BILATERAL BREAST CANCER

INCIDENCE AND SURVIVAL

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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.

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Kieran McCaul

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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.

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1 INTRODUCTION

1.1 Background

The occurrence of multiple primary cancers has been the subject of research since they were first described in the late 19th century (Billroth, 1889) and were interpreted as a sign of increased susceptibility to cancer (Lund, 1933; Warren and Ehrenreich, 1944; Thomas et al., 1948).

Similarly, in early studies specifically of breast cancer, bilateral breast cancer was also interpreted as indicating increased susceptibility to breast cancer (Kilgore, 1921; Warren and Gates, 1932; Warren and Ehrenreich, 1944; Thomas et al., 1948). This interpretation persists today, with studies published comparatively recently portraying women with bilateral breast cancer as being at increased genetic susceptibility to breast cancer (Carmichael et al., 2002; Bernstein et al., 2003).

While it may have seemed logical at that time to interpret bilateral breast cancer as a sign of increased susceptibility to breast cancer, this is nevertheless a hypothesis that has to be tested. Yet in previous studies it seemed that this hypothesis had come to be an established interpretation of bilateral breast without having been subjected to any rigorous investigation.

One consequence of this could be that epidemiological observations of bilateral breast cancer have been misinterpreted. If it is believed that women with bilateral breast cancer are highly susceptible women, then unusual epidemiological characteristics could simply be attributed to susceptibility.

A second consequence would be that possible alternative interpretations of bilateral breast cancer have not being considered.

One such alternative interpretation could be found if we dispense with bilateral breast cancer as a sign of susceptibility and instead interpret bilateral breast cancer as simply another occurrence of breast cancer. The view that bilateral breast cancer was a sign of high susceptibility to breast cancer was formed at a time when the process of carcinogenesis was poorly understood, and pre-dates the development of multistage carcinogenesis theory by more than twenty years.

While mathematical models of various configurations of this multistage process have been developed to give some insight into how carcinogenesis occurs, these models when applied to cancer in human populations have concentrated on the incidence of first primary cancers. While such models have been used to interpret the incidence of breast cancer, there are no multistage carcinogenesis models that explain both the incidence of first primary breast cancer and the incidence of bilateral breast cancer.

The effect of bilateral breast cancer on survival from breast cancer has also been investigated in many studies and, as will be apparent in my review of this literature, few of these studies have applied statistical techniques appropriate for determining this effect.

This thesis, therefore, has three principal aims:

- to re-evaluate the epidemiology of bilateral breast cancer;
- to determine the effect of a diagnosis of bilateral breast cancer on survival from breast cancer;
- and to critique the current interpretation that bilateral breast cancer is a sign of susceptibility to breast cancer and instead suggest an alternative interpretation based on multi-stage carcinogenesis theory.

1.2 The structure of this thesis

In the following chapter I have reviewed the literature on bilateral breast cancer concentrating on reports from studies of the epidemiology of bilateral breast cancer and also on those describing the survival of women with bilateral breast cancer.

At the end of my review I will outline the specific aims of my data analysis.

In Chapter 3, I describe the data source that I will be using in my analysis and the statistical methods used. The data I have used come from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI) and includes all breast cancers registered between 1973 and 2000 in the 11 cancer registries that contribute to the SEER program.

In Chapter 4, I will present the results of my analysis of these data. The first section of this chapter deals with the incidence of bilateral breast cancer and the second with the effect of bilateral breast cancer on survival from breast cancer.

In Chapter 5 I will discuss the results of my analysis and then present an interpretation of bilateral breast cancer in terms of a multistage model and discuss the implications of this.

2 LITERATURE REVIEW

2.1 Introduction

This review will examine the literature describing both the incidence of, and survival from, bilateral breast cancer. It is my aim to pay particular attention to the methods used in these studies and the conclusions drawn. In particular, early studies of bilateral breast cancer are of interest because it is in these that opinions about the incidence of bilateral breast cancer were first developed and methodological issues peculiar to bilateral breast cancer first arose.

The review has a number of sections and the first of these addresses issues involved in the classification and definition of bilateral breast cancer. Bilateral breast cancers are classified in the literature as being synchronous – occurring at the same time – or metachronous – occurring at some time after the diagnosis of the first primary breast cancer. This definition has been interpreted in a number of different ways. Bilateral breast cancers have been defined as synchronous in some studies if they occur within 6 months of the first breast cancer and, in other studies, if they occur within 1 year of the first breast cancer. At the very least this complicates comparison between studies.

The other issue concerning the definition of a bilateral breast cancer relates to the problem of discriminating a true new breast cancer from metastatic disease arising from the first breast cancer. I will review the various criteria that were developed to deal with this problem.

Following this, I will present a review of the epidemiological literature describing bilateral breast cancer. This will cover the incidence of bilateral breast cancer, age-related aspects of bilateral breast cancer, and risk factors for breast cancer that have

been examined in relation to bilateral breast cancer – family history, reproductive factors, etc. Finally, I will examine factors associated with the first breast cancer – stage, histology, hormone receptor status – and also factors associated with the treatment of the first breast cancer – the use of chemotherapy and radiotherapy.

Following this, I will review the literature describing survival from bilateral breast cancer.

In compiling this review MEDLINE was used to identify relevant papers. The keywords NEOPLASMS, SECOND PRIMARIES and BREAST NEOPLASMS in combination identified a large number of papers. These could be reduced to more manageable numbers using additional keywords and by further restricting them to papers for which these additional keywords were a focus of the paper. Thus papers dealing with survival could be identified by the inclusion of the keywords SURVIVAL ANALYSIS or SURVIVAL RATE. Similarly, papers dealing with the incidence of bilateral breast cancer could be identified by focused keywords of INCIDENCE or INCIDENCE RATE.

Cited reference searches were also used identify other relevant work.

Finally, while MEDLINE was useful for identifying relevant literature, it only covered papers published since 1966. To identify earlier work I resorted, in part, to textbooks on breast cancer that had a substantial chapter on bilateral or contralateral breast cancer with references to prior work such as Cutler (1962), Haagensen (1971), Haagensen et al. (1981) and Donegan and Spratt (1995). Of course, journal articles also include references to prior work, so it was possible to identify earlier work from these as well.

2.2 Definition of synchronous primaries

A feature of all studies conducted on bilateral breast cancer had been the classification of the second primary as either synchronous – occurring at the same time as the first primary – or metachronous – occurring at different times. While this is, at first glance, reasonably straightforward, the definition of 'at the same time' and hence what is regarded as a synchronous bilateral breast cancer, has varied over time.

In some studies, breast cancers diagnosed within 1 month of each other were regarded as being synchronous whereas in others, they were synchronous if they occurred within six months of each other, and in others, within one year of each other (Table 2-1). Since bilateral breast cancers that are not synchronous are metachronous, these definitions also affect the classification of metachronous bilateral breast cancers.

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

Time interval	Source
Same time	Kilgore (1921); Harrington (1946); Guiss (1954); Fitts and Patterson (1955); Farrow (1956); Moertel and Soule (1957); Robbins and Berg (1964); Leis et al. (1965); Shellito and Bartlett (1967); Bailey et al. (1980); Kelmendi et Ustaran and Meiss (1988)
1 month	Prior and Waterhouse (1981); Healey et al. (1993); Gollamudi et al. (1997); Yeatman et al. (1997)
2 months	Fracchia et al. (1985); Black et al. (1996)
68 days	Mose et al. (1997)
3 months	Kesseler et al. (1976); Pomerantz et al. (1989)
4 months	(1989); (1994).
6 months	Haagensen (1971); McCredie et al. (1975); Mueller and Ames (1978); Schell et al. (1982); Rosselli Del Turco et al. (1982); Burns et al. (1984); Michowitz et al. (1985); Robinson et al. (1993); Gustafsson et al. (1994); de la Rochefordiere et al. (1994); Broët et al. (1995); Bernstein et al. (2003).
1 year	Wilson and Alberty (1973); Sakamoto et al. (1978); Al-Jurf et al. (1981); Heron et al. (2000); Kaas et al. (2001)
5 years	Bloom et al. (1980)

When comparing estimates of the proportion of women diagnosed with synchronous bilateral breast cancer obtained from different studies, such differences in the definition of synchronous bilateral breast cancer create complications.

The earliest study is that of Kilgore (1921) who defined synchronous primaries as those diagnosed at the same time. The most recent study is that by Bernstein et al. (2003) who regarded any bilateral breast cancer occurring within one year of the first breast cancer diagnosis as synchronous. Of the studies represented, when an interval between first and second breast cancer was used to define synchronous bilateral breast cancer, it was most commonly 6 months.

While there are many definitions of synchronous bilateral breast cancer, few authors have presented a rationale for their definition.

Haagensen (1971) seems to have been the first to introduce a definition of synchronous bilateral breast cancer that allowed an interval between the two primaries. I can find no studies prior to this that invoked such a definition. He defined bilateral breast cancers that were diagnosed within 6 months of each other as synchronous and stated that this was done because of the assumption that the second primary existed at the same time as the first but was not diagnosed.

This assumption is undoubtedly true since estimates of breast tumour doubling times, while highly variable (Heuser et al., 1979; von Fournier et al., 1980; Peer et al., 1993; Brekelmans et al., 1996), nevertheless suggest that the latency period for breast cancer is of the order of years rather than months. Metachronous bilateral breast cancer diagnosed within eight or ten years of the first breast cancer are likely to have been present when the first breast cancer was diagnosed.

So there is some logic to Haagensen's assumption, but what is lacking is any reason for why he thought that tumours present at the same time should be treated in any analysis as if they were diagnosed at the same time.

Subsequent to Haagensen's publication, as we can see in Table 2-1, numerous other authors adopted this approach and defined synchronous bilateral breast cancers as those occurring within some fixed interval of time. Similarly, none of the authors of these papers provided any explanation or rationale for why synchronous bilateral breast cancers should be defined in this way.

It is difficult to find any clinical, biological or methodological justification for defining synchronous bilateral breast cancer in this way.

In terms of treatment, a woman presenting with synchronous bilateral breast cancer is a different clinical problem than a woman who presents with breast cancer and then again, 6 months later, with a second breast cancer in the contralateral breast. Therefore estimating the proportion of synchronous bilateral breast cancers by defining as synchronous any bilateral breast cancer that occurs within 6 months of the first is not estimating the extent of a particular clinical problem.

Significant methodological problems are introduced by allowing some interval of time between the first and second breast cancer when defining synchronous tumours. The occurrence of true synchronous bilateral breast cancers would be best summarised as a proportion of all breast cancers diagnosed. The occurrence of true metachronous bilateral breast cancers, on the other hand, would be best summarised by an incidence rate. If instead, synchronous bilateral breast cancers are defined to include metachronous bilateral breast cancers occurring within some interval of time since the

first breast cancer, then estimates of the proportion of synchronous bilateral breast cancers could vary between studies because of variations in short-term mortality.

Further problems are encountered if we wish to identify characteristics associated with diagnosis of synchronous bilateral breast cancer. True synchronous bilateral breast cancers are more likely to be associated with particular modes of detection, such as mammography (Hungness et al., 2000; Polednak, 2003). As a consequence, characteristics that are associated with the use of mammography, or tumour characteristics that are associated with detection by mammography, could appear to be associated with synchronous bilateral breast cancers.

The diagnosis of metachronous bilateral breast cancer within 6 months of the first breast cancer, on the other hand, is likely to be influenced by factors associated with treatment and follow-up of the first breast cancer. Consequently, if we define as synchronous any bilateral breast cancer occurring within 6 months of the first breast cancer, then any factors identified as being associated with synchronous bilateral breast cancer under this definition would be a mixture of detection and surveillance factors.

Finally, if one is attempting to estimate the survival of women with synchronous bilateral breast cancer, then by including in this group women who may have had their bilateral breast cancer up to 6 months (or even longer) after their first, we are defining at least part of this group on the basis of an event that occurred in their future. If this is not accounted for in the analysis, then estimates of survival in women with synchronous bilateral breast cancer will be biased to some extent.

In summary, there seems to be no compelling reason for defining as synchronous any bilateral breast cancers that occur within some interval of time since the first breast

cancer. On the contrary, there would seem to be a number of valid methodological reasons for not doing so.

2.3 Criteria for Diagnosis of Second Primaries

Malignant breast cancers can, like other cancers, metastasise and women can either be diagnosed with metastatic disease present or metastatic disease can become clinically evident some time later. While distant metastatic disease occurs most often in the bones, liver or brain (Cifuentes and Pickren, 1979), it can appear in the contralateral breast, although this appears to occur only rarely (Donegan, 1970). Therefore it is conceivable that metastatic disease occurring in the contralateral breast could be misclassified as a new primary breast cancer or, alternatively, a new contralateral breast cancer could be misclassified as metastatic disease arising from the first breast cancer. This is therefore a potential source of bias which, if it were occurring to a significant extent, could distort estimates of bilateral breast cancer incidence.

The possibility of this occurring was recognised in the very earliest studies of bilateral breast cancer and criteria were developed by various researchers in an attempt to minimise the impact of any bias that could result. These criteria are summarized in chronological order in Table 2-2. We can see that there was considerable variability in the criteria used to define a bilateral breast cancer and that some are so vague that it is difficult to see how they could be applied and achieve any reasonable degree of reliability. For example, the last of Warren and Gate's set of criteria (the probability of one being the metastasis of the other must be excluded) is more a statement of intent than a workable criterion.

If one applied the earliest criteria (Billroth, 1889) one would essentially be assuming that any second malignancy that occurred in the contralateral breast was metastatic

disease arising from the first breast cancer unless the histologies of both were different. This is an extremely restrictive criteria, particularly when one is dealing with breast cancer in which approximately 80% of tumours are infiltrating ductal carcinomas (Midler et al., 1952). In addition, many breast cancers contain multiple histological types – as many as 30% in a series reported by Qualheim and Gail (1957) – placing further doubt on the validity of this criterion..

When Midler et al. (1952) applied their criteria, more than half of the contralateral lesions that occurred in their series of patients were classified as metastatic disease. Similarly, when Guiss studied 1,521 women with breast cancer, 115 subsequently developed a malignancy in the contralateral breast, but after application of his criteria, all but 21 were excluded (Guiss, 1954). Kilgore applied Guiss's criteria to 131 cases of bilateral disease and excluded two thirds of these (Kilgore et al., 1956) and Smithers et al. (1952), using a variation of Guiss's criteria, excluded 56% of their series of 113 bilateral malignancies.

The problem with these criteria is that to achieve sensitivity their authors abandoned specificity. Robbins and Berg (1964) were roundly critical of these criteria, which they found to be arbitrary and 'remote from the facts of breast cancer behavior'. They proposed criteria that were based on the pathological appearance of primary breast cancer as distinct from the appearance of metastatic disease. While they could not assess the performance of their criteria because they did not review cases that had been previously classified as metastatic, their criteria do, at least, have better face validity than those previously proposed because they are based on well-described pathological features of primary breast cancer.

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

Author	Criteria
Billroth (1889)	each tumour had to have a different histological appearance; each tumour had to be in a separate organ; each tumour had to produce their own metastases.
Warren and Gates ((1932)	each of the tumours must present a definite picture of malignancy; each must be distinct; the probability of one being the metastasis of the other must be excluded.
Midler et al. ((1952)	eliminated all cases where lesions in the opposite breast followed lesions in the inner hemisphere of the other breast unless they were of different histological types.
Hubbard (1953)	required microscopic evidence of a tumour in both breasts.
Guiss (1954)	definite evidence that the first radical mastectomy was for breast cancer; a lapse of time, preferably two years, during which time there was no evidence of recurrence or metastatic disease; development of a clinically independent second primary in the other breast without evidence of metastatic development elsewhere; a clinical course for patient after the second breast cancer procedure that was compatible with a second primary lesion.
Robbins and Berg (1964)	Location. Second primary cancers could be expected to develop within breast tissue, most frequently in the upper outer quadrant and not in the fatty tail of the breast. Metastatic disease, on the other hand, will tend to appear in the fat at the periphery of the breast parenchyma, usually near the midline of the breast or in the fatty tail. Multiplicity of Growth. Metastases tend to be multiple and to show expansile growth rather than the infiltrating stellate, crablike growth characteristic of primary cancers. Contiguous In Situ Carcinoma. Primary breast cancers are most often observed with contiguous *in situ* carcinoma, whereas metastases are not.

(Cont) Summary of published criteria for the diagnosis of bilateral breast cancers.

Leis et al. (1965)	Same criteria as Robbins and Berg (1964) plus: a second primary was assumed when there was wide disparity in histological type; if the histology of both tumours was similar, a greater degree of nuclear differentiation in the second lesion was required; an interval of 5 years between the first and second lesion was required without and evidence of metastatic disease.
Haagensen (1971)	no evidence of local spread from the original tumour through the midline to the opposite breast; no demonstrable distant metastases from the first breast cancer.
Chaudary et al. (1984)	in-situ change in the contralateral lesion considered absolute proof; histological difference between the first and second malignancy; histological differentiation greater in the second lesion than in the first; in the absence of histological difference, no evidence of metastatic disease from the first malignancy was required.
Hislop et al. (1984)	the tumour in the second breast was infiltrating; the tumour was not associated with widespread metastatic disease; either the histological type of the second primary was distinct from the first, or the second primary was associated with in situ change.

This more promising approach by Robbins and Berg (1964) unfortunately had comparatively little impact on subsequent studies. Leis et al. (1965), for example, used a combination of Robbins and Berg's criteria and Guiss's, but also added, without any justification, that the second lesion had to exhibit greater degree of nuclear differentiation than the first. Haagensen (1971) restricted the diagnosis of a second primary to those where no distant metastases arising from the first breast cancer was evident, although there is no reason why a bilateral breast cancer could not occur in the presence of distant metastases. The criteria of Chaudary et al. (1984) and of Hislop et al. (1984) simply borrowed from the criteria of Robbins and Berg (1964), Leis et al. (1965), and Guiss (1954).

2.3.1 The Use of these Criteria in Studies of Bilateral Breast Cancer

The use of these criteria over time gives further evidence of the confusion and arbitrariness of methods used to classify second primary breast cancers. Moertel and Soule (1957) and Hubbard (1953) used Guiss's criteria, but modified the interval between successive malignancies to 6 months. Lewison and Neto (1971) borrowed from the criteria of Robbins and Berg (1964) and Leis et al. (1965), but also incorporated the time restrictions from Guiss's criteria. Wilson and Alberty (1973) used a combination of criteria gleaned from Guiss (1954), Huff (1969), and Kilgore (1921) and fixed the restriction on the interval between successive malignancies at 1 year. McCredie et al. (1975), Rosselli Del Turco et al. (1982), Schell et al. (1982) and Pomerantz et al. (1989) accepted a second malignancy as a new primary if there was no other evidence of metastatic disease, a component of Guiss's criteria. Egan (1976) used Robbins and Berg's criteria as did Bailey et al. (1980), in part, by requiring that both tumours have an in situ component.

Many studies reported either no criteria, no reference to previously published criteria, or vague pathological criteria (Huff, 1969; Kesseler et al., 1976; Kiang et al., 1980; Al-Jurf et al., 1981; Fracchia et al., 1985; Engin, 1994; Heron et al., 2000; Hungness et al., 2000).

Others simply relied on the judgement of the pathologist who first saw the tumour to distinguish between a new primary and metastatic disease (Slack et al., 1973; Mueller and Ames, 1978; Sakamoto et al., 1978; Adami et al., 1981; Broët et al., 1995; Kollias et al., 2001). This would also apply to the large number of studies that used breast cancer cases notified to cancer registries and thus relied on the classification of the breast cancer in these data (Prior and Waterhouse, 1978; Storm and Jensen, 1986; Horn et al., 1987; Horn and Thompson, 1988; Horn and Thompson, 1988; Parker et al., 1989; Bernstein et al., 1992; Boice et al., 1992; Brenner et al., 1993; Cook et al., 1996; Vaittinen and Hemminki, 2000; Bernstein et al., 2003).

2.3.2 Discussion

If metastatic disease were occurring in the contralateral breast and if it was frequently misdiagnosed as a new breast cancer, then this would result in over-estimation of the incidence of bilateral breast cancer. Alternatively, if true bilateral breast cancers were being frequently misdiagnosed as metastatic disease, this would result in under-estimation of the incidence of bilateral breast cancer.

While misdiagnoses could occur, there is no evidence that it occurs to an extent that would cause estimates of bilateral breast cancer incidence to be significantly biased.

Fisher et al. (1984) drew similar conclusions. When reporting the occurrence of bilateral breast cancer among women enrolled in one of the early National Surgical Adjuvant Breast Project (NSABP) Trials, they noted that while many studies raised the

issue of distinguishing between metastatic disease and a true new primary, the application of criteria to minimize this misclassification often led to the exclusion of large numbers of cases. They concluded that apart from autopsy studies, where detailed pathological analysis was often lacking, there was no information on how often metastatic disease would be confused with a new primary.

Robbins and Berg (1964) were quite scathing in their criticism of the criteria that had been developed to distinguish bilateral breast cancer from metastatic disease, concluding that application of the diagnostic criteria existing at that time, without any knowledge of the extent of the problem, could conceivably make the problem worse rather than better.

Some authors argued that while breast cancer could metastasise to the contralateral breast, it did so rarely, and that malignant lesions in the second breast were more likely to be a second primary rather than metastatic disease (Shellito and Bartlett, 1967; Egan, 1976). Donegan (1970), in a study of women with advanced breast cancer, found that only 3% of recurrences occurred in the contralateral breast.

Regardless of what may or may not be the extent of misclassification bias, most recent studies have dispensed with any criteria at all, deferring instead to the initial diagnosis recorded. This may reflect a greater confidence in the skills of the modern pathologist or, alternatively, it may also reflect the greater availability of computer-coded cancer registry data and hospital admissions data. Use of these data allows the outcomes of large numbers of breast cancer cases to be determined but, at the same time, makes it prohibitively expensive to individually review the pathological classification of each tumour.

While I can not draw any firm conclusions as to whether or not misclassification of metastatic disease is a significant source of bias, I can conclude that the ability to combine the results of many studies of bilateral breast cancer has been compromised by the plethora of diagnostic criteria used and by the propensity of various investigators to change these criteria.

2.4 Epidemiology of Bilateral Breast Cancer

2.4.1 Introduction

In recent years, a number of reviews of the epidemiology of bilateral breast cancer have appeared (Dawson et al., 1998; Chen et al., 1999; Bernstein et al., 2003). The main risk factors for bilateral breast cancer are:

- Young age at diagnosis of the first breast cancer which has been consistently described as increasing the risk of bilateral breast cancer.
- Lobular carcinoma. Women diagnosed with lobular carcinoma have been found to have an increased risk of bilateral breast cancer.
- A family history of breast cancer which has been found to increase the risk of bilateral breast cancer.
- The use of Tamoxifen in the treatment of breast cancer has been shown to reduce the risk of bilateral breast cancer.

