Pre-clinical Transition*	[6, 39]
	Sojourn Time Distributions*	[86, 40]
	Tumor Growth Distributions	[41]
Screening Impacts	Mammography Sensitivity (by age and tumor size)*	[80]
	Mammography Specificity (by age)*	[80]
	Clinical Breast Exam Sensitivity, Specificity*	[80]
	Magnetic Resonance Imaging Sensitivity, Specificity*	[80]
	Diagnostic Mammography Sensitivity, Specificity	[45]
Costs Related to Screening, Workup, and Treatment	Mammography and Clinical Breast Exam	[46, 47]
	Magnetic Resonance Imaging*	[46]
	Diagnostic Mammography	[46]
	Breast Biopsy	[46]
	Treatment by Stage	[27]
Indirect Costs	Lost Productive Time (lost wages)	[48]
Survival Models	By Age, Tumor Size, Nodal Status at Diagnosis, ER status, and Treatment	[6, 49, 50, 51] [52]
	Competing Risks by Age	[53]
	Quality of Life Adjustments by Treatment	[6, 54]

*= New or adjusted data inputs.

Table 3.2 : Model components and data inputs for high-risk analysis.

3.2 Model and Data Inputs

Certain factors associated with the level of breast cancer risk must be modified from the original average-risk cohort analysis in Chapter 2 to reflect the screening and tumor characteristics of women with a high-risk for breast cancer. These factors include the age-specific incidence, mean sojourn time or tumor growth rate, and the sensitivity and specificity of mammography, clinical breast exam, and MRI. We describe each of these new factors below, with specific data inputs and references found in Table 3.2.

3.2.1 Age-Specific Incidence

Because age-specific incidence estimates among high-risk women are not readily available, we estimated these values based on existing breast cancer risk assessment tools. There are several breast cancer risk assessment tools that have been developed, including the Gail[87], Claus[88], Tyrer[89], and BRCAPRO[90, 91, 92] models. Contrary to the others, the Gail model uses both hereditary and non-hereditary risk factors, and does not directly incorporate genotype information. The other models have an emphasis on genetic risk factors or require substantial pedigree information. Because our study does not focus on genetic risk, but rather a general increase in risk due to both genetic and non-genetic factors, we chose to use the Gail model in our analysis.

We used the Gail model as a template to obtain age-specific risk and thus age-specific incidence values, assuming certain medical, reproductive, and family history risk factors of age at menarche, age at first live birth, number of previous biopsies, and number of first-degree relatives with breast cancer. Using an online breast cancer risk assessment tool from the NCI based on the Gail model[85], we obtained 5-year and lifetime (up to age 90) risks assuming the following characteristics:

- Age at menarche: 7-11
- Age at first live birth: ≥ 30
- Number of previous biopsies: ≥ 1
- Number of first-degree relatives with breast cancer: > 1

These selected characteristics will yield a a more elevated risk for breast cancer than if milder characteristics (such as higher age of menarche or no previous live births) were chosen. The resulting lifetime risks ranged between about 25% to 50% for women ages 40 to 80. According to the ACS, annual MRI is recommended if a woman's lifetime risk is about 20-25% or more, but there is insufficient evidence to recommend MRI screening in women with lifetime risk of less than 20%[79].

For each group we calculated age-specific incidence rates from the computed hazard rates, where the incidence values ranged from about 0.6% to 2.5% for ages 30-79. Compared to the age-specific incidence rates used in Chapter 2 for the general population, the resulting age-specific incidence rates were about 10 times higher than the original values for our so-called high-risk group.

3.2.2 Tumor Characteristics

Women with increased-risk for breast cancer may experience faster tumor growth. Because of the likely shorter duration of the time spent in the preclinical state, we used shorter mean sojourn times of 1.0 years for women ≤ 50 and 1.9 years for women > 50 [86]. This shorter preclinical sojourn time accounts for the faster tumor growth.

3.2.3 Screening Impacts

The sensitivity and specificity of mammography and clinical breast exam differ between the general population and women with high-risk for breast cancer. Sensitivities have been shown to be lower in the subset of high-risk women, and specificities have

been shown to be higher for both screening modalities[80]. The lower sensitivities may be partially explained by the higher breast density of high-risk women who receive screening at a younger age, which contributes to difficult interpretation of the exams. Again, we assume age- and tumor size- specific sensitivity ($\beta_1(40,1) = 0.40$, $\beta_1(60,1) = 0.60$, $\beta_1(40,0.05) = 0.05$) and age-specific specificity ($\delta_1(40) = 0.95$, $\delta_1(60) = 0.98$) for mammography, and constant sensitivity ($\beta_2 = 0.178$) and specificity ($\delta_2 = 0.981$) for clinical breast exam reported in Kriege *et al.* (2004)[80]. Uncertainty is accounted for using a beta distribution for each sensitivity, where the parameters of the distribution are determined in a manner identical to that used for the general population in Chapter 2, where the effective sample sizes are $s_{MM} = 30$ and $s_{CBE} = 40$.

For MRI, we assume the specificity is constant ($\delta_3 = 0.90$), and the sensitivity is tumor-size specific, where the sensitivity is higher than that of mammography at the same tumor size ($\beta_3(0.05) = 0.25$, $\beta_3(1) = 0.71$) [80]. As before, we also add uncertainty for this exam, using $s_{MRI} = 30$. It is assumed that all three examination modalities work independently of each other in detecting breast cancer. A logit model is again used to model the age or tumor-size dependencies.

3.2.4 Costs

We have now added the cost of $996 for bilateral MRI[46] (2004 dollars), while all other costs remain the same as in Chapter 2.

3.2.5 Sensitivity Analysis

To assess how sensitive our model assumptions are to changes in the sensitivities of mammography and MRI, we used higher sensitivity estimates for mammography or clinical breast exam, according to the general population, using the same estimates from Chapter 2 [42, 44]. We also used milder characteristics from the GAIL model to generate lower lifetime risks ranging from about 7% to 17% and age-specific incidence values that ranged from about 0.06% to 0.8% for ages 30-79, which may still represent a cohort of higher risk relative to the general population (about 2.5 times higher than the original incidence values used for the general population in Chapter 2).

3.3 Results

The results in Table 3.3 show that every evaluated screening strategy extended life expectancy compared to no screening, but only a few strategies were more cost-effective compared to the alternatives. Other strategies were eliminated by simple or extended dominance.

For the high-risk cohort, strategies A, D, I, N, and b had lower costs per QALY saved than the alternatives. Strategies A, D, and I gave mammography alone every 2, 1, and 0.5 years, respectively, beginning at age 40. Strategy A saved about 5 days of life compared to no screening, costing $45,600 per QALY saved. Strategy D gained 3 days compared to strategy A, and strategy I gained 4 days compared to strategy D, costing an additional $99,300 per QALY compared to strategy D. Strategy N,

which gave mammography and clinical breast exam every six months from ages 30-79, cost an additional $228,700 per QALY saved compared to strategy I. Strategy b gave mammography and clinical breast exam every six months with the addition of MRI every year. Adding annual MRI resulted in 3 days gained compared to strategy N. This strategy which includes annual MRI is very expensive, costing more than $2 million to save one QALY compared to strategy N, the next cheapest cost-effective alternative.

The tradeoff plot for the high-risk cohort is found in Figure 3.1, corresponding to Table 3.3. Note that the strategies appear to be clustered into three groups, depending on whether or not the strategy uses MRI, and whether MRI is annual or biennial. Overall the dominated strategies fall below the line connecting the non-dominated alternatives. It is clear from both plots that there is a large tradeoff in costs to achieve a small gain in survival benefit as the efficiency frontier is followed upward.

We display the standard errors of the cost difference and gain in QALYs compared to no screening in Figure 3.2 (for total cost difference less than $7,000), Figure 3.3 (for total cost difference between $7,000 and $17,000), and Figure 3.4 (for total cost difference greater than $17,000). Based on the standard errors, it is clear that strategy V, which offers mammography and clinical breast exam every six months and MRI every two years from ages 30-79 may still be an efficient strategy and should not be ruled out from the efficiency frontier. All other strategies appear to fall significantly

Table 3.3 : Results of cost-effectiveness analysis in a high-risk cohort. Costs and QALYs are discounted at 3%. Strategies that are dominated or eliminated through extended dominance are indicated with '—'.

Strat	MM intv(age)	CBE intv(age)	MRI intv(age)	Total Cost ($)	QALYs (years)	Increm. QALYs gained	ICER
*	—	—	—	14,700	27.2381		
A	2(40-79)			15,300	27.2514	0.0134	45,600
B	2(40-79)	2(41-79)		15,600	27.2543	—	—
C	2(40-79)	2(40-79)		15,600	27.2535	—	—
D	1(40-79)			15,800	27.2585	0.0071	71,200
E	2(30-79)	2(30-79)		16,000	27.2559	—	—
G	2(30-79)	1(30-79)		16,400	27.2597	—	—
F	1(40-79)	1(40-79)		16,400	27.2617	—	—
H	1(40-79)	3(20-39), 1(40-79)		16,500	27.2633	—	—
I	0.5(40-79)			16,800	27.2684	0.0099	99,300
J	1(30-79)	1(30-79)		17,100	27.2669	—	—
K	2(30-79)	0.5(30-79)		17,200	27.2663	—	—
L	0.5(40-79)	0.5(40-79)		17,900	27.2718	—	—
M	1(30-79)	0.5(30-79)		18,000	27.2718	—	—
N	0.5(30-79)	0.5(30-79)		19,500	27.2801	0.0118	228,700
O	2(30-79)	2(30-79)	2(31-79)	24,500	27.2696	—	—
P	2(30-79)	2(30-79)	2(30-79)	24,900	27.2645	—	—
Q	2(30-79)	1(30-79)	2(30-79)	25,300	27.2668	—	—
R	1(30-79)	1(30-79)	2(30-79)	26,000	27.2729	—	—
S	2(30-79)	0.5(30-79)	2(30-79)	26,100	27.2716	—	—
T	1(30-79)	0.5(30-79)	2(30-79)	26,900	27.2767	—	—
U	2(30-79)	2(30-79)	1(30-79)	27,200	27.2688	—	—
V	0.5(30-79)	0.5(30-79)	2(30-79)	28,400	27.2840	—	—
W	2(30-79)	1(30-79)	1(30-79)	33,400	27.2763	—	—
X	1(30-79)	1(30-79)	1(30.5-79)	34,500	27.2834	—	—
Y	1(30-79)	1(30-79)	1(30-79)	34,600	27.2775	—	—
Z	2(30-79)	0.5(30-79)	1(30-79)	34,700	27.2794	—	—
a	1(30-79)	0.5(30-79)	1(30-79)	35,500	27.2814	—	—
b	0.5(30-79)	0.5(30-79)	1(30-79)	37,000	27.2881	0.0080	2,195,800

MM=Mammography; CBE=Clinical breast exam; MRI=Magnetic Resonance Imaging; intv=time interval between examinations (in years); age=age range; Increm=incremental
Total Cost: Mean total cost per woman in the complete cohort, rounded to the nearest $100
QALYs: Mean total expected quality-adjusted life years per woman from age 20
ICER: Incremental cost-effectiveness ratio (incremental cost/incremental QALYs gained compared to next least-expensive strategy)

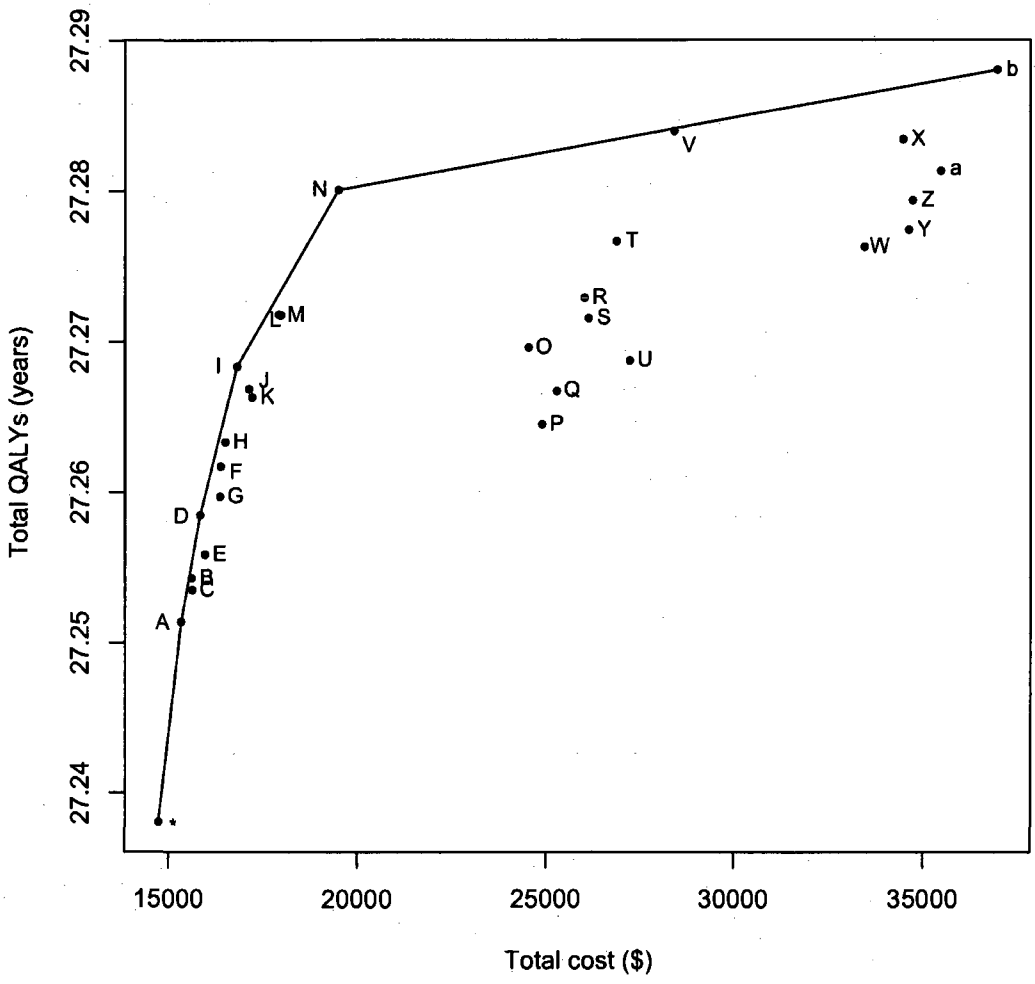


Figure 3.1 : Tradeoff plot for the high-risk cohort. X-axis is mean total cost in U.S. dollars. Y-axis is mean quality-adjusted life-years. Dominated strategies fall below the line of efficiency connecting the non-dominated alternatives (A,D,I,N,b).

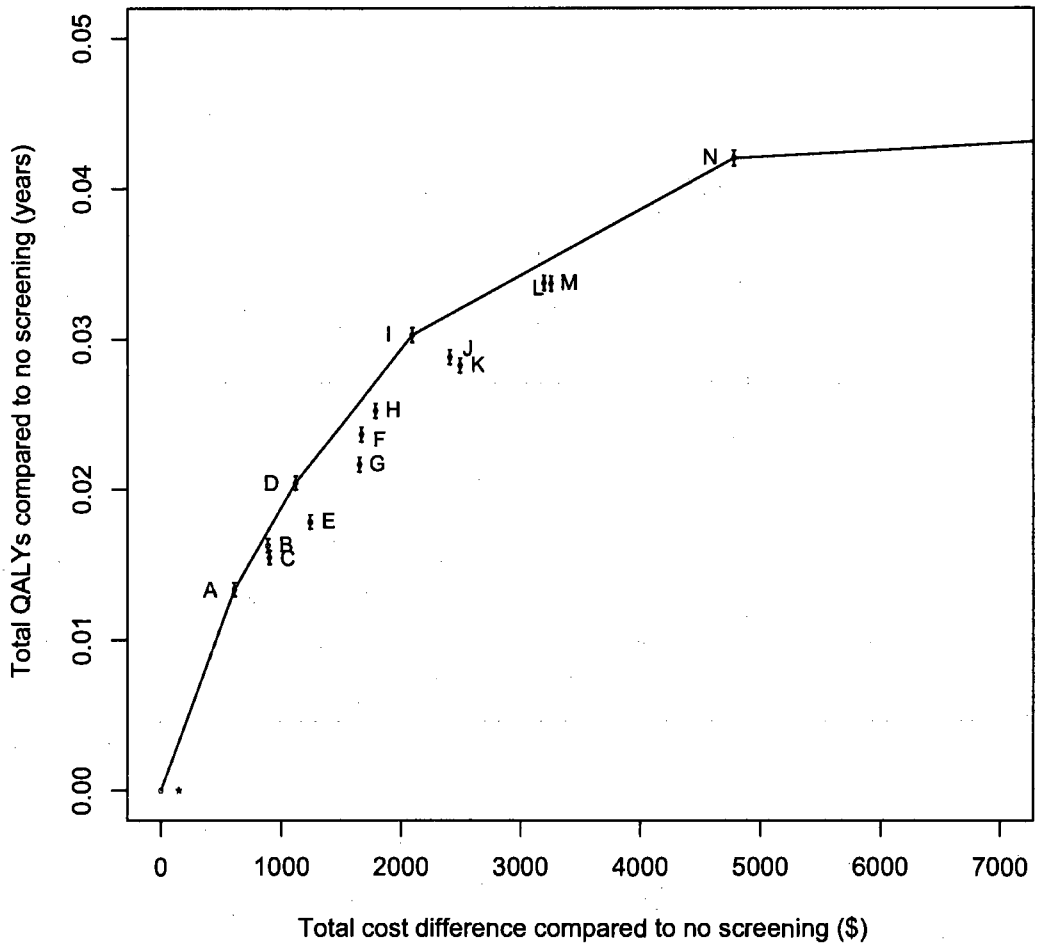


Figure 3.2 : Tradeoff plot of gains in QALY and difference in cost compared to no screening for the high-risk cohort. X-axis is mean total cost difference in U.S. dollars, ranging from $0 to $7,000. Y-axis is mean gain in quality-adjusted life-years. Standard error bars for the mean gain in QALYs (vertical) and mean total cost difference (horizontal endpoints) compared to no screening are shown.

