UNIVERSITY OF SOUTHAMPTON

FACULTY OF ENGINEERING, SCIENCE & MATHEMATICS

School of Mathematics

Behavioural Healthcare Modelling

Incorporating behaviour into healthcare simulation models: A breast cancer screening example

by

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Thesis for the degree of Doctor of Philosophy

June 2007

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

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Breast cancer is the second most common cancer in the UK. Early detection and treatment are key to halting disease progression and the ultimate survival of the patient. Mammography screening can detect breast tumours before symptoms occur, making screening for breast cancer an effective intervention to help to reduce mortality from the disease.

Simulation has been used for many years to evaluate the outcomes from medical interventions, and much research has focussed upon breast cancer screening policies. However in practice a screening policy can only be successful if people attend for the invited screen. This thesis discusses some of the issues involved in incorporating human factors in a simulation model of screening for breast cancer in a UK setting. Four different methods for approximating attendance at mammography screening were compared including one method derived from a psychological theory that was designed to predict human behaviour.

The research also uses the simulation model to compare the differences brought about by making different assumptions regarding the patterns and rates of breast tumour growth on the simulation outcomes.

Results indicate that different approaches to approximating attendance behaviour and cancer growth do produce significantly different simulation outcomes. However, the relative change in outcomes across different screening strategies remained roughly constant across the various approaches. Whilst this relative change was consistent, the changes in approach did lead to changes in the significance of differences between outcomes under different screening strategies. In light of these results caution is advised when interpreting simulation outcomes and emphasises the importance of comparing relative as opposed to actual simulation outcomes.

The benefit of incorporating a psychological model into the simulation came from enhanced simulation functionality and the ability to provide further insight into the effects of attitude changes on screening policies.

Contents

1 Introduction **1**

1.1 Background 1

1.2 Operational Research Models for Breast Cancer Screening 3

1.3 Research Objectives 4

1.3.1 Objectives Summary 6

1.4 Thesis Layout 6

2 Psychological Theory for the Modelling and Prediction of Health Related Behaviours **7**

2.1 Introduction 7

2.2 Traditional Models 8

2.2.1 Introduction 8

2.2.2 Health Belief Model 9

2.2.2.1 Introduction to the Health Belief Model 9

2.2.2.2 The HBM structure 9

2.2.2.3 Research using the HBM 11

2.2.2.4 Discussion 12

2.2.3 Health Locus of Control 12

2.2.3.1 Introduction 12

2.2.3.2 The Multidimensional Health Locus of Control Model 13

2.2.3.3 Research using Health Locus of Control 14

2.2.3.4 Discussion 14

2.2.4 Protection Motivation Theory 15

2.2.4.1 Background 15

2.2.4.2 The Protection Motivation Theory 15
2.2.4.3 Research Using PMT 17
2.2.4.4 Discussion 17
2.2.5 The Theory of Planned Behaviour 18
2.2.5.1 Background 18
2.2.5.2 Model Description 18
2.2.5.3 Research Using the TPB 21
2.2.5.4 Discussion 21
2.2.6 Social Cognitive Theory and Self Efficacy Theory 22
2.2.6.1 Background 22
2.2.6.2 The Social Cognitive Theory 22
2.2.6.3 Research Using SCT 23
2.2.6.4 Discussion 24
2.2.7 Motivational Models: Summary 24
2.3 Enaction Models 24
2.3.1 Introduction 24
2.3.2 Gollwitzer's Implementation Intentions 25
2.3.2.1 Research using Gollwitzer's Implementation Intentions 25
2.3.3 Bagozzi's Goal Theory 25
2.3.3.1 Research Using Bagozzi's Goal Theory 27
2.3.4 Enaction Models: Summary 27
2.4 Integrative Theories 27
2.4.1 Introduction 27
2.4.2 Major Theorists Model 28
2.4.2.1 Background 28
2.4.2.2 Model Proposal 28
2.4.3 Integrative Models: Summary 29
2.5 Stage Theories 30
2.5.1 Introduction 30
2.5.2 Health Action Process Approach 30

2.5.3 Heckhausen's Rubicon Model 31
2.5.4 Kuhl's Action Control Theory 32
2.5.5 The Transtheoretical Model 32
2.5.5.1 Structure of the Transtheoretical Stages of Change . . 33
2.5.5.2 Research Using the Transtheoretical Model 35
2.5.5.3 Discussion 35
2.5.6 The Precaution Adoption Process Model 36
2.5.6.1 The PAPM structure 36
2.5.6.2 Research Using the PAPM 37
2.5.6.3 Discussion 37
2.5.7 Stage Models: Summary 37
2.6 And the Rest 38
2.6.1 Other Models of Health Behaviour 39
2.7 Summary 39

3 Breast Cancer Behaviour **42**
3.1 Introduction 42
3.2 Overviews and Reviews 42
3.2.1 Systematic Review of the determinants of screening uptake . . . 43
3.2.2 Factors Affecting Population-based Screening in Sweden 44
3.2.3 Inequalities of Access to Cancer Screening 45
3.3 Individual Studies 46
3.3.1 Screening Behaviour 46
3.3.2 Breast Self-Examination Behaviour 49
3.3.3 Delay Seeking Help 53
3.3.4 Genetic Testing and Miscellaneous 54
3.4 Summary 55

4 Modelling approaches to breast cancer screening **56**
4.1 Analytical Models 57
4.2 Simulation models 58

4.3 Modelling psychology 63
4.4 A chosen modelling approach 67

5 A Discrete Event Simulation of Breast Cancer **69**
5.1 The Three Phase Approach 69
5.2 Model Structure 70
5.3 Model Inputs, Outputs, and Interface 72
5.3.1 Run Options 73
5.3.2 Cancer Options 73
5.3.3 Behaviour Options 74
5.3.4 Screening Options 74
5.3.5 Self Detection Options 74
5.3.6 Outputs 75
5.4 User Interface 76

6 Populating the Simulation Model Parameters **78**
6.1 Mortality Analysis 78
6.1.1 Mortality Summary 81
6.2 Tumour Growth 85
6.2.1 Summary 89
6.3 Age of Cancer Onset 93
6.4 Tumour Detection 96
6.4.1 Mammography Sensitivity 97
6.4.2 Detection by other means 99
6.4.3 Tumour Detection Summary 102
6.5 Survival 102
6.5.1 Survival Summary 108
6.6 Behavioural Data 110
6.6.1 The Theory of Planned Behaviour 110
6.6.2 Baker and Atherill's Compliance Model Data 116
6.7 Model Verification 117

6.8 Model Validation 118
6.8.1 Conceptual Model Validity 118
6.8.2 Operational Validity 119
6.8.3 Age of presentation 119
6.8.4 Proportion of screen-detected cancers 121
6.9 Experimental Set-Up 122

7 Results **126**
7.1 Introduction 126
7.2 Experimental Design 127
7.2.1 Mammography screening scenarios 127
7.2.2 Tumour Growth and Attendance Behaviour Options 128
7.2.3 Output statistics 128
7.3 Tumour Growth Assumptions 129
7.3.1 Numbers of cancers detected 129
7.3.2 Detection statistics 133
7.3.3 Life years saved 138
7.3.4 Summary of the screening scenario results and the effect of different assumptions of tumour growth 140
7.4 Attendance Behaviour Modelling 141
7.4.1 Number of cancers detected 142
7.4.2 Detection statistics 144
7.4.3 Life years saved 148
7.4.4 Attendance at invited breast screens 150
7.4.5 Summary of the effect of behavioural assumptions upon the simulation results 152
7.5 TPB Sensitivities 153
7.5.1 Summary of the TPB sensitivity results 159
7.6 TPB Increase vs Lowering the Age of First Screen 160
7.6.1 Experimentation Summary 161

8 Discussion **163**

8.1 Evaluation of Research Objectives 163
8.2 Limitations of the Research 166
8.3 Further Work 167
8.4 Conclusion 167

A Model Code **168**

B The Theory of Planned Behaviour Data **176**

C Results of Screening Scenarios Across Assumptions of Attendance Behaviour **179**

D Results of Screening Scenarios Across Different Assumptions of Tumour Growth **185**

E Results of Sensitivity Analysis Performed on the Theory of Planned Behaviour Variables **191**

F TPB Experimentation Results **193**

References **211**

List of Tables

1 Table of Thesis Abbreviations xvi

2.1 Reviews of HBM Studies, (Janz and Becker (1984); Harrison et al. (1992)) 11

2.2 Major Theorists involved in the workshop (Conner and Norman, 1995) 28

2.3 Variables Influencing Progression Through the PAPM (Weinstein et al., 1998) 37

2.4 Other Theories and Models Applied to Health Behaviour 39

4.1 Parameter values for S_n in Baker and Atherill (2002) 65

5.1 The B activities 70

6.1 Definitions and derivations of basic life table functions 79

6.2 Fit of $E(x)$ to $D(x_{20})$ and $D(x_{20}+n_{20})$ 81

6.3 Life table for women, based on death from all causes, 2002 83

6.4 Breast Cancer Eliminated Life Table Based on Data From 2002 84

6.5 Estimated parameters for the modified Gompertz model of tumour growth, Speer et al. (1984) 89

6.6 Percentage distribution of tumour size for the control group in the Swedish Two County Trial, Tabar et al. (2002) 100

6.7 Cured fraction of patients given tumour progression, mean range and 95% CI range over ages in brackets 107

6.8 Summary of variable values used within the simulation 109

6.9 The fitted β values from maximum likelihood calculations, and their confidence intervals 112

6.10 Percent detected by screening for each growth model under the assumption of local percentage attendance at 75%, (estimated from runs using 85% local attendance) 122

6.11 Percent detected by screening for each behaviour model under the assumption of exponential growth 122

6.12 Percent deviations of the confidence intervals from their mean outputs after 300 iterations for each behaviour model simulation (exponential growth, screening 51-69 every 3 years). 125

6.13 Percent deviations of the confidence intervals from their mean outputs after 300 iterations for each growth model simulation (local attendance, screening 51-69 every 3 years). 125

7.1 Start and end ages and interval frequency of screening invitations for each screening scenario 128

7.2 Comparison of Three Key Simulation Outputs Between the 75% Baseline TPB Run (Screening 45-69/3yrs) and Increasing the TPB Variables to Approximate 95% Attendance (Screening 51-69/3yrs). Where CI= Confidence interval. 161

B.1 Case Summary of data provided from Rutter (2000) for TPB variables 176

B.2 Summary statistics for dataset from Rutter (2000). 177

B.3 Spearman's Rho correlation statistics for data from Rutter (2000) . . . 178

C.1 Results from screening age 51 to age 63 every 3 years, by attendance behaviour option 180

C.2 Results from screening age 51 to age 69 every 3 years, by attendance behaviour option 181

C.3 Results from screening age 51 to age 63 every 2 years, by attendance behaviour option 182

C.4 Results from screening age 51 to age 69 every 2 years, by attendance behaviour option 183

C.5 Results from screening age 45 to age 69 every 3 years, by attendance behaviour option 184

D.1 Results for screening ages 51 to 63 every 3 years, by tumour growth pattern 186

D.2 Results for screening ages 51 to 69 every 3 years, by tumour growth pattern 187

D.3 Results for screening ages 51 to 63 every 2 years, by tumour growth pattern 188

D.4 Results for screening ages 51 to 69 every 2 years, by tumour growth pattern 189

D.5 Results for screening ages 45 to 69 every 3 years, by tumour growth pattern 190

E.1 TPB Sensitivity Results 192

F.1 Table of TPB experiment results to find the equivalent TPB values required to acheive similar results with todays screening programme as screening from age 45 would acheive 194

List of Figures

2.1 The Health Belief Model 10

2.2 Protection Motivation Theory 16

2.3 The TPB Structure 18

2.4 Gollwitzer's Implementation Intentions 25

2.5 Bagozzi's Goal Theory 26

5.1 Model Structure 70

5.2 User Interface for Inputs 76

5.3 User Interface at Run Time 77

5.4 User Interface Results 77

6.1 Cumulative Density Function of Mortality as Estimated From the Cause Eliminated Life Table 82

6.2 Mean growth pattern produced under each growth model with associated assumptions 90

6.3 Mean and percentile range of growth patterns modelled with the exponential tumour growth assumption 90

6.4 Mean and percentile range of growth patterns modelled with the Gompertz tumour growth assumption 91

6.5 Mean and percentile range of growth patterns modelled with the logistic tumour growth assumption 91

6.6 Mean and percentile range of growth patterns modelled with the stochastic modified Gompertzian tumour growth assumption 92

6.7 Cumulative distribution of age of breast cancer presentation in England in 2002 (ONS) 94

6.8 Derived Cumulative Age of Onset Distributions by Growth Pattern . . 97

6.9 Efficiency of mammographic detection by tumour size, Michaelson et al. (2003a) 99

6.10 Fit of the Erlang(3,0.85) distribution to the Swedish Two County Trial Control data of breast cancer detection sizes Tabar et al. (2002) 101

6.11 Fit of the Erlang(3,0.6) distribution to the non screen detected cancers at Massachussetts General Hospital, Michaelson et al. (2003a) 101

6.12 Selected distributions of self detection and mammography detection given tumour size 102

6.13 Tumour Progression as Modelled in the Simulation 106

6.14 Range of β values observed in bootstrapping, where bi is β_i for $i = 1, 2, 3, 4$.113

6.15 Plots of the Subjective Norm (X_2) scores against the PBC (X_3) scores given attendance for groups of low (1), medium (2), and high (3) scores for Attitude X_1. 114

6.16 Difference in π_i empirical distribution function for observed attenders and non attenders 115

6.17 Cumulative distribution for age of breast cancer detection in the UK in 2002 in comparison with simulation age of detection under each of the tumour growth assumptions and equivalent screening strategy, with assumed local' 75% attendance. 120

6.18 Cumulative distribution for the age of detection of breast cancer in the UK in 2002 in comparison to simulated output for each of the behaviour models and under equivalent screening strategies, with the assumption of 75% attendance where appropriate and exponential tumour growth. . 121

6.19 Means confidence intervals deviation from the mean with the number of iterations 124

7.1 The number of screen-detected breast cancers under different screening scenarios and tumour growth assumptions 130

7.2 Percent of detected tumours that were detected by mammography screening under different screening scenarios and tumour growth assumptions 130

7.3 Numbers of women invited to a screen while they have cancer 131

7.4 Relative difference between screening scenarios for the numbers of screen-detected cancers, under different assumptions of tumour growth 132

7.5 Average tumour diameters (mm) at detection under different screening and tumour growth assumptions 133

7.6 Relative difference of tumour size at detection between the screening scenarios for different tumour growth assumptions 134

7.7 Difference in tumour diameter (mm) at detection between screening scenarios for different tumour growth assumptions 134

7.8 Average time until tumour detection (for all detected tumours) by tumour growth option and screening scenario. 136

7.9 Significant findings between screening scenarios for the time to tumour detection (X = non significance) 136

7.10 Years earlier screen-detected tumours are detected relative to unscreened detection, by screening scenario and tumour growth pattern 137

7.11 Average of the total number of life-years saved by each screening scenario by assumption of tumour growth pattern (per 1,000 women) 138

7.12 Relative change in life-years saved in comparison to the current UK policy, by tumour growth pattern 139

7.13 Average number of screen-detected tumours for different screening scenarios and assumptions of attendance behaviour 142

7.14 Percent of detected tumours that were screen-detected for different screening policies and assumptions of attendance behaviour 143

7.15 Average tumour diameter (mm) at presentation of all detected tumours, over screening scenario and behavioural attendance option 145

7.16 Average time (years) from tumour onset until detection by screening scenario and assumption of attendance behaviour 146

7.17 Average number of years earlier that a tumour was detected by screening than it would have presented otherwise, by screening scenario and assumption of attendance behaviour 147

7.18 Relative increase and decrease in the average years earlier a tumour is detected by screening than would have naturally arisen, in comparison to the current UK policy, by attendance behaviour assumption and screening policy. 148

7.19 Average and 90% confidence intervals for the number of life-years saved over different screening scenarios and assumptions of attendance behaviour 149

7.20 The average number of women, per 1,000, who attended screening at least once across all screening scenarios by attendance behaviour assumption 150

7.21 Average number of attendances at screening of women who attended at least once, by screening scenario and attendance behaviour assumption 151

7.22 Relative number of attendances of women who attended screening invitations in comparison to the current UK screening policy by attendance behaviour assumption and screening scenario 151

7.23 The change in the percent of tumours detected by mammography screening for 10% changes in the TPB variables 155

7.24 Relative change in the percent of screen-detected tumours for 10% changes in the TPB variables 156

7.25 Relative change in the number of simulated women who attended mammography screening at least once for a 10% change in the TPB constructs156

7.26 Relative change in the average number of attendances at breast screening for women who attended screening with a 10% change in the TPB constructs 157

7.27 Relative change in tumour diameter for a 10% change in each of the TPB constructs 158

7.28 Change in the number of life-years saved for a 10% change in the TPB constructs 158

7.29 Relative change in the number of life-years saved for a 10% change in the TPB constructs in comparison to baseline 159

A.1 Simulation Modules (continued over the page) 170

A.2 Simulation Modules Continued 171

A.3 Simulation Classes (continued over the page) 172

A.4 Simulation Classes Continued 173

A.5 Simulation Collection Classes (continued over the page) 174

A.6 Simulation Collection Classes Continued 175

Acknowledgements

First and foremost I would like to thank my supervisors Paul Harper and Sally Brailsford for their help, support and advice throughout the research. Other people who deserve recognition include Professor Derek Rutter from the University of Kent for kindly sharing with me the results of his analysis without which the TPB modelling in this thesis would not have been possible, and Dr Joan Austoker from the University of Oxford whose advise and information regarding the psychology of screening uptake was invaluable. A big thank-you also goes out to the Southampton mammography screening unit personnel who were so helpful, open, and honest when providing me with information as to how breast screening is conducted at a local and national level in the UK, and representatives from the Oncology Department at Southampton University Hospitals NHS Trust whose feedback and advise regarding my epidemiological model of breast cancer was extremely useful.
I would also like to thank all of my friends, family, and colleagues for their continued support and advice, including amongst others Laurie, Emily, Katie, Helen, Christine, Lee, Mum and Dad.
Thank you all.

Abbreviations

Table 1 below provides a list of abbreviations and definitions used within this thesis.

Term	Definition
75% baseline	The baseline scenario for the further experimentation such that cancer growth was exponential, screening was from age 45 to 69 tri-annually, and TPB constructs had been manipulated to imply 75% overall attendance rates.
Attendance behaviour	Whether or not an individual attends a breast screening unit
Baseline	The scenario compared against such that cancer growth is exponential and behaviour is modelled using 75% local attendance.
BC	Breast cancer
BSE	Breast self examination
CI	Confidence interval
DES	Discrete event simulation
Equation model	Baker and Atherill's equation model for the prediction of attendance at UK breast screening units
HBM	Health Belief Model
Mod Gompertz	The modified Gomptertzian growth equation
ONS	UK Office of National Statistics
PBC	Perceived behavioural control construct
Scenario	See screening scenario
Screening scenario	A particular screening policy evaluated, for example the current UK strategy of screening from around age 51 to 69 every 3 years
SN	Subjective norm construct
TPB	Theory of Planned Behaviour
UKBCSP	The UK Breast Cancer Screening Programme
yrs	Years

Table 1: Table of Thesis Abbreviations

Chapter 1

Introduction

Operational Research (OR) techniques have been widely applied to the area of health care and health research. However, the expected outcomes of interventions, plans, or structural changes suggested by these models often differ from those observed in reality. In the real world, health care policy decisions, as well as operational decisions in health care planning, are made on the basis of Operational Research models. Therefore, it is important that these models reliably capture all aspects of the real-world system, as they can have great impact in practice.

The actions of people play a vital role in health care systems, resources, and disease progression. For example, when considering different, and/or, optimal disease interventions the participation of the patient, or potential patients, in the intervention must be considered. For the majority of models of health care systems the behaviour of the people involved in those systems is described by a single variable, e.g. the percentage of patients who comply with the regime or suggestion.

It is suggested that the observed gap between modelled expected outcomes and real outcomes may be in part due to the human behavioural aspects of the health care systems which are currently omitted from OR models. To this end it is intended to try to incorporate some psychological model(s) of health care behaviour, (or an amalgamation of several), into an OR model in an attempt to begin to bridge the gap between modelled and observed systems and increase the functionality and realism of the modelling work. It is believed that this will be one of the first serious attempts to incorporate behaviour at an individual level into a health care simulation model.

1.1 Background

Breast cancer and screening strategies for breast cancer were chosen as the application of the research, and there were a number of reasons for the choice.

Firstly, Southampton University have previous experience of modelling for the early detection of breast cancer. Secondly, breast cancer can be fatal and is the second most common cancer in the UK (see below), but with earlier detection and treatment prognosis can be significantly improved. Therefore, with an optimal strategy for a population, mammography screening may prevent premature death. Lastly, having perused the health behaviour literature, it became clear that attendance at cancer screening (and breast cancer screening) was an area that had been considered by a wealth of literature, many of which applied recognised psychological models to explain attendance behaviour, see Chapter 3 for more information.

Breast cancer is the second most common cancer in the UK with around 41,000 new cases diagnosed each year. Potential risk factors for the disease include age, a family history, previous breast cancer, early menarche and late menopause (Cancer Research UK, 2006).

Once diagnosed, treatment for breast cancer depends on factors such as the patient's age, and the type, size, and spread of the tumour, however, most patients will, at a minimum, undergo surgery to remove the tumour. This may be followed by radiotherapy, and/or chemotherapy. Many women will also receive hormonal therapy using drugs such as Tamoxifin or Arimidex.

Screening can be a useful tool to identify disease at an earlier stage in the natural history. The UK National Screening Committee define screening as follows.

> "Screening is a public health service in which members of a defined population, who do not necessarily perceive they are at risk of, or are already affected by a disease or its complications, are asked a question or offered a test, to identify those individuals who are more likely to be helped than harmed by further tests or treatment to reduce the risk of a disease or its complications."
>
> (UK National Screening Committee, 2006)

The Committee set out criteria for appraising the viability of national screening programmes that include criteria to ensure that the condition is serious enough to justify the intervention, that there should be an effective and safe screening test available, that the test should identify people at an earlier stage of the disease, that there is a suitable treatment for this stage of disease, and that the test is acceptable to the proposed screening population, (UK National Screening Committee, 2003).

As a life threatening disease that mammography screening may detect before symptoms occur, and with more effective treatments in the early stages, breast cancer satisfies the majority of the criteria laid out for a screening programme. The UK breast screening programme was introduced in 1988. Initially, mammography was

offered every three years to all women aged between 50 and 64, and to women aged 65 and over on request. From 2001 this was extended to women in England aged 65 to 70, and to women over 70 on request. In 2003-04, three quarters of women aged 50-64 invited for screening in England underwent screening for breast cancer, and over 1.4 million women are screened each year. Earlier detection and improved treatment has meant that survival rates have risen with the five-year survival rate up to 80 per cent for women diagnosed in 1998-2001 in England, (UK Office of National Statistics). Screening for breast cancer may help to identify tumours earlier and reduce the treatment required for the patient as well as improving overall prognosis.

1.2 Operational Research Models for Breast Cancer Screening

Analytical and simulation models are useful tools to aid decisions about which age groups to screen and how frequently. Traditionally, the clinical effectiveness of a new treatment or intervention has always been evaluated through a randomized controlled trial (RCT). In an RCT the test population is divided randomly whereby some patients receive the new treatment, and others receive either a placebo or the current best available treatment. A full scale trial, however, has considerable disadvantages in terms of cost and time. Simulation modelling can replicate the effects of the intervention in the trial population in a fraction of the time needed for a full scale RCT, and can then be used to conduct experiments which would be unethical or impractical to carry out in practice.

Simulation has been used to study optimal screening strategies for disease since as far back as the 1970's; Knox (1973) produced one of the earliest yet very comprehensive simulation models. Since that time many simulation models have considered screening strategies for breast cancer including more recent research using a simulation model called MISCAN in the Netherlands (Boer et al., 1998).

Even optimal screening programmes will only be successful, however, if screening uptake rates are sufficiently high within the target population. The majority of simulation models considering screening strategies for breast cancer treat screening uptake as a single global stand-alone variable. It may be the case, however, that comparisons between screening strategies alter when the behaviour of the patient is considered in more detail. It has been shown, for example, that screening uptake rates may be dependent upon, amongst others, factors such as patient age, attendance at previous screening tests, the method and type of invitation, and receiving a recommendation for attendance from a health professional, (Jepson et al., 2000).

A literature review was undertaken to investigate psychological theories applied to

breast cancer screening attendance and based upon these results it was decided that the Theory of Planned Behaviour could be used within an operational Research model of breast cancer screening. The Theory was chosen over other theories available since it is very well structured and clearly defined, and UK research has been undertaken using the theory that applied rigorous research methods and found positive predictive results regarding attendance at breast screening clinics, (Rutter, 2000). Other research has focussed purely on previous attendance and age (as opposed to psychological attributes) in order to predict breast cancer screening attendance in the UK (Baker and Atherill, 2002). It was decided that it might be interesting to investigate the differences that these two approaches may produce when modelling breast cancer screening strategies in the UK, and compare and contrast any differences against assumptions of standard percentage attendance at breast screening.

With this in mind, the primary objective of this research was to investigate the effects of different methods for modelling attendance at breast cancer screening units, and the effect that different assumptions of attendance would have upon results between simulations of different screening strategies for breast cancer within the UK.

1.3 Research Objectives

It was hoped that this research would form the first step towards answering key questions relating to, not only how best to incorporate human behaviour modelling into more traditional OR modelling and simulation, but also more fundamental questions such as can we even model human behaviour effectively, and if so, what effects different assumptions of behaviour make to modelled outcomes? While it is accepted that human behaviour is somewhat impossible to ever completely model and predict to a degree of absolute certainty, psychologists have been working for many years studying human behaviour and have identified factors significantly associated with behaviour and behaviour change.

How different assumptions of attendance behaviour effects simulated outcomes over different model runs (screening scenarios in this case), and how any differences between behavioural assumptions compare with differences brought about by other modelled variables (for example screening frequency or cancer growth pattern), was also a key research question. If different assumptions and models of human behaviour only produce small changes in the modelled outcomes, and/or, these changes are consistent over different model runs then the additional time and effort of researching and including further behavioural attributes in a simulation may not bring any additional value to the model. The results could be particularly interesting if different modelling approaches to attendance at breast screening produce differences in

modelled outcomes to such a degree that the preferred rank of screening age or frequency is changed. It is believed that this is one of the first pieces of research to specifically address these research questions, which could have far reaching implications for not only simulation within healthcare but all applications that require human input and behaviour as a primary driver to the outcome considered.

A discrete event simulation of breast cancer natural history, modelling women and breast cancer over time, requires the ability to model the progression and growth of the cancer. Exactly how human cancer growth progresses is understandably difficult to ascertain due to the ethics of following detected tumours progression without treatment. However, over the years a number of approaches have been developed with varying complexity, including assumptions of exponential, Gompertzian, and logistic growth. These approaches have been hypothesised based upon observations of tumour doubling times over time, however it has been difficult to ascertain the exact nature of tumour growth due to the wide variations observed that could fit a number of growth patterns. A popular decision when simulating the natural history of breast cancer is to assume exponential growth of the tumour (presumably due to the simple nature of the exponential assumptions), however the impact of this assumption is rarely investigated. As a secondary objective, therefore, this thesis reports upon the differences in results from a simulation model of breast cancer and screening for breast cancer, under four different assumptions of tumour growth, and over several different screening strategies.

To fulfil these two objectives, a discrete event simulation model of breast cancer was built in Microsoft Visual Basic, that modelled women over time. Each woman in the simulation may or may not develop breast cancer, and be invited for and attend screening for breast cancer. Breast cancer progression within the simulation is modelled using one of four different assumptions of tumour growth over time labelled exponential, logistic, Gompertz and modified Gompertz (a stochastic tumour growth pattern). Screening for breast cancer is carried out at ages that are specified by the user of the model and attendance at breast screening is modelled in one of four ways.

Attendance behaviour is approximated by either assuming a local percentage attendance (every woman has an x% chance of attending at each invitation, sampled at each invitation), a global percentage attendance (every woman has an x% chance of attending every screen and a 100-x% chance of attending no screens at all, sampled once at the first invitation and then fixed for the remainder), a probability for attendance (deduced on the basis of previous attendance rates and age of the individual and based on work done by Baker and Atherill (2002)), and lastly a probability based upon a psychological theory, the Theory of Planned Behaviour, (TPB).

1.3.1 Objectives Summary

To summarise, the objectives of this research are:

1. To investigate the effects of different methods of modelling attendance for breast cancer screening, using a model from the psychological literature on health-related behaviour (the Theory of Planned Behaviour) as well as a statistical model derived to predict attendance at UK screening clinics (Baker and Atherill (2002)), and two methods commonly used in OR models based on percentage attendance, for different screening policies.
2. To investigate the effects of using different models of tumour growth, (logistic, exponential, Gompertzian, and modified Gompertzian), for different screening policies.
3. To compare the effects of changes in behaviour with changes in screening policy.

1.4 Thesis Layout

The next Chapter introduces the reader to some of the psychological theories for the prediction of health behaviour, including the Theory of Planned Behaviour that has been incorporated within the simulation model reported in this thesis. Chapter 3 then discusses how these theories and ideas have been applied to the study of breast cancer and behaviours surrounding breast cancer. Chapter 4 introduces the methods and approaches others have used to model and analyse breast cancer progression and mammography screening strategies for the early detection of breast cancer. Chapters 5 and 6 go on to describe the structure of the simulation reported within this thesis, and how the parameters of the simulation model were populated respectively. The work to validate and verify the model and the experimental design are also described in Chapter 6, before presenting the results of the experimentation in Chapter 7. Lastly, discussion of the results and conclusions can be found in Chapter 8.

Chapter 2

Psychological Theory for the Modelling and Prediction of Health Related Behaviours

2.1 Introduction

The following sections discuss some of the cognitive psychological models and theories that exist for the prediction of health behaviour.
Each theory within psychology tends to have some supporting research or foundation, however, it is also often the case that there will be criticisms of the ideas and sometimes even conflicting research. This is due to the nature of psychological models and theories such that by their nature they cannot be 'proved' but only backed up, (or not), by research. This is because psychology is about understanding the human mind and personality and therefore it is difficult to ascertain sure facts.

This Chapter aims to talk about some of the more popular theories and models surrounding the prediction of health behaviour within the field of psychology, and it is hoped that due to their sustained popularity in literature these are the theories with some grounding.
Social cognition approaches (how individuals make sense of social situations) to predictive health related behaviour tend to take the form of a cost benefit analysis of outcomes. For example subjective expected utility theory (SEU, Savage (1954)), and expectancy value theory.

SEU theory (Savage, 1954) considers decisions as a function of the probability of an outcome and the expected utility of that outcome, summed over all possible outcomes

for each behaviour considered:

$$SEU_j = \sum_{i=1}^{i=m} P_{ij} \bullet U_{ij}$$

Where SEU_j is the subjective expected utility of behaviour j, P_{ij} is the perceived probability of outcome i given action j, and U_{ij} is the subjective utility of outcome i given action j.

Behaviours that have a high probability of producing valued outcomes will be chosen over other less desirable behaviours. In this way social cognitive models regard health behaviours to be predicted as the end result of a rational decision making process based upon deliberate processing of available information.

However, SEU theory does not provide much in the way of an explanation of the decision process, and more recent social cognition models elaborate on these ideas in order to try to explain, as well as predict, human behaviour (including health behaviour).

The following sections discuss some of the more popular social cognitive models (SCMs) of health behaviour and describe how they conceptualise the variables important in determining behaviour as well as the behaviour outcomes. Section 2.2 discusses five of the more traditional models for the prediction of health behaviour, while sections 2.3 and 2.4 introduce behavioural enaction and integrative models for health behaviour respectively. Section 2.5 discusses and describes stage models of behaviour, and Section 2.6 briefly mentions further theories of health behaviour that were uncovered in the literature but that, due to time and space constraints, are not discussed in detail here. Lastly, Section 2.7 summarises the theory discussed within the Chapter.

2.2 Traditional Motivational Cognitive Models

2.2.1 Introduction

This Section aims to discuss popular social cognition models (SCMs) of health behaviour. These models appear to be the more traditional and popular models of health behaviour that are discussed in psychological literature when considering the

prediction of health related behaviour.

Five models are discussed, the Health Belief Model (HBM), the Health Locus of Control (HLOC), Protection Motivation Theory (PMT), the Theory of Planned Behaviour (TPB), and Social Cognitive Theory (SCT).

These traditional theories and ideas form the basis for many of more recent ideas and theories and are still very popular in the field of behavioural health psychology, and so each is discussed in detail. The information and references within this Section are taken from the book "Predicting Health Behaviour" edited by Mark Conner and Paul Norman (Conner and Norman, 1995).

2.2.2 Health Belief Model

2.2.2.1 Introduction to the Health Belief Model

The Health Belief Model, (HBM), was one of the earliest models of health behaviour to be developed. It was created due to the requirement to find factors that influence health behaviour that may be changed or influenced, (unlike demographic variables shown to correlate with health behaviour), (Hockbaum, 1958; Rosenstock, 1966). The Health Belief Model was therefore constructed under the assumption that a persons health beliefs would influence their health behaviour and it would be possible to influence or alter these health beliefs in order to change the health behaviour. By the 1970s a series of studies had suggested that key health beliefs could aid the understanding of individual differences in health behaviour and interventions, (Sheeran and Abraham, 1995).

2.2.2.2 The HBM structure

Figure 2.1 illustrates the concept of the HBM. The idea is that there are two main constructs that influence health behaviour and these are threat perception and behavioural evaluation.

Threat perception is itself made up from two concepts, perceived susceptibility to a threat and the perceived severity of the threat in question. The threat is not the actual threat, but that perceived by the individual, and the perceived susceptibility to, and severity of, the threat combine to produce the threat perception. If the HBM were to be used in a mathematical model the method of combining the two constructs

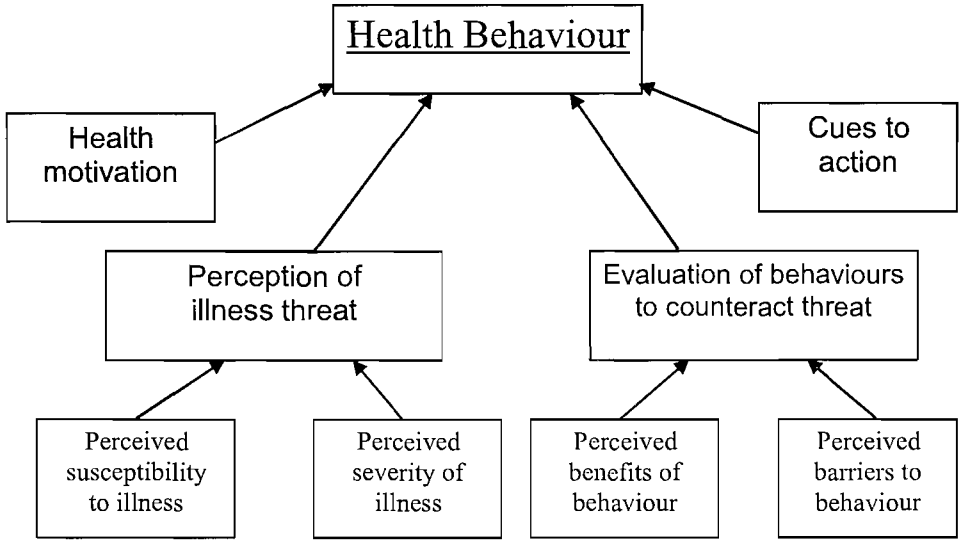


Figure 2.1: The Health Belief Model (Sheeran and Abraham, 1995)

would require consideration. Research into multiplying the two constructs in order to find a threat perception score has produced mixed results. One relationship found to be supported by literature is as follows,

$$\text{threat} = \text{susceptibility} + (\text{susceptibility x severity}),$$

while others suggest that severity must reach a threshold level first but once achieved, threat is a function of susceptibility alone, see Sheeran and Abraham (1995) for details.

Behavioural evaluation is also made up of two parts, the perceived benefits of carrying out the (preventative) behaviour and the perceived barriers to carrying out the behaviour (including psychological, physical, and monetary barriers or costs). The overall contribution of behavioural evaluation is usually found by subtracting the barriers from the benefits. However, in doing so important information may be lost. For example two people may have different scores for barriers and benefits, but when subtracted from one another their overall behavioural evaluation score may be the same, thus masking their individual differences.

In addition to threat perception and behavioural evaluation there are two further constructs thought to influence health behaviour within the HBM, and these are health motivation, and cues to action (triggers to considering action such as symptoms or campaigns).

As can be seen, (Figure 2.1), a disadvantage of the HBM is that there are no clear relationships defined between and within the constructs of the theory. The

relationships between the six constructs are not clearly explained and the constructs themselves left vague and open to interpretation. The lack of precise definitions of the constructs is important since changes in wording of questions can influence the response given, (Tversky and Kahneman, 1981). These attributes make the HBM difficult to interpret in terms of a mathematical model. It is not clear, for example, how health motivation affects the other constructs, or how psychological/demographic characteristics influence the beliefs that may be held.

2.2.2.3 Research using the HBM

The HBM has been applied to a wide spectrum of health behavioural questions which fall into roughly three broad areas, preventative behaviour, sick role behaviour (including compliance to medical regimes), and clinic use (e.g. visiting GPs), (Sheeran and Abraham, 1995). The majority of the studies used self reported measures of the six constructs, and some also include physiological, observational, or medical records. Longitudinal, (prospective), and retrospective designs have been implemented. However, it is worth noting that cross sectional studies are difficult to interpret as it is possible that behaviour could give rise to belief rather than vice versa, (Sheeran and Abraham, 1995).

Harrison et al. (1992) cited in Sheeran and Abraham (1995), conducted a meta analysis of HBM studies converting their results into a common effect size (Pearsons r). Of the 234 papers that Harrison et al. considered, only 16 were used since the remainder either did not measure all four constructs or did not show adequate controls for reliability and/or validity, thus highlighting again the problems of the vague model structure and definition. Harrison et al found that, overall, all of the HBM constructs were significantly correlated with health behaviour but that the correlates were low (see Table 2.1) and only accounted for between 0.5% and 4% of the variance in health behaviour observed.

Measure	Susceptibility	Severity	Benefits	Barriers
% of time construct is significant	81	65	78	89
Overall Correlation	0.15	0.08	0.13	-0.21

Table 2.1: Reviews of HBM Studies, (Janz and Becker (1984); Harrison et al. (1992))

It would appear that the four main constructs of the HBM are reliably correlated with health behaviour but that their effect is small. This may be due to important factors missing from the theory, a symptom of the vague definitions within the model, or due to the fact that the relations between the constructs are not considered but instead the constructs are considered as separate predictors of health behaviour. Furthermore it would appear that cues to action and health motivation constructs have been given less attention in research, (Sheeran and Abraham, 1995), perhaps

again due to the vague definitions they have been given that have been left to situational interpretation.

2.2.2.4 Discussion

The health belief model (HBM) is one of the more widely applied models for predicting health behaviour in cognitive psychology. However, for the purposes of quantitative modelling, it may not be an appropriate model due to the lack of precise definitions of constructs and their relations to one another. The HBM also fails to consider cognitions that have been shown to be good predictors of health behaviour such as intention formation, social norms, and locus of control, (see sections 2.2.3, 2.2.4, and 2.2.5 to follow). Given the lack of structure to the model, the HBM really remains little more than a list of six potentially important factors which may influence health behaviour.

2.2.3 Health Locus of Control

2.2.3.1 Introduction

The principle behind the Health Locus of Control (HLOC) model is that those who believe that they have more control over their health, through their actions, will be more likely to participate in healthy behaviour. The idea stemmed from Rotter's Social Learning theory (Rotter, 1954), which defines behaviour as a function of the expectancy that the behaviour will lead to an outcome, and the desirability (value) of the outcome in comparison to other outcomes.

From social learning theory Rotter developed the principle of locus of control (LOC) as a measure of the general expectancy that actions will lead to outcomes, (Rotter, 1966). People are said to have an external LOC if they believe that they do not have control over what happens to them in life, and an internal locus of control if they believe that their life is under their control and that they can shape their own future. This is measured using Rotter's internal-external scale, (Rotter, 1966).

Research has shown that people with internal locus of control may be more likely to expend effort in order to control their environment, take more responsibility for their actions, be more likely to seek out information, and take part in more autonomous decision making than those with an external locus of control e.g. (Strickland, 1978).

Today, the general LOC scale is widely applied as a measure of individual differences, but Rotter notes that when people have prior experience with a situation then specific expectancies of the situation have more predictive ability than general

expectancies, (Rotter, 1954).

It was theorised that, if people have an internal health locus of control (HLOC), then they would be more likely to take control of their health and participate in healthy behaviours. Since the general LOC scale failed to take account of the majority of the variance in health behaviours specific HLOC scales were developed. The most widely applied model today is called the Multidimensional Health Locus of Control, (MHLC) and this is described below.

2.2.3.2 The Multidimensional Health Locus of Control Model

Unlike the uni-dimensional general LOC scale the MHLC measures expectancy beliefs along three dimensions, internal HLC, powerful others HLC, and chance (fate) HLC. Here, internal and external HLC are not considered to be two extremes of one dimension but as orthogonal to one another with external HLC split into two distinct dimensions in itself, powerful others (the extent of belief that other people have control over life events), and chance or fate (the extent of belief that life is down to chance and not under the control of any person(s)).

The idea is that those with a high internal HLC will again be more likely to participate in health promoting behaviour, in comparison to those with high chance HLC who will be less likely to participate in healthy behaviours. Those who score highly on the powerful others HLC scale may be more likely to carry out activities that have been recommended by a professional or to attend clinics/follow regimes. However, no matter how strong the belief of control over their own health, no action will be taken if a person does not actually value their health (as per social learning theory, see Subsection 2.2.3.1).

Each of the three orientations are measured on a separate six point Likert scale collated from numerous responses on a questionnaire which has been successfully tested for reliability and validity. Further scales and variations to the theme have been developed but were not found to be as internally consistent as the MHLC developed by Wallston et al. (1978), see Conner and Norman (1995).

Health value tends to measured in one of two ways, either by finding an absolute value of health from the average of answers on a six point Likert scale, or by ranking health values amongst other values in order to gain a relative value of health, see Conner and Norman (1995).

2.2.3.3 Research using Health Locus of Control

The ideas of HLOC have been applied to many areas of health behaviour, the majority focussing upon specific preventative health behaviours such as exercise (Slemker et al., 1985), alcohol (Dean, 1991), condom use among the HIV positive (Kelley et al., 1990), breast examination (Redeker, 1989), smoking cessation (Shipley, 1982), and weight loss (Schifter and Ajzen, 1985).

Research has produced mixed results for supporting the HLOC model as a predictive model of health behaviour. Some results back the models ideas, while others find no evidence to support the theory, (Norman and Bennett, 1995). However, there have been criticisms of the research. Firstly the majority of research studies have failed to consider health value at all, or have considered it as an additive effect to expectancy beliefs rather than a moderator between expectancy beliefs and health behaviour, (Norman and Bennett, 1995). Secondly, the majority of the studies concentrate upon health behaviours which are familiar to the participants, and if measuring a specific behaviour correlation then a specific scale may be more appropriate than the general MHLC as a predictor of the behaviour (as social learning theory would suggest). It may be the case, for example, that different expectancy beliefs are held about different health situations, the subtleties of which are missed in the general scale. The studies that take these two ideas on board have been generally more successful in finding significant correlates with health behaviour, including general health and health values Weiss and Larsen (1990), and smoking cessation Georgiou and Bradley (1992), cited in (Norman and Bennett, 1995), but this is not always the case as found in an investigation into behaviour specific efficacy beliefs by Norman (1995), cited in (Norman and Bennett, 1995).

2.2.3.4 Discussion

Overall it would appear that the health locus of control theory, although sensible' on the surface, does not appear to be a strong predictor of health behaviour. Perhaps the idea is too simple and narrow to adequately explain the complexities associated with health behaviour, or perhaps further important variables also require inclusion (see further chapters).

Whatever the reason, it could be suggested that the HLOC/MHLOC model may not reliable enough to convert to a mathematical model of health behaviour at this time.

2.2.4 Protection Motivation Theory

2.2.4.1 Background

Protection Motivation Theory (PMT) was borne out of the study of fear arousing communication, considering whether such communication can directly or indirectly influence behaviour, and the cognitive processes involved in mediating behaviour change.

Two models formed the basis of PMT, the fear drive model, (Hovland et al., 1953), and the parallel response model, (Leventhal, 1970), both cited in Boer and Seydel (1995).

The fear drive model, (Hovland et al., 1953), states that fear acts to drive behaviour through increasing motivation. Upon the receipt of a fear arousing message, the motivation to follow the behaviour suggested in the message will increase in relation to the level of fear induced in order to reduce the unpleasant emotional response to the message. If following the behavioural advice succeeds in lowering the levels of fear then the behaviour will be reinforced and continued, else maladaptive behaviours may be undertaken to cope with the situation (e.g. denial of the threat, or avoidance of the message). Such maladaptive responses lead to unhealthy and risky behaviour such as smoking, failing to attend cancer screening etc.

The Parallel Response model, (Leventhal, 1970), considers the choice of maladaptive or adaptive responses to fear arousal as two control options, danger control (actions taken to reduce the physical threat to health), and fear control (actions taken to reduce the emotional threat). In contrast to the fear drive model, in this case it is considered to be the cognitive reaction of the individual to the message which governs the coping strategy they undertake.

Since research had found evidence to suggest a correlation between the level of fear arousal, and the perceived effectiveness of the advised action, with the adoption of advised behaviour, the effectiveness of different communications at increasing healthy behaviours appeared worthwhile considering.

2.2.4.2 The Protection Motivation Theory

Originally developed by Rogers in 1975, the PMT is illustrated in Figure 2.2. Upon the receipt of a threat response two appraisals are carried out, threat appraisal and coping appraisal. During threat appraisal the advantages of adopting a maladaptive response are considered alongside the perceived degree of threat, that is, the perceived vulnerability to, and severity of, the health problem. Fear arousal is

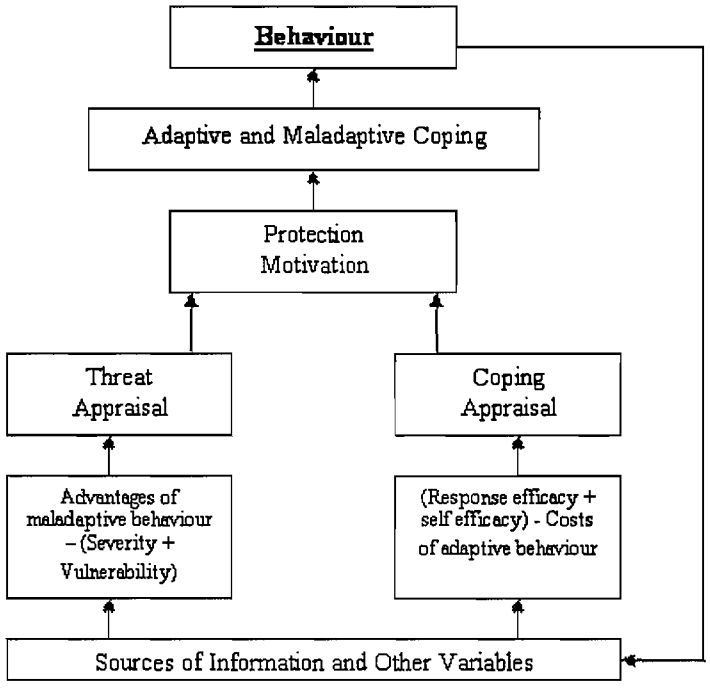


Figure 2.2: Protection Motivation Theory (Boer and Seydel, 1995)

assumed to indirectly relate to health behaviour by increasing the perceived vulnerability to, and severity of, the health issue.

The coping appraisal evaluates the response efficacy, the expectation that the behavioural response will reduce the threat, and self efficacy, the perceived ability to complete the behavioural intervention effectively. The efficacies of the behaviour are weighed up against the costs incurred to carry out the behaviour in order to produce the resulting coping appraisal of the situation. Adaptive responses are brought about by high perceptions of threat and a belief that the behaviour is possible, as well as effective, in reducing the threat placed against them without too much cost.

Protection motivation (PM) is a result of both threat and coping appraisal, and facilitates adaptive responses. As motivation to carry out (or not) an action, PM is best measured by intentions.

As pictured in Figure 2.2 the design of the PMT is well structured, with clear relations between constructs, perhaps making it more suitable to be applied in mathematical modelling than those considered in sections 2.2.2 and 2.2.3.

2.2.4.3 Research Using PMT

Research designed to study and test the PMT most often takes the form of presenting differing literature material to groups of subjects informing them of a health risk (real or fictional), and then inviting their reactions. Participants are asked to give their views of the severity, and personal vulnerability to the illness, their perceived self and response efficacy, and the degree of intention to engage in a suggested behaviour, on a Likert scale response sheet. The content of the messages presented to participants is varied in so far as how severe the illness is to be interpreted (by manipulation of the description of the problems that lack of action will lead to), the vulnerability of a typical person to the health risk in question (by emphasis on the low risks involved or high proportion of people who will be at risk), the response efficacy of the treatment suggested, and the self efficacy of completing the treatment (either explaining its good points and how simple it is to do, or focussing on the flaws of treatment and the difficulties involved in participation of the behaviour).

The PMT has been most often applied to health education campaigns in order to influence health behaviour. Some of the more popular areas of research include, for example, reducing alcohol intake (Stainback and Rogers, 1988), encouraging healthy lifestyles (Stanley and Maddux, 1986), diagnostic behaviour (Rippetoe and Rogers, 1987), and the prevention of disease (Tanner et al., 1991). Much of the research has found positive relations between the constructs and intentions to perform health behaviours. However, it would appear that only when new threats emerge does threat appraisal play a role in the adoption of health behaviour, e.g. (Brouwers and Sorrentino, 1993).

2.2.4.4 Discussion

Although in principle the PMT is little different from the Health Belief Model, sharing as it does three of the four major constructs severity, vulnerability and self efficacy, the PMT has been shown to be a "fruitful model for the prediction of intention to engage in preventative health behaviour", (Boer and Seydel, 1995). Perhaps its success in comparison to the troubles of the Health Belief Model lies in the inclusion of self efficacy, the variation of which has been shown to be important in predicting preventative health behaviour, see chapters 2.2.5 and 2.2.6. The clear layout of the PMT and preciseness of relations between its constructs, together with the research backing, may make this model more applicable to the introduction of mathematical modelling than those discussed in previous chapters. However, while research has shown an association with intention to perform behaviours, more research is required to demonstrate a strong link to behaviour (as opposed to just intention). The PMT is a strong model for the prediction of health behaviour on

paper, but with a few exceptions, it has received very little research attention so it is difficult to ascertain if the model would predict behaviour in practise. In order to use the PMT in a simulation model, it would be necessary to identify a successful piece of research applying the theory that was well structured and measured behaviour rather than intention. The results from this research could then be used to populate the simulation model parameters. The alternative would be to carry out the PMT research oneself which would be very costly both in terms of time and resources and would fall out of the scope and expertise of this research.

2.2.5 The Theory of Planned Behaviour

2.2.5.1 Background

The Theory of Planned Behaviour (TPB), is an elaboration of a previous model, the Theory of Reasoned Action (TRA), (Ajzen, 1988). Both models suggest that people make decisions based upon careful consideration of available information. The theories arose from the belief that our cognitive attitudes form a causal role in determining behaviour (when the attitudes are at the same level of consideration as the behaviour) and are described in turn below.

2.2.5.2 Model Description

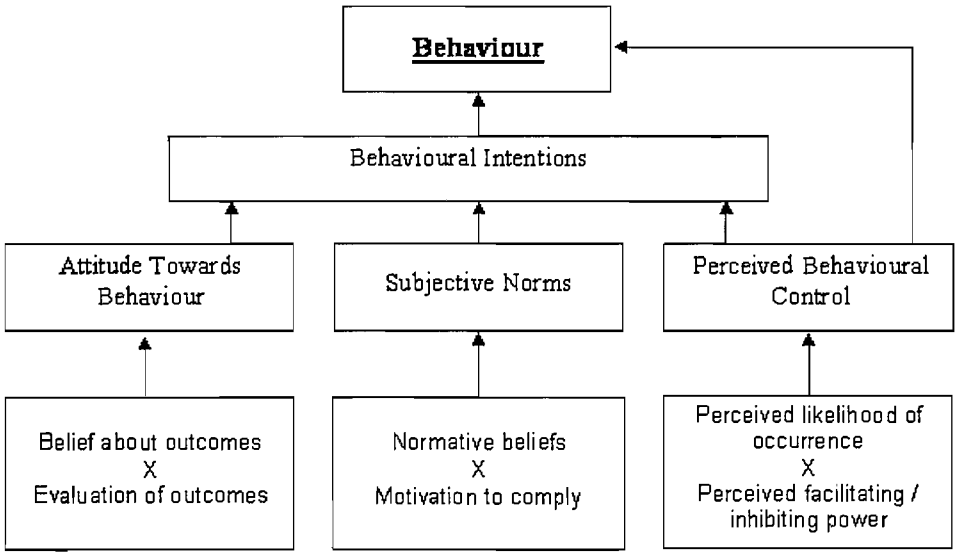


Figure 2.3: Structure of the Theory of Planned Behaviour (Conner and Sparks, 1995)

The idea of the TRA is that a persons attitudes shape his/her intentions to perform behaviour and these intentions (motivations to perform behaviours) themselves lead on to actions. Taking this idea a step further the TPB also considers perceptions of

control in order to extend the scope of the applicability of the theory by including more complex goals and tasks than only those easily performed. Figure 2.3 illustrates the idea behind the TPB.

The TPB examines behaviour as a linear regression function of behavioural intentions and perceived behavioural control, such that

$$B = w_1 BI + w_2 PBC$$

where B is behaviour, BI is behavioural intention, PBC is perceived behavioural control, and w_1 and w_2 are the regression weights.

The suggestion is that we will be more likely to participate in behaviours that we intend to carry out and that are under our control and we perceive them to be under our control, while we are prevented from carrying out behaviours that are not within our control. It is assumed that we will put more effort into desirable behaviours that we can control rather than behaviours we have little or no control over or which they do not wish to take part in, (Ajzen, 1988).

Intentions

The TPB considers three predictors of intentions to perform behaviours. 1. The attitude toward the behaviour, 2. Subjective norms relating to the behaviour, and 3. Perceived behavioural control. Attitude toward the behaviour refers to the overall evaluations of the behaviour by the individual. Subjective norms consist of a persons beliefs about whether significant others would approve of their participation in the behaviour, where significant other(s) are person(s) whose views in this domain are important to the individual. Perceived behavioural control is the extent to which the individual believes the behaviour in question is under his/her control, and draws parallels with the concept of self efficacy, see Subsection 2.2.6. Behavioural intention is itself then viewed as a regression function of these three variables,

$$BI_B = w_3 A_B + w_4 SN_B + w_5 PBC_B$$

where BI stands for behavioural intention, A is the individuals attitude to the behaviour B, SN the evaluated subjective norms relating to behaviour B, PBC the perceived behavioural control of the individual related to behaviour B, while w_3 to w_5 represent the relative weights assigned to the variables. The PBC variable has therefore a part to play in both the behavioural components and the intention components. Without PBC, equation for behavioural intention would represent the TRA.

Attitudes

The attitude component is considered as a function of the individuals salient beliefs representing the perceived consequences of the behaviour in question. The TPB regards consequences as expectancy value products (see Section 2.1), such that they are regarded as multiples of the expectancy that performance of the behaviour will bring about an outcome, and the desirability of this outcome,

$$A_B = \sum_{i=l}^{i=1} b_i \dot{e}_i$$

Where A_B is the attitude to behaviour B, b_i the belief that performing the behaviour B will lead to some consequence i, e_i the evaluation of the consequence i, and l the number of salient consequences.

It is not suggested that this calculation takes place for every decision made but that it is possible to store the information in memory for retrieval when required.

Subjective Norms

Subjective norms represent the perceptions of the views of others about whether or not the individual should participate in the particular behaviour. In the model this is quantified for each significant other by the multiple of, the significant others' view whether they should participate in the behaviour or not, with the individual's willingness to comply with this view.

$$SN_B = \sum_{j=1}^{j=m} nb_j \dot{m}c_j$$

Where SN is the subjective norm, nb_j the normative belief that significant other j approves of the behaviour, mc_j is the motivation to comply with significant other j, while m is the number of significant others considered for the behaviour.