In the following sections I will review the literature describing the epidemiology of bilateral breast cancer. I have chosen for review some of the very earliest studies through to the most recent research covering a period of some 80 years.

2.4.2 The Incidence of Bilateral Breast Cancer

The early literature describing the incidence of bilateral breast cancer is almost uniformly poor. I will summarize some of the early studies of bilateral breast cancer and then discuss briefly the main problems with these. These studies are shown in Appendix A. This is by no means a comprehensive list of early work, but is sufficient to highlight the common methodological and statistical problems that were prevalent prior to 1960.

A common problem with all papers cited in Appendix A was the lack of description of the methods used. All the studies cited were hospital-based and studied what were generally described as a consecutive series of patients. This would tend to imply that these series could be regarded as cohorts of breast cancer patients being followed until the diagnosis of a second breast cancer in the contralateral breast. This was not the case, however, as a number of authors admitted to including patients in their series who had been treated for their second breast cancer, but had had their first breast cancer treated elsewhere (Harrington, 1946; Guiss, 1954; Farrow, 1956). Others included such patients, but excluded them from any statistical calculations (Hubbard, 1953; Kilgore et al., 1956).

While descriptions of study design are lacking in these studies, the most serious problem is in the calculation of incidence. What was reported as incidence in these studies was simply the proportion of the women in each case series who developed a metachronous bilateral breast cancer over the period in which the patient were followed up.

It is not sufficient to simple record the proportion of women who are diagnosed with a bilateral breast cancer, since this will depend on the length of time the series of patients

has been followed-up. The patients in these studies were followed up for varying and unreported lengths of time and, as a consequence, the reported "incidences" are not incidence rates and are uninterpretable as estimates of cumulative risk.

This is not to say that researchers in this period were unaware of the problem. Kilgore (1921), for example, reviewing earlier work noted that interpreting percentages of cases that developed bilateral disease was difficult because these were the percentages of all patients in a series and took no account of the time interval between first and second lesions.

While these "incidences" are biased estimates of cumulative risk, they were nevertheless interpreted as valid estimates of risk, leading some to advocate prophylactic mastectomy of the contralateral breast because of the "high risk" of developing bilateral breast cancer (Pack, 1951; Guiss, 1954; Dobson, 1955).

While these early studies of bilateral breast cancer were marred by erroneous estimates of incidence, subsequent studies did calculate the person-years following diagnosis of the first breast cancer and derived from this an incidence rate. These papers are listed in Appendix B and cover a period from 1952 to the present.

There are 28 studies listed in this table, most are hospital-based studies, but population-based cancer registries provide the source of data for twelve (Schoenberg, 1977; Prior and Waterhouse, 1978; Hankey et al., 1983; Burns et al., 1984; Schenker et al., 1984; Harvey and Brinton, 1985; Storm and Jensen, 1986; Murakami et al., 1987; Robinson et al., 1993; Gajalakshmi et al., 1998; Vaittinen and Hemminki, 2000; Chen et al., 2001).

In this latter group of studies, cancer registries operating in Western countries produced similar incidence estimates ranging from 5.7 per 1,000 person-years (Robinson et al., 1993) to 7.1 per 1,000 person-years (Harvey and Brinton, 1985). The exception is the

study by Prior and Waterhouse (1978) where incidence was estimated to be 3.4 per 1,000 person-years. In this study, however, bilateral breast cancers were excluded if distant metastatic disease was evident when they were diagnosed. While the number of bilateral breast cancers excluded was not stated, such exclusions would tend to bias the estimate, so that a lower incidence estimate would not be unexpected.

For registries that were operating in non-Western countries – Israel (Schenker et al., 1984), Japan (Sakamoto et al., 1978; Murakami et al., 1987) and India (Gajalakshmi et al., 1998) – much lower estimates of bilateral breast cancer incidence were obtained.

The lower rates in India and Japan may not be unexpected, given that these countries experience much lower rates of breast cancer generally than countries in Western regions. For example, in 2001, the age-standardized rates (World Standard population) of breast cancer in Japan and India were 32.7 and 19.1 per 100,000 person-years respectively, whereas in the same period the rate was 101.1 per 100,000 person-years in the USA, 84.3 per 100,000 person-years in Canada, and 87.2 per 100,000 person-years in the UK. Thus, if the incidence of breast cancer in the population of all women is lower in countries like Japan and India than in western countries, one might expect that the incidence of bilateral breast cancer in the population of women with one breast cancer diagnosis would also be different.

It is also worth noting that one of the Japanese studies, (Sakamoto et al., 1978), while defining synchronous bilateral breast cancer as those occurring within 1 year of each other, incorporated all the synchronous bilateral breast cancers in their incidence calculation including those that were actually synchronous and would therefore have contributed no person-years to the denominator. This would therefore have produced an over-estimate of the true incidence rate.

While lower rates of bilateral breast cancer in India and Japan might not be unexpected, this is not so for Israel where the age-standardized rate of breast cancer in 2001 was 90.8 per 100,000 person-years, comparable to the rates in the USA, Canada, and the UK, so similar rates of bilateral breast cancer might be expected. The very low rate of bilateral breast cancer reported (1.1 per 1,000 person-years) reported in the Israeli study may, however, be an artefact due to methodological error. Compared to the other cancer registry-based studies reviewed, the Israeli study provided the least detail of their methods and, in particular, the method used to calculate person-time was poorly described.

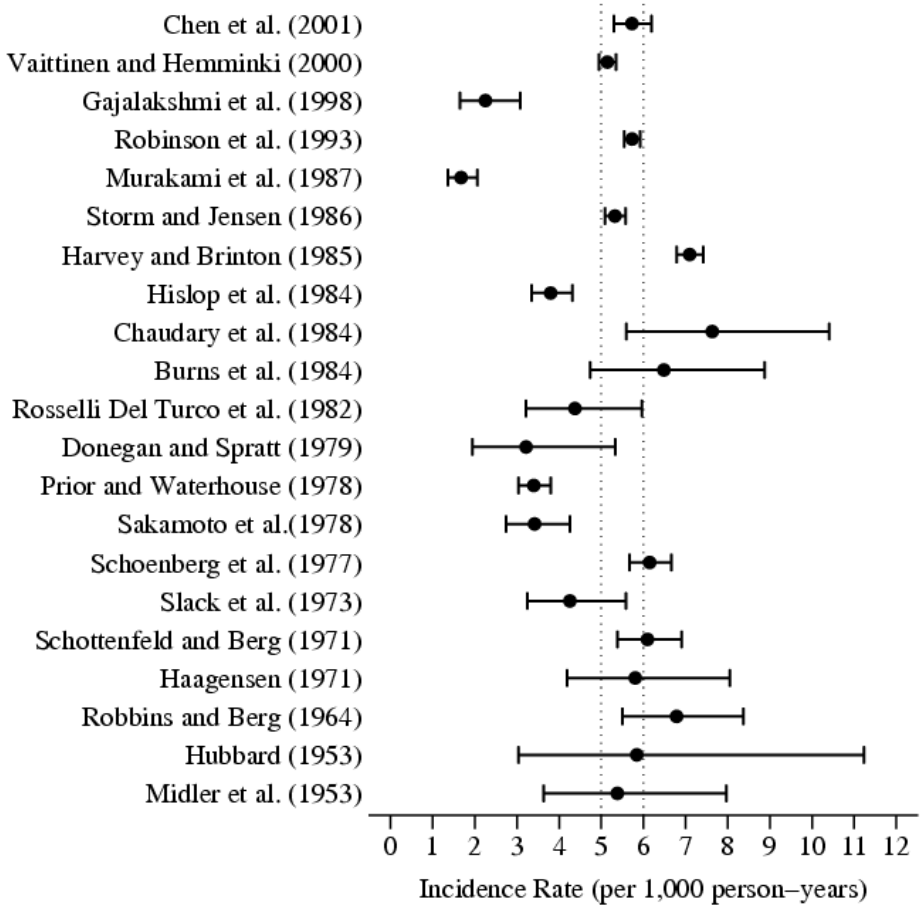
As outlined earlier, the criteria that used to discriminate between 'true' bilateral breast cancers and metastatic disease in the contralateral breast were never properly evaluated and, more than likely, excluded many cases of true bilateral breast cancer. The estimates obtained from some of the earlier studies may have been adversely affected by the use of these criteria. Midler et al. (1952), for example, excluded over 50% of the lesions that occurred in the contralateral breast in their series on this basis and similar exclusions were performed by McCredie et al. (1975) and by Prior and Waterhouse (1978). What is not clear from the description of their methods is what was done with the person-years of these women.

In addition, Prior and Waterhouse (1978) appear to have excluded some women from their study who had a second primary diagnosed after the closing date of the study – after follow-up had concluded. The implication is that they also excluded their person-years. In contrast, Midler et al. (1952), included women with bilateral breast cancer from outside the original cohort.

Thus when there was some detail in the description of methods used, it was possible to detect errors in the calculation of person-years at risk. In a number of studies reporting incidence rates, however, the methods were inadequately described and it was not possible to determine if person-years at risk had been calculated correctly (Haagensen, 1971; Schottenfeld and Berg, 1971; Mueller and Ames, 1978; Bailey et al., 1980; Rosselli Del Turco et al., 1982; Fisher et al., 1984; Hislop et al., 1984).

Figure 2-1 summarises the estimates of the incidence of metachronous bilateral breast cancer derived from the studies listed in Appendix B in a Forrest plot.

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



2.4.3 Annual Incidence of Bilateral Breast Cancer

A small number of studies calculated the annual incidence of bilateral breast cancer following diagnosis of the first breast cancer. The results of these are shown in Table 2-3. What is evident in all of these is that the annual incidence is comparatively constant over time. A constant incidence of cancer over time is quite unusual, yet no significance has been placed on this in any of these studies.

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

Years after first breast cancer	Robbins and Berg (1964)	Slack et al. (1973)	Sakamoto et al. (1978)	Donegan and Spratt (1979)	Rosselli Del Turco et al. (1982)	Chaudary et al. (1984)	Gajalakshmi et al. (1998)
1	7.945	4.389		3	5.7	7.86	
2	10.643	6.553	3.40	5	6.2	8.30	2.12
3	5.786	5.790	5.57	4	2.0	7.04	
4	4.398	1.590	2.92	8	3.4	4.69	
5	4.840	3.880	3.37	0	2.3	7.69	
6	9.229	0.823	2.73	3	3.2	5.52	
7	1.433		3.73	6	5.0	5.57	1.68
8	9.368		2.10		4.2	5.75	
9	6.711		1.59		9.2	16.72	
10	5.333		2.68			7.22	
11	13.270		4.02			3.79	
12	6.122		4.50			8.26	
13	4.381		5.17			5.03	
14	4.657		4.50			7.09	
15	0.000		3.38			8.62	
16	7.802		5.71			7.02	2.72
17	11.111		2.18				
18	5.970		4.98				
19	3.317		5.80				
20	12.903						
21	0.000						
22	12.270						

Robbins and Berg (1964) were the first to describe this constant incidence. They were principally interested in estimating the proportion of women who would get a bilateral breast cancer and to do this they calculated the annual incidence rate so that they could

then determine the cumulative risk. When they observed that the annual incidence rate appeared to be relatively constant over time they noted that this was unexpected because the incidence of breast cancer increases with age and, since their cohort of women with breast cancer was also ageing, they expected the incidence of bilateral breast cancer to also increase with age. They concluded that the absence of any increase over time was fortunate given the already high incidence of bilateral breast cancer.

The remaining studies (Slack et al., 1973; Donegan and Spratt, 1979; Rosselli Del Turco et al., 1982; Chaudary et al., 1984) all found relatively constant incidence rates and in most cases observed that this was similar to Robbins and Berg's finding, and concluded nothing more.

Other studies not presented in Table 2-3 also found a constant annual incidence of metachronous bilateral breast cancer, but graphed their results without presenting the actual data (Broët et al., 1995; Prior and Waterhouse 1978).

Most recently, Gao et al. (2003) reported the cumulative risk of bilateral breast cancer in a large series of patients diagnosed with either malignant or in situ breast cancer. At 5, 10, 15, and 20 years the risk of bilateral breast cancer diagnosis was, respectively, 3%, 6.1%, 9.1% and 12%, indicating a constant annual risk and also consistent with a constant annual incidence. This 20-year risk of 12% is approximately 1 in 8, essentially the same as found by Robbins and Berg (1964) 40 years earlier.

In summary, when studies have calculated the annual incidence of bilateral breast cancer it has been found to be constant over time.

2.4.4 Age and Bilateral Breast Cancer

Age is a major demographic risk factor for first primary breast cancer and a number of studies examined the relationship between age and risk of bilateral breast cancer. The studies, summarised in Appendix C, cover the period from 1964 to the present.

Broadly summarising the conclusions drawn from these studies, it was found that women first diagnosed with breast cancer at a young age (less than 50 years) were at increased risk of bilateral breast cancer. In addition, it was repeatedly observed that women with metachronous bilateral breast cancer were first diagnosed with breast cancer at younger ages on average than women who did not develop metachronous bilateral breast cancer. This observation was seen to support the theory that women who developed bilateral breast cancer were a highly susceptible group.

However, the relationship between age and the risk of bilateral breast cancer is more complex than the association between age and the risk of first primary breast cancer. With bilateral breast cancer there are now two ages to consider: the age at diagnosis of the first breast cancer; and the age at diagnosis of the second breast cancer.

Thus if we define a set of age groups based on the age at diagnosis of the first breast cancer we would be defining a set of cohorts of women – age-specific cohorts – who are now at risk of a bilateral breast cancer and, as these cohorts were followed over time, they would age, accumulating person-years in different age groups. We could therefore determine age-specific rates of bilateral breast cancer within each of these age-specific cohorts.

If women first diagnosed with breast cancer at a young age are at increased risk of bilateral breast cancer, what exactly does this mean? Of course these women will have a greater cumulative risk of developing bilateral breast cancer in their remaining life-

time than women first diagnosed with breast cancer at older ages. This is not what is meant by labelling them as a high risk group. What it should mean is that their age-specific rates of bilateral breast cancer were different – increased – compared to the same age-specific rates in women first diagnosed at older ages.

For example, if we consider women first diagnosed with breast cancer when aged 40 to 44 years we could, with sufficient follow-up, estimate their age-specific rate of bilateral breast cancer when they were aged 60 to 64 years. Equally so, this same age-specific rate could be estimated in other cohorts of women with breast cancer: women first diagnosed when they were aged 45 to 49 years, 50 to 54 years, 55 to 55 years, and 60 to 64 years. Would this 60 – 64 years age-specific rate in the 40 to 44 year and the 45 to 49 year age-specific cohorts be higher than in the older age-specific cohorts?

This has not been established in any previous studies.

In previous studies variety of different methods were used to investigate the relationship between age and the risk of bilateral breast cancer.

A number of studies reported age-specific incidence rates where the age was the age at first diagnosis (Haagensen, 1971; Hankey et al., 1983; Chaudary et al., 1984; Bernstein et al., 1992; Bernstein et al., 1992; Chen et al., 2001), whereas Bernstein et al. (2003) reported incidence rates by the age at diagnosis of bilateral breast cancer, and Robbins and Berg (1964) reported both separately. There are no studies that have reported the age-specific rates of bilateral breast cancer in women first diagnosed at younger ages and compared these to age-specific rates in older cohorts of women.

In those studies that reported incidence based on age at first diagnosed, the rate of bilateral breast cancer diagnosis was higher in women first diagnosed in younger age

groups, but these are essentially crude rates and do not take into account any possible difference in age-specific rates of bilateral breast cancer.

Studies that reported age-specific rates of bilateral breast cancer, ignored the age at first diagnosis. In these studies the age-specific rate of bilateral breast cancer was higher in younger age groups than in older age groups. If these rates were what was experienced by a cohort of young women with breast cancer as they aged, it would suggest that the increase in risk experienced by younger women was a transient effect and that they were only at increased risk while they were young and as they aged their rates approached those experienced by women first diagnosed at older ages.

The relationship between age and risk of bilateral breast cancer was further clouded by those studies that compared the observed number of bilateral breast cancers to the number expected based on population rates of first primary breast cancer (Prior and Waterhouse, 1978; Storm and Jensen, 1986). These studies drew erroneous conclusions concerning the risk of bilateral breast cancer in different age groups, inferring that young women with breast cancer were an extremely high risk group for bilateral breast cancer.

For example, consider the results presented by Prior and Waterhouse (1978) for age at first diagnosis of breast cancer. The ratio of observed to expected reported were 5.3 in the 15 to 44 age group, 3.0 in the 45 to 59 age group and 1.0 in those age more than 60 years. The meaning of these is clear. For women diagnosed with a first breast cancer when aged between 15 and 44 years, the number of bilateral breast cancers observed was over 5 times what would have been expected given population rates of breast cancer generally. For those aged between 45 and 59 years at first diagnosis there were 3 times as many bilateral breast cancers than would be expected and for those aged over

60 years at first diagnosis, the numbers of bilateral breast cancers observed were the same as would be expected.

Prior and Waterhouse (1978) inferred from these results that women first diagnosed with breast cancer at a young age (15 to 44 years) were at high risk for bilateral breast cancer compared to women first diagnosed with breast cancer at older ages.

This is not a valid interpretation of these results. These are indirect standardized rate ratios, but they are not comparable. While Prior and Waterhouse (1978) state that they have used population rates of breast cancer to determine the expected numbers of bilateral breast cancer in these three age cohorts, this is not what they have done. In fact, they have used rates from three different populations to determine the expected numbers. The expected number of bilateral breast cancer in the youngest cohort has been determined from population rates of women aged at least 15 years. The expected number of bilateral breast cancers in the oldest cohort has been determined from population rates of women aged at least 60 years.

Thus because different population rates are being used in the calculation of these ratios of observed to expected they are not comparable and no inference can be made concerning the risk of bilateral breast cancer across these different cohorts of women defined by their age at first diagnosis of breast cancer.

Finally, a number of studies calculated the average age at first diagnosis for women with or without metachronous bilateral breast cancer (Haagensen, 1971; Bailey et al., 1980; Adami et al., 1981; Rosselli Del Turco et al., 1982; Brenner et al., 1993; Healey et al., 1993; Abdalla et al., 2000). In these studies, women with metachronous bilateral breast cancer were consistently found to have had their first breast cancer at a younger

age, on average, than women with only one breast cancer and this was interpreted as further evidence of bilateral breast cancer being a sign of high susceptibility.

An alternative explanation is that this is simply an artefact of failing to account for mortality. In women with breast cancer, younger women will have a greater life expectancy in general than older women and therefore a higher cumulative risk of being diagnosed with bilateral breast cancer. Observing a younger average age at first diagnosis of breast cancer in women who subsequently are diagnosed with bilateral breast cancer would therefore be entirely expected and cannot be interpreted as a sign of increased risk or susceptibility.

2.4.5 Reproductive Factors and Bilateral Breast Cancer

The relationship between parity and first primary breast cancer is complex. Women who are nulliparous are at increased risk of breast cancer and, while the crude effect of the number of full-term pregnancies is protective, after controlling for age at first full-term pregnancy, the effect of subsequent pregnancies is no longer apparent (MacMahon et al., 1970). Late first full-term pregnancy, on the other hand, confers a risk greater than that experienced by nulliparous women.

With regard to the occurrence of bilateral breast cancer, a number of studies have examined the relationship between various reproductive factors and bilateral breast cancer. These, together with their results, are shown in Appendix D. Apart from the cohort study conducted by Bernstein et al. (1992), all were case-control studies.

Few studies considered age at first pregnancy. Adami et al. (1981) found protective effects for early age at first full-term pregnancy, but, while these effects could be considered to be large, the study was comparatively small and the results were not statistically significant. Similarly protective effects were also found in other studies,

but these too were not statistically significant (Hislop et al., 1984; Kato et al., 1986; Horn and Thompson, 1988). These studies either excluded nulliparous women from the comparison or, as in the Kato study, included the nulliparous women in the older age group.

The remaining studies (Horn and Thompson, 1988; Bernstein et al., 1992; Cook et al., 1996) simply dichotomised parity into nulliparous and parous and demonstrated small increases in risk associated with nulliparity, none of which were statistically significant.

Given that parity and age at first pregnancy have a complex association with risk of first primary breast cancer, it may be more prudent to conclude that these factors have yet to be properly investigated as to their role in the aetiology of bilateral breast cancer.

Reproductive factors such as age at menarche, age at menopause, and oral contraceptive use have been shown to be related to the risk of developing breast cancer. Early age at menarche has been consistently found to be associated with an increase in the risk of breast cancer as is the age at which regular menstrual cycles commence (Henderson et al., 1981; Hsieh et al., 1990; Kelsey et al. 1993). The association between age at menopause and subsequent risk of breast cancer is also well established in the literature. The risk of breast cancer has been estimated to increase by approximately 3% per year that menopause is delayed (Kelsey et al. 1993). Use of oral contraceptive has been shown to increase the risk of breast cancer among young women which was initially linked with long-term use in these women (Romieu et al., 1990; Thomas, 1991). A subsequent study, however, found that when use of oral contraceptives and duration of use were considered together, breast cancer risk was related to current or recent use with duration of use having no effect on risk, thus indicating that breast cancer risk was associated with recent use rather than duration of use (Collaborative Group on

Hormonal Factors in Breast Cancer, 1996). The increase in risk is generally modest and, after women cease taking oral contraceptives, the risk disappears within 10 years. Overall, the pattern of risk associated with use of oral contraceptives would tend to indicate that they are acting as a promoter in the latter stages of carcinogenesis.

While various studies have examined these factors in the development of bilateral breast cancer (Appendix D), little convincing evidence has been found that would suggest a role in the aetiology of bilateral breast cancer. These studies were, however, comparatively small and, in some, the effects found would be considered of practical significance indicating problems with statistical power (Hislop et al., 1984; Kato et al., 1986; Horn and Thompson, 1988). More importantly, however, the small sample sizes in these studies led to rather crude categorisations of exposures. For example, age at menarche (Horn and Thompson, 1988) or age at first birth (Hislop et al., 1984) were simply and arbitrarily dichotomised.

While existing evidence would suggest that reproductive factors are not associated with risk of bilateral breast cancer, I would conclude that as yet there have been no studies of sufficient size conducted that would adequately capture the complexity of reproductive exposures. Hence the question as to whether or not a relationship exists for some of the factors discussed above is as yet unanswered.