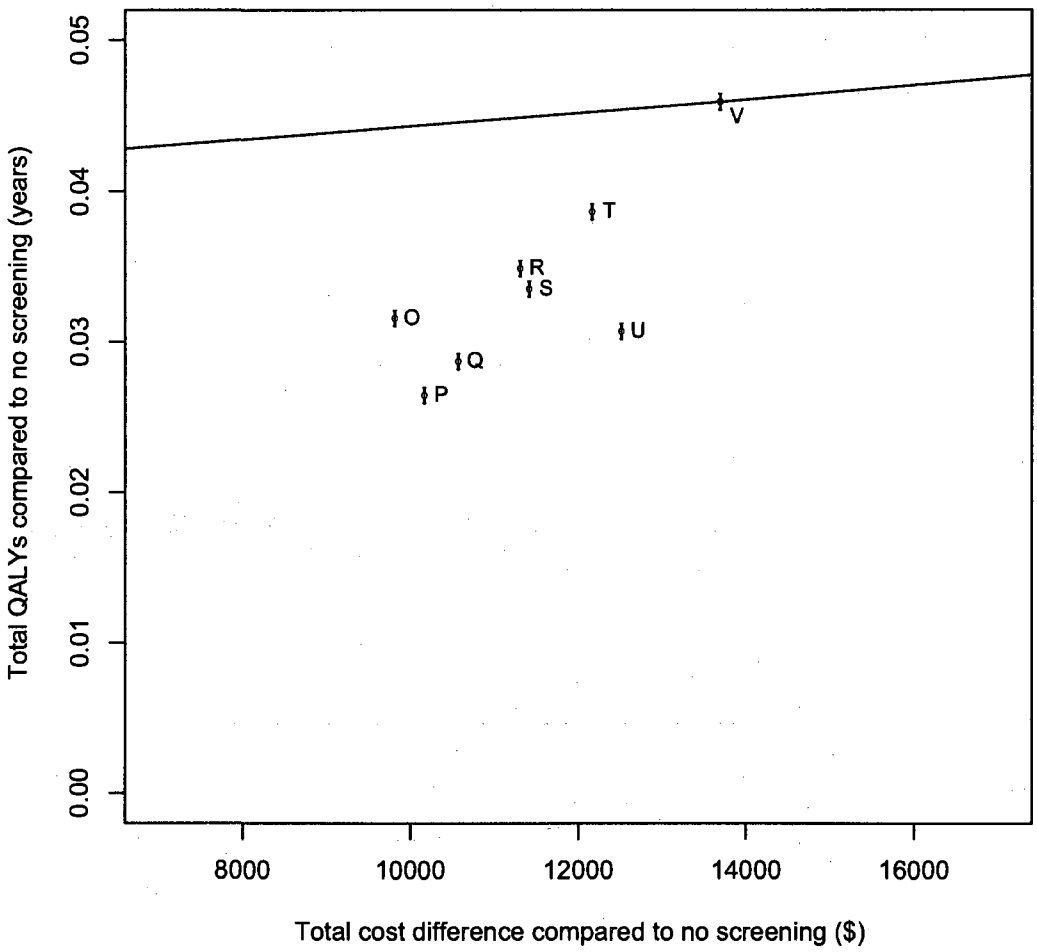


Figure 3.3 : Tradeoff plot of gains in QALY and difference in cost compared to no screening for the high-risk cohort. X-axis is mean total cost difference in U.S. dollars, ranging from $7,000 to $17,000. Y-axis is mean gain in quality-adjusted life-years. Standard error bars for the mean gain in QALYs (vertical) and mean total cost difference (horizontal endpoints) compared to no screening are shown.

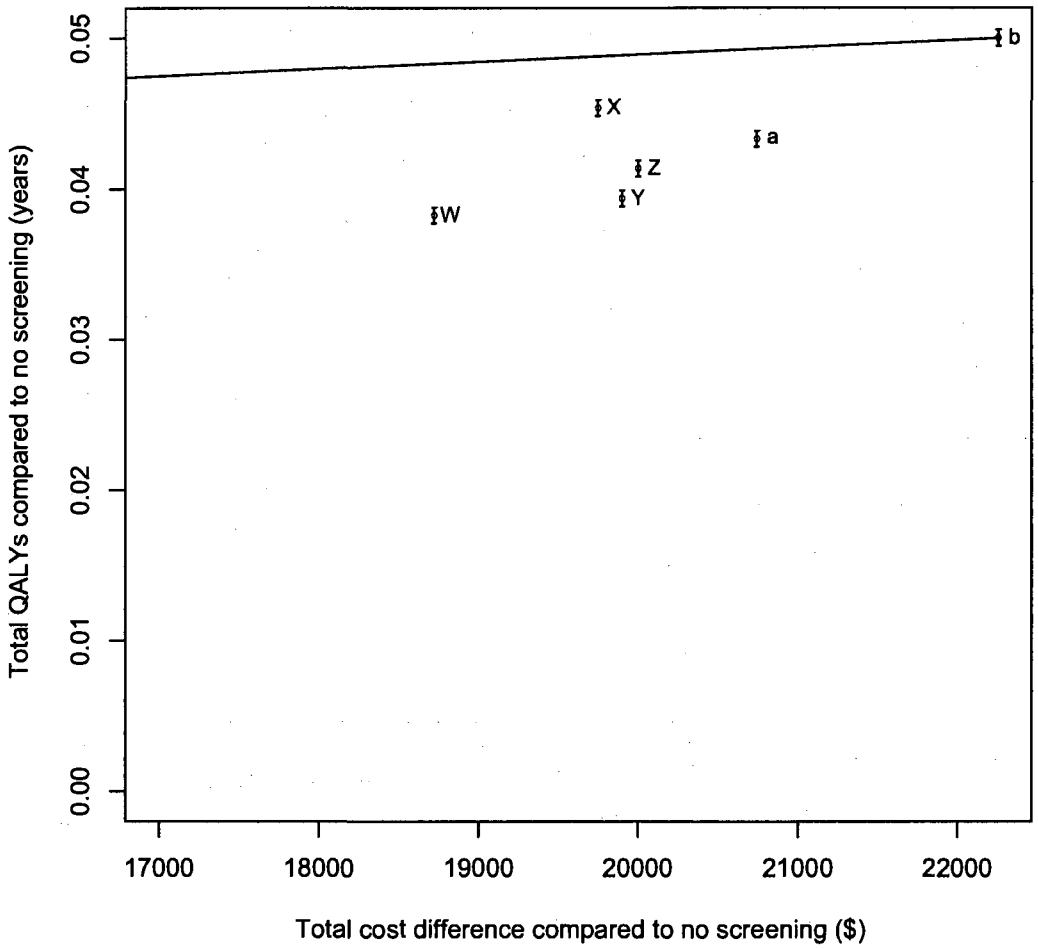


Figure 3.4 : Tradeoff plot of gains in QALY and difference in cost compared to no screening for the high-risk cohort. X-axis is mean total cost difference in U.S. dollars, from $17,000 and greater. Y-axis is mean gain in quality-adjusted life-years. Standard error bars for the mean gain in QALYs (vertical) and mean total cost difference (horizontal endpoints) compared to no screening are shown.

below the line of efficiency.

3.3.1 Sensitivity Analysis

When higher sensitivity values according to the general population are used for clinical breast exam, the results are different. The gain in survival for the strategies is higher compared to the original analysis using lower sensitivity, which may be explained by the clinical breast exam's increased effectiveness. The nondominated strategies become strategies B, G, K, N, V, and b in the high-risk cohort. Strategies B, G, and K reflect strategies which were not cost-effective when the clinical breast exam sensitivity was lower. For instance, strategy B, which offers mammography and clinical breast exam in alternating years from ages 40-79 becomes cost-effective while strategy A, which gives mammography alone biennially from ages 40-79 becomes dominated. Thus the sensitivity of clinical breast exam has a significant impact on the cost-effectiveness of the strategies.

When higher sensitivity values for mammography are used, there is less of an impact on the results. Although the survival gain is slightly higher, the overall results are not that different. We found that the strategies with a lower cost per QALY saved than the alternatives were the same, except strategy V became cost-effective when it was not in the original analysis, which used lower sensitivity for mammography. For this strategy, the higher sensitivity of mammography may make up for its less frequent MRI, making it more efficient than before. However, taking the standard

error into account, this strategy was essentially already an efficient strategy to begin with. The minimal impact of increasing mammography sensitivity may be partly attributed to the assumption that its sensitivity is always higher than that of clinical breast exam and smaller than that of MRI. Increasing its sensitivity within these limits does not really affect the order of effectiveness for the strategies of interest.

By using relatively lower incidence values of 0.06% to 0.8% for ages 30-79, the overall results are essentially identical to the analysis using higher incidence values. The expected total costs are lower, which may be due to less intense treatments, but otherwise the strategies with a lower cost per QALY gained were strategies A, D, I, N, V, and b. A simultaneous change in tumor characteristics together with the change in incidence may lead to a significant impact on the cost-effectiveness results.

3.4 Discussion

This study extends the analysis in Chapter 2 to a cohort of high-risk women for breast cancer. We account for differences in age-specific breast cancer incidence according to pre-specified characteristics under the GAIL model, tumor characteristics, and exam sensitivity and specificity among this population, and include a recently recommended screening exam in some of the studied strategies: magnetic resonance imaging. All costs due to screening, work-up, biopsies due to true-or false-positive examinations, and treatments are included.

Mammography alone every one or two years beginning at age 40, which are two

Table 3.4 : Results of sensitivity analysis in a high-risk cohort using a higher sensitivity value for clinical breast exam. Costs and QALYs are discounted at 3%. Strategies that are dominated or eliminated through extended dominance are indicated with '—'. Dominated strategies are indicated with '—'.

Strat	MM intv(age)	CBE intv(age)	MRI intv(age)	Total Cost ($)	QALYs (years)	Increm. QALYs gained	ICER
*	—	—	—	14,700	27.2380		
A	2(40-79)			15,300	27.2514	—	—
B	2(40-79)	2(41-79)		15,600	27.2598	0.0219	41,200
C	2(40-79)	2(40-79)		15,600	27.2568	—	—
D	1(40-79)			15,800	27.2590	—	—
E	2(30-79)	2(30-79)		15,900	27.2618	—	—
G	2(30-79)	1(30-79)		16,300	27.2720	0.0122	59,600
F	1(40-79)	1(40-79)		16,400	27.2678	—	—
H	1(40-79)	3(20-39), 1(40-79)		16,500	27.2716	—	—
I	0.5(40-79)			16,800	27.2678	—	—
J	1(30-79)	1(30-79)		17,100	27.2749	—	—
K	2(30-79)	0.5(30-79)		17,200	27.2853	0.0133	62,100
L	0.5(40-79)	0.5(40-79)		17,900	27.2791	—	—
M	1(30-79)	0.5(30-79)		17,900	27.2870	—	—
N	0.5(30-79)	0.5(30-79)		19,500	27.2904	0.0051	447,700
O	2(30-79)	2(30-79)	2(31-79)	24,500	27.2732	—	—
P	2(30-79)	2(30-79)	2(30-79)	24,900	27.2711	—	—
Q	2(30-79)	1(30-79)	2(30-79)	25,300	27.2753	—	—
R	1(30-79)	1(30-79)	2(30-79)	26,000	27.2782	—	—
S	2(30-79)	0.5(30-79)	2(30-79)	26,100	27.2867	—	—
T	1(30-79)	0.5(30-79)	2(30-79)	26,900	27.2892	—	—
U	2(30-79)	2(30-79)	1(30-79)	27,300	27.2752	—	—
V	0.5(30-79)	0.5(30-79)	2(30-79)	28,400	27.2927	0.0022	3,994,000
W	2(30-79)	1(30-79)	1(30-79)	33,400	27.2810	—	—
X	1(30-79)	1(30-79)	1(30.5-79)	34,400	27.2892	—	—
Y	1(30-79)	1(30-79)	1(30-79)	34,600	27.2808	—	—
Z	2(30-79)	0.5(30-79)	1(30-79)	34,700	27.2914	—	—
a	1(30-79)	0.5(30-79)	1(30-79)	35,400	27.2911	—	—
b	0.5(30-79)	0.5(30-79)	1(30-79)	37,000	27.2939	0.0012	6,928,600

MM=Mammography; CBE=Clinical breast exam; MRI=Magnetic Resonance Imaging; intv=time interval between examinations (in years); age=age range; Increm=incremental
Total Cost: Mean total cost per woman in the complete cohort, rounded to the nearest $100
QALYs: Mean total expected quality-adjusted life years per woman from age 20
ICER: Incremental cost-effectiveness ratio (incremental cost/incremental QALYs gained compared to next least-expensive strategy)

Table 3.5 : Results of sensitivity analysis in a high-risk cohort using higher sensitivity values for mammography. Costs and QALYs are discounted at 3%. Strategies that are dominated or eliminated through extended dominance are indicated with '—'.

Strat	MM intv(age)	CBE intv(age)	MRI intv(age)	Total Cost ($)	QALYs (years)	Increm. QALYs gained	ICER
*	—	—	—	14,700	27.2385		
A	2(40-79)			15,300	27.2547	0.0162	39,400
B	2(40-79)	2(41-79)		15,600	27.2561	—	—
C	2(40-79)	2(40-79)		15,600	27.2574	—	—
D	1(40-79)			15,800	27.2646	0.0099	49,100
E	2(30-79)	2(30-79)		15,900	27.2598	—	—
G	2(30-79)	1(30-79)		16,400	27.2639	—	—
F	1(40-79)	1(40-79)		16,400	27.2661	—	—
H	1(40-79)	3(20-39), 1(40-79)		16,500	27.2673	—	—
I	0.5(40-79)			16,800	27.2742	0.0096	104,900
J	1(30-79)	1(30-79)		17,100	27.2726	—	—
K	2(30-79)	0.5(30-79)		17,200	27.2683	—	—
L	0.5(40-79)	0.5(40-79)		17,900	27.2773	—	—
M	1(30-79)	0.5(30-79)		18,000	27.2770	—	—
N	0.5(30-79)	0.5(30-79)		19,500	27.2866	0.0124	214,200
O	2(30-79)	2(30-79)	2(31-79)	24,500	27.2720	—	—
P	2(30-79)	2(30-79)	2(30-79)	24,900	27.2668	—	—
Q	2(30-79)	1(30-79)	2(30-79)	25,300	27.2670	—	—
R	1(30-79)	1(30-79)	2(30-79)	26,000	27.2763	—	—
S	2(30-79)	0.5(30-79)	2(30-79)	26,100	27.2727	—	—
T	1(30-79)	0.5(30-79)	2(30-79)	26,900	27.2798	—	—
U	2(30-79)	2(30-79)	1(30-79)	27,300	27.2701	—	—
V	0.5(30-79)	0.5(30-79)	2(30-79)	28,400	27.2899	0.0033	2,664,100
W	2(30-79)	1(30-79)	1(30-79)	33,400	27.2769	—	—
X	1(30-79)	1(30-79)	1(30.5-79)	34,500	27.2871	—	—
Y	1(30-79)	1(30-79)	1(30-79)	34,600	27.2794	—	—
Z	2(30-79)	0.5(30-79)	1(30-79)	34,700	27.2802	—	—
a	1(30-79)	0.5(30-79)	1(30-79)	35,500	27.2829	—	—
b	0.5(30-79)	0.5(30-79)	1(30-79)	37,000	27.2913	0.0014	6,008,300

MM=Mammography; CBE=Clinical breast exam; MRI=Magnetic Resonance Imaging; intv=time interval between examinations (in years); age=age range; Increm=incremental
Total Cost: Mean total cost per woman in the complete cohort, rounded to the nearest $100
QALYs: Mean total expected quality-adjusted life years per woman from age 20
ICER: Incremental cost-effectiveness ratio (incremental cost/incremental QALYs gained compared to next least-expensive strategy)

Table 3.6 : Results of sensitivity analysis in a high-risk cohort where the age-specific incidence rates are lower than the original analysis. Costs and QALYs are discounted at 3%. Strategies that are dominated or eliminated through extended dominance are indicated with '—'.

Strat	MM intv(age)	CBE intv(age)	MRI intv(age)	Total Cost ($)	QALYs (years)	Increm. QALYs gained	ICER
*	—	—	—	13,100	27.3204		
A	2(40-79)			13,700	27.3340	0.0136	44,400
B	2(40-79)	2(41-79)		14,000	27.3373	—	—
C	2(40-79)	2(40-79)		14,000	27.3361	—	—
D	1(40-79)			14,200	27.3419	0.0079	63,800
E	2(30-79)	2(30-79)		14,400	27.3387	—	—
F	1(40-79)	1(40-79)		14,800	27.3453	—	—
G	2(30-79)	1(30-79)		14,800	27.3412	—	—
H	1(40-79)	3(20-39), 1(40-79)		15,000	27.3458	—	—
I	0.5(40-79)			15,200	27.3519	0.0100	98,400
J	1(30-79)	1(30-79)		15,600	27.3487	—	—
K	2(30-79)	0.5(30-79)		15,700	27.3475	—	—
L	0.5(40-79)	0.5(40-79)		16,300	27.3550	—	—
M	1(30-79)	0.5(30-79)		16,400	27.3529	—	—
N	0.5(30-79)	0.5(30-79)		18,000	27.3613	0.0093	298,600
O	2(30-79)	2(30-79)	2(31-79)	23,100	27.3509	—	—
P	2(30-79)	2(30-79)	2(30-79)	23,400	27.3461	—	—
Q	2(30-79)	1(30-79)	2(30-79)	23,800	27.3473	—	—
R	1(30-79)	1(30-79)	2(30-79)	24,600	27.3533	—	—
S	2(30-79)	0.5(30-79)	2(30-79)	24,700	27.3521	—	—
T	1(30-79)	0.5(30-79)	2(30-79)	25,500	27.3577	—	—
U	2(30-79)	2(30-79)	1(30-79)	25,800	27.3484	—	—
V	0.5(30-79)	0.5(30-79)	2(30-79)	27,000	27.3651	0.0038	2,346,200
W	2(30-79)	1(30-79)	1(30-79)	32,100	27.3563	—	—
X	1(30-79)	1(30-79)	1(30.5-79)	33,100	27.3635	—	—
Y	1(30-79)	1(30-79)	1(30-79)	33,300	27.3585	—	—
Z	2(30-79)	0.5(30-79)	1(30-79)	33,400	27.3601	—	—
a	1(30-79)	0.5(30-79)	1(30-79)	34,100	27.3619	—	—
b	0.5(30-79)	0.5(30-79)	1(30-79)	35,700	27.3676	0.0025	3,487,800

MM=Mammography; CBE=Clinical breast exam; MRI=Magnetic Resonance Imaging; intv=time interval between examinations (in years); age=age range; Increm=incremental
Total Cost: Mean total cost per woman in the complete cohort, rounded to the nearest $100
QALYs: Mean total expected quality-adjusted life years per woman from age 20
ICER: Incremental cost-effectiveness ratio (incremental cost/incremental QALYs gained compared to next least-expensive strategy)

strategies that are currently recommended guidelines for the general population, are cost-effective strategies compared to the alternatives in the high-risk population. Increasing the frequency to every six months is also cost-effective with an increased survival benefit but with a higher cost. For a program which includes mammography and clinical breast exam, giving these exams every six months beginning at age 30 is more life-saving than the strategies above, but quite expensive. Even more expensive, but more effective, is to add MRI every 1 or 2 years.

Thus it appears that even for a population with higher risk for breast cancer, the cheapest but still effective screening strategies among those considered are the ones that give mammography alone. For an added expense and only 3-4 days benefit compared to mammography alone, mammography and clinical breast exam may be combined every six months. The addition of MRI to the screening programs is more life-saving but much more expensive, and the high added expense must be considered when the gain in benefit is small.

If clinical breast exam had better performance among women of higher risk, more strategies combining mammography and clinical breast exam would be cost-effective. The sensitivity of this test makes a significant impact on which strategies are cost-effective. It is thus crucial that appropriate sensitivity estimates for clinical breast exam are used in such an analysis, and that the results are interpreted carefully, according to which estimates are assumed. On the other hand, given that the sensitivity of mammography is always larger than the sensitivity of clinical breast exam

and smaller than the sensitivity of MRI, any changes in the sensitivity of mammography within this boundary has little effect on the overall cost-effectiveness of the strategies.

While the American Cancer Society has issued recommendations to add MRI to mammography for women with increased-risk for breast cancer, our analysis indicates that adding periodic MRI to mammography screening is very expensive and the gain in survival is relatively small. Giving mammography with or without clinical breast exam is much cheaper and sacrifices only a small gain in benefit. It is possible that improvements in the administration and interpretation of MRI may make it a more effective screening exam, but because of its high expense, it may not be worth it to recommend regular periodic screening with MRI.

The limitations mentioned in Chapter 2 still apply to this analysis. In addition, data on women of increased breast cancer risk are currently limited in the literature. While clinical trials for MRI in a high-risk group for breast cancer are currently underway, there are no large randomized, controlled clinical trials that have been completed assessing the use of MRI as a mode of screening for healthy women at high-risk for breast cancer. We thus relied on the information that was readily available in the literature for use in our data inputs and models. If more updated information becomes available, it may be substituted into the models.

Overall, we report our findings from a societal perspective. Among an increased-risk population, a screening program which gives mammography alone beginning at

age 40 is the cheapest cost-effective option, and spending the money to add clinical breast exam or MRI does not add much benefit. However, if cost is not an issue, then the more ethically acceptable choice from a patient's perspective would be to give mammography and clinical breast exam every six months beginning at age 30, with MRI every 1 or 2 years. While it may be beneficial to give women of higher breast cancer risk earlier or more frequent exams with MRI, it is expensive and the costs required for the small benefit must be carefully considered.