Perceived Behavioural Control

Perceived behavioural control (PBC) is a measure of the individuals belief that they have the ability to complete the behaviour, and whether or not they really do. According to the TPB, PBC can be thought of as considering whether one has access, and control over, the necessary factors (resources etc) to perform the behaviour, whether or not they believe they have access to the resources, and how influential these factors are in facilitating completion of the behaviour. Influential factors may be either internal/personal such as psychological qualities and emotions, or external such as money, opportunities, or a dependence upon others,

$$PBC_B = \sum_{k=1}^{k=n} c_k \dot{p}_k$$

where c_k is the perceived likelihood of factor k, p_k is the perceived influential (facilitating or inhibiting) effect of factor k, and n is the number of factors considered relevant to the behaviour B.

2.2.5.3 Research Using the TPB

The TRA/TPB have been applied to the study of a range of health behaviours including sexual behaviour (Nucifora et al., 1993), health screening attendance (Norman, 1995), exercise (Goden et al., 1993), food choice (Towler and Shepherd, 1992), and breast self examination (McCaul et al., 1993).

Ajzen (1991) (cited in Conner and Sparks (1995)) wrote a review of studies using the TPB which were generally found to be supportive of the theory. The multiple correlations between behavioural intention, attitude, and subjective norms were found to be 0.71 over 16 different studies with the mean R between intention and behaviour as 0.51. Similarly Godin and Kok (1996) performed a literature review that identified 56 studies using the TPB to predict future behaviour. Their analysis also found a positive overall association between the TPB and behaviour, with the constructs of the TPB explaining 41% of the variance in intention, and 11.5% of the variance in behaviour above that explained by inention.

Over the years the TPB has grown in popularity and research has continued to support the theory for example more recently the TPB has also been successfully applied to the study of condom use (Sheeran and Taylor, 1999), and to diet (Conner et al., 2003).

2.2.5.4 Discussion

The Theory of Planned Behaviour is considered as a "..leading theoretical model..." (Rhodes and Courneya, 2003) and is perhaps one of the more promising predictive models of health behaviour for the future, (Conner and Sparks, 1995). The design and construction of the model is clear and well defined with a causational structure based upon equations.

Overall, the TPB is considered to be and has been found to be a significant predictor of both intention and behaviour, (Conner and Sparks, 1995; Ajzen, 1991; Godin and Kok, 1996). The attributes listed above may well make the TPB a prime candidate for the basis of a mathematical model of behaviour. Of the theoretical models discussed so far the TPB is both well defined, structured, and well researched with

positive findings.

However, there have been criticisms of the model urging caution to the assumptions of the validity of the model, not least that there is little evidence that communications can actually alter attitudes, and if so the effect that they have (Conner and Sparks, 1995). The inherent difficulty in measuring the constructs themselves reliably, (such as attitude and subjective norms), has also been pointed out (Conner and Sparks, 1995).

2.2.6 Social Cognitive Theory and Self Efficacy Theory

2.2.6.1 Background

Self Efficacy (SE) first appeared as a factor of behavioural modification in Bandura's Social Cognitive Theory (SCT) (Bandura, 1977).

Perceived self efficacy is the belief in the ability to excerpt control over ones environment. SE is not the same as unrealistic optimism, in so far as it is based upon experience, and leads to adventurous and challenging behaviour that is within reach of the individual.

The idea is that SE makes a difference to the whole process of how we think, feel, and how we act. The higher perceived SE a person possesses, the better their health and the higher their achievements, and they tend to be more socially integrated, (Bandura, 1977). In contrast, low perceived SE is thought to be associated with depression, anxiety and dependency, (Schwarzer and Fuchs, 1995).

2.2.6.2 The Social Cognitive Theory

Social Cognitive Theory (SCT) stipulates that all human action is due to forethought involving the following three factors.

1. Situation-Outcome Expectancies. These are the expectancies that outcomes will occur due to the environment and the situation rather than actions taken by the individual, i.e. the extent of belief that the world changes without personal engagement.
2. Action-Outcome Expectancies. These are the outcome expectancies relating to personal action.
3. Perceived Self Efficacy. This is the perceived degree of control over the actions required for the desirable outcome.

Under the first idea it is possible for beliefs to change in order to form defensive coping strategies in threatening situations, for example denial of the threat of a disease or vulnerability to it, while the last two include the option to cope with situations by providing the option to change the outcome through action.

Under SCT the likelihood of a health behaviour change will be affected by these three cognitions, (the expectancy of risk, the expectancy that behavioural change will reduce that risk, and the expectancy that the individual is capable of the behaviour change).

Self Efficacy is considered vital within this process, even more so than outcome expectancies since these are only considered during the formation of intentions alongside self efficacy (no intentions will be formed to change actions if it is not believed possible to see the actions through), whereas self efficacy is also a necessary controlling influence over the process leading to attempting and sustaining action.

The measurement of these variables should be situation specific wherever possible in order to increase the predictive ability of the theory (as before), and when considering addictive behaviour it has been suggested that SE be broken down into five categories, two concerning the prevention of undertaking addictive behaviours, and 3 addressing self efficacy issues relating to self change and relapse prevention.

2.2.6.3 Research Using SCT

The majority of research using SCT assesses the theory's ability to influence behaviour change. The theory has been applied in areas such as sexual risk behaviour (Kasen et al., 1992), physical exercise (Shaw et al., 1992), and weight control, (Bagozzi and Warshaw, 1990). In addition to this the SCT has been widely applied to areas of addiction and relapse, with success in coping in high stress situations linked to perceived control over the necessity to engage in the unwanted behaviour, (Schwarzer and Fuchs, 1995).

In most cases research has proved very supportive of the theory, and in some cases the further variables of the TRA were found to be non significant predictors of behaviour once the influence of SE had been taken account of, (Dzewaltowski, 1989; Beck and Lund, 1981).

Further to this in one study, after the receipt of cognitive behavioural treatment based upon the ideas of SCT, a group of patients suffering from rheumatoid arthritis reported less pain and joint inflammation (proposed to be due to enhanced coping strategies), and greater psychosocial functioning (O'Leary et al., 1988).

2.2.6.4 Discussion

Since it first appeared in Bandura's Social Cognitive Theory, self efficacy has been incorporated into other cognitive models of health behaviour, (see sections 2.2.4 and 2.2.5), so that social cognitive theory is now less of a standalone theory.

Its inclusion in modern theories of cognitive health processes outlines how effective self efficacy is in predicting health behaviour and accounting for its variance. Rather than concentrating on communicating risks and dangers, the idea here would suggest that emphasis should be placed upon increasing awareness of what (and how) people can change themselves, and pointing out what is to be gained by this in order to support and aid self efficacy beliefs.

2.2.7 Motivational Models: Summary

This Section has aimed to provide an introduction to some of the more traditional cognitive models used in psychology for the prediction of health behaviour. The information presented in this Chapter is taken from the book "Predicting Health Behaviour" edited by Conner and Norman (1995).

Although the theories and models do vary in their assumptions and structure, some parallels do exist and the core constructs are similar within the more popular models, such as self belief and self efficacy, benefits of the behaviour, barriers to the behaviour, and the severity of the illness/importance of the behaviour.

All the models have received a significant amount of attention in research and some papers have attempted to compare the predictive ability of each with that of the others.

The models and ideas that are more clearly defined and structured may be more suitable for the application of mathematical modelling or simulation. For this reason, perhaps the two more suitable models for inclusion in the currently reported research would be Protection Motivation Theory, and the Theory of Planned Behaviour.

2.3 Behavioural Enaction Models

2.3.1 Introduction

Behavioural enaction models build upon motivational models of health behaviour with an aim to bridging the gap between intentions to perform a behaviour and behavioural performance. Two behavioural enaction models are discussed in turn

below. These are Gollwitzer's Implementation Intentions and Bagozzi's Goal Theory.

2.3.2 Gollwitzer's Implementation Intentions

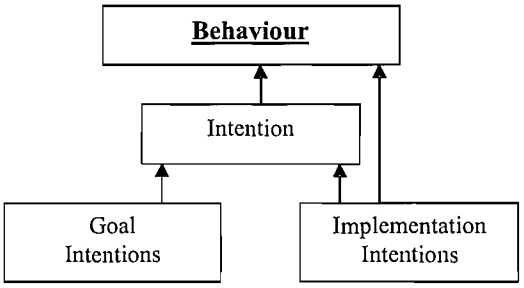


Figure 2.4: Gollwitzer's Implementation Intentions (cited in Conner and Norman (1995))

Gollwitzer's theory breaks the intention construct into two parts, goal intentions and implementation intentions, (see Figure 2.4).

Goal intentions are defined as the intentions to achieve a goal, while implementation intentions refer to plans as to how, when, and where, this goal will be translated into action.

Implementation intentions will lead on to performance when the conditions in the plans are met. This means that when the conditions of the plan are met, the individual is committed to action, almost handing control over to the environmental conditions once the intentions are formed.

2.3.2.1 Research using Gollwitzer's Implementation Intentions

Evidence has been found by Gollwitzer himself that forming plans and timetables for action increases the likelihood of performance of the action, (Gollwitzer, 1954), thus providing support for the idea of implementation intentions helping to predict performance. Initial findings by other researchers have also produced positive results including in areas such as breast self examination (Orbell et al., 1997) and exercise adoption and adherence (Kendierski, 1990).

However, despite the positive research findings where it has been studied, the model has not been widely researched, perhaps undeservedly.

2.3.3 Bagozzi's Goal Theory

Bagozzi introduced his Goal Theory in the early 1990's, (Bagozzi, 1992). He considered intentions as split into three categories, present oriented intentions

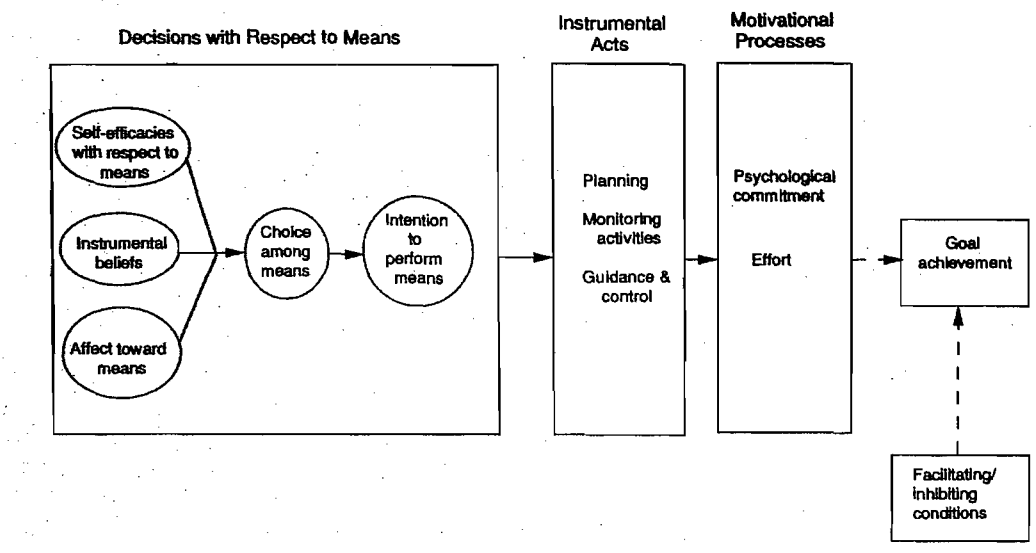


Figure 2.5: Bagozzi's Goal Theory, (Bagozzi, 1992)

(intentions to act immediately), future oriented intentions (intentions made at time point t_1 to act at time t_2), and goal oriented intentions.

Bagozzi argues that while traditional attitude theories, (e.g. the Theory of Planned Behaviour and the Theory of Reasoned Action), may apply to the first two categories of intention, problems arise for the theories when one intends to pursue a goal or target outcome.

Bagozzi's Goal Theory examines how and when intentions are translated into the achievement of a goal or target, and distinguishes between the intention to act and the intention to pursue a goal. Figure 2.5 depicts the theories account of the underlying processes from intention to action.

Once a goal intention is formed, the method a person chooses in order to pursue the goal will be influenced by his/her self confidence, the likelihood of goal attainment via the method, and his/her perception or the degree of pleasantness of the method.

According to Bagozzi (1992) goal intentions are brought about by desire, where desires are driven by attitudes, subjective norms, and goal efficacy.

Bagozzi argues that instrumental acts and motivational processes lie between intentions and goal achievement. Once the intention to perform an action is made, then this sets off implementation processes in order to decide how to achieve the goal. Plans are formulated in order to achieve the target, monitoring occurs to ensure that the acts are carried out effectively (and on time), with guidance and control required to change behaviours if monitoring suggests this is necessary.

It is motivational processes that Bagozzi suggests are the important driver to eventually achieving the goal(s) set out. Motivation is considered along two dimensions, psychological commitment, and effort. Commitment is taken to refer to "..the binding of the individual to 1) the decision to try to achieve the goal or perform a behaviour, and 2) the decision to use a particular means.", (Bagozzi (1992), p199). Bagozzi also recognises that goal achievement is not only influenced by the individual but may be influenced by the goal environment too, see Figure 2.5.

2.3.3.1 Research Using Bagozzi's Goal Theory

Bagozzi's goal theory has not been widely researched within health psychology, but the few studies that do exist may offer some support to the theory. Bagozzi and Edwards (1998) cited in Armitage and Conner (2000), for example found goal intentions had an effect upon the degree of effort and this in turn influenced the initiation of behaviour that determined the level of goal attainment.

2.3.4 Enaction Models: Summary

Behavioural enaction models help to bridge the gap between motivational models of behaviour and the implementation of the behaviour, with the achievement of a target. Since both of the models discussed concentrate on implementation intentions it has been suggested that this may be a valid construct that is certainly worth further consideration in research, (Armitage and Conner, 2000).

2.4 Integrative Models and Theories

2.4.1 Introduction

Over the years attempts have been made to integrate the various models of predictive and descriptive health psychology into one large umbrella model/theory.

Wallston and Wallston (1984), cited in (Schmidt et al., 1990), compared four major theories of health psychology and came to the conclusion that there are 6 variables that an integrative health model should include. These were attitude, vulnerability/threat, norms, motivation, habit, and facilitating conditions.

Other attempts at designing an integrative model of health psychology include the 'Integrative Conceptual Framework', (Moos, 1979), the 'Person-environment-interaction systems model', (Kar, 1986), and more recently the 'Major theorists model', (Fishbein et al., 2001), which is discussed below.

2.4.2 Major Theorists Model

2.4.2.1 Background

As the AIDS epidemic continued to unfold the National Institute of Mental Health (NIMH) brought together proponents of five of the more popular theories of health psychology in order to try to formulate a uniform approach to designing interventions primarily focussing upon safe sex and the use of condoms, (Fishbein et al., 2001). The theorists involved in the 3 day discussions are shown in Table 2.2.

Theorist	**Theory or Model**
A. Bandura	Social Cognitive Theory
M. Becker	Health Belief Model
F. Kanfer	Self-Regulation/Self control
M.Fishbein	Theory of Reasoned Action

Table 2.2: Major Theorists involved in the workshop (Conner and Norman, 1995)

2.4.2.2 Model Proposal

The theorists agreed upon 8 variables that account for health behaviour and these are listed below.

1. Intention
2. Environmental Constraints
3. Skills
4. Attitude
5. Norms
6. Self Standards
7. Emotion
8. Self Efficacy

The general assumptions were that a person will behave as he/she was previously until some stimulus, (either internal or external), alters his/her thoughts and affects one or more of the listed variables, and then his/her behaviour may change.

Intention was agreed to have the most influence upon behaviour, with the first three variables required in order for behaviour to take place. The last five variables then

influence, strengthen, and decide the direction of intention as well as occasionally affecting behaviour directly themselves.

Therefore, the theorists agreed that, in order to carry out a health behaviour it is first and foremost necessary to intend to carry it out, possess the relevant skills in order to carry out the behaviour, and there must be no obstacles preventing the behaviour from taking place. The final five variables play their part either directly or by affecting the intentions to carry out the behaviour in the following way. Intention will be strengthened if:

- the positive expected outcomes and attitudes outweigh the negative,
- more social pressure is felt to carry out the behaviour than not to,
- the behaviour is consistent with the person's self image,
- the behaviour elicits more positive than negative emotions in the individual
- the individual possesses self efficacy relating to the behaviour.

No consensus was found between the theorists as to the causal linking of the 8 variables, or the strength of their relation and inter-relationships. What was agreed was that the relative importance of each variable will vary, not only with the situation in question, but also with the population being considered. Therefore, it was felt appropriate to design interventions based upon research assessing the levels of each variable in order to gauge the areas that require enforcing or replacing. For example, if it was found that if intentions were low it would be appropriate to enforce intentions as the first step, but if intentions were already high it would be necessary to find out whether it was environmental constraints or lack of skills preventing the behaviour performance and then alter these as necessary.

2.4.3 Integrative Models: Summary

The idea of an integrative cognitive model for the prediction of health behaviour is a very appealing one. However, it would appear that to date no such model has become popular and therefore little research has been carried out in order to test/validate them, or indeed in order to populate a mathematical version with data.

Perhaps the reason for the apparent lack of popularity and research into this area is due to the difficulty in reaching a consensus of opinion across the disciplines in psychology as to how such health cognitions occur, and in forming the relationships between the constructs in any proposed model itself, (as is the case with the Major Theorists Model discussed above). That is not to say, however, that an integrative

model of health behaviour is not the way forward. Since many of the traditional models for the prediction of health behaviour do contain similar if not the same constructs, it is not inconceivable that a singular model or theorem could be designed to encapsulate the ideas from each without loosing the original concept.

When considering using an existing integrative model as the basis of a mathematical model of health behaviour it is suggested that at this time there may not be enough research finding support for the theories, or to populate the model with, and in the case of the more recent Major Theorists Model, structure is lacking for implementation. It would be possible to undertake new research to investigate how such models faired at predicting health behaviour and attendance at breast screening, however it was felt that this would be a huge undertaking requiring too much time and distract from the primary research objectives.

2.5 Stage Theories

2.5.1 Introduction

Stage theories consider health behaviour as made up of a number of discrete stages. The idea is that a person may reside in any one stage at a time and people within each stage will behave in qualitatively different ways and require different information and motivations to progress to the next stages on the way toward action itself.

According to Armitage and Conner (2000) the most prominent stage theories of behaviour suggested in psychology to date are the Health Action Process Approach (HAPA), Heckhausen's Rubicon Model, Kuhl's Action Control Theory, the Transtheoretical Model of Change, and the Precaution Adoption Process. These are discussed in turn below with more emphasis on the latter two models since they appear to be the two more popular theories.

There are also stage models of behaviour that are specific to a particular issue or behaviour, Weinstein et al. (1998) talk of stage theories addressing behaviours such as the delay in seeking medical care e.g. (Anderson et al., 1995), and AIDS risk reduction e.g. (Catania et al., 1990).

2.5.2 Health Action Process Approach

Schwarzer's Health Action Process Approach (HAPA) model comprises of two phases, the motivational phase and the volitional phase, (Schwarzer (1992) cited in Armitage and Conner (2000)).

The motivational phase is roughly equivalent to the ideas of SCT and TPB as described in sections 2.2.6 and 2.2.5, but with a few adjustments. Outcome expectancies only affect self efficacy if the individual in question has previous experience with the behaviour, otherwise their only impact is upon intentions. In addition, the threat construct, (from HBM in Subsection 2.2.2), is considered only as a more distal predictor of expectancies.

The volitional phase in HAPA comprises of three overlapping stages, planning, action, and maintenance of behaviour. Once a person has an intention to perform a behaviour they will begin to plan the related actions by imagining scenarios under which they will perform the behaviour. Movement into the action stage represents successful planning and is kept up if movement continues to the third volitional stage, that of maintenance.

The HAPA model brings together the two groups of theory discussed so far, the motivational models of health behaviour, describing how intentions are believed to be formed, and the behavioural enaction models, that attempt to describe how these intentions lead to behaviour. The model has, though, incurred criticism for its vagueness in describing the role social cognitive variables play at each stage in the volitional phase, (Armitage and Conner, 2000), and more clarity would be required in this area before the model could be fully tested, put into operation, or used in a simulation model.

2.5.3 Heckhausen's Rubicon Model

The model proposed by Heckhausen (1991), cited in Armitage and Conner (2000), is very similar to that of the HAPA model.

The Rubicon Model consists of four distinct stages,

1. Intention Formation, (selecting the appropriate behaviour by considering expected outcomes and then intend to perform the behaviour)
2. Post Decision, (Planning and preparation stage)
3. Action
4. Evaluation

The main difference between the Rubicon Model and HAPA is the inclusion of the evaluation stage containing attributes of causality and evaluation of the outcomes. The Rubicon Model is also more clearly structured with more closely defined discrete stages than those of the HAPA, rendering it more suitable to modelling and research.

However, despite its clearer definitions and attributes the Rubicon Model has received little research attention, (Armitage and Conner, 2000).

2.5.4 Kuhl's Action Control Theory

Kuhl (1981, 1985), cited in Bagozzi (1992); Armitage and Conner (2000), put forward two processes that aid the implementation of intentions, action control and implementation control. Action control is concerned with the successful implementation of the whole action, whereas implementation control is concerned with the implementation of step by step courses of behaviour leading to the end action.

Kuhl suggests seven intermediary control strategies that facilitate the successful completion of action including emotion control, motivation control and coping with failure. The mediating control strategies are influenced by self regulatory mechanisms. People with low self regulatory control capacity are said to be state oriented, and tend to engage in high amounts of planning and consideration related to past, present, and future, states before acting. Conversely those with high self regulatory control are said to be action oriented, and are more likely to act faster or immediately with little planning or deliberation.

Kuhl (1985) developed scales to measure action control, and these scales have been used in research to demonstrate that action oriented people show more likelihood to base their decisions on attitudes, whereas those high in state orientation based their decisions more upon social norms, (Bagozzi et al. (1992) cited in Bagozzi (1992)). Action orientation has also been shown to be influential in the successful implementation of intentions (Armitage and Conner, 2000).

Kuhls Action Control Theory looks promising on face value but requires clarification and more precise constructs before progress may be made through its application.

2.5.5 The Transtheoretical Model

The Transtheoretical Model suggests five stages of change, two principles of change, and ten processes of change governing movement through the stages.

The model was first conceptualised in the early 1980s, (Prochaska and DiClemente, 1983), when it was noticed that behavioural change appeared to unfold in stages. Ten processes of change, and two principles of change, emerged from an amalgamation of hundreds of theories of psychotherapy and behaviour change. These processes of change were reported to be used at different times during behaviour change by participants questioned about their efforts in giving up smoking, (Prochaska (1984),

cited in Prochaska et al. (1997)).

From initial studies in psychiatry and therapy, the Transtheoretical model went on to be applied to a broad range of health psychology and is now one of the leading stage theories in use.

2.5.5.1 Structure of the Transtheoretical Stages of Change

The core constructs of the transtheoretical model are five stages of change, ten processes of change, decisional balance, and self efficacy.

Stages of Change

Five stages of change are implied by the model, and are listed in the discussion that follows.

A linear progression through the stages is suggested, but at any stage a relapse may occur to a previous stage, leading to cyclic progression. Three revolutions has been suggested as common before stability returns, (Armitage and Conner, 2000). The rate of progression through the states is variable and it is possible for an individual to remain in one state and progress no further.

The distribution of people in each stage is said to vary with the situation considered, (Salovey et al., 1998).

The stages of the Transtheoretical Model are discussed in turn below.

Precontemplation People have no intention to change in the next 6 months. This may be due to their absence of knowledge or awareness of the threat or behaviour, or their perceived inability to carry out the behaviour.

Contemplation In this stage people are considering change within the next 6 months. They are aware of the benefits of the behaviour but also considering the disadvantages and barriers to the action.

Preparation Here an individual is actively committed to change within the next month. They may have attempted the behaviour (or change) in the past year but been unsuccessful, and have made plans and preparations in order to aid their behaviour.

Action This is the stage whereby people are actively engaged in the behaviour which requires effort and energy exertion by the individual. In order to qualify for membership of this stage, the behaviour alone may not be enough, but must reach the levels experts agree that will reduce the health risks. People may remain in this stage for any period from 1 day to 6 months.

Maintenance Typically after 6 months of action people enter the maintenance stage where they work to prevent a relapse to unhealthy behaviour. Individuals in this stage apply change processes less frequently than those in the action stage and are more confident that they will not relapse. Maintenance is estimated to last for any period from 6 months to 5 years (Prochaska et al., 1997).

Some behaviours also require a sixth stage which is called 'Termination', and this is applicable to addictions and repetitive behaviour. When in this final stage people are no longer tempted to stray from their healthy behaviour and self efficacy relating to the behaviour is strong.

Processes of change

The processes of change are the processes that people use in order to progress through the stages. There are 10 processes that were found to appear most often in the theories and received most empirical support and these are listed below, (Prochaska et al., 1997).

1. Consciousness raising
2. Dramatic relief
3. Self re-evaluation
4. Environmental re-evaluation
5. Self-liberation
6. Helping relationships
7. Counter-conditioning
8. Contingency management
9. Stimulus control
10. Social-liberation

The processes are not described in detail here, but the reader may wish to read more about them in Prochaska et al. (1997).

Decisional Balance

Decisional balance reflects an individual's appraisal of the situation, and the behaviour. The relative number of positive and negative beliefs about a behaviour is considered important for movement between stages. As progression takes place up the stages, the number of positive beliefs are said to increase and the negative beliefs

decrease. The idea has received empirical backing from a wide spectrum of health psychology and mathematical relations have been found between the positive and negative beliefs of change, and progression between some of the stages, (Prochaska et al., 1997).

Self-Efficacy

The construct of self efficacy has two parts, confidence and temptation. Confidence is derived from Bandura's Self Efficacy Theory, (Bandura, 1977), and refers to self efficacy, as has been discussed throughout this document. In addition, the Transtheoretical model also considers temptation as a minor part of self efficacy and here the intensity of urges to engage in habitual behaviour when in a difficult situation is addressed.

2.5.5.2 Research Using the Transtheoretical Model

Having been originally designed to study addictive behaviours, the Transtheoretical Model is now more widely applied in Health Psychology including in areas such as exercise, weight control, mammography utilisation, and safer sex, (Salovey et al., 1998). Empirical research has largely focussed upon the stages of change, with some support found for the model.

However, criticisms of the model have been made, some of which are discussed below. The majority of research testing the model has been cross-sectional in design thus making it even more difficult than usual to imply causation. It has been suggested that it may be more appropriate to find support for changes in the decisional balance, and processes of change, predicting movement across the suggested stages, (Salovey et al., 1998). Armitage and Conner (2000) criticise the model for the lack of clarity concerning the role of other variables in progression through, and within, each stage, and its lack of application in social cognitive terms. They also argue that there is little information provided as to why some people will be successful in achieving behaviour change and why others will not.

2.5.5.3 Discussion

The Transtheoretical Model was developed from practise and so has a very intuitive feel and is one of the more widely and commonly applied stage theories of health behaviour. Due to the stage based nature of the model, it lends itself to mathematical modelling quite neatly, however, the relations other variables have upon the movement through stages would need to be clarified if it were to be possible to quantify the model.

2.5.6 The Precaution Adoption Process Model

The Precaution Adoption Process Model (PAPM) was first conceptualised by Weinstein and Sandman (1992) and was later built upon by Weinstein et al. (1998). The model suggests seven stages of change until precautionary behaviour is adopted. The idea behind and structure of the PAPM is similar to that of the Transtheoretical model, (see Subsection 2.5.5.1), but the PAPM distinguishes between people who are unaware of a health issue, or risk, and those who are aware of the issue but have not applied much thought to it. A distinction is also drawn between people who have made the decision not to adopt the behaviour and those who have not yet considered adopting the behaviour.

2.5.6.1 The Precaution Adoption Process Model Structure

The model puts forward 7 stages through which people are thought to pass in their journey to adopting healthy behaviours, the stages are listed, and then described in turn, below.

1. Unaware of health issue
2. Aware of health issue
3. Contemplation
4. Planning
5. Action
6. Maintenance
7. Maintained

At an initial point in time it is presumed that the health issue or concern will not be known to the individual (stage one), once they have been made aware of the issue they have moved on to the second stage but may not be engaged in the issue, contemplation of the health issue and the risks/benefits of the behaviour is the third stage. After considering the issue people may make the decision not to take part in the recommended behaviour for now, (stage four), or to go forward and plan to carry out the behaviour, (stage five). When the planned behaviour(s) begin to take place then stage six is reached and, where relevant, a seventh stage may be reached once the behaviour is maintained.

The PAPM also identifies the factors relevant for, and against, transition between the stages, and these are both simpler and clearer than those of the Transtheoretical Model. These transition variables are summarised in Table 2.5.6.1.

Stage Transition	Variable
1-2	Knowledge
2-3	Perceptions of personal vulnerability
3-4	Beliefs about severity, susceptibility, and self efficacy
4-5	Pressures, situational constraints and obstacles

Table 2.3: Variables Influencing Progression Through the PAPM (Weinstein et al., 1998)

Stage classification is most often decided via questioning, for example asking if a person has heard of the health risk, and if so whether they have ever considered acting to reduce the risk etc. Unlike the Transtheoretical Model the PAPM does not take account of past behaviours, or time frames, when classifying people into each stage.

2.5.6.2 Research Using the PAPM

The PAPM has not been as widely applied as the Transtheoretical model, however studies have shown some support for the structure, although they do tend to be cross-sectional in design. The PAPM was originally applied to home radon testing (e.g.Weinstein and Sandman (1992)), but has also been applied to areas such as osteoporosis, (Blalock et al. (1996) cited in Weinstein et al. (1998)), and vaccinations, (Hammer (1997) cited in Weinstein et al. (1998)).

2.5.6.3 Discussion

The Precaution Adoption Process Model, although less popular than the Transtheoretical Stages of Change, does appear to be intuitive and natural in design, and offers a clearer idea of the factors of importance at each stage. However, it has been criticised, along with the Transtheoretical model, for not stating clearly the social cognitive variables being manipulated at each stage, (Armitage and Conner, 2000), and for the majority of the supporting research applying cross sectional designs, (Salovey et al., 1998).

2.5.7 Stage Models: Summary

Stage models of behaviour suggest that social cognitive influences on behaviour may be different at different stages of the behaviour change process. Each theory suggests a different number of stages but all agree that a separation exists between motivational processes and volitional processes. Armitage and Conner (2000) suggest that exactly what happens in the volitional stages of the behaviour process appear to be less clear in stage than in behavioural enaction models, (see Chapter 2.3), and

that the research studying them, although supportive, tends to be cross-sectional in nature, and can lack validity.

Weinstein et al. (1998) criticise the over tendency to use cross sectional designs in order to show support for the idea that behaviour change requires the movement through stages, arguing that differences between stages could also be due to pseudo stages (a continuum split into stages). Weinstein et al. instead ask for research to focus upon interventions that, according to the theories, should produce different effects at different stages in order to test the ideas.
By their nature, Stage theories of health behaviour may lend themselves quite nicely to mathematical modelling, especially to simulation modelling. Therefore, it is certainly worth considering applying the ideas within the more popular stage theories, (e.g. PAPM and the Transtheoretical Model), to simulation models involving health behaviour. Difficulties may arise, however, where there is less clarity as to how movement between the stages is negotiated, or indeed, as to whether the stages are really just different points along a continuum of change.

2.6 And the Rest

It would appear that the number of models of behaviour that may be, and have been, applied to health in the social sciences is ever growing, not to mention the suggested improvements and additions to each one, and the models specific to one behaviour or area. This is understandable since human behaviour can be regarded as nothing but complex and it would be difficult to find one model or theory that adequately identified all constructs in all situations.

Another issue is that the models and theories are just that, and in the social sciences the idea of 'proof' is somewhat impossible, therefore for each of the ideas there will be research to support them, and equally there will be criticisms and perhaps conflicting research. Of course some ideas are more widely accepted than others, and it is hoped that the more recognised and highly regarded models have been discussed in this Chapter.

Many more ideas and models were uncovered during the research for this Chapter and this Section aims to mention some of these, although will not discuss them in detail, in order to make the reader aware of their existence. It is also worth noting that this list will not be exhaustive and that many more theorems and models of health behaviour, or that may be applied to health behaviour, will exist in the literature.

Name	Comment or Description	Ref.	Cited in
Conflict Theory of Decisional Balance	Similar to HBM and PMT, emphasising the role of expected outcomes and belief in health behaviour and decisions	Velicer et al. (1985)	Carmody (1997)
Attribution Theory	Describing rules by which it is believed people use in order to draw logical cause and effect inferences about themselves and their environment. Has applications in health promotion and the causes of illness.	Heider (1958)	Salovey et al. (1998)
The Theory of Achievement Motivation and uncertainty orientation	Similar theory to Kuhl's Action Control Theory. The model has recently been assigned a mathematical reformulation which links individual differences in information processing to individual differences in motivation	Sorrentino et al. (1985)	N/A
Social Comparison Theory	Used to appraise how people cope with their own and others illness and judge how people appraise health information they receive. Assumes people draw perceptions by comparing themselves to others and seeking contact with people in similar situations	Festinger (1954)	Salovey et al. (1998)
Langlie's Social Network Model	Based upon the HBM and includes a social support dimension	Langlie (1977)	Schmidt et al. (1990)
The Preventative Behaviour Model	Based upon the HBM and assessed by the 'Prevention Index'	Beck and Lund (1981)	Schmidt et al. (1990)
The Theory of Social Behaviour	Designed to predict both specific and alternative behaviours. Includes physiological arousal and facilitating conditions as model parameters	Triandis (1977)	Schmidt et al. (1990)
Social Cognitive Health Behaviour Theory	Considers cognitive, emotional, and motivational conditions for maintaining health behaviour in social conditions.	Fuchs et al. (1989)	Schmidt et al. (1990)
PRECEDE	(Predisposing, Reinforcing and Enabling Forces in Educational Diagnosis and Evaluation). A health promotion and planning model.	Lazes et al. (1986)	Schmidt et al. (1990)
Health Education/ Promotion Planing Model	Based upon the HBM this model is again for the planning or health promotion and education. It has seven steps to be targeted at an individual or group.	Dignan and Carr (1987)	Schmidt et al. (1990)

Table 2.4: Other Theories and Models Applied to Health Behaviour

2.6.1 Other Models of Health Behaviour

2.7 Summary

This Chapter has aimed to provide an introduction to some of the popular and traditional cognitive models used in psychology for the prediction and study of health behaviour.

The Chapter began by discussing five traditional motivational models of health behaviour research, those of the Health Belief Model, Health Locus of Control, Protection Motivation Theory, The Theory of Planned Behaviour, and Social Cognitive Theory. A number of key constructs and ideas are repeated in several of the theories (e.g. self efficacy, intention formation, and benefits and barriers to the behaviour), each with slightly different ideas as to how they link together and which constructs are more influential.

All the models have received a significant amount of attention in research, with

varying degrees of success, and some papers have attempted to compare the predictive ability of each, with that of the others. However a tendency has been observed for research to be cross-sectional in design making a link with causation difficult to ascertain, and some of the theories lack a clearly defined structure between and within the variable constructs.

The models and ideas that are more clearly defined and structured may be more suitable for the application of mathematical modelling or simulation. For this reason, perhaps the two more suitable models for inclusion in the currently reported research would be Protection Motivation Theory, and the Theory of Planned Behaviour. However the Protection motivation Theory has received less research attention and the research that has been identified was not well designed such that it could not be used to fully approximate the theory in a simulation model. The Theory of Planned Behaviour has, however, been the subject of a large body of research considering health behaviours, and several well designed studies have applied the theory with success in a number of areas including attendance at breast cancer screening in the UK, (Rutter, 2000).

Behavioural enaction models help to bridge the gap between motivational models of behaviour, the implementation of the behaviour, and the achievement of a target. Two models were discussed, Gollwitzers Implementation Intentions and Bagozzi's Goal Theory. Since both of the models concentrate on implementation intentions (as a primary construct to behavioural enaction) it has been suggested that this may be a valid construct that is certainly worth further consideration in research, (Armitage and Conner, 2000). However, overall it was felt that there would not be enough well designed research available in order to incorporate integrative models into a simulation model, and that perhaps enaction models were more focussed upon predicting adherence to behavioural plans and goals than to general health behaviours.

Attempts have been made to integrate some of the more popular theories into one large umbrella theory. The idea of an integrative cognitive model for the prediction of health behaviour is a very appealing one. However, it would appear that to date no such model has become dominant nor widely applied, and therefore, little research has been carried out in order to test/validate such a model, or indeed in order to populate a mathematical version with data.

Perhaps the reason for the apparent lack of popularity and research into this area is due to the difficulty in reaching a consensus of opinion across the disciplines in psychology as to how such health cognitions occur, and in forming the relationships between the constructs in any proposed model itself, (as is the case with the Major Theorists Model).

That is not to say, however, that an integrative model of health behaviour is not the way forward. Since many of the traditional models for the prediction of health behaviour do contain similar if not the same constructs, it is not inconceivable that a singular model or theory could be designed to encapsulate the ideas from each without loosing the original concept.

When considering using an existing integrative model as the basis of a mathematical model of health behaviour it is suggested that at this time there may not be enough research finding support for the theories, or to populate the model with, and in the case of the more recent Major Theorists Model, structure is lacking for implementation.

Stage models of behaviour suggest that social cognitive influences on behaviour may be different at different stages of the behaviour change process. Each theory suggests a different number of stages but all agree that a separation exists between motivational processes and volitional processes. Armitage and Conner (2000) suggest that exactly what happens in the volitional stages of the behaviour process appear to be less clear in stage theories than in behavioural enaction models, (see Section 2.3), and that the research studying them, although supportive, tends to be cross-sectional in nature and can lack validity.

Weinstein et al. (1998) calls for research to focus upon interventions that, according to the theories, should produce different effects at different stages in order to test the ideas further.

By their nature Stage theories of health behaviour may lend themselves quite nicely to mathematical modelling, especially to simulation modelling. Therefore, it is certainly worth considering applying the ideas within the more popular stage theories, (e.g. PAPM and the Transtheoretical Model), to simulation models involving health behaviours. Difficulties may arise, however, where there is less clarity as to how movement between the stages is negotiated, or indeed, as to whether the stages are really just different points along a continuum of change. It was also felt that perhaps stage theories were more suitable to the study of behaviour change and help with monitoring addictive behaviours and change to combat destructive behaviours than to the uptake of general health behaviours.

Chapter 3

Breast Cancer Behaviour

3.1 Introduction

This Chapter summarises the research identified in literature review that considered the literature relating to behavioural issues surrounding breast cancer and breast cancer screening uptake. Within this Chapter the expression 'breast cancer behaviour' refers to any behaviour that may be associated with the prevention of, or the treatment of, breast cancer such as breast self examination, attendance and re-attendance at offered screening sessions, adherence to recall or recommended treatments, or the speed of seeking help for any identified change in the breast.

A small scale literature search was undertaken to find work citing behavioural issues surrounding such breast cancer behaviours, i.e. screening attendance, or breast self examination behaviour. Papers that considered these issues were identified and reviewed with an aim to advising any behavioural aspects to be added to a traditional OR model of breast cancer epidemiology.

This Chapter and its contents are not intended to be a full representation of all research into breast cancer behaviour, rather it is hoped to provide a summary of the more recent and predominant studies, reviews, and opinions.

The next Section (3.2) describes some of the reviews of the psychological literature relating to breast cancer behaviour, and Section 3.3 then discusses some of the individual studies found to be of relevance in more detail.

3.2 Overviews and Reviews

Three comprehensive papers were identified that summarised and reviewed the research concerning human factors relating to breast cancer with a focus upon

attendance at screening sessions. The first of these was a systematic review of the determinants of screening uptake in general, including breast cancer screening, and includes research conducted up to the end of 1998, (Jepson et al., 2000). The second is a Swedish paper which discusses five pieces of research examining factors affecting attendance at the population based mammography screening in Sweden, (Lagerlund, 2003). The paper also includes a summary of work conducted in other Countries with population based screening programmes for breast cancer, (including the UK). The most recent review considered inequalities in cancer screening and includes a discussion of 55 papers which examine factors affecting access to cancer screening among minority groups, (Chiu, 2003). This final review includes research published up to the end of 2002.

The information contained in each of these three reviews is summarised in turn below.

3.2.1 Systematic Review of the determinants of screening uptake

Jepson et al. (2000) published the systematic review with an aim to examining factors associated with the uptake of all screening regimes, including mammography screening for breast cancer. The paper also reviews and summarises literature relating to factors pertaining to the effectiveness of interventions for screening programmes, however the content of this part of the review is not discussed here.

Research was included in the review if it was published before the year 1999 and all factors thought to influence screening uptake were considered including demographic, sociological, psychological and economic factors. The review considered randomised control trials, quasi randomised control trials, cohort studies and case control studies.

In order to ensure some level of quality in the included research, studies were excluded if they measured determinants after screening had taken place rather than before, related to breast self-examination rather than mammography screening, the dependent variable was intention to attend rather than actual attendance, the design of the study was cross-sectional in nature, or if no multivariate analysis had been carried out upon the results. Sixty five papers met the criteria for the review, and of these, thirty four related specifically to factors affecting attendance at mammography screening.

It was hoped that a meta-analysis of the results of the research studies would be possible, however, statistical pooling of the information turned out to be inappropriate due to the heterogeneity of the study designs and data, and the lack of inclusion/publication within the multivariate analysis of determinants found to be insignificant in univariate analysis. Instead, a determinant was judged by the authors to be 'important' if it was investigated by more than three studies, and found to be a

significant predictor of attendance in more than half of those.

Of the papers considering breast cancer screening specifically, over 25 factors were investigated by at least 3 studies. Of these, the factors that appeared 'important' included insurance status, (not relevant in a UK setting), previous mammography behaviour, intention to attend, and receiving a recommendation from a doctor. The finding that intention was a significant predictor in more than half of the studies which examined it, supports the Theory of Planned Behaviour, (TPB), which stipulates that intention to act is the primary predictor of behaviour. However, across and within screening tests there was little other evidence to suggest that other constructs of the TPB, or other health behaviour models, are significant predictors of screening attendance, since attitudes, perceptions, and beliefs about screening did not consistently predict screening behaviour.

Based on the results it was concluded that it was worthwhile concentrating efforts on maximising attendance at the first screen since re-attendance rates are high given first attendance, and that personal recommendations for attendance from health professionals may be a way to accomplish this. The authors point out that although the inclusion criteria were tight, studies still varied in methodological quality, and generalisability, and they call for further well designed studies relating knowledge, attitudes, and beliefs, to screening attendance behaviour in the UK.

3.2.2 Factors Affecting Population-based Screening in Sweden

Lagerlund (2003) begins by discussing studies from outside Sweden that analyse factors affecting mammography screening attendance rates, and focuses in upon those within countries where mammography is offered as part of a national population based screening programme, such as the UK, since this is the system in Sweden.

The authors point out that differing results have been achieved within, and between, such studies with factors inconsistently being associated with attendance at breast cancer screening, and sometimes the direction of association has also been changeable. Consistent predictive factors that were highlighted in the discussion were marital status, (married women were generally more likely to attend screening sessions), and positive health behaviours, (such as regular dental check-ups).

It is suggested that some benefit can be gained by considering behavioural models such as the Health Belief Model, (HBM), since three of the four main constructs of the HBM have been shown to be predictive of screening attendance behaviour fairly consistently, with the relationship to susceptibility particularly strong. However, severity has rarely been found to be a significant predictor of screening behaviour, or indeed health behaviour in general.

Further factors believed to be predictive from the research discussed, included self efficacy, (which could offer some support for the Theory of Planned Behaviour), and once again recommendations from a health practitioner.

The main body of the overview paper describes five studies conducted in the Uppsala region of Sweden, aiming together to investigate factors associated with the uptake rate of mammography screening in Sweden, (currently fairly high at around 80% in Uppsala). The methodology of the studies varied with three of the five invoking a case control design, one a cohort design, and the last a focus group discussion. The results of the studies showed that employment status and home ownership were the only social economic variables to have a significant relationship to attendance in multivariate analysis of the case control studies. Other factors found to be related to attendance included alcohol consumption, recommendations from professionals, previous breast problems (both of the individual and those close to the individual), barriers to attendance, benefits of attendance, worry, nationality, cues to action, knowledge, and trust in the health care provider.

3.2.3 Inequalities of Access to Cancer Screening

In a literature review of inequalities of access to cancer screening, Chiu (2003) reviews 55 (of 129 papers due to time constraints) studies identified as relating to cancer screening up-take rates among minority groups published between 1998 and 2003. Five of the studies related specifically to the screening for breast cancer and factors affecting attendance at mammography screening. Designs and results of the studies varied, and determinant factors were sometimes contradictory. Of the non-psychological factors affecting up-take rates of cancer screening factors commonly found to be significantly associated with minority attendance were education, age, and physicians recommendations.

Five of the fifty five studies that were considered addressed beliefs in relation to minority attendance at cancer screening, four of which explicitly employed a theoretical framework (TPB/HBM). The author criticises the papers for theoretical inference and methodological failings. It is pointed out that the papers applied the models inconsistently and that results interpreted linear relationships of the variables to behaviour that are not suggested by theory.

The research did, though, highlight potential reasons for low attendance rates within minority groups, such as cultural values, (e.g. shyness), and traditional health beliefs, which could be barriers to attending cancer screening.

The review concludes by pointing out that, all too often, changes are sought in the individual rather than the system, and that disadvantaged groups may lack not just

income to attend screening, but also knowledge, prestige, and social support/communication. A call is made for more research into the low attendance at cancer screening by minority groups, and for ethnic monitoring in order to back up research.

3.3 Individual Studies

The majority of results that were found in the literature search related to breast cancer (BC) screening behaviour and focused on attendance at screening sessions, or breast self examination behaviour initiation or maintenance. Those studies identified which considered breast cancer screening behaviours are discussed in the next Section, followed by a summary of the breast self examination (BSE) papers, then a short Section addresses research which examines delay in help seeking associated with breast cancer, and lastly adherence to genetic testing for breast cancer is discussed.

3.3.1 Screening Behaviour

Of particular interest were studies that had attempted to relate current psychological models of behaviour to the health area of breast cancer and breast cancer screening. Yarbrough and Braden (2000) mention many theories as having been applied to breast cancer (BC) screening behaviours and these include social support theory, the cognitive transactional model, the multi-attribute utility model, the multiple health locus of control model, and a theory of care seeking behaviour. They found, though, that the psychological model most frequently applied (in America) was the Health Belief Model (HBM) and conducted a review of this research to assess the utility of the HBM as 'a guide for explaining or predicting breast cancer screening behaviours'.

Yarbrough and Braden found that the HBM was far from uniformly applied in the 16 studies that they reviewed. This is not surprising given the vague definitions and ambiguous constructs and relationships within the HBM itself. What is more, few of the studies measured all of the constructs, and none found, or considered, the relevant interactions between constructs. Although most of the research did find relationships between the measured constructs of the HBM and outcome measure (intention to attend mammography screening or the action of attending), Yarbrough and Braden were critical of the low proportion of variance in the outcome measure explained by the HBM constructs, as well as of the design, and generalisability of the studies. Indeed, of the studies that were identified for this review, those that applied the HBM to adherence to mammography screening recommendations were either cross-sectional in design (Champion, 1994), or, as Calnan (1984) found in his review of prospective studies, that although HBM variables were significant predictors of BC screening

attendance behaviour, the variance in behaviour explained by the HBM was low.

The Theory of Planned Behaviour (TPB) and its predecessor, the Theory of Reasoned Action (TRA), have also been used to study womens' attitudes to attendance at breast screening appointments. In contrast to Yarbrough and Braden (2000) this literature search found more papers applying the TRA/TPB to breast screening attendance than the HBM. All studies found some support for the TPBs ability to predict attendance (or intention to attend) at invited screening sessions, although again some had not used prospective designs and/or measured intention rather than behaviour, (Steele and Porche, 2005; Tolma et al., 2003; Braithwaite et al., 2002), and the ability to predict repeat attendance remains unclear, (Rutter, 2000; Drossaert et al., 2003).

In what appears to be a very comprehensive and robustly designed study Rutter tested the TPB's predictive power applied to attendance and re-attendance for BC screening, (Rutter, 2000). Rutter found that the TPB constructs, (attitude, perceived behavioural control, and subjective norms), could accurately predict attenders from non attenders for BC screening, as well as intention to attend, and could also distinguish between inclined/disinclined attenders/abstainers. What is more, attitude and subjective norms were found to predict behaviour independently of intention, supporting discussions for the TPB predicting the volitional as well as motivational stage of health behaviour. When considering re-attendance for breast screening three years later, however, the only significant predictor was attendance at the first screening session.

Braithwaite et al. (2002) have also applied the TPB to the prediction of attendance at breast screening. The study found that the TPB constructs of attitude and subjective norm did significantly predict intention to attend screening, as well as another proposed construct 'attitude to uncertainty'. However, having found that the TPB construct of perceived behavioural control did not significantly predict intention, the authors decided that the TPB was no better at predicting genetic BC screening intention than its predecessor the TRA, (differing only by its exclusion of perceived behavioural control as a construct). It is worth pointing out though, that the study questionnaire suffered from low internal validity for the questions relating to perceived behavioural control, was cross sectional in design, and proposed a theoretical situation to participants.

Montano and Taplin (1991) applied the TRA to 946 female attendees at subsequent screening units in Seattle. The prospective study found that the TRA could predict attendance, explaining 20% of the variance in behaviour.

More recently, Drossaert et al. (2003) used the TPB in a large prospective study considering attendance at organised mammography screening programmes in the

Netherlands. Questionnaires measuring TPB constructs were sent out to women who had been invited to a regular screening round and whose appointment date had passed. These measures were then used in order to try to predict re-attendance at the next two screening rounds (where individuals are invited biennially for screening as part of a national screening programme). It was found that the TPB was predictive of attendance behaviour, although much better at predicting initiation of behaviour (distinguishing between those who had refused the invitation before the study began and then attended at subsequent rounds and those who consistently non attended), than behaviour maintenance, (distinguishing between consistent attenders and those who dropped out having initially attended). Again the authors found that the variable most predictive of repeat attendance was past attendance. Drossaert et al. suggest from their results that interventions based upon the TPB should concentrate on improving the uptake of screening among those invited for the first time.

In an update to their research Drossaert et al. (2005) sent the same sample the questionnaire again, before and after the second and third screening invites were sent. The intention was to study whether or not the TPB could explain the drop out rate over time observed in many national screening programmes. They found, though, that the TPB variables remained constant over time, re-affirming their first result that the TPB may not be the best model to explain screening behaviour maintenance, although the drop out rate observed in their study was low and there was some evidence of selective attrition in study participation.

A further paper that applied the TPB to attendance behaviour at screening rounds for breast cancer, considered whether the believed importance of each measure for the constructs of the TPB affected the measures prediction of attendance behaviour, (Steadman and Rutter, 2005). Participants were sent questionnaires measuring the main constructs of the theory and asked to rank the sub measures for each construct as to which were the most important to them. They found that the top three rated measures for each construct (for each woman) performed just as well, and significantly, at predicting attendance as the full measures. All TPB constructs correlated with attendance behaviour, but only intention to attend significantly predicted behaviour in regression analysis (in contrast to Rutter (2000) where attitude and subjective norms were also significant predictors). Steadman and Rutter conclude that interventions may wish to concentrate upon a few of these most common 'important' issues, including the belief of having partner support, the ability to overcome access and transport issues, and the belief that mammography will allay fears or discover problems early.

Two studies were identified which investigated the transtheoretical stages of change and mammography attendance compliance, (Champion, 1994; Lipkus et al., 1996). Champion found in their cross-sectional home interview study that HBM variables

changed significantly across self reported stage of mammography uptake, (precontemplation, contemplation, and action/maintenance), and Lipkus et al. found that subjective risk of breast cancer significantly changed with stage of screening behaviour change, (women who perceived themselves to be of higher risk were more likely to be in later stages of change).

Self efficacy has also been associated with attendance at breast screening invitations, (Tolma et al., 2003). When questioning women who had no previous experience of mammography Tolma et al. found that self-efficacy was the best predictor of intention to be screened for breast cancer, accounting for more of the variance in intention than constructs of the TPB.

Using the Precaution Adoption Process Model and demographic variables Clemow et al. (2000) distinguished between interviewees who were either definitely planning, thinking about, or not planning to attend breast screening in a group of 2,507 women identified as under-utilisers of mammography in the US. Again, however the study measured reported intention to attend and not attendance behaviour itself.

Other studies that were identified considered socio-economic and general health status variables that may also explain the uptake of BC screening invitations. Some of the studies produced surprising results, for example alcohol consumption was found to be negatively related to the attendance at BC screening, (Harris et al., 2002), so that women who drank more were actually more likely to attend, indicating that perhaps drinking is not a good parameter by which to measure attitudes to health. However, the more robust studies that tested the psychological frameworks found socio-economic variables were no longer significant predictors of behaviour/intention once the model variables were accounted for, e.g. (Rutter, 2000).

3.3.2 Breast Self-Examination Behaviour

Around half of the identified papers applying psychological constructs to BC behaviour considered behaviours associated with breast self-examination (BSE). In the past it has been recommended that BSE be undertaken monthly as an alternative to, and in addition to, breast cancer screening, especially for younger women for whom mammography screening is not offered as routine. This is still the advice of some, including BreastCancer.org (BreastCancer.org) and the National Breast Cancer Foundation Inc, (National Breast Cancer Foundation, Inc), whereas the US preventative service task force (USPSTF) neither recommend nor discourage BSE performance, (US Preventative Services Task Force, 2002). There have been calls for BSE promotion to be abandoned altogether in favour of promoting general breast awareness in the UK (Austoker, 2003). Cancer Research UK now simply promote breast awareness rather than recommending regular BSE in light of research findings

that BSE may not offer any benefit in terms of identifying tumours at an earlier stage, (Cancer Research UK).

The majority of studies that were identified were studies assessing attitudes towards BSE outside the UK, so their generalisability to the UK setting may be called into question.

The majority of identified papers considering BSE applied the health belief model, (HBM), to the prediction of BSE performance or frequency. The review of the HBM by Yarbrough and Braden (2000) was quite critical of it's application to BC behaviour, (see Section 3.3.1), and included BSE research within its scope.

In one cross-sectional study, Lee et al. (2004) assessed the differences between the BSE health beliefs of Korean and Korean American women using the HBM variables. Using the Health Belief Model scale the authors sent 189 Korean and 146 American Korean women questionnaires that measured their attitudes and beliefs in relation to BSE. They found that Korean American women were significantly more likely to perform BSE, and their scores for perceived benefits, confidence, and motivation were also higher than those of Korean women. A further result showed that the two variables of perceived barriers and confidence in BSE, significantly explained BSE performance of Korean American and Korean women together.

A further paper tested the ability of the HBM to predict regular BSE in Thai migrants living in Brisbane Australia, (Jirojwong and Maclennan, 2002). The study found support for the use of the HBM although it suffers from many of the methodological issues described by Yarbrough and Braden (2000) in their review.

In a well designed study, Norman and Brain (2005) used the HBM to distinguish between low, medium, and high BSE performance by 567 UK women with a family history of breast cancer. BSE frequency was reported via a questionnaire nine months after the measurement of HBM variables. The measurement of the HBM included an expanded version of the perceived barriers construct that took into account self efficacy barriers, and the authors also collected information on past BSE performance. Analysis of the results revealed two groups of women in their sample, the infrequent BSE group, and the excessive BSE group. Those in the infrequent group were found to be significantly lower performers of BSE at time 1, to have higher self efficacy and emotional barriers, and score lower for beliefs relating to BSE benefits than those in medium or high/excessive BSE groups. In contrast those in the excessive BSE group, were found to have significantly lower self efficacy barriers relating to BSE, rate themselves as more worried about breast cancer, and believe breast cancer to be more severe than those in the other two groups. Here, results suggested that barriers to BSE performance, benefits of BSE performance, and worries about, and perceived severity of, breast cancer can all discriminate between

levels of BSE performance therefore lending support to the HBM. Norman and Brain note that severity is rarely found a predictor of BSE performance, and suggest that perhaps rather than predict the performance in the first place, the construct instead determines/distinguishes excessive performance of BSE. In light of their results the authors suggest that in order to increase the prevalence of BSE performance, interventions should focus upon increasing confidence and self efficacy relating to BSE performance, raise awareness of the appropriate frequency for performance and inform women about their real risk of BC.