2.4.6 Family History and Bilateral Breast Cancer

Women with a family history of breast cancer have an increased risk of being diagnosed with breast cancer. This risk is further increased if both the mother and the sister have a history of breast cancer and increased further if both mother and sister were diagnosed at an early age (Claus et al., 1990).

Studies listed in Appendix E investigated the relationship between family history and the occurrence of bilateral breast cancer.

In two studies (Horn and Thompson, 1988; Cook et al., 1996) defined family history as: mother with breast cancer; sister with breast cancer; or both. They were able to show that the risk of bilateral breast cancer was more elevated in women with an affected sister and less so in women with an affected mother. Anderson and Badzioch (1985), however, found that the risk associated with having an affected sister was different depending on whether her breast cancer was diagnosed before or after menopause.

The cohort study conducted by Bernstein et al. (1992) is the most detailed of those listed in Appendix E. They found increases in risk associated with family history defined as either mother or sister affected. They were also able to show that this risk was even more elevated if the mother or sister were diagnosed before age 45. Their most interesting finding, however, was in regard to the age-related risk of bilateral breast cancer compared to the age-related risk of unilateral breast cancer. In women with a first degree relative with breast cancer, the relative risk of first breast cancer declined with age. The relative risk of bilateral breast cancer, however, remained constant with age and was approximately double the risk of women with no exposed first degree relative.

2.4.7 Obesity and Bilateral Breast Cancer

The association between obesity and the risk of breast cancer has been subject of numerous studies and the results suggest that the effect of weight is strongly age dependent. For pre-menopausal women there is no effect of weight on the risk of breast cancer, but a positive relationship exists for older women (de Waard et al., 1977). Results from studies that have used body mass index (BMI) or as it is sometimes

known, Quetelet's index, are less clear and it seems that weight unadjusted for height is a better indicator of risk (Henderson et al., 1996).

There is a problem with modelling BMI as an independent effect. BMI is defined as weight divided by the square of the height and, in a regression model, BMI would therefore be the product of weight and the reciprocal of height squared – an interaction term. Consequently, such a model would be miss-specified if BMI was treated as a single independent effect without also including the independent effects of weight and the reciprocal of height squared (Kronmal, 1993). The finding by Henderson et al. (1996) is interesting because they treat height and weight as independent effects and avoid the use of BMI.

In a more recent study, Huang et al. (1997) initially suggested that the effect of BMI in post-menopausal women was mediated by their use of hormone replacement therapy (HRT), but in a subsequent study suggested that fat distribution might be more important in determining risk of breast cancer (Huang et al., 1999), an effect that remained after adjusting, incorrectly, by BMI as a single effect.

Appendix F summarizes the results from studies that have considered the role of obesity in the aetiology of bilateral breast cancer. Most of these studies employed Quetelet's index (BMI) as a measure of obesity. None of the studies obtained effects that were statistically significant and consequently there is little strong evidence of an association.

Given that obesity has an apparently complex relationship with risk of first primary breast cancer, it may be safe to conclude that as yet the role of obesity in the aetiology of bilateral breast cancer has not been adequately investigated.

2.5 The Effect of Characteristics of the First Breast Cancer

2.5.1 Cancer Stage and Bilateral Breast Cancer

Cancer stage is a construct that is designed to capture a measure of the extent of disease in a comparatively small number of categories. Staging involves consideration of the size of the tumour, the extent of any regional spread of the disease, and the presence of distant metastatic disease. Cancer staging criteria have been developed by the American Joint Committee on Cancer (AJCC) and by the International Union against Cancer (UICC). These were revised in 1992 so that both provided equivalent classifications of cancer stage thus ensuring that comparisons could be made between different regions or treatment centres using either system (American Joint Committee on Cancer, 1992). While there are still problems associated with cancer staging in general and with staging of breast cancer in particular, (Benson et al., 2003), breast cancer stage still remains an important prognostic factor, arguably the most important predictor of breast cancer survival.

A number of studies have examined the risk of bilateral breast cancer associated with the stage of the first breast cancer or with components of staging criteria such as number of positive nodes or tumour size (Appendix G). In general, the results from these studies are inconsistent. Slack et al. (1973), Hankey et al. (1983) and Storm and Jensen (1986) found effects that would tend to suggest an increase in risk of bilateral breast cancer with more advanced first breast cancers, whereas Haagensen (1971) found the opposite and Horn and Thompson (1988) found no relationship.

These inconsistencies likely reflect methodological differences between these studies. Storm and Jensen (1986), for example, used indirect standardised rate ratios as their measure of effect and computed these for different age cohorts and hence, as I have

already explained above, could not make valid inferences concerning risk of bilateral breast cancer.

In the case-control study conducted by Horn and Thompson (1988), the cases were bilateral breast cancers diagnosed between July 1975 and December 1983, but the controls were women with breast cancer alive at this time but who could have been first diagnosed at any time since 1935. No attempt was made to match on time since first diagnosis and they instead attempted to adjust for time since first diagnosis in their analysis. Since long-term survivors of breast cancer are likely to be women with localised breast cancers, their finding of no relationship with stage may reflect bias in their selection of controls.

In summary, I would conclude that the relationship between stage of the first breast cancer and subsequent risk of bilateral breast cancer has yet to be adequately investigated.

2.5.2 Histology and Bilateral Breast Cancer

Robbins and Berg (1964) were the first to demonstrate that the histology of the first breast cancer was associated with differences in the incidence of bilateral breast cancer. Lobular carcinoma, in particular, was associated with an increase in the risk of bilateral breast cancer.

Subsequent studies (Appendix H) have also found an increase in the risk of bilateral breast cancer associated with first breast cancers that were lobular (Horn et al., 1987; Horn and Thompson, 1988; Bernstein et al., 1992; Broët et al., 1995; Cook et al. (1996). Bernstein et al. (2003) also found an increase in incidence of bilateral breast cancer in young women initially diagnosed with medullary carcinoma.

Not all studies have found significant associations between lobular histology and subsequent risk of bilateral breast cancer (Hislop et al., 1984; Newman et al., 2001; Li et al., 2003). Of these, the study by Newman et al. (2001) should be discounted since it was a comparatively small matched case-control study which did not take the matching into account in the analysis. It is not immediately clear why the remaining two studies found no relationship. Hislop et al. (1984) did find that lobular histology was associated with synchronous bilateral breast cancer defined as any bilateral breast cancer occurring within one year of the first, but no effect for metachronous bilateral breast.

While the cohort study conducted by Li et al. (2003) was relatively small, it was of comparable size to the study conducted by Robbins and Berg (1964). They did, however, define metachronous bilateral breast cancer as occurring more than 6 months after the first breast cancer.

In summary, the available evidence would suggest that women initially diagnosed with lobular carcinoma are at increased risk of metachronous bilateral breast cancer.

2.5.3 Hormone Receptors and Bilateral Breast Cancer

Oestrogen and progesterone receptor levels are associated with survival in women with breast cancer. Women who are diagnosed with oestrogen receptor (ER) positive node-negative breast cancers experience lower risk of recurrence and better survival over a 4 to 6 year period than similar women with ER negative tumours (Henderson and Patek, 1998). There is also evidence of differences in the pattern of incidence of ER positive and ER negative breast cancers leading some to suggest that these represent two differing types of breast cancer, early-onset (pre-menopausal) breast cancer associated

with ER negativity and the other, late-onset (post-menopausal) breast cancer related to ER positivity (Anderson et al., 2002).

Comparatively few studies have examined subsequent risk of bilateral breast cancer according to the oestrogen receptor and progesterone receptor characteristics of the first breast cancer (Appendix I). Horn and Thompson (1988) found an increased risk of bilateral breast cancer in the first year following diagnosis of the first breast cancer associated with PR positive tumours. Mariani et al. (1997) found a reduced risk of bilateral breast cancer in pre-menopausal women associated with ER positive tumours and an overall reduced risk associated with PR positive lobular carcinomas. Li et al. (2003) found no association with either ER or PR in pre-menopausal women..

It is difficult to draw any overall conclusions from these studies.

2.5.4 Chemotherapy and Bilateral Breast Cancer

All studies that examined if the use of chemotherapy to treat the first breast cancer subsequently altered the risk of bilateral breast cancer have concluded that the risk was reduced in those women who had had chemotherapy (Appendix J).

The reduction in risk associated with the use of tamoxifen was particularly strong and in a meta-analysis of randomised controlled trials was associated with a significant reduction in the risk of bilateral breast cancer (Early Breast Cancer Trialists' Collaborative Group, 1998).

This has led to tamoxifen being considered as a preventative drug for women at high risk of breast cancer. In a randomised controlled trial, tamoxifen was shown to reduce the risk of breast cancer by approximately 50% in women who were breast cancer free (Fisher et al., 1998). A more recent randomised controlled trial in women with BRCA1

or BRCA2 mutations found a reduced risk of breast cancer in BRCA2-positive women but not BRCA1 positive women (King et al., 2001).

2.5.5 Radiotherapy and Bilateral Breast Cancer

A number of studies have considered treatment of the first breast cancer with radiotherapy and the subsequent risk of bilateral breast cancer (Appendix K). There is little convincing evidence of an effect in any of these. Most studies found small increases in risk associated with radiotherapy, but only after stratification by some other factor such as age at first diagnosis or time since first diagnosis of breast cancer.

Differences in study methods make synthesis of the results from these studies difficult, but any increases in risk of bilateral breast cancer associated with the use of radiotherapy in the treatment of the first breast cancer that were found were small and likely to be due to chance.

2.6 The Effect of Bilateral Breast Cancer on Survival

2.6.1 Introduction

There is a considerable literature reporting the results of studies that have attempted to estimate the effect that a diagnosis of bilateral breast cancer has on survival from breast cancer. Estimating this effect is not a trivial exercise and unless this is done correctly, quite erroneous conclusions can be drawn.

While it is tempting to view women with or without bilateral breast cancer as forming a natural dichotomy, this is not so. Women who are diagnosed with metachronous bilateral breast cancer have survived some period of time with unilateral breast cancer and then some period of time with bilateral breast cancer. Any analysis which fails to take this into account, could potentially produce biased survival estimates. If one used a

variable to record whether a women had unilateral or bilateral breast cancer, then for women with metachronous bilateral breast cancer, this variable would not be fixed, but time-dependent.

A method for incorporating time-dependent variables into a survival analysis was developed in 1972 (Cox, 1972), but was not available in popular statistical software programs until some decades after this. For example, time-dependent proportional hazards regression was not available in SAS until the early 1990s.

In the following two sections I will review the results of studies that have attempted to estimate the effect of bilateral breast cancer on survival. The first section will look at majority of these studies that have employed methods which ignored the time-dependent nature of metachronous bilateral breast cancers. These studies are not purely of historical interest, some are quite recent, but because they comprise the majority of studies conducted, their conclusions remain influential.

In the second section I will focus on those studies that have used time-dependent survival methods.

2.6.2 Studies not using Time-Dependent Proportional Hazards Methods

These studies are summarised in Appendix L and can be categorised into two groups depending on how they determined the survival of women with metachronous bilateral breast cancer. Some calculated this survival from date of diagnosis of the first breast cancer and others from date of diagnosis of the metachronous bilateral breast cancer. Only a small number of studies attempted to account for the interval between the first and second diagnosis in their analysis. These studies are discussed in the following sections according to the approach used.

2.6.2.1 Survival from date of diagnosis of the first breast cancer

A very common approach was to define all women with metachronous bilateral breast cancer as a group and then compare their survival from the date of diagnosis of the first breast cancer to the survival of a group of women who did not experience a bilateral breast cancer. Consequently, for women with metachronous bilateral breast cancer, their survival time while they had only a single unilateral breast cancer was falsely attributed to the bilateral breast cancer.

For example, if a woman had bilateral breast cancer diagnosed two years after her first breast cancer and then survived a further two years, studies of this type would have treated the overall survival of four years as if it were due to metachronous bilateral breast cancer rather than the final two years.

Not surprisingly, most studies using this approach found that women with metachronous bilateral breast cancer had better survival than women with unilateral breast cancer (Harrington, 1946; Cliffton and Young, 1951; Guiss, 1954; Wilson and Alberty, 1973; Bailey et al., 1980; Al-Jurf et al., 1981; Schell et al., 1982; Michowitz et al., 1985).

Only two studies concluded that there was no difference in survival (Slack et al., 1973; Mose et al., 1997), but both studies did in fact find differences in survival between the unilateral and metachronous groups of 8% and 10% respectively in favour of the metachronous bilateral breast cancer group. One study found poorer survival for women with metachronous bilateral breast cancer (Rosselli Del Turco et al., 1982).

The better survival of women with metachronous bilateral breast cancer was seen as a paradoxical result and various explanations were hypothesised to explain this. Some attributed the effect to better prognosis of the first breast cancer (Harrington, 1946;

Bailey et al., 1980; Al-Jurf et al., 1981), to immunological effects caused by the first breast cancer (Guiss, 1954) or the possibility of a host resistance mechanism (Wilson and Alberty, 1973).

This is not to say that these authors were unaware that being diagnosed with metachronous bilateral cancer required some period of time to elapse and that this could be influencing their results. Harrington (1946), for example, thought that this was the most likely explanation, but others placed no great significance on the survival benefit inherent in their definition of the metachronous bilateral cancer group.

Synchronous bilateral breast cancers can be compared to unilateral breast cancer survival without any difficulty, provided that no interval between first and second breast cancer is being used in the definition of synchronous.

Poorer survival for women with synchronous bilateral breast cancers compared to women with unilateral breast cancer was invariably observed leading some to conclude that having both breast cancers at the same time was a significant risk factor (Harrington, 1946; Wilson and Alberty, 1973; Bailey et al., 1980).

2.6.2.2 Survival from date of diagnosis of the second breast cancer

The most common approach taken by the studies listed in Appendix L was to determine the survival of women with metachronous bilateral breast cancer from the date of the second diagnosis. This approach, while correctly specifying the survival for the metachronous bilateral group, does so at the expense of the survival estimate in the unilateral group.

If we consider the example I gave above, a woman who has a metachronous bilateral breast cancer diagnosed two years after her first breast cancer diagnosis will now, using

this approach, contribute her time of observation following the second diagnosis to the metachronous group in the survival analysis. The first two years, however, which should be incorporated in the survival of women with unilateral breast cancer, is discarded. Using this approach, therefore, the survival of the unilateral group would be incorrectly specified, leading to an underestimate of the survival in women with unilateral breast cancer. Since the cumulative risk of metachronous bilateral breast cancer increases the longer a cohort is followed in time, this bias would likely become more pronounced in studies with longer periods of follow up.

Studies that employed this design in their survival analysis produced markedly different survival estimates for women with metachronous bilateral breast cancer than those discussed previously. In general, survival from metachronous bilateral breast cancer appeared to be poorer than survival in women with unilateral breast cancer (Moertel et al., 1961; Wanebo et al., 1985; Robinson et al., 1993; Gajalakshmi et al., 1999; Carmichael et al., 2002), although some studies found a better survival in the metachronous group (Burns et al., 1984; Péloquin et al., 1992).

2.6.2.3 The effect of the time interval between first and second breast cancer

While using the date of diagnosis of the metachronous bilateral breast cancer to calculated survival time may allow reasonably valid comparisons to be made with the survival of women with unilateral breast cancer, the interval between the first and second breast cancer is ignored.

A few studies attempted to examine the effect that the interval of time between the two breast cancers had on survival. In general all of these produced results that suggested that survival from metachronous bilateral breast cancer improved as the interval

between the two cancers increased (Farrow, 1956; Holmberg et al., 1988; Skowronek and Piotrowski, 2002; Bernstein et al., 2002)

2.6.3 Studies using Time-Dependent Proportional Hazards Methods

A more appropriate method for analysing the effect on survival is to model the occurrence of the second primary as a time-dependent variable. While Cox described this approach in 1972 (Cox, 1972), very few studies of bilateral breast cancer conducted after 1972 have utilized this method. The reasons for this are probably, in part, due to a lack of understanding of survival analysis methods, but also to the lack of availability of time-dependent modelling capabilities in commercially available statistical programs.

There are only five studies that I have identified that have estimated the effect of bilateral breast cancer on survival using time-dependent proportional hazards models. These are listed in Appendix M.

All of these provided an estimate of the effect of a metachronous bilateral breast cancer diagnosis on breast cancer survival using a single time-dependent variable. The results obtained all indicate that the diagnosis of the second cancer increased the risk of breast cancer death. Healey et al. (1993) found a diagnosis of metachronous bilateral breast cancer was associated with a 16% increase in risk of breast cancer death after adjusting for age and the tumour characteristics and treatment of the first breast cancer, whereas Black et al. (1996) and Kollias et al. (2001) found larger and somewhat similar effects: increases in risk of 56% and 67% respectively.

Black et al. (1996) provided their results further stratified by age (<50, ≥ 50 years) and stage of the first primary defined by the SEER historical staging classification as Stage 1 (localised, node negative) or Stage 2 (regional, node positive). These suggest that

effect of the second primary was independent of the stage of the first breast cancer, but elevated in women first diagnosed at ages less than 50 years.

Heron et al. (2000), Abdalla et al. (2000) and Kollias et al. (2001) all attempted to estimate the effect on survival of the interval between the first and second primary. Only Kollias et al. (2001) appears to have done this using a proportional hazards model with multiple time-dependent covariates and the interval-specific effects they found were similar to the estimate obtained using a single time-dependent effect. This would suggest that the time interval between the first and second breast cancer had little effect on the risk associated with a bilateral breast cancer diagnosis. Kollias et al. (2001) used only three time-dependent covariates, however, with the last of these estimating the effect of bilateral breast cancer diagnosis five or more years after the first breast cancer diagnosis. This may be too crude a classification to adequately estimate an effect if it exists.

2.7 Summary

The incidence of bilateral breast cancer has been estimated in a number of studies and, based on relatively recent large cohort studies is likely to be between 5 and 6 per 1,000 person-years. In studies that have examined the annual incidence of bilateral breast cancer, all have found it to be relatively constant over time.

Various risk factors for bilateral breast cancer have been found.

Women first diagnosed with breast cancer at a young age have been found to be at increased risk of bilateral breast cancer, but the evidence for this comes largely from studies that have estimated the crude incidence in different cohorts of women defined by their age at first diagnosis or from studies that have used inappropriate statistical methods (indirect standardisation or average age at first diagnosis). The age-specific

incidence of bilateral breast cancer in younger and older cohorts of women with breast cancer has yet to be properly investigated.

Women with lobular carcinoma have been found to be at increased risk of bilateral breast cancer in a number of studies. More recently an increase in the risk of bilateral breast cancer has also been found in women first diagnosed with medullary carcinoma.

A number of the established risk factors for breast cancer have also been investigated with respect to the risk of bilateral breast cancer. Little association has been found for various reproductive factors (for example, age at menarche, parity, age at first full-term pregnancy, age at menopause) or for obesity, but these results come from studies that were comparatively small and which classified these exposures somewhat crudely.

Similar criticism could be made of many of the studies that have examined family history of breast cancer as a risk factor for bilateral breast cancer, but all have found increases in risk associated with a positive family history.

While many studies that have examined the effect of metachronous bilateral breast cancer on survival from breast cancer, only quite recent studies have applied statistical techniques that would provide valid estimates of this effect . In these later studies the diagnosis of bilateral breast cancer has been associated with an increase in the risk of breast cancer mortality. Whether this risk is affected by the interval of time between the first and second diagnosis has yet to be adequately investigated.

2.8 The Aims of this Thesis

With regard to the incidence of bilateral breast cancer, this thesis has four principal aims:

- To describe the age-specific incidence of metachronous bilateral breast cancer in cohorts of women defined by their age at first diagnosis of breast cancer.

- To compare the average age at first diagnosis of breast cancer in women with unilateral breast cancer to the average age at first diagnosis of breast cancer in women with metachronous bilateral breast cancer.

- To describe the incidence of metachronous bilateral breast cancer in cohorts of women defined by the histology of their first breast cancer.

- To describe the incidence of metachronous bilateral breast cancer in cohorts of women defined by the stage of their first breast cancer.

With regard to the effect of diagnosis of bilateral breast cancer on survival from breast cancer, the principal aim of this thesis is:

- To estimate the effect of a bilateral breast cancer diagnosis on survival from breast cancer in different intervals of time since the first diagnosis of breast cancer.

Overall, the principal aim of this thesis is:

- To interpret the incidence of bilateral breast cancer in terms of multi-stage carcinogenesis theory and consider the implications of this on the incidence of breast cancer generally.

3 METHODS

3.1 Introduction

This analysis was conducted on cancer registry data for the period 1973 to 2000 obtained from the Surveillance, Epidemiology, and End Results (SEER) Program of the US National Cancer Institute (NCI). These data can be ordered free of charge via the SEER website (http://seer.cancer.gov/ current as of January 2004).

Since 1973, the SEER Program has collected data from 11 population-based cancer registries and three supplementary registries within the USA and, from this, published annual reports describing cancer incidence and survival data (see, for example, Ries et al., 1999). The locations of the population-based cancer registries that contribute their data to the SEER Program are shown in Table 3-1.

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

	Location of Registry	Year Registry Commenced	Year Registry Incorporated into SEER
1	San Francisco-Oakland SMSA	1969	1973
2	Connecticut	1935	1973
3	Metropolitan Detroit	1969	1973
4	Hawaii	1960	1973
5	Iowa	1973	1973
6	New Mexico	1966	1973
7	Seattle (Puget Sound)	1974	1974
8	Utah	1966	1973
9	Metropolitan Atlanta	1975	1975
10	San Jose-Monterey	1987	1992
11	Los Angeles	1972	1992

Cancer registries are chosen for inclusion in the SEER Program because they operate and maintain high quality, population-based, cancer reporting systems. The registries currently within the SEER Program cover approximately 14% of the U.S. population and are generally representative of this population with regard to social class indicators

such as levels of poverty and education. They do tend, however, to be somewhat over-representative of urban populations and have a higher proportion of foreign-born individuals than the general population (Hankey et al., 1999).

3.2 Study Design

I have conducted a cohort study of bilateral breast cancer. The cohort consists of all women with first primary breast cancer identified within the SEER data. Women in this cohort were then followed over time until death from breast cancer, death from any other cause, or until 31 December 2000.

The full date of diagnosis of cancers is not provided in the SEER data, only the month and year of diagnosis. Similarly, while the survival time is provided for each cancer, this is expressed as the total time in months and years from diagnosis to death, if the person has died during the period covered by the data, or 31st December 2000 otherwise. This was converted into total survival time in months. For women with bilateral breast cancer, there were two survival times and the difference between these defined the time between first and second diagnosis.

