BILATERAL BREAST CANCER

INCIDENCE AND SURVIVAL

Kieran McCaul

A thesis submitted for fulfilment of the requirements for the degree of Doctor of Philosophy

Discipline of Public Health
Faculty of Health Sciences
The University of Adelaide

July 2006
Declaration

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being made available in all forms of media, now or hereafter known.

Kieran McCaul
INTRODUCTION .................................................................................................................. 1

1.1 Background .................................................................................................................. 1

1.2 The structure of this thesis ........................................................................................ 3

LITERATURE REVIEW ...................................................................................................... 4

2.1 Introduction .................................................................................................................. 4

2.2 Definition of synchronous primaries .......................................................................... 6

2.3 Criteria for Diagnosis of Second Primaries ............................................................... 10
  2.3.1 The Use of these Criteria in Studies of Bilateral Breast Cancer ....................... 14
  2.3.2 Discussion ............................................................................................................... 15

2.4 Epidemiology of Bilateral Breast Cancer ................................................................... 17
  2.4.1 Introduction ........................................................................................................... 17
  2.4.2 The Incidence of Bilateral Breast Cancer ............................................................ 18
  2.4.3 Annual Incidence of Bilateral Breast Cancer ....................................................... 23
  2.4.4 Age and Bilateral Breast Cancer ......................................................................... 25
  2.4.5 Reproductive Factors and Bilateral Breast Cancer ............................................. 29
  2.4.6 Family History and Bilateral Breast Cancer ......................................................... 31
  2.4.7 Obesity and Bilateral Breast Cancer .................................................................... 32

2.5 The Effect of Characteristics of the First Breast Cancer ............................................ 34
  2.5.1 Cancer Stage and Bilateral Breast Cancer .......................................................... 34
  2.5.2 Histology and Bilateral Breast Cancer ................................................................. 35
  2.5.3 Hormone Receptors and Bilateral Breast Cancer ............................................... 36
  2.5.4 Chemotherapy and Bilateral Breast Cancer ...................................................... 37
  2.5.5 Radiotherapy and Bilateral Breast Cancer .......................................................... 38

2.6 The Effect of Bilateral Breast Cancer on Survival .................................................... 38
  2.6.1 Introduction ......................................................................................................... 38
  2.6.2 Studies not using Time-Dependent Proportional Hazards Methods .................. 39
  2.6.3 Studies using Time-Dependent Proportional Hazards Methods .......................... 43

2.7 Summary ..................................................................................................................... 44

2.8 The Aims of this Thesis ............................................................................................. 45

METHODS ......................................................................................................................... 47

3.1 Introduction ................................................................................................................. 47
3.2 Study Design

3.3 SEER Data items
   3.3.1 Person Identifiers
   3.3.2 Cancer Sequence Number
   3.3.3 Vital Status and Cause of Death
   3.3.4 Diagnostic Confirmation
   3.3.5 Type of Reporting Source
   3.3.6 Histology (Morphology)
   3.3.7 Breast Cancer Stage
   3.3.8 Radiotherapy Treatment

3.4 Data Extraction and Exclusions

3.5 Creation of Study Data File

3.6 Definition of Synchronous and Metachronous Bilateral Breast Cancer
   3.6.1 Synchronous Bilateral Breast Cancer
   3.6.2 Metachronous Bilateral Breast Cancer

3.7 Statistical methods
   3.7.1 Methods used in the Analysis of Bilateral Breast Cancer Incidence
   3.7.2 Methods used in the Survival Analysis
   3.7.3 Time-Dependent Proportional Hazards Models
   3.7.4 The use of Multivariate Models in this Analysis
   3.7.5 Statistical Software

4 RESULTS

4.1 Introduction

4.2 Exclusions

4.3 The Incidence of Metachronous Bilateral Breast Cancer
   4.3.1 Cancer Stage and Bilateral Breast Cancer Incidence
   4.3.2 Bilateral Breast Cancer Incidence and Age
   4.3.3 Bilateral Breast Cancer and Histology
   4.3.4 Race, Marital Status, Year of First Diagnosis, SEER Registry, Radiotherapy and Bilateral Breast Cancer Incidence