Umeh and Rogan-Gibson (2001) tested their hypothesis that threat perceptions would be a more powerful predictor of BSE performance than the other HBM constructs in younger people, since younger people were at less risk of breast cancer and the HAPA model implies that a given level of risk is required before a preventative behaviour is evaluated. Umeh and Rogan-Gibson sent a questionnaire to 178 women aged 18 to 35 which asked questions measuring the HBM constructs and whether or not BSE was performed regularly. The results revealed that severity and barriers were significant predictors of BSE performance (with barriers the most powerful predictor), although perceived benefits were found to correlate with reported regular BSE, and the authors comment that the results provide "qualified support for the HBM".

In a second study applying the HBM to the performance of BSE specifically in young women, Chouliara et al. (2004) assessed the differences in the performance of BSE in 18-26 year olds living in Greece and the UK. The study compared young Scottish beliefs and behaviours relating to BSE with those of young women in Greece since the two countries have different health care systems, different rates of BC (lower rates in Greece), and different levels of BSE and BC publicity (recent awareness campaigns in Scotland). The study measured all HBM constructs, and controlled for other factors such as family history of BC, marital status, etc. Chouliara et al. found that while the reported rates of BSE were similar between the two countries, the HBM scores did differ significantly. Scottish women in the study showed more knowledge of BSE performance, perceived more benefits to BSE, and demonstrated higher levels of internal HLOC. On the other hand the Greek women in the study were likely to rate their health as more valuable, perceive themselves to be more susceptible to BSE (even though they were less susceptible in reality), and have higher chance HLOC scores, than Scottish women in the study. The results suggest that while both sets of women were equally likely to perform BSE, they demonstrated different health beliefs relating to BSE, and so interventions and requirements to improve BSE and BC awareness may be culturally specific.

Overall, studies applying the HBM to BSE tended to find support for the theory, although in some cases this support was limited as not all of the HBM constructs significantly predicted behaviour. As noted by Yarbrough and Braden (2000), some

studies were not well designed. However, it is pleasing to note that more recent papers identified for this thesis did incorporate more appropriate designs and took account of confounding variables.

The HBM was not the only psychological model of behaviour identified as having been applied to the study of breast self examination behaviours, other models included HAPA, self efficacy, the transtheoretical stages of change, and PMT. Luszczynska and Schwarzer (2003) used the HAPA model to study BSE behaviour since they argue that most other research and models concentrate upon behavioural intentions whereas HAPA suggests planning, and maintenance are both important throughout the behaviour change process. Using this idea the authors argue that risk perceptions relating to breast cancer may be less important to the volitional stage of maintenance. The aim of the work was to test phase specific constructs of HAPA that had not previously been given much attention. In a two step trial Luszczynska and Schwarzer first tested the motivational phase of BSE in their 418 student participants, and informed the group about BSE practice and use. They then measured the self regulatory phase and behaviour change itself 12-15 weeks later. At each stage Participants intentions, planning, outcome expectancies, motivations and self efficacy were measured. The authors found that the reported rates of BSE increased between the two stages of the trial, and put forward their own model for inter-relationships between psychological constructs based upon the regression coefficient results. Overall, the strongest effect upon increasing BSE behaviour was associated with planning for the behaviour, and other significant effects were also found relating to intentions, and self efficacy. Evidence was also identified for different types of self efficacy relating to different stages of behaviour change.

Lechner et al. (2004) also found support for psychological constructs predicting BSE behaviours. In their longitudinal trial 364 women were questioned at three points in time, with results revealing that psychological constructs of intention, attitude, social influence and self efficacy explained 51% of the variance in BSE behaviour six months later.

Others have studied psychological theories applied to interventions to increase the uptake of BSE. Fry and Prentice-Dunn (2005) evaluated the effects of information sessions discussing and informing about breast cancer threats, survival rates, BSE techniques, effectiveness, and issues relating to BSE self efficacy, using the PMT. Participants were divided into two groups, a control group where they attended two sessions about general health and fitness, and an intervention group that received two sessions informing about breast cancer and BSE. PMT construct variables and BSE behaviours were measured before and after the sessions. The study found that the groups did not differ in their beliefs or BSE behaviours before the interventions, but that after the interventions the control group had significantly higher control and

threat appraisal scores in relation to breast cancer and BSE. Some three months after the trial, however, while the intervention group did still show higher levels of confidence in performing BSE, there was no measurable difference in BSE behaviour between the two groups.

In contrast, studying the effects of a BSE information video on a sample of 130 premenopausal women, Janda et al. (2002) found that while both the intervention and control group increased their performance of BSE over the trial period, the group shown the BSE video performed BSE more frequently than the control group at follow up three months later. Of the psychological predictors, having a social role model was shown to explain the greatest amount of variance in behaviour (although still low at 13%).

Lastly, Luszczynska (2004) also found that a breast self examination intervention was successful at increasing rates of BSE. Their results showed that phase specific (HAPA) self efficacy was a significant predictor of intention, planning, and behaviour in the intervention group, while results were less significant or non significant in the control group.

3.3.3 Delay Seeking Help

A third issue of interest identified in research was why women may delay in seeking help for BC symptoms. BSE is of limited assistance to speedy diagnosis and treatment if a woman identifies a change but does not seek assistance for several months.

Bish et al. (2005) reviewed literature with an aim of better understanding factors affecting delays in seeking help for breast symptoms. In the course of their review they found evidence that between 20-30% of women delay seeking help for breast symptoms by more than 3 months, and this can considerably affect their survival chances, reducing the average 5 year survival rate by as much as 12% (in comparison to those with shorter delays). As a result of their literature search considering the psychosocial factors affecting such delay in help seeking behaviour, Bish et al. have put forward their own proposed model of help seeking behaviour. This model proposes that intention is the foremost requirement for the behaviour itself, and forming intentions are attitudes to help seeking, and disclosure of symptoms which both require a knowledge of BC symptoms. The authors note that knowledge of symptoms of breast cancer and symptom appraisal my be affected by a person's age, ethnicity, access to medical care, and other sociodemographic factors.

Two further studies in the current search highlighted the importance of a womans knowledge of breast cancer symptoms. In the first, the most common reason given by

women for not seeking help sooner was that they considered the symptoms harmless, (Arndt et al., 2002), and in the other correctly identifying breast symptoms was the only variable to significantly predict intended help seeking behaviour across *all* age groups (Grunfield et al., 2003).

3.3.4 Genetic Testing and Miscellaneous

The uptake of genetic testing has also been a subject for psychological research. Helmes (2002) found that women with higher external locus of control, less knowledge of breast cancer genetic testing, and less education, were more likely to leave the decision regarding genetic testing to the medical providers. Jacobsen et al. (1997) used the transtheoretical stages of change model to measure 74 women's readiness to undergo genetic testing for breast cancer risk, and they found that, as expected, those with a positive decisional balance (pros of testing outweighing cons) were more likely to show greater readiness to proceed with testing.

Helmes et al. (2002) applies the full PMT model to test the motivation of women at mid-low risk of genetically linked BC to undergo genetic testing. Here, high protection motivation should lead to a choice not to undergo testing since the risk of breast cancer is low. The cross-sectional study measured protection motivation as the outcome rather than behaviour. Results failed to find significant predictors of protection motivation from the PMT constructs, but the author suggests a small change in the model which produced a better fit, explaining 50% of the variance in protection motivation. The new model suggested that vulnerability, fear, response efficacy and response costs are the important variables for predicting protection motivation for women at a low risk of developing genetically linked breast cancer. It is concluded that women should be better informed about the real risks of developing breast cancer in order to lower the high risk perceptions and worries surrounding the disease, and that women should also be educated as to the advantages and disadvantages of *not* undergoing genetic testing for breast cancer.

Psychological theories, principles and research have not been limited to the areas of breast cancer behaviour mentioned above, but have been applied to a wide range of issues surrounding and addressing breast cancer behaviours and attitudes. One further area of interest has been how women cope with breast cancer diagnosis, treatment, and survival. For example the effects of health locus of control and anxiety were investigated while considering depression in 109 breast cancer survivors/sufferers in Heuston, with the finding that anxiety mediated the effects of breast cancer LOC on depression (Naus et al., 2005). In addition two studies applied the TPB to investigate how the theory may influence a woman's decision whether or not to abide by recommendations of exercise during treatment for breast cancer,

(Jones et al., 2005; Courneya and Friedenreich, 1999).

3.4 Summary

This Chapter has provided an introduction to some of the work that has been carried out in order to study and help to understand behaviour relating to breast cancer.

The majority of the studies considered focussed upon attendance behaviour at breast cancer screening and a variety of psychological theories have been applied in the literature in an attempt to predict attendance based upon psychological beliefs and feelings. Two of the more commonly applied theories were the Theory of Planned Behaviour, and the Health Belief Model, both applied with varying success at predicting attendance behaviour. Much of the variation in the success of the studies may well lie in the study design, with many measuring intention to attend rather than the action of attendance directly, and/or using cross-sectional designs from which causality is even more difficult to infer than usual. Overall, however the Theory of Planned Behaviour appeared to be the more consistently successful model for the prediction of attendance at breast cancer screening, although the ability to predict subsequent screening attendance is still unproven (Rutter, 2000; Drossaert et al., 2003).

Other studies considered the psychological predictors and influences upon breast self examination behaviour. The majority of studies that were identified applied the Health Belief Model (HBM). The HBM is a vague model and as such its application and interpretation in the different studies varied, along with the quality of the design of the studies, producing inconsistent results. In two of the more successful studies, however, Norman and Brain (2005) suggest that rather than predicting the occurrence of BSE the HBM may be more useful to distinguish between regular and non regular performers, and Chouliara et al. (2004) found significantly different health beliefs between Scottish and Greek women.

Psychological research has been applied to many areas of breast cancer behaviour including breast self examination and screening attendance behaviour. A variety of psychological theories and approaches have been used to aid such research with varying success, however it is pleasing to see that some of the more recent and well designed studies have been more successful, and pooling results together our understanding of behaviour relating to breast cancer is gradually improving.

Chapter 4

Modelling approaches to breast cancer screening

Evidence for decision making in respect to cancer screening may come from randomised control trials or from estimated outcomes derived from computer and statistical models. Due to the costs and ethical considerations involved in conducting large scale randomised control trials, modelling may be more suitable for investigating the effects of different strategies and policies relating to the planning and evaluating of population based screening programmes. It seems logical, therefore, that the paper based research into cancer screening, and predictions, pre-date the first randomised controlled trials of the 1970's.

One of the first modelling approaches was by Zelen and Feinleib (1969), who modelled cancer screening using a Markov model assuming three states of cancer progression, from no disease, to a pre-clinical state (no clinical symptoms of disease), and lastly the state of clinical disease. The time a patient spent in each state was assumed to be exponential, and screening strategies were compared by considering the lead time, (the time from cancer onset to diagnosis).

Over the years a number of models were based on and around this early work, see (Duffy et al., 2001), and today numerous methods exist for the estimation of the impact of new policies and evaluation of current procedures. Bross et al. (1968) categorised screening models into two types, surface models and deep models. Surface models are those that consider the high level observable data such as incidence and mortality and estimate the effects of screening upon these trends using statistical analysis of available data. Surface models are useful for the evaluation of existing screening programmes and trials. Deep models by contrast consider the underlying process of the disease in the population that generate the high level trends, and are useful for assessing the impact of different scenarios that have not been investigated in clinical trials. It is these deep models that are necessary for the modelling work

required in this thesis, since we aim to investigate the effects of different screening policies given different levels of compliance to the programme. Deep models can then be further classified into analytical and computer simulation models, (Stevenson, 1995). Analytical models use direct estimates of a disease to produce estimated outcomes, whereas simulation models estimate the course of the disease in a hypothetical population both with and without screening in order to compare the scenarios. These two different methodologies are discussed in more detail in turn below.

4.1 Analytical Models

Most analytical models of cancer screening follow the framework of a Markov chain. These models typically assume disease progression as split up into a number of states, only one of which can be occupied by any one person at a time. For example states for breast cancer could include healthy, pre-clinical breast cancer (not clinically apparent), clinical breast cancer, and death from breast cancer. Transition to the next state is governed by the transition probabilities, which are not dependent on previous states but only upon the current state, and, when considering variations upon the basic model, possibly other factors such as time and age.

The first stochastic model of a disease process was developed by Fix and Newman (1951). Their model comprised two illness states (living a healthy life and being under treatment for cancer), and two death states, (death from cancer, and death from other causes or lost to observation). The first models to incorporate screening strategies for early cancer detection were developed in the 1960's e.g. Zelen and Feinleib (1969), (as above).

Among other such early work was that by Shahani and Crease (1977), who analysed two models to compare periodic with aperiodic screening strategies for the early detection of disease. The first model was a simple two state model taking each person from state S_0, no disease, to S_1, disease, with a transition time distribution, $f(t)$, that followed the Weibull distribution. Screening for disease took place at time x_i with intervals d_i. Three screening strategies were compared on the basis of the number of screens until diagnosis, the number of false positives, the delay in disease detection and the ratio $C_1 : C_2$, where C_1 is the cost of screening and C_2 is the cost of the delay in diagnosis. The three screening strategies compared were, X_A: periodic screening intervals, X_B: geometric screening intervals, and X_p: generated from the equation that follows:

$$\frac{F(x_i) - F(x_{i-1})}{1 - F(x_{i-1})} = p$$

where $p \in (0, 1)$. This last screening strategy matches the screening intervals to the

behaviour of the hazard rate $r(t)$, (the probability of getting the disease each year), represented by

$$r(t) = \frac{F(t)}{1 - F(t)}.$$

The analysis of this base model indicated that the last screening strategy, X_p was the most effective at detecting the disease under the assumptions of the model.

A second model then built on this first simple model, and this time assumed three states, no disease, disease, and death. Death is presumed to occur from either of the other two states, and progression from no disease to disease takes place in the absence of death. It was assumed that death and disease process were independent of each other. The results from this model were similar.

These basic models have a number of limitations however, for example most diseases, including breast cancer, tend to reach a symptomatic stage after a period of time when the patient would self refer, and it is also not appropriate to assume cancer and mortality are independent, since cancer can lead to early death particularly if left untreated.

4.2 Simulation models

Computer simulation models may also, and often do, follow a progressive state Markovian structure but tend to be more flexible and incorporate more detail in the modelling process than analytical models. In general, simulation models are capable of modelling more complex scenarios with more flexible assumptions than analytical models, but this does mean that the extra complexity requires more detailed data to inform the model, (Stevenson, 1995).

Simulation models themselves can vary in their approach from global modelling of flows of people through states dependent on a small number of factors alone such as age, (macrosimulation/systems dynamics), to the modelling of individuals through their life histories and cancer progression dependent upon previous events and individual characteristics, (microsimulation/discrete event simulation). Both methods offer the ability to demonstrate the relationships between variables and explore the effects of different scenarios and interventions. However, microsimulation may be more suitable for the modelling of cancer screening than macrosimulation, (Stevenson, 1995), since macrosimulation assumes a single homogeneous population which is unrealistic in todays society, and secondly it may be of use to investigate characteristics other than age to select groups for screening, (e.g. at risk groups).

Even when working to model the same trends, different choices of methodology can produce large differences in modelled outcomes. Boer et al. (2004) discuss the

differences in methodology employed by seven groups all considering the impact of screening and adjuvant therapy in the US between 1975 and 2000. They found that while six of the seven models were life history models, the assumptions and parameter estimation varied between them, and these variations led to large impacts on the surveillance of population trends considered.

Karnon (2003) recently compared the methodologies of Markov modelling and discrete event simulation (DES) for the economic evaluation of adjuvant therapies as treatments to help prolong relapse after primary breast cancer. The comparison of two models that were built as far as possible with the same structure and similar assumptions, was based upon the models ability to be flexible and the amount of analytical input required to run and evaluate the models. The discrete event simulation took three days to run, in comparison to the Markov model which only required an hour, and the former was also more difficult and time consuming to evaluate. When the outcomes of the models were compared, although there was variation between the two models, these differences were consistently in the same direction. When overall results were compared these results balanced each other out to produce extremely similar cost-effectiveness curves. Karnon concluded that while DES is more flexible, the Markov model was easier to develop and test, and produced similar results, so it was only useful to apply DES in special circumstances. One of these circumstances is when the areas of increased flexibility in DES apply to large proportions of the model, e.g. a large number of states with state-entry dependent probabilities.

Knox (1973) produced one of the earliest yet very comprehensive simulation models, which he later revised to include fewer states due to the complexity of information required to populate the model. According to Stevenson (1995) it was Parkin (1985) who proposed the idea of microsimulation for the modelling of cancer screening, in this case cervical cancer screening, and much work has subsequently focused on such an approach. This includes a working group at Erasmus University in the Netherlands who have developed a general framework for the microsimulation modelling of cancer screening named MISCAN (MIcrosimulation SCreening ANalysis), (Boer et al., 1998). This model has been applied to many areas of cancer screening over the years, including considering the cost effectiveness of shortening the screening interval of the NHS breast screening programme, (Boer et al., 1998).

MISCAN simulates the life histories of women both with and without different screening policies to compare the effects. The course of breast cancer is simulated as a Markov progression from no disease, through five pre-clinical states, and on to clinical disease. The pre-clinical states included an in-situ state and four invasive states according to the size of the tumour. It was assumed that if the cancer was not diagnosed then progression would take place to the next state. The two sink states in

the model were death from breast cancer and death from other causes, as is typical in such simulations. The time in pre-clinical states was assumed to be exponential, and the rates of progression to clinical disease were inferred from UK data. The sensitivity (the proportion of true positives detected within the subset of positive patients in the population that were tested) of mammography tests was assumed to be constant within each pre-clinical stage but increased with progression through the states from 0.4 to 0.95. Mortality and cost information were estimated based upon UK data sources, and attendance was modelled by assuming a percentage compliance reducing with age from 74.2% to 67.9%. Two scenarios were considered, shortening the screening interval of the UK screening programme from three to two years, and extending the age of final screening from 64 to 69 as standard. The main outcome measures of the model were the number of deaths prevented, the number of life years gained, and the cost of the screening scenario (per life years saved and per death prevented). The results suggested that while both scenarios would increase the number of deaths prevented (and the costs), expanding the age group eligible for screening would be the most cost effective policy.

A group of researchers in New Zealand produced a very similar model to the MISCAN model which used some of the same inputs and structure, in order to consider the benefits of population screening for breast cancer in New Zealand which has a similar cancer burden to the UK, (Szeto and Devlin, 1996). The model which was named MICROLIFE, simulates the same female population twice, with and without screening, and compares the cost effectiveness to the health service of treatment per discounted life saved. Again, the model splits the progression of cancer into different pre-clinical stages, with deaths from other causes informed from life tables, this time based upon the population of New Zealand with deaths from breast cancer removed. Attendance at the screening programmes was assumed to be 75%. When researching the costs of treatment, the authors found evidence of a wide range of treatments for breast cancer even within similar clinical groupings, which brought out the variability introduced by patient choice and physician preferences. This variation made the costs of treatment difficult to estimate and simulate. Their results revealed that, according to the model, screening women aged 50-64 every 3 years would be the most cost effective policy for New Zealand. Interestingly, this is the same policy that was standard across the UK until the upper age for screening was increased to 69 in recent years. Although screening every 3 years was the most cost effective policy considered with the modelling work, screening more frequently (biannually) was shown to save more lives.

An example of a Monte Carlo simulation to study breast cancer screening is work by Jansen and Zoeteleif (1997). This simulation was built with the aim of examining the benefits of various screening policies versus the risks associated with screening, and used real data from a study in Sweden (the chosen country for the application of the

research). The simulation took flows of women through time, and calculated the difference in tumour diameter between the spontaneously presented cancer populations and screening discovered populations in order to infer the differences in survival. Risks associated with breast screening were estimated using additive and multiplicative models informed from a study of TB re-weighted to apply to breast cancer, and other relevant input distributions were derived from literature that analysed the results of the Swedish two county trial of breast cancer.

The model was run for a group of one million women ten times, (and for mortality calculations was run for 133,000 women thirty times). The results showed that the optimal screening strategy was age dependent, with smaller screening intervals for younger women. Sensitivity analysis revealed little difference between additive or multiplicative assumptions of radiation risk in mammography screening, and assumptions regarding the tumour growth rates, age of tumour onset, age dependent survival, and the sizes of tumour detection, could alter the simulated lifetimes gained by screening by as much as 12, 10, 8, and 17% respectively. Screening was found to be optimal (overall) for women between the ages of 40 and 75, (screening older women lowered the net benefits by uncovering more dormant tumours that would not develop into clinical breast cancer, while screening younger women would increase the number of breast cancer cases due to screening exposure). Jansen and Zoeteleif conclude that it is more effective to screen the whole population (for breast cancer) less often than to screen a fraction of the population more frequently, thus it is important to have a high level of attendance at screening sessions.

Parmigiani (1998) used a stochastic compartmental equation difference model to study cost effective breast cancer screening strategies in the USA. The model took women through states of no cancer, detectable asymptomatic (pre-clinical) cancer, symptomatic (clinical) cancer, and death. Death can be reached from any of the other states, but progression through the cancer states was assumed to be in order. Transitions and sojourn times were estimated from a range of clinical trial and population registry data, and since times in and transitions to, the pre-clinical stage are unknown, these were estimated based on three different assumptions from previous research. Prognostic factors considered by the model were the size of the tumour, the number of observed metastases in the lymph nodes, and oestrogen receptor status (positive or negative). A range of assumptions were considered for the survival transitions and for mammogram efficiency, and QALYS were used to evaluate health outcomes and associated costs. Parmigiani found, in line with work discussed above, that it is most appropriate to screen more frequently at lower ages.

The models reported above all simulate breast cancer, and screening for breast cancer using clinically relevant stages of breast cancer and estimating parameters based upon a range of results from clinical trials and practitioner informed assumptions. A

second approach is to produce a statistical numerical model of breast cancer natural history and how screening would interrupt the progression and then to estimate the parameters of this model through fitting the input variables to observed datasets. This was the approach taken in early work by Schwartz (1978) who used a numerical simulation model to analyse the effects of screening interventions upon the disease burden from breast cancer. Screening took the form of a mammogram, clinical breast examination, and/or self examination. Progression through the no cancer (healthy), pre-clinical, and clinically surfaced states through to either death from cancer or death from other cases was described by a series of numerical equations. Tumours were assumed to grow exponentially, with one of two doubling time distributions (one assuming a higher proportion of slower growing tumours than the other). Two assumptions were also tested relating to the independence or dependence of mammogram sensitivity (the proportion of true positives detected within the subset of positive patients in the population that were tested) upon the result of the previous screen. All parameters of the model were fitted to observed data relating to clinical surfacing times and lymph node involvement using a pattern search procedure. The results revealed that the choice of growth rate distribution affected the results of the implied screening sensitivity by size of the tumour, especially for small tumours (less than one centimetre diameter), both for mammography screening and clinical breast examination sensitivity. When comparing different screening strategies the work implied that screening should be carried out as often as possible (to save the most lives), with clinical examinations starting at age 40, and adding mammography screening from age 50 through to age 70.

More recently Baker (1998) used a similar approach to fit their suggested statistical model of breast cancer screening to five datasets. The aim of their work was to find a cost effective screening strategy while minimizing life years lost to breast cancer. The model assumed Gompertzian tumour growth, with detection and self presentation both related to the size of the tumour. Cancer survival was first fitted to one of the datasets, since other model parameters relied upon it, and the resultant distribution was found to be dependant upon tumour size and growth rate. Using maximum likelihood estimation, the remaining model parameters were then fitted to the other 4 datasets. The results found that, amongst other findings, tumour detection was not a function of patient age (for the age group 50-64 they considered), and the model validated well against previous research and published findings. Of the screening policies considered under the fitted model, the authors concluded that the most cost effective population based screening strategy for the UK would be screening from age 48 to 61.5 with four screens in between spaced more frequently at lower ages. In conclusion the authors note that this optimal policy follows very closely what was the national screening policy in the UK at the time (screening at ages 50-64 at 3 yearly intervals), and that if given a choice whether to screen once more at a higher or lower

age, it would be most cost-effective to screen at the lower age (47-64 years). Their results agree with previously reported findings that screening is more effective at lower ages if conducted more frequently (Baker, 1998; Parmigiani, 1998). However their results differ from those of Boer et al. (1998) who recommended increasing the ages of screening up to 69 rather than decreasing the screening interval, although they did not report having analysed the effects of reducing the first invited age for screening.

4.3 Psychological modelling approaches

Using modelling in the social sciences is a relatively new advance, with its widespread use not taking hold until the 1990's, (Gilbert and Troitzch, 1999). Due to its ability to model individual variation, simulation is more relevant in order to investigate how individual characteristics affect the behaviour of the whole population, and to better understand interactions between individuals. Models have been built with the purpose of simulating choices of partner, demography changes over time, and the simulation of decisions and diagnosis. Arguably the most common use of simulation in the social sciences, however, is to test out different theories of human interaction and behaviour in a modelled society in order to evaluate the emergent effects on the population as a whole.

Whilst the early work in the social sciences used techniques such as game theory, cellular automata, and system dynamics, these early attempts were not popular since they were simulating predictions, whereas psychologists and social scientists tend to be more interested in the understanding and explanation of social phenomena, especially since in some cases a prediction may well affect the outcome in question.

Since then a number of techniques have been used to fulfil this criteria including microsimulation in the 1980's, multi-level models and multi-agent models in the 1990's for the analysis of social interactions, and more recently learning and evolutionary models for the exploration of language development and altruistic behaviour. Multi-level models and agent based models have proved particularly useful for the modelling of health risk-taking behaviours due to their ability to contain both a fixed element unchanging across communities (e.g. an average correlation) and a random part (2nd level), containing variances across different communities or individuals, see Cho et al. (1999) for more detail. For more information about the various methods employed in the social sciences for the modelling of different social behaviours and interactions the reader is referred to a book entitled 'Simulation for the Social Scientist' by Gilbert and Troitzch (1999).

Little work has been identified that includes the modelling of behaviour in standard Operational Research models (such as cancer screening models) at more than a global

level, i.e. the percentage of patients who attend each screen.

As part of their work to devise optimal scheduling techniques for breast cancer screening Baker and Atherill (2002) produced a model to estimate compliance of the public based upon data on 17,709 patients' attendance histories for up to five consecutive screens. The data were provided by the Centre for Cancer Epidemiology in Manchester. The model was based upon initial observations of the dataset that revealed previous attendance made current attendance more likely, with the first choice being particularly influential, and this influence being reduced with successive invitations. Their proposed model then gave extra weight to the first attendance/non attendance for each woman, and geometrically down-weighted the effects of previous attendance upon the calculation of the probability of current attendance. Age was also observed to have a small negative correlation with attendance, so age was also included as a parameter in the model. Baker and Atherill's final proposed model is outlined below.

The random variable X denotes attendance such that $X_i = 1$, if attendance takes place at the ith screen, and $X_i = 0$ otherwise. The model was then proposed for the logit of the nth screen, S_n, of the probability of attendance at the nth screen, p_n, such that for $n > 0$,

$$S_n = \alpha + \beta \left\{ \sum_{i=1}^{n} q^{n-i} \left(1 - (1+\rho) X_i\right) + c\left(1 - (1+\rho) X_1\right) \right\} + \eta a$$

$$S_0 = \alpha + \gamma + \eta a$$

and

$$p_n = \frac{1}{1 + S_n}$$

where a is the age of the woman and $\alpha, \beta, \rho, \eta, \gamma, q$ and c are constant parameters. The constant parameters were found from the data using the maximum likelihood method, and these values are given in Table 4.1. The model is an interesting concept and provides a nice bridge between the simple assumptions of percentage attendance usually applied in simulation models for cancer screening, and psychological models for the prediction of behaviour. The work reported in this thesis, therefore, decided to incorporate this equation for the prediction of attendance at breast screening as a method for modelling individual attendance (as opposed to assuming percentage probability attendance) but without the added work necessary to incorporate a psychology theory and supporting research.

Another notable exception is recent work by Brailsford and Schmidt (2003), who incorporated behaviour of the patient into an existing model for the examination of screening for diabetic retinopathy. The motivation behind the work was the finding that screening policies were highly sensitive to assumptions about compliance,

Model Parameter	Value
α	2.0010
β	-1.1740
q	0.454
γ	0.4297
c	0.3960
η	-0.0263
ρ	0.7158

Table 4.1: Parameter values for S_n in Baker and Atherill (2002)

(Davies et al., 2000). Each time an individual was invited for screening their compliance probability was calculated as,

$$compliance = v \times m \times p$$

where m is the motivation to comply, sampled as either low (0.6), medium (0.9) or high (1.0), the parameter v represents a scalar to deal with the history of compliance such that $v = 1 - (0.1)^{no.of previous visits}$, and p the approximated output of an agent based model named PECS. PECS is an architecture developed by Schmidt (2000) for the individual modelling of human behaviour. PECS incorporates four classes of state variables, physical, emotional, cognitive, and social status. Two different modes of behaviour can be modelled, named 'reactive' and 'deliberate', where the former is the intrinsic low level behaviour assumed to be modelled by a set of rules or equations, and the latter refers to deliberate behaviour involving the conscious pursuit of goals.

In Brailsford and Schmidt (2003) the equations and relations chosen were arbitrary and the aim of the work was to investigate the effects of deeper modelling of human behaviour within a discrete event simulation, rather than to produce a model that would necessarily accurately represent attendance behaviour. The results demonstrated variability in the outcome (years of sight saved), with different behavioural parameter assumptions, and importantly, variation when compared to an assumption of a fixed percentage attendance.

While it has been pointed out that system dynamics approaches are less useful to the study of breast cancer screening strategies, (Stevenson, 1995), the method has been applied to breast cancer screening in an interesting study that considers the interactions between the capacity of a screening unit, the number of regular mammograms performed by a radiographer, the quality of a mammogram, the location of screening units and the participation of the public (Gunes et al., 2004). The idea is that if a radiographer performs more mammograms more regularly their performance increases, thus leading to the detection of more cancers and saving more lives. However, if a particular radiographer is very busy then this implies that the screening unit is at capacity which could lead to queues and delays in the system

leading to fewer lives saved, and this could be further compounded by less participation from the invited individuals. Gunes et al. (2004) also consider the interactions between the location of the screening units, and ease of access/participation for eligible women (local versus central screening policies). Three sets of analysis were performed upon the model to assess the effects of improving the detection of breast cancers through mammography and the interaction between high quality readings and high waiting times alongside service decentralisation which could lead to more access but potentially at a lower quality. Their results revealed that an increase in population participation would only be beneficial if the system has enough capacity to cope with the increase in demand, this would aid the accurate reading of mammograms and the speedy diagnosis of further tests, as well as encouraging future participation. Decentralisation of screening units was only found to be beneficial if the quality of the readings could be maintained so as not to produce too many false positives and negatives that would both cost either lives or facilities and money.

Lastly, Wu et al. (2004) used a computer model of breast cancer to analyse the cost effectiveness of interventions to increase up-take among non compliant women in the USA. During their review of literature concerning interventions to increase mammography uptake published between 1999 and 2002, the authors identified six papers that studied the US population. They then grouped the interventions into 3 types, telephone counselling, physician based interventions, and clinic based interventions. Tailored telephone counselling involved qualified personnel using techniques based upon psychological theory, such as the Health Belief Model and the transtheoretical model, to help women overcome their barriers to mammography screening. Clinic based or physician based interventions involved more training for physicians to improve their counselling and interpersonal skills, and reminder calls from the clinic that an appointment is imminent.

Wu et al. took the mean pre and post compliance rates of the studies and any estimates of associated costs of the interventions, and used this analysis to compute inputs to a model of breast cancer control programmes named CAN*TROL. CAN*TROL is a computer simulation model which simulates the cost effectiveness of cancer control programmes. It moves a hypothetical population of women through one of 109 states and requires inputs relating to population statistics and cancer information such as incidence, prevalence, stage distribution, and treatment costs. The model predicts averages and not individual differences, and thus compliance with screening strategies is not modelled directly, the effects are instead inferred by the differences in stage proportions input to the model as implied by any change in compliance.

Results revealed that the most cost effective policy to introduce in order to target non-attenders on a large scale would be telephone counselling, however clinic based

interventions, while costing more, saved more lives (reducing breast cancer related mortality by 10.7% in comparison to a 6.5% reduction associated with telephone counselling interventions). When conducting a one way sensitivity analysis using the range of compliance and cost information, unsurprisingly, the most sensitive parameter to the cost effectiveness was the post intervention compliance rate (the interventions will only be cost effective if they produce an increase in compliance). The papers analysed by Wu et al. varied considerably in their success at increasing compliance rates in the intervention groups with increases on baseline compliance rates of as little as 2% above the rate observed in the control group in one study, up to 27% in another.

4.4 A chosen modelling approach

The aim of the research reported in this thesis was to investigate the effects of different assumptions of attendance behaviour at invited mammography screening in the UK, and compare the magnitude of any difference arising through different assumptions with those found by other modelling assumptions such as the tumour growth pattern.

In order to investigate this research aim we decided to build a discrete event simulation (DES) model of breast cancer and mammography screening for breast cancer. This simulation method was chosen due to the need to model women at an individual level if behaviour of each woman is to be included, and also due to the flexibility that it would provide for this purpose. DES is also a common tool for the Operational Researcher, and one of the aims of the research is to investigate methodologies for incorporating the modelling of human behaviour into everyday models and existing popular methodologies within this discipline.

Behaviour within the simulation is controlled by individual attributes sampled for each woman, and the values of these attributes then influence her choice behaviour such as whether or not to attend for screening in a way suggested by psychological theory (see Section 2). The chosen psychological theory to be considered was the Theory of Planned Behaviour (please see Chapters 2 and 3 for a description and explanation as to why the TPB was thought to be most appropriate). A second model, (Baker and Atherill's compliance model as described above), that used past behaviour to predict attendance at mammography screening, was also made available as an alternative behaviour model to use within the simulation. These two methods are compared with and contrasted against two methods for assuming percentage attendance named 'global' and 'local' percentage attendance (please see Chapter 6 for a full description and definition).

Modelling behaviour in this way was deemed as most appropriate since it models at an individual level as required, and also since the method is simple, and does not require knowledge outside DES. Furthermore, due to the psychological theories considered at this time there was no necessity to model interactions between women, but instead the simulation treats each individual separately as is the case in DES.

The next Chapter (Chapter 5) describes the structure of the simulation that was built to investigate the research aims, and this is followed by Chapter 6 which goes on to explain how the simulation variables and parameters were populated.

Chapter 5

A Discrete Event Simulation of Breast Cancer

A three phase discrete event simulation (DES) model has been built to model breast cancer and breast cancer screening policies, and it is this model that has been enhanced in order to include behavioural characteristics of the patients considered. The model is built in Microsoft Visual Basic 6.0 (SP5).

A discrete event simulation was chosen above other methods of modelling and simulation due to the need to model individual women with many attributes that affect their flow through the system. For further discussion of other modelling techniques please see Chapter 4.

5.1 The Three Phase Approach

The DES simulation runs using the three phase approach. This approach is so called as the simulation is run, (repeatedly until the end of the simulation), in three consecutive phases labelled A,B, and C, respectively.

When the simulation is run, the A phase is begun first. In this phase, also known as the time scan, a search is made of all events which are scheduled and finds the next event(s) that are due, makes a note of them, and moves the simulation clock forward to this point in time. An event is an action upon an entity (in this case a woman) in the simulation that has been scheduled, e.g. cancer onset, or an invitation to screening. For example, the next scheduled event may be that a woman is due for screening at time 35 and so the A phase would make a note of this as the next event to take place, and move the clock to time 35.

Once the next event(s) due in the simulation have been identified, the B phase

begins. In this phase of the simulation the 'B activities' that are due are then executed. B activities are operations that have a start or finishing time that can be predicted in advance, in this example invitation to a screening session at a particular age. Table 5.1 shows the B activities for the current breast cancer simulation model.

	Activity
1	Develop cancer
2	Be invited to a mammography screening session
3	Self detect the tumour
4	Die from breast cancer
5	Die from other causes

Table 5.1: The B activities

Finally, conditional activities, labelled 'C activities', whose conditions have been met, are executed in the simulation. These are activities that may be conditional on factors other than the simulation clock. C activities may be dependent upon parameters such as other events having occurred or resources that are available. At present, however, there are no C activities within the breast cancer simulation model. Instead, if conditions are satisfied, the dependent events are then scheduled. For example, death from breast cancer is scheduled upon completion of the activity 'develop cancer'.

Once all B and then all C activities that were due have been executed, the simulation then begins again at the A phase. This process is repeated continually, unless the system clock has reached the end of the specified simulation length, (default 100 years), or no more activities are scheduled.

5.2 Model Structure

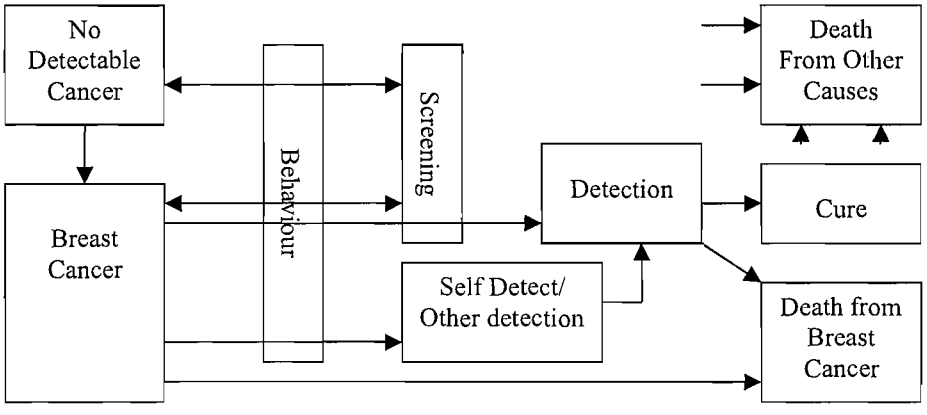


Figure 5.1: Model Structure

Figure 5.1 outlines the structure of the model. Each woman is taken through time from birth until death. During the course of her simulated life she may, or may not,

develop breast cancer, be invited to mammography screening, or attend a screening session.

If breast cancer develops then it could be detected either by mammography screening or by self detection, (through breast self examination, or through the development of clinical symptoms), both methods of detection may lead to 'cure' of the disease, or subsequent death from breast cancer, (unless natural death is scheduled to precede this). Whether a patient can ever be completely cured of breast cancer is difficult to determine since metastasis and death have been shown to appear up to 25 years after treatment for the primary tumour, and it is not until after this time that death rates from breast cancer patients begin to mirror that of the rest of the population, (Yakovlev et al., 1999), for more information please refer to Section 6.5.

At the beginning of the simulation each simulated woman is provided with a natural age of death, this is taken from UK life tables with deaths from breast cancer removed. Death for each woman then occurs at this age unless breast cancer develops, is not cured, and shortens her life span. Death from other causes can occur when the woman is in any other state of the model.

Screening for breast cancer occurs at ages specified by the user of the simulation model. The start age, end age, and intervals for screening are set by the user and the first screen is scheduled for all women in the simulation at the start of the model run. The probability of tumour detection at the screening session is based upon the size of the tumour at that point in time. The probability density curve of detection at different sizes is estimated from literature, please see Section 6.4 for details.

Each time a woman is called for screening, whether or not she attends is a function of her behavioural attributes. These attributes are stored in a class variable labelled 'behaviour'. The behaviour class stores each woman's behavioural attributes which include the five base elements of the Theory of Planned Behaviour, (see Section 2.2.5 for an explanation), and the seven parameters of Baker and Atherill's Compliance model, (see Section 4.3).

If the Theory of Planned Behaviour (TPB) is selected as the behavioural model, then for each simulated woman the value of three of the base elements of the TPB combine to predict the intention to attend for screening, and then the behaviour for attendance, in a manner suggested by literature, (Rutter, 2000). Otherwise, if Baker and Atherill (2002)'s compliance model is selected, then once invited for screening the model will calculate a probability of attendance dependent upon her previous attendance and the parameters of the compliance model, please see Section 6.6 for more information.

Two further options for the modelling of attendance behaviour are provided, and these are based upon more traditional percentage attendance assumptions. If either

option is selected then the user is invited to specify the percentage attendance that they wish to assume. The first option is that of 'local' percentage attendance, and the second a 'global' percentage attendance assumption. Local percentage attendance sets the probability of attendance at each invitation, so, for example if 70% attendance has been requested by the user, then at each screen a random number will be sampled and if less than or equal to 0.7 then the simulation will assume attendance. Global percentage attendance on the other hand sets the probability of attendance at each screen for each simulated woman at a global level, such that the random variable remains constant for each woman throughout the simulation. Therefore, although both percentage attendance options may ultimately lead to the same percentage attendance, in the case of global percentage attendance it is always the same simulated women who attend or do not attend at invited mammography screening, whereas for local percentage attendance a different subset of women may attend at each screen.

If a woman develops cancer then, if it is not detected by mammography screening, it will present naturally. The time of natural presentation is determined by the time it takes her individual tumour to reach a sampled diameter, and is scheduled at the start of the simulation. The sizes of natural presentation of breast cancers are taken from published literature before mammography screening was commonplace, see Section 6.4.

VB classes are used to manage the scheduling of tasks and facilitate the search for the next event. Classes are also used to store entity characteristics, for example growth parameters, behavioural attributes, and run statistics are all managed with separate classes. For a complete description of model code, and how the classes fit together, please see Appendix A.

5.3 Model Inputs, Outputs, and Interface

The user can select different options with which to run the model, and all major variables within the model may be adjusted by the user. A progress bar is provided as to how far along the simulation is, and once finished the user can select whether or not to view the summary results of the simulation.

When first run, the model presents the user with a number of input options, each of which have a default value. The options are separated into 5 groups each displayed on different tabs, labelled 'run options', 'cancer options', 'behaviour', 'screen', and 'self detection' respectively. These five groups are described in turn below.

5.3.1 Run Options

The first set of options available relate to the run options that may be set. Here it is possible to specify the number of iterations that the user wishes to run in order to gain average results. If more than one iteration is requested then the results that are presented are an average of the iterations that have been carried out. The default value is set at 300 since in validation trials it was found that around 250 iterations led to reasonable convergence of output statistics, see Section 6.9. It is also possible to change the number of women who are simulated in each of the iterations specified, this enables the opportunity to conduct one large iteration with more women instead of averaging over several iterations with fewer women, should this be required (due to computing constraints etc).

A user can also select where they would like outputs of the simulation to be recorded by selecting the folder where they would like the text file of summary statistics that are produced to be written. This summary text file is a comma separated file that displays all of the key statistics from each iteration of the simulation. An option button can also be found on this tab in order to request detailed results to be collected. Here, a text file will be produced for each iteration that stores information regarding the progress of each entity at different time steps in the model, as well as their key attributes such as age of cancer onset, cancer growth parameter, time from onset to detection, screen or natural presentation etc. These more detailed comma separated text files are useful for the verification and validation of the model.

5.3.2 Cancer Options

The next tab along contains user options relating to breast cancer itself, its prevalence and growth rate. Here the user can select the proportion of the simulated population that will be scheduled to have breast cancer. The default proportion is 1 since this maximises the efficiency of the model by comparing screening strategies within the breast cancer sub population rather than the larger population as a whole, due to requiring less computing power and time.

This is also where the user may select which type of tumour growth model they would like to assume for breast cancers. Four patterns of growth are available, exponential, Gompertzian, logistic, and a modified Gompertzian that allows stochastic growth rate rather than a fixed growth parameter (multiple) from onset. All four growth models allow individual variability regarding growth rates. For more details regarding the differences between the growth patterns and parameters please see Chapter 6.

5.3.3 Behaviour Options

The third tab provides the choice of behavioural theory to be used in order to determine compliance with the screening strategy to be modelled. The user may select one of four options, the Theory of Planned Behaviour (TPB), Baker and Atherill's compliance model, or percentage attendance as specified (either local or global).

The TPB is described in full in Chapter 2. Here the user may select to use this theory to model the attendance of individuals in the simulation at their invited screening appointments. For information as to how the TPB is approximated within the simulation please see Chapter 6.

Baker and Averill's compliance model and its inputs are described in Section 4.3. The model is based upon a statistical analysis of attendance probability at UK screening units with the primary predictors being age and previous attendance patterns.

Two options are provided for in order to model attendance as a percentage and these are labelled as 'local' and 'global' attendance as described above.

5.3.4 Screening Options

The screening tab presents the user with options for the screening scenario to be modelled. The user can select the start and end ages for screening and the desired screening interval (in years). It is assumed that all required screening strategies will consider fixed screening intervals.

The user may also alter the assumed detection probability of a tumour by the size of the tumour. This may be done by entering different values for the cumulative Weibull distribution than those that appear as default.

5.3.5 Self Detection Options

Under the last tab the user may select to run the simulation with a higher probability of self detection/natural detection than is run as default. The default distribution (labelled 'Tabar data') for the size of natural presentation is taken from size distributions before screening for breast cancer was commonplace. A second option is provided for the user to select a distribution of sizes based upon more recent analysis by Michaelson et al. (2003a) which assumes a higher probability of smaller tumours than the default distribution, this change is thought to be due to the skew in the size distributions introduced by analysing a screened population. For more information and precise parameters please refer to Chapter 6.

5.3.6 Outputs

The following statistics are recorded for each iteration of the simulation model.

- The number of women who developed cancer
- The number of women who did not develop cancer
- The number and proportion of women whose cancers were screen-detected
- The number of women whose cancers presented naturally
- The number of tumours that remained undetected
- The number of women who were invited to screening while they had breast cancer
- The number of women who were not invited to screening while they had cancer
- The number of women who attended screening at least once
- Of those who attended, the average number of times they attended screening
- The average diameter in millimetres of all cancers, screen-detected cancers, and self detected cancers, at presentation
- The average time from cancer onset to detection of all cancers, screen-detected cancers, and self detected cancers
- Of screen-detected cancers, the average number of years earlier the tumour was detected than the scheduled self detection date.
- Of screen-detected cancers, the sum of the life-years gained through earlier detection.

The above statistics and counts are collected for each iteration of a simulation and if multiple iterations are requested then the results window at the end of the simulation displays the averages across the iterations alongside the 95% confidence interval for this mean. Figure 5.4 provides a screenshot of the results window.

If required, the individual iteration results are also available as a comma separated text file written to the results folder of the directory that the user specified at the start of the simulation. This file will be named 'SummaryResults.txt'. If detailed outputs were requested by the user then a comma separated file is produced for each of the iterations that were run. These files will be written to the same directory and will be named 'ResultsX.txt', where X is the iteration number. These files provide information about each of the women within the simulation, such as her scheduled

cancer onset time, sampled cancer growth rate, whether they were screen-detected or not, and the time from tumour onset to detection. The files also provide output after each pass through of the three phase procedure, giving the clock time and the state of each woman in the simulation at that time (no cancer, undetected cancer, screen-detected cancer, other detected cancer, dead from natural causes or dead from breast cancer).

5.4 User Interface

A limited user interface is provided to the model operator. Upon starting the program executable an options screen is presented for choosing the various run options described in Section 5.3.1. Figure 5.2 below provides a snapshot of this screen.

Once the model is run via the menu commands, the run-time screen displays the progress of the simulation. A bar tells the operator how far along the run is within the current iteration, and a counter enables the user to know how many of the run iterations requested remain. Figure 5.3 provides a snapshot of this screen.

The last screen available to the user is the summary results screen. This provides the user with an overview of the simulation results, with the average outcomes over the iterations requested together with 95% confidence intervals for the individual means. An example of this summary result screen can be found in Figure 5.4.

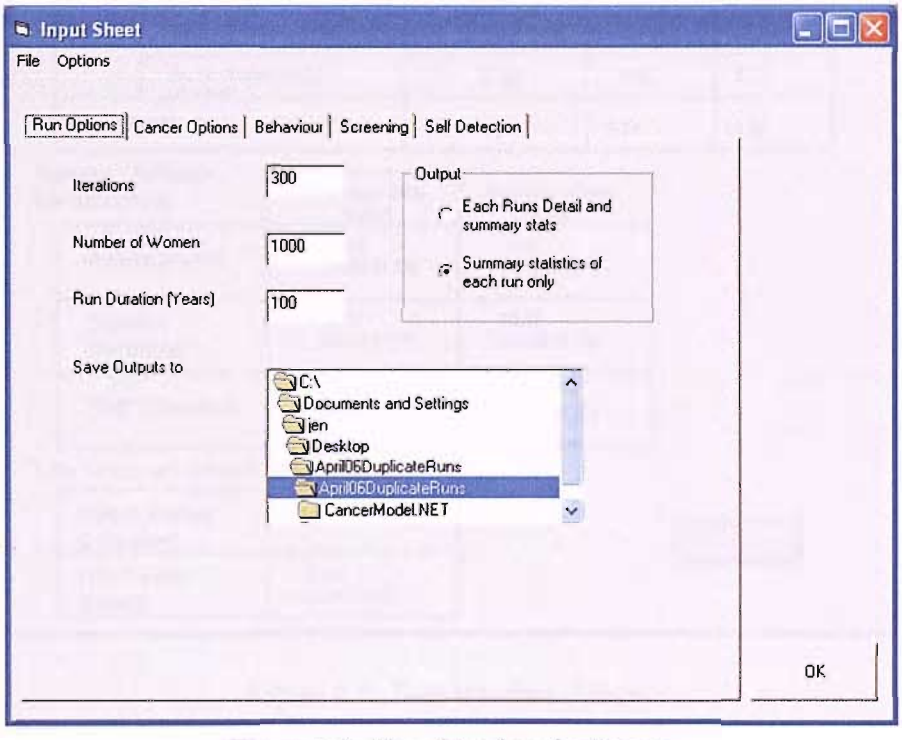


Figure 5.2: User Interface for Inputs

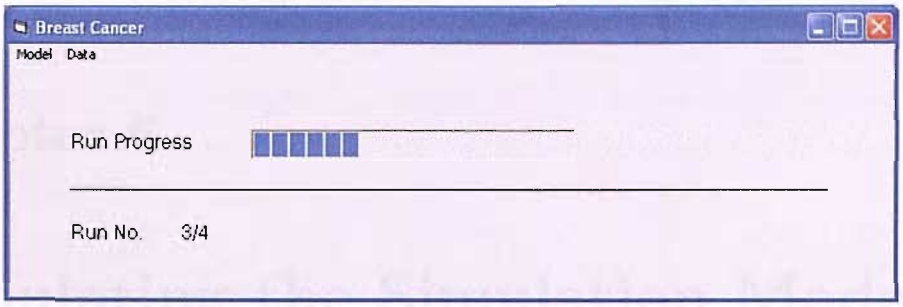


Figure 5.3: User Interface at Run Time

Results Overview

Counts	Average	Lower bound	Upper bound
Cancer	90	88.04	91.96
Screen Detected 24.42% (19.52:29.33)	18.5	13.6	23.4
Self Detected	57	57	57
Un-Detected	14.5	11.56	17.44
Screen invited while had cancer	46	38.16	53.84
Not Invited	44	38.12	49.88
Screen Attended (overall)	72.5	59.76	85.24
Av. No. Attendances (of attended)	5.03	4.68	5.37
No Cancer	10	8.04	11.96

Tumour statistics (of detected)	Average Size (mm)	Average Time (yrs)
Average (All)	21.60 (21.37:21.84)	14.82 (14.58:15.05)
Screen Detected	12.39 (10.04:14.75)	15.90 (15.38:16.43)
Self Detected	24.19 (23.23:25.15)	14.39 (13.72:15.07)

Life Years (of screen detected)

Years Earlier Detected	3.73 (2.57:4.89)
Life Years Saved	16.85 (15.04:18.67)

OK

Figure 5.4: User Interface Results

Chapter 6

Populating the Simulation Model Parameters

This chapter aims to outline the research reviewed in order to populate the variables (epidemiological and psychological) within the breast cancer discrete event simulation model.

The input variables for the model are split into four groups, those relating to the growth patterns of cancer, the detection of breast cancer, survival probabilities from breast cancer, mortality analysis, and psychological variables. These are discussed in turn below.

6.1 Mortality Analysis

In order to estimate any difference in life-years lost through different screening strategies, or modelling strategies, it was necessary to estimate the age of natural death (without breast cancer) for each woman in the simulation.

Two life tables were constructed based upon the figures provided by the Office of National Statistics (ONS) for deaths by age band in England and Wales. Basic life table functions were calculated, the definitions of which can be found in Table 6.1. For a detailed explanation as to how a life table is constructed please see Siegel and Swanson (2004).

The first life table was constructed based upon death from all causes in England and Wales. The data provided by the ONS was split into 20 age bands of roughly 5 years (see 6.1.1 for details). The width of the last age interval (n_{20}, ages 90+), was estimated using the interval specific death rate M_{90+}, and the fraction of the interval

it is assumed those who die in the interval live for, a_{90+}, such that,

$$n_{20} = \frac{1}{a} M_{20} = \frac{2}{M_{20}}$$

This produced a maximum upper age of death of 117. This is in line with predictions of highest attained age for a cohort born in England and Wales in 1966 which is expected to fall in the range 116-123, (Thatcher, Summer 1999).

Variable	Definition	Construction
x_i	The lower bound of the ith age interval in question (in years)	N/A
n_i	Width of the ith age interval in question (in years)	N/A
a_{x_i}	Fraction of the age interval lived by those in the cohort population who die in the age interval	0.5
pop_{x_i}	Estimated population in the age interval i	ONS figures
$deaths_{x_i}$	Observed number of deaths in the age interval i	ONS figures
M_{x_i}	Age specific death rate in interval i	$\frac{deaths_{x_i}}{pop_{x_i}}$
q_{x_i}	Conditional probability that an individual who has survived to start of the age interval i will die in the age interval.	$\frac{n_i M_{x_i}}{1+n_i(1-a_{x_i})M_{x_i}}$
p_{x_i}	Conditional probability that an individual entering age interval i will survive the age interval i.	$1 - q_{x_i}$
l_{x_i}	Life table cohort population at the beginning of age interval i.	$p_{(x_{i-1})} l_{(x_{i-1})}$
d_{x_i}	Number of life table deaths in the ith age interval	$l_{x_i} - l_{(x_{i+1})}$
L_{x_i}	Number of years lived during age interval i	$n\left(l_{x_{i+1}} + a_{x_i} d_{x_i}\right)$
T_{x_i}	Cumulative number of years lived by the cohort population in the age interval and all subsequent age intervals	$T_{(x_{i+1})} + L_{x_i}$
e_{x_i}	Life expectancy at the beginning of the age interval.	$\frac{T_{x_i}}{l_{x_i}}$

Table 6.1: Definitions and derivations of basic life table functions

In order to remove the probability of death from breast cancer from the life table a cause elimination life table was then constructed. Siegel and Swanson (2004) provide an explanation as to how to construct such a table and discuss the uses and pitfalls of the methodology. It is worth pointing out that cause elimination life tables may produce unrealistic results since by their nature they assume that eliminating the risk of breast cancer has no effect upon the risk of death from other causes.

The basic life table functions were then recalculated as follows, (the same notation is used as can be found in Table 6.1, however when referring to the function for the eliminated table, superscript of "$-bc$" will be used).

$$
\begin{aligned}
p_{x_i}^{-bc} &= p_{x_i}^{1-\frac{deaths_{x_i,bc}}{deaths_{x_i}}} \\
q_{x_i}^{-bc} &= 1 - p_{x_i}^{-bc} \\
l_0^{-bc} &= 100,000 \\
l_{x_i}^{-bc} &= p_{(x_i-n_i)}^{-bc} l_{(x_i-n_i)}^{-bc} \\
L_{x_i}^{-bc} &= l_{x_i}^{-bc}(n_i - f_{x_i}) + f_{x_i} l_{(x_i+n_i)}^{-bc}
\end{aligned}
$$

where $deaths_{x_i,bc}$ are the number of deaths in the interval i from breast cancer alone, and

$$f_{x_i} = \frac{n_i l_{x_i} - L_{x_i}}{l_{x_i} - l_{(x_i+n_i)}}.$$

In order to construct a cumulative probability distribution to sample age of death from within the simulation, the following calculations were performed using information from this breast cancer eliminated life table. Since l_x provides the estimate of the number of survivors at the start of interval i, the cumulative probability of survival $S(x_i + n_i)$ to the end of interval i for the cohort can be found by,

$$S(x_i) = \frac{l_{(x_i)}}{l_0}.$$

The cumulative probability of dying at the end of interval i, Dx_i, can then be found by

$$D(x_i) = 1 - S(x_i).$$

The distribution is then sampled in the simulation by generating a random number between zero and one, (denoted by U), and approximating the value for $D(U)$ using interpolation and assuming linear relationship as follows.
If $D(x_i) \leq U \leq D(x_i + n_i)$, then,

$$\hat{D}^{-1}(U) = \frac{n_i}{D(x_i + n_i) - D(x_i)}(U - D(x_i)n_i) \qquad for\ i = 1, 2, 3...19; U \leq D(x_{20}).$$

For the last interval a linear relation does not appear to be a reasonable assumption, (see Figure 6.1). Therefore Microsoft Excel was used to fit a modified exponential, $E(x)$, to the last two data points, (at ages 90 and 117). In order to help ensure continuity, the gradient of $E(x)$ at $x = 90$, $(E'(x_{90}))$, and the gradient of $\hat{D}(x)$ between $x = 85$ and $x = 90$, were set to be as close as possible. $E(x)$ and $E'(x)$ took the following form,

$$
\begin{aligned}
E(x) &= \alpha + \beta e^{-\gamma x} \\
E'(x) &= -\beta\gamma e^{-\gamma x}
\end{aligned}
$$

The method of least squares was used to fit $E(x)$ to the data points provided by the life table for $x = 90$ and $x = 117$, and the gradient difference at $x = 90$ was included in the least squares error with a weight of 10. Microsoft Excel's solver found the minimum error solution, and therefore $D(x)$, for $x > 90$, is approximated in the model as follows

$$\hat{D}(x) = 1.050 - 204.625e^{-0.071x} \qquad \text{for } x > 90.$$

Table 6.2 provides the resulting comparisons between values provided by the life table and those produced by $E(x)$, and Figure 6.1 illustrates the curve produced by the modified exponential.