Synchronous bilateral breast cancers were defined as those diagnosed in the same month and year. All other bilateral breast cancers were treated as metachronous.

The incidence of bilateral breast cancer was determined by identifying all women within the cohort who were subsequently diagnosed with metachronous bilateral breast cancer. For this analysis, women in the cohort contributed person-time from the date of diagnosis of their first breast cancer until the date of diagnosis of metachronous bilateral breast cancer, date of death from any cause, or 31 December 2000, whichever came first.

The effect of a diagnosis of metachronous bilateral breast cancer on survival from breast cancer was estimated using the same cohort of women. Survival was calculated from date of diagnosis of the first breast cancer until death from breast cancer. For those women who did not die from breast cancer, either dying from other causes or still alive on 31 December 2000, survival times were censored at these dates. The time from date of diagnosis of the first breast cancer and the date of diagnosis of metachronous bilateral breast cancer was used to define the occurrence of the bilateral breast cancer as a time-dependent effect.

3.3 SEER Data items

The format of the SEER data and a description of all variables contained within the data file are described in accompanying documentation (SEER, 2003). As of January 2004, this documentation was also available at the SEER Web-Site http://seer.cancer.gov/publicdata/documentation.html.

3.3.1 Person Identifiers

Each registry contributing to the SEER program identifies each person in their data by a unique identifier. Within the combined SEER data, each registry is identified by registry code and therefore each person is identified by the combined registry code and person identifier. Consequently it is possible to link all cancers for an individual within a registry.

It is not possible to identify persons diagnosed with cancer in one registry and who had subsequent cancer diagnoses outside of the geographic region covered by that registry.

3.3.2 Cancer Sequence Number

In addition to the person identifier, there is also a variable that codes the sequence in which cancers are diagnosed for a person with multiple cancer diagnoses. This sequence number identifies the first cancer, second cancer, third cancer, etc.

Of course, the first cancer recorded for a person in the SEER data may not necessarily be the first cancer that that person has had. The SEER registry collection begins in 1973, consequently there are likely to be a few women within the registry with a diagnosis of breast cancer who had a previous breast cancer diagnosed prior to 1973.

While most participating registries began contributing their data to the SEER program in 1973, many were operating and registering cancers prior to this (Anonymous, (Anonymous, 2003 #5690}). See Table 3-1 for the years when each Registry began operating. It should therefore be possible to use this sequence number to at least identify some, but not all, women who may have had a prior cancer diagnosis not recorded in the SEER data.

3.3.3 Vital Status and Cause of Death

For each record in the SEER data there is a variable that indicates if that person was alive at the end of the period of coverage or had died prior to this. For each person who has died, the cause of death is coded using ICD9 codes. Breast cancer deaths were any death coded to 174.

3.3.4 Diagnostic Confirmation

For each cancer in the SEER data there is a variable that indicates if the diagnosis of the cancer had been microscopically confirmed, either by positive histology, positive

exfoliative cytology, or positive microscopic confirmation. For this analysis, tumours that were not confirmed microscopically were regarded as not verified.

3.3.5 Type of Reporting Source

Notification of cancers can come to a cancer registry from a number of sources: hospital, laboratory, etc. A variable in the SEER data records the source of notification for each cancer registered. In particular, this variable identifies those cancer notifications that are from death certificates only, or where the cancer was an autopsy finding.

3.3.6 Histology (Morphology)

The coding schemes used in the SEER program have changed over time. Prior to 1976, the Manual of Tumor Nomenclature and Coding 1968 (MOTNAC) was used. From 1976, the International Classification of Diseases for Oncology 1976 (ICD-O) was used and the cases previously coded with MOTNAC were automatically recoded without review to ICD-O-2.

From 1986 to 1991, the International Classification of Diseases for Oncology, Field Trial Edition, 1986 was used and then the International Classification of Diseases for Oncology, Field Trial Edition, 1988. These were also converted to ICD-O-2. From 1992 the International Classification of Diseases for Oncology Version 2 was used.

I have used the ICD-O-2 morphology codes to construct eight breast cancer groups (Appendix N). Remaining histology codes were classified as ‘unspecified carcinoma’ or ‘other’.

The documentation accompanying the SEER data indicated that there were special morphology codes used by the SEER program to identify breast cancers with a lobular component. These were:

8522/3 Infiltrating duct carcinoma and lobular carcinoma
8523/3 Infiltrating duct carcinoma and lobular carcinoma in situ
8524/3 Intraductal carcinoma and lobular carcinoma in situ
8522/2 Intraductal carcinoma and lobular carcinoma in situ

No tumours coded 8523 or 8524 were found, however.

3.3.7 Breast Cancer Stage

Dealing with cancer stage of an extended period of time is problematic because staging definitions can change and because diagnostic technologies can change. Survival analyses, in particular, can be affected by changes in staging criteria that occur over time leading to the phenomena known as 'stage creep'.

To avoid this, I have used the SEER historical staging criteria for all analyses reported. This definition of cancer stage was derived from extent of disease categories originally developed by the End Results Group of the National Cancer Institute in 1967 and has been maintained, unchanged, over time (Young et al., 2001).

Tumours staged as localised (Stage 1) are invasive tumours that are still confined entirely within the organ of origin. Those classified as regional (Stage 2) have extended beyond the organ of origin into surrounding organs or tissues, or into regional lymph nodes. Those classified as distant (Stage 4) have spread to parts of the body that are remote from the site of the primary tumour either by direct extension or metastasis.

This summary stage variable has been used by the SEER program since its inception in 1973. It is missing for comparatively few breast cancers. Given that it has only three levels, it is clearly a more crude measure than the staging system developed by the American Joint Committee on Cancer (AJCC) or the TNM system of the International

Union against Cancer (IUCC). In Table 3-2, one can see that while the AJCC and TNM systems are comparable (and this is a result of efforts by the AJCC and the IUCC to make them so (Benson et al., 2003)), the use of only three levels in the SEER system only partially captures variation in the extent of disease. For example, node negative breast cancers are all classified as localised in the SEER system, but the AJCC and TNM systems allow further delineation based on the size of the tumour.

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

	T	N	M	SEER
Stage 0	Tis	N0	M0	In Situ
Stage I	T1	N0	M0	Local
Stage IIA	T0	N1	M0	Regional
	T1	N1	M0	Regional
	T2	N0	M0	Local
Stage IIB	T2	N1	M0	Regional
	T3	N0	M0	Local
Stage IIIA	T0	N2	M0	Regional
	T1	N2	M0	Regional
	T2	N2	M0	Regional
	T3	N1	M0	Regional
	T3	N2	M0	Regional
Stage IIIB	T4	Any N	M0	Distant
	Any T	N3	M0	Regional
Stage IV	Any T	Any N	M1	Distant

3.3.8 Radiotherapy Treatment

The use of radiotherapy in the treatment of a cancer has been coded in the SEER data since its inception. While there are a number of different categories in the coding scheme that is used, most records were coded as either no radiotherapy or beam radiotherapy. I have therefore recoded this variable to radiotherapy use: yes or no.

3.4 Data Extraction and Exclusions

I extracted all diagnoses of breast cancer in women that were either malignant (ICD9 174) or in-situ (ICD9 233) and to these data I applied the following four exclusions.

1. All women, and hence all their cancer diagnoses, were excluded if I could not be sure that the first breast cancer diagnosis recorded in the SEER data was indeed their first breast cancer diagnosis.

Since one of my aims was to investigate the incidence of bilateral breast cancer, it was important to ensure, within the limits of the data, that the first breast cancer recorded for a woman was indeed her first breast cancer. This is because I needed to be sure that the contralateral breast was at risk of breast cancer and, given the widespread use of mastectomy was a mode of treatment for breast cancer, this would be unlikely to be the case if the first breast cancer recorded in the SEER data was not in fact the first breast cancer diagnosed.

As explained earlier, the SEER data contain a variable that records a sequence number indicating the order in which cancer diagnoses are made for an individual. Within a registry, this variable indicates if a cancer diagnosis is the first cancer diagnosis known to that registry for an individual or the second, third, fourth, etc.

For all women with breast cancer, the date of diagnosis was used to identify the first breast cancer diagnosis recorded in the SEER data. For all women for whom the sequence number indicated that this was not their first cancer diagnosis, the remainder of the SEER data was searched to locate all prior cancers for these women. If all prior cancers could not be located within the SEER data, the possibility that these women had had a prior breast cancer could not be ruled out. These women were then excluded from further analysis.

2. All cancer diagnoses were excluded that were a result of a death certificate notification only or where the cancer was an autopsy finding.

A small proportion of cancers registered by SEER cancer registries are cancers where the only notification was a death certificate or where the cancer was detected at autopsy. These records were deleted because the former may be unreliable and the latter a chance finding. In either case, since these cases were diagnosed post mortem, survival times were missing and therefore they would not contribute to either incidence or survival studies. Note that in this instance I am only excluding the diagnosis. A woman with an earlier breast cancer diagnosis would remain in the analysis.

3. All women, and hence all their cancer diagnoses, were excluded if diagnostic confirmation was not present for all their breast cancer diagnoses.

This study was focussed specifically on bilateral malignant breast cancer. If the diagnosis of breast cancer could not be confirmed for all breast cancers then malignancy could not be confirmed.

4. All women, and hence all their cancer diagnoses, were excluded if laterality was not specified for all their cancer diagnoses.

In a study of bilateral breast cancer, it is obviously important to be able to determine which side (left or right) a breast cancer has been diagnosed so that it can be determined if any subsequent diagnosis is in the contralateral breast.

3.5 Creation of Study Data File

Once these exclusions were applied, all breast cancers for each woman were sorted by date of diagnosis, the first of these was then assumed to be the first breast cancer diagnosis for that woman. For the majority of women this was their only diagnosis of breast cancer and these I will refer to as having unilateral breast cancer. For women

with another breast cancer diagnoses, the first diagnosis in the contralateral breast was identified and these women I will refer to as having bilateral breast cancer. All other diagnoses were then discarded and the following 6 mutually exclusive groups were defined. These were:

Group 1: All women with unilateral in-situ breast cancer;

Group 2: All women with unilateral malignant breast cancer;

Group 3: All women with bilateral in-situ breast cancer;

Group 4: All women with bilateral malignant breast cancer;

Group 5: All women with bilateral breast cancer – the first in-situ and the second malignant;

Group 6: All women with bilateral breast cancer – the first malignant and the second in-situ.

For my analysis, I was only interested in malignant breast cancer so the first, third, and fifth groups were excluded and only the second, fourth and sixth groups were used. Note: the sixth group is retained because women in this group have unilateral malignant breast cancer at first diagnosis and, until diagnosis of the contralateral in-situ breast cancer, they were legitimately at risk of a contralateral malignant breast cancer. The diagnosis of in situ breast cancer in these women is a censoring event.

3.6 Definition of Synchronous and Metachronous Bilateral Breast Cancer

3.6.1 Synchronous Bilateral Breast Cancer

The SEER data do not provide the exact date of diagnosis of breast cancer, only the month and year of diagnosis. Consequently, after constructing the dataset as described

above, for all women with bilateral breast cancer, those that had the same month and year of diagnosis were defined as having synchronous bilateral breast cancer.

3.6.2 Metachronous Bilateral Breast Cancer

All women with bilateral breast cancers where the month and year of diagnosis of both cancers was different were defined as having metachronous bilateral breast cancer.

3.7 Statistical methods

3.7.1 Methods used in the Analysis of Bilateral Breast Cancer Incidence

The incidence of metachronous bilateral breast cancer was determined by dividing the total number of women with a metachronous diagnosis by the total person-years of observation accumulated by all women at risk. Person-years were determined from the date of diagnosis of the first breast cancer until the date of diagnosis of the metachronous bilateral breast cancer. For women diagnosed with a metachronous in-situ breast cancer in the contralateral breast, the time to this second diagnosis contributed to the total person-years. For women who were not diagnosed with a metachronous bilateral breast cancer, person-years of observation were calculated until death from any cause or until 31 December 2000, whichever came first.

Multivariate analyses of the incidence of metachronous bilateral breast cancer were performed using Poisson regression. To examine the effect of a factor on the incidence of bilateral breast cancer, I first fitted a model containing only the factor of interest and then additional covariates were added to the model, thus estimating the effect of the factor of interest adjusted for these covariates.

More detail concerning the approach I have taken when using regression models is provided below in Section 3.7.4 on page 60.

3.7.2 Methods used in the Survival Analysis

All survival analyses were conducted from date of diagnosis of the first breast cancer until date of death from breast cancer. Women who died from causes other than breast cancer had their survival times censored at their date of death. All women who were alive at the end of follow-up (31 December 2000) had their survival times censored at this date.

Crude estimates of survival to death from breast cancer were obtained using the method of Kaplan and Meier (1958) and proportional hazards regression was used to model breast cancer survival (Cox, 1972). The proportional hazards assumption was tested using the method of Grambsch and Therneau (1994) and visually checked by graphing Schoenfeld residuals (Schoenfeld, 1982). Ties in survival times were broken using Efron's method (Efron, 1977).

3.7.3 Time-Dependent Proportional Hazards Models

The effect on survival of a diagnosis of a metachronous bilateral breast cancer was determined using time-dependent proportional hazard regression. To investigate how this effect may alter depending on the time interval between first and second breast cancer in those women with metachronous bilateral breast cancer, the survival was partitioned into 19 one-year intervals. Within each of these intervals, a time-dependent variable was defined that captured the occurrence of a metachronous bilateral breast cancer. The effect of a diagnosis of metachronous bilateral breast cancer was therefore estimated in discrete one-year intervals following the diagnosis of the first breast cancer. This allowed not only the relative risk associated with a diagnosis of metachronous bilateral breast cancer to be estimated, but also the functional form of this relative risk over time.

The standard proportional hazards regression model defines the hazard rate, *h*, at some time *t* given a set of risk factors or covariates **Z** as:

$$h(t \mid \mathbf{Z}) = h_0(t)\exp(\boldsymbol{\beta}\mathbf{Z}) = h_0(t)\exp\left(\sum_{i=1}^{n}\beta_i Z_i\right)$$

where $h_0(t)$ is an arbitrary baseline hazard rate, $\mathbf{Z} = (Z_1, \ldots, Z_n)$ is a series (or vector) of risk factors, and $\boldsymbol{\beta} = (\beta_1, \ldots, \beta_p)$ is a vector of regression parameters. In this model, the risk factors, Z_i, are known initially at time zero and remain fixed thereafter.

If there are covariates that change over time, these can be included in the model by defining them as time-dependent covariates. For example, the occurrence of a bilateral breast cancer could be modelled as a binary covariate, *X*, that changed value at some time *t*, where *t* was the time since diagnosis of the first breast cancer.

Prior to time *t* the bilateral breast cancer has not been diagnosed ($X = 0$) and at time *t* and thereafter, it has been diagnosed ($X = 1$). A model incorporating a single binary time-dependent variable would have the following form:

$$h(t \mid \mathbf{Z}, X(t)) = h_0(t)\exp\left(\boldsymbol{\beta}\mathbf{Z} + \boldsymbol{\beta}^t X(t)\right) = h_0(t)\exp\left(\sum_{i=1}^{n}\beta_i Z_i + \beta^t X(t)\right)$$

where $X(t) = \begin{cases} 0 \text{ if no bilateral breast cancer has been diagnosed at time, } t \\ 1 \text{ if a bilateral breast cancer was diagnosed at time, } t \end{cases}$

In this model, the covariate *X* changes value at some time *t* and the coefficient, β^t, estimates the change in risk associated with the change in the covariate *X*, in other words the change in risk associated with a diagnosis of bilateral breast cancer.

Using a single time-dependent covariate to model the diagnosis of bilateral breast cancer will therefore produce a single estimate of β^t and so implicitly assumes that the change in risk is the same regardless of when the bilateral breast cancer occurs.

To examine the effect of a bilateral breast cancer diagnosis at different times since the first diagnosis, a model with multiple time-dependent covariates was used. The time since the first breast cancer diagnosis was partitioned into 1-year intervals for the first 19 years after the initial breast cancer and a final interval representing 20 or more years. Within each of these 20 intervals of time, a time-dependent covariate was fitted to estimate the effect of a bilateral breast cancer diagnosis in that interval.

This model had the following form:

$$h\left(t \mid \mathbf{Z}, \mathbf{X}(t)\right) = h_0(t)\exp\left(\boldsymbol{\beta}\mathbf{Z} + \boldsymbol{\beta}^t\mathbf{X}(t)\right) = h_0(t)\exp\left(\sum_{i=1}^{n}\beta_i Z_i + \sum_{j=1}^{m}\beta_j^t X_j(t)\right)$$

for $j = 1,\ldots,19$ one-year time intervals

and $X_j(t) = \begin{cases} 0 \text{ if no bilateral breast cancer was diagnosed by time } t, \text{ where } t < j \\ 1 \text{ if a bilateral breast cancer was diagnosed by time } t, \text{ where } j-1 < t < j \end{cases}$

and $X_{20}(t) = \begin{cases} 0 \text{ if no bilateral breast cancer was diagnosed at any time } t \\ 1 \text{ if a bilateral breast cancer was diagnosed by time } t, \text{ where } t > 19 \text{ years} \end{cases}$

This model estimates 20 time-dependent effects, β_j^t, one for each of the 20 intervals of time since first diagnosis of breast cancer and therefore allows the estimate of the change in risk associated with a bilateral breast cancer diagnosis to vary depending on the interval of time between the first and second diagnoses.

3.7.4 The use of Multivariate Models in this Analysis

The strategy that was used to model these data is at variance with what would describe as "normal practice". In general, when estimating the effect of some exposure on the risk of some disease outcome, confounding effects of other variables would be assessed

using the “change-in-estimate” method (Mickey and Greenland, 1989; Maldonado and Greenland, 1993).

This is not a strategy used this analysis. As will be evident in the results, very few variables were strongly associated with the incidence of bilateral breast cancer. Accordingly, their influence as potential confounders was correspondingly weak. If the “change-in-estimate” approach had been used to select variables and a criterion for confounding had been a 20% change in the effect measure, for example, then in many instances no variables would have met this criterion.

Instead a standard set of variables are used in each multivariate model. Given the level of statistical power in this study, the loss of precision caused by adding unnecessary variables to the model was negligible.

The use of Poisson regression to model bilateral breast cancer rates may also require some justification. Often when modelling the incidence of disease events with Poisson regression, the residuals display more variability than would be expected, a phenomena called over-dispersion or extra-Poisson variability. When this occurs, standard error estimates for the coefficients estimated by the model will be erroneous as will the results of any statistical tests derived from these. When over-dispersion is present, negative binomial regression models are used instead of Poisson regression models.

A formal test for over-dispersion can be conducted via a likelihood ratio test comparing the fit of a Poisson model with that obtained via negative binomial regression. Using this approach, no evidence of over-dispersion was detected in this analysis of the rates of bilateral breast cancer incidence. Consequently, Poisson regression was used for all analyses.

3.7.5 Statistical Software

All analyses were performed using Stata Release 9 (StataCorp, College Station, Texas).

4 RESULTS

4.1 Introduction

The results of the statistical analysis in this chapter are presented in two parts, the first dealing with the analysis of the incidence of bilateral breast cancer and the second with the effect of a bilateral breast cancer diagnosis on breast cancer survival.

In the next section (Section 4.2) I have briefly documented the effects of the various exclusions that I applied to the SEER breast cancer data, which were outlined in Section 3.4.

The analysis of the incidence of metachronous bilateral breast cancer (Section 4.3) is divided into a number of subsections, each dealing with a particular aspect of bilateral breast cancer incidence: stage of the first breast cancer and incidence of bilateral breast cancer (Section 4.3.1); age and bilateral breast cancer incidence (Section 4.3.2); and the incidence of bilateral breast cancer by the histology of the first breast cancer (Section 4.3.3).

The remainder of this chapter is devoted to an analysis of the effect of a bilateral breast cancer on breast survival. In Section 4.4.1 is an analysis of breast cancer survival overall, providing crude survival estimates for each of the variables that are potential covariates in the analysis of the effect of bilateral breast cancer diagnosis. Also in this section, proportional hazards regression was used to obtain an initial model for breast cancer survival and the proportionality assumption was tested to identify covariates for which this assumption could be problematic.

I analysed the survival of women with synchronous and metachronous bilateral breast cancer separately (Sections 4.5 and 4.6, respectively). While a single model

incorporating both synchronous and metachronous bilateral breast cancers might be considered more desirable, this is difficult to achieve when covariates describing tumour characteristics are to be used. For example, for metachronous bilateral breast cancer tumour stage can be modelled as the stage of the first breast cancer and the stage of the second – two covariates, the second being time-dependent. For synchronous bilateral breast cancer, however, there are no "first" or "second" tumours. A different coding of stage is therefore required in order to provide suitable contrasts of risk.

Tests of the proportional hazards assumption suggested that the hazards associated with most of the covariates were not proportional, but examination of Schoenfeld residuals suggested that this was not the case. The large sample size was evidently allowing the statistical test of the proportional hazards assumption to detect quite small differences. Consequently, only one covariate, stage of the first breast cancer, showed evidence of lack of proportionality and subsequent analyses were conducted separately by stage of the first breast cancer.

Analysis of survival of women with metachronous bilateral breast cancer began with comparatively simple time-dependent models and progressed towards more complex models. The first models therefore incorporated the occurrence of a bilateral breast cancer as a single time-dependent effect (Section 4.6.1). In subsequent models I partitioned the survival period into one-year intervals and used multiple time-dependent covariates within each of these in order to capture variation in the hazard ratio with time since the first breast cancer (Section 4.6.3). At this point, I had not included the stage of either the first or second breast cancers, so I first produced survival models separately by stage of the first breast cancer (Section 4.6.4) and then using these, produced further models which incorporated the stage of the second breast cancer as a time-dependent effect (Section 4.6.5).

4.2 Exclusions

In the SEER dataset there were 1,695,240 cancer records for 1,542,671 women and among these there were 467,138 women with 498,543 diagnosed breast cancers either malignant or in situ.

From these the following exclusions were made:

- Women were excluded if their first breast cancer diagnosis was not their first cancer diagnosis and their previous diagnoses could not be located in the SEER dataset (n=18,319).
- Breast cancers were excluded if they were diagnosed at autopsy (n=2,771).
- Women were excluded if any of their breast cancers were not histologically confirmed (n=5,209)
- Women were excluded if laterality was missing for any of their breast cancers (n=2,834).

After these exclusions, there remained 438,005 women with breast cancer of whom 24,404 had a bilateral breast cancer diagnosis. From these, the following six mutually exclusive groups were identified.