4.4 Survival from First Breast Cancer
   4.4.1 Univariate Analysis
   4.4.2 Initial Multivariate Analysis
   4.4.3 Implications for the following Analysis

4.5 Survival – Synchronous Bilateral Breast Cancer
   4.5.1 Coding Stage for Synchronous Bilateral Breast Cancer
   4.5.2 Survival by Stage of Synchronous Bilateral Breast Cancers
List of Tables

Table 2-1: Time intervals used to define synchronous bilateral breast cancers in various studies published between 1921 and 2003.............................. 6

Table 2-2: Summary of published criteria for the diagnosis of bilateral breast cancers. ........................................................................................................ 12

Table 2-3: Annual incidence per 1,000 person-years of bilateral breast cancer following diagnosis of the first breast cancer........................................ 23

Table 3-1: Location of US cancer registries contributing to SEER data collection. ..47

Table 3-2: Comparison of AJCC, TNM, and SEER Summary Stage coding............. 53

Table 4-1: Stage of first breast cancer and the incidence of bilateral breast cancer (per 1,000 person-years). ................................................................. 68

Table 4-2: Observed and expected bilateral breast cancers following diagnosis of a first breast cancer staged as distant. .................................................... 74

Table 4-3: Age at diagnosis of first breast cancer and the incidence of metachronous bilateral breast cancer (per 1,000 person-years)............................. 77

Table 4-4: Age-specific relative rates of bilateral breast cancer within age cohorts defined by age at first diagnosis of breast cancer.................................... 83

Table 4-5: The average age at diagnosis of first primary breast cancer. ............... 86

Table 4-6: Average age at first diagnosis of breast cancer conditioning on survival. 88

Table 4-7: Histology of first breast cancer and the incidence of metachronous bilateral breast cancer (per 1,000 person-years)......................................... 89

Table 4-8: Crude and adjusted† incidence rate ratios (IRR) for histology of the first breast cancer. ......................................................................................... 90

Table 4-9: Incidence of bilateral breast cancer in the first three years and subsequent years in sub-cohorts of women with infiltrating ductal carcinoma, lobular carcinoma, and medullary carcinoma................................. 94

Table 4-10: Crude and adjusted incidence rate ratios of bilateral breast cancer in the first three years and in subsequent years by histology of the first breast cancer................................................................. 95

Table 4-11: Incidence of bilateral ductal carcinomas and bilateral lobular carcinoma following initial ductal and lobular carcinomas. .................. 100
Table 4-12: Crude and adjusted incidence rate ratios of ductal carcinomas in women with initial ductal or lobular carcinomas by time since first breast cancer....................................................................................................... 101

Table 4-13: Crude and adjusted incidence rate ratios of bilateral lobular carcinomas in women with initial ductal or lobular carcinomas by time since first breast cancer....................................................................................................... 102

Table 4-14: Crude and adjusted incidence rate ratios of bilateral ductal carcinomas in women with initial ductal or medullary carcinomas by time since first breast cancer. ........................................................................................... 103

Table 4-15: Crude and adjusted incidence rate ratios of bilateral medullary carcinomas in women with initial ductal or medullary carcinomas by time since first breast cancer. ........................................................................................... 103

Table 4-16: Race and the incidence of metachronous bilateral breast cancer (per 1,000 person-years). .......................................................................................... 106

Table 4-17: Crude and adjusted IRR of bilateral breast cancer for race..................... 106

Table 4-18: Marital status and the incidence of metachronous bilateral breast cancer (per 1,000 person-years). ................................................................. 107

Table 4-19: Crude and adjusted IRR of bilateral breast cancer for marital status. ..... 108

Table 4-20: Incidence of bilateral breast cancer by year of diagnosis of first breast cancer and year of diagnosis of the bilateral breast cancer. .................... 110

Table 4-21: Crude and adjusted IRR of bilateral breast cancer by year of diagnosis of the first breast cancer and of the bilateral breast cancer. .................... 111