This leads to an approximation of x (age) at $U > D(x_{20})$ of

$$\hat{D}^{-1}(U) = -\frac{ln\left[(U-\alpha)/\beta\right]}{\gamma} \qquad \text{for } U > D(x_{20}).$$

6.1.1 Mortality Summary

The age of natural death, (x), is sampled for each entity in the simulation as follows,

1. Generate U that follows $Uniform(0, 1)$
2. If $U \leq D(x_{20})$, then $x = \frac{n_i}{D(x_i+n_i)-D(x_i)}(U - D(x_i)n_i)$, for $i = 1, 2, 3...19$; $D(x_i) \leq U \leq D(x_i + n_i)$.
3. Else if $U > D(x_{20})$, then $x = -\frac{ln[(U-\alpha)/\beta]}{\gamma}$.

Variables	E(x)	Objective	Error squared
x=117	1.000010	1.000000	9.283E-11
x=90	0.707525	0.707520	2.837E-11
Gradient at x=90	0.024350	0.024371	4.398E-09
Sum of errors squared			4.519E-09

Table 6.2: Fit of $E(x)$ to $D(x_{20})$ and $D(x_{20} + n_{20})$

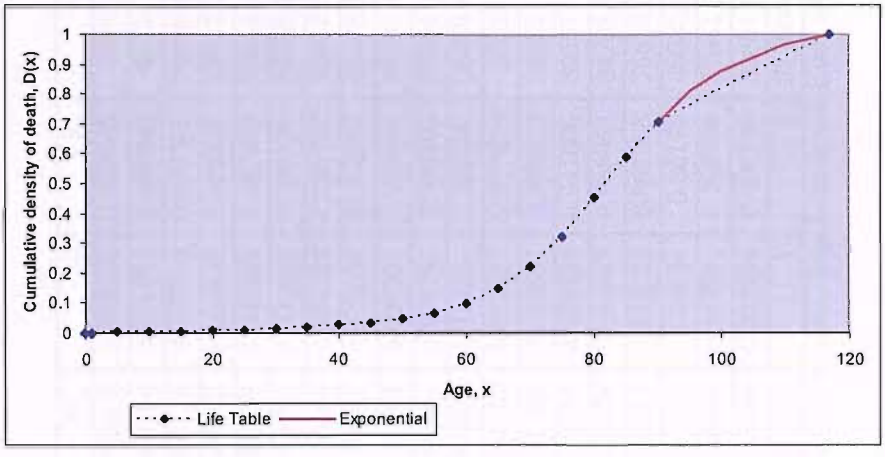


Figure 6.1: Cumulative Density Function of Mortality as Estimated From the Cause Eliminated Life Table

Age interval	x	n	a_x	pop_x	$deaths_x$	M_x	q_x	p_x	l_x	d_x	L_x	T_x	e_x
<1	0	1	0.1	286578	590	0.002059	0.002055	0.997945	100000	205.4969	998.05	8100715	81.00715
1-4	1	4	0.5	1190935	315	0.000264	0.001057	0.998943	99794.5	105.526	398967	8000900	80.17376
5-9	5	5	0.5	1589671	197	0.000124	0.000619	0.999381	99688.98	61.75066	498290.5	7601933	76.25651
10-14	10	5	0.5	1682098	280	0.000166	0.000832	0.999168	99627.23	82.88465	497928.9	7103643	71.30222
15-19	15	5	0.5	1605366	833	0.000519	0.002591	0.997409	99544.34	257.9256	497076.9	6605714	66.35951
20-24	20	5	0.5	1604841	1243	0.000775	0.003865	0.996135	99286.42	383.7592	495472.7	6108637	61.5254
25-29	25	5	0.5	1675878	1442	0.00086	0.004293	0.995707	98902.66	424.5879	493451.8	5613164	56.75443
30-34	30	5	0.5	2008254	2028	0.00101	0.005036	0.994964	98478.07	495.9796	491150.4	5119712	51.98835
35-39	35	5	0.5	2095368	2649	0.001264	0.006301	0.993699	97982.09	617.4018	488366.9	4628562	47.23886
40-44	40	5	0.5	1900649	3549	0.001867	0.009293	0.990707	97364.69	904.8007	484561.4	4140195	42.52255
45-49	45	5	0.5	1687178	5066	0.003003	0.014901	0.985099	96459.89	1437.385	478706	3655634	37.89797
50-54	50	5	0.5	1722995	7849	0.004555	0.022521	0.977479	95022.5	2139.975	469762.6	3176928	33.43343
55-59	55	5	0.5	1640427	11921	0.007267	0.035687	0.964313	92882.53	3314.672	456126	2707165	29.14612
60-64	60	5	0.5	1299609	15800	0.012158	0.058994	0.941006	89567.85	5284.006	434629.3	2251039	25.13222
65-69	65	5	0.5	1199502	22884	0.019078	0.091047	0.908953	84283.85	7673.801	402234.7	1816410	21.5511
70-74	70	5	0.5	1125490	33374	0.029653	0.138032	0.861968	76610.05	10574.62	356613.7	1414175	18.4594
75-79	75	5	0.5	998878	43961	0.04401	0.19824	0.80176	66035.43	13090.88	297449.9	1057561	16.01506
80-85	80	5	0.5	785717	44343	0.056436	0.247291	0.752709	52944.55	13092.72	231990.9	760111.5	14.35675
85-90	85	5	0.5	458664	32790	0.07149	0.303252	0.696748	39851.82	12085.16	169046.2	528120.6	13.25211
90+	90	26	0.5	269073	20807	0.077328	1	0	27766.67	27766.67	359074.4	359074.4	12.93185

Table 6.3: Life table for women, based on death from all causes, 2002

Age interval	x	n	a_x^{-bc}	$deaths_{x,all}$	$deaths_{x,bc}$	pop_x^{-bc}	M_x^{-bc}	q_x^{-bc}	p_x^{-bc}	l_x^{-bc}	f_x^{-bc}	L_x^{-bc}	T_x^{-bc}	e_x^{-bc}
<1	0	1	0.1	590		286,578	0.002059	0.002055	0.997945	100000	0.90	99815	8183092	81.83
1-4	1	4	0.5	315		1,190,935	0.000264	0.001057	0.998943	99795	2.00	398967	8083277	81.00
5-9	5	5	0.5	197		1,589,671	0.000124	0.000619	0.999381	99689	2.50	498291	7684310	77.08
10-14	10	5	0.5	280		1,682,098	0.000166	0.000832	0.999168	99627	2.50	497929	7186020	72.13
15-19	15	5	0.5	833		1,605,366	0.000519	0.002591	0.997409	99544	2.50	497077	6688091	67.19
20-24	20	5	0.5	1,243	1	1,604,841	0.000774	0.003862	0.996138	99286	2.50	495473	6191014	62.36
25-29	25	5	0.5	1,442	17	1,675,878	0.000850	0.004242	0.995758	98903	2.50	493466	5695540	57.59
30-34	30	5	0.5	2,028	96	2,008,254	0.000962	0.004799	0.995201	98483	2.50	491235	5202075	52.82
35-39	35	5	0.5	2,649	229	2,095,368	0.001155	0.005758	0.994242	98011	2.50	488643	4710839	48.06
40-44	40	5	0.5	3,549	363	1,900,649	0.001676	0.008346	0.991654	97446	2.50	485199	4222196	43.33
45-49	45	5	0.5	5,066	552	1,687,178	0.002675	0.013289	0.986711	96633	2.50	479955	3736997	38.67
50-54	50	5	0.5	7,849	820	1,722,995	0.004080	0.020192	0.979808	95349	2.50	471932	3257042	34.16
55-59	55	5	0.5	11,921	1051	1,640,427	0.006626	0.032592	0.967408	93424	2.50	459506	2785110	29.81
60-64	60	5	0.5	15,800	983	1,299,609	0.011401	0.055428	0.944572	90379	2.50	439370	2325604	25.73
65-69	65	5	0.5	22,884	1044	1,199,502	0.018208	0.087080	0.912920	85369	2.50	408262	1886233	22.09
70-74	70	5	0.5	33,374	1215	1,125,490	0.028573	0.133358	0.866642	77935	2.50	363694	1477971	18.96
75-79	75	5	0.5	43,961	1444	998,878	0.042565	0.192400	0.807600	67542	2.50	305223	1114278	16.50
80-85	80	5	0.5	44,343	1422	785,717	0.054627	0.240403	0.759597	54547	2.50	239952	809055	14.83
85-90	85	5	0.5	32,790	1184	458,664	0.068909	0.294102	0.705898	41434	2.50	176704	569104	13.74
90+	90	27	0.5	20,807	1055	269,073	0.073408	1.000000	0.000000	29248	12.93	392399	392399	13.42

Table 6.4: Breast Cancer Eliminated Life Table Based on Data From 2002

6.2 Tumour Growth

The epidemiological model of breast cancer requires information about the growth rate and pattern of breast cancer in women. This growth rate is used to increase the tumour size over time, as appropriate, in order to alter both the chances of detection and prognosis information.

Exactly how best to model human cancer growth is understandably difficult to ascertain due to the ethics of following a detected tumour's progression without treatment. However, over the years a number of approaches of varying complexity have been developed.

Outlined below are a few of the classical growth patterns found to approximate tumour growth in the literature. While other more sophisticated models exist that include the simulation of chemicals and treatment on the growth of the tumour, (e.g. Jiang et al. (2004); Sachs et al. (2001)), we believed that the simple classical models would be adequate for the simulation model described in this thesis.

The rate of tumour growth can be represented by a differential equation of the form:

$$\frac{dN}{dt} = f(N)$$

where N is the number of cells in a tumour, t represents the time, and f some differentiable function. In order to calculate the volume and diameter of the tumour at any one time it is assumed that tumour growth is spherical, see formula 6.2, and that the volume of one cell is $10^{-6}mm^3$ as assumed by Spratt et al. (1993b). Therefore, the volume and diameter of a tumour can be calculated at any time such that,

$$V(t) = 10^{-6} \cdot N(t) \tag{6.1}$$

$$D(t) = 2\sqrt[3]{\frac{3V(t)}{4\pi}} \tag{6.2}$$

where $V(t)$, and $D(t)$ are the volume and diameter of the tumour at time t respectively, (in millimetres).

A popular simplistic approach to the mathematical modelling of tumour growth has been to assume exponential growth, and this has been shown to be adequate when allowances are made for large individual variations in growth rate, (Atkinson et al., 1983). Here $f(N) = KN$ where K is a constant of growth that does not vary with time.

Under this model the number of cells, $N(t)$, within the tumour increase at a constant

doubling time, α, with time, t, such that,

$$N(t) = N(0) \cdot e^{\frac{t \cdot ln(2)}{\alpha}} \tag{6.3}$$

In their review article of the growth rates of tumours Friberg and Mattson (1997) identify five large studies of the doubling times of untreated breast cancers (as estimated from serial mammograms) and report their findings. The results cover more than 800 patients and show considerable variation in doubling times from 30 days to infinity, with an estimated median across the studies of approximately 180 days.

Previous research has found that the distribution of variation in breast cancer tumour growth rates across populations can be described by a Lognormal. Therefore, Microsoft Excel's solver was used to find a Lognormal distribution such that the mean was 180 days and the probability of 30 days or less was chosen as 0.01. These assumptions led to the doubling times under the Exponential option in the breast cancer model following a Lognormal distribution. The log doubling times were therefore assumed to be normally distributed with mean 5.19 and standard deviation 0.77. Since the simulation model described in this thesis works in years as units of time rather than days, the input time to the equation was multiplied by 365 days before the calculation of tumour volume at that time was performed.

However, as Wolf points out the exponential assumption of tumour growth is a '..mathematical projection of cells in virtual circumstances', (Wolf, 2001). That is, in reality a tumour is inhibited in growth at first by the supply of nutrients and in later stages by the neovascularisation (the process of vascularisation of a tissue involving the development of new capillary blood vessels; vascularisation of tumours is usually a prelude to more rapid growth and often to metastasis) in the tumour tissue, whereas the exponential model assumes sufficient nutrients and space for growth. The assumption of a constant growth rate has also been disputed by clinical data, for example Spratt et al. (1993a) found evidence of doubling times as low as 7051 days which under exponential growth assumptions would lead to a tumour life of 578 years. For these reasons it has been suggested that the exponential growth law should be ruled out as a viable model for the natural history of breast cancer, (Clare et al., 2000).

A second and popular model is the Gompertzian population growth model. The Gompertzian model considers the increase in the number of cells in a tumour as a function of the number of cells present and satisfies the differential equation:

$$\frac{dN}{dt} = -\beta \cdot N \cdot ln(N/K)$$

Here, β is the exponential decay rate of growth, and K the limiting size of the tumour, (carrying capacity).

The Gompertz model not only fits well with theory but has been shown to fit well to both in vivo studies of breast tumour growth, (Norton et al., 1976), and to published serial mammography data, (Norton and Simon, 1977; Norton, 1988; Spratt et al., 1993b). Norton (1988) for example found the following solution best approximated observed breast cancer growth patterns,

$$N(t) = N(0)e^{\left\{log\left(\frac{N(\infty)}{N(0)}\right)\left(1-e^{-bt}\right)\right\}} \tag{6.4}$$

where, if t is in months then $N(0) = 1$, $N(\infty) = 3.1 * 10^{12}$, and b is Lognormally distributed with the log mean -2.9, and standard deviation 0.71. Since the simulation model described in this thesis uses years as unit time, the input time was multiplied by 12 before a calculation of tumour size was performed for this equation.

A third simple model for tumour growth is the generalised logistic growth population model. Forms of Logistic equation have been shown to provide the best fit to tumour growth observed via mammograms when compared to the exponential and Gompertzian growth models, while the exponential growth equation provided the least good fit, (Spratt et al., 1993a,b). The logistic model assumes density dependent growth and its differential equation is as follows,

$$\frac{dN}{dt} = b \cdot N\left[1 - \left(\frac{N}{K}\right)^c\right]$$

where N, K, and t are as before (in days), b is the intrinsic growth rate, and c is the generalising factor. Note that if $c = 1$ then the standard logistic is produced and as c tends to infinity an exponential is approximated. The model has the solution for $c > 0$ as follows,

$$N(t) = N(\infty)\left[1 + e^{-c(bt+d)}\right]^{-\frac{1}{c}} \tag{6.5}$$

where

$$d = -\left(\frac{1}{c}\right) ln\left[\left(\frac{N(\infty)}{N(0)}\right)^c - 1\right]$$

The model that best fit the data was found from the records of 113 patients who had three serial mammograms with evidence of tumour size over time. It was assumed tumour volume began at $10^{-6}mm^3$ at $t = 0$, and $N(\infty)$ was set to 2^{40} cells. Results found that the best fit came from setting $c = 0.25$ and $d = -27.72$, (where t is in days).

The individual variation in the intrinsic growth rate, b, was then investigated by considering the records of 448 patients with at least 2 size recordings from serial mammograms. The intrinsic growth rate was found to be approximately Lognormally distributed, although the fit was not statistically significant. Spratt et al. cite other evidence that the variation in breast cancer growth has been shown to be Lognormally distributed, and therefore, for the purpose of this analysis, a Lognormal

distribution was fitted to the percentage points provided by Spratt et al.. This was done using Palisade's BestFit add on for MS Excel which produced a Lognormal fit to the data with the log variable having mean -5.84 and standard deviation 1.04. The simulation model described in this thesis works in years rather than days, so all times were multiplied by 365 before tumour volume calculations were performed.

In their comparison of different models of tumour sizes, Hart et al. (1998) found that data from the first screen of the Swedish Two County mammography trial were inconsistent with the exponential, logistic, and Gompertz laws. Instead they found that the best tumour growth model that fit to the data was a parabolic growth function, (Power Law). The Power Law is a broad family of growth rates and includes the exponential. The Power Law differential equation takes the following form:

$$\frac{dN}{dt} = k \cdot N^{\lambda}$$

where λ indicates the mode of tumour growth, (linear at zero to exponential at one), and k is a constant of growth.

The value of λ found to fit the trial data the best was approximately 0.5 indicating Parabolic growth, a rate that declines with the square root of the tumour mass. This rate of growth is slower than the exponential which has a constant decline in growth, but appears to be more significant in the clinical size ranges than the Logistic and Gompertz size specific rate reductions, (Hart et al., 1998). The differential equation evaluates as follows,

$$N(t) = (kt(1-\beta) + c)^{\frac{1}{1-\beta}}$$

However, due to the methods employed in the paper by Hart et al. (1998), no values or ranges were supplied for c and so this pattern of tumour growth has not been included as a growth model within the scope of this thesis.

Demicheli (2001) argues that continuous growth models cannot explain the long lasting recurrence risks associated with breast cancer, and that cancer growth may undergo periods of dormancy. Demicheli goes on to present results that support his theory. In order to explain similar observations of plateaux in tumour growth, Speer et al. (1984) produced a stochastic modification to the basic Gompertz model whereby the intrinsic growth rate is varied with time producing stepwise growth patterns. The Speer et al. model builds on the original Gompertzian model and simulates tumour growth by changing α with a probability A_4 every 5 days as described in equation 6.6, where A_3 and A_4 are random numbers between 0 and 1.

$$\alpha = \frac{\alpha}{1 + Rnd \cdot A_3} \tag{6.6}$$

Speer et al. then demonstrated how their model fit to three different breast cancer

data sets and in doing so produced estimates for the values of the variables within their modified Gompertzian model of breast cancer growth, see Table 6.5.

Variable	Estimate
λ_0	0.4 (/day)
A_3	0.3
A_4	0.008
α_0	0.03(/day)

Table 6.5: Estimated parameters for the modified Gompertz model of tumour growth, Speer et al. (1984)

Further support for the notion of periods of non growth in breast cancer tumours was found in a review conducted by Retsky et al. (1990), who point out that taking averages of tumour growth doubling times or omitting slower growing tumours from the analysis smooths out individual variation. They conclude that considering irregular kinetics and stochastic growth patterns may be more appropriate when modelling individual breast cancers (as opposed to modelling populations).

Since the idea of non continuous growth has some support, the modified Gompertzian model as suggested by Speer et al. has been included as a growth pattern for breast cancer within the reported simulation model. To limit the calculations, the times of change for alpha, and the new alpha values are taken from a set of paired values that have been previously sampled from the distributions suggested. For a full description of the methodology, please refer to Section 6.3.

6.2.1 Summary

Four patterns of tumour growth are available to choose from within the model. Only one pattern can be used for any one analysis at one time, and the selection is made via the input options screen from the user interface.

It is assumed that breast tumours grow spherically, (see equation (6.2)), and where equations provide density rather than volume, it is assumed that a single cell has volume $10^{-6}mm^3$.

The four growth options to choose from are to assume exponential growth over time, equation (6.3), Gompertzian growth, equation (6.4), a generalised Logistic (6.5), or a stochastic variation upon Gompertzian growth such that the growth rate changes over time with probabilities and values as defined in equation (6.6) and Table 6.5.

Figure 6.2 plots the difference between the mean growth pattern over time produced by each of the different models. Here, the growth pattern is produced using the overall mean of the growth parameter distribution (not the mean once logged), and the modified Gompertzian distribution is calculated with the mean time to next α

change (624 days) set constant each time, and using the median change in α such that $Rnd_2 = 0.5$.

Figures 6.3 through 6.6 provide an indication as to the range of growth patterns produced within each model by illustrating the mean pattern produced as above, but also the patterns produced by the 10th, 50th, and 90th percentiles of the growth distributions. The modified Gompertzian distribution in Figure 6.6 illustrates the given percentiles of the distribution for the next change, while the change in α is kept constant at the median ($Rnd_2 = 0.5$).

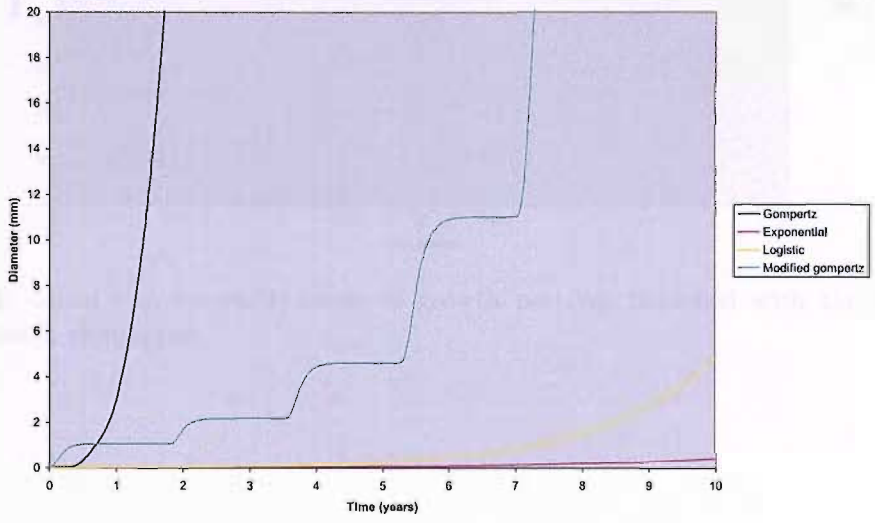


Figure 6.2: Mean growth pattern produced under each growth model with associated assumptions

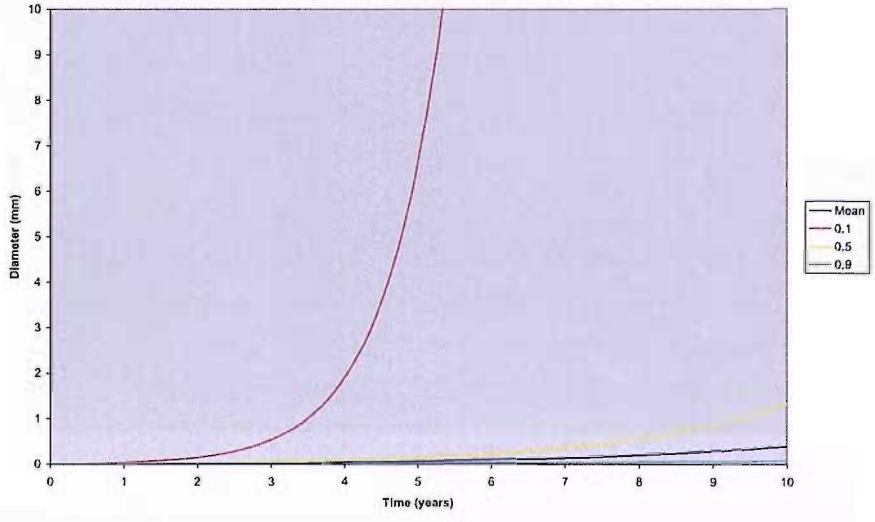


Figure 6.3: Mean and percentile range of growth patterns modelled with the exponential tumour growth assumption

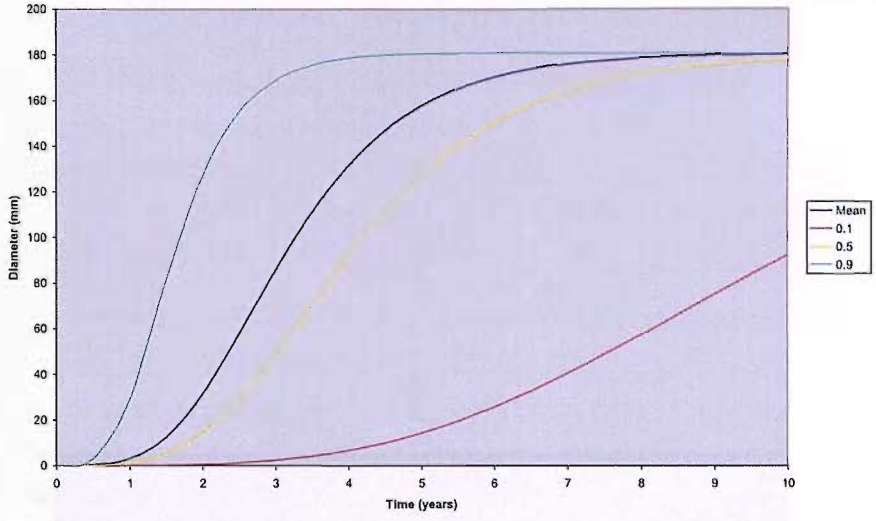


Figure 6.4: Mean and percentile range of growth patterns modelled with the Gompertz tumour growth assumption

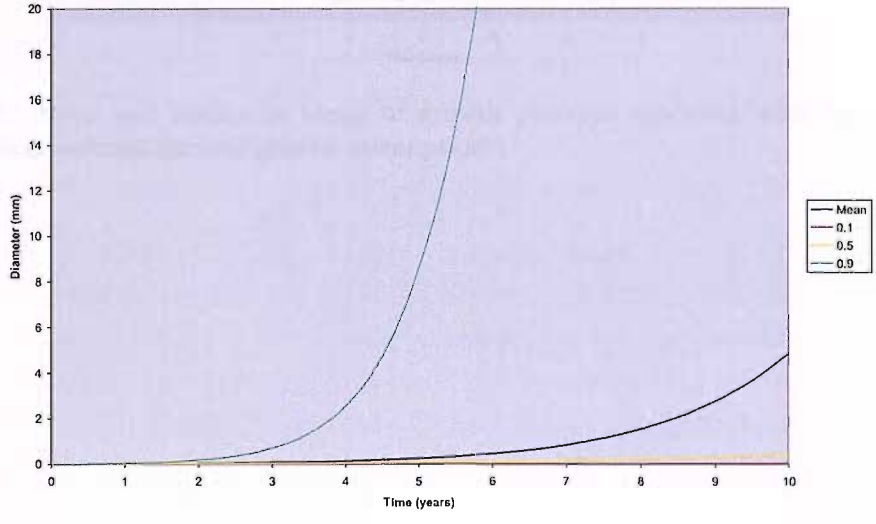


Figure 6.5: Mean and percentile range of growth patterns modelled with the logistic tumour growth assumption

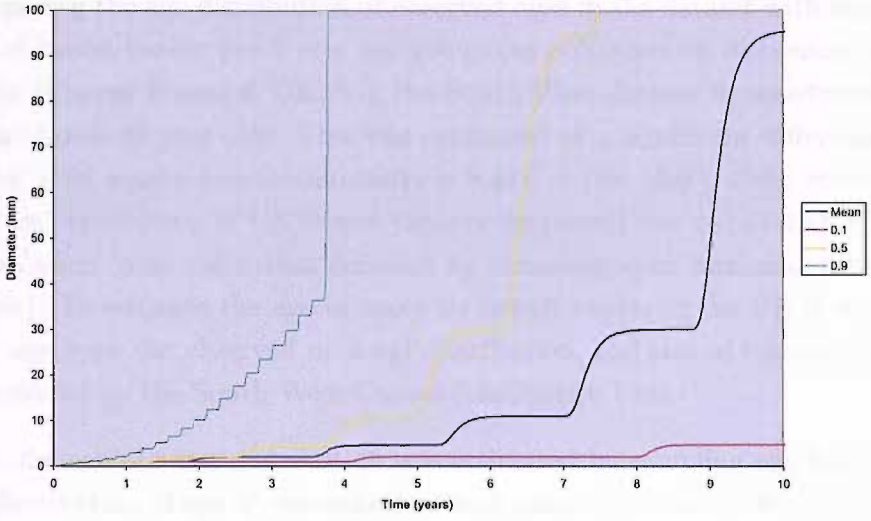


Figure 6.6: Mean and percentile range of growth patterns modelled with the stochastic modified Gompertzian tumour growth assumption

6.3 Age of Cancer Onset

At the beginning of the simulation it is necessary to sample the age of tumour onset for each woman in order to make it possible to schedule tumour onset.

Data were obtained from the South West Cancer Intelligence Unit in England who record details of all breast cancers in the South West of England. The database contains all recorded patients between 1981 and 2000, and provides, among other statistics, the patients age at diagnosis (in years), and the recorded diameter of the tumour (in millimetres).

The dataset was sorted and any entries removed for which the tumour width was zero or missing, or the age of the patient not provided. This left a database of 26,298 patients with an average age of 61.45 and tumour diameter of 24.4mm. However, when comparing the age distribution of observed ages in the dataset with the reported incidence of breast cancer per 5 year age group (as published on the cancer research UK website (Cancer Research UK, b)), the South West dataset demonstrated a lower proportion of over 85 year olds. This was confirmed as a significant difference at the 5% level by a chi square test ($teststatistic = 8.84E-168, 13df$). Data relating to the observed size distribution of UK breast cancers diagnosed was not available for the whole population (only the subset detected by mammography screening producing a bias sample). To estimate the age of onset for breast cancer in the UK it was decided to sample age from the observed national distribution, and size of tumour from the dataset provided by the South West Cancer Intelligence Unit.

Therefore, the age of onset distribution was estimated by sampling age from the national distribution of age at presentation, and tumour size was sampled from the distribution observed in the South West dataset at random, before back-calculating to find the age of the tumour (given its size) for each of the four tumour growth theories in turn, and subtracting this age from the patient age to estimate age of onset.

The national distribution of age at breast cancer presentation was estimated from Office of National Statistics records of incidences of breast cancer by 5 year age bands per 100,000 population in England in 2002, see Figure 6.7. Linear interpolation was used to provide the probability of presentation between two cumulative points at the maximum of an age band, however this did not appear appropriate for the final age band. Figure 6.7 shows the result of a function ($f(x)$ as below), fitted to the last age band with the gradient at age (x) 85 included in the least squares fitted with a weight of 10. The upper age limit of the last age band was set at 101, as this was the highest age observed in the South West dataset. The function $f(x)$ that was fitted to the last band was as follows,

$$f(x) = \alpha + \beta e^{-\gamma x}$$

where $\alpha = 1.01$, $\beta = -72221.87$, and $\gamma = 0.16$ to 2dp.

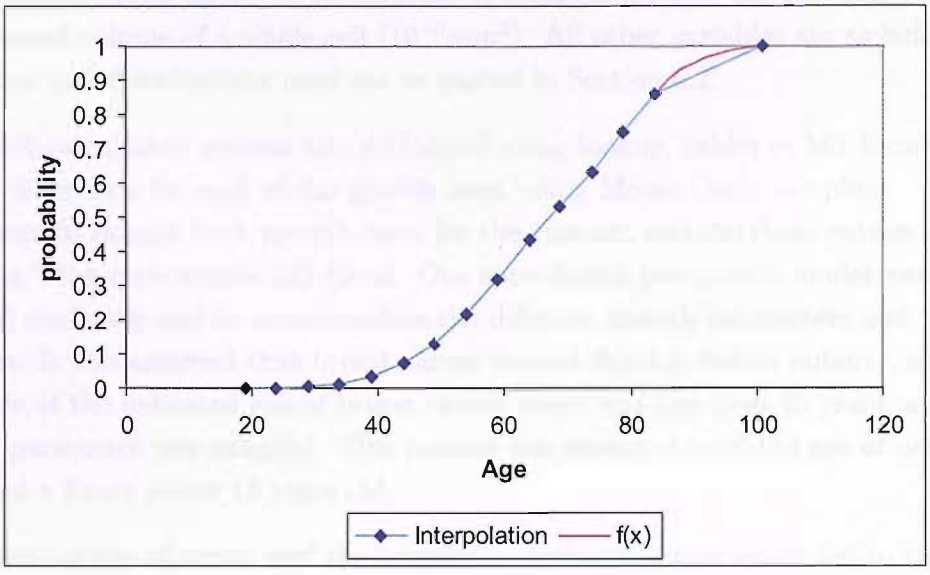


Figure 6.7: Cumulative distribution of age of breast cancer presentation in England in 2002 (ONS)

The size of tumour, for the given age band, was randomly sampled (with replacement) from the relevant age band subset of the South West dataset, and a back-calculation was performed to find the age of the tumour, and therefore the age of the individual at the time of tumour onset, given growth parameters appropriately sampled.

The exponential, logistic, and Gompertz functions could all be re-arranged to approximate the age of the tumour, t in years, as follows.

Logistic

$$t = \frac{1}{365b}\left[\left(\frac{-1}{c}\right) ln\left(\left(\frac{N(D)}{N(\infty)}\right)^{-c} - 1\right) - d\right] \tag{6.7}$$

Exponential

$$t = \left(\frac{\alpha}{365}\right)\frac{ln(\frac{N(D)}{N(0)})}{ln(2)} \tag{6.8}$$

Gompertz

$$t = -\frac{1}{12b}\left[1 - \left(\frac{log(N(D))}{log(N(\infty))}\right)\right] \tag{6.9}$$

where $N(D)$ is the number of cells at detection, estimated by calculating the volume of the tumour based upon the assumption of spherical growth and dividing this by the assumed volume of a single cell ($10^{-6}mm^3$). All other variables are as before and the values and distributions used are as quoted in Section 6.2.

This back-calculation process was performed using lookup Tables in MS Excel for 100,000 iterations for each of the growth laws, using Monte Carlo sampling techniques to sample both growth rates for the tumour, and database entries each time, via VBA code within MS Excel. One spreadsheet per growth model was built to avoid confusion and to accommodate the different growth parameters and patterns. It was assumed that breast cancer cannot develop before puberty, and therefore, if the indicated age of breast cancer onset was less than 15 years, a new growth parameter was sampled. This process was repeated until the age of onset indicated a figure above 15 years old.

The resulting age of onset, and the sampled growth parameter which led to the age derivation were both recorded for each iteration. At the start of the simulation model described in this thesis, the model reads in paired values for the age of cancer onset and growth parameters from text files appropriate to the chosen pattern of tumour growth. This methodology of using paired samples as inputs to the simulation model was chosen above the possibility of randomly assigning new growth variables and age of onsets to individuals within the simulation sampled from independent distributions. This decision was made to try to control for the large variations in tumour growth rates assumed (see Section 6.2), and to ensure that the tumours would reach a detectable size at appropriate ages. To save computing time and resources, the values were read in in order, but start at a random place within the data (txt) file(s).

Due to the more complex nature of the stochastic modified Gompertzian model of tumour growth, it was not possible to back-calculate the age of the tumour based upon size via one simple formula. Instead, in this case, the time the tumour had been growing to reach the sampled size was estimated within each iteration as follows.

Since the modified Gompertzian growth model assumes that the growth parameter α of the basic Gompertz equation may change every 5 days with probability $A_4 = 0.008$, it was assumed that this probability of change was uniform across the 5 day period and so the probability of change in any one day was calculated as $C_1 = A_4/5 = 0.0016$. The time until the next change in α can then be compared to the number of Bernoulli trials required until a success is observed, with the probability of success in any one trial equal to C_1. The time to the next change in α was then measured as a sample from a geometric distribution with parameter $C_1 = 0.0016$.

A spreadsheet model was built in MS Excel which provided up to ten new times for a

change in α, (each a random sample from the geometric distribution with C_1 the probability of success), plus the time of the previous change(s), and a sampled size and age at detection as before. This approach assumed a maximum of 10 steps in the growth pattern over the life time of the tumour which appeared to be a reasonable assumption given the original research measured around 5 changes per tumour on average, and limiting the number of possible changes helped to reduce required computing power and memory.

Alongside these times of α change, a new value for α at this time was calculated, using the formula provided by the modified Gompertzian model. It was then possible to use lookup Tables to ascertain the volume of a tumour under the sampled values, in steps of 5 day intervals. This was calculated in 5 day intervals for 40 years. It was assumed that by 40 years, a tumour would have reached a detectable size.

The back-calculation of time from tumour onset until a sampled size could then be estimated (with an accuracy of a few days). The times and values of the sampled αs, as well as the time of tumour onset, were all recorded for each of the 100,000 iterations of the back-calculation. These parameters are then read into the simulation model as paired values of tumour onset and growth parameters in order to ensure that the tumour reaches a detectable size at an appropriate age, and in an attempt to control some of the variation within the model.

Figure 6.8 shows the resulting distributions found for the age of cancer onset under the different tumour growth assumptions. It can be seen that the differing assumptions of the models lead to a large (up to 20 year) difference in assumed growth times for breast tumours until detection, with the Gompertzian model providing the shortest growth times, and the logistic model the longer growth times.

6.4 Tumour Detection

This Section aims to describe the methods used to model the probability of tumour detection (by mammography screening or otherwise) within the simulation model, and to explain the reasons for the chosen approach.

Since cost effectiveness of screening programmes is not a prime objective of the current research, mammogram specificity (the probability of a true negative being correctly identified) has not been included in the simulation model. If cost effectiveness of mammography screening was of interest then the specificity of the screens would be an important variable to measure as it would provide the rate of over-diagnosis (false positives) at the screening unit which would lead to a cost in terms of follow-up appointments and tests. The next Section introduces literature pertaining to the probability of tumour detection via mammography screening, and

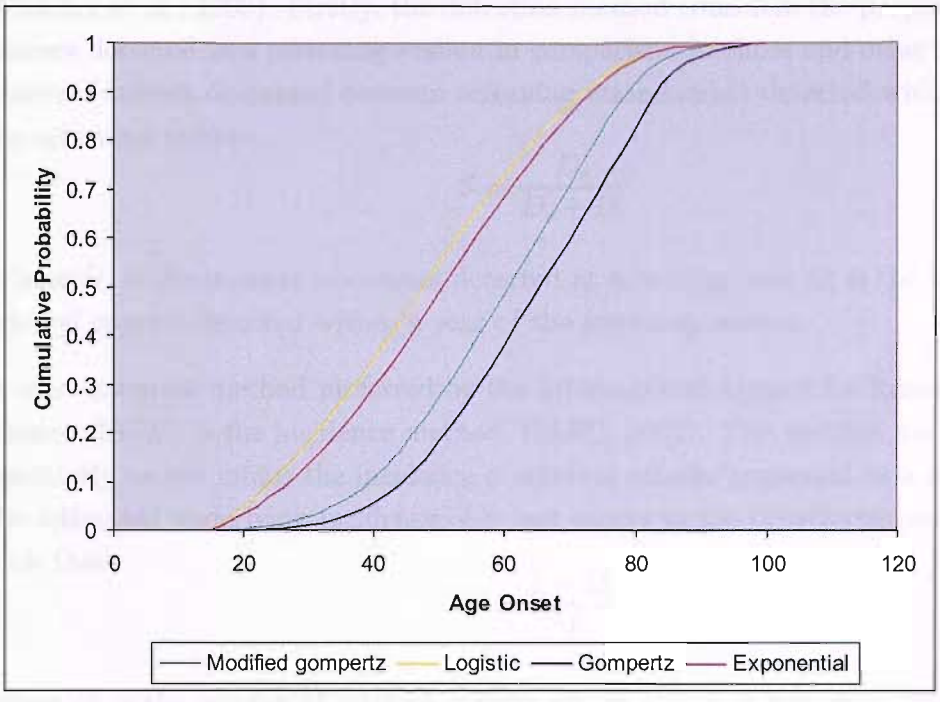


Figure 6.8: Derived Cumulative Age of Onset Distributions by Growth Pattern

presents the chosen method of approximation within the breast cancer simulation model. This is followed by an explanation of how detection by other means (self detection via breast self examination or presentation of symptoms) is handled within the discrete event simulation model.

6.4.1 Mammography Sensitivity

The sensitivity S of a test is usually defined as the proportion of true positives found in the proportion of the population that was tested, such that in the case of cancer screening

$$S = \frac{D_s}{N_+}$$

where S is the screening test sensitivity, D_s the number of true positive screening results, and N_+ the underlying number of people screened who did have cancer. Ideally, a test would be 100% sensitive and always find a cancer should it exist, however this would be extremely difficult in the case of breast cancer given the differences in breast tissue and breast tumours themselves.

The underlying numbers of women who have breast cancer in a population is difficult to determine (since tests cannot be 100% sensitive), and so estimates of mammogram sensitivity have varied. Two methods of reporting mammography sensitivity have been observed in the literature, the 'detection' method and the 'incidence' method

(Fletcher et al., 1993). Firstly, the detection method considers the proportion of cancers detected at a screening session in comparison to those and other interval cancers (cancers diagnosed between screening attendances) detected within a year of the screening session.

$$S = \frac{D_s}{D_s + D_i}$$

Where D_s is the number of cancers detected at screening, and D_i is the number of interval cancers detected within a year of the screening session.

A more accurate method preferred by the International Agency for Research on Cancer (IARC) is the incidence method, (IARC, 2002). This method expresses sensitivity as one minus the incidence of interval cancers expressed as a proportion of the estimated underlying incidence of breast cancer in the considered population, such that

$$S = \frac{1 - D_i}{\hat{I}}$$

where D_i is the number of interval cancers within a year of screening, and $\hat{I}$ is the estimated underlying incidence in the population.

Numerous attempts have been made to estimate the sensitivity of mammography based on data from controlled trials, quasi trials, and from population-based screening programmes. The IARC Breast Cancer Screening Handbook cites several of these with results ranging from 68% up to around 90% for the detection method. The quoted results from the incidence method produced lower estimates ranging between 52% and 82%.

Mammography sensitivity has been shown to vary with age, (the younger the patient the less sensitive the procedure). This may be in part due to the density of the breast which is thought to have a negative association with mammographic sensitivity, (Michaelson et al., 2003b). Other factors that can affect the variability of the mammograms sensitivity and quality include the optical density of the machine itself, the quality of the processing, the examination technique (position and compression of the breast), and the performance of the radiologist reading the film, (IARC, 2002).

The size of the tumour would appear to be an obvious factor for determining the likelihood of a mammogram detecting the tumour, however little research has been identified addressing this issue. The only paper found to date to estimate the efficiency of mammography given the size of the tumour is also believed by the authors to be the first of its kind. Michaelson et al. (2003a) produced estimates for the sizes at which breast cancers become detectable by screening. Data from 810 invasive carcinoma diagnosed at Massachusetts General Hospital between 1990 and 1999 were used to estimate mammography efficiency by two methods. Firstly, the

sizes of tumours at previous mammography screens were estimated by back-calculating from the size at discovery (absolute efficiency method), and secondly a comparison was made between the efficiency at and around the mid-point of the size of detected tumours and from this estimated efficiency at other sizes, (relative efficiency method).

Both methods produced similar results, and Figure 6.9 shows the estimated distribution of detection sizes for screened cancers as produced by Michaelson et al. via the absolute efficiency method.

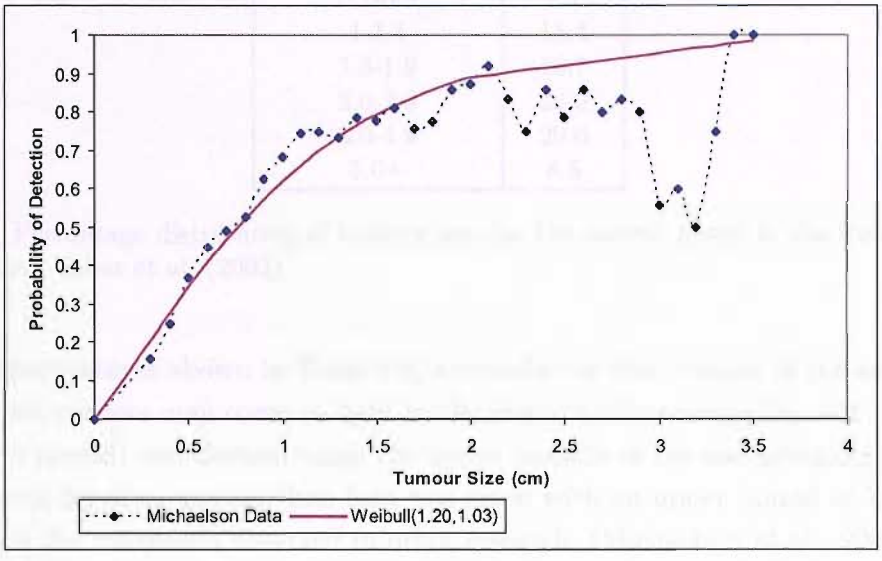


Figure 6.9: Efficiency of mammographic detection by tumour size, Michaelson et al. (2003a)

A distribution was fitted to this data using Palisades' BestFit for Windows version 2.0d. Although the statistical best fit to the data was produced by a PearsonIV, no closed form exists for the cumulative PearsonIV for sampling, so instead a Weibull was used. The data were found to fit the cumulative Weibull(1.2,1.03) with a confidence of 95% by the chi-squared method, and Figure 6.9 demonstrates the fit.

Each time a woman attends screening in the model, a calculation is then made based upon this Weibull distribution as to the probability of detection $p(x)$, such that

$$p(x) = 1 - e^{-\left(\frac{x}{1.03}\right)^{1.2}}$$

where x is the size (diameter) of the tumour in cm at the time of screening.

6.4.2 Detection by other means

In order to compare the efficiency of mammography regimes it is necessary to estimate the times at which the tumour would have come to light by other means rather than

having been detected by mammography as part of a screening programme.

Tabar et al. (2002) report on the results of the Swedish Two County Trial which was a randomised control trial of invitation to breast cancer screening conducted in Sweden in the 1970s. Included in the analysis is a breakdown of the sizes of tumours presenting in the passive study population (the control group not invited to screening). The size frequencies of tumours from this population are provided in Table 6.6.

Tumour Size (cm)	Percent
0.1-0.9	7.1
1-1.4	15.4
1.5-1.9	19.7
2.0-2.9	29.0
3.0-4.9	20.0
5.0+	8.8

Table 6.6: Percentage distribution of tumour size for the control group in the Swedish Two County Trial, Tabar et al. (2002)

From the percentages shown in Table 6.6, a cumulative distribution of the sizes at which breast cancers may come to light in the absence of screening (by self detection or by other means) was derived using the upper bounds of the size groupings. The last category, for sizes greater than 5cm was given with an upper bound of 7.5cm since this is the maximum observed in other research, (Michaelson et al., 2003a). Palisades' BestFit for windows version 6.0d was then used to fit a distribution to the cumulative data. The data followed the Erlang(3,0.85) distribution with a confidence level of greater than 95% by the chi-squared statistic. Figure 6.10 shows the fit to the cumulative data.

When a breast cancer initiation is scheduled in the simulation model, a natural time of discovery is also scheduled. This natural discovery time is calculated from the size of discovery which is set to follow Erlang(3,0.85).

More recently Michaelson et al. (2003a) also produced estimates of the distributions of breast cancers detected without screening. Their data may be a slight underestimate since the sample is taken from the same population (Massachussetts General Hospital) as discussed in Section 6.4.1, therefore the distribution of 'other detected' cancers may be skewed as some breast cancers that could otherwise have been detected at larger sizes may have been found via mammography screening at a smaller size. Indeed, the median of Michaelson et al.'s 'other detected' distribution is 1.5cm rather than approximately 2cm as suggested by Tabar et al.'s data. It may be the case, however, that self detection sizes have reduced due to increased awareness, and for this reason an option to use the distribution suggested by Michaelson's data has been included within the simulation model.

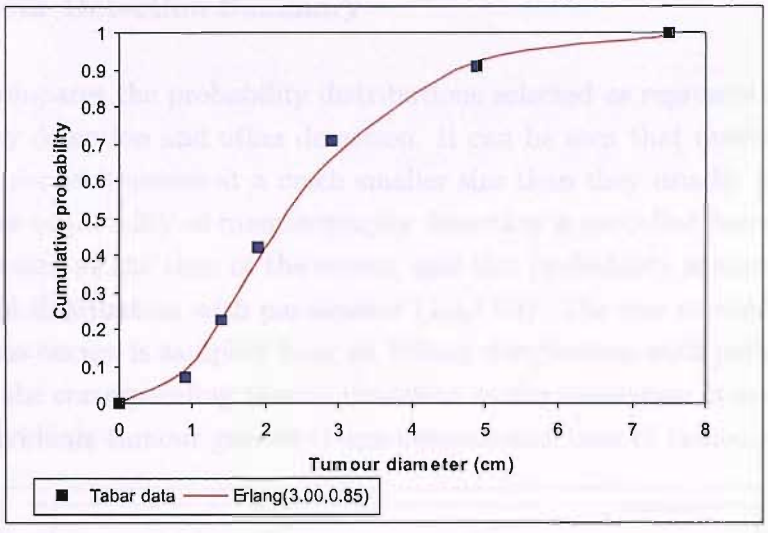


Figure 6.10: Fit of the Erlang(3,0.85) distribution to the Swedish Two County Trial Control data of breast cancer detection sizes Tabar et al. (2002)

As above, Palisades' BestFit for Windows was used to fit a distribution to the cumulative probabilities provided by Michaelson et al.'s results. The best fit was given by an Erlang(3,1.7) which provided a significant fit at the 95% confidence level by the chi-squared statistic. Figure 6.11 demonstrates the fit to the data.

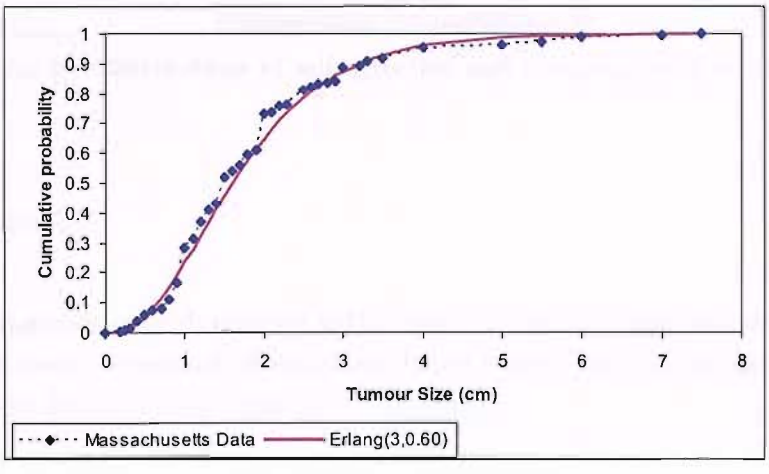


Figure 6.11: Fit of the Erlang(3,0.6) distribution to the non screen detected cancers at Massachussetts General Hospital, Michaelson et al. (2003a)

During a simulation model run, a time for self detection is scheduled for each woman. A size of self detection will first be calculated using the appropriate generator and then the time-to-discovery derived as appropriate, based upon the individuals tumour growth characteristics (sampled appropriately as previously discussed in Section 6.2).

6.4.3 Tumour Detection Summary

Figure 6.12 compares the probability distributions selected as representing mammography detection and other detection. It can be seen that mammography has the ability to detect tumours at a much smaller size than they usually present otherwise. The probability of mammography detection is modelled based upon the size of the tumour at the time of the screen, and this probability is approximated with a Weibull distribution with parameters (1.2,1.03). The size at which detection by other means occurs is sampled from an Erlang distribution with parameters (0.85,3), and the corresponding time of detection in the simulation is calculated based upon the individuals tumour growth characteristics and time of tumour onset.

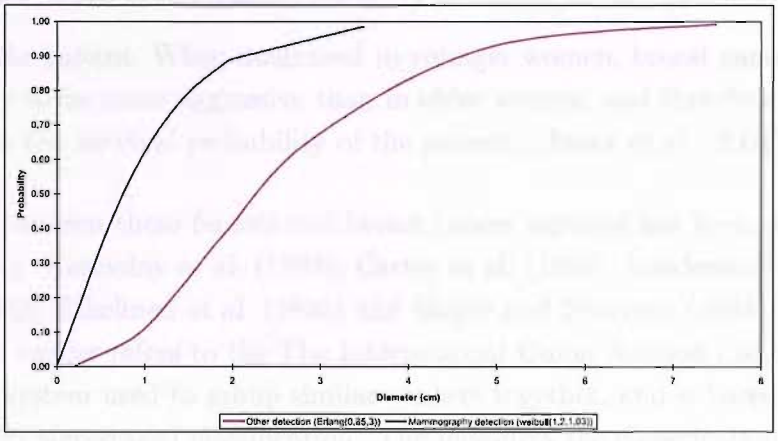


Figure 6.12: Selected distributions of self detection and mammography detection given tumour size

6.5 Survival

A patient's prognosis once diagnosed with breast cancer is dependent upon a number of factors, the most recognised of which are listed below, (BMJ Publishing Group (2004), and The Breast Clinic (1997)).

1. *The 'stage' of the cancer*, see discussion that follows.
2. *Tumour size.* As tumour size increases the expected survival rates decrease.
3. *Lymph node involvement.* The presence of cancer cells in the axillary lymph glands of a patient indicates that the tumour has spread at least as far as the lymph nodes, with the chances of distal spread (metastasis spread to other regions) more likely the more nodes affected.
4. *Hormonal status.* Whether the tumour is sensitive to oestrogens, inferring oestrogen is required to aid tumour growth. This helps to indicate how well the

tumour will respond to post operative chemotherapy.

5. *Tumour grade.* Tumour grade (measured as 3 grades) is a measure of tumour cell characteristics, and how close they are to breast cells. The higher the grade, the more abnormal the cells, and the lower the survival rates of patients, (The Breast Clinic, 1997).

6. *Tumour pathology.* Tumour pathology relates to the type of tumour which may be non malignant (ductal carcinoma in situ, DCIS), malignant (ductal cancer), or of an unusual type. DCIS has the best survival probability as it is non malignant and confined to the breast so removal should approximate a cure if diagnosed correctly. Ductal cancer on the other hand has a worse prognosis than other types of malignant cancer, (The Breast Clinic, 1997).

7. *Age of the patient.* When diagnosed in younger women, breast cancer has a tendency to be more aggressive than in older women, and therefore age can influence the survival probability of the patient, (Jimor et al., 2002).

The relation between these factors and breast cancer survival has been much researched (e.g. Koscielny et al. (1988); Carter et al. (1989); Sunderland and McGuire (1990); Eskelinen et al. (1992) and Meyer and Province (1994)).
The 'stage' of cancer refers to the The International Union Against Cancer's classification system used to group similar cancers together, and is based on a TNM (Tumour Node Metastasis) classification. The measures the classification system considers are, the size of the tumour, lymph node involvement (local spread), and whether metastasis is apparent (distal spread). Five stages describe the cancer progression, varying from a non-malignant cancer in situ, with no lymph node involvement or metastasis, (stage 0), to a tumour with both nodal involvement and metastatic spread, (stage IV). As the stage of breast cancer increases, the expected survival rates decrease, (BMJ Publishing Group, 2004).

Survival statistics for breast cancer are most often given in terms of the proportion of patients who would be expected to survive for a period of time after treatment. Due to the nature of the statistics the results are often not up to date. Statistics considering the impact of new advances in treatment and prevention, or survival given no treatment, are understandably rare. The good news is, though, that modern treatments and earlier interventions do appear to be leading to improving survival rates for breast cancer, with one study results even indicating a 1% reduction in risk for patients with recurrent breast cancer, with each increasing year, (Giordano et al., 2004).

As previously discussed, a patients probability of survival will be dependent upon a number of variables, some of which may be unknown at the time of diagnosis, and others which may still be unknown to scientists. Therefore, modelling approaches for

the prediction of patient outcomes can take many forms ranging from complicated approaches with many input variables and stochastic analysis, to more basic and broad approaches giving less precise estimates of survival.

An example of the more comprehensive approach is that by Pittman et al. (2004) who consider including genetic information as well as the usual clinical information, as inputs for the prediction of breast cancer recurrence. Their approach uses statistical classification and decision tree modelling to evaluate the inclusion of genetic information to the modelled recurrence probability. Results indicated a significant increase in predictive power by including the genetic information, with the capacity for up to 90% sensitivity and specificity for the individual prediction of disease recurrence. Of the clinical inputs, lymph node involvement, (and the number of nodes involved), was the most significant risk factor for recurrence, and they concluded that traditional tree models for the prediction of disease outcomes can be improved by the inclusion of genomic data.