Group 1	Unilateral in-situ breast cancer	46,828 women
Group 2	Unilateral malignant breast cancer	365,335 women
Group 3	Bilateral in-situ breast cancer	1,439 women
Group 4	Bilateral malignant breast cancer	18,379 women
	a) metachronous	13,955 women
	b) synchronous	4,424 women
Group 5	Bilateral breast cancer, the first in-situ and the second malignant	2,196 women
Group 6	Bilateral breast cancer, the first malignant and the second in-situ	3,828 women
	a) metachronous	3064 women
	b) synchronous	766 women

The analysis of the incidence of bilateral breast cancer was based only on the occurrence of metachronous malignant bilateral breast cancers in women first diagnosed with malignant breast cancer. The data file for this analysis therefore contained all

women with unilateral malignant breast cancer (Group 2, 365,335 women), all women with metachronous bilateral malignant breast cancers (Group 4a; 13,955 women), and all women with a malignant breast cancer at their first diagnosis and a subsequent metachronous bilateral in-situ diagnosis (Group 6a; 3064 women). The latter group were at risk of malignant bilateral breast cancer until the diagnosis of their in situ bilateral tumour and contributed person-years to the incidence calculation, but the in-situ cancers were not counted.

In summary, the analysis of the incidence of metachronous bilateral breast cancer was based on a cohort of 382,354 women, 13,955 of whom subsequently developed malignant bilateral breast cancer during the period of follow-up.

These data were also used for the analysis of the effect of a metachronous bilateral breast cancer diagnosis on survival.

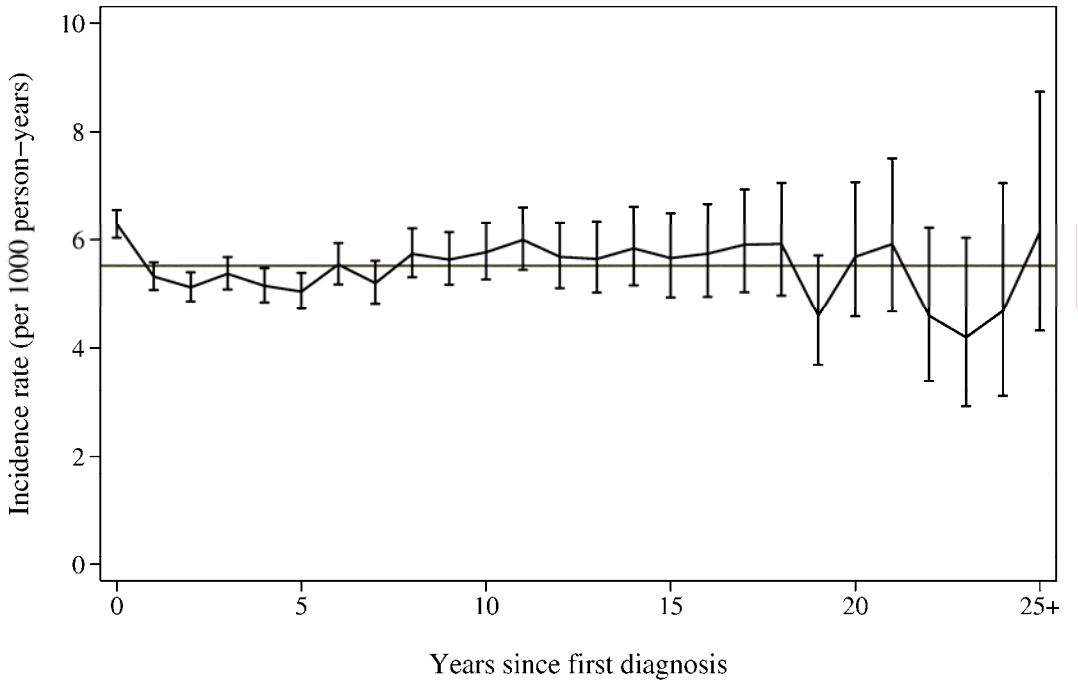
Women diagnosed with synchronous malignant bilateral breast cancer (Group 4b; 4424 women) were used to estimate the effect of a synchronous bilateral breast cancer diagnosis on breast cancer survival.

4.3 The Incidence of Metachronous Bilateral Breast Cancer

The cohort of 382,354 women with first malignant breast cancer were followed over time until the date of the diagnosis cancer in the contralateral breast, the date of death, or the end of follow-up (31 December 2000). A total of 2,528,435.33 person-years of observation accrued and 13,955 malignant breast cancers in the contralateral breast were observed resulting in a crude incidence of bilateral breast cancer of 5.52 per 1,000 person-years (95% CI: 5.43 – 5.61).

To determine the annual incidence of bilateral breast cancer, the total person-years of the cohort were partitioned into one-year intervals since first diagnosis and the number of metachronous bilateral breast cancers diagnosed in each one-year interval determined. The annual incidence and associated 95% confidence intervals of bilateral breast cancer following the diagnosis of the first breast cancer is shown below in Figure 4-1. The horizontal line in this figure is set at 5.52 per 1,000 person-years, the overall crude incidence. While the incidence of bilateral breast cancer was elevated in the first year and slightly below the average incidence for the next 5 years, there was little change in the incidence in the remaining years and no evidence of an increase in incidence over the 25-year period following diagnosis of the first breast cancer.

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



4.3.1 Cancer Stage and Bilateral Breast Cancer Incidence

The incidence of bilateral breast cancer in sub-cohorts of women defined by the stage of their first breast cancer is shown below in Table 4-1, where stage was classified as Stage

1 (localised), Stage 2 (regional) or Stage 4 (distant) according to the SEER definition described previously (Section 3.3.7, page 52). The incidence was also calculated for those first primary breast cancers where the stage was missing.

It is evident that the incidence of bilateral breast cancer is associated with stage of first primary (Table 4-1). In the sub-cohort of women initially diagnosed with Stage 2 (regional) breast cancer, the incidence of bilateral breast cancer was 5.68 per 1,000 person-years compared to 5.38 per 1,000 person-years in the sub-cohort of women with Stage 1 (localised) breast cancer. In the sub-cohort with Stage 4 (distant) breast cancer the incidence was higher, 7.39 per 1,000 person-years. If stage was missing, the incidence was virtually the same as the overall crude incidence.

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

Stage of the first breast cancer	Index Breast Cancers	Metachronous Breast cancers	Person-years (× 1000)	Rate	95% CI	
Stage 1: Localised	222,550	8561	1592.5302	5.38	5.26	5.49
Stage 2: Regional	128,459	4669	822.3973	5.68	5.52	5.84
Stage 4: Distant	21,497	386	52.2259	7.39	6.69	8.17
Missing	9,848	339	61.2288	5.54	4.98	6.16

There has been concern in the literature regarding the possibility of metastatic disease from the first breast cancer occurring in the contralateral breast and being misclassified as a new primary (Section 2.3, page 10). If this were occurring to any significant extent, then a higher incidence of bilateral breast cancer in women with advanced breast cancer would be expected because more advanced breast cancers are more likely to produce metastases. The results in Table 4-1 could therefore be indicative of misclassification of metastatic disease.

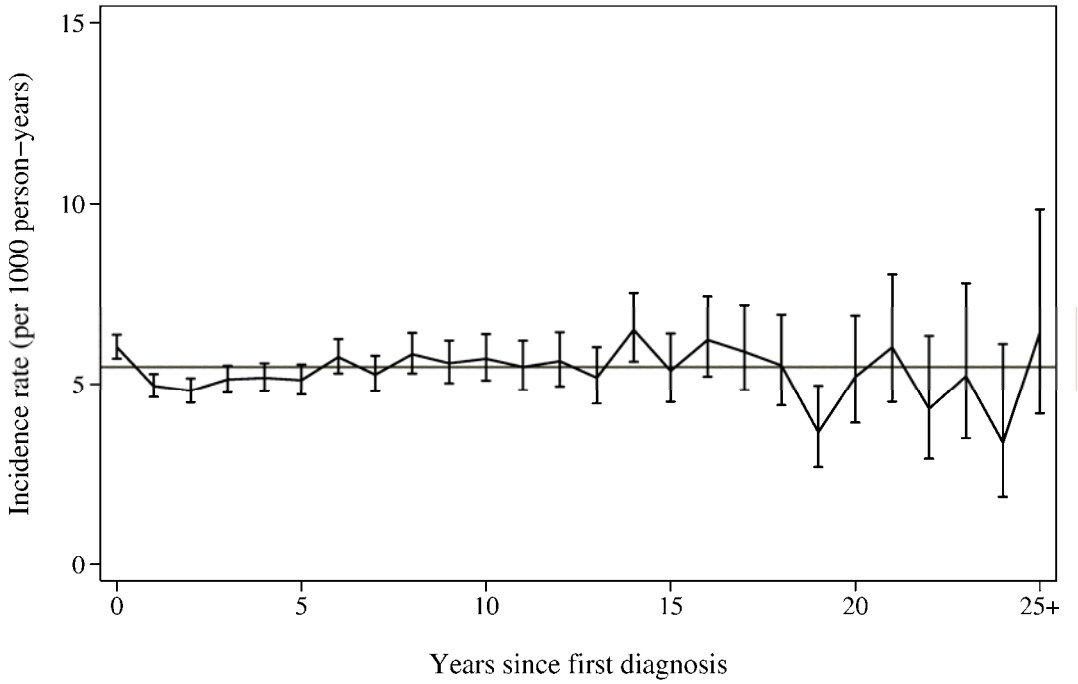
If significant misclassification of metastatic disease was occurring, however, we would also expect to see a pattern of bilateral breast cancer incidence over time since the first diagnosis that was similar to what one would see if examining the incidence of recurrence of breast cancer in women with advanced breast cancer. In other words, a higher bilateral breast cancer incidence in the first few years after diagnosis of the first breast cancer would be expected since this is when the risk of recurrence is high.

4.3.1.1 The annual incidence in women with Stage 1 breast cancer

The annual incidence of bilateral breast cancer in the sub-cohort of women with Stage 1 breast cancer is shown in Figure 4-2. The horizontal line is set at 5.52 per 1,000 person-years – the overall crude incidence.

The incidence in the first year is (6.03 per 1,000 person-years; 95% CI: 5.71 – 6.37), significantly higher than the overall rate, yet this is a cohort of women with localised disease and no evidence of metastatic disease in the axillary nodes when first diagnosed. This elevated incidence in the first year is unlikely to be due to misclassification of metastatic disease in this cohort of women. Further, if we look at the incidence in the years immediately after the first year, the incidence is attenuated. This pattern of incidence is actually more indicative of an ascertainment or surveillance effect in the first year following the initial diagnosis.

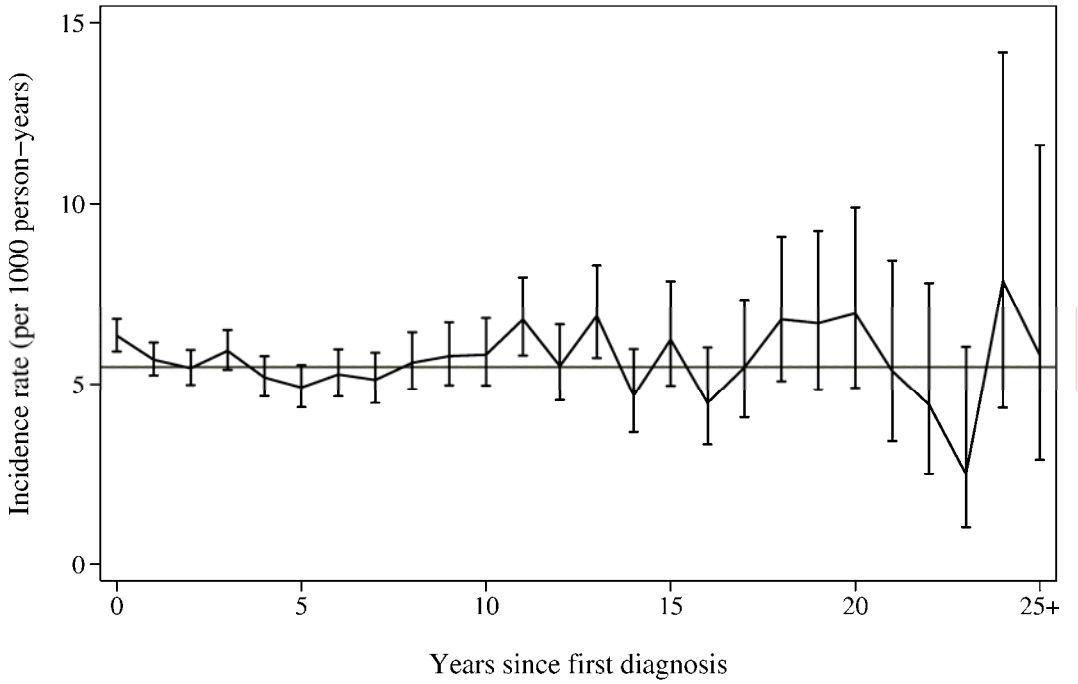
Figure 4-2: Annual incidence of bilateral breast cancer following Stage 1 (localised) first breast cancers.



4.3.1.2 The annual incidence in women with Stage 2 breast cancer

A similar pattern of incidence can be seen in the sub-cohort of women with Stage 2 breast cancer (Figure 4-3). The incidence rate in the first year is 6.34 per 1,000 person-years (95%CI: 5.91 – 6.81) and attenuated in the years immediately following this. In subsequent years, the rates become more variable, but in most the associated 95% confidence intervals include the overall crude rate of 5.52 per 1,000 person-years.

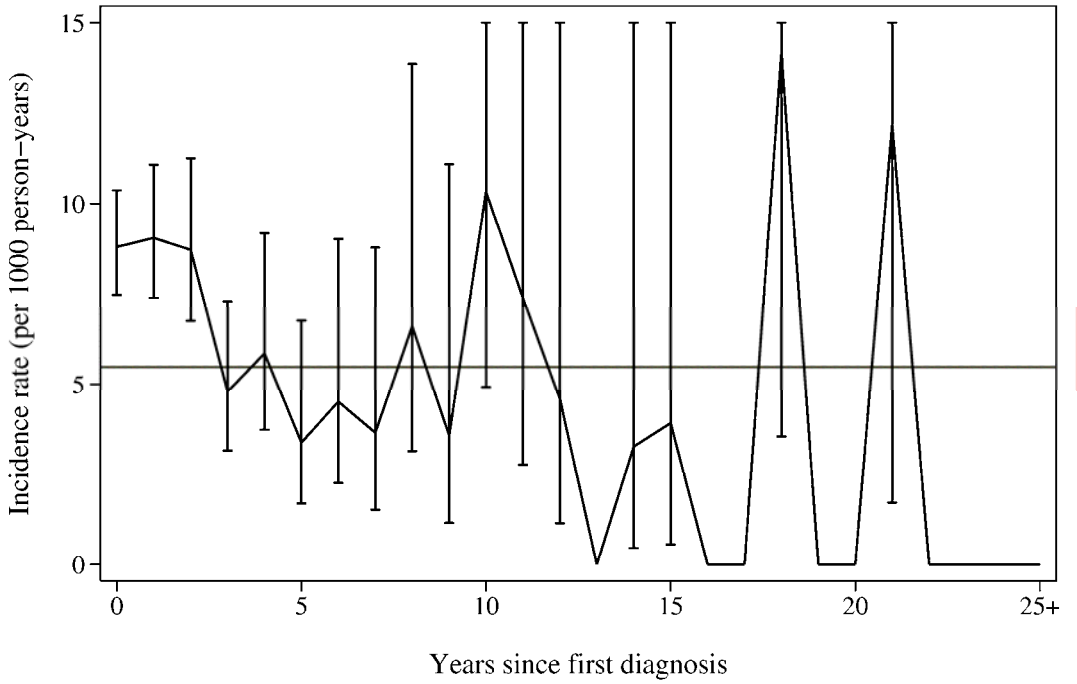
Figure 4-3: Annual incidence of bilateral breast cancer following a regional staged first breast cancer.



4.3.1.3 The annual incidence in women with Stage 4 breast cancer

A very different pattern emerges if we consider the annual incidence rates of bilateral breast cancer in the sub-cohort of women diagnosed with Stage 4 breast cancer (Figure 4-4). Note, to constrain the scale of this figure to be the same as in the previous figures, I have truncated the upper 95% confidence intervals at 15 per 1,000 person-years. In this sub-cohort, rates of bilateral breast cancer were elevated in the first three years – 8.80 per 1,000 person-years (95%CI: (7.47 – 10.36) in the first year, 9.04 per 1,000 person-years (7.39 – 11.07) in the second, and 8.72 per 1,000 person-years (6.75 – 11.26) in the third.

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



The possibility that misclassification of metastatic disease has occurred to some extent in these first three years is difficult to dismiss. These are women for whom distant metastatic disease was present at the time of their first breast cancer diagnosis and the emergence of further metastases at distant sites is highly likely.

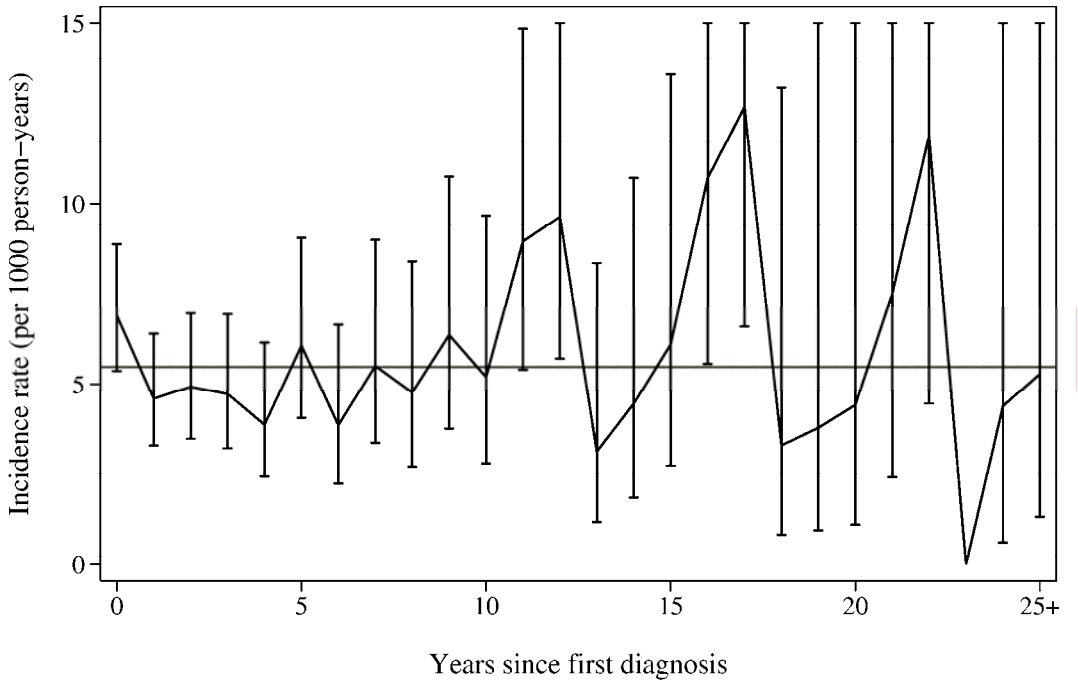
Alternatively, a plausible argument could also be made that these elevated rates in the first three years are a result of surveillance since these are women with advanced disease at their first diagnosis and will no doubt be more intensively followed.

4.3.1.4 The annual incidence in women with unstaged breast cancer

Not all breast cancers in this series were staged. For some women this information was missing. The annual incidence of bilateral breast cancer for these women is shown in Figure 4-5. There were only 9,848 women with unstaged first breast cancers and only 339 metachronous bilateral breast cancers observed during the course of follow-up,

consequently the confidence intervals are quite broad and the rates more erratic. Nevertheless, the incidence in the first year is elevated as was observed for the Stage 1 and Stage 2 breast cancers and there is little evidence of a consistent departure from the overall rate of 5.52 per 1,000 person-years.

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



4.3.1.5 Misclassification or surveillance effect?

Returning to the incidence of bilateral breast cancer in women with Stage 4 breast cancers, I can compare the number of bilateral breast cancers observed in each year following the initial breast cancer with the numbers expected. I have calculated two sets of expected numbers, the first using the rates of bilateral breast cancer observed in the sub-cohort of women with Stage 1 breast cancer and the second using the rates of bilateral breast cancer observed in the Stage 1 and Stage 2 sub-cohorts combined.

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

Years since first breast cancer diagnosis	Observed bilateral breast cancers	Person-years (x 1000)	Using rate for localized breast cancers		Using rate for localized and regional breast cancers combined	
			Expected	Excess	Expected	Excess
0	143	16.25425	87.4	55.6	89.0	54.0
1	94	10.39325	55.9	38.1	56.9	37.1
2	59	6.76983	36.4	22.6	37.1	21.9
3	22	4.58367	24.6	-2.6	25.1	-3.1
4	19	3.24600	17.4	1.6	17.8	1.2
5	8	2.36750	12.7	-4.7	13.0	-5.0
6	8	1.77408	9.5	-1.5	9.7	-1.7
7	5	1.36883	7.4	-2.4	7.5	-2.5
8	7	1.06008	5.7	1.3	5.8	1.2
9	3	0.83900	4.5	-1.5	4.6	-1.6
10	7	0.67775	3.6	3.4	3.7	3.3
11	4	0.54183	2.9	1.1	3.0	1.0
12	2	0.43617	2.3	-0.3	2.4	-0.4
13	0	0.35625	1.9	-1.9	2.0	-2.0
14	1	0.30575	1.6	-0.6	1.7	-0.7
15	1	0.25517	1.4	-0.4	1.4	-0.4
16	0	0.20917	1.1	-1.1	1.1	-1.1
17	0	0.17392	0.9	-0.9	1.0	-1.0
18	2	0.14092	0.8	1.2	0.8	1.2
19	0	0.11850	0.6	-0.6	0.6	-0.6
20	0	0.09725	0.5	-0.5	0.5	-0.5
21	1	0.08192	0.4	0.6	0.4	0.6
22	0	0.06708	0.4	-0.4	0.4	-0.4
23	0	0.05225	0.3	-0.3	0.3	-0.3
24	0	0.03317	0.2	-0.2	0.2	-0.2
25+	0	0.02283	0.1	-0.1	0.1	-0.1
Total	386	52.22642	280.5	105.5	286.1	99.9

Regardless of which rate is used to determine the expected counts of bilateral breast cancers (there is little difference between the two), the excess of bilateral breast cancers in women with Stage 4 breast cancer occurs almost entirely within the first three years. The higher overall incidence rate of bilateral breast cancer in these women is therefore due to the raised incidence rates in the first three years following this diagnosis.