Table 4-22: SEER registry and the incidence of metachronous bilateral breast cancer (per 1,000 person-years).......................................................................... 112

Table 4-23: Crude and adjusted † IRR of bilateral breast cancer for SEER registry. .. 113

Table 4-24: Radiotherapy treatment of first breast cancer and the incidence of metachronous bilateral breast cancer (per 1,000 person-years). ............. 113

Table 4-25: Crude and adjusted † IRR of bilateral breast cancer for the use of radiotherapy to treat the first breast cancer. ............................................ 114

Table 4-26: Survival from breast cancer by histology................................................. 122

Table 4-27: Crude and adjusted estimates of relative risk of death from breast cancer....................................................................................................... 125

Table 4-28: Tests for proportional hazards assumption............................................ 129
Table 4-29: Comparison of results from full model, stage-stratified model, and stage-specific models. .................................................................132

Table 4-30: Stage distribution of synchronous bilateral breast cancers ...........137

Table 4-31: Relative risk of breast cancer death by stage for unilateral and bilateral breast cancers .....................................................................139

Table 4-32: Results of test of proportional hazards assumption by stage of unilateral and synchronous bilateral breast cancers. .........................139

Table 4-33: Relative risk of breast cancer death by stage for unilateral and bilateral breast cancers both Stage 1 (localised) versus women with unilateral Stage 1 (localised) breast cancers† ........................................................................141

Table 4-34: Relative risk of breast cancer death for women with synchronous bilateral breast cancers both Stage 2 (regional) or one Stage 1 (localised) and one Stage 2 (regional), versus women with unilateral Stage 2 (regional) breast cancers† ..............................................................................141

Table 4-35: Relative risk of breast cancer death by stage for unilateral and bilateral breast cancers .........................................................................142

Table 4-36: Effect of diagnosis of metachronous bilateral breast cancer on survival – single time-dependent variable† ........................................145

Table 4-37: Effect of diagnosis of a metachronous bilateral breast cancer on survival by stage of the first breast cancer – single time-dependent variable† .................................................................147

Table 4-38: Effect of diagnosis of metachronous bilateral breast cancer on risk of death from breast cancer by time since first breast cancer diagnosis. ..........148

Table 4-39: Effect of a metachronous bilateral breast cancer on risk of death from breast cancer by time since diagnosis of first breast cancer and stage of first breast cancer ........................................................................151

Table 4-40: Effect of stage of metachronous bilateral breast cancer on risk of death from breast cancer by stage of the first breast cancers. .....................154

Table 4-41: Effect of stage of metachronous bilateral breast cancer on risk of death from breast cancer by time since diagnosis of Stage 1 (localised) first breast cancers ..............................................................................155

Table 4-42: Effect of stage of metachronous bilateral breast cancer on risk of death from breast cancer by time since diagnosis of Stage 2 (regional) first breast cancers† .................................................................158

Table 4-43: Crude and adjusted estimates of relative risk of death from breast cancer .......................................................................................162
Table 4-44: Effect of stage of metachronous bilateral breast cancer on risk of death from breast cancer by stage of the first breast cancers............................ 163

Table 4-45: Effect of stage of metachronous bilateral breast cancer on risk of death from breast cancer by stage of the first breast cancers............................ 164
# Table of Figures

Figure 2-1: Incidence of metachronous bilateral breast cancer obtained from various studies (1953 – 2001). ................................................................. 22

Figure 4-1: The incidence of bilateral breast cancer by year since diagnosis of the first breast cancer. ................................................................. 67

Figure 4-2: Annual incidence of bilateral breast cancer following Stage 1 (localised) first breast cancers. ................................................................. 70

Figure 4-3: Annual incidence of bilateral breast cancer following a regional staged first breast cancer................................................................. 71

Figure 4-4: Annual incidence of bilateral breast cancer following a distant staged first breast cancer. ................................................................. 72

Figure 4-5: Annual incidence of bilateral breast cancer following an unstaged first breast cancer. ................................................................. 73