Useful to health professionals are prognostic scoring tools that combine several different clinical indicators for prognosis, to produce one overall score. Such scores and techniques are useful in order to combine the different information into one scale and to group patients by risk status. A well used example of such a tool is the Nottingham Prognostic Index (NPI). The NPI considers three prognostic indicators, tumour size, lymph node stage, and histological grade, and computes a prognostic score as follows,

$$NPI = 0.2S + \eta + \gamma$$

where S is the tumour size in centimetres, γ is the histological grade of the tumour (1= good, 2= moderate, 3= poor), and η is the lymph node stage (1= node negative, 2=less then three metastatic nodes, 3 = four or more metastatic lymph nodes), The Breast Clinic (1997).

The NPI is commonly used to group patients into one of three prognostic groups, good' ($NPI < 3.5$), moderate' ($3.5 \leq NPI \leq 5.4$), and poor' ($NPI > 5.4$). The three groups of patients have very different prognoses, with the good' category relating to about 85% survival after five years, reducing to 70% for the moderate' group, and 50% for the 'poor' category, (The Breast Clinic, 1997). The Index has been validated and applied frequently e.g. Galea et al. (1992). It has been pointed out, though, that with the change in presentation of breast cancer due to national screening programmes, the statistical weighting and cut-off points in the index may have changed since it was formulated in the 1980's, (Anderson).

Modelling for the prediction of survival

The breast cancer simulation model described in this thesis takes women through time, and advances the cancer by increasing the size of the tumour. Therefore, other

information such as histological grade and lymph node stage would require estimation from the size of the tumour. It may be simpler and less costly (in terms of simulation run time and size as well as an increase in variability so perhaps error), to estimate prognosis on the basis of tumour size alone. Publicly available survival statistics for breast cancer are rarely available by size of the tumour. The yearly audit of screen detected cancers contains survival analysis by each of the major prognostic indicators including size of the tumour, (Programme and of Breast Surgery at BASO, 2002). However, these statistics are calculated from screen detected cancers alone, and it may be the case that survival distributions from interval detected cancers, or other non screen detected cancers, differ from those of screen detected cancers.

Published survival rates from breast cancer are also available based upon follow up studies from the Swedish two county trials. Here survival statistics are broken down by size, nodal status and histological type, but it is not clear whether the statistics refer only to the study population (i.e. those invited to screening) or include the passive study population (those not invited for screening until after the trial), (Laslo et al., 2000).

Michaelson et al. (2003b) produce an equation for relating tumour diameter to survival for breast cancer, based upon three groups of previously published survival rates. Michaelson et al. approximate the survival of a fraction of women (F) from breast cancer for approximately 15 years, by

$$F = e^{-QD^Z}$$

where D is the diameter of the tumour and Q,Z are constants.
When compared to previously published survival data, their model was shown to be a strong predictor, and Q and Z were found to be roughly 0.006 and 1.3 respectively.

Michaelson et al. show that their model is consistent with biological mechanisms leading to lethal metastasis, with probabilities based upon the number of tumour cells or tumour cell days. Their model therefore takes account of metastasis without specifically considering its presence in an individual, but instead calculates an overall probability of 15 year survival (F) for a given population.

While this relation can tell us the probability of survival to 15 years, it cannot provide an estimate of when death may occur in the time interval. In order to approximate a time to any death from breast cancer (as the simulation model requires) two percentage points could be used to estimate the parameters of a Weibull distribution. The tumour size equation suggested by Michaelson et al. (2003b) provides a percentage point at roughly 15 years, and while other work has attempted to consider relations between tumour size and subsequent survival, they have grouped tumour size into large bands, and/or excluded cases whereby metastasis was already

present therefore skewing the results, (Verschraegen et al. (2005); Engel et al. (2003); Carter et al. (1989)).

The ultimate cause of death from breast cancer is believed to be from tumour metastasis, and survival has been shown to be unrelated to tumour size once metastasis has occurred, Engel et al. (2003). The association between breast cancer size and survival is, under this hypothesis, due to the association between the probability of, and lifetime of, metastasis with tumour size. Thus if it is possible to simulate the time at which metastasis occurs then it should also be possible to simulate life expectancy. Figure 6.13 provides a schematic illustration of this idea, where t_0 is the initial time of tumour onset, t_1 the time of tumour metastasis, t_2 the time that this metastasis is diagnosed, C_0, C_1 and C_2 are the probability of cure given the time of diagnosis A, and $D1$ and $D2$ the time of natural death from breast cancer and death from breast cancer if treated, respectively.

The time at which tumours metastasise has been studied by many authors, (Kendal, 2001; Engel et al., 2003; Heimann and Hellman, 2000). Koscienly et al. (1984) produced estimates of the size of the primary tumour when metastasis is inevitable, by considering the distribution of metastasis and recurrence upon follow-up given the size of the primary tumour at diagnosis. This distribution of primary tumour size forms the basis for the threshold value t_1 in the model, and was found to be Lognormally distributed with the log values taking mean 3.16ml and standard deviation 2.62ml. The time the tumour takes to grow to this volume is calculated by considering that tumour growth is spherical according to the appropriate growth model (see Section 6.2).

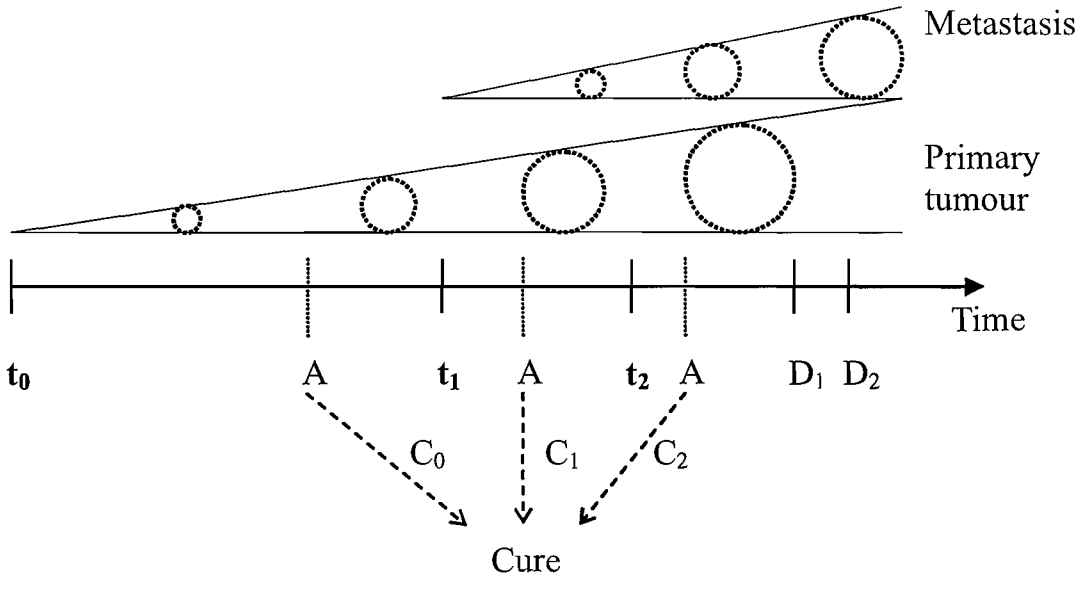


Figure 6.13: Tumour Progression as Modelled in the Simulation

From Figure 6.13, A is the time of tumour diagnosis (regardless of the type of detection). Under this hypothesis, if detection of the tumour occurs before metastasis, ie ($t_1 > A$), then the patient should not die from breast cancer or suffer any recurrences once the primary tumour has been removed, (assuming that the operation is 100% successful in removing the whole tumour). Therefore the probability of cure before metastatic spread is inevitable is 1, ie $C_1 = 1$.

If, on the other hand detection of the primary tumour occurs after the occurrence of metastasis then at some point this metastasis will become troublesome and may ultimately lead to death at time D2, (if natural death does not precede this time).

Whether a patient can ever be completely cured of breast cancer is difficult to determine since metastasis and death have been shown to appear up to 25 years after treatment for the primary tumour, and it is not until after this time that death rates from breast cancer patients begin to mirror that of the rest of the population, (Yakovlev et al., 1999). Estimates of the cured fraction of breast cancer patients given the stage of the primary tumour at diagnosis have been made, (Myasnikova et al., 2000; Yakovlev et al., 1999). Since stage three refers to the diagnosis of distant metastasis, this can give an idea of the likelihood of cure for patients once metastasis is at a stage to be diagnosed ($t > t_2$), and results for grade two can provide a rough estimation of the cure rate for patients with early metastasis ($t_1 < t > t_2$). Table 6.7 provides a summary of the findings by Yakovlev et al. and the corresponding values used within the simulation for calculating the probability of cure from breast cancer. These probabilities are derived as the mean of the means across the age groups studied (not weighted by the numbers in each group since this information was not provided). The probability of cure before metastasis was taken to be 1 as indicated previously.

Stage	Yakovlev et al. (1999)	DES Simulation Parameter
1 - Local	0.7-0.75(0.65-0.79)	
2 - Regional	0.37-0.42(0.28-0.48)	$C_1 = 0.39$
3 - Distant	0.09-0.15(0.01-0.23)	$C_2 = 0.125$

Table 6.7: Cured fraction of patients given tumour progression, mean range and 95% CI range over ages in brackets

If the cancer is not considered as cured then the patient will be scheduled to die from breast cancer. The time to death from breast cancer once metastasis has been diagnosed and treated has been shown to be roughly 2 years, regardless of primary tumour size at diagnosis, (Carter et al., 2003; Engel et al., 2003).

The time from the initiation of metastasis until the primary tumour reaches a detectable size has been estimated to be on average 45 months or just under 4 years, (Koscienly et al. (1985), 18 doubling times multiplied by the median doubling time for metastasis of 2.5 months). In this paper the time-to-diagnosis of metastasis was

considered to be fixed in terms of the doubling time of the tumour in question, at 18 doubling times. The variation in the time-to-detection is then associated with the achieved variation in metastasis doubling time modelled. The variation interval assumed for the metastasis doubling time was between 0.49 and 13.1 months, corresponding to a time range until discovery of 8.82 months to 19.65 years. The standard deviation used to estimate the metastasis doubling time (assumed to follow a Lognormal distribution) in the paper is 2.316 months.

In this simulation, time-to-diagnosis of the metastasis is considered to be 18 times the sampled metastasis doubling time. Metastasis doubling time is taken to follow the same distribution as assumed in Koscienly et al.'s work which is Lognormally distributed with logged values taking mean 0.92 months and standard deviation 0.84 months. Death (D_2) is scheduled to follow 2 years later. This approach assumes that metastasis doubling times are unrelated to the doubling times of the primary tumour.

It may also be the case that the breast cancer goes undiagnosed, and that death occurs before treatment can take effect. Data concerning untreated breast cancers are understandably rare, however not unheard of. Bloom et al. (1962) considered the natural history of 356 patients who died in Middlesex hospital between 1805 and 1933 (untreated due to a lack of treatment for cancers at that time). They found that the time from symptom onset (as reported by the patient) until death ranged from 2 months to 219 months (or just over 18 years), with a mean of 2.9 years. The cumulative survival rates provided in the paper were fitted to a Gamma(1.53,2.20) distribution by BestFit v2.0d and it is this distribution that is used to determine the time from the onset of symptoms until death (in years) if the breast cancer is not treated. The time to the onset of symptoms is modelled as the time of self or other detection, see Section 6.4.2.

However, since it is presently assumed that all tumours will eventually self detect if not detected by screening, and upon self detection a woman will seek medical advice, this functionality is not currently utilised by the model. The theory is left within the code, however, so that future work may investigate the effects of delay in seeking help.

6.5.1 Survival Summary

The discrete event simulation reported in this thesis assumes that metastasis is the ultimate cause of death from breast cancer, and that detection before metastasis occurs will lead to effective treatment and the prevention of death from the disease.

The time of metastasis is derived from a distribution of sizes for the primary tumour when metastasis is inevitable. It is then assumed that, if the primary tumour is detected before the metastasis is detectable, then the patient has a higher chance of

Variable	Value	Note
t1	t0 + time to size(exp(normal(3.16ml,2.62ml)))	Size in volume ml
t2	t1 + (18/12)*exp(normal(0.92,0.84))	years
C0	1	
C1	0.39	
C3	0.125	
D1	time to symptoms + 12*Gamma(1.53,2.20)	Time to symptoms = self detection
D2	t2 + 2	years

Table 6.8: Summary of variable values used within the simulation

effective treatment, than if the tumour becomes apparent after this time. The time until the metastasis becomes detectable is sampled appropriately for each individual.

Table 6.5.1 summarises the distributions used within the model for the various time-scales and probabilities as depicted in Figure 6.13.

6.6 Behavioural Data

As previously discussed, the simulation model assigns behavioural attributes to each simulated woman which then control her behaviour within the model. Behaviour modelling is restricted to considering attendance at each invited screening session for each woman modelled. The particular behavioural variables of relevance, and the way that they combine to affect the simulated pathway for each woman, is governed by the chosen psychological theory. The user has the option of modelling the attendance at invited mammography screening sessions using either local or global percentage attendance, the Theory of Planned Behaviour (TPB, see chapter 2), or Baker and Atherill's compliance model, (Baker and Atherill, 2002), as discussed in Section 4.3.

The options for local and global percentage attendance are described in detail in Chapter 5, and require no further data input/analysis beyond the user input of the percentage of people who attend screening. As such these two options are not described here. Instead, the modelling for the Theory of Planned Behaviour (TPB) and the equation option for approximating attendance at breast screening are described in the sections that follow.

6.6.1 The Theory of Planned Behaviour

This Section aims to describe the method by which the Theory of Planned Behaviour (TPB) was implemented within the breast cancer discrete event simulation. For a full description of the Theory of Planned Behaviour, please refer to Chapter 2.

The Theory of Planned Behaviour outlines three main constructs of attitude, subjective norms, and perceived behavioural control (PBC), relating to a behaviour, that influence intention and the action of the behaviour, (please see Section 2.2.5 for a full description of the model). In order to use this theory within the simulation model it was necessary to have a quantitative measure of the models constructs and relations. This required estimates of the distributions and correlations between the three main constructs, as well as their interactions, and regression weights, to predict both intention to perform the behaviour, and the behaviour itself. Research was identified that had tested the Theory of Planned Behaviour for predicting attendance at breast cancer screening (see Chapter 3). An author of a recent such piece of research within the UK, (Rutter from Rutter (2000) discussed in Chapter 3), was contacted and kindly agreed to share the data that had been collected for the study.

The dataset is in an SPSS data file, and records the responses of 2058 randomly sampled women from three health authorities in the UK. The questionnaire comprises demographic and socio-economic information, as well as recognised measures for the

qualitative constructs in the Theory of Planned Behaviour. The questionnaire was sent out to the random sample of women before they were invited for their screening session. Answers to the majority of questions were requested on an ordinal rating scale, and the final calculated measures of attitude to mammography, subjective norms relating to mammography screening, and PBC in relation to screening attendance, are all scale variables calculated from the rating scale responses. Tables B.1 and B.2, (in Appendix B), provide summary statistics for these three variables as well as for the ordinal variable intention to attend, (measured on a 5 point ordinal scale ranging from definitely yes to definitely no).

The dataset also includes the attendance/non-attendance information for each woman at the subsequent screening session, as well as the next screening session three years later, collected from the relevant mammographic screening clinics.

Analysis of Data
Cases for which values for any of the three predictor variables were missing (attitude, subjective norms, or PBC), or for whom attendance information was missing, were removed from the analysis. This left a sample of 1846 cases, 1586 of whom attended their invited screening session, and 283 who did not.

Under the Theory of Planned Behaviour the three variables, attitude, perceived behavioural control, and subjective norms, combine in a linear regression equation to predict intention to attend. Intention to attend and PBC then go on to predict the behaviour itself with their own regression weights. If this is the case then it should also be possible to model attendance as a direct function of the three predictor variables (attitude, subjective norms, and PBC), and effectively skip the intermediate variable of intention, as shown below.

$$\begin{aligned} Intention &= \gamma(Attitude, SubjectiveNorms, PBC) \\ Attendance &= \delta(PBC, Intention) \\ &= \delta\left(PBC, \gamma(Attitude, SubjectiveNorms, PBC)\right) \\ &= \eta(PBC, Attitude, SubjectiveNorms) \end{aligned}$$

for some linear functions γ, δ, and η.

Since attendance (y) is a binary response variable, (either the person attended or they did not), the probability of attendance, π, can be considered as the result of a Bernoulli trial with probability π of success. The probability π can then be modelled as a linear function of the inputs attitude, subjective norms, and PBC, denoted X_1, X_2 and X_3 respectively. In order to ensure π lies between 0 and 1, a logistic

transformation is performed such that

$$ln\left(\frac{\pi\left(\underline{X},\underline{\beta}\right)}{1-\pi\left(\underline{X},\underline{\beta}\right)}\right) = \beta_1 + \beta_2 X_1 + \beta_3 X_2 + \beta_4 X_3$$

or

$$\pi\left(\underline{X},\underline{\beta}\right) = \frac{exp\left(\beta_1 + \beta_2 X_1 + \beta_3 X_2 + \beta_4 X_3\right)}{1 + exp\left(\beta_1 + \beta_2 X_1 + \beta_3 X_2 + \beta_4 X_3\right)}$$

where $\underline{X} = (X_1, X_2, X_3)^T$, and $\underline{\beta} = (\beta_1, \beta_2, \beta_3, \beta_4)^T$.

The parameters β_i for $i = 1, 2, 3, 4$ were calculated using the method of maximum likelihood. The log of the likelihood was minimised, where

$$LogLikelihood = \sum_{j:y_i=1} ln\left(\pi(\underline{X}_j,\underline{\beta})\right) + \sum_{j:y_i=0} ln\left(1-\pi(\underline{X}_j,\underline{\beta})\right)$$

For $j = 1, 2..1846$.

The minimum was found using the Nelder-Mead optimisation algorithm with a confidence level of 0.05.

Table 6.9 shows the resulting values of β_i for $i = 1, 2, 3, 4$. For more information regarding logistic regression with Binomial response variables, the reader is referred to Krzanowski (1996).

Parameters	**Estimates**	**Lower 95% Limit**	**Upper 95% Limit**	**BootStrap Lower CI Limit**	**BootStrap Upper CI Limit**
β_1	-1.34546742	-2.13826322	-0.552671	-2.12407139	-0.5139070
β_2	0.008027605	-0.001097429	0.01715264	-0.00112037	0.017595029
β_3	0.014644905	0.008482051	0.02080776	0.008865912	0.020940595
β_4	0.155316327	0.092143516	0.21848914	0.091814396	0.21792617

Table 6.9: The fitted β values from maximum likelihood calculations, and their confidence intervals

Confidence limits for $\underline{\beta}$ were obtained using bootstrapping methodology as follows. The sample of observed values, $\underline{X}_j$ for $j = 1, 2...1846$, were used as the basis of a population from which new samples of the same size were created. Each time, the minimum log-likelihood vales for $\underline{\beta}$ was found for the particular new sample in question. This re-sampling was conducted 1,000 times and the 95% confidence limits for $\underline{\beta}$ taken to be the 500th and 1500th values of the ranked ranges observed for each β_i, $(i = 1, 2, 3, 4)$. Table 6.9 provides the results. For more information about bootstrapping, its application and uses, please see Davidson and Hinkley (1997).

When the range of the values for $\underline{\beta}$ were plotted in scatter plots across the re-sampling runs, $\underline{\beta}_j$, it could be seen that the behaviour of the $\underline{X}_j$ were not particularly skewed and that assumptions of normality would not be unreasonable (for $j = 1, 2...1846$), see Figure 6.14. The asymptotic confidence limits were then also

calculated for comparison, see Table 6.9 for results.

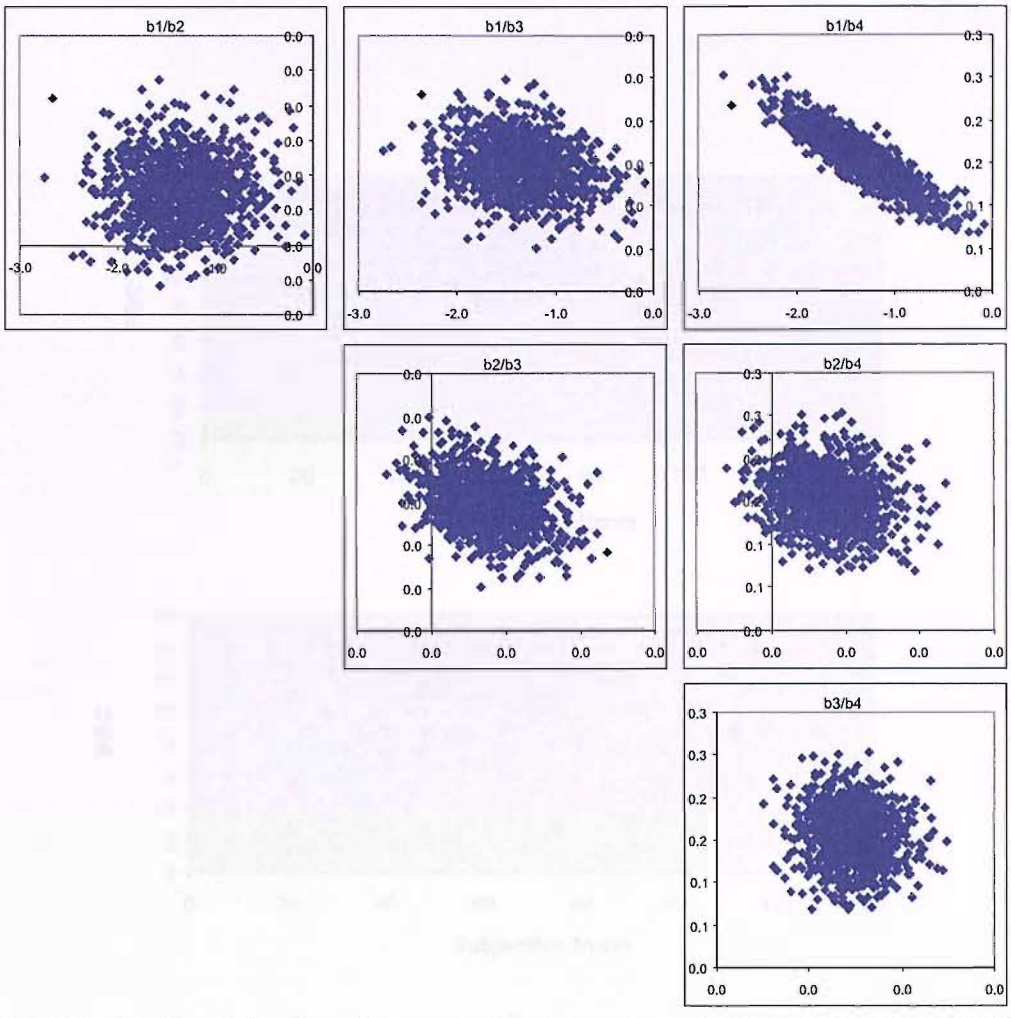


Figure 6.14: Range of β values observed in bootstrapping, where bi is β_i for $i = 1, 2, 3, 4$.

The lower confidence interval for β_2 crosses zero, indicating that X_1 (attitude to mammography screening), may not be a significant predictor within this sample. Figure 6.15 helps to demonstrate the effects of $\underline{X}$ upon attendance, y. As the least significant variable, the data were first grouped by ranking X_1 and dividing the data into three sections, where X_1 was low (group 1), medium (group 2), and high (group 3). Scatter plots were then created comparing the relationship between subjective norm scores (X_2), and PBC scores (X_3), given attendance, for each observed case from the sample. As can be seen, while the attitude scores may not be statistically significant, they appear to have a nonlinear effect upon the probability of high PBC scores in the sample of non-attendees.

The fit of the logistic model to the prediction of π can be seen from the range of the confidence limits around the β_i's (Table 6.9). Figure 6.16 demonstrates the logistic models effect upon the probability of attendance, by plotting the empirical distribution function of the π_j for the observed sample $j = 1, 2...1846$, given actual

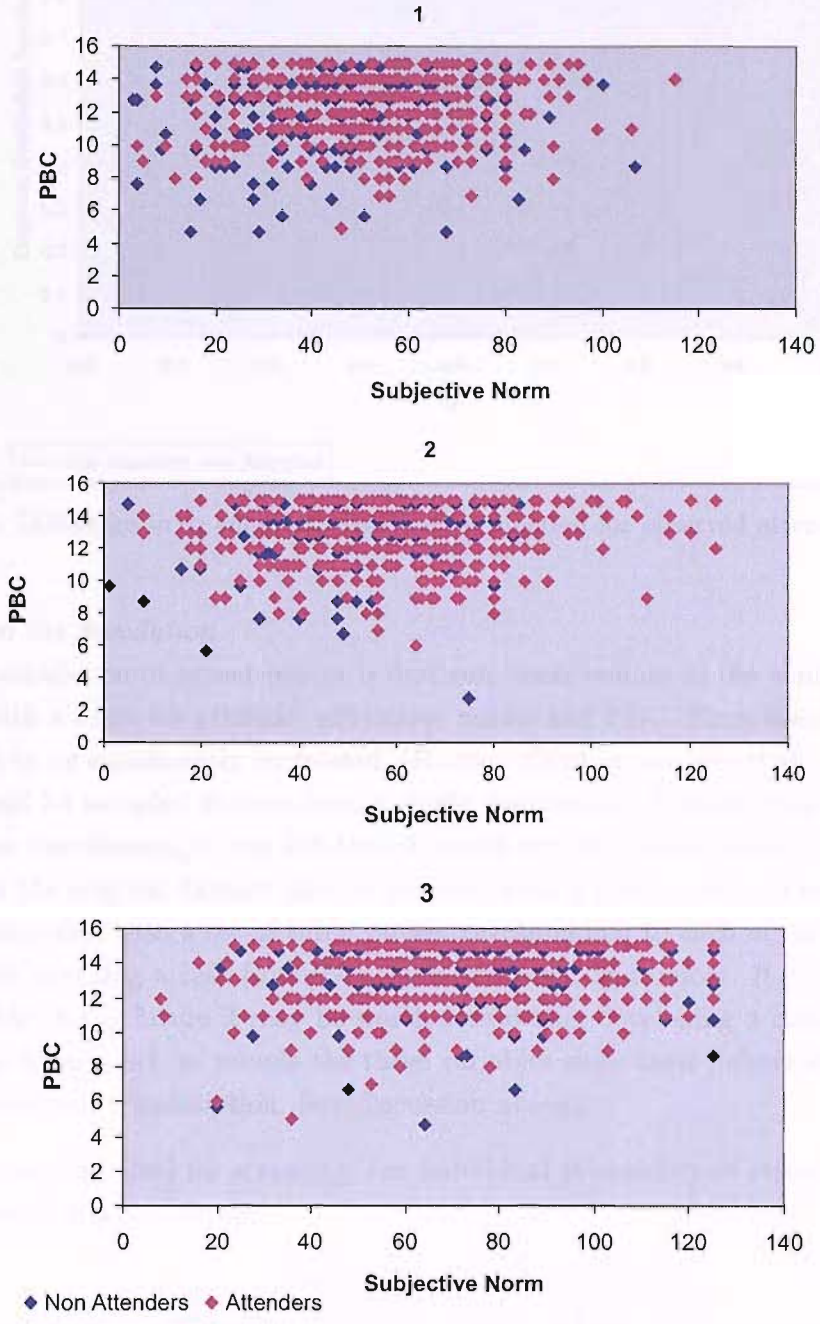


Figure 6.15: Plots of the Subjective Norm (X_2) scores against the PBC (X_3) scores given attendance for groups of low (1), medium (2), and high (3) scores for Attitude X_1.

attendance.

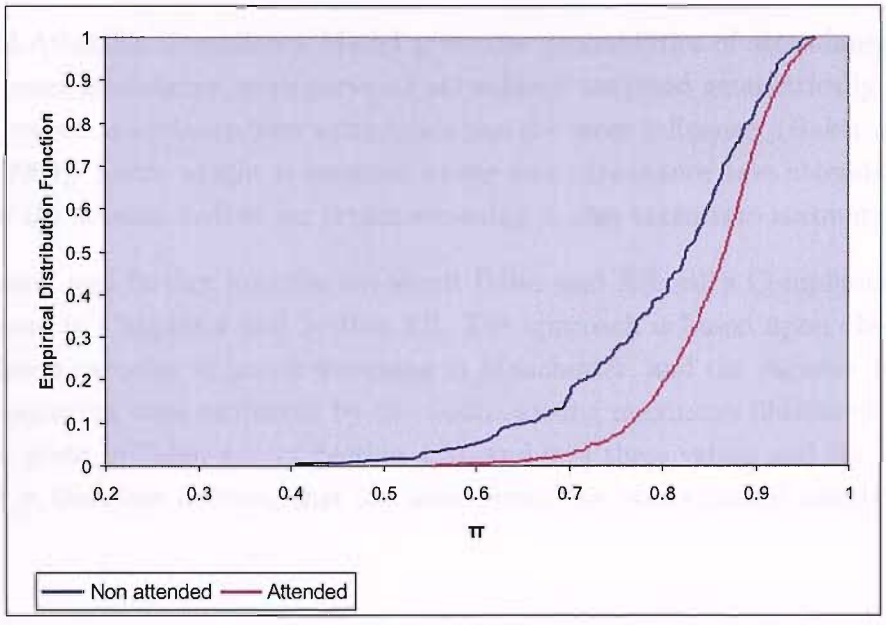


Figure 6.16: Difference in π_i empirical distribution function for observed attenders and non attenders

Sampling in the Simulation

When the simulation of breast cancer is first run, each woman in the simulation is provided with a score for attitude, subjective norms and PBC. Since these variables were found to be significantly correlated, (Rutter, 2000), it was felt that these three values should be sampled at once from a single distribution. Rather than create a multivariate distribution, it was felt that it would not be inappropriate to sample the values from the original dataset since it provided such a large sample. Each simulated woman is provided with a set of three values corresponding to each of the three variables, by selecting a case from the original data set, at random. It is noted, however, that in the future it may be worth considering developing a multivariate distribution from which to sample the three variables since their behaviour does not rule out a normality assumption, (see discussion above).

When a woman is called for screening, her individual probability of attendance, π, is calculated such that, as above,

$$\pi\left(\underline{X},\underline{\beta}\right) = \frac{exp\left(\beta_1 + \beta_2 X_1 + \beta_3 X_2 + \beta_4 X_3\right)}{1 + exp\left(\beta_1 + \beta_2 X_1 + \beta_3 X_2 + \beta_4 X_3\right)}.$$

where the β_i's (for $i = 1, 2, 3, 4$) take the values given in Table 6.9. If a random number between zero and one is greater than this calculated π then the woman will not attend this particular screening session, and if it is less than or equal to π then they will attend.

6.6.2 Baker and Atherill's Compliance Model Data

Baker and Atherill's Compliance Model generates probabilities of attendance based upon previous attendance, with previous attendance weighted geometrically so that the most recent attendance/non attendance has the most influence, (Baker and Atherill, 2002). Extra weight is assigned to the first attendance/non attendance, and the age of the woman invited for breast screening is also taken into account.

The equation and further information about Baker and Atherill's Compliance Model can be found in Chapter 4 and Section 4.3. The approach is based upon observations of attendance patterns at breast screening in Manchester, and the variable values from the equation were estimated by the authors using maximum likelihood. These values are given in Table 4.1 (in Section 4.3), and it is these values and the equation described in the same Section, that are used within the breast cancer simulation model.

6.7 Model Verification

It is important that any simulation code is adequately verified in order to ensure that the code accurately represents the conceptual design of the simulation. The following methods were employed in order to ensure that the model code for the simulation reported within this thesis was reliable and valid.

Major class modules to the simulation were first built as standalone modules outside of the main simulation. This was done in Visual Basic for Applications for MS Excel, and inputs, relevant workings, and outputs were fed to worksheets to enable visibility of processes within the code. Sampled values were also recorded in order to compare with the expected distributions. This was done for each of the growth pattern assumptions in the model, as well as for the equation and TPB behaviour models, cancer onset, mortality, survival from breast cancer, and tumour detection.

A combination of interactive debugging (stopping the code when specific routines are called or values change, and setting values to force an event), and running the code under simplified conditions (for example with only a few individuals, or iterations, and/or forcing all women to attend screening), helped to ensure that the code modules interacted well with one another and that events were being scheduled and managed as they should be.

Tracing was performed throughout the build of the simulation, and several times before the results were run. This involved stepping through the code one step at a time, and noting down values assigned to ensure consistency within the code. In this way, once complete, it was possible to follow' individual women (entities) through the simulation over time, and ensure that they were screened, self detected, and died at the appropriately sampled times, and that the tumour grew at appropriate rates. Although the individual pieces of code had been verified as above, this tracing helped ensure that the code worked as a package and that consistency was maintained. This was carried out at least once for each of the growth patterns and behaviour options within the model in turn, as well as once for each of the screening programmes investigated, (under exponential growth and local percentage attendance assumptions).

6.8 Model Validation

> "Validation is the process of determining whether a simulation model is an accurate representation of the system, for the particular objectives of the study"
>
> Law and McComas (2001)

It was important that not only did the code that made up the simulation model accurately represent the models concepts, but also that the concepts themselves were fit for modelling the different breast cancer screening strategies considered within this study.

Sargent (1991) discuss two aspects of model validity, conceptual model validation, and operational validity. The following two sections discuss each of these validation concepts in relation to the discrete event simulation described in this thesis.

6.8.1 Conceptual Model Validity

Conceptual model validity refers to the face validity of the models theories and assumptions. In this case, does the simulation model described in this thesis simulate the effects of screening mammography in the UK accurately enough such that the effects of different behavioural assumptions within the model may be compared? It is hoped that the answer to this question is "yes", and we now describe how this was achieved.

The modelled theory of the natural history of breast cancer was put together after substantial consideration of the literature pertaining on breast cancer simulation models (see Chapter 4 for details), and the structure of this simulation model is comparable to many of the simulations, and current theories of breast cancer development. While the natural history of breast cancer is not modelled at its most detailed level (for example no explicit account is taken of tumour grade or stage, rather tumour size governs prognosis within the model) it was felt that making such simplifications did not have a detrimental impact upon the aim of the modelling work which was to explore the effects of different behavioural modelling, upon the simulation outcomes.

Since the literature revealed that there was no consensus as to the pattern of tumour growth, four of the most prevalent widely used patterns of tumour growth were included within the analysis for comparison. This decision was made as it was not clear what effect making assumptions of tumour growth pattern may have upon the outcome of the behaviour analysis, and it was felt important to ensure that no single

assumption of tumour growth was made that could lead to skewed or misleading results.

The theory of planned behaviour (TPB) was chosen as the psychological theory to include in the simulation model. This decision was again taken on the basis of a literature review of predictive behavioural theories regarding health behaviours (see Chapter 2). The TPB was found to be a popular model, and was also regarded as more formally structured therefore lending itself more easily to being tested, measured, and modelled.

In addition to consulting the literature, experts in the field were contacted and their opinions sought regarding both the natural history of breast cancer and how this is approximated within the model, and also the choice of psychological model and the method(s) by which behaviour should be modelled within the simulation.

6.8.2 Operational Validity

Operational validity refers to whether or not the outputs of a simulation model are accurate enough for the purpose of the analysis. The most appropriate method by which to ensure the breast cancer simulation model produced appropriate results appeared to be to compare the outcomes of the simulation with observations under the UK national screening policy.

6.8.3 Age of presentation

The Cancer Research UK website documented the number of newly diagnosed cases (and rates) of breast cancer by age group within the UK during 2002, (Cancer Research UK, b). At this time the UK screening policy was to screen women from age 50 every 3 years up until age 64, and in 2002 a 75% attendance rate at invited screens was achieved. Therefore the simulation model was run, for each of the growth and behaviour modelling assumptions in turn, with a screening policy of starting to screen at age 51 and ending invitations at age 63, with invitations every 3 years within this period. 5 iterations of the simulation were completed under each setting, each time simulating 1000 women over 100 years, with detailed results collected. The results were then used to generate samples of simulated individuals who had their breast cancer detected either via mammography screening or by self detection, and the age at which they were detected. This led to a sample of well over 900 cases for each simulation setting. The empirical distribution function of this age at detection was then compared to the cumulative distribution function of the distribution of new cases diagnosed in the UK during 2002.

Figures 6.17 and 6.18 demonstrate the results from this analysis, and show that the simulated distributions of the age of detection of breast cancer follow the observed spread of ages very well. No formal tests have been carried out to assess whether or not the simulated age of detection distributions follow the same distribution as observed in 2002 since a hypothesis test would assume that the two scenarios are the same, however in this case we are simulating rather than replicating a system and so this assumption may not be valid (Law and McComas, 2001).

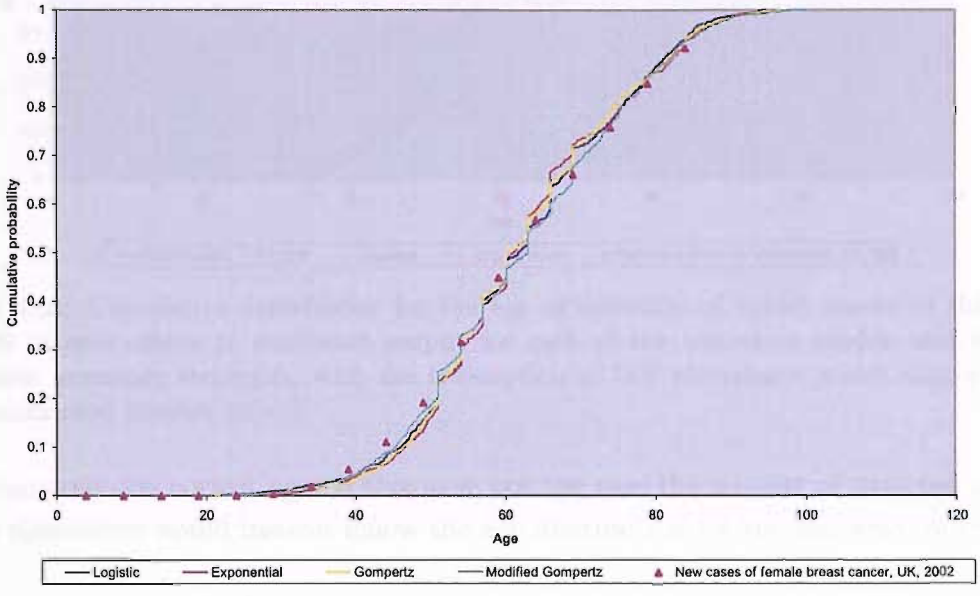


Figure 6.17: Cumulative distribution for age of breast cancer detection in the UK in 2002 in comparison with simulation age of detection under each of the tumour growth assumptions and equivalent screening strategy, with assumed local' 75% attendance.

It can be seen that the simulated age of breast cancer detections followed a similar distribution to that observed in the UK in 2002. Noticeable jumps in the probabilities are apparent at the screening ages for the simulated output, but not from the national dataset. This is due to the simulation modelling inviting all individuals for screening at the same age, whereas in practise the UK breast screening rounds invite women by area in 3 year cycles so not all women will attend screening at the same ages.

Figures 6.17 and 6.18 help to validate a number of the simulation model assumptions. Firstly, the age of onset of breast cancer was back-calculated from a sampled age of breast cancer detection. This sample came from the same age dataset, however, the figures for rates per population of breast cancer incidence versus age were used to calculate the distribution. Therefore, the result that the distribution of the absolute numbers of new cases of breast cancer in 2002 matches the age distribution of detected cancers in the simulations helps to validate that not only are breast cancers simulated to reach a detectable size at an appropriate age, but that they are then detected at the appropriate age, and in addition to this, that death occurs at

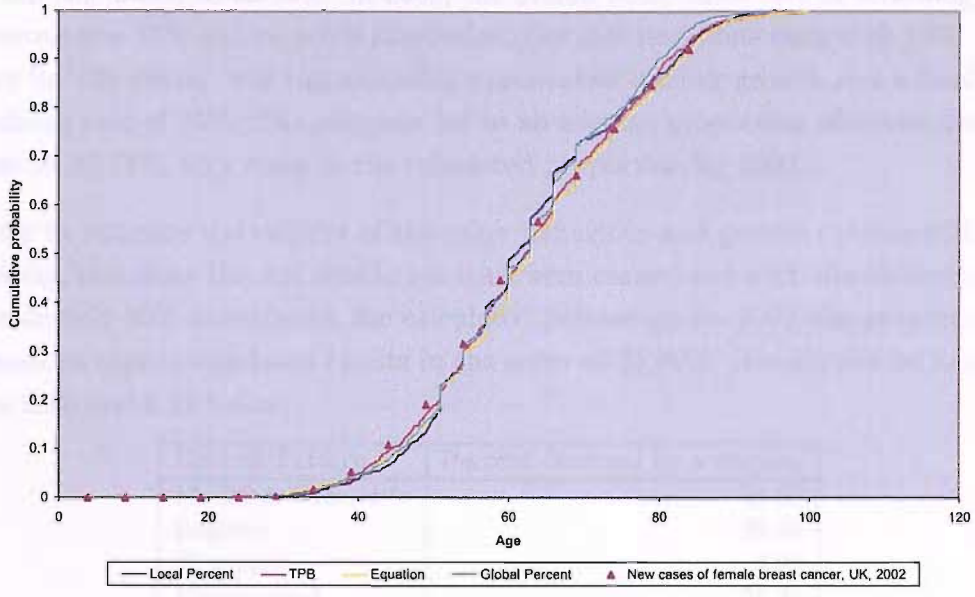


Figure 6.18: Cumulative distribution for the age of detection of breast cancer in the UK in 2002 in comparison to simulated output for each of the behaviour models and under equivalent screening strategies, with the assumption of 75% attendance where appropriate and exponential tumour growth.

approximately the correct age. If this were not the case the number of detected cases in the simulation would instead follow the age distribution for the incidence rates.

6.8.4 Proportion of screen-detected cancers

At the end of the financial year, an audit of the UK breast screening programme is carried out, and key results from the year published in bulletins for each Country. Among the results published are the number of breast cancers that were detected by the mammography rounds within the period. The 2002-03 bulletin for England report gave a breakdown, by age group, of all screen detected cancers during the year, (Programme, 2004). These figures included non invasive tumours, so to provide an estimate of the number of invasive tumours detected it was assumed that 20% of detected tumours were non-invasive as supported by the literature, (Sloane Project, 2002). From this it was possible to calculate the approximate proportion of newly detected breast cancers that were detected via the breast cancer screening programme in 2002, and compare this with the percent detected by screening output from the simulation model when run with screening policy to start at age 51 every 3 years until age 63.

The results from the full model runs (300 iterations, 1000 women, 100 years) were used as comparisons to allow for convergence of the outputs. The proportion of all reported screen detected breast cancers by the breast screening programme in 2002

was then calculated as 22.96%. In 2002, the overall acceptance rate of screening invitations was 75% and so a full simulation, (for 300 iterations each with 1000 women for 100 years), was run assuming exponential tumour growth and a local attendance rate of 75%. The outcome led to an average proportion of screen detected cancers of 22.73%, very close to the calculated proportion for 2002.

In order to estimate the validity of the other behaviour and growth options within the model, and since the full simulation runs were carried out with the assumption of approximately 85% attendance, the calculated percentage for 2002 was proportionally increased to expect simulated results in the order of 25.90%. Results can be found in Tables 6.10 and 6.11 below.

Growth Pattern	Percent detected by screening
Modified Gompertz	20.39
Logistic	29.93
Gompertz	9.20
Exponential	25.26

Table 6.10: Percent detected by screening for each growth model under the assumption of local percentage attendance at 75%, (estimated from runs using 85% local attendance)

Behaviour Model	Percent detected by screening
Equation	20.78021323
Local	25.26140433
Global	23.9442253
TPB	25.06105864

Table 6.11: Percent detected by screening for each behaviour model under the assumption of exponential growth

As can be seen in Tables 6.10 and 6.11, with the exception of Gompertzian growth assumptions, all other results indicate that between 20% and 30% of cancers that were detected in the simulation runs were detected by screening. This falls in line with the expected 25%, therefore adding confidence that the modelling assumptions are suitable, with the possible exception of the assumptions surrounding Gompertzian growth (see the results in Chapter 7 for a discussion).

6.9 Experimental Set-Up

Due to the stochastic nature of the simulation, each iteration of the model will produce very slightly different results, with the variation in summary statistics and confidence intervals reducing as the number of women simulated in the iteration increases. A choice therefore existed as to whether to fix the number of women simulated, or the number of iterations, and then optimise the other such that the results of the simulation converged. It was decided to fix the number of women who are simulated during each iteration at 1,000 women. This choice was made on the

basis of computing power and simulation run time. As the number of women simulated increases, the simulation takes longer to run due to the increase in complexity and array sizes required. However, as some of the model parameters are read in from input files at the start of each iteration, this also takes time. Having experimented with the model, it appeared that simulating 1,000 women was best to satisfy this speed trade off.

To insure that enough iterations of the model were run such that the results were reliable, an experiment was run for 1,000 iterations under exponential growth assumptions with a 75% local attendance rate at screening which was conducted from age 51 to 69 every 3 years. The outputs of these iterations were then analysed to find the number of iterations required for convergence using the confidence interval method as described in Robinson (2004). This method involved calculating the mean of the outputs up to the current iteration, and the confidence interval for this mean (using the student t distribution). The point at which the deviation of the confidence interval from the mean reaches an acceptable level provides the number of iterations required for the modelling purposes. In this case there are 18 outputs from the simulation model (see Chapter 5), and as pointed out in Law and Kelton (1991), the Bonferroni inequality demonstrates that if a significance level (α) of 5% (i.e. 95% confidence interval) is used to calculate confidence intervals for 20 outputs, then the probability of all the intervals containing their means is 0. Therefore, the 5% significance level was divided by 18 before use in the interval calculations such that

$$\alpha = \frac{0.05}{n} \tag{6.10}$$

where n is the number of outputs, in this case 18 ($n = 18$, $\alpha = 0.05/18 = 0.0028$). A percentage deviation from the mean of 5% was considered sufficiently small, and Figure 6.19 shows how the deviations reduced for the output variables as the number of iterations increased.

As can be seen from Figure 6.19, by 250 iterations, all of the output variables' confidence intervals were below 5% deviation from their means. The output variable seen to be the last to converge to this level was that for the number of life-years saved by the screening policy. This is logical since the output depends on many other outputs, and therefore has greater variance than the others (for example it requires screen-detection to have taken place, together with early detection to have delayed death from breast cancer beyond the time of natural death for the individual).

On the basis of these results, it was decided that 300 iterations would be sufficient as a default number with which to run the results. Once the result runs were completed, the analysis was repeated with the outputs from all the simulation runs with screening from 51 to 69 years every 3 years, to check that suitable output convergence had

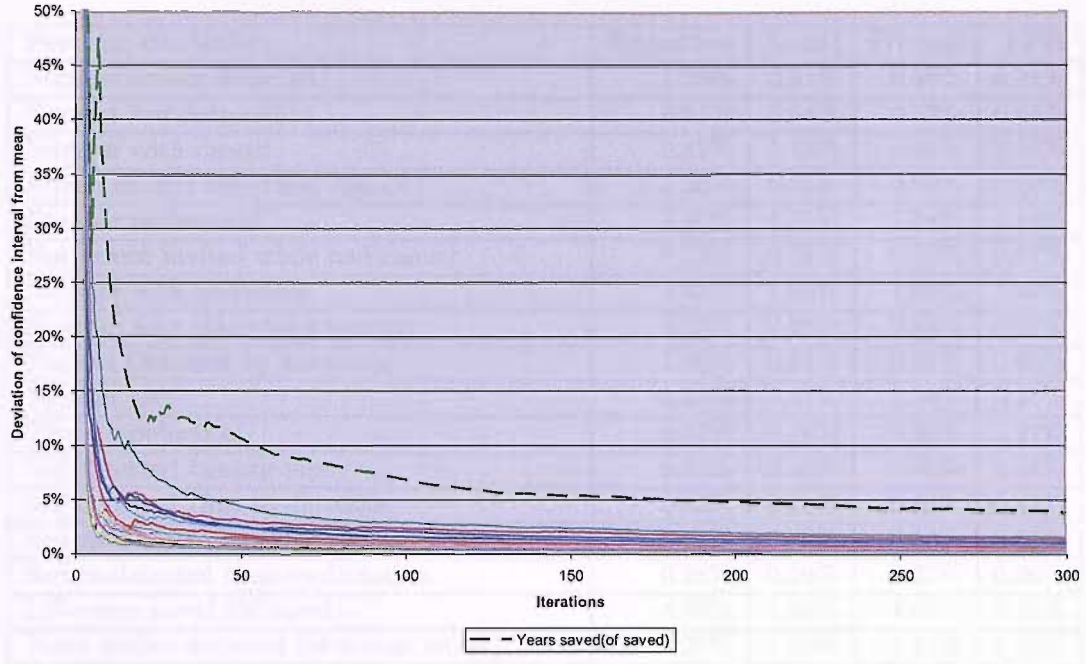


Figure 6.19: Means confidence intervals deviation from the mean with the number of iterations

indeed taken place. Tables 6.12 and 6.13 display the resulting percent deviation of the confidence intervals from their mean outputs after the 300 iterations in each case.

As Tables 6.12 and 6.12 show, in the vast majority of cases, the percent deviation from their means of the confidence interval for the outputs (over the 300 iterations) remains at less than 5%, and in all cases is less than 7%. These results helped to provide reassurance to the author that the mean results used for the analysis of the different scenario results reported in this thesis, had converged to an acceptable level for the desired purpose.

Percent deviation	Equation	Local	Global	TPB
Number screen-detected	1.05%	0.91%	0.98%	0.94%
Number self detected	0.51%	0.54%	0.52%	0.54%
Number with cancer	0.17%	0.18%	0.19%	0.18%
Screen invited while had cancer	0.56%	0.51%	0.50%	0.50%
Number undetected	1.30%	1.35%	1.34%	1.18%
Not screen invited while had cancer	0.73%	0.73%	0.75%	0.67%
Number with no cancer	1.48%	1.55%	1.66%	1.52%
Number who attended screening	0.35%	0.26%	0.34%	0.27%
Percent Detected by screening	1.00%	0.85%	0.91%	0.90%
Tumour size	0.43%	0.47%	0.48%	0.47%
Time-to-detection	0.37%	0.36%	0.36%	0.37%
Self detected tumour size	0.39%	0.38%	0.41%	0.44%
Self detected time-to-detection	0.43%	0.41%	0.43%	0.42%
Screen-detected tumour size	0.45%	0.48%	0.53%	0.51%
Screen-detected time-to-detection	0.28%	0.29%	0.27%	0.26%
Life-years saved (of saved)	4.63%	3.86%	4.07%	4.12%
Years earlier detected (of screen found)	1.31%	1.09%	1.17%	1.16%
Average number of attendances (of attended)	0.36%	0.23%	0.26%	0.28%

Table 6.12: Percent deviations of the confidence intervals from their mean outputs after 300 iterations for each behaviour model simulation (exponential growth, screening 51-69 every 3 years).

Percent deviation	Mod Gompertz	Logistic	Gomp-ertz	Expon-ential
Number screen-detected	1.10%	0.82%	1.71%	0.91%
Number self detected	0.51%	0.58%	0.40%	0.54%
Number with cancer	0.26%	0.17%	0.30%	0.18%
Screen invited while had cancer	0.63%	0.46%	0.68%	0.51%
Number undetected	1.61%	1.34%	2.79%	1.35%
Not screen invited while had cancer	0.73%	0.71%	0.63%	0.73%
Number with no cancer	1.24%	1.61%	1.02%	1.55%
Number who attended screening	0.29%	0.28%	0.28%	0.26%
Percent detected by screening	1.05%	0.75%	1.65%	0.85%
Tumour size	0.49%	0.47%	0.37%	0.47%
Time-to-detection	0.37%	0.39%	0.52%	0.36%
Self detected tumour size	0.41%	0.41%	0.36%	0.38%
Self detected time-to-detection	0.38%	0.51%	0.52%	0.41%
Screen-detected tumour size	0.46%	0.49%	0.49%	0.48%
Screen-detected time-to-detection	0.30%	0.31%	0.35%	0.29%
Life-years saved (of saved)	4.59%	4.05%	6.24%	3.86%
Years earlier detected (of screen found)	1.17%	1.03%	2.36%	1.09%
Average number of attendances (of attended)	0.28%	0.28%	0.26%	0.23%

Table 6.13: Percent deviations of the confidence intervals from their mean outputs after 300 iterations for each growth model simulation (local attendance, screening 51-69 every 3 years).

Chapter 7

Results

7.1 Introduction

This Chapter aims to describe the effects and differences brought about by using each of the available behavioural options within the model. It will also explain the differences observed in the simulation results by using each of the four tumour growth patterns.

For each of the tumour growth options (Gompertz, Exponential, Logistic, and Modified Gompertz) and behavioural options (Theory of Planned behaviour - TPB, Local and global percentage, and Baker and Atherill's equation model) outlined previously, a full simulation (1000 women simulated over 100 years for 300 iterations) has been run once for each of four different screening policies. The idea was to compare any differences that may exist between the modelling options that may affect the effects brought about by screening more often, or for longer, than current policy dictates.

The next Section describes the experimental design used to create the results reported in this Chapter, and this is followed in Section 7.3 by the results comparing each of the four tumour growth patterns over the different screening strategies. Section 7.4 then demonstrates the effects of the four different modelling approaches to attendance behaviour that are available within the simulation, and goes on to focus upon the sensitivities of the Theory of Planned Behaviour variable inputs on the results of simulation runs using this theory. Finally, Section 7.6 reports results from experiments to find approximate increases in the UK populations TPB constructs that would bring about the same increase in attendance and screening benefits as lowering the current age of first screen to age 45.

7.2 Experimental Design

7.2.1 Mammography screening scenarios

The discrete event simulation model of breast cancer and screening for breast cancer allows the user to choose the age at which mammography population screening should be simulated to begin and end, as well as the frequency of the screening intervals within these years. It was infeasible to run all possible combinations of start, end, and interval ages for screening, and therefore, a few carefully selected screening scenarios were chosen as these represented realistic extensions to the current mammography screening programme in the UK.

The current UK policy is to screen women from around age 50 until approximately age 70 at 3 year intervals. Since the simulation model invites women for screening at exactly the same age (unlike the reality of the UK Breast Cancer Screening Programme-UKBCSP), this scenario was converted to a policy of screening between the ages of 51 and 69, every 3 years. This is then used as the baseline simulation screening scenario to which all other screening policies are compared.

Until 2002 the UK Breast screening programme only screened up to age 64 as standard, and therefore a natural choice of screening scenario was to reduce the upper age of screening. The second scenario considered in this Chapter was therefore screening from 51 to 63 every 3 years, in order to compare the simulated improvement in results from extended screening.

It was also of interest to investigate the effects of screening more frequently than every 3 years, and so two more screening scenarios take the start and end ages for screening in the above screening scenarios, but instead of screening every 3 years, simulate screening every 2 years. These scenarios will help to compare the difference between adding screening at a later age (as the UKBCSP have chosen to do) or screening more frequently, and/or both together.

As well as increasing the maximum age of screening, the last scenario lowers the standard age for inviting women to be screened to 45. Here, women are invited to screening every 3 years from age 45 until age 69. This last scenario will aid the trade-off between altering the current UK national screening policy by either inviting younger women for screening or by decreasing the screening interval of those currently invited to 2 years rather than 3.

Table 7.1 summarises the five screening scenarios considered in this Chapter.

Scenario	Start Age	End Age	Frequency
1	51	69	3 years
2	51	63	3 years
3	51	69	2 years
4	51	63	2 years
5	45	69	3 years

Table 7.1: Start and end ages and interval frequency of screening invitations for each screening scenario

7.2.2 Tumour Growth and Attendance Behaviour Options

The aim of the experimentation was to assess the differences in model output under different behavioural and cancer growth assumptions. A baseline setting of local attendance and exponential tumour growth pattern was chosen. These two options were considered appropriate markers for comparison, since they have been observed as popular assumptions when modelling the natural history of breast cancer and tumour screening interventions (see Chapter 4). The percentage attendance chosen for the baseline local (and global) percentage attendance was set at 84.664% since this falls in line with the average attendance rate brought about by the model's interpretation of the Theory of Planned Behaviour (TPB).