Chapter 4
Utility Function

4.1 Background

While a simulation model has its advantages of modeling disease history and assessing the benefits and costs directly for a given set of different screening programs (a local optimum) simultaneously, a mathematical model can be a useful tool for searching for an optimal screening schedule (a global optimum) but under potentially more strict model assumptions.

Despite broad attention to modeling the general screening process, less attention has been given to the optimization of examination schedules for screening examinations using mathematical models. Optimal examination schedules may be determined by factors such as the initial age to begin a screening examination program, the intervals between subsequent examinations, and the number of examinations. Works by Parmigiani[93], Tsodikov and Yakovlev[94], Shahani and Crease[95], Lee and Zelen[96], and Zelen[59] are examples of efforts to address optimal examination schedules in the setting of early detection. We give brief and general reviews of these approaches, then present our proposed mathematical model under two frameworks.

Parmigiani (1993) took a decision theoretic approach, where the decision space consists of all possible sequences of examination times. Optimal schedules are chosen

to minimize the risk $R(\tau)$, or total expected loss due to an examination schedule τ, accounting for the expected number of examinations and the expected losses due to mortality, morbidity, costs, and other factors associated with the disease. He considered the effect of age on the optimal schedule of examinations by modeling age-specific incidence and age-specific competing risks. Although his formula for finding the optimal examination schedule is general enough, he can only solve the problem under a few very special cases: 1. when there is only one exam; and 2. under perfect exam sensitivity. He concluded that optimal periodic examinations (with a constant interval) can be derived only under restrictive assumptions (such as sensitivity=1), and non-periodic screening intervals for different age cohorts may maximize benefit instead.

Tsodikov and Yakovlev (1991) addressed the problem of optimal screening with non-periodic examinations using a minimum delay time approach and a minimum cost approach. In the minimum delay time approach, the number of exams is assumed to be fixed, and the problem is to construct the screening schedule given the fixed number of exams that maximizes the benefit through minimization of the expected delay time. The minimum cost approach was used to find the optimal schedule of examinations (and thereby the optimal number of exams) by minimizing the total costs due to screening and late detection of the disease.

Alternatively, Lee and Zelen (1998) considered two different approaches to select the optimal screening schedule, specifically with applications to breast cancer. The

first was the threshold method which selects examination schedules within a screening horizon according to a preselected threshold value, such as the probability of an individual being in the preclinical state. Examinations are carried out when an individual's risk status reaches that threshold. The second approach was schedule selection based on schedule sensitivity, defined as the ratio of expected number of diagnosed cases to the total expected number of cases. This approach does not give a unique solution. The combination of these two methods allows for the evaluation of screening schedules based on the tradeoffs between schedule sensitivity and costs.

Similar to Tsodikov and Yakovlev (1991), Zelen (1993) assumed a fixed cost (or number of exams) while maximizing the health benefit. In Zelen's approach, he considers a screening horizon $[0, T]$ for a fixed number of examinations at times $0 = t_0, t_1, ..., t_n = T$ and general formulations for probability of detection at screening (screening detection) and probability of diagnosis between screening (interval detection). Instead of minimizing the expected delay time, Zelen's approach seeks to maximize a weighted difference between screening and interval detected cases.

The following general expressions were derived by Zelen for the probability that the disease is detected at the ith screening exam when the sensitivity is $0 < \beta \leq 1$ $(D_i(\beta))$, and the probability that an individual is incident at age t after i exams

$(I_i(\beta,t))$:

$$
\begin{aligned}
D_0(\beta) &= \beta P(t_0) \\
D_i(\beta) &= \beta\left\{\sum_{j=0}^{i-1}(1-\beta)^{i-j}P_j(t_j)Q_j(t_i-t_j)+\int_{t_{i-1}}^{t_i} w(x)Q(t_i-x)dx\right\}, i=1,...,n \\
I_i(\beta,t) &= \sum_{j=0}^{i-1}(1-\beta)^{i-j}P_j(t_j)q_j(t-t_j)+\int_{t_{i-1}}^{t} w(x)q(t-x)dx, i=1,...,n,
\end{aligned}
$$

where $w(t)$ is the preclinical transition rate, $P(t)$ is the prevalence of disease at time t, $q(t)$ is the probability density function of the sojourn time, and $Q(t)$ is the survival function for $q(t)$, and $P_i(t_i)q_i(t) = \int_{t_{i-1}}^{t_i} w(x)q(t_i-x+t)dx$.

Using these formulations, Zelen proposed a utility function that represents a weighted difference between the probability of screening detection and the probability of interval detection for a screening program with $n+1$ examinations:

$$
U_{n+1} = A\sum_{i=0}^{n} D_i(\beta) - B\sum_{i=1}^{n} I_i(\beta),
$$

where the weights A and B are non-negative and $A > B$. The weights may, for example, represent the probability of a cure when disease is found through a screening examination or an interval case. The idea is to maximize the utility with a screening schedule which will yield a large number of screening detections and a smaller number of clinical incidence cases between exams.

The utility function is thus a function of screening sensitivity, disease incidence,

and the preclinical sojourn time distribution. In particular, Zelen assumes a stable disease model, where transition into the preclinical state $H \rightarrow P$ is independent of age. The optimal values $\{t_i\}$ are then found by maximizing the utility function under these assumptions, where the $\{t_i\}$ define the optimal spacing of examinations. Although the assumption of a stable disease model significantly simplifies the formulations, it can be unrealistic for a potentially long screening horizon.

In the current work, we extend Zelen's approach under the more general assumption of a non-stable disease model by taking into consideration age-dependent preclinical incidence of disease, as well as costs of screening exams and the dollar value of benefit. We will explore two frameworks for the utility function given the estimated age-dependent preclinical incidence, screening sensitivity, and sojourn time distribution:

1. **Equal Intervals** We will derive the optimal number of examinations within a specified screening horizon $[t_0, T]$, with $t_n = T$ and assuming that the intervals between exams are equal.

2. **Fixed Budget** We will derive the optimal ages of examinations within a specified screening horizon $[t_0, T]$, with $t_n \leq T$, given the number of examinations (fixed budget) and allowing the intervals between examinations to be unequal.

4.2 Proposed Models

In each proposed framework, we consider the following general form for the utility function which includes a cost deduction:

$$U = Value\ Of\ Benefit - Cost\ Of\ Screening,$$

where the *Value of Benefit* denotes the dollar value of the benefit due to a screening program, and *Cost of Screening* denotes the cost of screening examinations in that screening program. Then the goal will be to maximize U, or the value of the benefit when costs for screening are deducted.

Using Zelen's expressions as a template, we present two proposed frameworks to find the optimal screening schedule under a non-stable disease model. In both frameworks, $w(x)$, the age-dependent transition rate from $H \rightarrow P$ is assumed to be a continuous function of the form $k_1 x - k_0$ where k_1 and k_0 are constants, and $w(x) = 0$ for $x < \frac{k_0}{k_1}$. For instance, for $\frac{k_0}{k_1} = 20$, the transition rate is zero for ages $x < 20$. We assume that $\frac{k_0}{k_1} \leq t_0$. The probability density function for the sojourn time is assumed to be exponential with mean $\mu = \frac{1}{\lambda}$. We present proofs of the existence of a solution for both scenarios and some numerical optimization results.

4.2.1 Framework 1: Equal Intervals

Although the earlier settings in previous works showed that choosing equal intervals may not be optimal unless the exam sensitivity is one[93, 59], it may have practical

advantages in its convenience and feasibility of enforcement. Under the assumption of equal intervals, we present a utility function where the number of exams (n), or equivalently the interval between exams (Δ), in a screening schedule is unknown. The n (or Δ) which maximizes the utility function will define the optimal schedule when exams are equally spaced.

Presentation of Model

Using Zelen's expressions for $D_i(\beta)$ and $I_i(\beta, t)$, we define the utility function as follows:

$$\begin{aligned} U(n) &= Value\ Of\ Benefit(n) - Cost\ Of\ Screening(n) \\ &= C_1 \left(A \sum_{i=0}^{n} D_i(\beta) - B \sum_{i=1}^{n} I_i(\beta) \right) - C_2(n+1). \end{aligned}$$

We assume that the $Benefit$ is the difference in cure rates between those found on examination compared to interval cases, where A is the probability of a cure when disease is found through screening, B is the probability of a cure for an interval case, C_1 is the average dollar value of survival benefit due to one life cured, and C_2 is the average cost of a screening exam. We assume a fixed screening horizon of ages $[t_0, T]$, and assume that $n+1$ examinations at times $t_0, t_1, \ldots, t_n = T$ are equally-spaced at

intervals of $\Delta = t_i - t_{i-1}$. Then the following expressions follow:

$$\begin{aligned} \Delta &= \frac{T - t_0}{n} \\ t_i &= t_0 + i\Delta \\ &= t_0 + \frac{i}{n}(T - t_0), i = 1, \ldots, n. \end{aligned}$$

Using these expressions in the utility function, we can find the n^* that maximizes $U(n)$, and therefore solve for the optimal Δ^*.

Proof for Existence of Solution

In the derivations below, we first simplify the problem to eliminate the summations, using properties of the geometric series, then use Taylor series expansion to approximate $U(n)$. Note that the term $D_0(\beta)$ is not dependent on n, and may thus be excluded in the proof. We begin by rewriting

$$D_i(\beta) = \beta \left\{ \sum_{j=0}^{i-1} (1-\beta)^{i-j} P_j(t_j) Q_j(t_i - t_j) + \int_{t_{i-1}}^{t_i} w(x) Q(t_i - x) dx \right\}$$

with expressions for $P_j(t_j)q_j(t)$ and $P_j(t_j)Q_j(t_i - t_j)$. The proof is given under an exponential assumption with mean $\mu = \frac{1}{\lambda}$ for the sojourn time distribution.

For $j = 0$,

$$\begin{aligned} P_0(t_0)q_0(t) &= \int_0^{t_0} w(x)q(t_0 - x + t)dx \\ &= \int_0^{t_0} k_1 x\lambda \exp(-\lambda(t_0 - x + t))dx - \int_0^{t_0} k_0\lambda \exp(-\lambda(t_0 - x + t))dx \\ &= \mu k_1 \exp(-\lambda(t + t_0)) + k_1(t_0 - \mu)\exp(-\lambda t) \\ &\quad - k_0 \exp(-\lambda t) + k_0 \exp(-\lambda(t_0 + t)), \end{aligned}$$

and

$$\begin{aligned} P_0(t_0)Q_0(t_i - t_0) &= \int_{t_i - t_0}^{\infty} P_0(t_0)q_0(t)dt \\ &= \int_{t_i - t_0}^{\infty} (\mu k_1 \exp(-\lambda(t + t_0)) + k_1(t_0 - \mu)\exp(-\lambda t) \\ &\quad -k_0 \exp(-\lambda t) + k_0 \exp(-\lambda(t_0 + t)))\, dt \\ &= \mu^2 k_1 \exp(-\lambda t_i) + k_1\mu(t_0 - \mu)\exp(-\lambda(t_i - t_0)) \\ &\quad - \mu k_0 \exp(-\lambda(t_i - t_0)) + \mu k_0 \exp(-\lambda t_i). \end{aligned}$$

For $j > 0$,

$$\begin{aligned} P_j(t_j)q_j(t) &= \int_{t_{j-1}}^{t_j} w(x)q(t_j - x + t)dx \\ &= \int_{t_{j-1}}^{t_j} k_1 x\lambda \exp(-\lambda(t_j - x + t))dx - \int_{t_j - 1}^{t_j} k_0\lambda \exp(-\lambda(t_j - x + t))dx, \end{aligned}$$

and

$$\begin{aligned}
P_j(t_j)Q_j(t_i - t_j) &= \int_{t_i-t_j}^{\infty} P_j(t_j)q_j(t)dt \\
&= \int_{t_i-t_j}^{\infty}\int_{t_{j-1}}^{t_j} k_1 x\lambda \exp(-\lambda(t_j+t))\exp(\lambda x)dxdt \\
&\quad - \int_{t_i-t_j}^{\infty}\int_{t_{j-1}}^{t_j} k_0\lambda \exp(-\lambda(t_j+t))\exp(\lambda x)dxdt \\
&= \int_{t_i-t_j}^{\infty} k_0 \exp(-\lambda(t_j+t))dt \int_{t_{j-1}}^{t_j} \lambda\exp(\lambda x)dx \\
&\quad - \int_{t_i-t_j}^{\infty} k_1 \exp(-\lambda(t_j+t))dt \int_{t_{j-1}}^{t_j} \lambda x\exp(\lambda x)dx \\
&= k_1\mu\exp(-\lambda t_i)\left((t_j-\mu)\exp(\lambda t_j) - (t_{j-1}-\mu)\exp(\lambda t_{j-1})\right) \\
&\quad - k_0\mu\exp(-\lambda t_i)(\exp(\lambda t_j) - \exp(\lambda t_{j-1})).
\end{aligned}$$

Also,

$$\begin{aligned}
\int_{t_{i-1}}^{t_i} w(x)Q(t_i-x)dx &= \int_{t_{i-1}}^{t_i} k_1 x\exp(-\lambda(t_i-x))dx - \int_{t_{i-1}}^{t_i} k_0\exp(-\lambda(t_i-x))dx \\
&= k_1\mu\exp(-\lambda t_i)\left((t_i-\mu)\exp(\lambda t_i) - (t_{i-1}-\mu)\exp(\lambda t_{i-1})\right) \\
&\quad - k_0\mu + k_0\mu\exp(-\lambda(t_i-t_{i-1})).
\end{aligned}$$

Then using the above expressions, we rewrite $D_i(\beta)$:

$$
\begin{aligned}
D_i(\beta) &= \beta\left\{\sum_{j=0}^{i-1}(1-\beta)^{i-j}P_j(t_j)Q_j(t_i-t_j)+\int_{t_{i-1}}^{t_i}w(x)Q(t_i-x)dx\right\} \\
&= \beta\{(1-\beta)^i(\mu^2k_1\exp(-\lambda t_i)+k_1\mu(t_0-\mu)\exp(-\lambda(t_i-t_0)) \\
&\quad -\mu k_0\exp(-\lambda(t_i-t_0))+\mu k_0\exp(-\lambda t_i)) \\
&\quad +\sum_{j=1}^{i-1}(1-\beta)^{i-j}\{k_1\mu\exp(-\lambda t_i)((t_j-\mu)\exp(\lambda t_j)-(t_{j-1}-\mu)\exp(\lambda t_{j-1})) \\
&\quad -k_0\mu\exp(-\lambda t_i)(\exp(\lambda t_j)-\exp(\lambda t_{j-1}))\} \\
&\quad +k_1\mu\exp(-\lambda t_i)((t_i-\mu)\exp(\lambda t_i)-(t_{i-1}-\mu)\exp(\lambda t_{i-1})) \\
&\quad -k_0\mu+k_0\mu\exp(-\lambda(t_i-t_{i-1}))\} \\
&= \beta k_1\mu\exp(-\lambda t_i)\{(1-\beta)^i\mu+(1-\beta)^i(t_0-\mu)\exp(\lambda t_0) \\
&\quad +(1-\beta)^{i-1}((t_1-\mu)\exp(\lambda t_1)-(t_0-\mu)\exp(\lambda t_0)) \\
&\quad +(1-\beta)^{i-2}((t_2-\mu)\exp(\lambda t_2)-(t_1-\mu)\exp(\lambda t_1))+\ldots \\
&\quad +(1-\beta)((t_{i-1}-\mu)\exp(\lambda t_{i-1})-(t_{i-2}-\mu)\exp(\lambda t_{i-2})) \\
&\quad +((t_i-\mu)\exp(\lambda t_i)-(t_{i-1}-\mu)\exp(\lambda t_{i-1}))\} \\
&\quad -\beta k_0\mu\exp(-\lambda t_i)\{(1-\beta)^i\exp(\lambda t_0)-(1-\beta)^i \\
&\quad +(1-\beta)^{i-1}(\exp(\lambda t_i)-\exp(\lambda t_0))+(1-\beta)^{i-2}(\exp(\lambda t_2)-\exp(\lambda t_1))+\ldots \\
&\quad +(1-\beta)(\exp(\lambda t_{i-1})-\exp(\lambda t_{i-2}))+\exp(\lambda t_i)-\exp(\lambda t_{i-1})\} \\
&= \beta k_1\mu\exp(-\lambda t_i)\{(1-\beta)^i\mu+(1-\beta)^{i-1}(t_0-\mu)\exp(\lambda t_0)(-\beta)+\ldots \\
&\quad +(t_{i-1}-\mu)\exp(\lambda t_{i-1})(-\beta)+(t_i-\mu)\exp(\lambda t_i)\} \\
&\quad -\beta k_0\mu\exp(-\lambda t_i)\{-(1-\beta)^i+(1-\beta)^{i-1}\exp(\lambda t_0)(-\beta)+\ldots \\
&\quad +\exp(\lambda t_{i-1})(-\beta)+\exp(\lambda t_i)\}
\end{aligned}
$$

$$= \beta k_1 \mu \exp(-\lambda t_i) \left\{ (1-\beta)^i \mu + \sum_{j=0}^{i-1} (1-\beta)^{i-j-1} (t_j - \mu) \exp(\lambda t_j)(-\beta) + (t_i - \mu) \exp(\lambda t_i) \right\}$$
$$- \beta k_0 \mu \exp(-\lambda t_i) \left\{ -(1-\beta)^i + \sum_{j=0}^{i-1} (1-\beta)^{i-j-1} \exp(\lambda t_j)(-\beta) + \exp(\lambda t_i) \right\}.$$

Then since $t_j - \mu = t_0 - \mu + j\Delta$, we can rewrite $D_i(\beta)$ as

$$\beta k_1 \mu \left\{ \mu(1-\beta)^i \exp(-\lambda t_i) - (t_0 - \mu)\beta \exp(-\lambda\Delta) \sum_{j=0}^{i-1} (1-\beta)^{i-j-1} \exp(-\lambda(i-j-1)\Delta) \right.$$
$$\left. -\Delta\beta \exp(-\lambda\Delta) \sum_{j=1}^{i-1} j(1-\beta)^{i-j-1} \exp(-\lambda(i-j-1)\Delta) + (t_i - \mu) \right\}$$
$$- \beta k_0 \mu \left\{ -(1-\beta)^i \exp(-\lambda t_i) - \beta \exp(-\lambda\Delta) \sum_{j=0}^{i-1} (1-\beta)^{i-j-1} \exp(-\lambda(i-j-1)\Delta) + 1 \right\}.$$