Figure 4-6: The incidence of bilateral breast cancer by year since diagnosis of the first breast cancer; excluding women with Stage 4 (distant) initial breast cancers. ............................................................. 76

Figure 4-7: Age-specific incidence by age at diagnosis of first breast cancer .......... 79

Figure 4-8: Age-specific incidence of bilateral breast cancer by age at diagnosis of first breast cancer................................................................. 81

Figure 4-9: Overall age-specific incidence of bilateral breast cancer .................... 85

Figure 4-10: Annual incidence of bilateral breast cancer by histology of the first breast cancer; SEER 1973 to 2000......................................................... 92

Figure 4-11: Incidence of bilateral ductal and lobular carcinomas following initial ductal and lobular carcinomas. .................................................. 97

Figure 4-12: Incidence of bilateral ductal and medullary carcinomas following initial ductal and medullary carcinomas......................................... 98

Figure 4-13: Survival to death from breast cancer............................................. 115

Figure 4-14: Survival to death from breast cancer by age at diagnosis. ............... 116

Figure 4-15: Survival to death from breast cancer by marital status at diagnosis.... 117

Figure 4-16: Survival to death from breast cancer by race. ............................... 118

Figure 4-17: Survival to death from breast cancer by tumour stage. ................... 119
Figure 4-18: Survival to death from breast cancer by period of diagnosis. .......... 120
Figure 4-19: Survival to death from breast cancer, by cancer registry. ............... 121
Figure 4-20: Survival to death from breast cancer by histology. ....................... 122
Figure 4-21: Survival to death from breast cancer by treatment with radiotherapy.... 123
Figure 4-22: Schoenfeld residuals for stage of first breast cancer. ...................... 130
Figure 4-23: Survival by stage for unilateral and synchronous bilateral breast cancers. .................................................................................................... 136
Figure 4-24: Survival by stage for unilateral and synchronous bilateral breast cancers. .................................................................................................... 138
Figure 4-25: Schoenfeld residuals for unilateral Stage 2 (regional) breast cancers. .... 140
Figure 4-26: Hazard associated with stage of first breast cancer. ......................... 146
Figure 4-27: Effect of a metachronous bilateral breast cancer on risk of death from breast cancer by time since diagnosis of first breast cancer† .............. 149
Figure 4-28: Effect of a metachronous bilateral breast cancer on risk of death from breast cancer by time since diagnosis of Stage 1 (localised) first breast cancers† ........................................................................................................ 152
Figure 4-29: Effect of a metachronous bilateral breast cancer on risk of death from breast cancer by time since diagnosis of Stage 2 (regional) first breast cancers† ........................................................................................................ 153
Figure 4-30: Effect of a metachronous Stage 1 (localised) bilateral breast cancer on risk of death from breast cancer by time since diagnosis of Stage 1 (localised) first breast cancers† ........................................................................................................ 156
Figure 4-31: Effect of a metachronous Stage 2 (regional) bilateral breast cancer on risk of death from breast cancer by time since diagnosis of Stage 1 (localised) first breast cancers† ........................................................................................................ 156
Figure 4-32: Effect of a metachronous Stage 4 (distant) bilateral breast cancer on risk of death from breast cancer by time since diagnosis of Stage 1 (localised) first breast cancers† ........................................................................................................ 157
Figure 4-33: Effect of a metachronous Stage 1 (localised) bilateral breast cancer on risk of death from breast cancer by time since diagnosis of Stage 2 (regional) first breast cancers† ........................................................................................................ 159
Figure 4-34: Effect of a metachronous Stage 2 (regional) bilateral breast cancer on risk of death from breast cancer by time since diagnosis of Stage 2 (regional) first breast cancers† ........................................................................................................ 159
Figure 4-35: Effect of a metachronous Stage 4 (distant) bilateral breast cancer on risk of death from breast cancer by time since diagnosis of Stage 2 (regional) first breast cancers†........................................................................................................160

Figure 5-1: Age-specific incidence of breast cancer; SEER 1989 – 1993. ...............175

Figure 5-2: The Armitage-Doll carcinogenesis model.............................................192

Figure 5-3: Schematic representation of Moolgavkar’s two-stage carcinogenesis model. ..................................................................................................................195
Abstract

Introduction

This study re-examined the epidemiology of bilateral breast cancer with regard to the age at diagnosis and histology of the first breast cancer, and examined the effect of bilateral breast cancer on breast cancer survival.