The effects of varying the behavioural and tumour growth assumptions within the simulation model were then modelled by selecting each option in turn and evaluating each screening scenario, comparing results with one another. For consistency, when measuring the effect of the behavioural assumptions within the simulation, the baseline assumption of exponential tumour growth was chosen, and when considering the different growth patterns, the baseline assumption of local attendance was chosen.

For each of the 7 resulting combinations of attendance and tumour growth options, the model was run 5 times, once for each of the screening scenarios discussed in Section 7.2.1 above. Every simulation was run for 100 years, with 1000 women and repeated for 300 iterations.

Results of the attendance behaviour assumptions can be found in Section 7.4, and growth patterns in Section 7.3.

7.2.3 Output statistics

The results presented in this Chapter and in Appendixes C and D are, for each output, the average of the results over the 300 iterations run within each simulation. Standard deviations of the 300 values for each output were also calculated in order to derive confidence intervals for the means. To reduce error upon comparisons, the significance level α used to derive the confidence interval (using the student t

distribution), was divided by the total number of outputs to be compared (18 outputs, for five screening scenarios, and each of 4 either tumour growth or behavioural assumptions led to a result of 360). A 90% confidence interval was constructed such that

$$Interval = \bar{x} \pm t_{n-1,1-\alpha}\frac{\sigma}{\sqrt{n}}$$

where α was the significance level such that $\alpha = 0.05/360$, $n = 300$ was the number of iterations the average was taken over, and σ the standard deviation of the selected output.

7.3 Tumour Growth Assumptions

The following discussion summarises the effects of varying the assumed pattern of tumour growth within the simulation model. For full results and statistics the reader is referred to Appendix D. Four patterns of tumour growth are considered, labelled exponential, logistic, Gompertz, and modified Gompertz (or mod Gompertz for short) respectively. For details as to the nature of each growth pattern and how the parameters were assigned, please refer to Chapter 6.

7.3.1 Numbers of cancers detected

The aim of any national screening programme is to detect the disease at an earlier stage than it would have naturally presented, and to do so consistently. Therefore, both the number and proportion of screen-detected cancers found in each simulations were of particular interest.

Figure 7.1 shows the average number of screen-detected cancers found from each simulation run, along with their 90% confidence intervals. Figure 7.2 shows the percentage of detected cancers that were screen-detected under each screening scenario and tumour growth pattern. The results show that the least number of screen-detected cancers occurred when the simulations were screening from age 51-63 every 3 years. This was the old UK national policy, and the result was expected as this scenario covers the least range of ages, providing less opportunity to detect the cancer. Screening the same age ranges every 2 years can, however, be seen to significantly increase the number of screen-detected cancers.

It appears that the current UK policy may do better still though, as the simulated number of screen-detected cancers increases further under the scenario where screening starts at age 51 and continues every 3 years until age 69 (akin to the current UK practice). This result is statistically significantly higher than the numbers

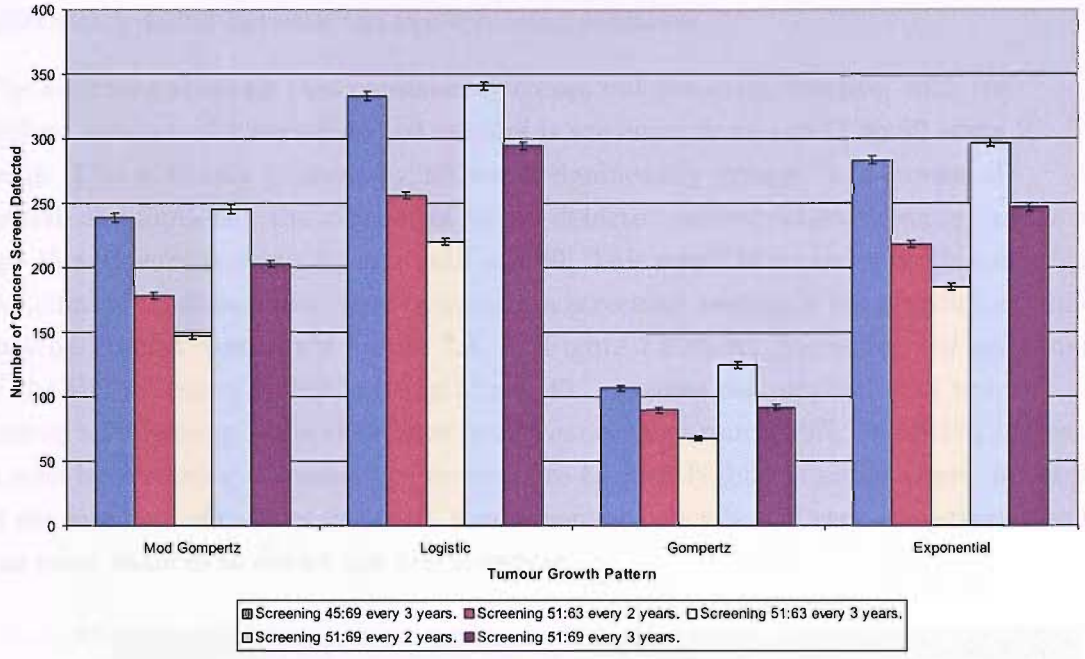


Figure 7.1: The number of screen-detected breast cancers under different screening scenarios and tumour growth assumptions

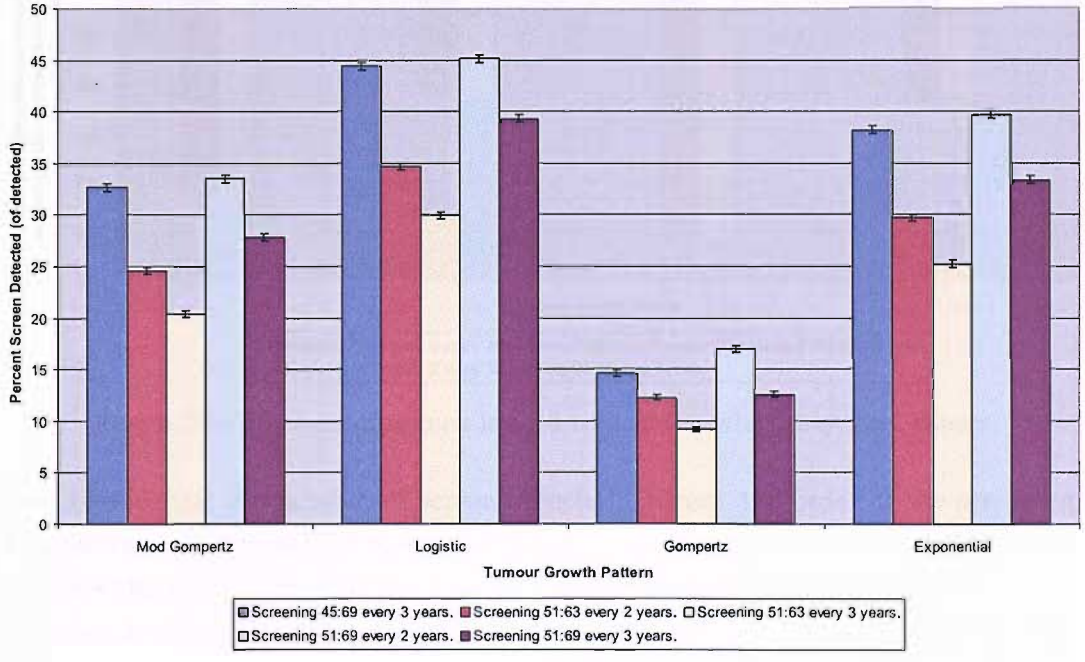


Figure 7.2: Percent of detected tumours that were detected by mammography screening under different screening scenarios and tumour growth assumptions

simulated when screening within ages 51 to 63 every 2 years for all tumour growth options bar the Gompertzian pattern of tumour growth, where no significant difference is found between the two screening scenarios.

The screening strategy that consistently comes out the most effective, with the highest number of screen-detected cancers is screening from age 51 to 69 every 2 years. This is closely followed by, although significantly greater than (under all growth assumptions), the number of screen-detected cancers when screening begins at age 45 and screens every 3 years until age 69. This result is echoed when considering the number of women who were invited to a screening session in the simulation while they had breast cancer, see Figure 7.3. As Figure 7.3 shows, increasing the age range of the UK screening policy to begin at age 45, increases the proportion of women invited to screening while they have breast cancer by around 15%. A smaller increase is seen by screening the same age range more frequently, but as noted above, in terms of the numbers of cancers detected, this screening policy is still very competative as it has more chances to detect the breast cancer.

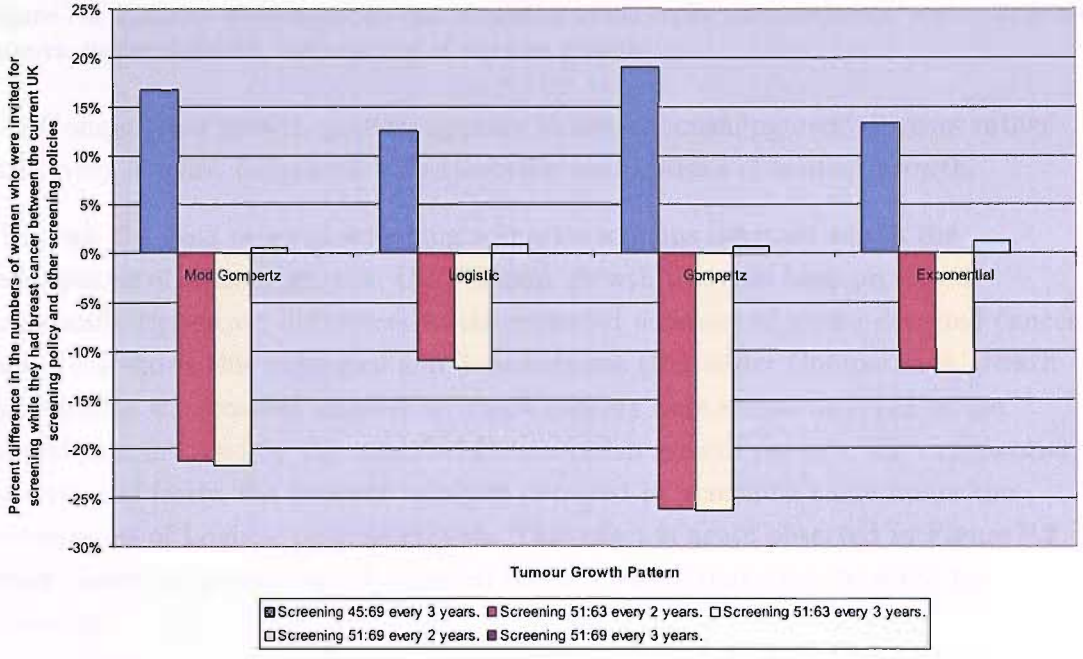


Figure 7.3: Numbers of women invited to a screen while they have cancer

When considering the number of screen-detected cancers, the order of the screening scenarios remains constant across the different assumptions of tumour growth. Figure 7.4 shows the percentage difference in the number of screen-detected cancers simulated in comparison to the current UK policy screening scenario (51-69 every 3 years). This Figure demonstrates that the proportional changes in the number of screen-detected cancers remains comparatively stable across the different tumour growth assumptions, with the possible exception of the Gompertzian growth pattern.

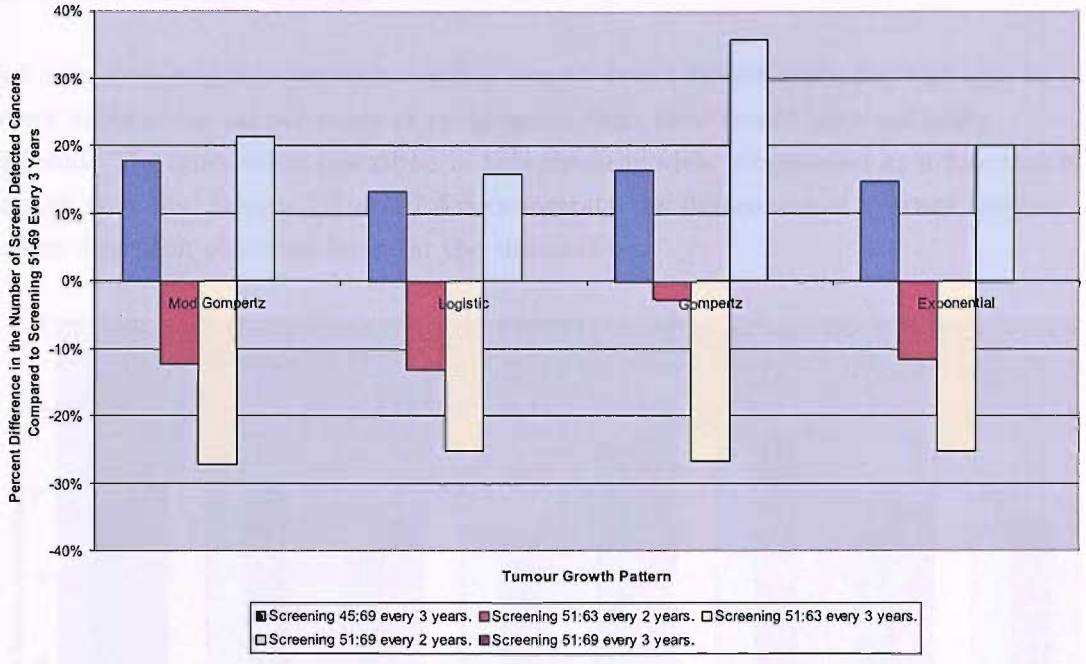


Figure 7.4: Relative difference between screening scenarios for the numbers of screen-detected cancers, under different assumptions of tumour growth

The Gompertzian growth pattern appears to favour screening every 2 years rather than every 3 years, compared with the other assumptions of tumour growth.

Although the rank order of screening scenarios remains constant across the assumptions of tumour growth, the different growth patterns have produced statistically significant differences in the expected numbers of screen-detected cancers. Figure 7.1 shows this difference and demonstrates that under Gompertzian growth assumptions the smallest number of breast cancers were screen-detected in the simulations, followed by the modified Gompertzian growth pattern, the exponential pattern, and lastly, the greatest numbers detected by screening came under the assumptions of Logistic tumour growth. This effect is again observed in Figure 7.2 which shows the percentage of detected breast cancers that were detected by screening.

As discussed in Chapter 6, the approximate percentage of screen-detected cancers in the UK in 2002, (screening from age 50 to 64 every 3 years), was around 23%. The results for the percent screen-detected when screening between ages 51 and 63 every 3 years found that screen-detected cancers accounted for around 9%, 20%, 25%, and 30% of all detected cancers given Gompertzian, modified Gompertzian, exponential, and logistic growth assumptions respectively. Therefore, it may be that the assumptions made surrounding Gompertzian growth are questionable.

7.3.2 Detection statistics

Not only does mammography screening aim to detect breast tumours, but also to detect them at an earlier stage of progression than they would have naturally surfaced. The simulation described in this thesis models progression as a function of tumour size, and figures 7.5 and 7.6 demonstrate the differences of average tumour size at detection observed between the simulations.

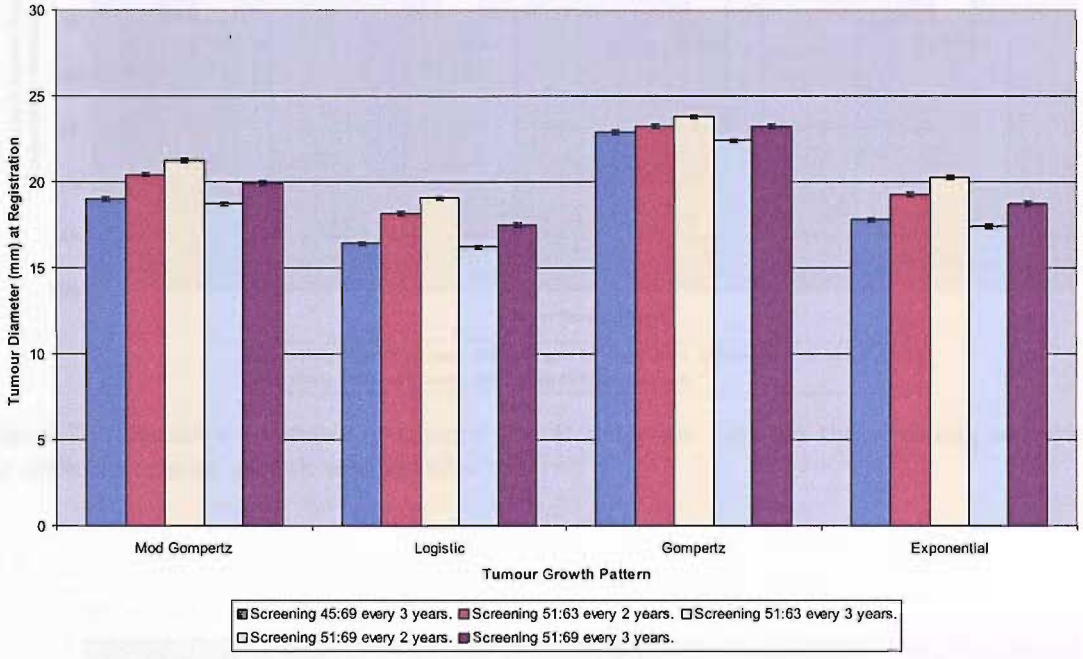


Figure 7.5: Average tumour diameters (mm) at detection under different screening and tumour growth assumptions

Figures 7.5 and 7.7 reveal that, as could be expected as screening is increased (either in frequency or in length of years screened) the average size of all detected tumours is decreased. This is due to an increase in the numbers of tumours detected by screening, as reported above, and screening detecting smaller tumours than those that arose naturally.

With the exception of the Gompertzian assumptions of tumour growth, all differences in screening scenario produced statistically significant differences within the tumour diameters at detection. Figure 7.7 provides a picture as to the degree of this difference relative to the screening scenario corresponding to the present UK policy.

The results indicate that the change in UK policy to screen up to age 70 rather than age 64 reduces the average tumour diameter more than decreasing the screening interval from two to three years within the previous age range (50-63), (with the exception of the Gompertzian growth model results which showed no significant difference between the two scenarios). These results are in line with results by Boer

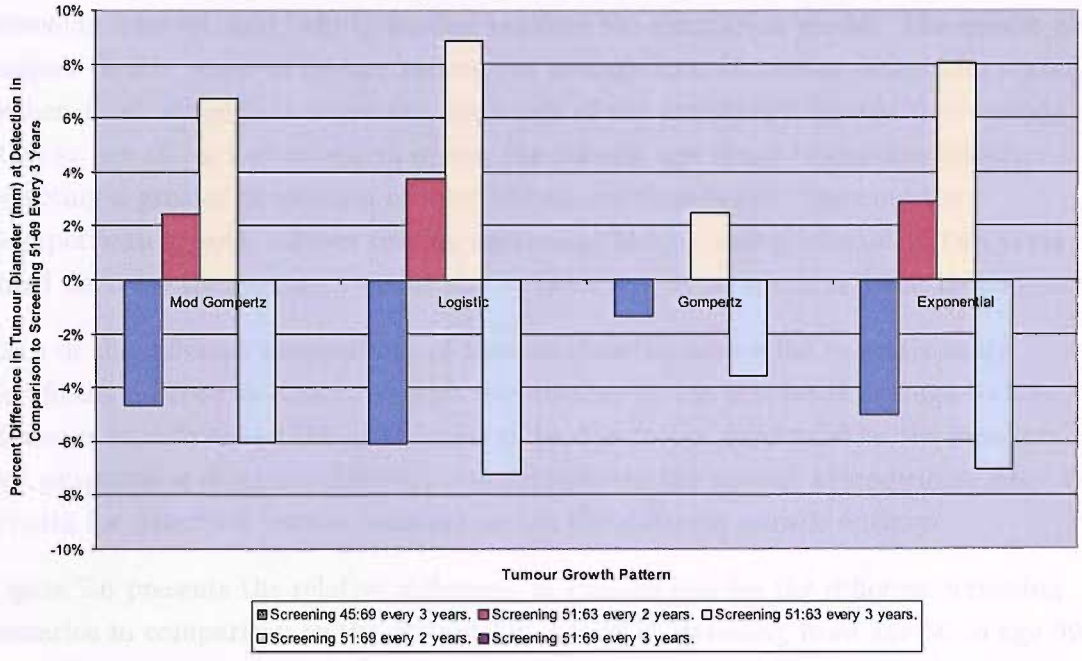


Figure 7.6: Relative difference of tumour size at detection between the screening scenarios for different tumour growth assumptions

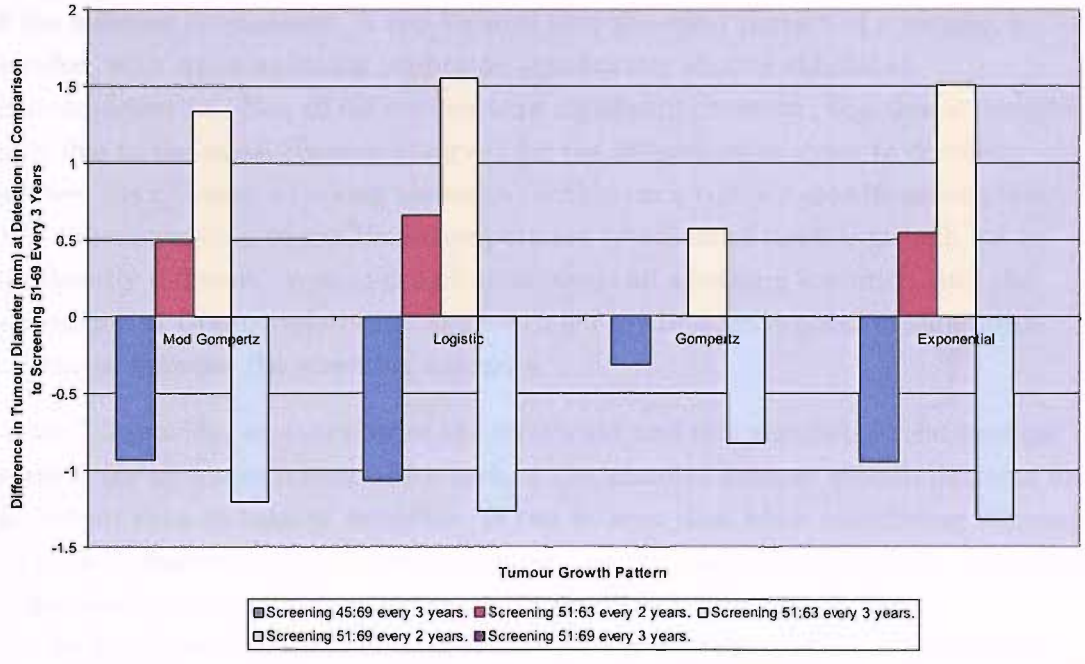


Figure 7.7: Difference in tumour diameter (mm) at detection between screening scenarios for different tumour growth assumptions

et al. (1998), whose simulation analysis recommended that the UK's old policy be extended by increasing the maximum age of screening rather then decreasing the screening interval, and help to further validate the simulation model. The results also suggest that in order to further reduce the average tumour size at detection, it would be beneficial either to increase the age range of the population invited to screening to start at age 45, or better still to screen the current age range biennially, therefore detecting a greater proportion of interval cancers than before. Ignoring the Gompertzian growth pattern results, decreasing the screening interval to two years could decrease the average tumour size at detection by as much as 1mm in diameter.

Each of the different assumptions of tumour growth pattern led to statistically significant differences compared with one another in the simulated average tumour diameter at detection. This is believed to be due to the differences in the numbers and proportions of screen-detected cancers between the growth assumptions, since the criteria for detection remain constant across the different growth options.

Figure 7.6 presents the relative difference in tumour size for the different screening scenarios in comparison to the current UK policy of screening from age 50 to age 69. It can be seen that, with the exception of Gompertzian growth assumptions, the degree of tumour diameter change remains approximately constant across the remaining three tumour growth patterns considered.

A further factor that influences the probability of tumour progression is the age of the breast tumour before diagnosis. Figure 7.8 demonstrates the results found in each of the different simulations. It can be seen that the same pattern of screening is revealed, with more screening leading to significantly shorter simulated times-to-detection. Not all differences were significant, however, and this is thought to be due to the small changes observed for the differences in times to discovery between the different screening scenarios (within each tumour growth assumption). Only the assumption of modified Gompertzian (stochastic) tumour growth led to significantly different times-to-detection between all screening scenarios, and the assumption of Gompertzian tumour growth led to the least number of significant differences between the screening scenarios.

Figure 7.9 provides an overview of the significant and non significant relationships between the screening scenarios for each of the assumed tumour growth patterns for the output time to tumour detection. It can be seen that when considering reducing the time-to-discovery of the average tumour, in three out of the four cases according to the simulation model, it would make no significant difference to the time-to-detection if the screening policy in the UK was changed to screening fewer age groups but more often (51 to 63 years biennially). There was also a non significant difference found (again in three of the four growth assumptions) between screening the current age groups more frequently (51 to 69 biennially) and increasing

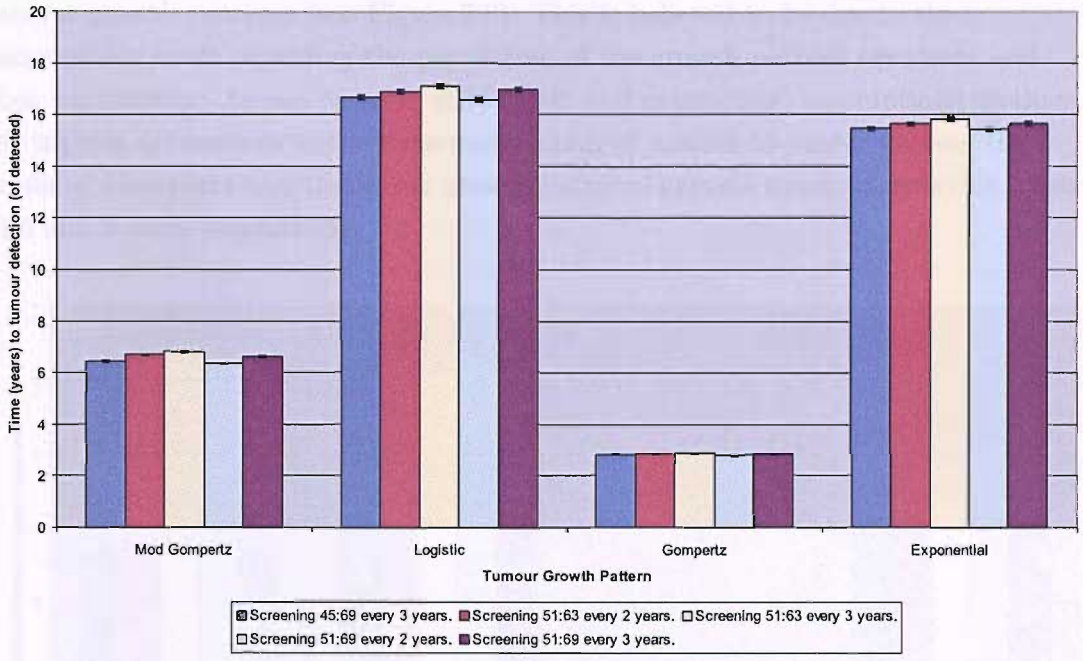


Figure 7.8: Average time until tumour detection (for all detected tumours) by tumour growth option and screening scenario.

Time to tumour discovery	Mod. Gompertz					Logistic					Gompertz					Exponential				
	51:63 every 3 years.	51:69 every 3 years.	45:69 every 3 years.	51:63 every 2 years.	51:69 every 2 years.	51:63 every 3 years.	51:69 every 3 years.	45:69 every 3 years.	51:63 every 2 years.	51:69 every 2 years.	51:63 every 3 years.	51:69 every 3 years.	45:69 every 3 years.	51:63 every 2 years.	51:69 every 2 years.	51:63 every 3 years.	51:69 every 3 years.	45:69 every 3 years.	51:63 every 2 years.	51:69 every 2 years.
Screening 51:63 every 3 years.							X					X		X						
Screening 51:69 every 3 years.						X			X		X		X	X					X	
Screening 45:69 every 3 years.										X		X		X	X					X
Screening 51:63 every 2 years.							X				X	X	X		X		X			
Screening 51:69 every 2 years.								X					X					X		

Figure 7.9: Significant findings between screening scenarios for the time to tumour detection (X = non significance)

the age range of screening down to a start age of 45 (45 to 69 triennially).

While the results did not always indicate significant differences for time-to-detection within the growth patterns, a significant difference can be clearly seen between the tumour growth patterns (see Figure 7.8). This is believed to be due to the assumptions made regarding the populating of the growth pattern equations and their parameters. As can be seen, the logistic and exponential assumptions produce the highest estimations of the time-to-detection of around 16 years, whereas the modified Gompertz and Gompertz growth patterns provide times-to-detection closer to 6 and 3 years respectively.

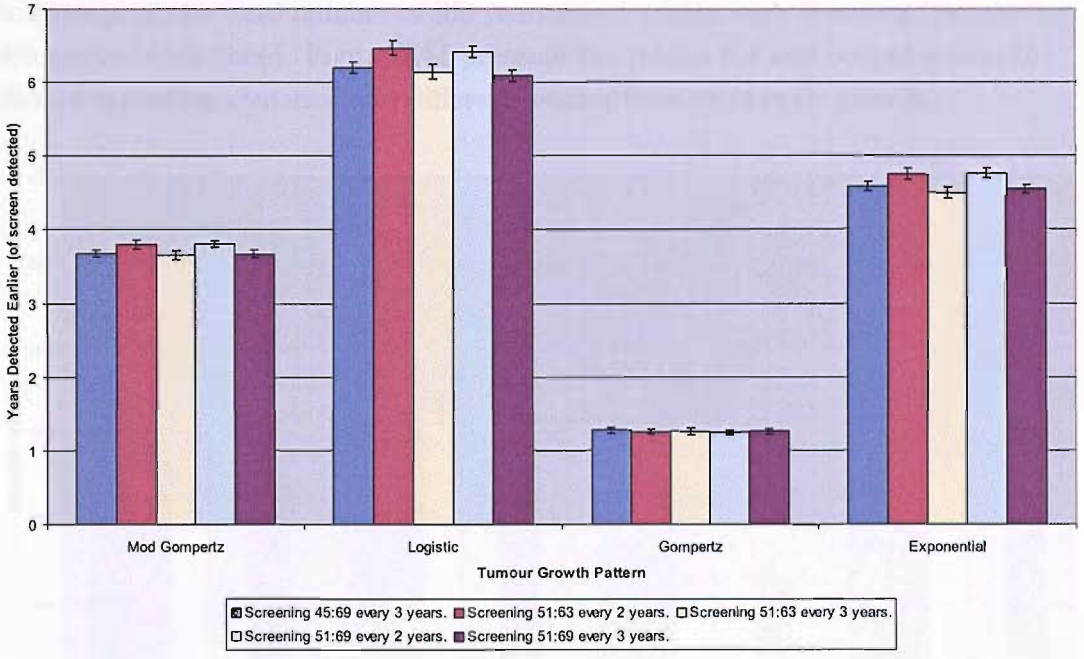


Figure 7.10: Years earlier screen-detected tumours are detected relative to unscreened detection, by screening scenario and tumour growth pattern

When considering only screen-detected tumours, it can be seen (Figure 7.10) that the simulations suggest screen-detected tumours are detected between 1 and 6 years earlier than they would have arisen naturally, depending on the assumption of tumour growth used within the model. In line with the time-to-discovery, the least benefit of screening is brought about by the Gompertzian pattern of tumour growth, and the largest benefit by the logistic pattern.

However, in contrast to the results of the average time to tumour detection, here a tumour is detected sooner than it would have otherwise have been if screening was more frequent (i.e. every two years rather than every three years). This makes sense as biennial screening has the potential to find the tumours that are screen-detected one year earlier than triennial screening. The biennial screening scenarios produce significantly higher results than the triennial screening scenarios in all cases, (for the

average years a screen-detected tumour is detected earlier than if screening had not taken place), with the exception of those within the Gompertz tumour growth pattern.

7.3.3 Life years saved

The ultimate aim of screening for breast cancer is to reduce breast cancer related mortality. If a screening policy does not save lives then it could be argued that it is not effective as it may simply increase the number of years a patient is aware of the disease and the time undergoing treatment. One output of the simulation model is the average of the total number of life-years saved within each iteration (simulating 1000 women each time). Figure 7.11 presents the results for this output across the different screening scenarios and different assumptions of tumour growth.

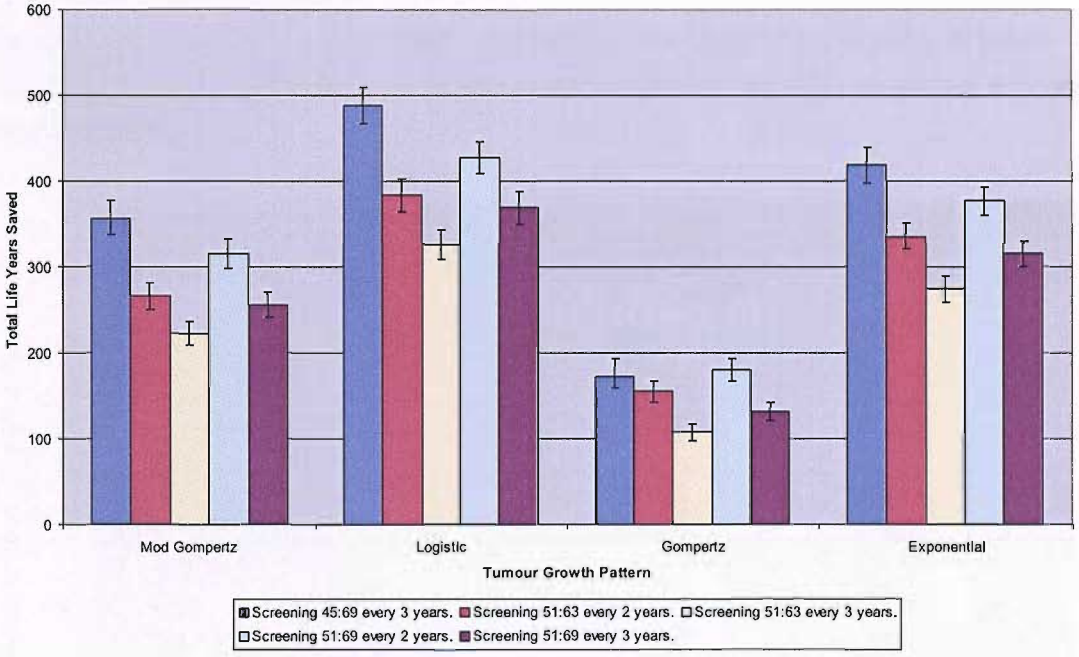


Figure 7.11: Average of the total number of life-years saved by each screening scenario by assumption of tumour growth pattern (per 1,000 women)

It can be seen in Figure 7.11 that in all cases but the Gompertzian assumption of tumour growth, screening a larger age range produced the highest numbers of lives saved (screening 45 to 69 triennially). The number of life-years saved by this screening scenario produced significantly higher results than screening from age 51 to 69 every 2 years in all cases except the Gompertzian assumption of tumour growth. Although the number of tumours detected was lower when extending the age group of screening, than screening more frequently, (since the additional tumours that are detected are in younger women), this leads to more life-years saved when a life is

saved in the simulation.

Screening from age 51 to age 69 every two years rather than every 3 years (as the current UK policy) produces the second highest number of life-years saved, with significantly higher results in all but the Gompertzian tumour growth screening scenarios. Figure 7.12 indicates that if the UK policy were extended to screen from age 45, then the number of life-years saved in the UK could be increased by around 30%. Alternatively, screening the same age groups, but every two years rather than three years could increase the number of life-years saved by around 20%. This is an important finding, and cost not withstanding, if the aim of the UK screening policy is to save lives then it may well be worth decreasing the screening interval to two years, or to lower the age for the first invited screen to age 45. In order to understand the full cost-benefit (both in terms of the increase in costs due to the extra number of mammograms required, and the increase in treatment and overdiagnosis) a full cost model would be required.

The previous UK policy (up to 2002) of screening from age 51 to 63 every 3 years consistently led to significantly fewer life-years saved than all other screening scenario policies analysed.

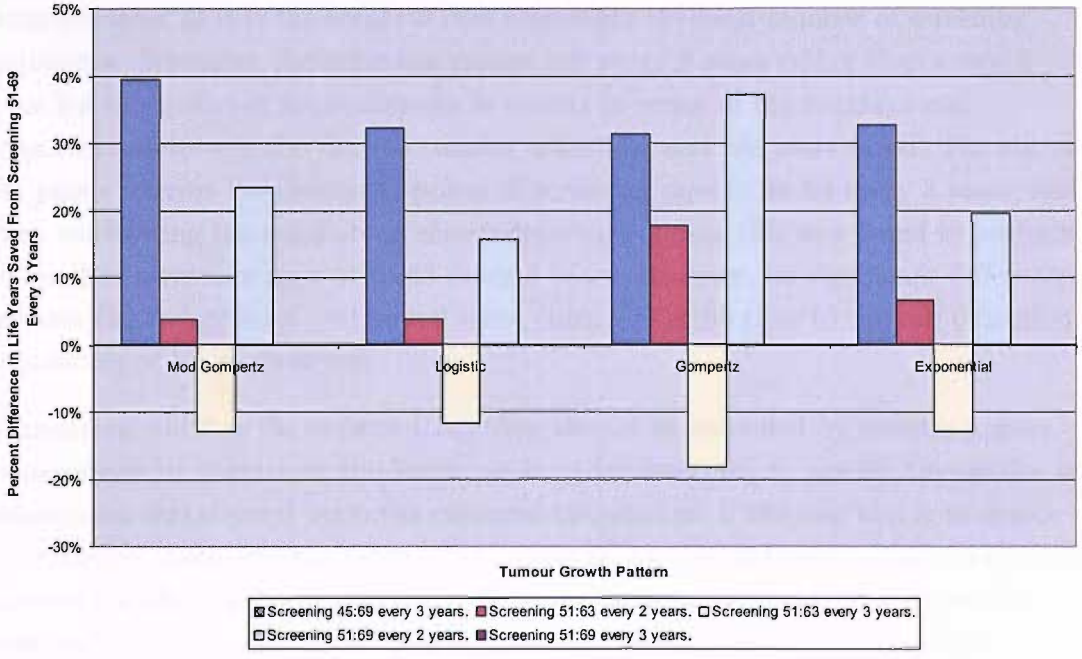


Figure 7.12: Relative change in life-years saved in comparison to the current UK policy, by tumour growth pattern

From Figure 7.11 it can be seen that a significant difference is obtained between life-years saved across the different assumptions of tumour growth. This result could be very important if decisions regarding strategy that takes account of cost per life years saved are made upon the basis of a simulation model. The logistic and

exponential tumour growth patterns provide the most optimistic estimate of the numbers of life-years that screening strategies may save (per 1000 women with breast cancer), while the assumption of Gompertzian growth produces the most pessimistic results. However, it can be seen from Figure 7.12 that the relative change in simulated life-years saved remains fairly constant across tumour growth assumptions, with the possible exception of Gompertzian growth which can be seen to favour the biennial screening scenarios.

7.3.4 Summary of the screening scenario results and the effect of different assumptions of tumour growth

The results presented so far in this Chapter have compared the effects of different assumptions of tumour growth within the simulation model across five different screening scenarios. This Section summarises the findings so far by first discussing the overall ranking of screening scenario by outcome, followed by the differences brought about by different assumptions of tumour growth.

The screening scenario which consistently led to the least desirable results across all simulation outputs was that of screening from age 51 to 63 every 3 years. This result is unsurprising as it is the scenario that represents the least number of screening invitations. Screening the same age ranges but every 2 years rather than every 3 years led to significant improvements in results in terms of the numbers and proportions detected, the time to tumour detection, and life-years saved. The current UK policy mirrors the simulated policy of screening ages 51 to 69 every 3 years, and when considering the numbers of screen-detected cancers, this was found to perform better than screening ages 51 to 63 every 3 years. However, no significant differences between the two policies were found when considering the time to tumour detection, or numbers of life-years saved.

Considering whether the current UK policy should be extended by screening more frequently or by decreasing the lower age limit for screening to age 45, the results are inconclusive and depend upon the outcome in question. If the sole aim is to detect more cancers, then screening every 2 years would be the preferred option (and would increase the life-years saved by 20%). However, if the objective is to increase the years earlier that tumours are detected than they would naturally occur, or to increase the total number of life-years saved (by 30%), then the choice of screening from age 45 to 69 but every 3 years would be preferred.

Overall, the choice of tumour growth model made little difference to the *relative* increase or decrease in output brought about by each different screening scenario. However, the assumptions surrounding the Gompertzian model of tumour growth displayed less significant differences between screening scenarios and demonstrated a

bias toward biennial screening in comparison to the other assumptions of tumour growth. This bias and difference in results is thought to be due to the very short doubling times assumed within the growth pattern, since the tumour grows very quickly and so there is less time to detect it by screening and thus biennial screening will be more likely to detect more cancers in comparison to triennial screening.

The different assumptions of tumour growth did however, interestingly, lead to significantly different actual (as opposed to relative) outcomes. The most desirable outcomes were modelled using the logistic pattern of tumour growth followed by the exponential, modified Gompertzian, and lastly the least desirable outcomes overall were associated with simulations run using the Gompertzian pattern of tumour growth. Of particular note is the large difference brought about by the different assumptions of tumour growth upon the simulated numbers of life years saved. This result is of particular importance since decisions with regard to screening strategies are often made upon the cost per life years saved, and even though cost is not included in this model it is not unreasonable to assume that a difference in the numbers of life years saved may also lead to a difference in cost per life years saved. The observed difference in absolute results across assumption of tumour growth is important, and helps to demonstrate that when simulating breast cancer (or indeed any cancer) screening policies in this way, it is best to compare relative rather than absolute outcomes between different screening scenarios even if the baseline model validates well.

7.4 Attendance Behaviour Modelling

Four options are provided within the simulation model for the approximation of attendance behaviour at invited screening sessions. These behavioural options are, local and global percentage attendance, the Theory of Planned Behaviour (TPB) and Baker and Averills' attendance equation (abbreviated to 'equation' from now on). Each method of approximating attendance was described in detail in Chapter 5.

This Section outlines the results of using each of the four behavioural models in turn to approximate attendance at invited mammography screening sessions, and compares and contrasts the differences produced between the methods. The same five screening scenarios are considered as used to compare assumptions of tumour growth, and these were outlined in Section 7.2.1. In all cases an assumption of exponential tumour growth has been made, and where appropriate the percentage attendance set to 84.66%. The results presented are a summary of the full results, and for detailed results over all scenarios and outputs the reader is referred to Appendix C.

7.4.1 Number of cancers detected

The primary aim of screening for a disease is to diagnose the disease at an earlier time in the natural history of the disease, and to do so for a large enough proportion of the screened population that the costs and efforts involved in the process are outweighed by the gain in reducing the severity of the disease burden.

One measure of effectiveness of a screening policy for breast cancer is therefore the number (and proportion) of screen-detected cancers over the life of the policy. This Section first of all discusses the differences in the numbers and proportions of screen-detected cancers brought about by the different screening policies, before reviewing how these differences are affected by the different methods for modelling attendance at the breast screening clinics.

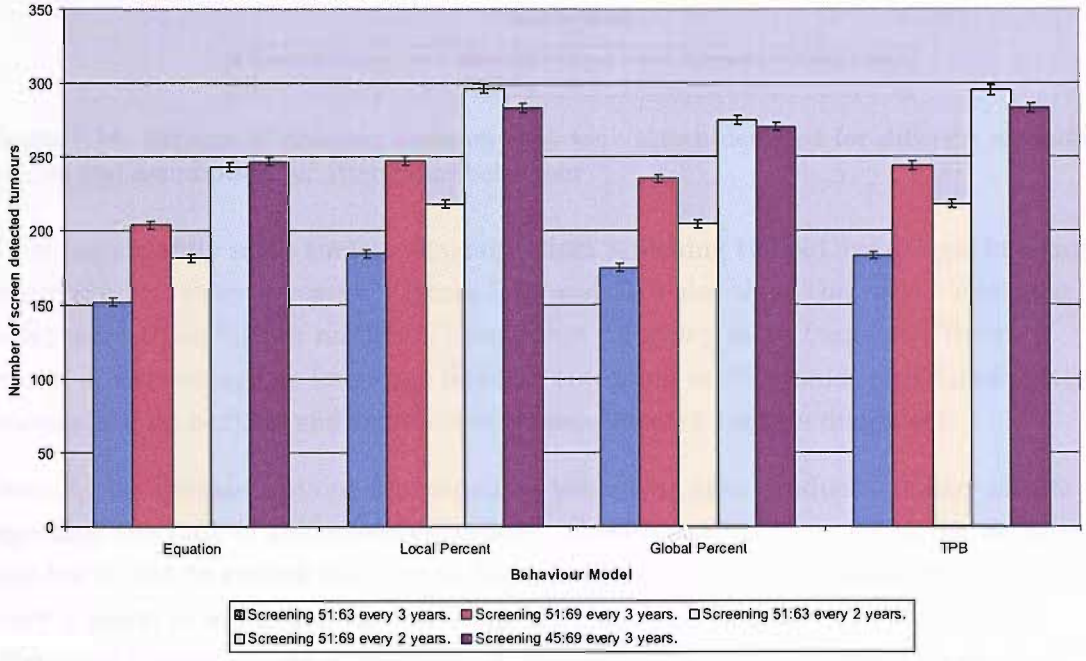


Figure 7.13: Average number of screen-detected tumours for different screening scenarios and assumptions of attendance behaviour

Figures 7.13 and 7.14 demonstrate the average numbers and proportions of screen-detected cancers (and their 90% confidence intervals) for each of the screening scenarios, and over each of the four assumptions of attendance behaviour. It can be seen that, in all cases, the lowest number and proportions of screen-detected cancers from the simulation are brought about by screening from age 51 until age 63, every 3 years. This was the screening scenario designed to match the previous UK national screening policy, and the results indicate that a significant increase in numbers and proportions of breast cancers detected should have been achieved by increasing the upper age limit of screening to 70 (and under these modelling conditions this brings

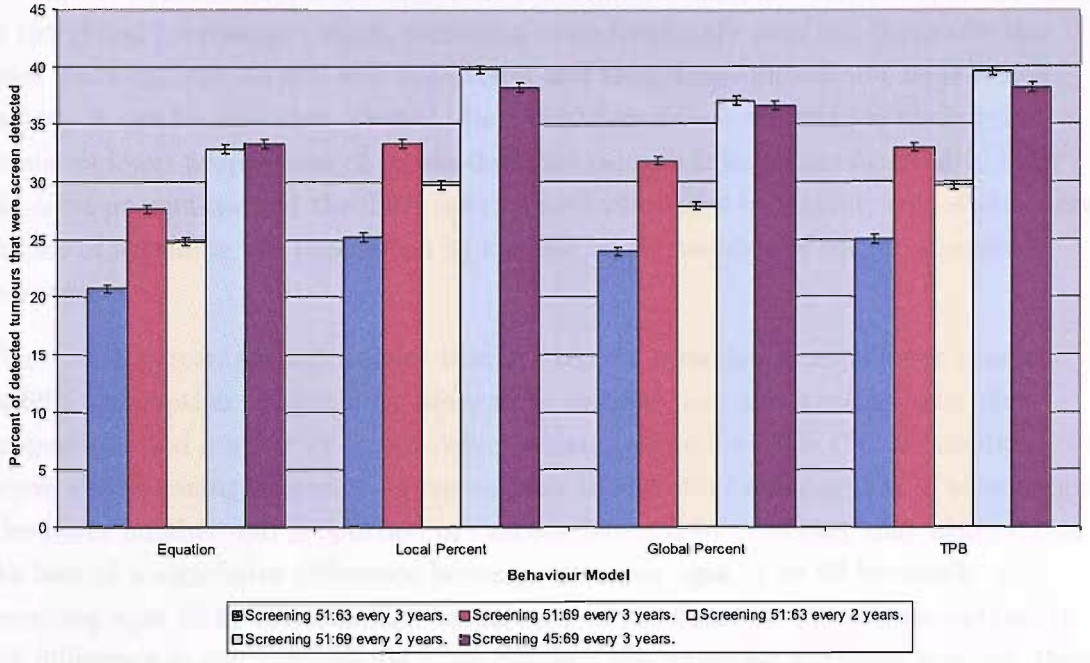


Figure 7.14: Percent of detected tumours that were screen-detected for different screening policies and assumptions of attendance behaviour

about significantly more tumour diagnosis than screening the old age groups but more frequently, i.e. every 2 years). Figures 7.13 and 7.14 also show that if the screening policy were to be further modified, then either screening more frequently (every 2 years), or decreasing the lower age limit for screening to 45, would both significantly increase the proportion and numbers of screen-detected cancers diagnosed.

Overall, the different options for modelling behaviour have produced similar results regarding the rank of the screening policies. However, when it comes to the decision whether or not to extend the current UK screening policy by screening the same ages every 2 years, or extending the lower age limit for screening down to 45 from 50, differences appear. These differences can be seen in Figure 7.14, which shows that when using the equation method to predict attendance, or when using the global percentage attendance option, no significant differences are apparent between the two screening scenarios (when considering the output of the numbers of breast cancers diagnosed by screening). However, if the simulation is run using either the local percentage or the TPB assumptions of attendance behaviour then the favoured policy to increase the proportion of screen-detected cancers is to screen the same age group as at present (51:69) but more frequently (biennially). This result is not entirely unexpected since both local percent and the TPB modelling methods lead to individual probabilities of attendance at each invitation.

When considering the global percentage option in the model however, the logic for this option dictates that although the same percentage of individuals will attend each

screen, the subset who attend each time will remain constant. Therefore, in the case of the global percentage option, screening more frequently may not be as effective since some individuals will still not attend and their tumours will not be detected. Indeed, it can be seen that, overall, the global percentage attendance assumption produces lower proportions of screen-detected cancers than those observed in both the local percentage and the TPB options for attendance behaviour, who stand more chance of screening the population as a whole as the number of invited screens increases.

The overall percentage attendance that the equation model infers is lower than the 84.66% assumption produced by other three options, and this explains why the proportions and number of screen-detected cancers are lower for this assumption across the screening scenarios, in comparison to the other assumptions of attendance. The lower number and proportion of cancers detected by screening may also explain the lack of a significant difference between screening ages 51 to 69 biennially and screening ages 45 to 69 triennially in the case of the equation attendance option. If the difference in the numbers detected between the screening scenarios is small, then a large sample would be required to produce significance, (and results from the other behavioural assumptions demonstrate that the difference may well be small), and since a lower proportion attend each screen under the equation option, a smaller sample of screen-detected cancers would be expected. The result is interesting, however, since the equation attendance behaviour option was derived from empirical data from a UK breast screening unit, it follows that the attendance proportion reflected should be realistic at least at the relevant local area level, and hence, there may be no difference between lowering the screening interval and decreasing the lower age limit for screening within the current UK policy unless a higher percentage attendance can be achieved.

7.4.2 Detection statistics

As well as detecting tumours via mammography screening, the aim of screening for breast cancer is also to detect these tumours at an earlier stage in their natural history than they would have been detected naturally, therefore potentially leading to more successful, less invasive treatment and fewer deaths from breast cancer.

This Section describes the differences between, and across, the different methods of attendance behaviour modelling considered, and the different screening scenarios, when considering the average tumour time-to-detection, the average number of years earlier screen-detected tumours were simulated to be detected than they would have naturally arisen, and the average size of a detected tumour at diagnosis.

Figure 7.15 demonstrates how the average tumour size, and confidence interval for

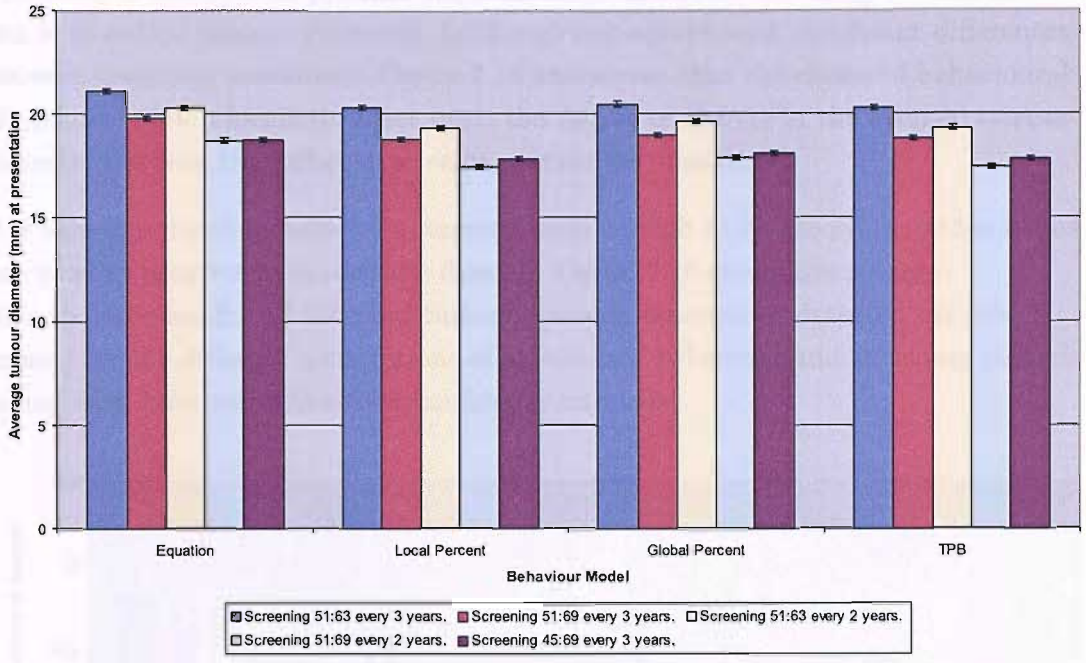


Figure 7.15: Average tumour diameter (mm) at presentation of all detected tumours, over screening scenario and behavioural attendance option

the average, changes with the different screening scenarios considered, and over the different options for attendance behaviour. It can be seen that, once again, the screening policy that leads to the largest tumour diameters on average is the old UK national policy of screening from age 51 to age 63 every 3 years. Increasing the upper limit for screening to 69 (as the UK has done) significantly reduces the size of the average tumour at presentation by around a millimetre in diameter. Reducing the size of tumour at diagnosis is beneficial since the size of tumour is one indication of the tumours progression through its natural life cycle (please refer to Chapter 6 for more detail).

Again, in all cases, the current UK policy leads to smaller tumours than the simulation predicts would have been the case had the UK kept the screening ages to between 51 and 63 but screened every two years rather than every three. However, as for the case of the number of tumours detected by screening, when it comes to assessing whether it would be best to extend the current UK policy by screening more frequently or by screening a larger age range, the difference in the diameter of the tumours at presentation is not always statistically significant. No significant difference is found between the two screening scenarios when the behavioural options of global percent, and the equation model are run. When the simulation is run using the TPB or local percent attendance, however, the results indicate that the preferred screening scenario in order to reduce the tumour size the most would be to decrease the current screening interval from three years to two.

The behavioural options produce the same ranking for the screening policies if the aim is to reduce tumour diameter, (although not always with significant differences between screening scenarios). Figure 7.15 also shows that the choice of behavioural attendance option has little effect upon the degree of change in the average tumour diameter between the different screening strategies considered.

It is also important to detect the tumour early enough in its life cycle so that it has less time to progress to metastatic disease. Figure 7.16 shows the average time-to-detection for all detected tumours (screen-detected or detected via other means) for the different assumptions of attendance behaviour and screening scenarios (along with their respective 90% confidence intervals).