Now let $D_n = \sum_{i=1}^{n} D_i(\beta)$. Then using the sum of the geometric series $\sum_{i=0}^{n} ar^i = a\left(\frac{1-r^{n+1}}{1-r}\right)$, we have

$$\begin{aligned}
D_n &= \beta k_1 \mu^2 \sum_{i=1}^{n} (1-\beta)^i \exp(-\lambda t_i) \\
&\quad - k_1 \mu \beta^2 (t_0 - \mu) \exp(-\lambda\Delta) \sum_{i=1}^{n} \sum_{j=0}^{i-1} (1-\beta)^{i-j-1} \exp(-\lambda(i-j-1)\Delta) \\
&\quad - \beta^2 k_1 \mu \Delta \exp(-\lambda\Delta) \sum_{i=1}^{n} \sum_{j=1}^{i-1} j(1-\beta)^{i-j-1} \exp(-\lambda(i-j-1)\Delta) + \beta k_1 \mu \sum_{i=1}^{n} (t_i - \mu) \\
&\quad + \beta k_0 \mu \sum_{i=1}^{n} (1-\beta)^i \exp(-\lambda t_i) \\
&\quad + \beta^2 k_0 \mu \exp(-\lambda\Delta) \sum_{i=1}^{n} \sum_{j=0}^{i-1} (1-\beta)^{i-j-1} \exp(-\lambda(i-j-1)\Delta) - \sum_{i=1}^{n} \beta k_0 \mu \\
&= \beta k_1 \mu^2 \sum_{i=1}^{n} X_i - k_1 \mu \beta^2 (t_0 - \mu) \exp(-\lambda\Delta) \sum_{i=1}^{n} Y_i - \beta^2 k_1 \mu \Delta \exp(-\lambda\Delta) \sum_{i=1}^{n} Z_i \\
&\quad + \beta k_1 \mu \sum_{i=1}^{n} (t_i - \mu) + \beta k_0 \mu \sum_{i=1}^{n} X_i + \beta^2 k_0 \mu \exp(-\lambda\Delta) \sum_{i=1}^{n} Y_i - n\beta k_0 \mu,
\end{aligned}$$

where

$$\begin{aligned}
\sum_{i=1}^{n} (t_i - \mu) &= \sum_{i=1}^{n} (t_0 + i\Delta - \mu) \\
&= n(t_0 - \mu) + \frac{n(n+1)}{2}\Delta \\
&= nt_0 - n\mu + \frac{n+1}{2}(T - t_0) \\
&= \frac{(T - t_0)}{2} + \frac{n}{2}(T + t_0 - 2\mu),
\end{aligned}$$

$$\begin{aligned}
\sum_{i=1}^{n} X_i &= \sum_{i=1}^{n}(1-\beta)^i \exp(-\lambda t_i) \\
&= \sum_{i=1}^{n}(1-\beta)^i \exp(-\lambda(t_0 + i\Delta)) \\
&= \exp(-\lambda t_0)\sum_{i=1}^{n}\{(1-\beta)\exp(-\lambda\Delta)\}^i \\
&= \exp(-\lambda t_0)(1-\beta)\exp(-\lambda\Delta)\frac{1-\{(1-\beta)\exp(-\lambda\Delta)\}^n}{1-(1-\beta)\exp(-\lambda\Delta)} \\
&= \exp(-\lambda t_0)(1-\beta)\exp(-\lambda\Delta)\frac{1-(1-\beta)^n\exp(-\lambda(T-t_0))}{1-(1-\beta)\exp(-\lambda\Delta)},
\end{aligned}$$

$$\begin{aligned}
\sum_{i=1}^{n} Y_i &= \sum_{i=1}^{n}\sum_{j=0}^{i-1}(1-\beta)^{i-j-1}\exp(-\lambda(i-j-1)\Delta) \\
&= \sum_{j=0}^{n-1}\sum_{i=j+1}^{n}\{(1-\beta)\exp(-\lambda\Delta)\}^{i-j-1} \\
&= \sum_{j=0}^{n-1}\frac{1-\{(1-\beta)\exp(-\lambda\Delta)\}^{n-j}}{1-(1-\beta)\exp(-\lambda\Delta)} \\
&= \frac{1}{1-(1-\beta)\exp(-\lambda\Delta)}\left\{n - \frac{1-(1-\beta)^n\exp(-\lambda\Delta(n))}{1-(1-\beta)\exp(-\lambda\Delta)}(1-\beta)\exp(-\lambda\Delta)\right\},
\end{aligned}$$

and

$$
\begin{aligned}
\sum_{i=1}^{n} Z_i &= \sum_{i=1}^{n}\sum_{j=1}^{i-1} j(1-\beta)^{i-j-1}\exp(-\lambda\Delta(i-j-1)) \\
&= \sum_{j=1}^{n-1} j \sum_{i=j+1}^{n} \{(1-\beta)\exp(-\lambda\Delta)\}^{i-j-1} \\
&= \sum_{j=1}^{n-1} j \frac{1-\{(1-\beta)\exp(-\lambda\Delta)\}^{n-j}}{1-(1-\beta)\exp(-\lambda\Delta)} \\
&= \frac{1}{1-(1-\beta)\exp(-\lambda\Delta)} \left\{ \frac{n(n-1)}{2} - \sum_{j=1}^{n-1} j\{(1-\beta)\exp(-\lambda\Delta)\}^{n-j} \right\} \\
&= \frac{1}{1-(1-\beta)\exp(-\lambda\Delta)} \left\{ \frac{n(n-1)}{2} + \sum_{j=1}^{n-1}(n-j)\{(1-\beta)\exp(-\lambda\Delta)\}^{n-j} \right. \\
&\quad \left. - \sum_{j=1}^{n-1} n\{(1-\beta)\exp(-\lambda\Delta)\}^{n-j} \right\} \\
&= \frac{1}{1-(1-\beta)\exp(-\lambda\Delta)} \left\{ \frac{n(n-1)}{2} + \sum_{j=1}^{n-1}(n-j)\{(1-\beta)\exp(-\lambda\Delta)\}^{n-j} \right. \\
&\quad \left. - n\frac{1-\{(1-\beta)\exp(-\lambda\Delta)\}^{n-1}}{1-(1-\beta)\exp(-\lambda\Delta)}(1-\beta)\exp(-\lambda\Delta) \right\} \\
&= \frac{1}{1-(1-\beta)\exp(-\lambda\Delta)} \left\{ \frac{n(n-1)}{2} \right. \\
&\quad + (1-\beta)\exp(-\lambda\Delta)\frac{1-n\{(1-\beta)\exp(-\lambda\Delta)\}^{n-1}+(n-1)\{(1-\beta)\exp(-\lambda\Delta)\}^{n}}{(1-(1-\beta)\exp(-\lambda\Delta))^2} \\
&\quad \left. -n(1-\beta)\exp(-\lambda\Delta)\frac{1-\{(1-\beta)\exp(-\lambda\Delta)\}^{n-1}}{1-(1-\beta)\exp(-\lambda\Delta)} \right\}.
\end{aligned}
$$

Next we rewrite $I_n(\beta,t) = \sum_{j=0}^{i-1}(1-\beta)^{i-j}P_j(t_j)q_j(t-t_j) + \int_{t_{i-1}}^{t} w(x)q(t-x)dx$. Here, we need expressions for $P_j(t_j)q_j(t-t_j)$:

For $j = 0$,

$$\begin{aligned} P_0(t_0)q_0(t-t_0) &= \int_0^{t_0} w(x)q(t-x)dx \\ &= \int_0^{t_0} k_1 x\lambda\exp(-\lambda(t-x))dx - \int_0^{t_0} k_0\lambda\exp(-\lambda(t-x))dx \\ &= k_1\exp(-\lambda t)\{(t_0-\mu)\exp(\lambda t_0)+\mu\} - k_0\exp(-\lambda t)\{\exp(\lambda t_0)-1\}. \end{aligned}$$

For $j > 0$,

$$\begin{aligned} P_j(t_j)q_j(t-t_j) &= \int_{t_{j-1}}^{t_j} w(x)q(t-x)dx \\ &= \int_{t_{j-1}}^{t_j} k_1 x\lambda\exp(-\lambda(t-x))dx - \int_{t_{j-1}}^{t_j} k_0\lambda\exp(-\lambda(t-x))dx \\ &= k_1\exp(-\lambda t)\{(t_j-\mu)\exp(\lambda t_j) - (t_{j-1}-\mu)\exp(\lambda t_{j-1})\} \\ &\quad - k_0\exp(-\lambda t)\{\exp(\lambda t_j) - \exp(\lambda t_{j-1})\} \end{aligned}$$

Also,

$$\begin{aligned} \int_{t_{i-1}}^{t} w(x)q(t-x)dx &= \int_{t_{i-1}}^{t} k_1 x\lambda\exp(-\lambda(t-x))dx - \int_{t_{i-1}}^{t} k_0\lambda\exp(-\lambda(t-x))dx \\ &= k_1(t-\mu) - k_1\exp(-\lambda t)(t_{i-1}-\mu)\exp(\lambda t_{i-1}) \\ &\quad - k_0 + k_0\exp(-\lambda(t-t_{i-1})). \end{aligned}$$

Using these expressions we write

$$
\begin{aligned}
I_i(\beta,t) &= \sum_{j=0}^{i-1}(1-\beta)^{i-j}P_j(t_j)q_j(t-t_j)+\int_{t_{i-1}}^{t}w(x)q(t-x)dx \\
&= (1-\beta)^i\{k_1\exp(-\lambda t)\{\underbrace{(t_0-\mu)\exp(\lambda t_0)}_{a_0}+\mu\}-k_0\exp(-\lambda t)(\underbrace{\exp(\lambda t_0)}_{b_0}-1)\} \\
&\quad+\sum_{j=1}^{i-1}(1-\beta)^{i-j}\{k_1\exp(-\lambda t)\{\underbrace{(t_j-\mu)\exp(\lambda t_j)}_{a_j}-\underbrace{(t_{j-1}-\mu)\exp(\lambda t_{j-1})}_{a_{j-1}}\} \\
&\quad-k_0\exp(-\lambda t)(\underbrace{\exp(\lambda t_j)}_{b_j}-\underbrace{\exp(\lambda t_{j-1})}_{b_{j-1}})\} \\
&\quad+k_1(t-\mu)-k_1\exp(-\lambda t)\underbrace{(t_{i-1}-\mu)\exp(\lambda t_{i-1})}_{a_{i-1}}-k_0+k_0\exp(-\lambda t)\underbrace{\exp(\lambda t_{i-1})}_{b_{i-1}} \\
&= k_1\exp(-\lambda t)\{(1-\beta)^i a_0+(1-\beta)^i\mu+(1-\beta)^{i-1}a_1-(1-\beta)^{i-1}a_0 \\
&\quad+(1-\beta)^{i-2}a_2-(1-\beta)^{i-2}a_1+\ldots+(1-\beta)a_{i-1}-(1-\beta)a_{i-2}-a_{i-1}\} \\
&\quad+k_1(t-\mu)-k_0\exp(-\lambda t)\{(1-\beta)^i b_0-(1-\beta)^i+(1-\beta)^{i-1}b_1-(1-\beta)^{i-1}b_0 \\
&\quad+(1-\beta)^{i-2}b_2-(1-\beta)^{i-2}b_1+\ldots+(1-\beta)b_{i-1}-(1-\beta)b_{i-2}-b_{i-1}\}-k_0 \\
&= k_1\exp(-\lambda t)\{(1-\beta)^i\mu+(1-\beta)^{i-1}a_0(-\beta)+\ldots+(1-\beta)a_{i-2}(-\beta)+a_{i-1}(-\beta)\} \\
&\quad+k_1(t-\mu)-k_0\exp(-\lambda t)\{-(1-\beta)^i+(1-\beta)^{i-1}b_0(-\beta)+\ldots \\
&\quad+(1-\beta)b_{i-2}(-\beta)+b_{i-1}(-\beta)\}-k_0 \\
&= k_1\exp(-\lambda t)\left\{(1-\beta)^i\mu-\beta\sum_{j=0}^{i-1}(1-\beta)^{i-j-1}(t_j-\mu)\exp(\lambda t_j)\right\}+k_1(t-\mu) \\
&\quad+k_0\exp(-\lambda t)\left\{(1-\beta)^i+\beta\sum_{j=0}^{i-1}(1-\beta)^{i-j-1}\exp(\lambda t_j)\right\}-k_0.
\end{aligned}
$$

Then integrating out the t, we get

$$
\begin{aligned}
I_i(\beta) &= \int_{t_{i-1}}^{t_i} I_i(\beta,t)dt \\
&= k_1 \int_{t_{i-1}}^{t_i} \exp(-\lambda t)dt \left\{ (1-\beta)^i \mu - \beta \sum_{j=0}^{i-1} (1-\beta)^{i-j-1}(t_j - \mu)\exp(\lambda t_j) \right\} \\
&\quad + \int_{t_{i-1}}^{t_i} k_1(t-\mu)dt + k_0 \int_{t_{i-1}}^{t_i} \exp(-\lambda t)dt \left\{ (1-\beta)^i + \beta \sum_{j=0}^{i-1} (1-\beta)^{i-j-1}\exp(\lambda t_j) \right\} \\
&\quad - \int_{t_{i-1}}^{t_i} k_0 dt \\
&= k_1\mu(\exp(-\lambda t_{i-1}) - \exp(-\lambda t_i)) \left\{ (1-\beta)^i \mu - \beta \sum_{j=0}^{i-1} (1-\beta)^{i-j-1}(t_j - \mu)\exp(\lambda t_j) \right\} \\
&\quad + \frac{1}{2}k_1(t_i - \mu)^2 - \frac{1}{2}k_1(t_{i-1} - \mu)^2 \\
&\quad + k_0\mu(\exp(-\lambda t_{i-1}) - \exp(-\lambda t_i)) \left\{ (1-\beta)^i + \beta \sum_{j=0}^{i-1} (1-\beta)^{i-j-1}\exp(\lambda t_j) \right\} \\
&\quad - k_0(t_i - t_{i-1}) \\
&= k_1\mu(1-\exp(-\lambda\Delta))\exp(-\lambda t_{i-1}) \left\{ (1-\beta)^i \mu - \beta \sum_{j=0}^{i-1} (1-\beta)^{i-j-1}(t_j - \mu)\exp(\lambda t_j) \right\} \\
&\quad + \frac{1}{2}k_1((t_i - \mu) - (t_{i-1} - \mu))((t_i - \mu) + (t_{i-1} - \mu)) \\
&\quad + k_0\mu(\exp(-\lambda t_{i-1}) - \exp(-\lambda t_i)) \left\{ (1-\beta)^i + \beta \sum_{j=0}^{i-1} (1-\beta)^{i-j-1}\exp(\lambda t_j) \right\} \\
&\quad - k_0(t_i - t_{i-1}) \\
&= k_1\mu(1-\exp(-\lambda\Delta)) \Big\{ (1-\beta)^i \mu \exp(-\lambda(t_i - \Delta)) \\
&\quad -\beta \sum_{j=0}^{i-1} (1-\beta)^{i-j-1}(t_0 + j\Delta - \mu)\exp(-\lambda\Delta(i-j-1)) \Big\} \\
&\quad + \frac{1}{2}k_1\Delta(t_i + t_{i-1} - 2\mu) + k_0\mu(1-\exp(-\lambda\Delta)) \Big\{ (1-\beta)^i \exp(-\lambda(t_0 - \Delta)) \\
&\quad +\beta \sum_{j=0}^{i-1} (1-\beta)^{i-j-1}\exp(-\lambda\Delta(i-j-1)) \Big\} - k_0(t_i - t_{i-1}).
\end{aligned}
$$

Now let $I_n = \sum_{i=1}^{n} I_i(\beta)$. Then

$$
\begin{aligned}
I_n &= k_1\mu^2(1-\exp(-\lambda\Delta))\exp(\lambda\Delta)\sum_{i=1}^{n}(1-\beta)^i\exp(-\lambda t_i) \\
&\quad - k_1\beta\mu(1-\exp(-\lambda\Delta))(t_0-\mu)\sum_{i=1}^{n}\sum_{j=0}^{i-1}(1-\beta)^{i-j-1}\exp(-\lambda\Delta(i-j-1)) \\
&\quad - k_1\beta\mu(1-\exp(-\lambda\Delta))\Delta\sum_{i=1}^{n}\sum_{j=1}^{i-1}j(1-\beta)^{i-j-1}\exp(-\lambda\Delta(i-j-1)) \\
&\quad + \frac{1}{2}k_1\Delta\sum_{i=1}^{n}(t_i+t_{i-1}) - k_1\mu\Delta n \\
&\quad + k_0\mu(1-\exp(-\lambda\Delta))\exp(\lambda\Delta)\sum_{i=1}^{n}(1-\beta)^i\exp(-\lambda t_i) \\
&\quad + k_0\mu\beta(1-\exp(-\lambda\Delta))\sum_{i=1}^{n}\sum_{j=0}^{i-1}(1-\beta)^{i-j-1}\exp(-\lambda\Delta(i-j-1)) - k_0\Delta \\
&= k_1\mu^2(\exp(\lambda\Delta)-1)\sum_{i=1}^{n}X_i - k_1\mu\beta(t_0-\mu)(1-\exp(-\lambda\Delta))\sum_{i=1}^{n}Y_i \\
&\quad - k_1\mu\beta\Delta(1-\exp(-\lambda\Delta))\sum_{i=1}^{n}Z_i + \frac{1}{2}k_1\Delta\sum_{i=1}^{n}(t_i+t_{i-1}) - k_1\mu\Delta n \\
&\quad + k_0\mu(\exp(\lambda\Delta)-1)\sum_{i=1}^{n}X_i + k_0\beta\mu(1-\exp(-\lambda\Delta))\sum_{i=1}^{n}Y_i - k_0\Delta n,
\end{aligned}
$$

where X_i, Y_i, and Z_i are defined as before, and

$$
\begin{aligned}
\sum_{i=1}^{n}(t_i+t_{i-1}) &= (t_1+t_n)\frac{n}{2} + (t_0+t_{n-1})\frac{n}{2} \\
&= (t_0+\Delta+t_0+n\Delta)\frac{n}{2} + (t_0+t_0+(n-1)\Delta)\frac{n}{2} \\
&= n(2t_0+n\Delta) \\
&= \frac{T-t_0}{\Delta}(T+t_0).
\end{aligned}
$$

We next use Taylor series expansion to approximate each expression D_n and I_n. For

D_n we expand $\sum_{i=1}^n X_i$, $\exp(-\lambda\Delta)\sum_{i=1}^n Y_i$, and $\Delta\exp(-\lambda\Delta)\sum_{i=1}^n Z_i$ at zero: We use

$$\exp(-\lambda\Delta) = 1 - \lambda\Delta + \frac{\lambda^2}{2}\Delta^2 + O(\Delta^3),$$

and let

$$\begin{aligned} g(\Delta) &= \{1-(1-\beta)\exp(-\lambda\Delta)\}^{-1} \\ &= g(0) + g'(0)\Delta + \frac{g''(0)}{2}\Delta^2 + O(\Delta^3), \end{aligned}$$

where

$$\begin{aligned} g(0) &= \beta^{-1} \\ g'(\Delta) &= -\{1-(1-\beta)\exp(-\lambda\Delta)\}^{-2}\{-(1-\beta)\exp(-\lambda\Delta)\}(-\lambda) \\ g'(0) &= -\lambda\beta^{-2}(1-\beta) \\ g''(\Delta) &= -\lambda(1-\beta)\exp(-\lambda\Delta)(-\lambda)(1-(1-\beta)\exp(-\lambda\Delta))^{-2} \\ &\quad -\lambda(1-\beta)\exp(-\lambda\Delta)(-2)(1-(1-\beta)\exp(-\lambda\Delta))^{-3}(-(1-\beta)\exp(-\lambda\Delta))(-\lambda) \\ g''(0) &= \lambda^2(1-\beta)\beta^{-2} + 2\lambda^2(1-\beta)^2\beta^{-3} \\ &= \frac{\lambda^2(1-\beta)(2-\beta)}{\beta^3}. \end{aligned}$$