Methods

A cohort of US women with breast cancer was identified using cancer registry data for the period 1973 to 2000 obtained from the Surveillance, Epidemiology, and End Results (SEER) Program. In this cohort, incidence cases of bilateral breast cancer were identified and rates calculated per 1,000 person-years and the effect on survival of a diagnosis of a bilateral breast cancer was determined using time-dependent proportional hazard regression.

Results

The overall incidence of bilateral breast cancer was 5.5 per 1,000 person-years and, apart from an elevation in incidence in the first year, was constant over time.

In age-cohorts of young women, age-specific rates of bilateral breast cancer were found to decline as these women aged, approaching the incidence observed in older age cohorts. In older age-cohorts, age-specific rates were comparatively constant until age 75-79 years, after which age-specific rates began to decline regardless of age at first diagnosis.
Differences in the crude incidence of bilateral breast cancer in sub-cohorts of women with lobular carcinoma (6.56 per 1,000 person-years) and infiltrating ductal carcinoma (5.31 per 1,000 person-years) were largely explained by differential incidence in the first year following diagnosis of the first breast cancer.

Diagnosis of bilateral breast cancer increased the risk of breast cancer mortality, independent of the interval between the first and second breast cancer. Stage of both the first and second breast cancers was found to be the most important determinant of risk.

**Conclusions**

This study found that the pattern of age-specific incidence of bilateral breast cancer was consistent with effects already well established in the literature describing the incidence of first primary breast cancer – pre-menopausal effects in young women and under-ascertainment in older women.

Estimates of the incidence of bilateral breast cancer were subject to bias caused by an elevation in the incidence in the first year following diagnosis of the first breast cancer. This was most likely an effect of increased surveillance. This explained to a large extent, associations between the histology of the first breast cancer and the incidence of bilateral breast cancer observed in earlier studies.

This study challenged the currently accepted view that bilateral breast cancer was a sign of increased susceptibility to breast cancer. Instead it is argued that the constant annual incidence of bilateral breast cancer suggests a final, discrete stage in a multistage carcinogenesis process. It is further argued that the observed incidence of bilateral breast cancer allows us to estimate the incidence of breast cancer in the population.
among women reaching this final stage within their lifetime. It is conservatively estimated that by age 75 to 79 years only half the women in the population have reached this final stage.

This implies that in half the population of women, breast cancer either never initiates or progresses so slowly that the final stage of carcinogenesis is not reached within their lifetime.
Acknowledgments

I could not have completed this work without the help and support I received from a number of people.

Most thanks must go to my wonderful partner Jane. Over the many years it has taken me to complete this work she has had to put up with my moodiness, occasional bouts of depression, odd working hours, and general grumpiness. Jane read though a number of drafts of my thesis and provided me valuable feedback. Her support and encouragement has always been unwavering.

I am especially grateful for the support and guidance of my three supervisors: Associate Professor Phillip Ryan, Associate Professor David Roder and Associate Professor Patricia Solomon. They have patiently read drafts of this thesis which would arrive infrequently and without warning, providing me with excellent comments when I most needed them.

Special thanks must also go to my friend and colleague Associate Professor Lin Fritschi who read through a number of drafts of this thesis and provided me with sound advice and encouragement.

The staff of Oriel’s café in Subiaco who kept me supplied me with coffee and a place to plug in my laptop. Open 24-hours a day, Oriel’s became a second workplace for me early in the morning.

Thank you to friends and colleagues in the Epidemiology Branch of the South Australian Health Commission (now the South Australian Department of Human
Services) for their support and particularly to the staff of the Commission’s library who helped me so much in the early stages of this thesis.