It is difficult to draw any firm conclusions regarding the presence of any significant misclassification of metastatic disease as bilateral breast cancer in this sub-cohort of

women. While the elevated rates of bilateral breast cancer observed in these women could be interpreted as evidence of misclassification, it could be equally argued that they are a result of an extended period of surveillance.

The elevated rate seen in the first year following diagnosis of Stage 1 and Stage 2 breast cancers is more consistent with an effect of increased surveillance, particularly in those women with Stage 1 breast cancer where the occurrence of metastatic disease at any distant site within a year of diagnosis would be unlikely. It seems equally unlikely that, in the sub-cohort of women with Stage 2 breast cancer, there would be significant numbers developing metastatic disease in the contralateral breast within one year of their diagnosis and that it would be misclassified to an extent likely to cause bias.

If the elevation in the rate in the first year were caused by surveillance, then lower rates in the subsequent few years would be expected and this is what is observed in both the Stage 1 and Stage 2 sub-cohorts. It seems more likely that the elevated rates of bilateral breast cancer in the first year in these cohorts are an effect of surveillance.

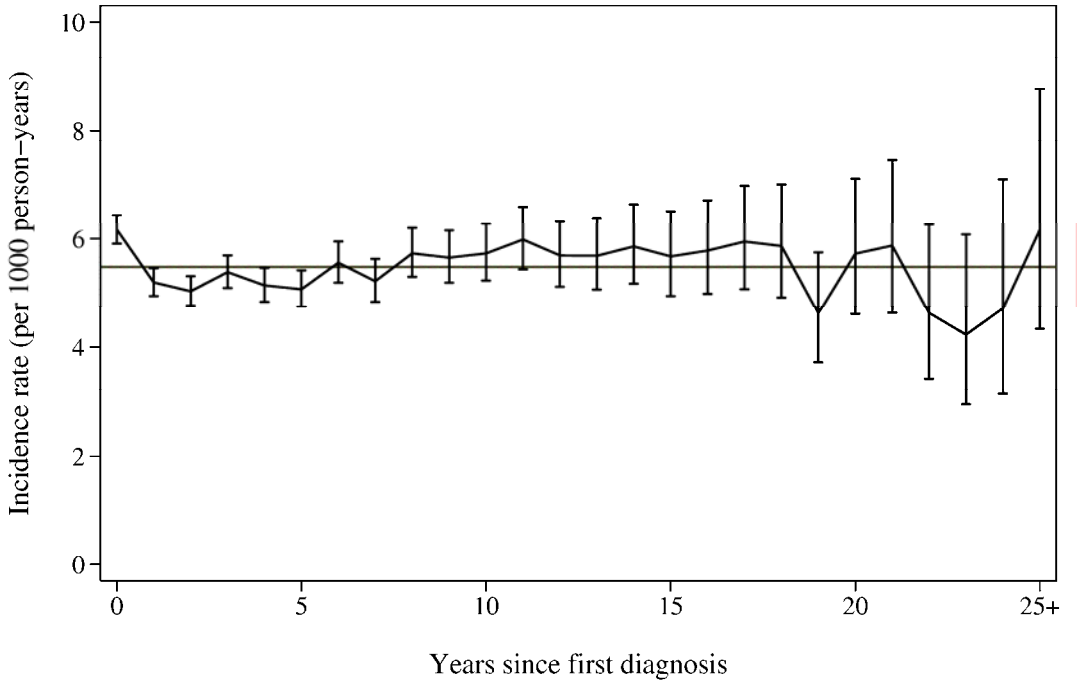
Regardless of the cause of this elevation in rates, it is a form of bias. While confined, as it is, to the first year in women with Stage 1 or Stage 2 breast cancer, its effect can be isolated in analysis. In women with Stage 4 breast cancer, this bias affects the rates in the first three years and accounting for this will complicate any analysis.

Given that women with Stage 4 breast cancer account for only 5.6% of all women in this study and contribute only 2.1% of the total person-years and 2.8% of the bilateral breast cancers observed, their influence in any overall analysis will be minimal. I will therefore exclude them from further analysis.

All subsequent analyses will now be based on a cohort of 360,857 women with a first breast cancer that was Stage 1 (localised), Stage 2 (Regional) or where stage was missing. There were 13,569 bilateral breast cancers observed in these women over

2,476,156.3 person-years, giving an overall incidence of 5.5 per 1,000 person-years (95% CI: 5.39 – 5.57). The annual incidence of bilateral breast cancer for these women is shown in Figure 4-6 and is little changed from Figure 4-1.

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.



4.3.2 Bilateral Breast Cancer Incidence and Age

Women who were in younger age groups when first diagnosed with breast cancer have been regarded as a high risk group for bilateral breast cancer and this would imply that their age-specific rates of bilateral breast cancer would be different from the age-specific rates in women first diagnosed at older ages. The aim of this section is to see if this is the case.

The average age at first diagnosis of breast cancer has also been found in a number of studies to be associated with bilateral breast cancer, with women who are diagnosed with a bilateral breast cancer being younger on average than women who have unilateral

breast cancer. This has been interpreted as evidence that women who are diagnosed with bilateral breast cancer are a highly susceptible group. I will also investigate this further in this section.

4.3.2.1 Age at first diagnosis

The rates of bilateral breast cancer incidence in sub-cohorts of women defined by their age at diagnosis of their first breast cancer are shown in Table 4-3.

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

Age at Diagnosis of the First Breast Cancer	Index Breast Cancers	Metachronous Breast Cancers	Person-years (x 1000)	Rate	95% CI	
<40	25,490	1209	193.6758	6.24	5.90	6.60
40-44	26,911	979	204.4586	4.79	4.50	5.10
45-49	36,357	1462	278.6584	5.25	4.98	5.52
50-54	38,519	1500	290.3038	5.17	4.91	5.44
55-59	39,322	1634	298.8024	5.47	5.21	5.74
60-64	41,083	1808	312.3456	5.79	5.53	6.06
65-69	42,515	1860	302.9544	6.14	5.87	6.43
70-74	39,572	1431	251.1853	5.70	5.41	6.00
75-79	33,019	1003	183.0095	5.48	5.15	5.83
80-84	21,714	469	102.9683	4.55	4.16	4.99
85+	16,355	214	57.7942	3.70	3.24	4.23

There is some variability in the incidence rates between age groups, with women who were first diagnosed when aged less than 40 years having an elevated rate of bilateral breast cancer. There also appears to be a trend towards increasing incidence of bilateral breast cancer as we move from the sub-cohort of women first diagnosed when aged 40-44 years (incidence 4.79 per 1,000 person-years) through to those aged 65-69 years when first diagnosed (incidence 6.14 per 1,000 person-years). In older sub-cohorts, the incidence declines.

These are not, it should be stressed, age-specific rates of bilateral breast cancer. For example, the 25,490 women who were first diagnosed with breast cancer when aged under 40 years are a cohort of women and the 193675.8 person-years of observation in this cohort, together with the 1,209 bilateral breast cancers that occurred during this time, have accumulated in different age groups as this cohort has aged.

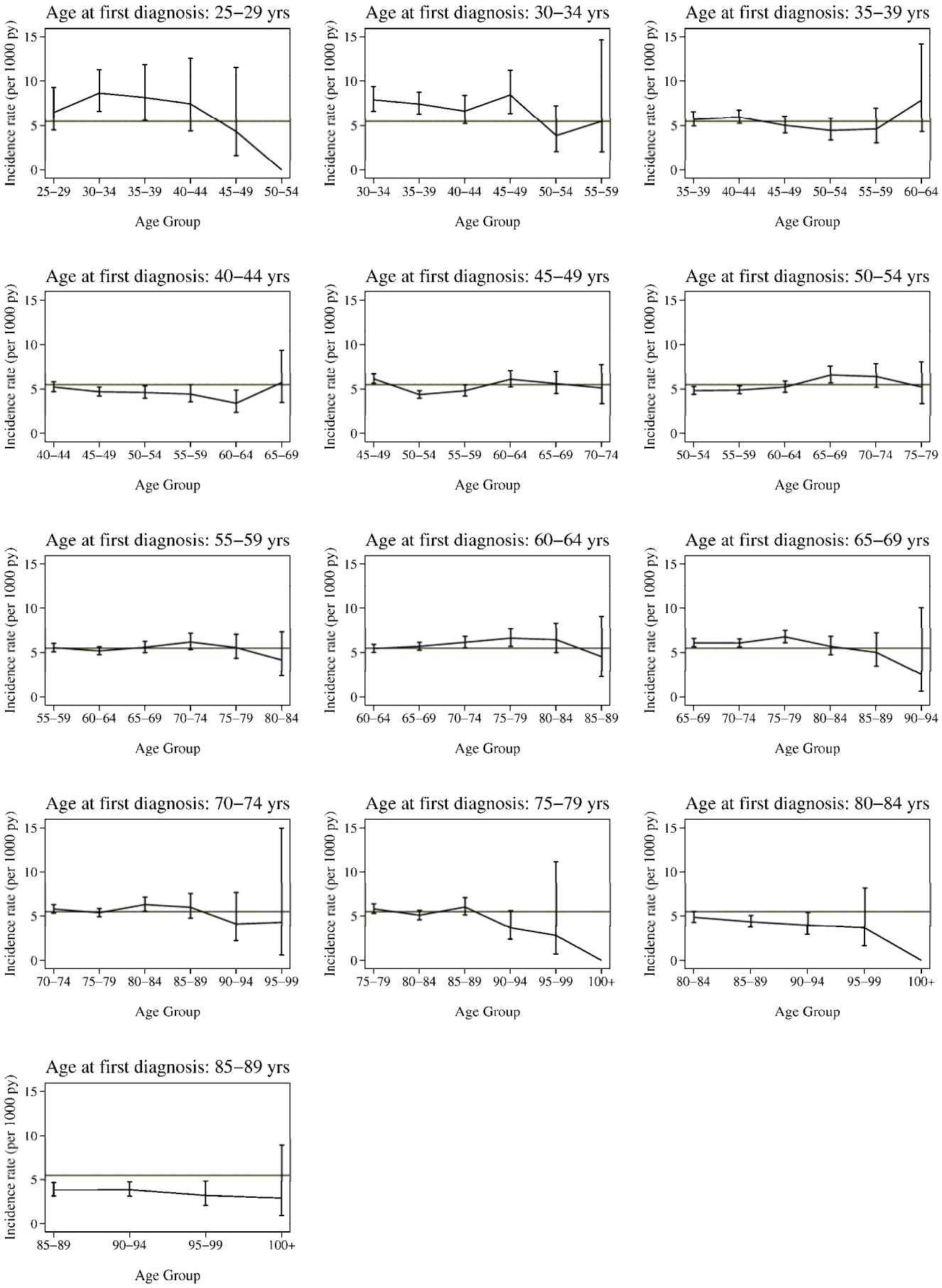
What are presented in Table 4-3 are crude incidence rates for a number of cohorts of women defined by their age at first diagnosis of breast cancer. Before we can make any clear inference concerning the association between age and the incidence of bilateral breast cancer we must disentangle the age at diagnosis of the first breast cancer from the age at diagnosis of the second breast cancer.

4.3.2.2 Age-specific incidence of bilateral breast cancer

To establish what is happening to the incidence of bilateral breast cancer as women age, 13 sub-cohorts of women were defined based on their age when first diagnosed with breast cancer in 5-year age groups from 25-29 years up to 85-89 years.

Within each of these sub-cohorts, age-specific incidence rates of bilateral breast cancer were calculated. These are presented in Figure 4-7, together with their associated 95% confidence intervals. The horizontal line in each of these graphs indicates the overall crude incidence of bilateral breast cancer, 5.48 per 1000 person-years.

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



As is evident from the 95% confidence intervals, the estimates of age-specific rates in the younger sub-cohorts of women are less precise than those in older sub-cohorts. Similarly, there is a general loss of precision as each sub-cohort ages. If we leave aside the issue of precision for the moment, we can see differences between some cohorts, but also similarities.

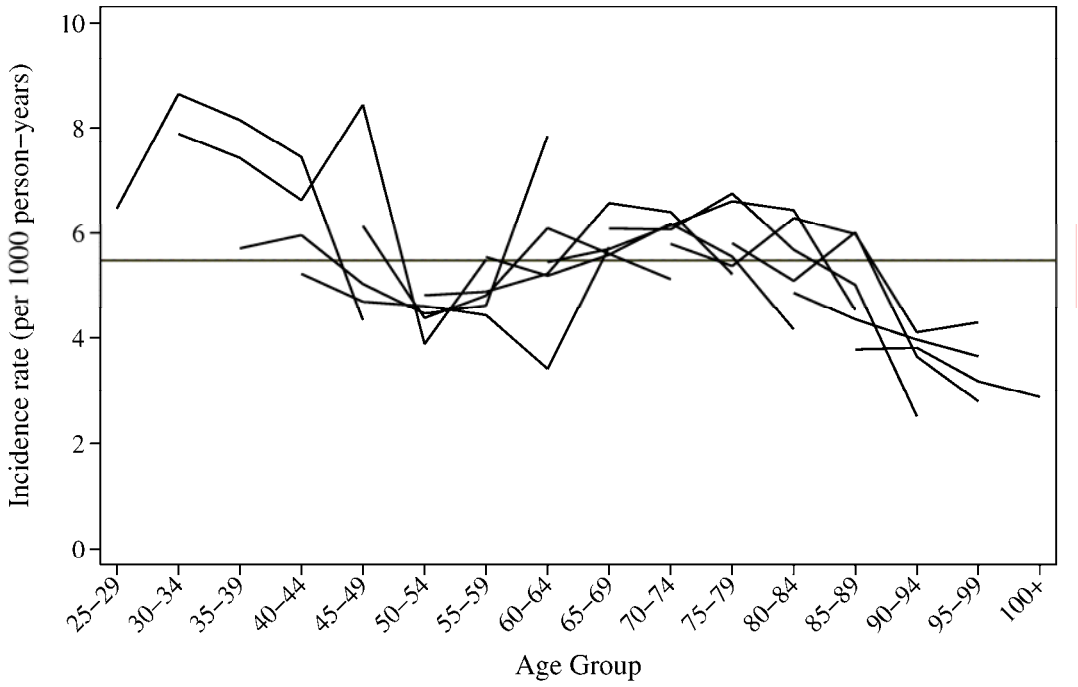
For example, in the youngest sub-cohort (25-29 years) the age-specific rate increases initially, but then declines over the next 15 years. By the time this sub-cohort is aged 45-49 years their incidence rate is 4.00 per 1,000 person-years.

In the sub-cohort aged 30 to 34 years when first diagnosed with breast cancer, the age-specific rates of bilateral breast cancer show a general decline with age, apart from the rate when aged 45-54 years which is elevated.

In older sub-cohorts, the age-specific rates are comparatively constant until we reach the 65-69 sub-cohort. In this and in older sub-cohorts, age-specific rates appear to decline after age 85-89.

In Figure 4-8, I have overlaid the age-specific incidence rates for each of the cohorts presented in Figure 4-7. The rates are quite erratic for younger women, where the number of bilateral breast cancers observed are small, and also towards the end of each series. There is, however, some general similarity in the trajectories each of these cohorts takes as they age.

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



There is reasonable evidence here that the risk of a bilateral breast cancer diagnosis is largely a function of age rather than age-at-first-diagnosis. If we refer back to Table 4-3 where the overall rates by age at first diagnosis were presented, we can see that in the sub-cohort of women first diagnosed at an age less than 40 years, the rate of bilateral breast cancer was higher than in any other sub-cohort. We can see in Figure 4-8, however, that this higher incidence rate is actually averaging across a series of age-specific rates that are, in general, declining as these women age.

We can also see in Table 4-3 that women who are older when first diagnosed with breast cancer have, overall, lower rates of bilateral breast cancer incidence, but we can see (Figure 4-8) that these too are averaging across a series of age-specific rates that in general begin to decline after age 85-89 regardless of the age at first diagnosis.

On the basis of these observations, it would appear that if age at diagnosis of the first breast cancer is exerting any influence on bilateral breast cancer incidence, it is comparatively minor compared to the influence of age at diagnosis of the bilateral breast cancer.

I have tested this formally using Poisson regression to model age-specific rates of bilateral breast cancer within each cohort of women defined by their age at first diagnosis of breast cancer. These results are presented in Table 4-4 and are arranged so that the age-specific relative rates of bilateral breast cancer run from left to right for each age-specific cohort and, therefore, down each column of the table are the age-specific relative rates from successively older cohorts of women. The reference level is the 50 to 54 year age-specific rate of bilateral breast cancer in women who were aged 50 to 54 years when diagnosed with their first breast cancer. The p-values in each column across the bottom of this table test for equality of the relative rates in the column. In other words they test for equality of the age-specific relative rates across age-specific cohorts.

For example, if we consider the 40 to 44 age-specific rate of bilateral breast cancer, there are four age cohorts that contribute to this rate: the 25 to 29 age cohort (RR = 1.66), 30 to 34 age cohort (RR = 1.37), 35 to 39 age cohort (RR = 1.31), and 40 to 44 age cohort (RR = 1.06). Overall, there are a significant differences in these 40 to 44 age-specific rates across the different age-specific cohorts (p=0.05). Similarly, there are significant differences across age-specific cohorts in the 35 to 39 age-specific relative rates (p = 0.007), the 45 to 49 age-specific relative rates (p = 0.004), and the 85 to 89 age-specific relative rates (p = 0.026). For the other age-specific relative rates, however, there is comparatively little heterogeneity by age cohort.

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

Age, First breast cancer	Age, Second Breast Cancer													
	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89	90-94	95-99
25-29	1.87 1.39-2.52	1.77 1.18-2.65	1.66 0.96-2.88	0.72 0.23-2.28										
30-34	1.56 1.27-1.92	1.62 1.33-1.98	1.37 1.04-1.81	1.78 1.27-2.49	0.71 0.34-1.47	1.02 0.31-1.47								
35-39		1.17 0.98-1.39	1.31 1.11-1.54	1.08 0.86-1.36	0.87 0.62-1.21	0.95 0.59-1.53	1.90 0.97-3.73							
40-44			1.06 0.92-1.23	1.04 0.89-1.21	0.98 0.80-1.19	0.95 0.72-1.25	0.70 0.45-1.08	1.39 0.77-2.51						
45-49				1.26 1.11-1.44	0.96 0.83-1.11	1.03 0.86-1.23	1.26 1.00-1.58	1.17 0.85-1.62	1.02- 0.58-1.79					
50-54					1.00 (ref)	1.08 0.94-1.25	1.11 0.93-1.33	1.38 1.11-1.73	1.39 1.02-1.89	1.21 0.69-2.11				
55-59						1.14 1.00-1.30	1.15 1.00-1.32	1.20 1.01-1.42	1.32 1.06-1.65	1.22 0.88-1.70	0.93 0.47-1.84			
60-64							1.13 1.00-1.29	1.28 1.12-1.46	1.33 1.13-1.57	1.35 1.08-1.69	1.33 0.94-1.87	0.81 0.34-1.93		
65-69								1.27 1.12-1.44	1.35 1.18-1.54	1.46 1.23-1.72	1.20 0.94-1.54	1.06 0.69-1.64	0.61 0.15-2.54	

(Cont.)

Age, First breast cancer	Age, Second Breast Cancer													
	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89	90-94	95-99
70-74									1.22 1.08-1.39	1.21 1.05-1.39	1.36 1.13-1.63	1.31 0.98-1.74	0.92 0.47-1.76	0.99 0.14-7.25
75-79										1.24 1.08-1.41	1.14 0.98-1.33	1.26 1.02-1.56	0.73 0.45-1.18	0.61 0.15-2.49
80-84											1.03 0.87-1.21	0.98 0.81-1.19	0.91 0.65-1.27	0.83 0.37-1.89
85+												0.82 0.65-1.03	0.83 0.65-1.06	0.75 0.49-1.16
p value	0.300	0.007	0.050	0.004	0.900	0.788	0.061	0.730	0.567	0.249	0.111	0.026	0.927	0.974

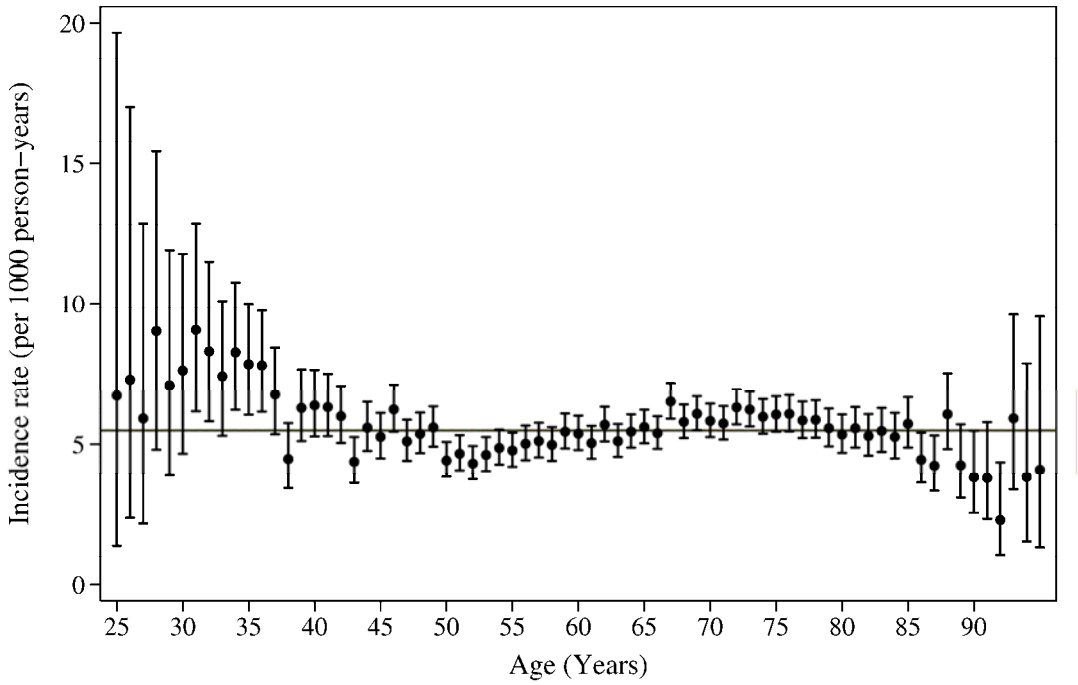
† Adjusted for registry, race, year of diagnosis, marital status, stage, histology and radiotherapy.

Any heterogeneity in the age-specific relative rates therefore appears to be largely confined to the younger age groups.