Then we can write

$$\{1-(1-\beta)\exp(-\lambda\Delta)\}^{-1} = \frac{1}{\beta} - \frac{\lambda(1-\beta)}{\beta^2}\Delta + \frac{\lambda^2(1-\beta)(2-\beta)}{2\beta^3}\Delta^2 + O(\Delta^3)$$

and we also have

$$\begin{aligned}(1-\beta)^n &= (1-\beta)^{\frac{(T-t_0)}{\Delta}} \\ &= o(\Delta^L)\end{aligned}$$

for any $L > 0$. Then we have

$$\begin{aligned}\sum_{i=1}^{n} X_i &= \exp(-\lambda t_0)(1-\beta)\exp(-\lambda\Delta)\frac{1-(1-\beta)^n\exp(-\lambda(T-t_0))}{1-(1-\beta)\exp(-\lambda\Delta)} \\ &= \exp(-\lambda t_0)(1-\beta)\{1-\lambda\Delta+O(\Delta^2)\}\left\{\frac{1}{\beta}-\frac{\lambda(1-\beta)}{\beta^2}\Delta+O(\Delta^2)\right\}+o(\Delta^L) \\ &= \exp(-\lambda t_0)\frac{1-\beta}{\beta}-\exp(-\lambda t_0)(1-\beta)\left(\frac{\lambda(1-\beta)}{\beta^2}+\frac{\lambda}{\beta}\right)\Delta+O(\Delta^2) \\ &= \exp(-\lambda t_0)\frac{1-\beta}{\beta}-\exp(-\lambda t_0)\frac{\lambda(1-\beta)}{\beta}\Delta+O(\Delta^2),\end{aligned}$$

$$
\begin{aligned}
&\exp(-\lambda\Delta)\sum_{i=1}^{n} Y_i \\
&= \frac{\exp(-\lambda\Delta)}{1-(1-\beta)\exp(-\lambda\Delta)}\left\{n - \frac{1-(1-\beta)^n\exp(-\lambda(T-t_0))}{1-(1-\beta)\exp(-\lambda\Delta)}(1-\beta)\exp(-\lambda\Delta)\right\} \\
&= \frac{\exp(-\lambda\Delta)}{1-(1-\beta)\exp(-\lambda\Delta)}\left\{n - \frac{(1-\beta)\exp(-\lambda\Delta)}{1-(1-\beta)\exp(-\lambda\Delta)} + o(\Delta^L)\right\} \\
&= \frac{\exp(-\lambda\Delta)}{1-(1-\beta)\exp(-\lambda\Delta)}\left\{n + \frac{1-(1-\beta)\exp(-\lambda\Delta)}{1-(1-\beta)\exp(-\lambda\Delta)} - \frac{1}{1-(1-\beta)\exp(-\lambda\Delta)} + o(\Delta^L)\right\} \\
&= \left(1-\lambda\Delta+\frac{\lambda^2}{2}\Delta^2+O(\Delta^3)\right)\left(\frac{1}{\beta}-\frac{\lambda(1-\beta)}{\beta^2}\Delta+\frac{\lambda^2(1-\beta)(2-\beta)}{2\beta^3}\Delta^2+O(\Delta^3)\right)\times \\
&\quad \left\{n+1-\left(\frac{1}{\beta}-\frac{\lambda(1-\beta)}{\beta^2}\Delta+O(\Delta^2)\right)\right\}+o(\Delta^L) \\
&= \left\{\frac{1}{\beta}-\left(\frac{\lambda}{\beta}+\frac{\lambda(1-\beta)}{\beta^2}\right)\Delta+\left(\frac{\lambda^2}{2\beta}+\frac{\lambda^2(1-\beta)}{\beta^2}+\frac{\lambda^2(1-\beta)(2-\beta)}{2\beta^3}\right)\Delta^2+O(\Delta^3)\right\}\times \\
&\quad \left\{\frac{T-t_0}{\Delta}-\frac{1-\beta}{\beta}+\frac{\lambda(1-\beta)}{\beta^2}\Delta+O(\Delta^2)\right\}+o(\Delta^L) \\
&= \frac{T-t_0}{\beta}\frac{1}{\Delta}-\left\{(T-t_0)\frac{\lambda}{\beta^2}+\frac{1-\beta}{\beta^2}\right\}+\left\{\frac{1-\beta}{\beta}\left(\frac{\lambda}{\beta^2}\right)+\frac{\lambda(1-\beta)}{\beta^3}+(T-t_0)\lambda^2\frac{(2-\beta)}{2\beta^3}\right\}\Delta \\
&\quad +O(\Delta^2) \\
&= \frac{T-t_0}{\beta}\frac{1}{\Delta}-\left\{(T-t_0)\frac{\lambda}{\beta^2}+\frac{1-\beta}{\beta^2}\right\}+\left\{\frac{2\lambda(1-\beta)}{\beta^3}+(T-t_0)\lambda^2\frac{(2-\beta)}{2\beta^3}\right\}\Delta+O(\Delta^2),
\end{aligned}
$$

and

$$
\begin{aligned}
&\Delta \exp(-\lambda\Delta) \sum_{i=1}^{n} Z_i \\
&= \frac{\Delta \exp(-\lambda\Delta)}{1-(1-\beta)\exp(-\lambda\Delta)} \left(\frac{n(n-1)}{2}\right) \\
&\quad + \frac{\Delta \exp(-\lambda\Delta)}{1-(1-\beta)\exp(-\lambda\Delta)} \left\{ \frac{(1-\beta)\exp(-\lambda\Delta)}{(1-(1-\beta)\exp(-\lambda\Delta))^2} + o(\Delta^L) \right\} \\
&\quad - \frac{\Delta \exp(-\lambda\Delta)}{1-(1-\beta)\exp(-\lambda\Delta)} \left\{ \frac{n(1-\beta)\exp(-\lambda\Delta)}{1-(1-\beta)\exp(-\lambda\Delta)} + o(\Delta^L) \right\} \\
&= \frac{(T-t_0)\exp(-\lambda\Delta)}{1-(1-\beta)\exp(-\lambda\Delta)} \left\{ \frac{(T-t_0)}{2\Delta} - \frac{1}{2} \right\} + \frac{\Delta \exp(-\lambda\Delta)}{(1-(1-\beta)\exp(-\lambda\Delta))^3} (1-\beta)\exp(-\lambda\Delta) \\
&\quad - \frac{(T-t_0)\exp(-\lambda\Delta)}{1-(1-\beta)\exp(-\lambda\Delta)} \left\{ \frac{1}{1-(1-\beta)\exp(-\lambda\Delta)} - 1 \right\} + o(\Delta^L) \\
&= (T-t_0)^2 \left(1 - \lambda\Delta + \frac{\lambda^2}{2}\Delta^2 + O(\Delta^3)\right) \times \\
&\quad \left(\frac{1}{\beta} - \frac{\lambda(1-\beta)}{\beta^2}\Delta + \frac{\lambda^2(1-\beta)(2-\beta)}{2\beta^3}\Delta^2 + O(\Delta^3)\right) \frac{1}{2\Delta} \\
&\quad - \frac{1}{2}(T-t_0)(1-\lambda\Delta+O(\Delta^2)) \left(\frac{1}{\beta} - \frac{\lambda(1-\beta)}{\beta^2}\Delta + O(\Delta^2)\right) \\
&\quad + \Delta(1+O(\Delta))(1-\beta)(1+O(\Delta))(\beta^{-3}+O(\Delta)) \\
&\quad - (T-t_0)(1-\lambda\Delta+O(\Delta^2)) \left(\frac{1}{\beta} - \frac{\lambda(1-\beta)}{\beta^2}\Delta + O(\Delta^2)\right) \times \\
&\quad \left\{ \left(\frac{1}{\beta} - \frac{\lambda(1-\beta)}{\beta^2}\Delta + O(\Delta^2)\right) - 1 \right\} + o(\Delta^L) \\
&= (T-t_0)^2 \left\{ \frac{1}{\beta} - \left(\frac{\lambda}{\beta} + \frac{\lambda(1-\beta)}{\beta^2}\right)\Delta + \left(\frac{\lambda^2}{2\beta} + \frac{\lambda^2(1-\beta)}{\beta^2} + \frac{\lambda^2(1-\beta)(2-\beta)}{2\beta^3}\right)\Delta^2 \right\} \frac{1}{2\Delta} \\
&\quad - \frac{1}{2}(T-t_0) \left\{ \frac{1}{\beta} - \left(\frac{\lambda}{\beta} + \frac{\lambda(1-\beta)}{\beta^2}\right)\Delta + O(\Delta^2) \right\} + \frac{1-\beta}{\beta^3}\Delta \\
&\quad - (T-t_0) \left\{ \frac{1}{\beta} - \left(\frac{\lambda}{\beta} + \frac{\lambda(1-\beta)}{\beta^2}\right)\Delta \right\} \left\{ \frac{1-\beta}{\beta} - \frac{\lambda(1-\beta)}{\beta^2}\Delta \right\} + O(\Delta^2) \\
&= (T-t_0)^2 \left\{ \frac{1}{2\beta}\frac{1}{\Delta} - \frac{\lambda}{2\beta^2} + \frac{\lambda^2(2-\beta)}{2\beta^3}\frac{\Delta}{2} \right\} - \frac{1}{2}(T-t_0)\frac{1}{\beta} + \frac{1}{2}(T-t_0)\frac{\lambda}{\beta^2}\Delta + \frac{1-\beta}{\beta^3}\Delta \\
&\quad - (T-t_0) \left\{ \frac{1-\beta}{\beta^2} - \left(\frac{\lambda(1-\beta)}{\beta^3} + \frac{\lambda(1-\beta)}{\beta^3}\right)\Delta \right\} + O(\Delta^2) \\
&= \frac{(T-t_0)^2}{2\beta}\frac{1}{\Delta} + \left\{ \frac{-(T-t_0)(1-\beta)}{\beta^2} - \frac{T-t_0}{2\beta} - \frac{(T-t_0)^2\lambda}{2\beta^2} \right\} \\
&\quad + \left\{ \frac{(T-t_0)^2\lambda^2(2-\beta)}{4\beta^3} + \frac{(T-t_0)\lambda}{2\beta^2} + \frac{1-\beta}{\beta^3} + \frac{2\lambda(1-\beta)(T-t_0)}{\beta^3} \right\} \Delta + O(\Delta^2).
\end{aligned}
$$

Thus, omitting terms of $O(\Delta^2)$, we get

$$
\begin{aligned}
D_n &= \sum_{i=1}^{n} D_i(\beta) \\
&= \beta k_1 \mu^2 \sum_{i=1}^{n} X_i - k_1 \mu \beta^2 (t_0 - \mu) \exp(-\lambda\Delta) \sum_{i=1}^{n} Y_i - \beta^2 k_1 \mu \Delta \exp(-\lambda\Delta) \sum_{i=1}^{n} Z_i \\
&\quad + \beta k_1 \mu \sum_{i=1}^{n} (t_i - \mu) + \beta k_0 \mu \sum_{i=1}^{n} X_i + \beta^2 k_0 \mu \exp(-\lambda\Delta) \sum_{i=1}^{n} Y_i - \sum_{i=1}^{n} \beta k_0 \mu \\
&= \beta k_1 \mu^2 \left\{ \exp(-\lambda t_0) \frac{1-\beta}{\beta} - \exp(-\lambda t_0) \frac{\lambda(1-\beta)}{\beta^2} \Delta \right\} \\
&\quad - k_1 \mu \beta^2 (t_0 - \mu) \left\{ \frac{T-t_0}{\beta} \frac{1}{\Delta} - \left((T-t_0) \frac{\lambda}{\beta^2} + \frac{1-\beta}{\beta^2} \right) \right. \\
&\quad \left. + \left(\frac{2\lambda(1-\beta)}{\beta^3} + (T-t_0)\lambda^2 \frac{(2-\beta)}{2\beta^3} \right) \Delta \right\} \\
&\quad - k_1 \mu \beta^2 \left\{ \frac{(T-t_0)^2}{2\beta} \frac{1}{\Delta} + \left(\frac{-(T-t_0)(1-\beta)^2}{\beta^2} - \frac{T-t_0}{2\beta} - \frac{(T-t_0)^2 \lambda}{2\beta^2} \right) \right. \\
&\quad \left. + \left(\frac{(T-t_0)^2 \lambda^2 (2-\beta)}{4\beta^3} + \frac{(T-t_0)\lambda}{2\beta^2} + \frac{1-\beta}{\beta^3} + \frac{2\lambda(1-\beta)(T-t_0)}{\beta^3} \right) \Delta \right\} \\
&\quad + \beta k_1 \mu \left\{ \frac{T-t_0}{2} + \frac{(T+t_0-2\mu)(T-t_0)}{2} \frac{1}{\Delta} \right\} \\
&\quad + \beta k_0 \mu \left\{ \exp(-\lambda t_0) \frac{1-\beta}{\beta} - \exp(-\lambda t_0) \frac{\lambda(1-\beta)}{\beta} \Delta \right\} + k_0 \mu \beta^2 \left\{ \frac{T-t_0}{\beta} \frac{1}{\Delta} \right. \\
&\quad \left. - \left((T-t_0) \frac{\lambda}{\beta^2} + \frac{1-\beta}{\beta^2} \right) + \left(\frac{2\lambda(1-\beta)}{\beta^3} + (T-t_0)\lambda^2 \frac{(2-\beta)}{2\beta^3} \right) \Delta \right\} - \beta k_0 \mu (T-t_0) \frac{1}{\Delta} \\
&= -k_1 \mu \beta (T-t_0) \left\{ \underbrace{(t_0 - \mu) + \frac{T-t_0}{2} - \frac{T+t_0-2\mu}{2} - \beta k_0 \mu (T-t_0) + \beta k_0 \mu (T-t_0)}_{0} \right\} \frac{1}{\Delta} \\
&\quad + \left\{ k_1 \mu^2 (1-\beta) \exp(-\lambda t_0) + k_1 \mu \beta^2 (t_0 - \mu) \left((T-t_0) \frac{\lambda}{\beta^2} + \frac{1-\beta}{\beta^2} \right) \right. \\
&\quad \left. - k_1 \mu \left(-(T-t_0)(1-\beta)^2 - \frac{(T-t_0)}{2} \beta - (T-t_0)^2 \frac{\lambda}{2} \right) + \beta k_1 \mu \frac{(T-t_0)}{2} \right\} \\
&\quad + k_0 \mu \exp(-\lambda t_0)(1-\beta) - k_0 \mu ((T-t_0)\lambda + 1 - \beta) \\
&\quad + \left\{ -k_1 \mu^2 \exp(-\lambda t_0) \lambda (1-\beta) - k_1 \mu (t_0 - \mu) \left(\frac{2\lambda(1-\beta)}{\beta} + \frac{\lambda^2 (T-t_0)(2-\beta)}{2\beta} \right) \right. \\
&\quad - k_1 \mu \left((T-t_0)^2 \frac{\lambda^2 (2-\beta)}{4\beta} + \frac{(T-t_0)\lambda}{2} + \frac{1-\beta}{\beta} + \frac{2\lambda(1-\beta)(T-t_0)}{\beta} \right) \\
&\quad \left. - k_0 \exp(-\lambda t_0)(1-\beta) + k_0 \frac{2(1-\beta)}{\beta} + k_0 (T-t_0) \frac{\lambda(2-\beta)}{2\beta} \right\} \Delta,
\end{aligned}
$$

where we recall that $\Delta = \frac{T-t_0}{n}$. We may now denote D_n as

$$D_n \doteq a_0 + a_1 \frac{1}{n} + O\left(\frac{1}{n^2}\right).$$

This approximation is more accurate when n is relatively large (or Δ is small).

For I_n we similarly expand $(\exp(\lambda\Delta) - 1)\sum_{i=1}^n X_i$, $(1 - \exp(-\lambda\Delta))\sum_{i=1}^n Y_i$, and $\Delta(1 - \exp(-\lambda\Delta))\sum_{i=1}^n Z_i$ to get:

$$\begin{aligned}(\exp(\lambda\Delta) - 1)\sum_{i=1}^n X_i &= (\lambda\Delta + O(\Delta^2))\left(\exp(-\lambda t_0)\frac{1-\beta}{\beta} + O(\Delta)\right) \\ &= \frac{\exp(-\lambda t_0)\lambda(1-\beta)}{\beta}\Delta + O(\Delta^2),\end{aligned}$$

$$\begin{aligned}&(1 - \exp(-\lambda\Delta))\sum_{i=1}^n Y_i \\ &= \frac{\left(\lambda\Delta - \frac{\lambda^2}{2}\Delta^2\right)}{1 - (1-\beta)\exp(-\lambda\Delta)}\left\{n - \frac{(1-\beta)\exp(-\lambda\Delta)}{1 - (1-\beta)\exp(-\lambda\Delta)}\right\} + O(\Delta^2) \\ &= \left\{\lambda(T-t_0) - \frac{\lambda^2}{2}(T-t_0)\Delta\right\}\left\{\frac{1}{\beta} - \frac{\lambda(1-\beta)}{\beta^2}\Delta\right\} \\ &\quad - \lambda\Delta\left(\frac{1}{\beta} + O(\Delta)\right)(1-\beta)(1-\lambda\Delta)\left(\frac{1}{\beta}\right) + O(\Delta^2) \\ &= \lambda(T-t_0)\frac{1}{\beta} - \left\{\frac{\lambda^2(T-t_0)}{2\beta} + \frac{\lambda^2(T-t_0)(1-\beta)}{\beta^2} + \frac{\lambda(1-\beta)}{\beta^2}\right\}\Delta + O(\Delta^2),\end{aligned}$$

and

$$
\begin{aligned}
&\Delta(1-\exp(-\lambda\Delta))\sum_{i=1}^{n} Z_i \\
&= \Delta\frac{\left(\lambda\Delta-\frac{\lambda^2}{2}\Delta^2+O(\Delta^3)\right)}{1-(1-\beta)\exp(-\lambda\Delta)}\left\{n\left(\frac{n}{2}-\frac{1}{2}\right)\right. \\
&\quad \left.+\frac{(1-\beta)\exp(-\lambda\Delta)}{(1-(1-\beta)\exp(-\lambda\Delta))^2}-\frac{n(1-\beta)\exp(-\lambda\Delta)}{1-(1-\beta)\exp(-\lambda\Delta)}\right\}+o(\Delta^L) \\
&= (T-t_0)\left\{\lambda\Delta-\frac{\lambda^2}{2}\Delta^2\right\}\left\{\frac{1}{\beta}-\frac{\lambda(1-\beta)}{\beta^2}\Delta\right\}\left(\frac{n}{2}-\frac{1}{2}\right) \\
&\quad +(T-t_0)\left\{\frac{1}{\beta}-\frac{\lambda(1-\beta)}{\beta^2}\Delta\right\}\lambda\Delta\frac{-(1-\beta)}{\beta}+O(\Delta^2) \\
&= (T-t_0)\left\{\frac{\lambda}{\beta}-\frac{\lambda^2\Delta}{2\beta}\right\}\left(\frac{\Delta n}{2}-\frac{\Delta}{2}\right)+(T-t_0)\left\{\frac{-(1-\beta)\lambda\Delta}{\beta^2}\right\}+O(\Delta^2) \\
&= \frac{(T-t_0)^2\lambda}{2\beta}-\left\{\frac{(T-t_0)^2\lambda^2}{4\beta}+\frac{(T-t_0)\lambda}{2\beta}+\frac{(T-t_0)\lambda(1-\beta)}{\beta^2}\right\}\Delta+O(\Delta^2).
\end{aligned}
$$