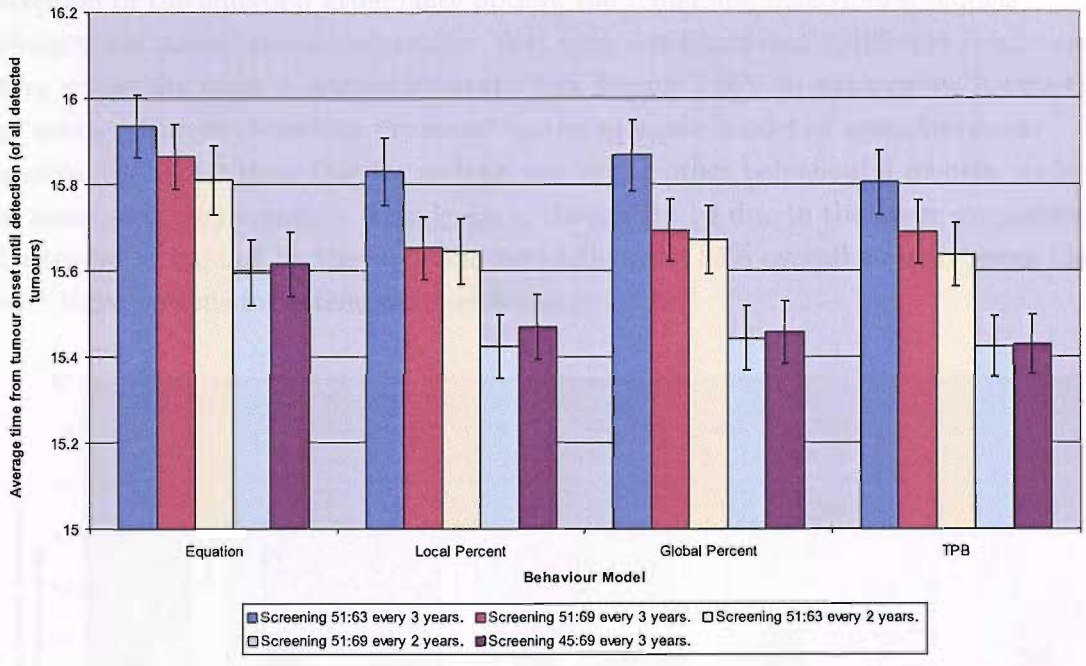


Figure 7.16: Average time (years) from tumour onset until detection by screening scenario and assumption of attendance behaviour

As can be seen from Figure 7.16, as the number of screens an individual is invited to increases, the average age of her tumour before detection is decreased. However, the difference in average time-to-detection brought about by screening policy is not always significant. Not surprisingly the policy that produced the longest average times-to-detection was screening from age 51 to age 63 every 3 years (the previous UK policy) but when using the equation and the TPB options for behavioural modelling, this policy did not produce significantly longer times-to-detection than increasing the upper age limit to 69 (as in the current policy). Here, across the behavioural options, no significant difference was found between the simulated times-to-detection of detected tumours when screening ages 51 to 69 every 3 years and screening ages 51 to 63 every 2 years. This result is in contrast to the findings

reported previously that in order to increase the number of screen-detected tumours it was better to screen up to age 69 every three years than to lower the maximum age limit to 63 but screen biennially rather than triennially.

The screening policies that produced the lowest times-to-detection (consistently across behavioural assumptions) were again, screening the current age ranges more frequently (51 to 69 every 2 years), and increasing the age range for screening (45 to 69 every 3 years), although no significant difference in average time-to-detection was found between the two screening strategies.

Although, as noted above, the choice of behavioural option did affect whether two of the screening scenarios produced different times-to-detection or not, with the exception of the equation attendance option, the remaining behavioural models produced estimated times-to-detection that were not significantly different from each other across the same screening strategies (see Figure 7.16). In some cases, however, the average time-to-detection produced by the equation model of attendance was significantly higher than that for at least one of the other behavioural models, under the same screening scenario. This is again thought to be due to the lower proportion of attendance implied by the equation model than the 85% overall assumed from the other three options for attendance behaviour.

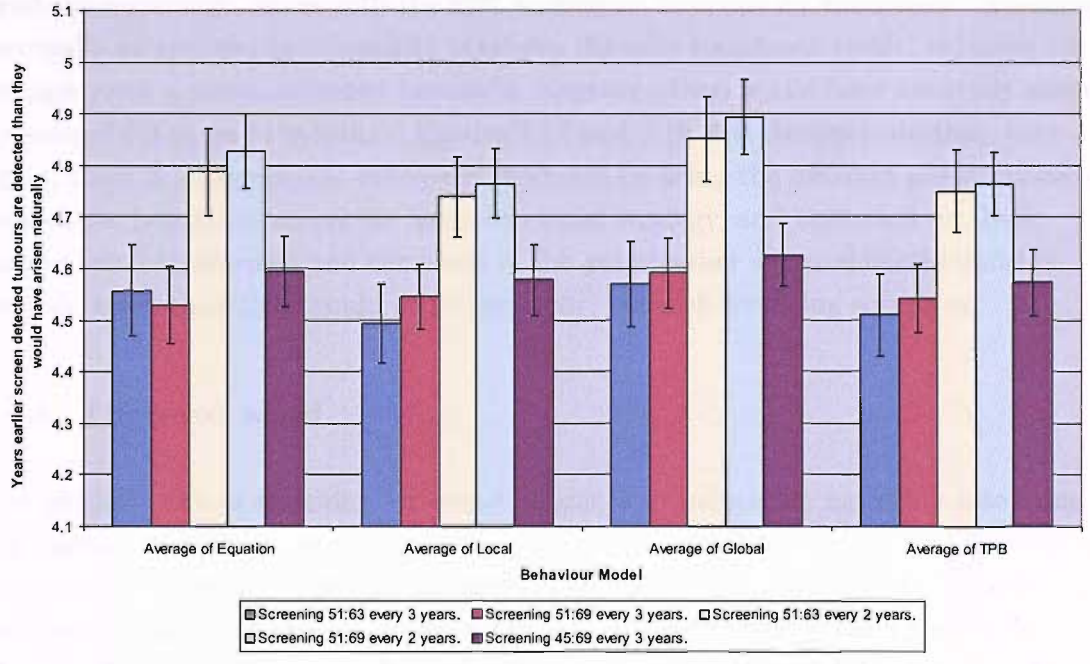


Figure 7.17: Average number of years earlier that a tumour was detected by screening than it would have presented otherwise, by screening scenario and assumption of attendance behaviour

Figure 7.17 shows the average number of years earlier that screen-detected tumours in the simulations were detected than they would have been detected naturally

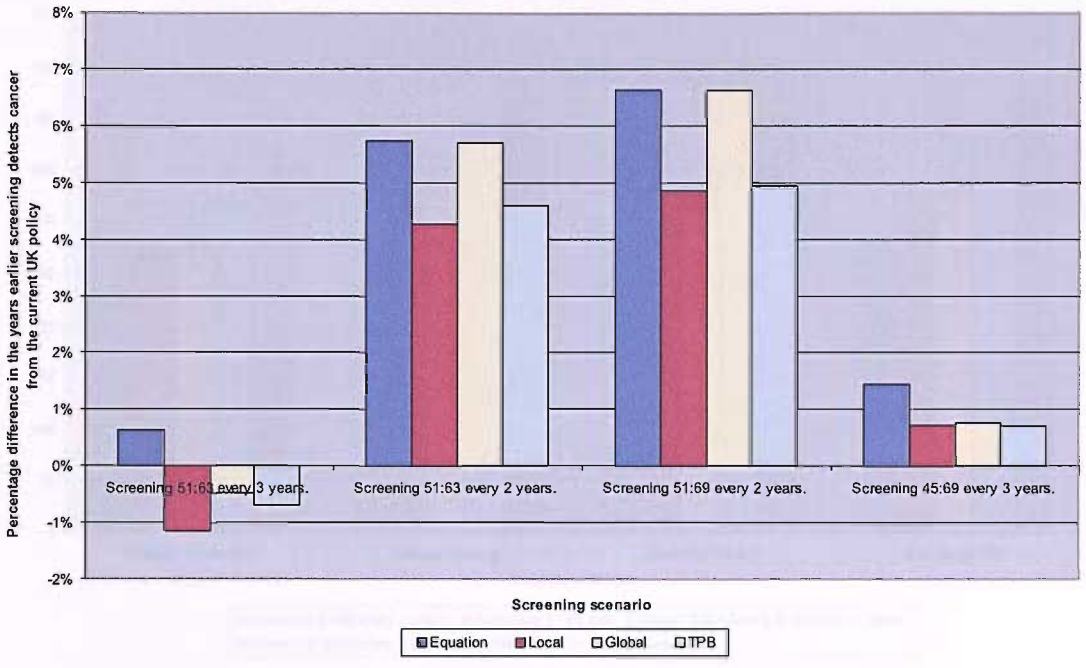


Figure 7.18: Relative increase and decrease in the average years earlier a tumour is detected by screening than would have naturally arisen, in comparison to the current UK policy, by attendance behaviour assumption and screening policy.

(without screening), along with the 90% confidence intervals for the means. Screening biennially as opposed to triennially produces the only significant result, reducing the average years a screen-detected tumour is diagnosed than would have naturally arisen by around 0.3 years (4 months). Figures 7.17 and 7.18 also demonstrate that, once again, there is no significant difference produced by using the different assumptions of attendance behaviour across the same screening strategy, and they each produce similar relative increases and decreases in the years earlier screen-detected cancers were detected than they would occur naturally, between screening scenarios.

7.4.3 Life years saved

The ultimate aim of screening for breast cancer is to reduce the mortality rate from the disease. A popular method of comparing different interventions in healthcare is to compare the difference in projected life-years saved by each intervention. This Section outlines the results of the simulation runs, across the different screening scenarios considered, and the four attendance behaviour options within the simulation, with regards to the estimated life-years saved in each run.

Figure 7.19 outlines the results for the change in life-years saved over the different screening scenarios considered within this thesis. It can be clearly seen that, so far as the assumptions made within this simulation model are concerned, the screening

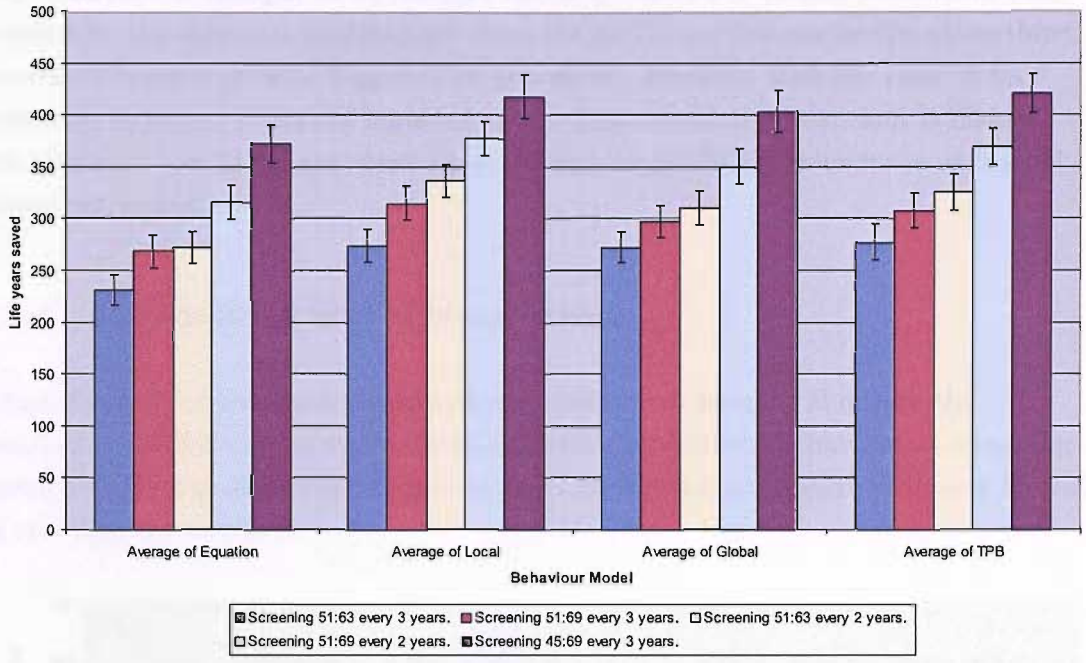


Figure 7.19: Average and 90% confidence intervals for the number of life-years saved over different screening scenarios and assumptions of attendance behaviour

scenario that would lead to the highest number of life-years saved is to screen from age 45 to age 69, every 3 years. This agrees with the findings across tumour growth assumptions (see Section 7.3) and would make sense since it is the only policy that screens from ages 45 to 50, and the younger the person is when a cancer is detected, the greater the potential number of life-years saved should the tumour be detected early enough to save a life.

The old UK national policy of screening from age 51 to 63 every 3 years can be seen to provide the lowest average number of life-years saved (although in two of the attendance behaviour assumptions, TPB and global percentage, the difference between this and the current policy of screening up to age 69 was insignificant). Interestingly, when considering the number of life-years saved, over all methods of attendance behaviour modelling, there was no significant difference found between screening from age 51 to 63 every 2 years, and the current UK national policy of screening from roughly age 51 to age 69, every 3 years.

As has been seen across all results in this Section, little variation exists across the different methods of modelling attendance behaviour at screening invitations, and Figure 7.19 also depicts that the local percentage, global percentage, and TPB options all produced results that were not significantly different from each other across the same screening scenarios. The equation option for modelling attendance behaviour produced lower estimates for the average number of life-years saved than did the other three methods, and some of these differences were significant. Again,

this difference is thought to be brought about by the lower overall attendance rate implied by the equation models logic than the 84.7% implied across the other three models of tumour growth. Figure 7.19 also shows, however, that the rank of the screening scenarios when the equation method of attendance behaviour is chosen, remains the same as for the other three options for modeling attendance at invited breast screening.

7.4.4 Attendance at invited breast screens

Since this part of the thesis deals with any differences brought about by the simulation models chosen approach to modelling attendance behaviour at screening invitations, it was also interesting to explore the attendance results produced by each of the different methods.

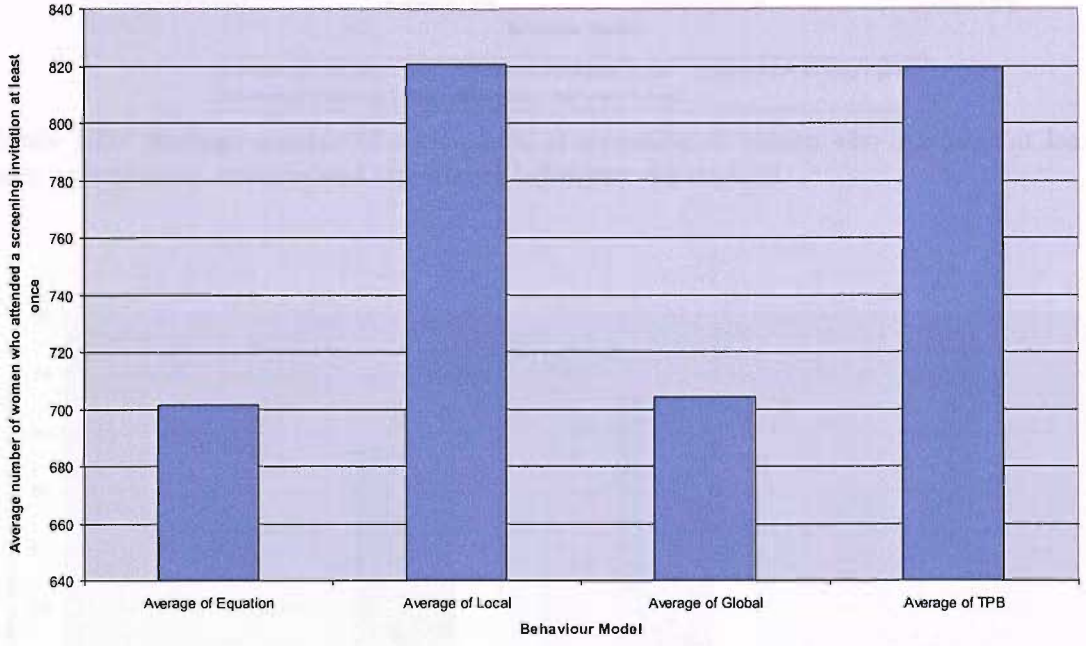


Figure 7.20: The average number of women, per 1,000, who attended screening at least once across all screening scenarios by attendance behaviour assumption

For each behaviour model, the number of women who attended at least once did not vary greatly according to the screening scenario. However, Figure 7.20 shows that there were significant differences brought about by the different behavioural assumptions. It can be seen that the TPB assumptions and local percentage attendance options produced very similar results regarding the numbers of women who attended the simulated screening units at least once during the iteration, whereas the numbers implied by the global percentage option and the equation were lower by around 100 women (out of the 1,000 women simulated in each iteration).

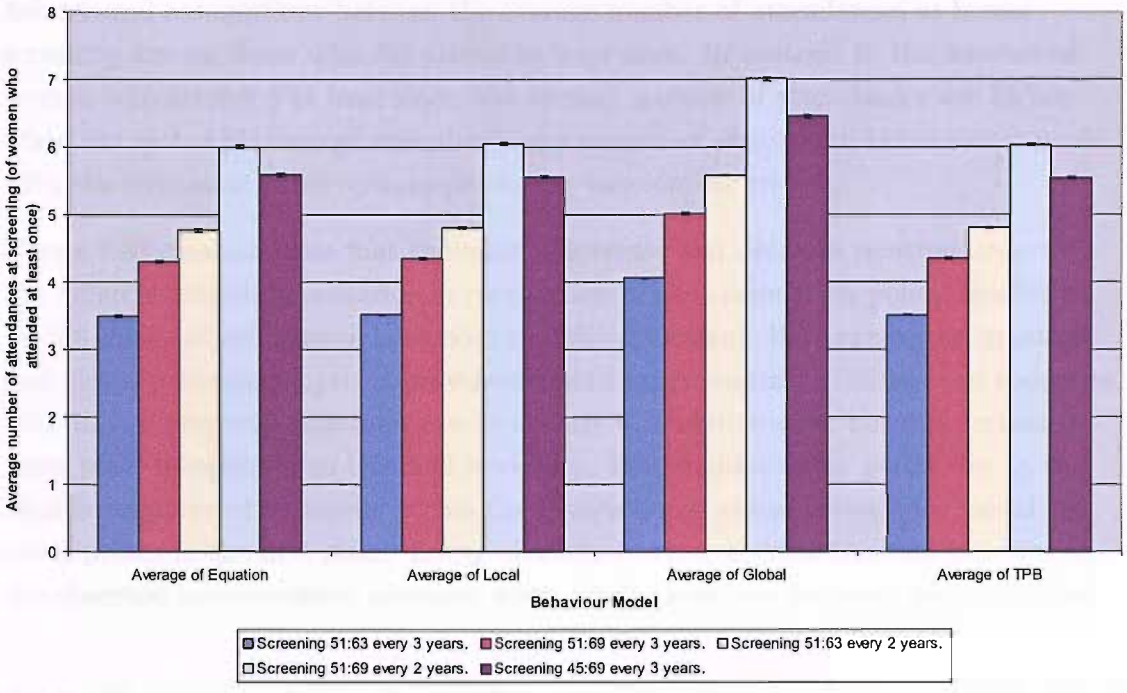


Figure 7.21: Average number of attendances at screening of women who attended at least once, by screening scenario and attendance behaviour assumption

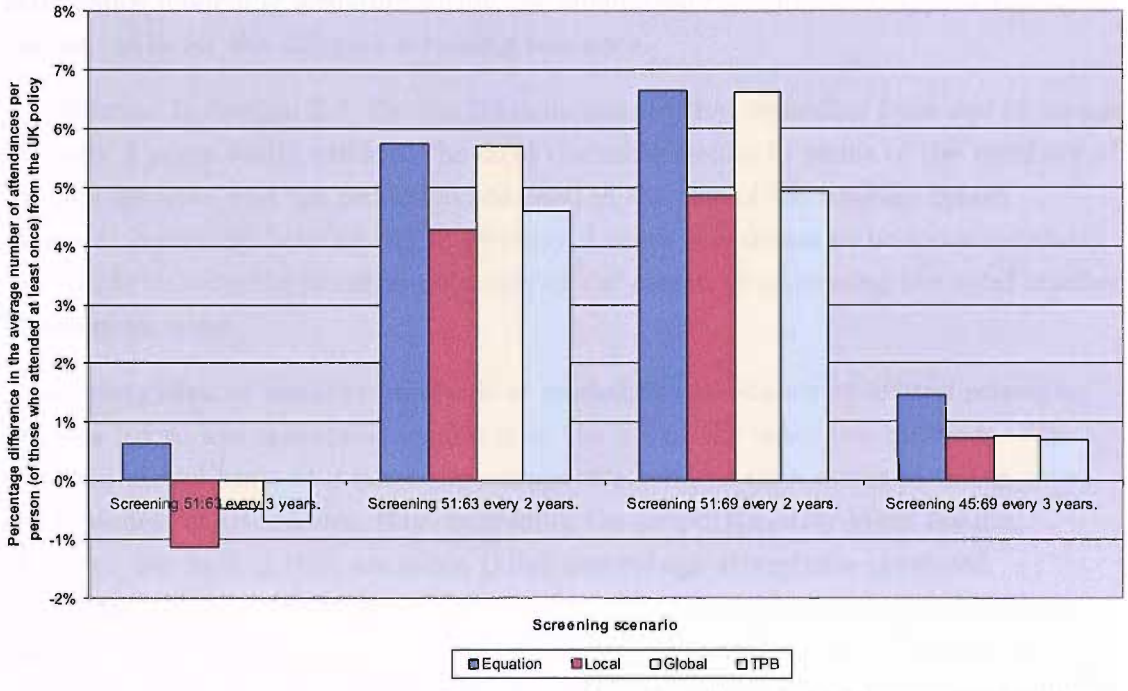


Figure 7.22: Relative number of attendances of women who attended screening invitations in comparison to the current UK screening policy by attendance behaviour assumption and screening scenario

Figures 7.21 and 7.22 depict the differences brought about by the different behavioural assumptions between the average number of attendances at breast screening among those who did attend at least once. In contrast to the number of women who attended at least once, the average number of attendances are higher when the global percentage attendance assumption of attendance behaviour is made, with the remaining three options producing very similar results.

Figure 7.22 demonstrates that the relative increase and decrease in attendance over the different screening scenarios in comparison to the current UK policy, is affected by the choice of attendance behaviour modelling method. Here again, the equation and global percentage options provide different proportionate increases and decreases, with higher proportionate increases in average attendance when biennial screening takes place as opposed to triennial screening. This result may be partly due to the smaller numbers of attendees within the equation and global attendance modelling assumptions in the first place. Lower absolute starting conditions could have led to the observed proportionate increases when similar absolute increases are introduced.

7.4.5 Summary of the effect of behavioural assumptions upon the simulation results

The results presented above indicate that overall, the different behavioural attendance modelling available within the simulation model lead to approximately similar ranks for the different screening scenarios.

As observed in Section 7.3, the results demonstrate that screening from age 51 to age 69 every 2 years would produce the most desirable results in terms of the numbers of cancers detected and the reduction obtained in the size of the average cancer. However, screening from age 45 to 69 every 3 years was shown to be more beneficial in regards to reducing times-to-detection of the cancer or increasing the total number of life-years saved.

Using the global or equation methods of modelling attendance at invited screening sessions led to less favourable results than the use of the other two methods. The equation model leads to a lower percentage of attendees than assumed in the other three models of attendance, thus explaining the proportionately lower results. However, the finding that assuming global percentage attendance produced significantly different outcomes to those of the local percentage suggest that the method by which a simulation model chooses to model attendance is important to the modelled outcome. Although the rank of the different screening policies was the same irrespective of which attendance model was used, the global percentage assumptions led to lower numbers of screen-detected cancers, and in some cases these lower counts produced insignificant differences between the screening scenarios (under the global

attendance assumptions), that were significant under different assumptions of attendance.

Modelling that assumed local percentage or TPB attendance, however, produced more desirable results (with an increase in the number of detected tumours of around 7% over global percentage assumptions). The two methods were shown to produce very similar proportional and actual results across the different model outputs and through different screening scenarios. In two cases, however, the TPB led to insignificant differences between outputs from screening ages 51 to 63 every 3 years, and increasing the upper age limit to 69 (still screening triennially). The differences between the same outputs under the same screening scenarios were significant under local attendance behaviour assumptions. The differences between the two approaches to behaviour modelling may be due to the more structured approach of the TPB, which may assign very low probabilities of attendance to some individuals who may never attend, whereas the local percentage assumptions imply that all women in the simulation have an equal chance of attending each screen. As has been seen from the results of the global percentage attendance, assuming that the same women attend each time at screening produces less desirable results. Since the TPB provides values to psychological variables for each simulated individual that do not change during the simulation and go on to predict likelihood of attendance, the TPB assumptions in this thesis can lead to the same individual repeatedly attending or non-attending (although not necessarily all of the time as with the global percentage option). Therefore, the added structure for the probability of attendance brought about by the assumptions within the TPB method of attendance modelling (as opposed to the local percentage attendance option) may explain the slight reduction in desirable results.

7.5 TPB Sensitivities

The results in Section 7.4 have helped to verify that using the Theory of Planned Behaviour (TPB) to model attendance behaviour at breast screening units produces very similar results to the assumptions of local percentage attendance. The advantage of the TPB, however, is that it can provide additional insight into the impact of psychological changes in a population upon the attendance at, and therefore overall performance of, screening for breast cancer.

This Section outlines the results of a small scale sensitivity analysis involving the three main variables of the TPB that were included in this analysis, those of attitude, subjective norm, and perceived behavioural control (PBC). The analysis considers the simulated effects of population changes in the three psychological constructs.

Attitude toward the behaviour refers to the overall evaluations of the behaviour by

the individual. Attitude toward a behaviour may be changed by a number of external factors such as advertising campaigns (promoting breast awareness or the severity and importance of early detection for breast cancer), or negative press (for example press attention to research findings that population mammography screening is not effective). Subjective norms consist of a persons beliefs about whether significant others would approve of their participation in the behaviour, where a significant other(s) are person(s) whose views in this domain are important to the individual. Subjective norms may be altered by a shift in general opinion in society due to an overall shift in attitudes, or by direct communications with the individuals concerned. Perceived behavioural control is the extent to which the individual believes the behaviour in question is under his/her control, and draws parallels with the concept of self efficacy. An individuals PBC can again be affected by a number of internal and external factors including confidence, depression, self efficacy, and the real ability to travel to the screening unit (in turn affected by distance from home, transport, time, and expense).

Jepson et al. (2000) summarise and evaluate literature relating to factors pertaining to the effectiveness of interventions for screening programmes, including breast screening programmes. Their results revealed a mix of success by interventions to increase scores relating to psychological constructs (such as those in the TPB), and studied interventions such as telephone reminders before appointments, telephone and face to face counselling (covering the reasons behind and importance of screening as well as what is involved in the screening process), personal advice from a GP, mail-shots and informative videos.

The next paragraph outlines the methodology used in the sensitivity analysis that focused upon the TPB variables, followed by a description of the results from this methodology.

When the simulation is run with the TPB, at the beginning of a simulation each woman in the model is provided with a sampled value for each of the three TPB variables considered, taken from a background population. The populations used for the constructs were derived from literature (please refer to Chapter 6 for details). To analyse how sensitive the results of the simulation are to each of these three variables, the background distributions of the variables were individually increased and then decreased by 10% in turn before running the simulation, and then they were simultaneously increased and decreased by 10% to view the collective impact. This analysis was carried out with the baseline settings reported in Section 7.2 such that screening took place from age 51 to 69 every 3 years, and an assumption of exponential tumour growth was made.

This Section outlines the main effects of the sensitivity changes and how the results of the simulation altered with these small changes in the TPBs behavioural

constructs. Appendix E contains the full results for all outputs and all changes.

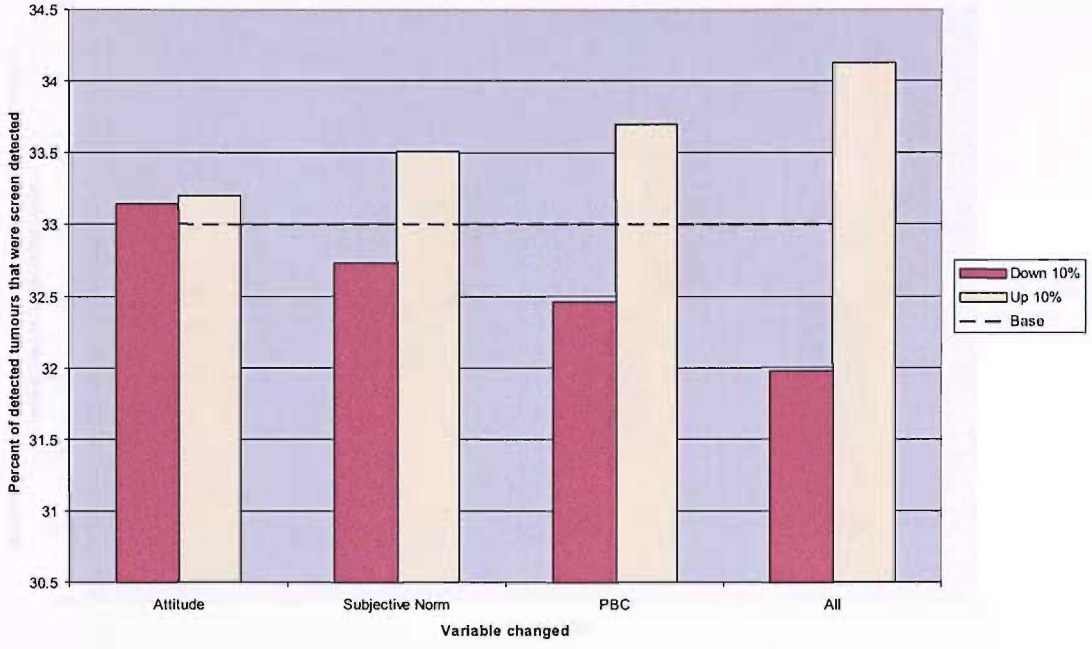


Figure 7.23: The change in the percent of tumours detected by mammography screening for 10% changes in the TPB variables

Figures 7.23 and 7.24 provide the absolute and relative change in the percent of breast tumours that were screen-detected with the 10% change in each of the TPB constructs. The results show that, as expected from the analysis in Chapter 6 and the weights of the logistic regression (the smallest weight associated with the attitude construct, and the largest with PBC), the construct that has the largest effect upon the outcome is perceived behavioural control (PBC), followed by subjective norms, and lastly, attitude. It appears that the change in attitude construct did not have a significant effect upon the percent of screen-detected cancers since a rise in the proportion of screen-detected cancers is observed even when the value of the construct is reduced, (modelling the effect of a 10% negative swing in attitudes to mammography screening). This is thought to be due to the insignificant effect of Attitude in the study from which the data for the TPB approximation in the simulation were derived, and confidence limits would be expected to cross zero (see Chapter 6 for details). The effect of PBC and subjective norms however, appears roughly linear, with an approximate 3% and 2% change respectively in the percent of tumours detected by mammography screening for each 10% change in the construct.

The relationship between the TPB constructs and the number of women who attend for screening at least once is less clear as Figure 7.25 depicts. Here it can be seen that while the constructs of subjective norm and PBC appear to have an effect upon the number of women who attend at least once, the effect is much smaller (of the order of

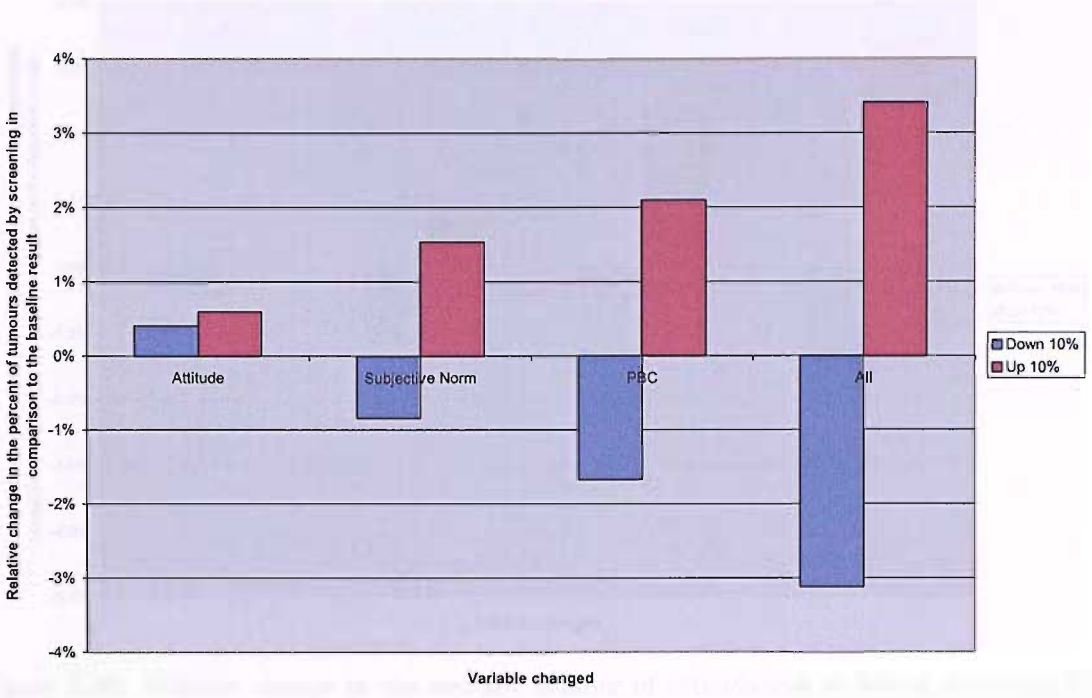


Figure 7.24: Relative change in the percent of screen-detected tumours for 10% changes in the TPB variables

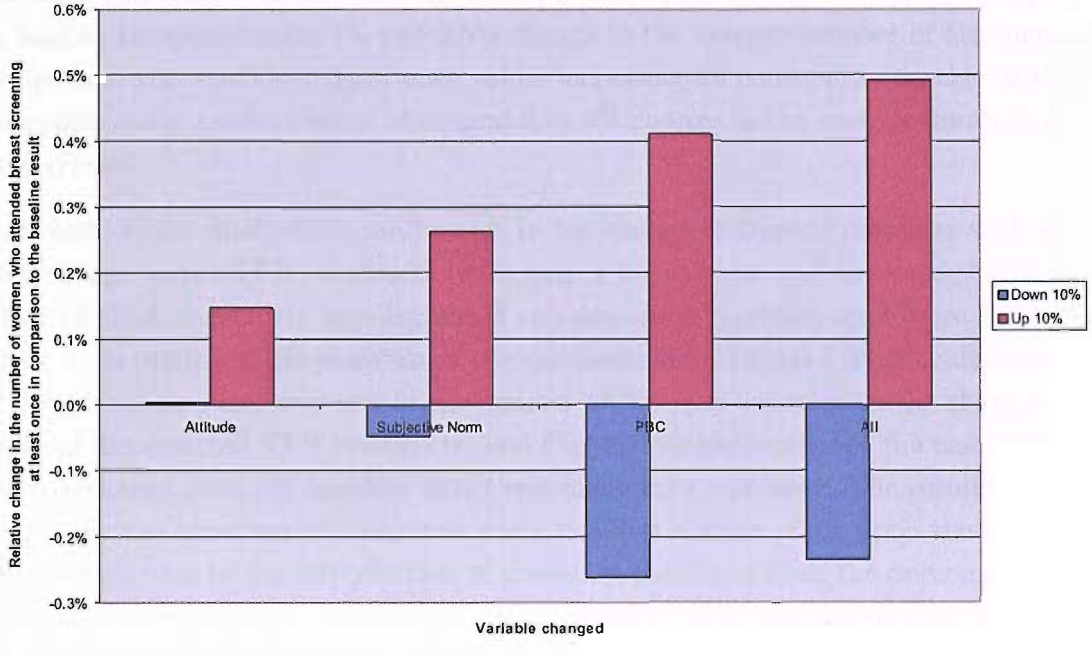


Figure 7.25: Relative change in the number of simulated women who attended mammography screening at least once for a 10% change in the TPB constructs

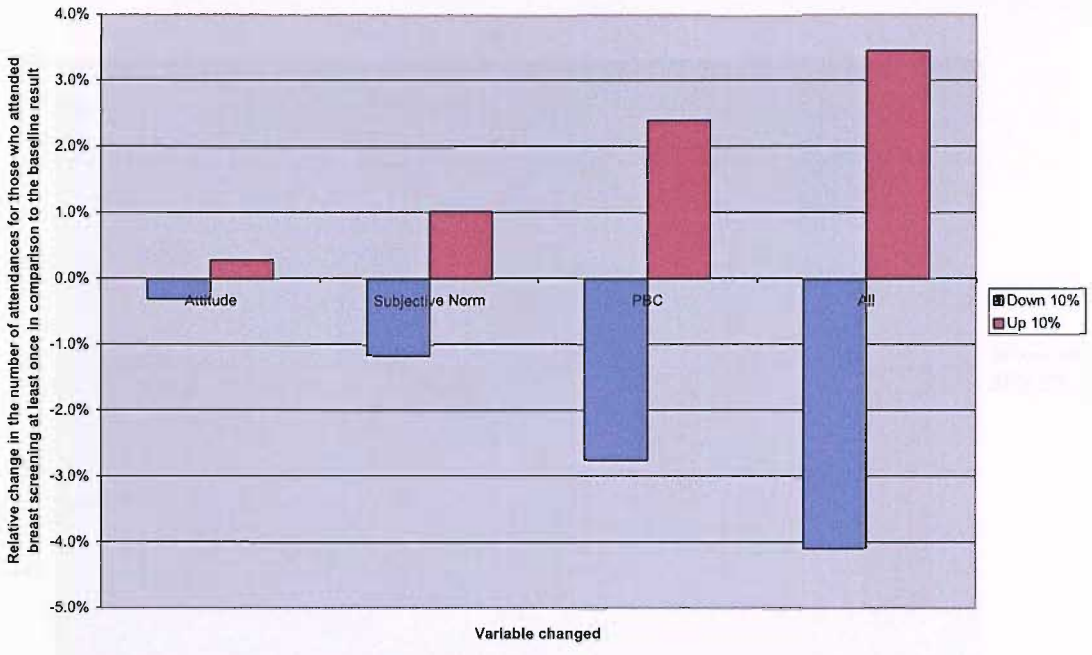


Figure 7.26: Relative change in the average number of attendances at breast screening for women who attended screening with a 10% change in the TPB constructs

less than half a percent for a 10% change in each construct respectively). In contrast to this, however, Figure 7.26 reveals that the average number of attendances for those who did attend screening does show a consistent change with each 10% alteration in the TPB constructs. In this case the constructs of subjective norm and PBC appear to lead to an approximate 1% and 2.5% change in the average number of attendances per person who attends at least once, while increasing all constructs together leads to an approximate additive effect of around 3 to 4% change in the average number of attendances.

Although only a small effect can be seen in the change in tumour diameter with a 10% change in the TPB constructs (with only a 1% increase and decrease observed when all three constructs were increased and decreased together, see Figure 7.27), the effect upon predicted life-years saved is more noticeable. Figure 7.28 provides the observed increase and decrease in the number of life-years saved with the change in value of the sampled TPB constructs, and Figure 7.29 demonstrates the associated relative change from the baseline that these differences represent. The results show that while the construct of subjective norm now has a lower effect upon the outcome than before (due to the introduction of greater variability within the outcome), PBC can still be seen to influence the simulation output of life-years saved. Figure 7.29 shows that even a 10% increase in PBC could potentially lead to a 2% increase in the number of life-years saved, and if all constructs were increased together then this Figure could rise to as much as 4%.

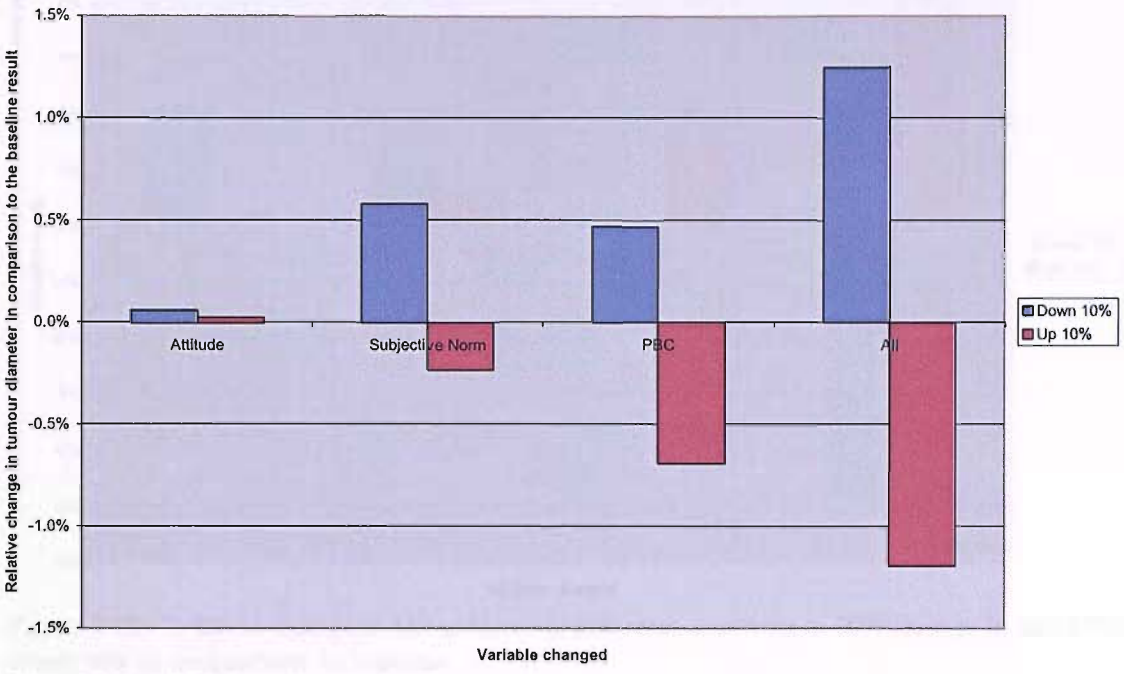


Figure 7.27: Relative change in tumour diameter for a 10% change in each of the TPB constructs

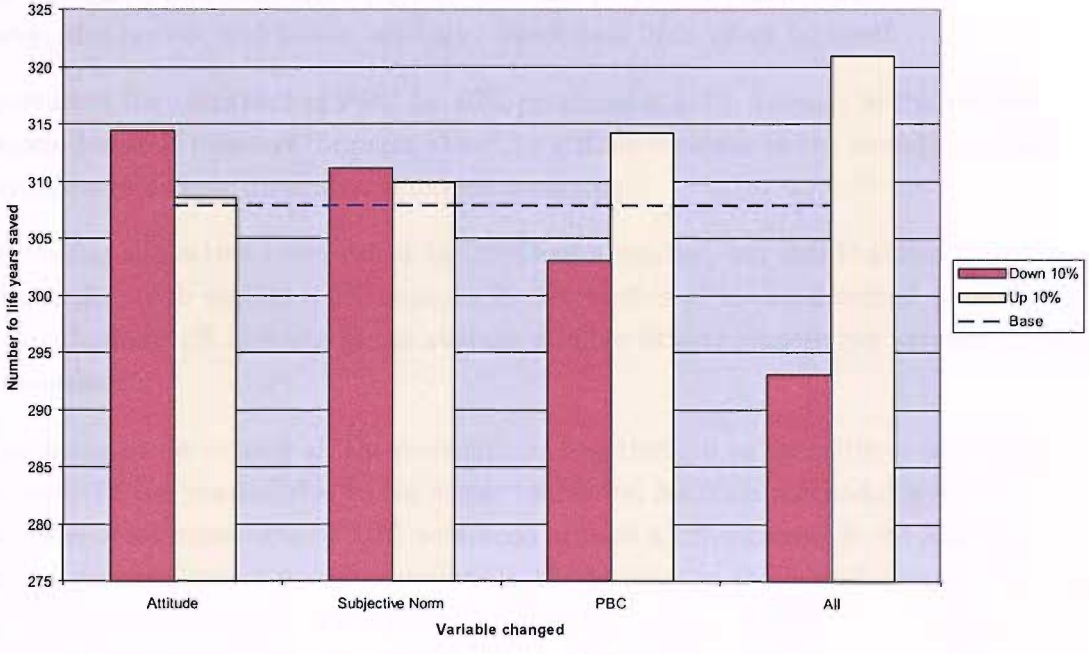


Figure 7.28: Change in the number of life-years saved for a 10% change in the TPB constructs

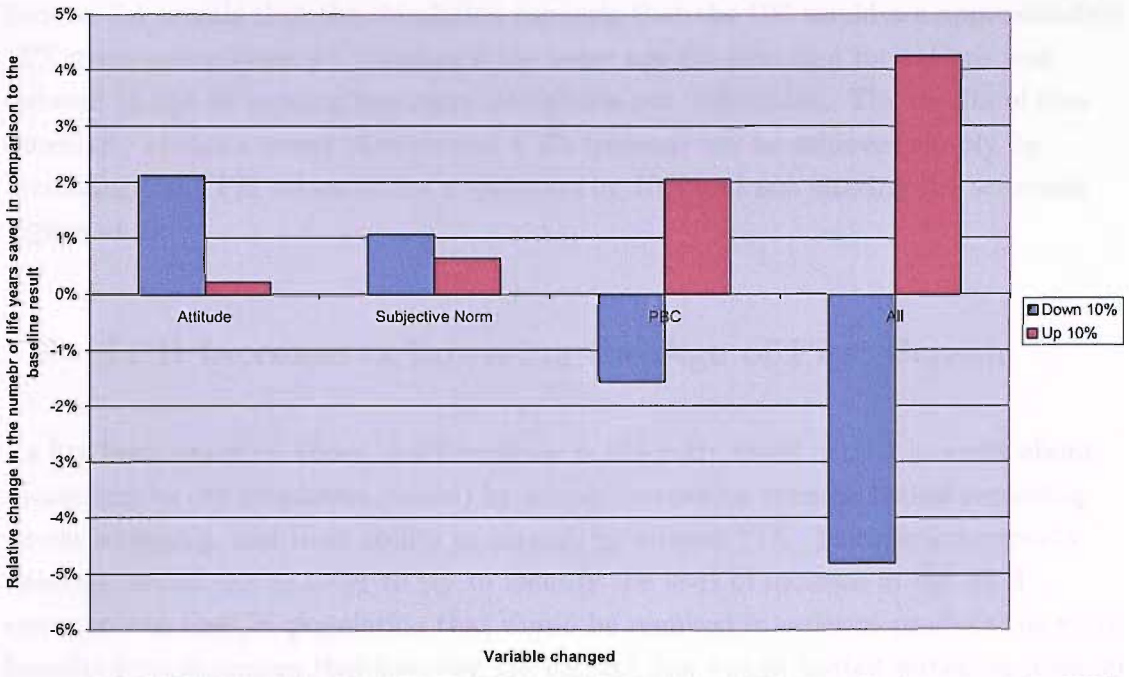


Figure 7.29: Relative change in the number of life-years saved for a 10% change in the TPB constructs in comparison to baseline

7.5.1 Summary of the TPB sensitivity results

The results of the simulation sensitivity results reveal that (in line with the make-up of the linear regression function modelling), the rank effect of the TPB constructs on the measured outcomes from high to low were perceived behavioural control, subjective norms, and finally, attitude, which had little effect by itself.

Increasing the construct of PBC by 10% produced a 2-3% increase in the number of screen-detected tumours, brought about by a 2.5% increase in the average number of attendances among those who attended screening.

Increasing subjective norm values by 10% had a smaller, but still beneficial impact on the results, with around a 2% increase in the number of screen-detected cancers, and approximately 1% increase in the average number of attendances per attendee in the simulations.

Increasing or decreasing all three constructs together led to an additive increase or decrease in the results (due to the linear regression function methodology). An increase of all constructs by 10% produced around a 4% increase in the number of screen-detected breast tumours, around a 1% decrease in the overall average diameter of tumours at detection, and an approximate 4% increase in the total number of life-years saved by screening. This is roughly the increase in life-years saved modelled by increasing the maximum age of screening from 63 to 69 (screening every 3 years in both scenarios) as implemented in the UK policy.

Section 7.4 reveals that the simulation suggests that the UK would see approximately 15% more screen-detected tumours if the lower age for screening invitations was reduced to age 45 (adding two more invitations per individual). The results of this sensitivity analysis reveal that around a 4% increase can be achieved simply by increasing the TPB values of the population by 10% and not altering the screening regime at all.

7.6 TPB Increase vs Lowering the Age of First Screen

As has been reported above, a 4% increase in life-years saved can be brought about (according to the simulation model) by simply increasing womens beliefs regarding breast screening, and their ability to attend, by around 10%. This Section reports analysis carried out in order to try to identify the level of increase in the TPB constructs in the UK population that would be required in order to produce the extra benefits from screening that lowering the current first age of invited screening from 50 to 45 would bring (as predicted by the simulation model).

Current attendance at invited screening in UK breast screening units stands at around 75%, whereas the baseline approximation of the TPB in the reported simulation model provides on average around 85% attendance. Therefore, to estimate a baseline approximation of the UK populations TPB characteristics, the sampled values for each of the TPB constructs in each simulation were reduced by 17%, providing (on average) a 75% attendance result. This method makes the simplistic assumption that the relationship between TPB constructs remain stable as the values of the constructs changes, which may or may not be the case, and also assumes that the subset of results in the experiment by Rutter (2000) may be generalised to the UK population, and so results should be treated with appropriate caution.

A simulation run was then made using these TPB populations to sample from, which simulated 1,000 women, 300 times, under the extension to the current UK screening policy of screening from age 45 to age 69 every 3 years. This run will be named the 75% baseline run in this thesis, in order to avoid confusion with the previous baseline runs. The results of this 75% baseline run can be found in Appendix F.

Experimentation was then carried out in order to find the required proportional increases in the TPB constructs in order to produce similar benefits (to those observed by lowering the age of invited screening to 45), but using the current UK screening policy (screening from age 51 to 69 triennially). In other words, by how much would the population TPB construct values need to increase in order to produce similar benefits as lowering the age of screening to age 45 from age 51?

Three of the simulation outputs were used in order to compare the results of the

TPB implied attendance	**75% Baseline**			**95% Attendance**		
Screen scenario	**45-69/3yrs**			**50-69/3yrs**		
Statistic	**Mean**	**Upper 90% CI**	**Lower 90% CI**	**Mean**	**Upper 90% CI**	**Lower 90% CI**
Number of cancers screen detected	**268.07**	270.46	265.69	**265.80**	267.98	263.62
Percent of detected cancers detected by screening	**36.17**	36.47	35.88	**35.81**	36.09	35.53
Life years saved	**389.20**	403.77	374.62	**345.09**	357.36	332.81

Table 7.2: Comparison of Three Key Simulation Outputs Between the 75% Baseline TPB Run (Screening 45-69/3yrs) and Increasing the TPB Variables to Approximate 95% Attendance (Screening 51-69/3yrs). Where CI= Confidence interval.

experimentation, and these were: the number of screen-detected cancers, the proportion of screen-detected cancers, and the life-years saved by the screening strategy. The results found that in order to find similar numbers, and proportions, of breast cancers as by lowering the age of screening, the TPB constructs needed to be increased by 74.77% on the 75% baseline result, (around 45% increase on the population data provided by Rutter (2000)), leading to an attendance rate at screening units of around 95%. Full results of this run can be found in Appendix F.

Table 7.2 presents the results from this final experimentation, as well as the results of the 75% Baseline run for comparison. 90% confidence limits are displayed and from these it can be seen that no significant difference was found between the numbers or proportions of screen-detected cancers were found between the two runs. However, Table 7.2 also shows that, despite finding similar proportions of tumours, a significant difference was observed between the numbers of life-years saved predicted by the model, with significantly lower numbers of life-years saved associated with the run that increased the TPB variables above the 75% baseline rates, but screened at the current UK policy ages. This result is not entirely unexpected, as screening lower ages (as in the 75% baseline run) will detect tumours in younger women who have the potential to live longer than older women (on average) and so overall, the number of life-years saved by this earlier detection will be greater.

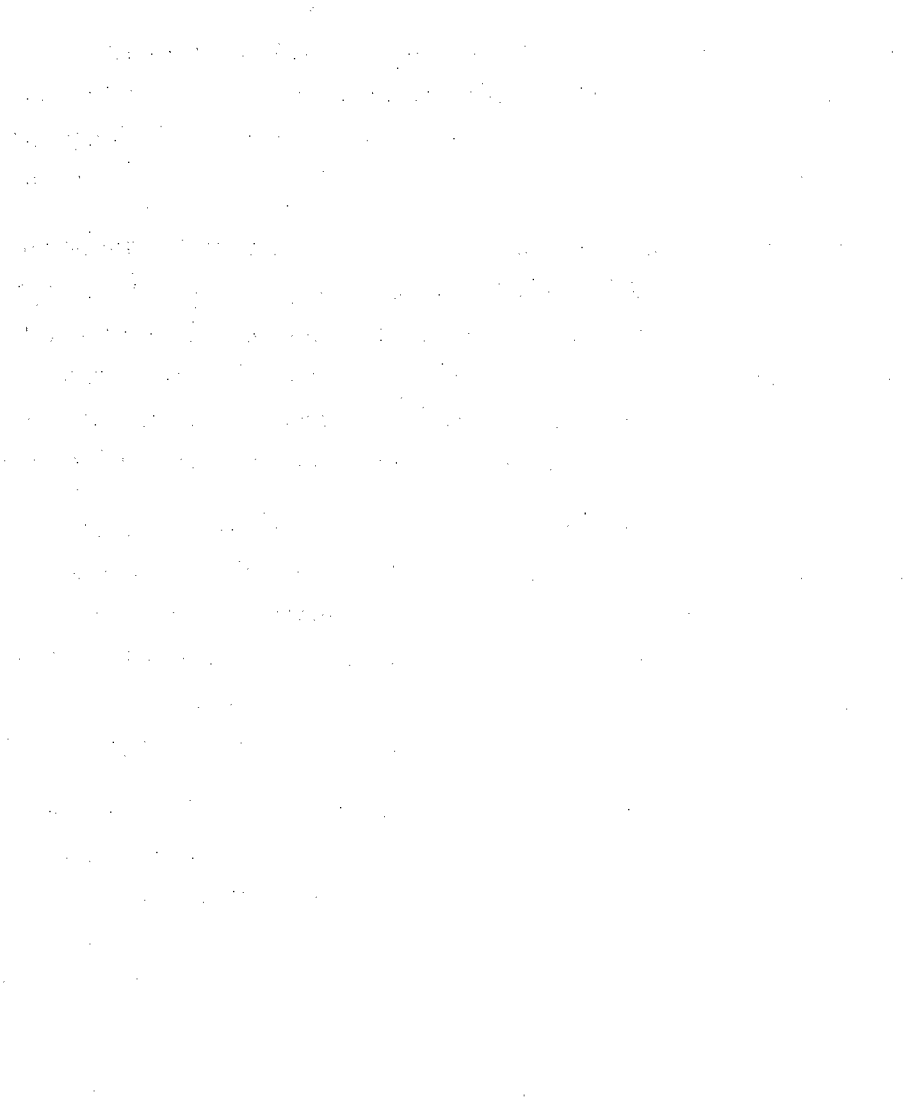
7.6.1 Experimentation Summary

This Section reported the results of experimentation to find the required increase in the UK populations current TPB variables that would be required to produce similar screening benefits as keeping the population TPB variables constant but starting to screen at a lower age (age 45 as opposed to 51).

It was estimated that an increase of around 75% in the UK TPB variables associated

with breast cancer screening could lead to similar numbers and proportions of screen-detected breast cancers as would be observed if the screening policy was changed to reduce the age of invited screening down to age 45.

However, although similar numbers of cancers would be detected, reducing the age of screening would lead to a higher number of life-years saved through screening, by detecting breast cancers in younger individuals.



Chapter 8

Discussion

Operational Research (OR) techniques have been widely applied to the area of health care and health research. However, the expected outcomes of interventions, plans, or structural changes suggested by these models often differ from those observed in reality.

The actions of people play a vital role in health care systems, resources, and disease progression. For example, when considering different and or optimal disease interventions the participation of the patient, or potential patients, in the intervention must be considered. For the majority of models of health care systems, the behaviour of the people involved in those systems is described by a single variable, e.g. the percentage of patients who comply with the regime or procedure.

It is suggested that the observed gap between modelled expected outcomes and real outcomes may be in part due to the human behavioural aspects of the health care systems which are currently omitted from OR models. To this end this thesis attempts to begin to incorporate psychological theory of health care behaviour into an OR model in order to start to bridge the gap between modelled and observed systems and increase the functionality and realism of the simulation model.

It is believed that this thesis describes one of the first serious attempts to incorporate behaviour at an individual level into a health care simulation model. The aim of the research was to investigate the benefits and differences that this approach brings against the extra time required for the building and researching of the model as well as the running time of the simulation.

8.1 Evaluation of Research Objectives

The research objectives for the work reported in this thesis are provided in Chapter 1, Section 1.3. This Section discusses the findings from considering each of the three

objectives in turn.