In order to understand what might be going on with the age-specific rates of bilateral breast cancer, I calculated overall age-specific rates ignoring the age at first diagnosis completely. Also, because of the large number of women with breast cancer in this dataset, I calculated these age-specific rates by individual ages (Figure 4-9).

In this figure we can see that the age-specific rates appear to be highest, approximately 8 per 1,000 person-years, around age 30 years. There is then a general decline in age-specific incidence so that by age 50 to 54 the incidence is approximately 4.5 per 1,000 person-years. After this the rates begin to increase again reaching approximately 6 per 1,000 person-years at age 70 to 74 after which they decline again.

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



There is a danger in over-interpreting this figure. The age-specific rates presented are from age 35 to age 95, a span of some 60 years. The SEER data I have used for this analysis, however, covers 1973 to 2000, a 27 year period. Therefore I have at most only a 27 year follow-up on the women in my analysis, so there is no guarantee that the age-specific rates in Figure 4-9 are the age-specific rates that would be experienced by a cohort of women with breast cancer followed for 60 years.

4.3.2.3 The average age of bilateral breast cancer patients

Before finishing with the issue of age and bilateral breast cancer incidence, I need to deal with the issue of average age at diagnosis of the first breast cancer. A number of studies have reported that women who had bilateral breast cancer had their first breast cancer at an earlier age on average than women who had not had bilateral breast cancer (discussed in Section 2.4.4, page 25). This was seen as further evidence that women with bilateral breast cancer were a highly susceptible group – they had their first breast cancer at a younger age and then had a second breast cancer.

In the current analysis, the average age of women with unilateral breast cancer and the average age at first diagnosis of breast cancer in women who were subsequently diagnosed with bilateral metachronous breast cancer were calculated (Table 4-5). In the latter the average age was 58.70 years whereas in the former, the unilateral breast cancer cases, the average age was 61.31 years. The difference is 2.29 years.

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

	Unilateral	Bilateral	All
n	347,288	13,569	360,857
Mean	60.99	58.70	60.91
SD	14.48	13.45	14.45

This is not a large difference, but regardless of how large the difference may be, the question is, is it a valid comparison?

The problem with this comparison is that at the time of the first diagnosis of breast cancer, all of these women have unilateral breast cancer: there is no group of women with bilateral breast cancer. This bilateral group forms over time as bilateral breast cancers are diagnosed. Consequently a crude comparison such as this may find differences that are associated with bilateral breast cancer, but it may also find differences that are due to survival or, to put it another way, differences that are related to all-cause mortality. Thus by making crude comparisons between groups of women with unilateral and bilateral breast cancer and failing to take into account the formation of the bilateral group over time, we may detect the influence of factors strongly related to all-cause mortality – a factor such as age, for example.

In Table 4-6 I have constructed a series of comparisons between women with and without bilateral breast cancer and each comparison is conditional on both groups being alive at the end of a fixed period of observation.

The first comparison, for example, is conditioning on 1 year of survival. For all women diagnosed with breast cancer who are still alive at the end of one year, the average age of those who have also had a bilateral breast cancer within that year is 60.77 years which is very similar to the average age of women who have not had a bilateral breast cancer, 60.60 years.

If we move forward in time and consider all women alive 5 years after their diagnosis of breast cancer, the average age at first diagnosis for those women who also had a metachronous bilateral breast cancer is 59.98 years and for those without a bilateral diagnosis it is 59.59 years. Once again, very little difference.

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

	Unilateral	Bilateral	Difference
Conditioning on 1 year survival			
Average Age	60.60	60.77	0.17
SD	14.29	13.91	
Conditioning on 5 years survival			
Average Age	59.59	59.98	0.39
SD	13.58	13.50	
Conditioning on 10 years survival			
Average Age	57.51	58.42	0.90
SD	12.65	12.80	
Conditioning on 15 years survival			
Average Age	54.78	55.92	1.13
SD	11.60	11.85	
Conditioning on 20 years survival			
Average Age	52.14	53.27	1.13
SD	10.21	10.53	

In each of the subsequent comparisons – conditioning on 10 years survival, 15 years survival, and 20 years survival – the same result is observed. There is little difference in average age at first diagnosis of breast cancer between women with metachronous bilateral breast cancer and women without bilateral breast cancer. There is certainly no indication, in any of these comparisons, that women with metachronous bilateral breast cancer have their first breast cancer diagnosed at a younger age, on average, than women without bilateral breast cancer.

What is apparent, however, is that the average age at first diagnosis decreases as we condition on longer periods of survival and this is why there was an apparent difference in average age at first diagnosis in Table 4-5. Women who were still alive 20 years after their first diagnosis of breast cancer had an average age at diagnosis of 52 years in

Table 4-6, much younger that the overall average age of women when diagnosed with breast cancer (60.9 years in Table 4-5).

For women with newly diagnosed breast cancer, those who are younger will have an overall lower risk of all-cause mortality and hence a greater overall life expectancy than those who are older when diagnosed with breast cancer. Having a greater life expectancy means that they are exposed to the risk of bilateral breast cancer for a longer period of time and so their cumulative or lifetime risk of bilateral breast cancer will be higher than in older women. The often reported difference in the average age at first diagnosis of breast cancer between women with and without metachronous bilateral breast cancer is therefore nothing more than an artefact of failing to account for the competing risk of mortality.

4.3.3 Bilateral Breast Cancer and Histology

The crude incidence of bilateral breast cancer by the histology of the first breast cancer is shown below in Table 4-7.

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

Histology of the first breast cancer	Index Breast Cancers	Metachronous Breast cancers	Person-years (x 1000)	Rate	95% CI	
Infiltrating Ductal Carcinoma	257,014	9232	1740.0503	5.31	5.20	5.41
Comedocarcinoma	6,885	261	52.0524	5.01	4.44	5.66
Papillary Carcinoma	1,563	69	11.7466	5.87	4.64	7.44
Mucinous Carcinoma	9,030	328	60.8096	5.39	4.84	6.01
Lobular Carcinoma	40,526	1562	238.2870	6.56	6.24	6.89
Tubular Carcinoma	4,411	145	27.9904	5.18	4.40	6.10
Medullary Carcinoma	7,034	450	67.4176	6.67	6.09	7.32
Sarcoma	1,125	29	8.2116	3.53	2.45	5.08
Carcinoma Unspecified	8,161	347	61.4782	5.64	5.08	6.27
Other	25,108	1146	208.1125	5.51	5.20	5.83

As has been observed in some previous studies reviewed in Section 2.5.2, crude rates of bilateral breast cancer in the sub-cohorts of women with lobular carcinoma (6.56 per 1,000 person-years) and with medullary carcinoma (6.67 per 1,000 person-years) are higher than in the sub-cohort of women with infiltrating ductal carcinoma (5.31 per 1,000 person-years).

These differences in crude rates of bilateral breast cancer are not explained by other factors (Table 4-8). The rates in the sub-cohort of women with a lobular carcinoma were 23% higher than those in the infiltrating ductal carcinoma sub-cohort and this relative effect was altered only marginally after multivariate adjustment (27%). Similarly, for women in the medullary carcinoma sub-cohort where rates of bilateral breast cancer were 25% higher than in the infiltrating ductal carcinoma sub-cohort, this relative effect was attenuated slightly after adjustment (19%).

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

Histology	Crude Estimates			Adjusted Estimates		
	IRR	95% C. I.		IRR	95% C. I.	
Infiltrating Ductal Carcinoma	1.00			1.00		
Comedocarcinoma	0.93	0.82	1.06	0.95	0.84	1.08
Papillary Carcinoma	1.14	0.90	1.45	1.14	0.90	1.45
Mucinous Carcinoma	1.03	0.92	1.15	1.03	0.92	1.16
Lobular Carcinoma	1.23	1.17	1.30	1.27	1.20	1.34
Tubular Carcinoma	0.99	0.84	1.17	1.03	0.87	1.22
Medullary Carcinoma	1.25	1.13	1.38	1.19	1.07	1.31
Sarcoma	0.67	0.46	0.99	0.66	0.45	0.97
Carcinoma Unspecified	1.11	0.98	1.26	1.05	0.92	1.19
Other	1.04	0.98	1.11	0.99	0.93	1.06

† Adjusted for age at bilateral diagnosis, registry, race, year of diagnosis, marital status, stage, and radiotherapy.

We can also see that for women originally diagnosed with breast sarcoma, adjusted rates of bilateral breast cancer are 34% lower than those observed in the infiltrating ductal carcinoma sub-cohort. The 1,125 women with first primary breast sarcoma represent

only 0.31% of all women in this series and only 0.21% of all the person-years observed and are not likely to be influential in any analysis of bilateral breast cancer incidence.

In the remainder of this section, while I will report results for all histological types, I will concentrate primarily on the incidence of bilateral breast cancer in the sub-cohorts of women with infiltrating ductal carcinomas, lobular carcinomas, and medullary carcinomas. Together, these sub-cohorts of women represent 84% of all women with breast cancer in this series, 83% of the total person-years observed and 83% of all bilateral breast cancers observed.

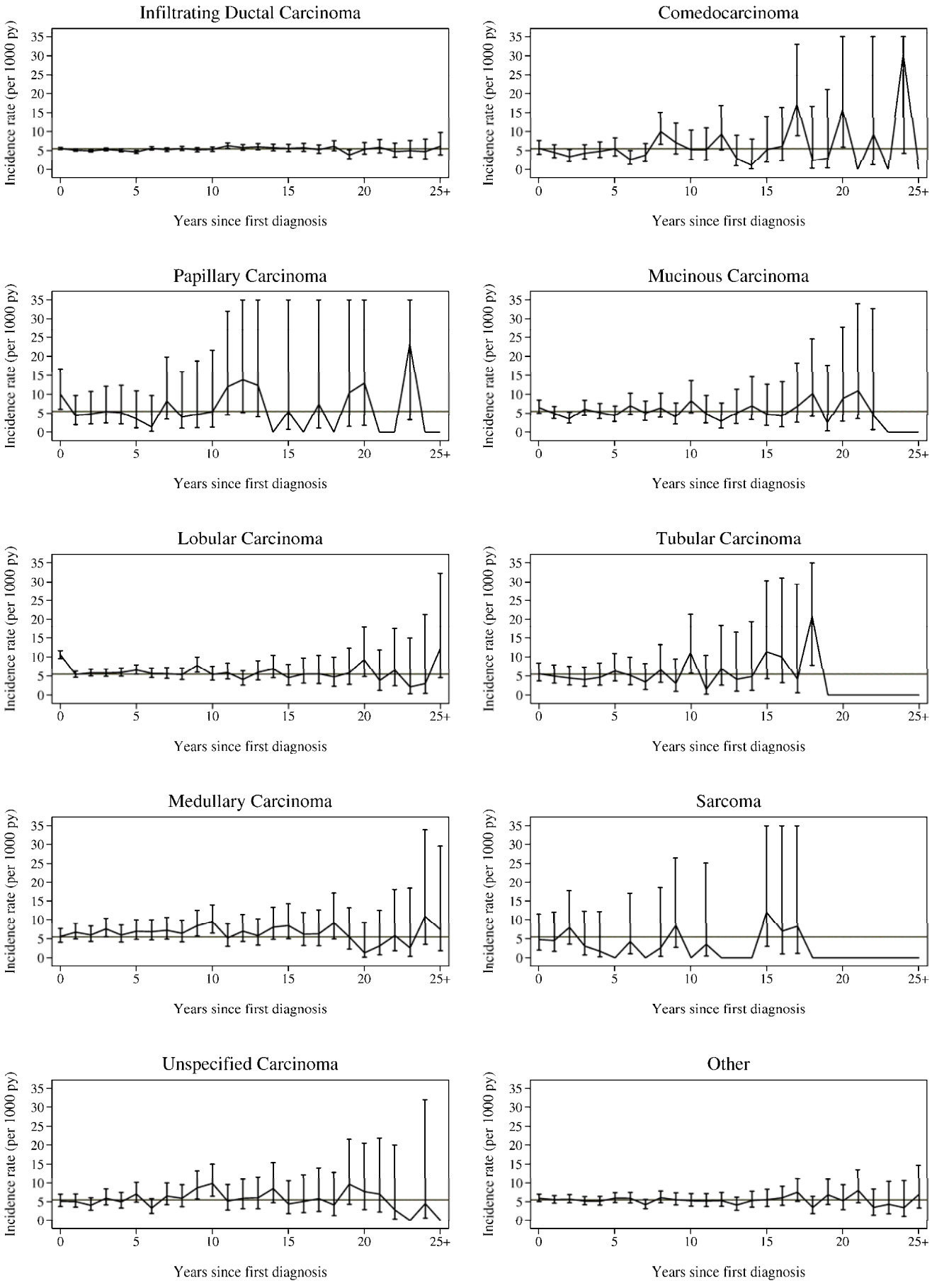
4.3.3.1 Annual incidence of bilateral breast cancer by histology

I have calculated the annual incidence of bilateral breast cancer by the histology of the first breast cancer and these are shown in Figure 4-10. Note that to preserve the same scale on the y-axis for all of the graphs I have truncated the upper 95% confidence interval at 35 per 1,000 person-years in some of these figures. In each graph, the horizontal line corresponds to the overall incidence of bilateral breast cancer – 5.48 per 1000 person-years.

In the sub-cohort of women with infiltrating ductal carcinoma the incidence of bilateral breast cancer is constant. There is no indication of any tendency for the incidence rates to increase or decrease over 25 years of follow-up.

In the sub-cohort of women with lobular carcinoma the incidence of bilateral breast cancer is quite high in the first year but, subsequent to this, there is little evidence of any tendency for the incidence to increase or decrease over time nor does it appear to be markedly different from 5.48 per 1000 person-years, the overall incidence of bilateral breast cancer.

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



This suggests that the association between lobular carcinoma and bilateral breast cancer is limited to the incidence in the first year and, subsequent to this there is little association between lobular carcinoma and bilateral breast cancer incidence.

In the medullary carcinoma sub-cohort, there is also little evidence of any tendency for the incidence of bilateral breast cancer to increase or decrease over time, but the impression is that these rates appear slightly higher than the overall incidence of bilateral breast cancer. In contrast to the incidence observed in the lobular carcinoma sub-cohort, however, there is no evidence of any elevation in the incidence in the first year.

To tease out these early effects on bilateral breast cancer incidence, I calculated the incidence of bilateral breast cancer separately for the first three years following diagnosis of the first breast cancer, and then for all subsequent years combined. These are presented for the sub-cohorts of women with infiltrating ductal carcinoma, lobular carcinoma and medullary carcinoma in Table 4-9 and for remaining sub-cohorts in Appendix O.

In the sub-cohort of women with infiltrating ductal carcinoma, the incidence of bilateral breast cancer 3 or more years after diagnosis was 5.35 per 1,000 person-years and slightly elevated above this in the first year (5.55 per 1,000 person-years).

In the lobular carcinoma sub-cohort, the incidence of bilateral breast cancer in the first year was 10.57 per 1,000 person-years and three or more years after diagnosis it was only 5.89 per 1,000 person-years, slightly higher than in the infiltrating ductal carcinoma sub-cohort.

In the medullary carcinoma sub-cohort the rates of bilateral breast cancer 3 or more years after diagnosis was 6.91 per 1,000 person-years, appreciably higher than observed in the infiltrating ductal carcinoma sub-cohort.

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.

	Time (years)	Metachronous breast cancers	Person-years (x1000 years)	Rate	95% CI	
Infiltrating Ductal Carcinoma	0-1	1351	243.3900	5.55	5.26	5.85
	1-2	1111	216.5100	5.13	4.84	5.44
	2-3	936	189.0336	4.95	4.64	5.28
	3+	5823	1091.1206	5.35	5.21	5.49
Lobular Carcinoma	0-1	396	37.4800	10.57	9.57	11.66
	1-2	176	32.4920	5.42	4.67	6.28
	2-3	163	27.8802	5.85	5.01	6.82
	3+	827	140.4357	5.89	5.50	6.30
Medullary Carcinoma	0-1	38	6.8082	5.58	4.06	7.67
	1-2	42	6.2711	6.70	4.95	9.06
	2-3	34	5.6856	5.98	4.27	8.37
	3+	336	48.6527	6.91	6.21	7.69

The results from a Poisson regression analysis of these rates in the infiltrating ductal carcinoma, lobular carcinoma and medullary carcinoma sub-cohorts are shown in Table 4-10. Results for the remaining sub-cohorts are shown in Appendix P. The reference level for all rate ratios in Table 4-10 is the rate of bilateral breast cancer observed three or more years after diagnosis in the infiltrating ductal carcinoma sub-cohort. Both crude and multivariate adjusted incidence rate ratios are presented.

In the sub-cohort of women with infiltrating ductal carcinoma, the adjusted rate of bilateral breast cancer in the first year following diagnosis was 5% higher than the rate three or more years after diagnosis, but for all practical purposes there was little

difference in rates across the time periods considered, nor for that matter were there any notable differences between the crude and adjusted rate ratios.

In the sub-cohort of women with lobular carcinoma however, the adjusted rate of bilateral breast cancer in the first year following diagnosis was double the rate observed three or more years after diagnosis in the infiltrating ductal carcinoma sub-cohort. Three or more years after diagnosis, however, the rate of bilateral breast cancer in the lobular carcinoma sub-cohort was only 12% higher than observed in the infiltrating ductal carcinoma sub-cohort.

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.

		Crude Estimates			Adjusted Estimates		
Histology	Interval	IRR	95% C.I.		IRR	95% C.I.	
Infiltrating Ductal Carcinoma	0-1	1.03	0.97	1.10	1.05	0.94	1.18
	1-2	0.96	0.90	1.02	0.98	0.89	1.08
	2-3	0.94	0.87	1.00	0.96	0.88	1.05
(ref)	3+	1.00			1.00		
Lobular Carcinoma	0-1	1.98	1.78	2.19	2.08	1.80	2.40
	1-2	1.01	0.87	1.18	1.07	0.91	1.27
	2-3	1.10	0.94	1.29	1.18	0.99	1.39
	3+	1.10	1.02	1.18	1.12	1.04	1.21
Medullary Carcinoma	0-1	1.08	0.78	1.50	1.02	0.73	1.43
	1-2	1.14	0.82	1.58	1.08	0.77	1.51
	2-3	1.12	0.79	1.58	1.05	0.74	1.50
	3+	1.29	1.15	1.44	1.23	1.10	1.38

† Adjusted for age at bilateral diagnosis, registry, race, year of diagnosis, marital status, stage, and radiotherapy.

For women with medullary carcinomas, the rate of bilateral breast cancer in the first three years following diagnosis were not appreciably different from the rate in women with ductal carcinoma three or more years after diagnosis. However, the rate in the medullary carcinoma sub-cohort three or more years after diagnosis was 23% higher than the equivalent rate in women with ductal carcinoma.

Thus, by partitioning out what appear to be early and differential ascertainment effects, the association between lobular carcinoma and bilateral breast cancer incidence is considerably weaker than suggested by the overall crude comparison presented in Table 4-8, but the association between medullary carcinomas and bilateral breast cancer incidence remains.

4.3.3.2 The histology of the bilateral breast cancer

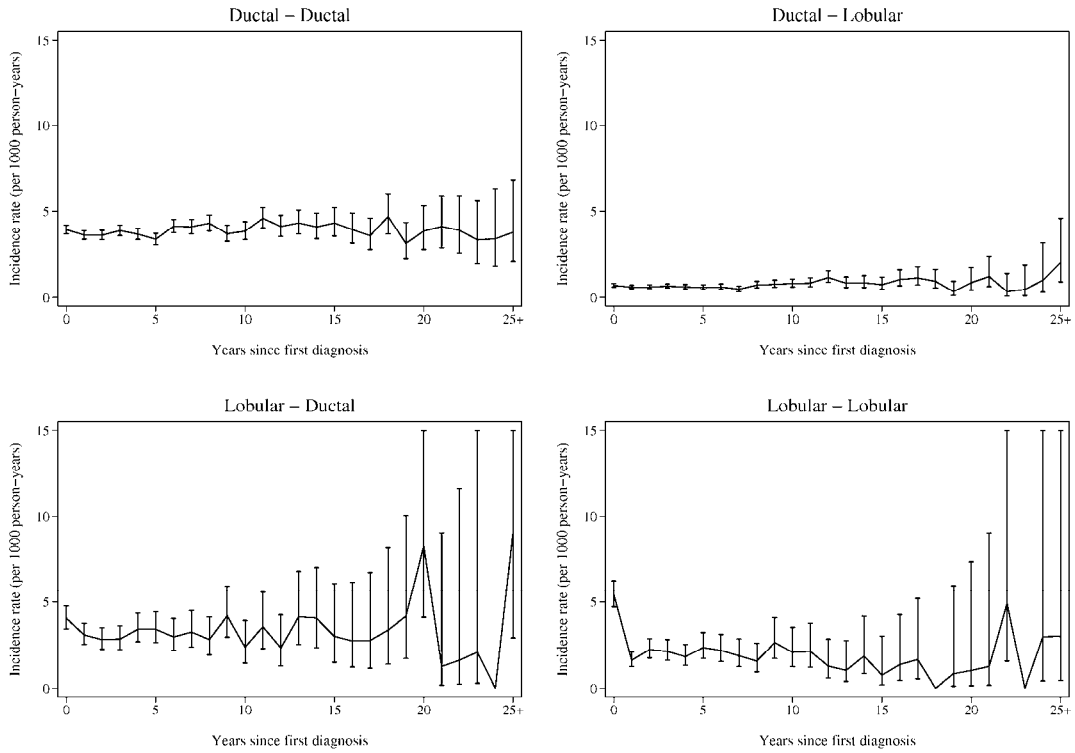
While these results tend to explain why previous studies (reviewed in Section 2.5.2) have found an association between lobular carcinoma and bilateral breast cancer incidence, a more fundamental question remains unanswered. Why should the histology of the first breast cancer influence the incidence of bilateral breast cancer, particularly the incidence in the first year?

To answer this question it is necessary consider the histology of the bilateral breast cancer. Thus far, all rates calculated have been based on the occurrence of bilateral breast cancers of any histological type in sub-cohorts of women defined by the histology of their first breast cancer. In the following analysis I have examined the rates of bilateral infiltrating ductal, bilateral lobular and bilateral medullary carcinoma and I have restricted my analysis to first breast cancers that were infiltrating ductal, lobular or medullary.

Figure 4-11 shows the annual incidence of bilateral infiltrating ductal carcinoma in the sub-cohort of women whose first breast cancer was an infiltrating ductal carcinoma (labelled Ductal-Ductal) and for the sub-cohort of women whose first breast cancer was a lobular carcinoma (labelled Lobular-Ductal). Similarly, I have estimated the incidence of bilateral lobular carcinoma in the infiltrating ductal carcinoma sub-cohort

(labelled Ductal-Lobular) and in the lobular carcinoma sub-cohort (labelled Lobular-Lobular).