Omitting terms of $O(\Delta^2)$ gives

$$
\begin{aligned}
I_n &= \sum_{i=1}^{n} I_i \\
&= k_1\mu^2(\exp(\lambda\Delta)-1)\sum_{i=1}^{n} X_i - k_1\mu\beta(t_0-\mu)(1-\exp(-\lambda\Delta))\sum_{i=1}^{n} Y_i \\
&\quad - k_1\mu\beta\Delta(1-\exp(-\lambda\Delta))\sum_{i=1}^{n} Z_i + \frac{k_1}{2}(T^2-t_0^2) - k_1\mu(T-t_0) \\
&\quad + k_0\mu(\exp(\lambda\Delta)-1)\sum_{i=1}^{n} X_i + k_0\beta\mu(1-\exp(-\lambda\Delta))\sum_{i=1}^{n} Y_i - k_0(T-t_0) \\
&= k_1\mu^2\left\{\frac{\exp(-\lambda t_0)\lambda(1-\beta)}{\beta}\Delta\right\} \\
&\quad -k_1\mu\beta(t_0-\mu)\left\{\lambda(T-t_0)\frac{1}{\beta} - \left(\frac{\lambda^2(T-t_0)}{2\beta} + \frac{\lambda^2(T-t_0)(1-\beta)}{\beta^2} + \frac{\lambda(1-\beta)}{\beta^2}\right)\Delta\right\} \\
&\quad - k_1\mu\beta\left\{\frac{(T-t_0)^2\lambda}{2\beta} - \left(\frac{(T-t_0)^2\lambda^2}{4\beta} + \frac{(T-t_0)\lambda}{2\beta} + \frac{(T-t_0)\lambda(1-\beta)}{\beta^2}\right)\Delta\right\} \\
&\quad + \frac{k_1}{2}(T^2-t_0^2) - k_1\mu(T-t_0) + k_0\exp(-\lambda t_0)\frac{1-\beta}{\beta}\Delta + k_0\beta\mu\left\{\lambda(T-t_0)\frac{1}{\beta}\right. \\
&\quad \left. - \left(\frac{\lambda^2(T-t_0)}{2\beta} + \frac{\lambda^2(T-t_0)(1-\beta)}{\beta^2} + \frac{\lambda(1-\beta)}{\beta^2}\right)\Delta\right\} - k_0(T-t_0) \\
&= \underbrace{-k_1(t_0-\mu)(T-t_0) - \frac{k_1(T-t_0)^2}{2} + \frac{k_1(T^2-t_0^2)}{2} - k_1\mu(T-t_0)}_{0} \\
&\quad + \left\{\frac{k_1\mu\exp(-\lambda t_0)(1-\beta)}{\beta} + \frac{k_1\lambda(t_0-\mu)(T-t_0)(2-\beta)}{2\beta} + \frac{k_1(t_0-\mu)(1-\beta)}{\beta}\right. \\
&\quad + \frac{k_1(T-t_0)^2\lambda}{4} + \frac{k_1(T-t_0)(2-\beta)}{2\beta} + \frac{k_0\exp(-\lambda t_0)(1-\beta)}{\beta} - \frac{k_0\lambda(T-t_0)}{2} \\
&\quad \left. - \frac{k_0\lambda(T-t_0)(1-\beta)}{\beta} - \frac{k_0(1-\beta)}{\beta}\right\}\Delta,
\end{aligned}
$$

where $\Delta = \frac{T-t_0}{n}$. We may thus denote I_n as

$$I_n \doteq b_1\frac{1}{n} + O\left(\frac{1}{n^2}\right).$$

Then using the above expressions, we can derive the conditions for the existence of a

unique maximum of $U(n)$. We have

$$\begin{aligned} U(n) &= C_1\{AD_n - BI_n\} - C_2(n+1) \\ &= C_1 A\left(a_0 + a_1\frac{1}{n}\right) - C_1 B\left(b_1\frac{1}{n}\right) - C_2(n+1) + O\left(\frac{1}{n^2}\right). \end{aligned}$$

Now let $\frac{1}{n} = x$ and

$$\begin{aligned} h(x) &= C_1 A(a_0 + a_1 x) - C_1 B(b_1 x) - C_2\left(\frac{1}{x} + 1\right) \\ h'(x) &= C_1 A a_1 - C_1 B b_1 + C_2\frac{1}{x^2} \\ h''(x) &= \frac{-2C_2}{x^3}. \end{aligned}$$

To find the critical point of $h(x)$ we set $h'(x) = 0$:

$$C_1 A a_1 - C_1 B b_1 + C_2\frac{1}{x^2} = 0.$$

The only critical point of $h(x)$, x_c, satisfies

$$x_c^2 = \frac{C_2}{C_1(Bb_1 - Aa_1)},$$

where

$$
\begin{aligned}
a_1 &= (T-t_0)\left\{k_1\left(-\mu\exp(-\lambda t_0)(1-\beta)-2(t_0-\mu)\frac{(1-\beta)}{\beta}-\frac{\lambda(t_0-\mu)(T-t_0)(2-\beta)}{2\beta}\right.\right.\\
&\quad \left.-(T-t_0)^2\frac{\lambda(2-\beta)}{4\beta}-\frac{(T-t_0)}{2}-\frac{\mu(1-\beta)}{\beta}-\frac{2(1-\beta)(T-t_0)}{\beta}\right)\\
&\quad \left.+k_0\left(-\exp(-\lambda t_0)(1-\beta)+\frac{2(1-\beta)}{\beta}+\frac{(T-t_0)\lambda(2-\beta)}{2\beta}\right)\right\}\\
&= (T-t_0)\left\{k_1\left(-\mu\exp(-\lambda t_0)(1-\beta)-\frac{(2-\beta)\lambda(T-t_0)}{\beta}(\frac{T+t_0}{2}-\mu)\right.\right.\\
&\quad \left.-\frac{T-t_0}{2}-\frac{(2T-\mu)(1-\beta)}{\beta}\right)\\
&\quad \left.+k_0\left(-\exp(-\lambda t_0)\frac{(1-\beta)}{\beta}+\frac{2(1-\beta)}{\beta}+\frac{(T-t_0)\lambda(2-\beta)}{2\beta}\right)\right\}
\end{aligned}
$$

and

$$
\begin{aligned}
b_1 &= (T-t_0)\left\{k_1\left(\frac{\mu\exp(-\lambda t_0)(1-\beta)}{\beta}+\frac{\lambda(t_0-\mu)(T-t_0)(2-\beta)}{2\beta}+\frac{(t_0-\mu)(1-\beta)}{\beta}\right.\right.\\
&\quad \left.+\frac{(T-t_0)^2\lambda}{4}+\frac{(T-t_0)(2-\beta)}{2\beta}\right)\\
&\quad \left.+k_0\left(\frac{\exp(-\lambda t_0)(1-\beta)}{\beta}-\frac{\lambda(T-t_0)}{2}-\frac{-\lambda(T-t_0)(1-\beta)}{\beta}-\frac{1-\beta}{\beta}\right)\right\}.
\end{aligned}
$$

It is easy to show that $a_1 < 0$ and $b_1 > 0$ under the assumption that $\frac{k_0}{k_1} < t_0$. This condition is easily satisfied under practical settings. Therefore, since

1. $a_1 < 0$, $b_1 > 0$, and $\frac{C_2}{C_1} > 0$, and

2. $h''(x) < 0$ for any $x > 0$,

$\frac{C_2}{C_1(Bb_1-Aa_1)} > 0$, $h(x)$ is concave, and $x_c = \sqrt{\frac{C_2}{C_1(Bb_1-Aa_1)}}$ is the unique maximum of $h(x)$.

Equivalently, the optimal Δ^* of the approximate utility function $U(n) \doteq C_1A(a_0 +$

$a_1\frac{1}{n}) - C_1B(b_1\frac{1}{n}) - C_2(n+1)$ can be obtained from the optimal n^*:

$$\begin{aligned} n^* &= \frac{1}{x_c} \\ &= \sqrt{\frac{C_1(Bb_1 - Aa_1)}{C_2}}, \\ \Delta^* &= \frac{(T - t_0)}{n^*} \\ &= (T - t_0)\sqrt{\frac{C_2}{C_1(Bb_1 - Aa_1)}}. \end{aligned}$$

In order to have $n^* \geq 1$, we require

$$\frac{C_1(Bb_1 - Aa_1)}{C_2} \geq 1.$$

This condition is easily satisfied.

4.2.2 Framework 2: Fixed Budget

This framework may address a realistic issue of a limited budget of healthcare in society. Under a fixed budget, or equivalently a fixed number of examinations, we present a utility function where given the starting age t_0, the ages of examination $\{t_1 \ldots t_n\}$ are unknown. In this scenario, the $\{t_i\}_{i=1\ldots n}$ which maximize the utility function will define the optimal schedule for a prespecified number of exams and screening horizon.

Presentation of Model

Using Zelen's expressions for $D_i(\beta)$ and $I_i(\beta, t)$, we define the utility function for a screening program with $n+1$ exams at times $t_0, t_1, \ldots, t_n$ as follows:

$$\begin{aligned} U(t_1, \ldots, t_n) &= Value\ Of\ Benefit(t_1, \ldots, t_n) - Cost\ Of\ Screening(t_1, \ldots, t_n) \\ &= C_1 \left(A \sum_{i=0}^{n} D_i(\beta, t_0, \ldots, t_i) - B \sum_{i=1}^{n+1} I_i(\beta, t_0, \ldots, t_i) \right) - C_2(n+1), \end{aligned}$$

with the first exam at a known age t_0. Again, we assume that the *Benefit* is the difference in cure rates between those found on examination compared to interval cases, where A is the probability of a cure when disease is found through screening, B is the probability of a cure for an interval case, C_1 is the average dollar value of survival benefit due to one life cured, and C_2 is the average cost of a screening exam.

We fix the age of first examination (t_0) and the maximum age of examination (T), for example $t_0 = 40$ and $T = 79$ according to current screening guidelines. We are thus searching for the optimal schedule of $n+1$ examinations at times t_0, t_1, ..., t_n which may be unequally-spaced at intervals of Δ_1, Δ_2, ..., Δ_n. We can find the optimal exam times t_0, t_1, ..., $t_n \leq T$ and therefore the optimal intervals Δ_1, Δ_2, ..., Δ_n that maximize the utility function $U(t_1, \ldots, t_n)$.

The proof that a solution exists under this framework is simple.

Proof for Existence of Solution

We can prove that $U(t_1, ..., t_n)$ achieves a maximum at some $t_1^*, ..., t_n^*$ by using the Extreme Value Theorem:

Extreme Value Theorem. *Suppose that H is a nonempty subset of $\mathbf{R}^n$ and $f : H \to \mathbf{R}$. If H is compact, and f is continuous on H, then $M := sup\{f(\mathbf{x}) : \mathbf{x} \in H\}$ and $m := inf\{f(\mathbf{x}) : \mathbf{x} \in H\}$ are finite real numbers. Moreover, there exist points $\mathbf{x}_M$, $\mathbf{x}_m \in H$ such that $M = f(\mathbf{x}_M)$ and $m = f(\mathbf{x}_m)$.*

Clearly, we have a closed and finite set in $\{(t_1, \ldots, t_n) : t_0 \leq t_1 \leq t_2 \leq \ldots \leq t_n \leq T\}$ since the examination ages are bounded by the starting and ending ages t_0 and T. It is also clear that since the utility function U consists of continuous functions, it is continuous on the compact set $\{(t_1, \ldots, t_n) : t_0 \leq t_1 \leq t_2 \leq \ldots \leq t_n \leq T\}$. Therefore, a maximum exists at some $t_1, ..., t_n$.

4.3 Numerical Results

We apply the theoretical results to finding the optimal screening program under the two separate frameworks.

4.3.1 Illustration of Framework 1

To illustrate the results for finding the optimal number of equally spaced exams within a fixed screening interval, we specify certain parameter values for the expression $U(n)$. We assume that an optimal screening program within a fixed interval $[t_0, T]$ will have

$n+1$ examinations at times $t_0, t_1, \ldots, t_n = T$ in equal intervals of Δ, where $\frac{T-t_0}{\Delta} = n$. Other parameter assumptions are listed in Table 4.1, which are all based on realistic estimators from previous studies. The cure rates $A = 0.8$ and $B = 0.52$ were estimated based on a long-term follow-up study of survival in breast cancer patients[97]. We consider a range of reasonable values for the mean sojourn time and sensitivity of mammography examination. The ratio of the cost of examination to value of life saved ($\frac{C_1}{C_2}$) is varied at \$50, \$100, or \$200, where we choose value of life saved using the commonly accepted threshold stating that a year of life is worth \$50,000. Thus if the expected gain in survival for screening versus interval detection in a cohort of sreened women (who may or may not develop the disease) is 2, 4, or 7 months, then the value of life saved is \$7,500, \$15,000, or \$30,000 based on a \$50,000 per year threshold value.

Parameter	Value
Starting age of screening	$t_0 = 40$
Ending age of screening	$T = 80$
Cure rate (screening-detected)	$A = 0.8$
Cure rate (clinically detected)	$B = 0.52$
Sojourn time distribution	$Expo(\mu)$, $\mu = \{1, 2, 3\}$
Exam sensitivity	$\beta = \{0.7, 0.8, 0.9\}$
Value of life saved by cure	$C_1 = \{\$7,500, \$15,000, \$30,000\}$
Exam cost	$C_2 = \$150$

Table 4.1 : Parameter assumptions under Framework 1.

The values k_0 and k_1 in the preclinical incidence function $w(x)$ are chosen to approximately reflect an age-dependent incidence function of a population with average-risk for breast cancer and an increased-risk for breast cancer (Figure 4.1). According

to these assumptions, the Δ (and thus n) that maximizes U was found using the R function **optimize** (Tables 4.2 through 4.4), where the optimal number of examinations $n^* = \frac{T-t_0}{\Delta^*}$ is rounded down to the nearest integer. A visualization of the utility function versus n is shown in Figure 4.2 for the case $\frac{C_1}{C_2} = 100$, $\beta = 0.8$, and $\mu = 3$ for the two risk scenarios, showing the concavity of the function.

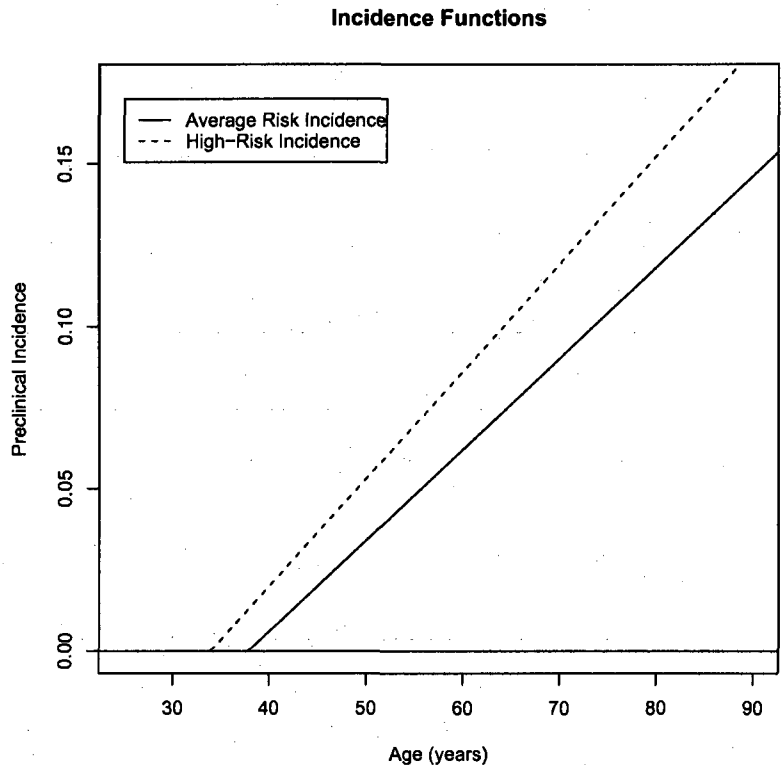


Figure 4.1 : Plot of preclinical incidence functions for average- and high-risk groups.

We observed that the study results are reasonable. The optimal schedule in an average-risk population for a mean sojourn time of $\mu = 2$ in Table 4.2 gives exams in approximately one year intervals, which is fairly consistent with current guidelines. As the mean sojourn time (μ) increases, Δ^* increases (exams are less frequent). It

		Increased-Risk $k_1 = 0.0033$ $k_0 = 0.112$	Average-Risk $k_1 = 0.0028$ $k_0 = 0.106$
$\mu = 1$	$\beta = 0.7$	$n^* = 57, \Delta^* = 0.699$	$n^* = 42, \Delta^* = 0.932$
	$\beta = 0.8$	$n^* = 55, \Delta^* = 0.716$	$n^* = 43, \Delta^* = 0.930$
	$\beta = 0.9$	$n^* = 54, \Delta^* = 0.738$	$n^* = 42, \Delta^* = 0.939$
$\mu = 2$	$\beta = 0.7$	$n^* = 47, \Delta^* = 0.840$	$n^* = 37, \Delta^* = 1.066$
	$\beta = 0.8$	$n^* = 45, \Delta^* = 0.888$	$n^* = 36, \Delta^* = 1.111$
	$\beta = 0.9$	$n^* = 42, \Delta^* = 0.939$	$n^* = 34, \Delta^* = 1.161$
$\mu = 3$	$\beta = 0.7$	$n^* = 41, \Delta^* = 0.963$	$n^* = 33, \Delta^* = 1.206$
	$\beta = 0.8$	$n^* = 38, \Delta^* = 1.031$	$n^* = 33, \Delta^* = 1.275$
	$\beta = 0.9$	$n^* = 36, \Delta^* = 1.102$	$n^* = 29, \Delta^* = 1.350$

Table 4.2 : Table of optimal n and Delta under different scenarios for $\frac{C_1}{C_2} = \$50$, or equivalently if $C_2 = \$150$, then $C_1 = \$7500$, or the value of about 2 months.

		Increased-Risk $k_1 = 0.0033$ $k_0 = 0.112$	Average-Risk $k_1 = 0.0028$ $k_0 = 0.106$
$\mu = 1$	$\beta = 0.7$	$n^* = 95, \Delta^* = 0.418$	$n^* = 75, \Delta^* = 0.528$
	$\beta = 0.8$	$n^* = 90, \Delta^* = 0.442$	$n^* = 75, \Delta^* = 0.551$
	$\beta = 0.9$	$n^* = 85, \Delta^* = 0.468$	$n^* = 69, \Delta^* = 0.577$
$\mu = 2$	$\beta = 0.7$	$n^* = 74, \Delta^* = 0.534$	$n^* = 60, \Delta^* = 0.659$
	$\beta = 0.8$	$n^* = 69, \Delta^* = 0.575$	$n^* = 56, \Delta^* = 0.704$
	$\beta = 0.9$	$n^* = 64, \Delta^* = 0.619$	$n^* = 53, \Delta^* = 0.752$
$\mu = 3$	$\beta = 0.7$	$n^* = 63, \Delta^* = 0.625$	$n^* = 52, \Delta^* = 0.766$
	$\beta = 0.8$	$n^* = 58, \Delta^* = 0.679$	$n^* = 48, \Delta^* = 0.827$
	$\beta = 0.9$	$n^* = 54, \Delta^* = 0.737$	$n^* = 44, \Delta^* = 0.890$

Table 4.3 : Table of optimal n and Delta under different scenarios for $\frac{C_1}{C_2} = \$100$, or equivalently if $C_2 = \$150$, then $C_1 = \$15000$, or the value of about 4 months.

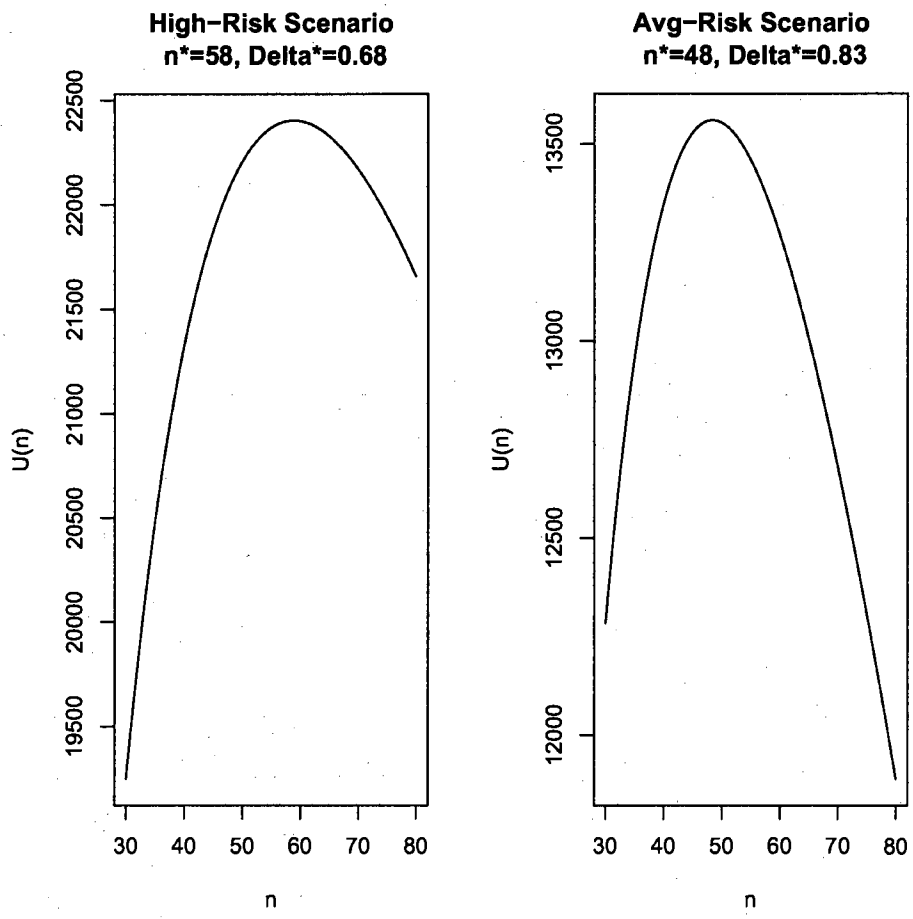


Figure 4.2 : Plots of utility function against n when $\frac{C_1}{C_2} = \$100$, $\beta = 0.8$, $\mu = 3$, under the high-risk ($k_1 = 0.0033$, $k_0 = 0.112$) and average-risk ($k_1 = 0.0028$, $k_0 = 0.106$) scenarios.