1. **To investigate the effects of different methods of modelling attendance for breast cancer screening, using a model from the psychological literature on health-related behaviour (the Theory of Planned Behaviour) as well as a statistical model derived to predict attendance at UK screening clinics (Baker and Atherill (2002)), and two methods commonly used in OR models based on percentage attendance, for different screening policies.**

To answer this research question a discrete event simulation of breast cancer and screening policies for breast cancer was built and populated with data from literature as appropriate. The model contained four different options for the approximation of attendance behaviour at the invited screening sessions. The results have found that different approaches to attendance behaviour did produce significantly different modelled outcomes. However, although the actual outcomes across the different attendance models differed, the relative effects of changing screening scenario were found to be stable across the four chosen methods for approximating attendance behaviour. In some cases the differences between the four approaches to attendance behaviour led to differences as to whether or not two different screening policies produced significantly different results. This finding is important and emphasises the need to treat simulation results with caution and not be too quick to assume a policy has, or does not have, additional benefit without taking into account the assumptions implicit in the simulation design.

One of the four attendance behaviour models was based upon a psychological theory of behaviour (the Theory of Planned Behaviour), designed to predict an individuals behaviour based upon their subjective beliefs surrounding the behaviour, (including the outcomes associated with the behaviour, and what others will think about the behaviour in question). The results of the work reported in this thesis found that using an approximation of this psychological model in the simulation in order to predict attendance at breast cancer screening, provided similar results to an assumption of percentage attendance. This could mean that in some cases it would not be worthwhile incorporating the additional behavioural detail into a simulation. However, the added information provided by the psychological theory could aid the evaluation of different psychological changes in the population, (through interventions to increase the uptake of screening, or by negative press associated with the benefits of process of screening), against changes in screening policy. The research therefore finds that the question as to whether or not the additional time and effort required to incorporate a psychological theory is worthwhile depends on the aim of the research in question.

2. To investigate the effects of using different models of tumour growth for different screening policies.

Four cancer growth patterns were considered in the simulation model, those of Gompertzian, Logistic, modified Gompertzian, and Exponential. Assumptions of Gompertzian growth produced some outcomes that were not validated and indicated that the short doubling times that were used to populate the Gompertzian distribution may not be appropriate. Results from the remaining three methods, and associated doubling times, all validated well, and the results found no reason to further accept nor reject any of the remaining three assumptions.

The results of the experimentation found that each of four different assumptions of tumour growth, and their associated parameters, led to significantly different modelled outcomes, with an especially notable difference brought about for the number of life years saved simulated. This outcome is of particular importance since screening decisions may be made on the basis of the simulated number and cost of lives saved and this outcome has been shown to vary with assumptions of tumour growth. However, again the rank order of the different screening strategies considered remained constant regardless of the assumption of tumour growth within the simulation. This outcome helps to re-enforce the importance of comparing relative outcomes as opposed to actual outcomes in all simulation models of real life systems.

3. To compare the effects of changes in behaviour with changes in screening policy.

Results comparing screening scenarios revealed that the simulation model suggested the UK could see approximately 15% more screen-detected tumours if the lower age for screening invitations was reduced to age 45 (adding two more invitations per individual). The results of this sensitivity analysis demonstrated that around a 4% increase in the number of screen-detected cancers could be achieved simply by altering psychological attitudes of the population by 10% (and therefore increasing the attendance rate at screening units) and not altering the screening regime at all. Moreover, further analysis estimated that if the Theory of Planned Behaviour constructs in the UK population could be increased by 75%, (a 45% increase on the baseline figures reported in the work by Rutter (2000) and as used in the analysis in this thesis), then similar numbers and proportions of breast cancers could be diagnosed via screening as by changing the current screening regime to screen from age 45 (as opposed to age 50 as is standard today).

8.2 Limitations of the Research

This is not a cost-effectiveness analysis. The work has not attempted to attach financial costs to mammography or treatment. Therefore no conclusions can be drawn about the real-life applicability of the results since it would be necessary to take into account the relative costs of different screening programmes to evaluate the cost per life year saved. In practice, health policy makers would need to trade this off against other potential use of the money and take into account the savings in terms of life years (or Quality Adjusted Life Years) saved. A cost-effectiveness analysis would also need to take into account the rates of over-diagnosis at screening, another factor that is not addressed in the research described here.

Data for the Theory of Planned Behaviour model was limited to the women in the Rutter study. The work was not able to generalise to a UK population. Moreover, it did not fit (and sample from) a multivariate distribution function, thus restricting the simulated population to the empirical observed data. It was also assumed that the relation between the constructs of the variables of the TPB would remain stable if the values of the individual constructs were to change. In addition no consideration was made as to how the TPB variables might be changed in practice, in order to achieve the 10% increase or decrease discussed in Chapter 7, (via improving psychological constructs associated with mammography screening through telephone counseling, advertising campaigns, and GP advice, or by reducing the barriers to screening such as travel distance and transport costs), nor the cost implications associated with such a change.

The author has not modelled behaviours associated with breast self examination in any of the four options for approximating behaviour within the simulation model. Nor has the research considered any possible correlation between the practise of self examination and attendance at breast screening or the values of psychological constructs in the Theory of Planned Behaviour. Furthermore the Theory of Planned Behaviour was the only psychological theory that was used in order to attempt to incorporate into the analysis, and it is possible that different results may have been achieved if an alternative psychological framework had been the focus.

The simulation model that was built to study the research questions makes a number of assumptions regarding breast cancer and screening for breast cancer. Firstly, the model assumes that breast cancers grow spherically. Secondly, the model links survival from breast cancer directly to the size of the tumour and does not take into account further prognostic indicators as discussed in Section 6.5. The simulation model also assumes that women are invited to screening at exact and specific ages as opposed to practise in the UK population whereby women are screened in regional patterns and invited if they have not been invited for three years or if they have now,

or are about to, pass their 50th Birthday.

8.3 Further Work

The first step would be to attach costs as described in Section 8.2, in order to carry out a full cost-effectiveness analysis and compare screening policies in terms of cost per life year saved.

It would be very interesting (but time-consuming) to carry out a larger empirical study to collect data for the TPB model (or alternatively one of the umbrella models discussed in Chapter 2), and perform the necessary statistical analysis to in order to develop a multivariate distribution from which to sample. It might be possible to work with marketing researchers, either to carry out an empirical study or to do secondary data collection from the literature, in order to quantify the effects of health education campaigns, and other interventions designed to affect health-related behaviour.

It would be interesting to incorporate some of the other psychological models discussed in Chapter 2, in particular the more recent integrative models of health behaviour.

It would of course be possible to develop behavioural models for screening for other diseases. An obvious candidate is diabetic retinopathy where there is a large literature on screening (see for example Brailsford and Schmidt (2003)). Models for screening for other cancers (cervical, prostate, testicular, and bowel cancers) could also potentially benefit from this approach.

8.4 Conclusion

This was believed to be the first serious attempt to model health-related behaviour in a detailed, individual way using psychological variables. There was a significant data collection and modelling effort and it remains unclear from this study whether the benefits of modelling in such detail will always outweigh the cost of this effort. However, the potential impact of including behavioural variables in simulation models goes far beyond healthcare. Any human activity system depends ultimately on the role played by the people within that system. These ideas could carry over into manufacturing industry, defence and every other arena where simulation plays a key role.

Appendix A

Model Code

The discrete event simulation model is built in Microsoft Visual Basic 6.0 and makes use of the three phase discrete event simulation methodology. Chapter 5 provides an overview of the models schema, and this Chapter attempts to describe the models' code structure in more detail, however it is not the intention to provide full code documentation.

The main body of the code is split into two modules, named 'BreastCancer' and 'Executive' respectively. The Executive module contains subroutines and procedures that govern the three phase procedure and access routines for other classes and modules within the simulation to gain information about the state of the system such as the current clock time. The BreastCancer module contains routines and procedures that are specific to the breast cancer scenario, including the code relating to the specific B-Phase events of the three phase methodology such as code governing screening for breast cancer, and entity parameter initialisation.

Figures A.1 and A.2 provide an overview of the main routines and procedures contained within these two modules and how they interact with each other, the list is not exhaustive but is intended to inform a high level picture of how the simulation works. Here it can be seen that the user runs the model by selecting 'Model' then 'Run' from the models' menu bar, which calls, for each iteration of the simulation, the initialisation routine in the BreastCancer module followed by the Simulate routine within the Executive.

Statistics and parameters relating to particular entities (women) within the simulation are stored and accessed via user defined collection classes containing objects which bring together parameters and functions grouped into topics appropriately. For example, the collection object Growth contains many Growth objects, one for each entity in the simulation which is scheduled to have, or already has breast cancer. Each Growth object stores, for that individual, their growth parameters, and the 'TumourSizeNow' method of the object allows the calculation of

the entities tumour diameter (in millimetres) at any point in time by using the other growth properties within the object, (and the current simulation clock time as passed to the function).

There are 23 class modules within the simulation code, 9 of which are collection classes. The main class objects and collections of class objects are detailed in Figures A.3 and A.4 and are colour coded. All collection classes are shown with blue headings, and all class objects with orange headings. Figures A.5 and A.6 give an indication of how the classes are used within the module level code to search for and alter an entities properties throughout the simulation. Here, an argument is shaded in blue if its code directly refers to a collection class object, and orange if it refers to a class object.

Form: Runtime

User input	Model:Run
Code	call mnuRun

Procedure Name	mnuRun
Description	For each iteration, initialises the classes and variables, then runs the simulation
Arguments	For integer =1 to number of iterations Call BreastCancer:Initialise Call Executive:Simulate Next iteration Calculate summary results.

Module: Executive

Procedure Name	NewEntity
Description	Adds a new entity to the classes of Growth and Women
Arguments	Growth.Add Entity.Add

Procedure Name	ScheduleCancerOnset, ScheduleSelfDetection, ScheduleDeath, ScheduleScreen
Description	Adds a new object (of the type specified) to the scheduler.
Arguments	Schedule.Object.Add. where object is the relevant acivity to be scheduled.

Procedure Name	Simulate
Description	Calls the three phase procedures A,B, and C in turn until the end of the iterations run length
Arguments	Do while Clock < iteration duration Aphase Bphase Update progress bar Do events Loop Call Finished.

Procedure Name	Aphase
Description	Searches for the next scheduled event in the scheduler
Arguments	NextEvent = runduration + 100 Find the next scheduled event in the scheduler by searching through Schedule.Cancer, schedule.Screen, Schedule.Death, Schedule.CancerDeath Record the time of the next event (NextEvent), and the unique IDs of the entities with these timecells (mstrEntityToAction()) as well as the event they are due for in their women class Clock = NextEvent Update entity ages.

Procedure Name	Bphase
Description	Carry out the actions due at this timestep
Arguments	For integer = 1 to number of entities scheduled with an event at this clock time Select the action they are due for (Woman(ID).NextTransition) Case Die from natural causes Call BreastCancer:BDie Case GetCancer Call BGetCancer Case GoToScreen If Behaviour(ID).Attend = true then Call BreastCancer:BGetScreened, and add an attendance to their behaviour class Else schedule next screen, and change Behaviour(ID).PreviousAttend = false Case SelfDetecting Call BreastCancer:BSelfDetect Case CancerDying Call BreastCancer:BDieFromCancer End Select Next integer.

Figure A.1: Simulation Modules (continued over the page)

Module: BreastCancer

Procedure Name	Initialise
Description	Initialises the classes and variables for each entity (woman), scheduling cancer onset, first screens, and natural death.

Arguments	Reset all global counts to zero
	For integer = 1 to number of entities
	Assign an identifier (W & integer)
	Add entity to the Behaviour class collection
	If they get cancer then
	Add entity to OnsetEntity class collection
	Call Executive: NewEntity to add basic entity attributes
	Call Executive: ScheduleCancerOnset, ScheduleSelfDetection, ScheduleDeath
	Else
	Add entity to OnsetEntity class collection without onset and growth attributes
	Call Executive: ScheduleDeath to schedule natural death
	End if
	Call Executive: ScheduleScreen to schedule the first screen
	Next integer.

Procedure Name	BDie
Description	Moves an entity to the state of natural death and de-schedules all events for that entity
Arguments	Move the entity from the state they are in to the natural death state and update counts of women in each state appropriately. De-schedule all events for the entity.

Procedure Name	BGetCancer
Description	Moves an entity form the state of no cancer to cancer
Arguments	Alters the state of the entity to 'cancer' and updates the counts of entities in each state to reflect the change. De-schedule cancer onset for the entity Call Executive:ScheduleDeath to schedule their death from cancer.

Procedure Name	BGetScreened
Description	Finds out if the tumour would be detected by screening at this time and if so moves the state of the entity to screen found, re-scheduling CancerDeath as appropriate.
Arguments	De-schedule this screen If the entity currently has cancer then Find the current size of the tumour (using Growth class) If the probability of detection at that size is greater than a random number then the tumour is detected Move the state of the entity to screen found De-schedule self discovery of the tumour Re-schedule death from cancer based on current tumour size Else Schedule the next screen Else schedule the next screen.

Procedure Name	BSelfDetect
Description	Moves the entity from the cancer state to self found/other detected state and update figures appropriately.
Arguments	De-schedule this time of self discovery De-schedule any screening scheduled Re-schedule cancer death Update counts in each state appropriately.

Procedure Name	BDieFromCancer
Description	Remove the entity form their current state to that of dead from breast cancer.
Arguments	De-schedule this death and natural death De-schedule any other activities scheduled for the entity Update counts of the numbers of entities in each state appropriately.

Figure A.2: Simulation Modules Continued

Class Objects

Object Class: Behaviour Object		
Description	A group of behavioural attributes belonging to a particular entity	
Attributes	Name	Description
	ID	Unique identifying key
	Attitude	Individuals score for attitude construct of TPB
	SubNorm	Individuals score for subjective norm construct of TPB
	PBC	Individuals score for perceived behavioural control construct of TPB
	PreviousAttend	Boolean variable describes whether or not individual attended the previous screening invitation.
	AttendCount	Count of the individuals attendances at breast screening.
	Attendance()	Array of bytes describing the attendance pattern for the individual, where i stands for the ith invitation, and 1 indicates an attendance, 0 a non attendance.
	GlobalAttend	The probability of attendance for the individual for the 'global' percentage attendance scenario
	Invitations	The number of invitations to screening that the entity has received.
Methods	Name	Purpose
	Attend	Pulls together the individuals behavioural attributes to calculate a probability of attendance, and then uses Monte Carlo sampling to determine if attendance takes place or not.
	AddAttendance	Adds to the count of attendances for the individual

Object Class: CancerOnset Object		
Description	A time of cancer onset for an individual	
Attributes	Name	Description
	ID	Unique identifying key
	TimeCell	The clock time for the particular entities' cancer onset

Object Class: Screen Object		
Description	The time of the next screen due for an individual	
Attributes	Name	Description
	ID	Unique identifying key
	TimeCell	The clock time for the particular entities' mammography screen

Object Class: Death Object		
Description	The time of death for an individual	
Attributes	Name	Description
	ID	Unique identifying key
	TimeCell	The clock time for the particular entities' scheduled death from any causes

Object Class: SelfDetect Object		
Description	The time of self or other detection for an individual	
Attributes	Name	Description
	ID	Unique identifying key
	TimeCell	The clock time for the particular entities' time to self detect the tumour.

Object Class: Growth Object		
Description	A group of parameters describing the growth and size of an individuals tumour at a particular point in time	
Attributes	Name	Description
	ID	Unique identifying key
	TimeOnset	Time of tumour onset
	GrowthVariable	The growth variables sampled for the individual when the object was added to the collection
	GrowthType	The growth pattern selected for the current simulation
	TimeFromMetOnsetToDet	The sampled time from metastasis onset until metastasis detection sampled upon object creation
	TimeToMetastasis	The time it takes from onset to metastasis given the individual growth attributes. Calculated using MetDetectionTime, and TimeOnset.
	SizeWhenMetastasis	Stores the sampled size of primary tumour when metastasis occurs.
Functions	Name	Description
	TumourVolumeNow	Calculates the volume of the spherical tumour at a given time according to the chosen growth pattern. Uses the Duration function.
	Duration	Provides the time the tumour has been growing based upon the clock time and time of onset
Methods	TumourSizeNow	Calculates the tumour diameter (in mm) at the clock time from the tumour volume assuming the tumour is spherical. Uses the Duration, and TumourVolumeNow functions.
	TimeFromStartToSize	Calculates how long, from onset, a tumour with the growth characteristics of the object would take to reach a given diameter (in mm).
	MetDetectionTime	Calculates and returns the time of metastasis for the individual, based upon the size of the tumour at metastasis as sampled upon addition to the collection, the growth variable, and using the function TimeFromStartToSize.

Figure A.3: Simulation Classes (continued over the page)

Object Class: Scheduler		
Description	An object containing the collection classes of all scheduled activities	
Attributes	Name	Description
	Screen	Is a Screen collection class
	CancerDeath	Is a Death collection class
	NaturalDeath	Is a Death collection class
	SelfDetection	Is a SelfDetect collection class
	Cancer	Is a Cancer collection class

Object Class: Statistics Object		
Description	An object containing an individuals cancer statistics for use in calculating summary statistics and for outputs to detailed text files.	
Attributes	Name	Description
	ID	Unique identifying key relating to a particular entity
	SizeAtDet	The size of the tumour at detection
	TypeDet	A usertype providing the type of detection, screen detected or other.
	AgeAtDet	Age at detection
	TimeSelfDied	The time of cancer death scheduled based upon survival at the time and tumour size at natural detection
	TimeCaughtEarlier	If screen detected, the time difference between scheduled self detection and time of screen detection is recorded.
	TimeDied	The actual time of death of the individual

Object Class: Woman Object		
Description	An object containing the key attributes of each entity	
Attributes	Name	Description
	ID	Unique identifying key relating to a particular entity
	State	The current cancer state of the entity, e.g. no cancer, screen detected, dead etc
	NextTransition	The next event scheduled for the entity
	Age	Current age of the entity
	FoundState	Whether cancer was screen detected or not
	TimeDies	Time of entity death

Figure A.4: Simulation Classes Continued

Collection Class Objects

Collection Class: Behaviour Collection		
Description	A collection of class objects Behaviour	
Methods	Name	Purpose
	Add	Adds a Behaviour object for an entity to the collection. Provides them with relevant behavioural attributes sampled as necessary.
	Count	Provides a count of the number of elements in the collection at any one time
	Item	Allows retrieval from the behaviour class by key identifier
	NewEnum	Enables For..Next loops through the collection
	Remove	Removes an entities Behaviour object from the behaviour collection
Functions	Name	Purpose
	Initialise	If the theory of planned behaviour is selected then the routine reads in the set of behaviour parameters from the relevant file for each entities random selection when added to the collection.

Collection Class: Cancer Collection		
Description	A collection of class objects Cancer, to schedule cancer onset	
Methods	Name	Purpose
	Add	Adds a CancerOnset object for an entity to the collection. Provides each entity added with a cancer onset time to be searched through by the scheduler
	Count	Provides a count of the number of elements in the collection at any one time
	Item	Allows retrieval from the Cancer class by key identifier
	NewEnum	Enables For..Next loops through the collection
	Remove	Removes an entities CancerOnset object from the Cancer collection, therefore de-scheduling cancer onset.

Collection Class: Death Collection		
Description	A collection of class objects Death, to schedule natural death.	
Methods	Name	Purpose
	Add	Adds a Death object for an entity to the collection. Provides each entity added with a time of natural death to be searched through by the scheduler
	Count	Provides a count of the number of elements in the collection at any one time
	Item	Allows retrieval from the Death class by key identifier
	NewEnum	Enables For..Next loops through the collection
	Remove	Removes an entities Death object from the Death collection, therefore de-scheduling natural death.

Collection Class: Screen Collection		
Description	A collection of class objects Screen, to schedule the next screen for that entity.	
Methods	Name	Purpose
	Add	Adds a Screen object for an entity to the collection. Provides each entity added with a time of next screen invitation to be searched through by the scheduler
	Count	Provides a count of the number of elements in the collection at any one time
	Item	Allows retrieval from the Screen class by key identifier
	NewEnum	Enables For..Next loops through the collection
	Remove	Removes an entities Screen object from the Screen collection, therefore de-scheduling their next screen.

Collection Class: SelfDetect Collection		
Description	A collection of class objects SelfDetect, to schedule the self detection for that entity.	
Methods	Name	Purpose
	Add	Adds a SelfDetect object for an entity to the collection. Provides each entity added with a time to self detect to be searched through by the scheduler
	Count	Provides a count of the number of elements in the collection at any one time
	Item	Allows retrieval from the SelfDetect class by key identifier
	NewEnum	Enables For..Next loops through the collection
	Remove	Removes an entities SelfDetect object from the SelfDetect collection, therefore de-scheduling their time to self detect.

Figure A.5: Simulation Collection Classes (continued over the page)

Collection Class: Statistics Collection		
Description	A collection of class objects Statistics, to store statistics relating to that entity from the iteration	
Methods	Name	Purpose
	Add	Adds a Statistics object for an entity to the collection. Provides each entity added with key statistics useful for result calculations
	Count	Provides a count of the number of elements in the collection at any one time
	Item	Allows retrieval from the Statistics class by key identifier
	NewEnum	Enables For..Next loops through the collection
	Remove	Removes an entities Statistics object from the Statistics collection.

Collection Class: Entity Collection		
Description	A collection of class objects Entity, to store key information about each entity (woman)	
Methods	Name	Purpose
	Add	Adds a Entity object for an entity to the collection. Provides each entity added with key information such as their current age and cancer state.
	Count	Provides a count of the number of elements in the collection at any one time
	Item	Allows retrieval from the Entity class by key identifier
	NewEnum	Enables For..Next loops through the collection
	Remove	Removes an entities Entity object from the Entity collection, and therefore from the simulation.

Collection Class: Growth Collection		
Description	A collection of class objects Growth, to store information relating to the cancer growth of an entity.	
Methods	Name	Purpose
	Add	Adds a Growth object for an entity to the collection. Provides each Growth added with key information such as growth rate, and size when metastasis occurs etc.
	Count	Provides a count of the number of elements in the collection at any one time
	Item	Allows retrieval from the Growth class by key identifier
	NewEnum	Enables For..Next loops through the collection
	Remove	Removes an entities Growth object from the Growth collection.
Functions	Name	Purpose
	SizeWhenMetastasis	Calculates the a size of cancer when metastasis could occur based upon the distribution proposed by Koscienly (1984)
	Readin	Reads in the selected subset of growth parameters from the relevant file for each entities use within the iteration.
	ReadinStoc	When the modified gompertz (stochastic) growth function is selected, this function reads in the selected subset of growth parameters and timings for those parameters from the relevant file for each entities use within the iteration.

Collection Class: Onset Collection		
Description	A collection of class objects CancerOnset, to find and return the time of cancer onset for each entity.	
Methods	Name	Purpose
	Add	Adds an Onset object for an entity to the collection. Provides each entity added with a sampled age of inset read in from the relevant input file.
	Count	Provides a count of the number of elements in the collection at any one time
	Item	Allows retrieval from the Onset class by key identifier
	NewEnum	Enables For..Next loops through the collection
	Remove	Removes an entities CancerOnset object from the Onset collection.
Functions	Name	Purpose
	Readin	Reads in the selected subset of age of cancer onsets from the relevant file for each entities use within the iteration.

Figure A.6: Simulation Collection Classes Continued

Appendix B

The Theory of Planned Behaviour Data

Rutter kindly made available data relating to a study of the Theory of Planned Behaviour (TPB) and how well the theory predicted attendance at three UK screening units over two rounds of invitations, (Rutter, 2000). The study is described in Chapter 3 and the dataset and analysis of the dataset in Chapter 6. Tables B.1 and B.2 provide summary statistics relating to the TPB constructs within the dataset and Table B.3 shows the correlations observed between the measured TPB variables.

Construct of TPB	Screening attendance	Cases					
		Valid		Missing		Total	
		N	Percent	N	Percent	N	Percent
Intention to attend	did not attend	278	84.0%	53	16.0%	331	100.0%
	attended	1,559	90.3%	168	9.7%	1,727	100.0%
Attitude	did not attend	278	84.0%	53	16.0%	331	100.0%
	attended	1,559	90.3%	168	9.7%	1,727	100.0%
Subjective Norms	did not attend	278	84.0%	53	16.0%	331	100.0%
	attended	1,559	90.3%	168	9.7%	1,727	100.0%
PBC	did not attend	278	84.0%	53	16.0%	331	100.0%
	attended	1,559	90.3%	168	9.7%	1,727	100.0%

Table B.1: Case Summary of data provided from Rutter (2000) for TPB variables

Construct	Screening attendance	Statistic		Value
Intention to attend	did not attend		Mean	3.79
		95% Confidence Interval for Mean	Lower Bound	3.66
			Upper Bound	3.92
			Median	4.00
			Std. Deviation	1.11
			Minimum	1.00
			Maximum	5.00
	attended		Mean	4.52
		95% Confidence Interval for Mean	Lower Bound	4.49
			Upper Bound	4.55
			Median	5.00
			Std. Deviation	0.65
			Minimum	1.00
			Maximum	5.00
Attitude	did not attend		Mean	24.23
		95% Confidence Interval for Mean	Lower Bound	22.10
			Upper Bound	26.36
			Median	22.00
			Std. Deviation	18.03
			Minimum	-33.00
			Maximum	70.00
	attended		Mean	29.66
		95% Confidence Interval for Mean	Lower Bound	28.91
			Upper Bound	30.42
			Median	29.00
			Std. Deviation	15.23
			Minimum	-24.00
			Maximum	76.00
Subjective Norms	did not attend		Mean	54.25
		95% Confidence Interval for Mean	Lower Bound	51.19
			Upper Bound	57.31
			Median	50.50
			Std. Deviation	25.93
			Minimum	1.00
			Maximum	125.00
	attended		Mean	65.05
		95% Confidence Interval for Mean	Lower Bound	63.87
			Upper Bound	66.23
			Median	65.00
			Std. Deviation	23.71
			Minimum	4.00
			Maximum	125.00
Perceived Behavioural Control	did not attend		Mean	12.22
		95% Confidence Interval for Mean	Lower Bound	11.92
			Upper Bound	12.51
			Median	13.00
			Std. Deviation	2.47
			Minimum	5.00
			Maximum	15.00
	attended		Mean	13.06
		95% Confidence Interval for Mean	Lower Bound	12.97
			Upper Bound	13.15
			Median	13.00
			Std. Deviation	1.76
			Minimum	5.00
			Maximum	15.00

Table B.2: Summary statistics for dataset from Rutter (2000).

Construct		Attitude	Subjective Norm	PBC
Attitude	Correlation Coefficient	1.000	0.398	0.298
	Sig. (2-tailed)		0.000	0.000
	N	2,029	1,868	2,001
Subjective Norm	Correlation Coefficient	0.398	1.000	0.210
	Sig. (2-tailed)	0.000		0.000
	N	1,868	1,881	1,858
PBC	Correlation Coefficient	0.298	0.210	1.000
	Sig. (2-tailed)	0.000	0.000	
	N	2,001	1,858	2,024

Table B.3: Spearman's Rho correlation statistics for data from Rutter (2000)

Appendix C

Results of Screening Scenarios Across Assumptions of Attendance Behaviour

This Appendix provides the detailed results from all of the outputs from the simulation runs reported in Section 7.4 that consider the effect of tumour growth assumptions upon simulated outcomes. The Tables that follow provide the mean and 90% confidence intervals for the mean, of all of the simulation outcomes for each run.

The 90% confidence intervals are generated via methodology described in Section 7.2.

Where Global = global percentage attendance, local = local percentage attendance, TPB = the Theory of Planned Behaviour, and equation = the equation option for modelling attendance behaviour.

Output Variable	Average				90% Confidence interval for the average (mean plus and minus result)			
	Equation	Local	Global	TPB	Equation	Local	Global	TPB
Number of cancers screen detected	151.550	184.777	175.260	183.480	2.596	2.723	2.547	2.631
Number detected by other means	577.780	546.657	556.760	548.710	3.591	3.412	3.567	3.592
Number of women who got cancer	896.023	895.687	896.120	896.170	2.093	2.292	2.255	2.091
Number of women screen invited while had cancer	464.733	468.047	467.277	467.703	3.432	3.277	3.501	3.730
Number of cancers that were not detected	166.693	164.253	164.100	163.980	2.600	2.399	2.427	2.524
Number of women not screen invited while had cancer	431.290	427.640	428.843	428.467	3.413	3.145	3.373	3.547
Number of women who did not get cancer	103.977	104.313	103.880	103.830	2.093	2.292	2.255	2.091
Number of women who attended screening at least once	678.310	802.820	689.300	801.297	3.423	2.560	2.994	2.806
Percent of detected cancers detected by screening	20.780	25.261	23.944	25.061	0.346	0.354	0.340	0.350
Average tumour diameter (mm) at registration	21.094	20.258	20.470	20.309	0.110	0.110	0.120	0.109
Average time (years) to detection	15.934	15.829	15.867	15.804	0.073	0.079	0.083	0.075
Average diameter (mm) of tumour at detection if detected by other means	24.054	23.741	23.873	23.748	0.120	0.119	0.122	0.114
Average time (years) to detection if detected by other means	15.302	14.952	15.142	14.936	0.084	0.086	0.084	0.078
Average diameter (mm) of tumour if screen detected	9.922	9.987	9.687	10.018	0.056	0.061	0.054	0.060
Average time to detection (years) if screen detected	18.355	18.544	18.186	18.347	0.014	0.025	0.012	0.013
Life years saved	230.855	274.372	272.120	277.888	14.642	15.155	14.932	16.548
Years earlier detected if screen detected	4.557	4.493	4.569	4.509	0.089	0.078	0.083	0.080
Average number of attendances (of those who attended at least once)	3.492	3.519	4.068	3.511	0.013	0.010	0.011	0.010

Table C.1: Results from screening age 51 to age 63 every 3 years, by attendance behaviour option

Output Variable	Average				90% Confidence interval for the average (mean plus and minus result)			
	Equation	Local	Global	TPB	Equation	Local	Global	TPB
Number of cancers screen detected	203.950	247.000	235.260	244.297	2.731	2.892	2.952	2.937
Number detected by other means	532.353	493.397	503.940	495.923	3.493	3.382	3.353	3.425
Number of women who got cancer	895.583	895.853	895.603	896.177	1.982	2.070	2.224	2.014
Number of women screen invited while had cancer	529.697	533.303	532.070	531.680	3.766	3.501	3.428	3.434
Number of cancers that were not detected	159.280	155.457	156.403	155.957	2.653	2.678	2.682	2.349
Number of women not screen invited while had cancer	365.887	362.550	363.533	364.497	3.424	3.373	3.473	3.128
Number of women who did not get cancer	104.417	104.147	104.397	103.823	1.982	2.070	2.224	2.014
Number of women who attended screening at least once	679.390	801.337	689.790	799.743	3.081	2.687	3.002	2.775
Percent of detected cancers detected by screening	27.700	33.360	31.825	33.004	0.354	0.362	0.372	0.379
Average tumour diameter (mm) at registration	19.796	18.751	18.984	18.828	0.108	0.114	0.116	0.113
Average time (years) to detection	15.862	15.652	15.693	15.689	0.076	0.073	0.073	0.074
Average diameter (mm) of tumour at detection if detected by other means	23.570	23.162	23.353	23.188	0.117	0.112	0.124	0.130
Average time (years) to detection if detected by other means	14.862	14.147	14.446	14.190	0.082	0.075	0.079	0.076
Average diameter (mm) of tumour if screen detected	9.776	9.898	9.610	9.905	0.057	0.061	0.065	0.064
Average time to detection (years) if screen detected	18.494	18.679	18.315	18.766	0.013	0.017	0.015	0.029
Life years saved	268.607	315.157	297.359	308.093	15.900	15.585	15.488	16.227
Years earlier detected if screen detected	4.528	4.545	4.591	4.541	0.076	0.063	0.069	0.067
Average number of attendances (of those who attended at least once)	4.299	4.351	5.024	4.346	0.020	0.013	0.017	0.016

Table C.2: Results from screening age 51 to age 69 every 3 years, by attendance behaviour option

Output Variable	Average				90% Confidence interval for the average (mean plus and minus result)			
	Equation	Local	Global	TPB	Equation	Local	Global	TPB
Number of cancers screen detected	181.543	218.290	204.793	218.067	2.707	2.680	2.636	2.756
Number detected by other means	550.203	516.680	530.410	516.793	3.740	3.768	3.198	3.360
Number of women who got cancer	896.150	896.307	896.467	895.223	2.106	2.291	2.064	2.214
Number of women screen invited while had cancer	467.087	470.793	469.720	470.613	3.399	3.372	3.421	3.529
Number of cancers that were not detected	164.403	161.337	161.263	160.363	2.757	2.706	2.534	2.508
Number of women not screen invited while had cancer	429.063	425.513	426.747	424.610	3.427	3.540	3.407	3.407
Number of women who did not get cancer	103.850	103.693	103.533	104.777	2.106	2.291	2.064	2.214
Number of women who attended screening at least once	684.320	804.747	690.993	805.207	3.470	2.684	3.254	2.756
Percent of detected cancers detected by screening	24.813	29.706	27.854	29.675	0.367	0.362	0.337	0.358
Average tumour diameter (mm) at registration	20.283	19.295	19.623	19.325	0.122	0.122	0.113	0.119
Average time (years) to detection	15.810	15.644	15.672	15.637	0.080	0.077	0.079	0.073
Average diameter (mm) of tumour at detection if detected by other means	24.007	23.603	23.859	23.687	0.133	0.125	0.122	0.127
Average time (years) to detection if detected by other means	15.214	14.763	14.984	14.753	0.088	0.078	0.085	0.080
Average diameter (mm) of tumour if screen detected	8.929	9.090	8.662	9.022	0.047	0.056	0.055	0.057
Average time to detection (years) if screen detected	17.685	17.673	17.415	17.702	0.008	0.025	0.022	0.014
Life years saved	271.758	336.155	310.306	325.953	15.234	15.563	16.080	17.488
Years earlier detected if screen detected	4.788	4.739	4.852	4.750	0.085	0.079	0.082	0.080
Average number of attendances (of those who attended at least once)	4.764	4.812	5.587	4.802	0.020	0.015	0.016	0.015

Table C.3: Results from screening age 51 to age 63 every 2 years, by attendance behaviour option

Output Variable	Average				90% Confidence interval for the average (mean plus and minus result)			
	Equation	Local	Global	TPB	Equation	Local	Global	TPB
Number of cancers screen detected	243.310	296.553	274.807	295.260	3.018	3.121	3.137	3.234
Number detected by other means	497.317	449.883	468.473	450.720	3.667	3.256	3.676	3.493
Number of women who got cancer	895.543	896.787	896.277	894.900	2.215	2.238	2.161	2.198
Number of women screen invited while had cancer	534.307	540.237	535.237	540.240	3.509	3.760	3.586	3.529
Number of cancers that were not detected	154.917	150.350	152.997	148.920	2.594	2.647	2.642	2.583
Number of women not screen invited while had cancer	361.237	356.550	361.040	354.660	3.272	3.565	3.323	3.271
Number of women who did not get cancer	104.457	103.213	103.723	105.100	2.215	2.238	2.161	2.198
Number of women who attended screening at least once	686.293	806.150	688.897	804.590	3.312	2.740	3.210	2.714
Percent of detected cancers detected by screening	32.853	39.727	36.974	39.580	0.387	0.373	0.402	0.400
Average tumour diameter (mm) at registration	18.720	17.433	17.871	17.444	0.113	0.116	0.119	0.104
Average time (years) to detection	15.595	15.424	15.443	15.423	0.077	0.073	0.074	0.072
Average diameter (mm) of tumour at detection if detected by other means	23.601	23.065	23.369	23.017	0.117	0.122	0.125	0.115
Average time (years) to detection if detected by other means	14.594	13.921	14.329	13.902	0.077	0.079	0.080	0.080
Average diameter (mm) of tumour if screen detected	8.671	8.902	8.486	8.911	0.045	0.051	0.058	0.060
Average time to detection (years) if screen detected	17.645	17.630	17.332	17.774	0.009	0.020	0.020	0.016
Life years saved	316.024	377.109	350.160	369.401	16.322	16.862	17.209	17.874
Years earlier detected if screen detected	4.829	4.765	4.894	4.765	0.072	0.066	0.072	0.061
Average number of attendances (of those who attended at least once)	6.005	6.057	7.013	6.034	0.028	0.020	0.027	0.022

Table C.4: Results from screening age 51 to age 69 every 2 years, by attendance behaviour option

Output Variable	Average				90% Confidence interval for the average (mean plus and minus result)			
	Equation	Local	Global	TPB	Equation	Local	Global	TPB
Number of cancers screen detected	246.763	283.480	270.513	283.210	3.058	3.164	2.982	3.127
Number detected by other means	493.027	458.683	468.847	458.000	3.439	3.525	3.658	3.690
Number of women who got cancer	896.280	895.580	895.393	896.087	2.180	2.234	2.250	2.102
Number of women screen invited while had cancer	602.643	604.550	602.107	603.427	3.441	3.505	3.436	3.419
Number of cancers that were not detected	156.490	153.417	156.033	154.877	2.285	2.583	2.644	2.535
Number of women not screen invited while had cancer	293.637	291.030	293.287	292.660	3.135	3.329	3.301	3.153
Number of women who did not get cancer	103.720	104.420	104.607	103.913	2.180	2.234	2.250	2.102
Number of women who attended screening at least once	779.443	888.870	761.273	888.880	3.063	1.989	2.923	2.165
Percent of detected cancers detected by screening	33.355	38.197	36.591	38.212	0.388	0.397	0.390	0.408
Average tumour diameter (mm) at registration	18.744	17.810	18.079	17.810	0.122	0.111	0.117	0.108
Average time (years) to detection	15.615	15.470	15.457	15.428	0.076	0.075	0.073	0.068
Average diameter (mm) of tumour at detection if detected by other means	23.372	22.846	23.176	22.928	0.126	0.140	0.125	0.125
Average time (years) to detection if detected by other means	14.543	13.941	14.242	13.828	0.082	0.078	0.087	0.074
Average diameter (mm) of tumour if screen detected	9.473	9.609	9.284	9.638	0.069	0.058	0.063	0.062
Average time to detection (years) if screen detected	17.781	17.957	17.488	17.966	0.027	0.012	0.008	0.015
Life years saved	372.338	417.927	403.376	420.791	17.724	21.208	19.951	18.849
Years earlier detected if screen detected	4.594	4.578	4.626	4.573	0.069	0.069	0.062	0.065
Average number of attendances (of those who attended at least once)	5.592	5.555	6.449	5.546	0.024	0.018	0.021	0.018

Table C.5: Results from screening age 45 to age 69 every 3 years, by attendance behaviour option

Appendix D

Results of Screening Scenarios Across Different Assumptions of Tumour Growth

This Appendix provides the detailed results from all of the outputs from the simulation runs reported in Section 7.3 that consider the effect of tumour growth assumptions upon simulated outcomes. The Tables that follow provide the mean and 90% confidence intervals for the mean, of all of the simulation outcomes for each run.

The 90% confidence intervals are generated via methodology described in Section 7.2.

Where Mod Gom = Modified Gompertzian tumour growth assumption.

Output Variable	Average				90% Confidence interval for the average (mean plus and minus result)			
	Mod Gom	Logistic	Gompertz	Exponential	Mod Gom	Logistic	Gompertz	Exponential
Number of cancers screen detected	147.363	220.227	67.190	184.777	2.632	2.797	1.796	2.723
Number detected by other means	575.267	515.620	663.340	546.657	3.161	3.326	3.420	3.412
Number of women who got cancer	828.393	906.370	770.603	895.687	2.736	2.134	3.073	2.292
Number of women screen invited while had cancer	344.277	486.150	274.880	468.047	3.443	3.449	3.082	3.277
Number of cancers that were not detected	105.763	170.523	40.073	164.253	2.160	2.754	1.446	2.399
Number of women not screen invited while had cancer	484.117	420.220	495.723	427.640	3.652	3.360	3.275	3.145
Number of women who did not get cancer	171.607	93.630	229.397	104.313	2.736	2.134	3.073	2.292
Number of women who attended screening at least once	789.143	800.833	799.867	802.820	2.759	3.091	3.013	2.560
Percent of detected cancers detected by screening	20.388	29.927	9.197	25.261	0.341	0.351	0.242	0.354
Average tumour diameter (mm) at registration	21.268	19.050	23.801	20.258	0.119	0.111	0.111	0.110
Average time (years) to detection	6.807	17.118	2.882	15.829	0.032	0.087	0.020	0.079
Average diameter (mm) of tumour at detection if detected by other means	24.089	22.972	24.628	23.741	0.122	0.117	0.118	0.119
Average time (years) to detection if detected by other means	7.067	15.725	2.790	14.952	0.032	0.100	0.020	0.086
Average diameter (mm) of tumour if screen detected	10.306	9.921	15.643	9.987	0.002	0.013	0.002	0.009
Average time to detection (years) if screen detected	5.806	20.486	3.757	18.544	0.020	0.069	0.020	0.077
Life years saved	222.966	326.475	107.644	274.372	14.226	16.754	9.970	15.155
Years earlier detected if screen detected	3.654	6.142	1.259	4.493	0.067	0.101	0.043	0.078
Average number of attendances (of those who attended at least once)	3.561	3.448	3.606	3.519	0.010	0.010	0.010	0.010

Table D.1: Results for screening ages 51 to 63 every 3 years, by tumour growth pattern

Output Variable	Average				90% Confidence interval for the average (mean plus and minus result)			
	Mod Gom	Logistic	Gompertz	Exponential	Mod Gom	Logistic	Gompertz	Exponential
Number of cancers screen detected	202.513	294.377	91.627	247.000	2.846	3.080	2.008	2.892
Number detected by other means	526.830	455.200	639.777	493.397	3.463	3.386	3.266	3.382
Number of women who got cancer	828.550	905.683	771.157	895.853	2.713	1.947	2.979	2.070
Number of women screen invited while had cancer	439.903	550.580	373.093	533.303	3.542	3.260	3.256	3.501
Number of cancers that were not detected	99.207	156.107	39.753	155.457	2.046	2.671	1.422	2.678
Number of women not screen invited while had cancer	388.647	355.103	398.063	362.550	3.650	3.220	3.217	3.373
Number of women who did not get cancer	171.450	94.317	228.843	104.147	2.713	1.947	2.979	2.070
Number of women who attended screening at least once	789.160	802.207	799.650	801.337	2.890	2.918	2.829	2.687
Percent of detected cancers detected by screening	27.766	39.272	12.526	33.360	0.372	0.376	0.264	0.362
Average tumour diameter (mm) at registration	19.930	17.499	23.226	18.751	0.124	0.104	0.109	0.114
Average time (years) to detection	6.582	16.963	2.847	15.652	0.031	0.084	0.019	0.073
Average diameter (mm) of tumour at detection if detected by other means	23.680	22.442	24.273	23.162	0.125	0.119	0.111	0.112
Average time (years) to detection if detected by other means	6.901	14.547	2.713	14.147	0.034	0.095	0.018	0.075
Average diameter (mm) of tumour if screen detected	10.207	9.867	15.829	9.898	0.005	0.020	0.004	0.009
Average time to detection (years) if screen detected	5.747	20.734	3.733	18.679	0.022	0.083	0.017	0.069
Life years saved	255.678	369.338	131.571	315.157	15.027	19.148	10.507	15.585
Years earlier detected if screen detected	3.671	6.091	1.253	4.545	0.055	0.080	0.038	0.063
Average number of attendances (of those who attended at least once)	4.438	4.236	4.506	4.351	0.016	0.015	0.015	0.013

Table D.2: Results for screening ages 51 to 69 every 3 years, by tumour growth pattern

Output Variable	Average				90% Confidence interval for the average (mean plus and minus result)			
	Mod Gom	Logistic	Gompertz	Exponential	Mod Gom	Logistic	Gompertz	Exponential
Number of cancers screen detected	177.807	255.997	89.203	218.290	2.737	2.761	2.140	2.680
Number detected by other means	546.800	483.493	640.810	516.680	3.532	3.337	3.358	3.768
Number of women who got cancer	829.553	905.890	770.993	896.307	2.763	2.083	3.121	2.291
Number of women screen invited while had cancer	346.697	490.660	275.560	470.793	3.551	3.387	3.389	3.372
Number of cancers that were not detected	104.947	166.400	40.980	161.337	2.220	2.797	1.297	2.706
Number of women not screen invited while had cancer	482.857	415.230	495.433	425.513	3.273	3.183	3.621	3.540
Number of women who did not get cancer	170.447	94.110	229.007	103.693	2.763	2.083	3.121	2.291
Number of women who attended screening at least once	792.743	804.533	805.657	804.747	2.714	3.116	2.804	2.684
Percent of detected cancers detected by screening	24.536	34.619	12.216	29.706	0.350	0.346	0.281	0.362
Average tumour diameter (mm) at registration	20.419	18.151	23.224	19.295	0.113	0.113	0.120	0.122
Average time (years) to detection	6.648	16.895	2.840	15.644	0.030	0.095	0.018	0.077
Average diameter (mm) of tumour at detection if detected by other means	23.972	22.989	24.395	23.603	0.123	0.125	0.120	0.125
Average time (years) to detection if detected by other means	7.041	15.366	2.752	14.763	0.031	0.103	0.018	0.078
Average diameter (mm) of tumour if screen detected	9.454	8.999	14.828	9.090	0.002	0.008	0.004	0.006
Average time to detection (years) if screen detected	5.486	19.725	3.487	17.673	0.027	0.075	0.020	0.067
Life years saved	265.524	383.608	154.898	336.155	15.453	18.952	12.373	15.563
Years earlier detected if screen detected	3.790	6.468	1.250	4.739	0.057	0.099	0.038	0.079
Average number of attendances (of those who attended at least once)	4.899	4.684	5.025	4.812	0.015	0.016	0.015	0.015

Table D.3: Results for screening ages 51 to 63 every 2 years, by tumour growth pattern

Output Variable	Average				90% Confidence interval for the average (mean plus and minus result)			
	Mod Gom	Logistic	Gompertz	Exponential	Mod Gom	Logistic	Gompertz	Exponential
Number of cancers screen detected	245.640	340.913	124.350	296.553	3.206	3.079	2.457	3.121
Number detected by other means	487.330	414.203	607.383	449.883	3.499	3.337	3.314	3.256
Number of women who got cancer	829.317	906.200	771.107	896.787	2.610	2.156	2.800	2.238
Number of women screen invited while had cancer	442.403	555.710	375.960	540.237	3.568	3.686	3.396	3.760
Number of cancers that were not detected	96.347	151.083	39.373	150.350	2.051	2.427	1.388	2.647
Number of women not screen invited while had cancer	386.913	350.490	395.147	356.550	3.513	3.340	3.555	3.565
Number of women who did not get cancer	170.683	93.800	228.893	103.213	2.610	2.156	2.800	2.238
Number of women who attended screening at least once	791.830	804.663	804.833	806.150	2.896	3.102	2.715	2.740
Percent of detected cancers detected by screening	33.512	45.148	16.992	39.727	0.412	0.374	0.325	0.373
Average tumour diameter (mm) at registration	18.726	16.232	22.402	17.433	0.108	0.104	0.110	0.116
Average time (years) to detection	6.342	16.595	2.803	15.424	0.031	0.092	0.019	0.073
Average diameter (mm) of tumour at detection if detected by other means	23.491	22.379	23.955	23.065	0.123	0.115	0.114	0.122
Average time (years) to detection if detected by other means	6.802	14.040	2.666	13.921	0.032	0.089	0.019	0.079
Average diameter (mm) of tumour if screen detected	9.301	8.805	14.890	8.902	0.003	0.016	0.002	0.014
Average time to detection (years) if screen detected	5.417	19.636	3.440	17.630	0.025	0.084	0.017	0.062
Life years saved	315.567	427.638	180.599	377.109	16.877	18.489	13.029	16.862
Years earlier detected if screen detected	3.801	6.419	1.237	4.765	0.047	0.080	0.031	0.066
Average number of attendances (of those who attended at least once)	6.204	5.837	6.398	6.057	0.024	0.022	0.023	0.020

Table D.4: Results for screening ages 51 to 69 every 2 years, by tumour growth pattern

Output Variable	Average				90% Confidence interval for the average (mean plus and minus result)			
	Mod Gom	Logistic	Gompertz	Exponential	Mod Gom	Logistic	Gompertz	Exponential
Number of cancers screen detected	238.640	333.383	106.670	283.480	3.182	3.285	2.224	3.164
Number detected by other means	492.757	417.823	623.883	458.683	3.686	3.456	3.347	3.525
Number of women who got cancer	829.093	906.397	770.087	895.580	2.633	2.155	2.939	2.234
Number of women screen invited while had cancer	513.373	619.360	444.337	604.550	3.493	3.522	3.505	3.505
Number of cancers that were not detected	97.697	155.190	39.533	153.417	1.989	2.535	1.278	2.583
Number of women not screen invited while had cancer	315.720	287.037	325.750	291.030	3.183	3.220	3.420	3.329
Number of women who did not get cancer	170.907	93.603	229.913	104.420	2.633	2.155	2.939	2.234
Number of women who attended screening at least once	878.413	887.943	890.653	888.870	2.523	2.285	2.328	1.989
Percent of detected cancers detected by screening	32.629	44.380	14.600	38.197	0.416	0.398	0.294	0.397
Average tumour diameter (mm) at registration	18.998	16.430	22.912	17.810	0.118	0.106	0.117	0.111
Average time (years) to detection	6.409	16.668	2.822	15.470	0.029	0.091	0.017	0.075
Average diameter (mm) of tumour at detection if detected by other means	23.385	21.975	24.183	22.846	0.123	0.113	0.118	0.140
Average time (years) to detection if detected by other means	6.817	14.182	2.671	13.941	0.032	0.096	0.017	0.078
Average diameter (mm) of tumour if screen detected	9.983	9.475	15.441	9.609	0.002	0.014	0.002	0.011
Average time to detection (years) if screen detected	5.591	19.736	3.682	17.957	0.024	0.075	0.021	0.069
Life years saved	356.622	488.427	172.710	417.927	18.473	20.861	13.506	21.208
Years earlier detected if screen detected	3.672	6.197	1.268	4.578	0.045	0.076	0.035	0.069
Average number of attendances (of those who attended at least once)	5.630	5.442	5.729	5.555	0.019	0.019	0.018	0.018

Table D.5: Results for screening ages 45 to 69 every 3 years, by tumour growth pattern

Appendix E

Results of Sensitivity Analysis Performed on the Theory of Planned Behaviour Variables

Table E.1 provides the means from the 300 iterations run for each of the sensitivity simulations performed as described in Chapter 7. Each of the three constructs of the Theory of Planned Behaviour (TPB) were increased, and then decreased (by 10%) relative to their baseline values discussed in Chapter 6.
Where SN= Subjective norm, PBC= Perceived behavioural control as before.

Direction change/ Variable change	Up 10%				Baseline				Down 10%			
	Attitude	SN	PBC	All	Attitude	SN	PBC	All	Attitude	SN	PBC	All
Number of cancers screen detected	246.13	248.27	249.97	252.70	244.30	244.30	244.30	244.30	244.91	242.51	240.19	236.41
Number detected by other means	495.24	492.62	491.92	487.69	495.92	495.92	495.92	495.92	494.17	498.47	499.96	502.99
Number of women who got cancer	896.83	897.05	896.35	895.35	896.18	896.18	896.18	896.18	895.35	896.66	896.37	896.11
Number of women screen invited while had cancer	534.09	533.95	535.17	534.19	531.68	531.68	531.68	531.68	532.99	533.76	533.13	533.73
Number of cancers that were not detected	155.45	156.16	154.46	154.96	155.96	155.96	155.96	155.96	156.27	155.68	156.22	156.71
Number of women not screen invited while had cancer	362.74	363.10	361.19	361.16	364.50	364.50	364.50	364.50	362.36	362.90	363.25	362.38
Number of women who did not get cancer	103.17	102.95	103.65	104.65	103.82	103.82	103.82	103.82	104.65	103.34	103.63	103.89
Number of women who attended screening at least once	800.92	801.85	803.02	803.68	799.74	799.74	799.74	799.74	799.77	799.36	797.65	797.86
Percent of detected cancers detected by screening	33.20	33.51	33.70	34.13	33.00	33.00	33.00	33.00	33.14	32.73	32.46	31.98
Average tumour diameter (mm) at registration	18.84	18.79	18.70	18.61	18.83	18.83	18.83	18.83	18.84	18.94	18.92	19.07
Average time (years) to detection	15.69	15.66	15.67	15.61	15.69	15.69	15.69	15.69	15.67	15.68	15.69	15.73
Average diameter (mm) of tumour at detection if detected by other means	23.25	23.24	23.20	23.15	23.19	23.19	23.19	23.19	23.25	23.28	23.23	23.32
Average time (years) to detection if detected by other means	14.20	14.16	14.19	14.10	14.20	14.20	14.20	14.20	14.20	14.20	14.22	14.29
Average diameter (mm) of tumour if screen detected	9.94	9.91	9.84	9.86	9.90	9.90	9.90	9.90	9.97	9.98	9.95	10.04
Average time to detection (years) if screen detected	18.68	18.68	18.65	18.47	18.76	18.76	18.76	18.76	18.61	18.70	18.68	18.74
Life years saved	308.56	309.81	314.18	320.96	307.86	307.86	307.86	307.86	314.39	311.12	303.05	293.07
Years earlier detected if screen detected	4.55	4.52	4.52	4.53	4.54	4.54	4.54	4.54	4.54	4.53	4.55	4.52
Average number of attendances (of those who attended at least once)	4.36	4.39	4.45	4.49	4.34	4.34	4.34	4.34	4.33	4.29	4.22	4.17

Table E.1: Sensitivity results from screening age 51 to age 69 every 3 years, for baseline TPB values and increasing or decreasing the TPB parameter values by 10% in turn (exponential growth assumed)

Appendix F

TPB Experimentation Results

This Appendix provides the detailed results from all of the outputs from the two runs reported in Section 7.6 that estimated the increase in TPB values required in the UK population in order to provide as much benefit with todays' screening strategy as would be expected by lowering the first invited age of screening to 45. Table F.1 provides the mean and 90% confidence intervals for the mean, of all of the simulation outcomes for both the reported 75% baseline, and TPB run with equivalent 95% attendance (for a discussion of the terms, please see Section 7.6).

The 90% confidence intervals are generated via methodology described in Section 7.2.

TPB implied attendance	75% Baseline			95% Attendance		
Screening scenario	45-69/3yrs			50-69/3yrs		
Statistic	Mean	Upper 90% CI	Lower 90% CI	Mean	Upper 90% CI	Lower 90% CI
Number of cancers screen detected	**268.07**	270.46	265.69	**265.80**	267.98	263.62
Number detected by other means	**472.94**	475.39	470.49	**476.54**	479.09	473.99
Number of women who got cancer	**896.77**	898.34	895.20	**895.33**	896.90	893.77
Number of women screen invited while had cancer	**602.94**	605.50	600.38	**535.99**	538.61	533.38
Number of cancers that were not detected	**155.76**	157.55	153.97	**152.99**	154.89	151.10
Number of women not screen invited while had cancer	**293.83**	296.16	291.50	**359.34**	361.90	356.78
Number of women who did not get cancer	**103.23**	104.80	101.66	**104.67**	106.23	103.10
Number of women who attended screening at least once	**882.94**	884.50	881.38	**809.02**	810.89	807.16
Percent of detected cancers detected by screening	**36.17**	36.47	35.88	**35.81**	36.09	35.53
Average tumour diameter (mm) at registration	**18.23**	18.31	18.15	**18.27**	18.36	18.18
Average time (years) to detection	**15.53**	15.59	15.48	**15.55**	15.60	15.49
Average diameter (mm) of tumour at detection if detected by other means	**22.99**	23.08	22.90	**23.08**	23.17	22.99
Average time (years) to detection if detected by other means	**14.06**	14.12	14.00	**13.95**	14.01	13.90
Average diameter (mm) of tumour if screen detected	**9.75**	9.80	9.70	**9.70**	9.75	9.65
Average time to detection (years) if screen detected	**18.09**	18.14	18.04	**18.37**	18.42	18.31
Life years saved	**389.20**	403.77	374.62	**345.09**	357.36	332.81
Years earlier detected if screen detected	**4.56**	4.61	4.52	**4.57**	4.62	4.52
Average number of attendances (of those who attended at least once)	**5.10**	5.11	5.09	**4.80**	4.81	4.79

Table F.1: Table of TPB experiment results to find the equivalent TPB values required to acheive similar results with todays screening programme as screening from age 45 would acheive

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