		Increased-Risk $k_1 = 0.0033$ $k_0 = 0.112$	Average-Risk $k_1 = 0.0028$ $k_0 = 0.106$
$\mu = 1$	$\beta = 0.7$	$n^* = 149, \Delta^* = 0.267$	$n^* = 121, \Delta^* = 0.328$
	$\beta = 0.8$	$n^* = 139, \Delta^* = 0.287$	$n^* = 113, \Delta^* = 0.351$
	$\beta = 0.9$	$n^* = 129, \Delta^* = 0.309$	$n^* = 106, \Delta^* = 0.375$
$\mu = 2$	$\beta = 0.7$	$n^* = 113, \Delta^* = 0.352$	$n^* = 93, \Delta^* = 0.428$
	$\beta = 0.8$	$n^* = 104, \Delta^* = 0.384$	$n^* = 86, \Delta^* = 0.464$
	$\beta = 0.9$	$n^* = 95, \Delta^* = 0.418$	$n^* = 79, \Delta^* = 0.502$
$\mu = 3$	$\beta = 0.7$	$n^* = 95, \Delta^* = 0.418$	$n^* = 79, \Delta^* = 0.506$
	$\beta = 0.8$	$n^* = 87, \Delta^* = 0.459$	$n^* = 72, \Delta^* = 0.552$
	$\beta = 0.9$	$n^* = 79, \Delta^* = 0.502$	$n^* = 66, \Delta^* = 0.601$

Table 4.4 : Table of optimal n and Delta under different scenarios for $\frac{C_1}{C_2} = \$200$, or equivalently if $C_2 = \$150$, then $C_1 = \$30000$, or the value of about 7 months.

makes sense that if the preclinical duration is longer, examinations may be spaced further apart. Also, as the exam sensitivity (β) increases, Δ^* increases. Better exam performance may allow for more reliability of the exam and thus less frequent examinations. We also observed that when the incidence is higher, the optimal time between examinations is smaller, requiring more frequent examinations among a higher-risk group.

Depending on the ratio of costs $\frac{C_1}{C_2}$, the optimal n and Δ varied. As the ratio increased, the optimal Δ became smaller. This may reflect that when the value of life to be gained is much greater than the cost for screening, there may be more incentive to spend more money on additional screening, which leads to more frequent and intensive screening exams.

4.3.2 Illustration of Framework 2

We illustrate the results for finding an optimal set of exam times $t_1, \ldots, t_n \leq T$ within a screening horizon $[t_0, T]$ given the assumptions in Table 4.5. We investigate a range of starting and ending ages for screening under various combinations of mean sojourn times and exam sensitivities. We illustrate the difference in optimal exam times under the given number of exams: 5 and 10 ($n = 4, 9$), using the same estimates of k_0 and k_1 for the preclinical incidence $w(x)$ as in the previous illustration. Note that under this framework, the optimal exam times do not depend on the costs for exam or life value.

Parameter	Value
Starting age of screening	$t_0 = \{40, 50\}$
Maximum age of screening	$T = \{60, 80\}$
Cure rate (screening-detected)	$A = 0.8$
Cure rate (clinically detected)	$B = 0.52$
Sojourn time distribution	$Expo(\mu)$, $\mu = \{2, 4\}$
Exam sensitivity	$\beta = \{0.8, 0.6\}$
Number of Exams	$n + 1 = \{5, 10\}$

Table 4.5 : Parameter assumptions under Framework 2.

Given these assumptions, we use the R function optim to find the set of exam times $t_1, \ldots, t_n$ that maximize U. The results are listed in Tables 4.6- 4.7.

We made the following general observations. First, an increase in mean sojourn time and exam sensitivity led to an increase in intervals between exams, which again makes intuitive sense. It also makes sense that the intervals between exams are shorter for shorter screening horizons and longer for longer screening horizons. The intervals

			$\beta = 0.8$, $\mu = 2$		$\beta = 0.8$, $\mu = 4$		$\beta = 0.6$,$\mu = 2$		$\beta = 0.6$, $\mu = 4$	
		t_0	40	50	40	50	40	50	40	50
$T = 60$	$n = 4$	t_1,Δ_1	49.80,9.80	52.89,2.89	48.69,8.69	52.82,2.82	50.62,10.62	52.95,2.95	49.68,9.68	52.90,2.90
		t_2,Δ_2	53.56,3.76	55.38,2.50	53.19,4.50	55.47,2.65	54.06,3.43	55.39,2.44	53.83,4.15	55.58,2.68
		t_3,Δ_3	56.57,3.01	57.62,2.24	56.84,3.65	57.88,2.41	56.76,2.70	57.52,2.13	57.14,3.31	57.98,2.40
		t_4,Δ_4	59.19,2.62	59.67,2.05	60.00,3.16	60.00,2.12	59.09,2.33	59.45,1.93	60.00,2.86	60.00,2.02
	$n = 9$	t_1,Δ_1	44.84,4.84	51.19,1.19	44.13,4.13	51.00,1.00	45.86,5.86	51.14,1.14	44.97,4.97	50.78,0.78
		t_2,Δ_2	47.65,2.81	52.47,1.27	46.96,2.83	52.32,1.32	48.59,2.72	52.47,1.33	47.78,2.80	52.20,1.42
		t_3,Δ_3	49.95,2.29	53.68,1.21	49.35,2.39	53.58,1.26	50.75,2.17	53.71,1.25	50.10,2.32	53.55,1.34
		t_4,Δ_4	51.96,2.01	54.84,1.16	51.48,2.13	54.79,1.21	52.63,1.88	54.89,1.18	52.14,2.05	54.83,1.28
		t_5,Δ_5	53.79,1.83	55.96,1.12	53.44,1.96	55.96,1.17	54.32,1.69	56.02,1.13	54.01,1.87	56.05,1.23
		t_6,Δ_6	55.48,1.70	57.04,1.08	55.27,1.83	57.09,1.13	55.88,1.56	57.10,1.08	55.74,1.73	57.23,1.18
		t_7,Δ_7	57.08,1.59	58.08,1.04	57.00,1.73	58.19,1.10	57.34,1.46	58.14,1.04	57.37,1.63	58.37,1.14
		t_8,Δ_8	58.58,1.51	59.09,1.01	58.64,1.64	59.26,1.07	58.71,1.38	59.14,1.00	58.92,1.55	59.47,1.10
		t_9,Δ_9	60.00,1.42	60.00,0.91	60.00,1.36	60.00,0.74	60.00,1.29	60.00,0.86	60.00,1.08	60.00,0.53
$T = 80$	$n = 4$	t_1,Δ_1	65.36,25.36	65.37,15.37	61.32,21.32	62.02,12.02	66.49,26.49	66.49,16.49	62.86,22.86	63.25,13.25
		t_2,Δ_2	70.47,5.11	70.48,5.11	68.32,7.00	68.69,6.67	71.18,4.69	71.18,4.69	69.23,6.37	69.43,6.18
		t_3,Δ_3	74.61,4.13	74.61,4.13	73.90,5.58	74.10,5.41	74.91,3.73	74.91,3.73	74.23,5.00	74.34,4.91
		t_4,Δ_4	78.22,3.62	78.23,3.62	78.75,4.85	78.84,4.74	78.15,3.24	78.15,3.24	78.54,4.31	78.59,4.25
	$n = 9$	t_1,Δ_1	56.08,16.08	56.83,6.83	51.90,11.90	55.67,5.37	58.09,18.09	58.35,8.35	54.08,14.08	56.26,6.26
		t_2,Δ_2	60.51,4.43	60.99,4.16	57.23,5.33	59.58,4.21	62.22,4.13	62.38,4.03	59.13,5.05	60.54,4.28
		t_3,Δ_3	64.07,3.55	64.41,3.42	61.50,4.27	63.22,3.64	65.48,3.26	65.60,3.22	63.12,3.99	64.13,3.59
		t_4,Δ_4	67.17,3.10	67.42,3.01	65.23,3.73	66.51,3.29	68.30,2.82	68.39,2.79	66.56,3.44	67.31,3.18
		t_5,Δ_5	69.97,2.80	70.16,2.74	68.61,3.38	69.55,3.04	70.84,2.53	70.90,2.51	69.66,3.10	70.21,2.90
		t_6,Δ_6	72.56,2.59	72.70,2.54	71.73,3.12	72.39,2.84	73.17,2.33	73.21,2.31	72.52,2.85	72.90,2.69
		t_7,Δ_7	74.99,2.43	75.09,2.39	74.66,2.93	75.08,2.69	75.34,2.17	75.37,2.16	75.18,2.67	75.43,2.53
		t_8,Δ_8	77.28,2.30	77.35,2.26	77.43,2.77	77.64,2.56	77.39,2.05	77.41,2.04	77.70,2.52	77.83,2.40
		t_9,Δ_9	79.47,2.19	79.50,2.16	80.00,2.57	80.00,2.36	79.34,1.95	79.35,1.94	80.00,2.30	80.00,2.17

Table 4.6 : Increased-risk scenario: Table of optimal Δ_i and t_i under different scenarios for $T = \{60, 80\}$, $t_0 = \{40, 50\}$, $\beta = \{0.6, 0.8\}$, $\mu = \{2, 4\}$, $n = \{4, 9\}$, $A = 0.8$, $B = 0.52$, and $k_1 = 0.0033$, $k_0 = 0.112$.

			$\beta = 0.8$, $\mu = 2$		$\beta = 0.8$, $\mu = 4$		$\beta = 0.6$,$\mu = 2$		$\beta = 0.6$, $\mu = 4$	
		t_0	40	50	40	50	40	50	40	50
$T = 60$	$n = 4$	t_1,Δ_1	50.93,10.93	53.08,3.08	49.90,9.90	52.99,2.99	51.68,11.68	53.23,3.23	50.91,10.91	53.18,3.18
		t_2,Δ_2	54.35,3.42	55.58,2.50	53.95,4.06	55.62,2.63	54.79,3.10	55.65,2.42	54.60,3.70	55.82,2.63
		t_3,Δ_3	57.07,2.72	57.77,2.19	57.22,3.26	57.98,2.35	57.23,2.44	57.71,2.07	57.55,2.94	58.12,2.31
		t_4,Δ_4	59.43,2.37	59.76,1.99	60.00,2.78	60.00,2.02	59.33,2.10	59.56,1.84	60.00,2.45	60.00,1.88
	$n = 9$	t_1,Δ_1	46.35,6.35	51.28,1.28	45.48,5.48	51.12,1.12	47.43,7.43	51.28,1.28	46.57,6.57	51.01,1.01
		t_2,Δ_2	48.95,2.60	52.59,1.30	48.20,2.71	52.46,1.34	49.88,2.45	52.64,1.36	49.16,2.59	52.45,1.44
		t_3,Δ_3	51.03,2.08	53.81,1.22	50.41,2.22	53.73,1.26	51.82,1.93	53.90,1.25	51.26,2.10	53.79,1.34
		t_4,Δ_4	52.84,1.81	54.97,1.16	52.36,1.95	54.93,1.20	53.49,1.67	55.07,1.17	53.10,1.84	55.05,1.26
		t_5,Δ_5	54.48,1.64	56.07,1.10	54.14,1.78	56.08,1.15	54.99,1.50	56.17,1.10	54.77,1.67	56.25,1.20
		t_6,Δ_6	55.99,1.52	57.13,1.06	55.80,1.65	57.19,1.11	56.38,1.39	57.22,1.05	56.32,1.55	57.39,1.14
		t_7,Δ_7	57.41,1.42	58.14,1.02	57.35,1.56	58.26,1.07	57.67,1.29	58.23,1.01	57.77,1.45	58.49,1.10
		t_8,Δ_8	58.76,1.35	59.13,0.98	58.83,1.48	59.30,1.04	58.90,1.22	59.19,0.97	59.14,1.38	59.54,1.06
		t_9,Δ_9	60.00,1.24	60.00,0.87	60.00,1.17	60.00,0.70	60.00,1.10	60.00,0.81	60.00,0.86	60.00,0.46
$T = 80$	$n = 4$	t_1,Δ_1	66.07,26.07	66.07,16.07	62.54,22.54	62.93,12.93	67.16,27.16	67.16,17.16	64.00,24.00	64.21,14.21
		t_2,Δ_2	70.97,4.90	70.97,4.90	69.16,6.62	69.36,6.43	71.65,4.49	71.65,4.49	70.01,6.01	70.12,5.91
		t_3,Δ_3	74.93,3.95	74.93,3.95	74.43,5.27	74.54,5.18	75.21,3.56	75.22,3.56	74.73,4.72	74.79,4.67
		t_4,Δ_4	78.38,3.46	78.38,3.46	79.01,4.58	79.06,4.52	78.30,3.09	78.30,3.09	78.80,4.07	78.82,4.04
	$n = 9$	t_1,Δ_1	57.50,17.50	57.83,7.83	53.76,13.76	55.97,5.97	59.38,19.38	59.48,9.48	55.85,15.85	57.12,7.12
		t_2,Δ_2	61.70,4.20	61.91,4.08	58.76,5.00	60.22,4.25	63.29,3.91	63.36,3.87	60.57,4.72	61.37,4.25
		t_3,Δ_3	65.06,3.36	65.21,3.30	62.75,4.00	63.81,3.60	66.38,3.09	66.42,3.07	64.29,3.72	64.86,3.49
		t_4,Δ_4	67.99,2.93	68.10,2.89	66.24,3.48	67.02,3.21	69.04,2.66	69.08,2.65	67.50,3.21	67.92,3.06
		t_5,Δ_5	70.63,2.65	70.72,2.62	69.39,3.15	69.96,2.94	71.43,2.39	71.46,2.39	70.40,2.89	70.70,2.78
		t_6,Δ_6	73.08,2.45	73.14,2.42	72.30,2.92	72.71,2.74	73.64,2.20	73.65,2.19	75.55,2.49	73.28,2.57
		t_7,Δ_7	75.37,2.29	75.41,2.27	75.04,2.73	75.30,2.59	75.69,2.05	75.70,2.05	77.90,2.35	75.69,2.41
		t_8,Δ_8	77.54,2.17	77.56,2.15	77.63,2.59	77.75,2.46	77.62,1.94	77.63,1.93	80.00,2.10	77.98,2.29
		t_9,Δ_9	79.60,2.06	79.61,2.05	80.00,2.37	80.00,2.25	79.46,1.84	79.47,1.84	78.80,4.07	80.00,2.02

Table 4.7 : Average-risk scenario: Table of optimal Δ_i and t_i under different scenarios for $T = \{60, 80\}$, $t_0 = \{40, 50\}$, $\beta = \{0.6, 0.8\}$, $\mu = \{2, 4\}$, $n = \{4, 9\}$, $A = 0.8$, $B = 0.52$, and $k_1 = 0.0028$, $k_0 = 0.106$.

between exams consistently decrease with age, as expected. It is interesting to note that across the two different risk scenarios, Δ^* decreases under the increased-risk scenario for the first interval only, so that the first examination is sooner than in the average-risk scenario. The need for screening at an earlier age for higher risk patients is thus recognized in the model, although the subsequent exams may not necessarily need to be more frequent.

4.4 Discussion

We have shown with mathematical proofs that a solution exists for two proposed frameworks for finding optimal screening programs under a nonstable disease model while incorporating costs, and explored the solutions under various scenarios. Under the first proposed framework, we can find the optimal number of examinations (or optimal interval between exams) in a given screening horizon, assuming that the exams are equally spaced. Under an age-dependent incidence function, equal spacing between examinations may not be optimal. However, for policy or administration purposes, recommending screening at equal intervals may be more feasible to enforce. This framework also accounts for costs of screening and the dollar value of life saved by being cured through screening detection versus clinical detection.

Under the second proposed framework, the optimal ages of examination may be found for a specified number of exams within a specified screening horizon. Thus, if the number of exams is known, we can find the best times to give them. For example,

if a budget exists that can only afford a certain number of exams within a particular age interval, then we can find the optimal ages of examination within that interval. This may be helpful for healthcare in society, where total funds may be limited.

Our models are limited since they specify particular forms for the incidence function and sojourn time distribution. Realistically, a linear assumption for the preclinical incidence may not be practical, and while it has been shown to be a satisfactory model, an exponential sojourn time distribution may not necessarily be the best, but is practically the only parametric model currently used in the literature. However, both assumptions allow for simple derivations of the expressions and make it easier to derive the proofs. It may be of interest in future work to explore different parametric functions for the preclinical incidence or other representative distributions for the sojourn time.

We also did not account for costs for false-positive exams in the utility functions, and did not include a component for competing risks for death. To more realistically model the costs and benefits of a screening program, it may be useful to find a way to incorporate these issues into the models.

One other possible adjustment to the model would be to consider the utility as a sum of screening and interval detections, rather than a difference. We believe that the current work which subtracts interval detections from screening detections better reflects the benefit due to screening examinations. The sum of the two terms may be considered ion a future analysis as an alternative approach.

It should be noted that while the simulation analyses accounted for components of discounting of costs and benefits, and lost wages, the utility function presented here does not. Thus the two separate approaches should be carefully interpreted given the assumptions of each.

Overall we have explored two possible models for finding the optimal number of exams (or equal intervals between exams) or the optimal ages of examinations for a specified number of examinations under particular assumptions, namely a nonstable disease model. These models may be useful in determining public health recommendations in screening for breast cancer while accounting for the tradeoff between costs and benefits, and provide a more global solution to screening policies than a simulation-based approach.

Chapter 5

Conclusions

We have taken both empirical and theoretical approaches to the problem of optimal screening strategies for breast cancer. In the microsimulation models, the analyses are limited to a select set of screening strategies, while the theoretical approach has the ability to search for a true global optimum under certain model assumptions. In each case, we have explored both approaches in two different risk sets to account for differences among the general population and an increased-risk group. Both approaches incorporate components that have not been extensively explored in the literature.

For the general population, we conducted a comprehensive microsimulation analysis of the impact of a set of screening strategies on a cohort of women, which included all relevant costs from screening to treatment. The screening strategies under consideration included current recommended guidelines from major cancer societies as well as combinations of mammography and clinical breast exam. In previous studies, costs beyond screening have often been excluded, and the investigated screening programs have focused on mammography alone, ignoring the impact of clinical breast exam. We found several screening strategies among those studied that were more cost-effective compared to the alternatives. The cheapest one was that which offered mammography and clinical breast exam in alternating years from ages 40-79, while the most

expensive was the recommendation from the American Cancer Society, which begins screening with clinical breast exam every three years beginning at age 20, then continues with both mammography and clinical breast exam annually from ages 40-79. Although the American Cancer Society recommendation is more life-saving, the cost is very high for a small gain in benefit compared to the cheaper alternatives. If funds are not limited, the strategy from the American Cancer Society is favorable, but under a more realistically constrained budget, it may be more cost-effective to select the strategy which gives mammography and clinical breast exam from ages 40-79 in alternating years. This strategy is still effective, and cheaper, and should be easily enforceable in health policy.

To extend the analysis to an increased-risk population, we made relevant adjustments to the cohort of women according to age-specific incidence and tumor characteristics, and added screening strategies that began screening at an earlier age and combined the use of MRI. Although recent developments have led to its recommendation for women at increased-risk, we found that strategies offering MRI are expensive and may not provide much of an increase in survival benefit. In fact, certain strategies offering more frequent mammography alone or mammography and clinical breast exam are much cheaper and do not sacrifice much benefit compared to the strategies that include MRI. In a high-risk cohort, offering mammography and clinical breast exam every six months from ages 30-79 with the addition of annual or biennial MRI can be cost-effective. The use of these programs which include MRI depends on

society's willingness to pay the high expense for adding MRI to screening policies for women of increased-risk for breast cancer. However, the cheaper strategies that exclude MRI may actually be favorable, sacrificing only small gains in benefit.

In future work, we may improve the simulation models by updating them with more current data inputs as they become available. The more accurate and current the inputs are, the more useful the results may be to health policy makers. There are many ways in which the model may be added to or made more complex to more accurately represent screening and treatment procedures. For instance, we may want to add updated treatment regimens such as axillary or sentinel lymph node dissection, and account for possible overdiagnosis due to cases of ductal carcinoma in situ. It may also be interesting in a future study to directly incorporate genetic dispositions into the microsimulation models to better assess the risk status of each individual in the cohort.

Under the theoretical model, we introduced a utility function that incorporates both a nonstable disease model and cost components. Assuming a nonstable disease model in place of a stable disease model is more realistic since breast cancer incidence has been shown to increase with age. We showed that under two frameworks, a solution exists and both give reasonable results. The Equal Intervals model may be more practical for use in health policy, while the Fixed Budget model may be useful under realistic budget constraints.

As part of the theoretical model, the use of an alternative preclinical incidence

function which better represents the trend in age-specific incidence may be more appropriate in future analyses. A linear relationship between incidence and age is convenient but may not be realistic. Finally, since our models do not account for costs due to false-positive exams or the effects of competing risks, these would be the next logical components to be added.

This work was intended to contribute to decisions in health policy related to the early detection of breast cancer. Although this work has focused on breast cancer screening, the methods may be applied to the early detection of other cancers or diseases with some adjustments to the natural history model or other data inputs where necessary. In both the empirical and theoretical approaches, decisions related to the tradeoff between reasonable costs and desired benefits must be considered in choosing the best screening program.

Bibliography

[1] Ries LAG, Eisner MP, Kosary CL, et al. SEER cancer statistics review, 1975-2002. National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/csr/1975_2002/. Accessed 2007.

[2] Berry DA, Cronin KA, Plevritis SK, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med.* 2005;353:1784-1792.

[3] American Cancer Society. Detailed guide: breast cancer. Can breast cancer be found early? http://www.cancer.org/. 2006.

[4] National Cancer Institute. Breast cancer: screening and testing. http://www.cancer.gov/cancertopics/screening/breast/. Accessed 2007.

[5] U.S. Preventive Services Task Force. Screening for breast cancer. http://www.ahrq.gov/. Accessed 2007.

[6] Parmigiani G. *Modeling in medical decision making.* West Sussex, England: John Wiley and Sons, Ltd; 2002.

[7] Shen Y, Parmigiani G. A model-based comparison of breast cancer screening strategies: mammograms and clinical breast examination. *Cancer Epidemiol Biomarkers Prev.* 2005;14(2):529-532.

[8] Shen Y, Parmigiani G. Optimization of breast cancer screening modalities. In:

Nikoulina M, Commenges D, Huber C, eds. *Probability, Statistics, and Modelling in Public Health.* USA: Springer Science and Business Media, Inc.; 2006:405-420.

[9] vanOortmarssen G, Boer R, Habbema J. Modeling issues in cancer screening. *Stat Meth Cancer Screen.* 1995;4:33-54.

[10] Gorlova O, Kimmel M, Henschke C. Modeling of long-term screening for lung carcinoma. *Cancer.* 2001;92(6):1531-1540.

[11] Mandelblatt JS, Jacobson WF Lawrence SM Womack D, Yi B, et al. Benefits and costs of using HPV testing to screen for cervical cancer. *JAMA.* 2002;287(18):2372-2381.

[12] Zelen M, Feinleib M. On the theory of screening for chronic diseases. *Biometrika.* 1969;56(3):601-614.

[13] Day NE, Walter SD. Simplified models of screening for chronic disease: estimation procedures from mass screening programmes. *Biometrics.* 1984;40:1-14.

[14] Flehinger B, Kimmel M. The natural history of lung cancer in a periodically screened population. *Biometrika.* 1987;43(1):127-144.

[15] Berry DA. Benefits and risks of screening mammography for women in their forties: a statistical appraisal. *J Natl Cancer Inst.* 1998;90:1431-1439.

[16] Fletcher S, Black W, Harris R, Rime B, Shapiro S. Report of the international

workshop on screening for breast cancer. *J Natl Cancer Inst.* 1993;85(20):1643-1665.

[17] Jatoi I. Breast cancer screening *Am J Surg.* 1999;177:518-524.

[18] Olsen O, Goetzsche PC. Cochrane review on screening for breast cancer with mammography. *Lancet.* 2001;358:1340-1342.

[19] Fletcher S, Elmore J. Mammographic screening for breast cancer. *N Engl J Med.* 2003;348(17):1672-1680.

[20] Salzmann P, Kerlikowske K, Phillips K. Cost-effectiveness of extending screening mammography guidelines to include women 40 to 49 years of age. *Ann Intern Med.* 1997;127(11):955-965.

[21] Carter R, Glasziou P, vanOortmarssen G, et al. Cost-effectiveness of mammographic screening in Australia. *Aust J Public Health.* 1993;17:42-50.

[22] Eddy DM. Screening for breast cancer. *Ann Intern Med.* 1989;111(5):389-399.

[23] Elixhauser A. Costs of breast cancer and the cost-effectiveness of breast cancer screening. *Int J Technol Assess Health Care.* 1991;7:604-615.

[24] Lindfors KK, Rosenquist CJ. The cost-effectiveness of mammographic screening strategies. *JAMA.* 1995;274:881-884.

[25] Rosenquist CJ, Lindfors KK. Screening mammography beginning at age 40 years. *Cancer.* 1998;82:2235-2240.

[26] Kattlove H, Liberati A, Keeler E, Brook RH. Benefits and costs of screening and treatment for early breast cancer: development of a basic benefit package. *JAMA*. 1995;273(2):142-148.

[27] Mandelblatt J, Schechter C, Yabroff K, et al. Benefits and costs of interventions to improve breast cancer outcomes in African American women. *J Clin Oncol.* 2004;22(13):2554-2566.

[28] Mandelblatt J, Schechter C, Yabroff K, et al. Toward optimal screening strategies for older women. *J Gen Intern Med.* 2005;20:487-496.

[29] Stout NK, Rosenberg MA, Trentham-Dietz A, Smith MA, Robinson SM, Fryback DG. Retrospective cost-effectiveness analysis of screening mammography. *J Natl Cancer Inst.* 2006;98(11):774-782.

[30] Boer R, deKoning H, Threlfall A, et al. Cost-effectiveness of shortening screening interval or extending age range of NHS breast screening programme: computer simulation study. *BMJ.* 1998;317:376-379.

[31] Mandelblatt J, Saha S, Teutsch S, et al. The cost-effectiveness of screening mammography beyond age 65 years: a systematic review for the US Preventive Services Task Force. *Ann Intern Med.* 2003;139(10):835-842.

[32] Shen Y, Zelen M. Screening sensitivity and sojourn time from breast cancer early detection trials: mammograms and physical examinations. *J Clin Oncol.*

2001;19(15):3490-3499.

[33] Barton MB, Harris R, Fletcher SW. Does this patient have breast cancer? The screening clinical breast examination: should it be done? How? *JAMA.* 1999;282:1270-1280.

[34] Bobo J, Lee N, Thames SF. Findings from 752081 clinical breast examinations reported to a national screening program from 1995 through 1998. *J Natl Cancer Inst.* 2000;92:971-976.

[35] Oestreicher N, Lehman CD, Seger DJ, Buist DSM, White E. The incremental contribution of clinical breast examination to invasive cancer detection in a mammography screening program. *Am J Roentgenol.* 2005;184(2):428-432.

[36] Kerlikowske K, Salzmann P, Phillips KA, Cauley JA, Cummings SR. Continuing screening mammography in women aged 70 to 79 years: impact on life expectancy and cost-effectiveness. *JAMA.* 1999;282:2156-2163.

[37] Wong IO, Kuntz KM, Cowling BJ, Lam CL, Leung GM. Cost-effectiveness of mammography screening for Chinese women. *Cancer.* 2007;110(4):885-895.

[38] Moolgavkar SH, Stevens RG, Lee JAH. Effect of age on incidence of breast cancer in females. *J Natl Cancer Inst.* 1979;62:493-501.

[39] Parmigiani G, Skates S. Estimating the age of onset of detectable asymptomatic cancer. *Math Comput Model.* 2001;33:1347-1360.

[40] Walter SD, Day NE. Estimation of the duration of pre-clinical disease state using screening data. *Am J Epidemiol.* 1983;118:865-886.

[41] Peer P, vanDijck J, Hendriks J, Holland R, Verbeek A. Age-dependent growth rate of primary breast cancer. *Cancer.* 1993;71:8547-3551.

[42] Kolb T, Lichy J, Newhouse J. Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations. *Radiology.* 2002;225:165-175.

[43] Elmore J, Barton MB, Moceri VM, Polk S, Arena PJ, Fletcher SW. Ten-year risk of false-positive screening mammograms and clinical breast examinations. *N Engl J Med.* 1998;338(16):1089-1096.

[44] Elmore J, Armstrong K, Lehman C, Fletcher S. Screening for breast cancer. *JAMA.* 2005;293(10):1245-1256.

[45] National Cancer Institute. Breast Cancer Surveillance Consortium. http://breastscreening.cancer.gov/data/benchmarks/table7.html/. Accessed 2007.

[46] Plevritis SK, Kurian AW, Sigal BM, et al. Cost-effectiveness of screening BRCA1/2 mutation carriers with breast magnetic resonance imaging. *JAMA.* 2006;295(20):2374-2384.

[47] MAG Mutual Healthcare Solutions, Inc.;*MAG Mutual Healthcare Solutions' 2004 physicians' fee and coding guide.* 2003.

[48] Day JC, Newburger EC. The big payoff: educational attainments and synthetic estimates of work-life earnings. US Census Bureau. 2002.

[49] Wood W, Weiss R, Tormey D, Holland J, Henry P, Leone L. A randomized trial of CMF versus CMFVP as adjuvant chemotherapy in women with node-positive stage II breast cancer: a CALGB study. *World J Surg.* 1985;9:714-718.

[50] Wood W, Budman D, Korzun A, Cooper M, Younger J, Hart R. Dose and dose intensity of adjuvant chemotherapy for stage II node-positive breast carcinoma. *N Engl J Med.* 1994;330:1253-1259.

[51] Perloff M, Norton L, Korzun A, Wood W, Carey R, Gottlieb A. Postsurgical adjuvant chemotherapy of stage II breast carcinoma with or without crossover to a non-cross-resistant regimen: a cancer and leukemia group B study. *J Clin Oncol.* 1996;14:1589-1598.

[52] Mariotto AB, Feuer EJ, Harlan LC, Abrams J. Dissemination of adjuvant multi-agent chemotherapy and tamoxifen for breast cancer in the United States using estrogen receptor information: 1975-1999. *J Natl Cancer Inst Monogr.* 2006;36:7-15.

[53] Cancer Surveillance Research Program, National Cancer Institute. The Surveil-

lance, Epidemiology, and End Results (SEER) program. http://www-seer.ims.nci.nih.gov/. 1998.

[54] Earle CC, Chapman RH, Baker CS, et al. Systematic overview of cost-utility assessments in oncology. *J Clin Oncol.* 2000;18:3302-3317.

[55] Petitti D. *Meta-analysis, decision analysis, and cost-effectiveness analysis.* 2nd edition. New York, New York: Oxford University Press, Inc.; 2000.

[56] Hunink M, Glasziou P, Siegel J, et al. *Decision making in health and medicine: integrating evidence and values.* New York, New York: Cambridge University Press; 2001.

[57] Shen Y, Zelen M. Parametric estimation procedures for screening programmes: stable and nonstable disease models for multimodality case finding. *Biometrika.* 1999;86(3):503-515.

[58] Straatman H, Peer PG, Verbeek AL. Estimating lead time and sensitivity in a screening program without estimating the incidence in the screened group. *Biometrics.* 1997;53:217-229.

[59] Zelen M. Optimal scheduling of examinations for the early detection of disease. *Biometrika.* 1993;80(2):279-293.

[60] Peer P, Verbeek A, Straatman H, Hendriks J, Holland R. Age-specific sensitivities of mammographic screening for breast cancer. *Breast Cancer Res Treat.*

1996;38:153-160.

[61] Shen Yu, Yang Y, Inoue LYT, Munsell M, Miller A, Berry D. Role of detection method in predicting breast cancer survival: analysis of randomized screening trials. *J Natl Cancer Inst.* 2005;97:1195-1203.

[62] Cong XJ, Shen Y, Miller AB. Estimation of age-specific sensitivity and sojourn time in breast cancer screening studies. *Stat Med.* 2005;24(20):3123-3138.

[63] Kerlikowske K, Carney PA, Geller B, et al. Performance of screening mammography among women with and without a first-degree relative with breast cancer. *Ann Intern Med.* 2000;133(11):855-863.

[64] National Comprehensive Cancer Network. Clinical practice guidelines in oncology. http://www.nccn.org/. Accessed 2007.

[65] Yankaskas BC, Cleveland RJ, Schell MJ, Kozar R. Association of recall rates with sensitivity and positive predictive values of screening mammography. *Am J Roentgenol.* 2001;177:543-549.

[66] Gur D, Sumkin JL, Hardesty LA, et al. Recall and detection rates in screening mammography. *Cancer.* 2004;100(8):1590-1594.

[67] Shen Y, Wu D, Zelen M. Testing the independence of two diagnostic tests. *Biometrics.* 2001;57:1009-1017.

[68] Singletary SE, Allred C, Ashley P, et al. Revision of the American Joint Committee on Cancer staging system for breast cancer. *J Clin Oncol.* 2002;20(17):3628-3636.

[69] Shen Y, Dong W, Esteva FJ, Kau S, Theriault RL, Bevers T. Are there racial differences in breast cancer treatments and clinical outcomes for women treated at M.D. Anderson Cancer Center? *Breast Cancer Res Treat.* 2006;102:347-356.

[70] Barlow WE, Taplin SH, Yoshida CK, Buist DS, Seger D, Brown M. Cost comparison of mastectomy versus breast-conserving therapy for early-stage breast cancer. *J Natl Cancer Inst.* 2001;93(6):447-455.

[71] National Cancer Institute. Chemoprevention of estrogen receptor negative breast cancer preclinical studies. http://grants1.nih.gov/grants/guide/rfa-files/RFA-CA-03-005.html/. 2002.

[72] Parmigiani G, Berry D, Winer E, Tebalsi C, Iglehart JD, Prosnitz L. Is axillary lymph node dissection indicated for early-stage breast cancer? A decision analysis. *J Clin Oncol.* 1999;17(5):1465-1473.

[73] Hogan C, Lunney J, Gabel J, Lynn J. Medicare beneficiaries' costs of care in the last year of life. *Health Aff.* 2001;20(4):188-195.

[74] Bureau of Labor Statistics. Consumer Price Index. http://data.bls.gov/cgi-bin/surverymost/. Accessed 2007.

[75] Cronin KA, Mariotto AB, Clarke LD, Feuer EJ. Additional common inputs for analyzing impact of adjuvant therapy and mammography on U.S. mortality. *J Natl Cancer Inst Monogr.* 2006;36:26-29.

[76] Owens DK. Interpretation of cost-effectiveness analyses. *J Gen Intern Med.* 1998;13(10):716-717.

[77] Jemal A, Tiwari RC, Murray T, et al. Cancer Statistics, 2004 *CA Cancer J Clin.* 2004;54:8-29.

[78] Smith RA, Saslow D, Sawyer KA, et al. American Cancer Society guidelines for breast cancer screening: update 2003. *CA Cancer J Clin.* 2003;53:141-169.

[79] Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammogrpahy. *CA Cancer J Clin.* 2007;57:75-89.

[80] Kriege Mieke, Brekelmans CTM, Boetes C, et al. Efficacy of magnetic resonance imaging and mammography for breast cancer screening in women with a familial or genetic predisposition. *N Engl J Med.* 2004;351:427-437.

[81] Leach MO, Brown J, Coulthard A, et al. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). *Lancet.* 2005;365:1769-1778.

[82] Warner E, Plewes DB, Hill KA, et al. Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. *JAMA.* 2004;292:1317-1325.

[83] Kuhl CK, Schrading S, Leutner CC, et al. Surveillance of "high risk" women with proven or suspected familial (hereditary) breast cancer: first mid-term results of a multi-modality clinical screening trial [abstract]. *Proc Am Soc Clin Oncol.* 2003;22:2.

[84] Griebsch I, Brown J, Boggis C, et al. Cost-effectiveness of screening with contrast enhanced magnetic resonance imaging vs X-ray mammography of women at a high familial risk of breast cancer. *Br J Cancer.* 2006;95:801-810.

[85] National Cancer Institute. Breast cancer risk assessment tool. http://www.cancer.gov/bcrisktool/. Accessed 2007.

[86] Chen THH, Kuo HS, Yen MF, Lai MS, Tabar L, Duffy SW. Estimation of sojourn time in chronic disease screening without data on interval cases. *Biometrics.* 2000;56(1):167-172.

[87] Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst.* 1989;81:1879-1886.

[88] Claus EB, Risch N, Thompson WD. Autosomal dominant inheritance of early-

onset breast cancer. Implications for risk prediction. *Cancer.* 1994;73:643-651.

[89] Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. *Stat Med.* 2004;23:1111-1130.

[90] Berry DA, Parmigiani G, Sanchez J. Probability of carrying a mutation of breast-ovarian cancer gene BRCA1 based on family history. *J Natl Cancer Inst.* 1997;89:227-238.

[91] Parmigiani G, Berry D, Aguilar O. Determining carrier probabilities for breast cancer-susceptibility genes BRCA1 and BRCA2. *Am J Hum Genet.* 1998;62:145-158.

[92] Berry DA, Iverson ES, Gudbjartsson DF, et al. BRCAPRO validation, sensitivity of genetic testing of BRCA1/BRCA2, and prevalence of other breast cancer susceptibility genes. *J Clin Oncol.* 2002;20:2701-2712.

[93] Parmigiani G. On optimal screening ages. *JASA.* 1993;88:622-628.

[94] Tsodikov AD, Yakovlev AY. On the optimal policies of cancer screening. *Math Biosci.* 1991;107(1):21-45.

[95] Shahani AK, Crease DM. Towards models of screening for early detection of disease. *Adv Appl Prob.* 1977;9:665-680.

[96] Lee SJ, Zelen M. Scheduling periodic examinations for the early detection of disease: applications to breast cancer. *JASA.* 1998;93(444):1271-1281.

[97] Rosen PR, Groshen S, SAigo PE, Kinne DW, Hellman S. A long-term follow-up study of survival in stage I (T1N0M0) and stage II (T1N1M0) breast carcinoma. *J Clin Oncol.* 1989;7:355-366.