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

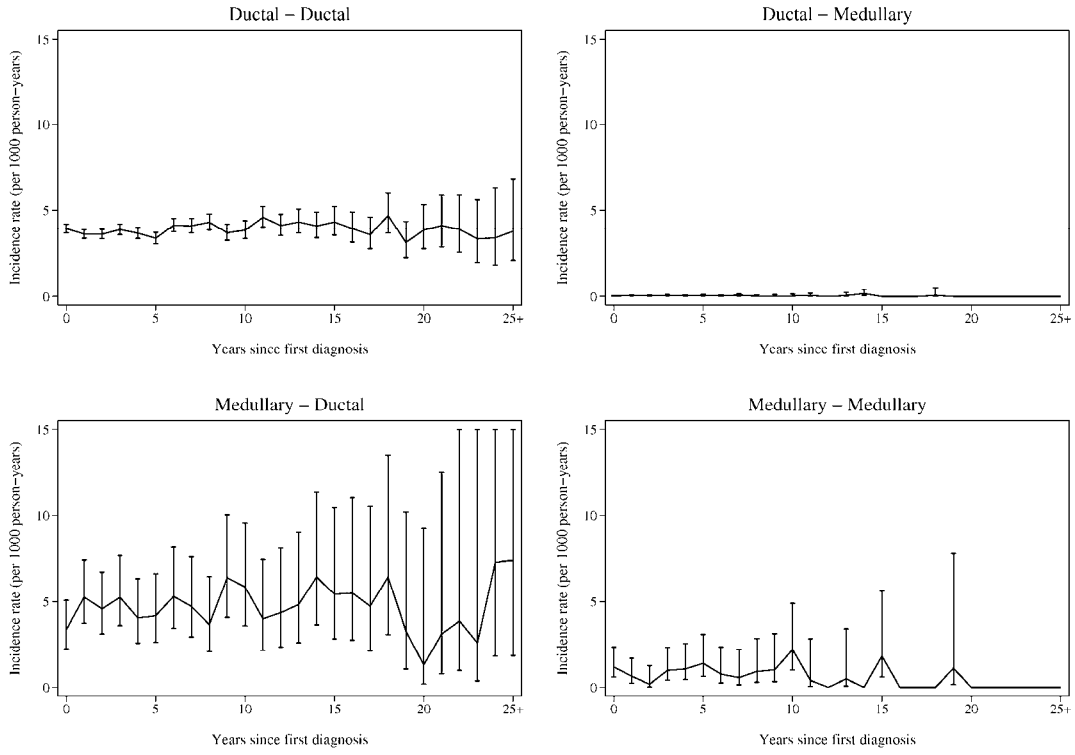


There are a number of striking features in these graphs. First, consider the incidence in the first year following the initial breast cancer diagnosis. If the first breast cancer was an infiltrating ductal carcinoma, the incidence in the first year only is slightly elevated regardless of whether we are looking at the incidence of bilateral ductal or bilateral lobular carcinoma. If, however, the first breast cancer was lobular, the incidence of bilateral ductal carcinoma is more obviously elevated and the elevation in incidence of bilateral lobular carcinoma is quite striking.

Second, and perhaps more importantly, the overall incidence of bilateral lobular carcinoma is much higher in the sub-cohort of women with lobular carcinomas than in the sub-cohort of women with an infiltrating ductal carcinoma.

In the next series of graphs (Figure 4-12), the annual incidence of bilateral infiltrating ductal carcinoma in the sub-cohort of women with infiltrating ductal carcinoma (Ductal-Ductal, the same as presented in Figure 4-11) is compared with the annual incidence in the sub-cohort with medullary carcinoma (labelled Medullary-Ductal). Similarly, I have estimated the incidence of bilateral medullary carcinoma in the sub-cohort of women with infiltrating ductal carcinoma (labelled Ductal-Medullary) and in the sub-cohort of women with medullary carcinoma (labelled Medullary-Medullary).

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



Once again there are different effects in the first year following the initial breast cancer, but the most striking feature is the overall difference in the incidence of bilateral medullary breast cancer which appears to be much higher if the first breast cancer is medullary and appreciably lower if the first breast cancer was infiltrating ductal.

As I have done previously, I have combined the period three or more years after the initial breast cancer and calculated the crude incidence rates of bilateral breast cancer in

this period together with the incidence in the first three years individually. These rates are presented in Table 4-11.

In the infiltrating ductal carcinoma sub-cohort three or more years after a diagnosis, the rate of bilateral infiltrating ductal carcinoma was 4.41 per 1,000 person-years, the rate of bilateral lobular carcinoma was 0.83 per 1,000 person-years, and the rate of bilateral medullary carcinoma was 0.05 per 1,000 person-years. The rate of these three bilateral carcinomas combined is therefore 5.29 per 1,000 person-years.

In contrast, in the lobular carcinoma sub-cohort three or more years after diagnosis, the incidence of bilateral infiltrating ductal carcinoma was 3.32 per 1,000 person-years, lower than the rate observed following an initial ductal carcinoma, but the rate of bilateral lobular carcinoma was 2.34 per 1,000 person-years almost three times the incidence observed in the infiltrating ductal carcinoma sub-cohort. The rate of bilateral infiltrating ductal and lobular carcinomas combined is 5.65 per 1,000 person-years.

Finally, in the medullary carcinoma sub-cohort three or more years after diagnosis, the incidence of bilateral infiltrating ductal carcinoma was 5.20 per 1,000 person-years, higher than the rate observed in the infiltrating ductal sub-cohort (4.41 per 1,000 person-years) and the rate of bilateral medullary carcinoma was 0.80 per 1,000 person-years – 16 times higher than observed in the infiltrating ductal carcinoma sub-cohort. The rate of these two histological types combined is 5.21 per 1,000 person-years.

Table 4-11: Incidence of bilateral ductal carcinomas and bilateral lobular carcinoma following initial ductal and lobular carcinomas.

	Time (years)	Metachronous breast cancers	Person-years (× 1000)	Rate	95% CI	
Infiltrating Ductal Carcinoma sub-cohort:						
Infiltrating Ductal Carcinoma	0-1	953	243.3866	3.92	3.67	4.17
	1-2	780	216.5096	3.60	3.36	3.86
	2-3	679	189.0336	3.59	3.33	3.87
	3+	4261	1091.1206	3.91	3.79	4.02
Lobular Carcinoma	0-1	173	243.3866	0.71	0.61	0.83
	1-2	130	216.5096	0.60	0.51	0.71
	2-3	117	189.0336	0.62	0.52	0.74
	3+	777	1091.1206	0.71	0.66	0.76
Medullary Carcinoma	0-1	7	243.3866	0.03	0.01	0.06
	1-2	13	216.5096	0.06	0.03	0.10
	2-3	9	189.0336	0.05	0.02	0.09
	3+	52	1091.1206	0.05	0.04	0.06
Lobular Carcinoma sub-cohort:						
Infiltrating Ductal Carcinoma	0-1	152	37.4795	4.06	3.46	4.75
	1-2	101	32.4916	3.11	2.56	3.78
	2-3	79	27.8802	2.83	2.27	3.53
	3+	454	140.4357	3.23	2.95	3.54
Lobular Carcinoma	0-1	203	37.4795	5.42	4.72	6.22
	1-2	53	32.4916	1.63	1.25	2.14
	2-3	63	27.8802	2.26	1.77	2.89
	3+	275	140.4357	1.96	1.74	2.20
Medullary Carcinoma sub-cohort:						
Infiltrating Ductal Carcinoma	0-1	23	6.8082	3.38	2.24	5.08
	1-2	33	6.2711	5.26	3.74	7.40
	2-3	26	5.6856	4.57	3.11	6.72
	3+	234	48.6527	4.81	4.23	5.47
Medullary Carcinoma	0-1	8	6.8082	1.18	0.59	2.35
	1-2	4	6.2711	0.64	0.24	1.70
	2-3	1	5.6856	0.18	0.02	1.25
	3+	39	48.6527	0.80	0.59	1.10

In Table 4-12, I have concentrated on two groups of women, those whose first breast cancers were infiltrating ductal carcinomas or lobular carcinomas, and I have used Poisson regression to model the incidence of bilateral infiltrating ductal carcinoma in the first three years separately and then in all years combined after this. The reference rate is the rate of bilateral infiltrating ductal carcinoma in the infiltrating ductal carcinoma sub-cohort three or more years after diagnosis.

There is very little difference between the crude and adjusted rate ratios. Three or more years after diagnosis, the rate of bilateral ductal carcinoma in the lobular sub-cohort is 15% lower than the rate in the infiltrating ductal sub-cohort.

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.

		Crude estimates			Adjusted estimates		
Initial Breast Cancer sub-cohort	Time (Years)	IRR	95% C.I.		IRR	95% C.I.	
Ductal Carcinoma	0-1	1.00	0.93	1.07	0.97	0.90	1.05
	1-2	0.92	0.85	1.00	0.90	0.83	0.98
	2-3	0.93	0.85	1.01	0.91	0.84	0.99
(ref)	3+	1.00			1.00		
Lobular Carcinoma	0-1	1.06	0.90	1.25	1.08	0.91	1.27
	1-2	0.79	0.64	0.97	0.80	0.65	0.98
	2-3	0.73	0.58	0.91	0.74	0.59	0.93
	3+	0.83	0.75	0.91	0.85	0.77	0.94

† Adjusted for age at bilateral diagnosis, registry, race, year of diagnosis, marital status, stage, and radiotherapy.

If we now consider the rate of bilateral lobular carcinoma in these same women (Table 4-13), we can see that in the lobular sub-cohort the rate of bilateral lobular carcinoma is, after adjustment, over two and a half times greater than in the infiltrating ductal carcinoma sub-cohort.

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.

Initial Breast Cancer sub-cohort		Time (Years)	Crude estimates IRR	95% C.I.		Adjusted estimates IRR	95% C.I.	
Ductal Carcinoma		0-1	1.00	0.84	1.18	1.03	0.87	1.23
		1-2	0.86	0.71	1.04	0.89	0.73	1.07
		2-3	0.87	0.71	1.06	0.89	0.72	1.08
	(ref)	3+	1.00			1.00		
Lobular Carcinoma		0-1	7.48	6.38	8.77	7.30	6.20	8.60
		1-2	2.27	1.70	3.02	2.20	1.65	2.94
		2-3	3.22	2.48	4.18	3.12	2.40	4.05
		3+	2.67	2.31	3.07	2.59	2.25	2.99

† Adjusted for age at bilateral diagnosis, registry, race, year of diagnosis, marital status, stage, and radiotherapy.

In the first year after diagnosis, the rate of bilateral lobular in the infiltrating ductal sub-cohort was almost the same as the rate three or more years after diagnosis (IRR = 1.03). In the lobular carcinoma sub-cohort, the IRR was 7.30.

If we now consider women whose first breast cancers were either medullary or ductal carcinomas and use Poisson regression to model the incidence of bilateral ductal carcinoma we obtain the results shown in Table 4-14.

There is comparatively little difference between crude and adjusted relative rate estimates in the infiltrating ductal carcinoma sub-cohort, whereas in the medullary sub-cohort the relative rates have all been attenuated slightly by adjustment for other variable.

While differences in relative rates in the first three years could be due to chance, three or more years after their initial diagnosis, the rate of bilateral ductal carcinoma in the medullary carcinoma sub-cohort was 18% higher than in the infiltrating ductal carcinoma sub-cohort.

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.

Initial Breast Cancer	Time (Years)	Crude estimates IRR	95% C.I.		Adjusted estimates IRR	95% C.I.	
Ductal Carcinoma	0-1	1.00	0.93	1.07	0.97	0.90	1.04
	1-2	0.92	0.85	1.00	0.90	0.83	0.98
	2-3	0.93	0.85	1.01	0.91	0.83	0.99
(ref)	3+	1.00			1.00		
Medullary Carcinoma	0-1	0.88	0.58	1.34	0.80	0.52	1.22
	1-2	1.22	0.84	1.77	1.11	0.77	1.62
	2-3	1.15	0.77	1.72	1.06	0.71	1.58
	3+	1.23	1.08	1.41	1.18	1.03	1.36

† Adjusted for age at bilateral diagnosis, registry, race, year of diagnosis, marital status, stage, and radiotherapy.

In these same women, relative rates of bilateral medullary carcinoma were also estimated (Table 4-15). Once again relative rate estimates in the medullary carcinoma sub-cohort are attenuated after adjustment for other variables, markedly so in this instance.

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.

Initial Breast Cancer	Time (Years)	Crude estimates IRR	95% C.I.		Adjusted estimates IRR	95% C.I.	
Ductal Carcinoma	0-1	0.62	0.28	1.37	0.38	0.17	0.84
	1-2	1.29	0.70	2.38	0.84	0.45	1.58
	2-3	1.02	0.50	2.08	0.72	0.35	1.48
(ref)	3+	1.00			1.00		
Medullary Carcinoma	0-1	25.41	12.06	53.54	6.96	3.06	15.79
	1-2	10.32	3.22	33.07	3.16	0.95	10.48
	2-3	3.79	0.52	27.45	1.29	0.18	9.49
	3+	15.45	10.05	23.75	8.92	5.73	13.90

† Adjusted for age at bilateral diagnosis, registry, race, year of diagnosis, marital status, stage, and radiotherapy.

In the infiltrating ductal carcinoma sub-cohort, the rate of medullary bilateral breast cancer in the first year after diagnosis was 62% lower than the rate three or more years after diagnosis.

In the medullary carcinoma sub-cohort rates of bilateral medullary carcinoma were elevated above the reference rate at all times after diagnosis (the reference rate being the rate of bilateral medullary carcinoma three or more years after diagnosis in the infiltrating ductal carcinoma sub-cohort). In the first year following diagnosis the rate of bilateral medullary carcinoma was nearly seven times the reference rate, three or more years after diagnosis it was almost nine times the reference rate.

This analysis of bilateral medullary carcinoma is one of the few instances in this study where statistical adjustment for other factors has produced noticeable changes in relative rate estimates. By running a series of simpler Poisson models, each with histology and only one other covariate, I was able to ascertain that age at diagnosis of the bilateral breast cancer and, to a lesser extent, year of diagnosis of the first breast cancer were responsible for these strong confounding effects.

In the sub-cohort of women with medullary carcinoma, 28.4% of person-years were accumulated and 40% of bilateral breast cancers were diagnosed in ages younger than 50 years. In contrast, in the sub-cohort of women with infiltrating ductal carcinoma, only 16.4% of person-years accumulated and only 17.3% of bilateral breast cancers were diagnosed in ages younger than 50 years.

In conclusion, while the histology of the first breast cancer appears to be associated with the subsequent incidence of bilateral breast cancer, particularly lobular and medullary carcinomas, these are largely a function of differential incidence in the first year following diagnosis of the first breast cancer. This occurs because the distribution of

histological types occurring bilaterally is dependent on the histology of the first breast cancer.

4.3.4 Race, Marital Status, Year of First Diagnosis, SEER Registry, Radiotherapy and Bilateral Breast Cancer Incidence

In this analysis of bilateral breast cancer incidence I have concentrated primarily on the relationship between age and histological type and, in doing so, I have made use of Poisson regression models to adjust for the effects of other factors such as race, marital status, year of diagnosis, SEER registry, and use of radiotherapy in the treatment of the first breast cancer. While regression models are used to control for the confounding effects of other variables, in the results I have presented in the previous sections there was in most models very little evidence of significant confounding, with the crude incidence rate ratios being very similar to the adjusted rate ratios. In fact, it was only in the analysis of the incidence of bilateral medullary carcinoma that significant confounding was detected.

When we are interested in the relationship between two variables, for example, the incidence of bilateral breast cancer and some exposure variable, then a confounder would be a variable that was associated with the incidence of bilateral breast cancer but also associated with the exposure. As I will show in this section, those variables that I have treated as potential confounders – race , marital status, year of diagnosis, SEER registry, and use of radiotherapy – are associated with the incidence of bilateral breast cancer, but the strength of these associations are invariably quite weak and, as a consequence, so are the resulting confounding effects.

4.3.4.1 Race and the incidence of bilateral breast cancer

In the SEER data, race is reported as white, black, or other, where the latter includes Asian, Latino, and Native American women. The incidence of bilateral breast cancer in these three sub-cohorts of women is shown in Table 4-16 and the crude and adjusted relative rate estimates obtained from Poisson regression are shown in Table 4-17.

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

Race	Index Breast Cancers	Metachronous Breast cancers	Person-years (x 1000)	Rate	95% CI	
White	311,441	11942	2179.3741	5.48	5.38	5.58
Black	26,977	1020	158.3444	6.44	6.06	6.85
Other	20,839	599	128.7052	4.65	4.30	5.04

By examining the 95% confidence intervals around these rate estimates we can see that the crude rate in black women is significantly higher than that observed in white women whereas the rate for women in the 'other' category is significantly lower.

The crude incidence rate ratios shown in Table 4-17 are indicative of relatively weak association between race and the incidence of bilateral breast cancer. The crude rate in black women is 18% higher than in white women and, for women in the 'other' category, it is 17% lower.

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

Race	Crude estimates			Adjusted estimates†		
	IRR	95% C.I.		IRR	95% C.I.	
White	1.00			1.00		
Black	1.18	1.10	1.26	1.17	1.10	1.26
Other	0.83	0.76	0.91	0.90	0.81	0.99

† Adjusted for age at bilateral diagnosis, registry, histology, year of diagnosis, marital status, stage, and radiotherapy.

After multivariate adjustment for other covariates these effects were modified, although not to an extent that would indicate that any of the other covariates was a source of significant confounding. The adjusted rate in black women is 17% higher in white women and such a week effect is unlikely to have exerted much of a confounding effect in prior analyses, particularly when one considers that black women contribute only 158244 person-years to the whole cohort, 6.4% of the total person-years.

4.3.4.2 Marital status and the incidence of bilateral breast cancer

In sub-cohorts of women defined by their marital status when first diagnosed with breast cancer there was some variation in the crude rates of bilateral breast cancer. Women who were married formed the largest sub-cohort, contributing 63.1% of the total person-years of observation. Rates of bilateral breast cancer in the sub-cohorts of women who were divorced or widowed were similar to those in the married sub-cohort, whereas rates in the single and separated sub-cohorts were noticeably elevated – 6.01 per 1,000 person-years and 6.21 per 1,000 person-years respectively.

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

Marital Status	Index Breast Cancers	Metachronous Breast cancers	Person-years (x 1000)	Rate	95% CI	
Single	37,745	1244	207.15575	6.01	5.68	6.35
Married	214,428	8264	1525.45425	5.42	5.30	5.54
Separated	6,599	280	45.11517	6.21	5.52	6.98
Divorced	31,696	1069	191.30933	5.59	5.26	5.93
Widowed	81,284	2430	449.31233	5.41	5.20	5.63

The crude and adjusted incidence rate ratios for marital status relative to the rate in the married sub-cohort are shown in Table 4-19 and indicate that marital status is only weakly associated with the incidence of bilateral breast cancer. While the crude rate in

the separated sub-cohort was 16% higher than in the married sub-cohort, the adjusted rate ratio was only 1.05. The rate in the single sub-cohort was largely unaffected by statistical adjustment for other covariates, but a rate ratio of 1.13 is indicative of only very weak association with bilateral breast cancer incidence.

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

Marital Status		Crude estimates			Adjusted estimates †		
		IRR	95% C.I.		IRR	95% C.I.	
Single		1.12	1.05	1.19	1.13	1.06	1.20
Married	(ref)	1.00			1.00		
Separated		1.16	1.03	1.31	1.05	0.93	1.19
Divorced		1.03	0.97	1.10	1.05	0.98	1.12
Widowed		1.01	0.97	1.06	1.03	0.98	1.08

† Adjusted for age at bilateral diagnosis, registry, race, histology; year of diagnosis, stage, and radiotherapy.

4.3.4.3 Year of diagnosis and the incidence of bilateral breast cancer

In Table 4-20 the incidence of bilateral breast cancer is presented separately by year of diagnosis of the first breast cancer – sub-cohorts defined by year of diagnosis – and then by year of diagnosis of the bilateral breast cancer – period-specific rates ignoring year of first diagnosis. In both instances, year has been categorised in 3-year groups, with the exception of the first period, 1973 to 1976, which is four years.

In sub-cohorts of women defined by their year of first diagnosis we would expect rates of bilateral breast cancer to be most affected by exposures experienced at the time of the first breast cancer. For example, the use of tamoxifen would tend to reduce the risk of bilateral breast cancer (Fisher et al., 1989; Rutqvist et al., 1991).

Population screening mammography would also affect these rates but it is difficult to predict what the overall effect would be. Screening women without breast cancer would tend to increase detection of synchronous bilateral breast cancers thus reducing the

incidence of metachronous bilateral breast cancer in the years immediately after this. For women screen detected with unilateral breast cancer, however, lead time would be added to their subsequent person-years. If they were to continue to be screened after this, however, then bilateral breast cancers would be detected earlier. These effects are acting in opposite directions, so it is difficult to foresee what the net effect of these would be.

Using the year of diagnosis of the bilateral breast cancer will estimate period-specific rates and these would be more likely affected by exposures that affect women either newly diagnosed with breast cancer or with a history of breast cancer.

Tamoxifen use, for example, might be expected to produce a more noticeable effect on rates in the later periods, but its effect on these period-specific rates would depend on the extent to which it was used primarily to treat newly diagnosed breast cancer. If few women with a history of breast cancer were offered tamoxifen, then tamoxifen use would tend to have a less noticeable effect of these period-specific rates.

Population screening might be expected to have a more immediate effect on these rates, particularly if we assume that women with a history of breast cancer would be more likely to be screened than women in the general population.

If we look at the rates of bilateral breast cancer in sub-cohorts of women based on the year of first diagnosis we can see that there was a general decline in bilateral breast cancer incidence after 1982 (Table 4-20).

If, however, we look at the period-specific rates based on the year of diagnosis of the bilateral breast cancer, these suggest that lower rates were only evident after 1992.

Poisson regression models of bilateral breast cancer rates for both year of first diagnosis and year of bilateral breast cancer diagnosis were fitted and the crude and adjusted incidence rate ratios estimated from these are shown Table 4-21.

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.

	Metachronous Breast cancers	Person-years (x 1000)	Rate	95% CI	
Year of diagnosis of the first breast cancer					
1973-1976	2020	355.7838	5.68	5.44	5.93
1977-1979	1566	268.1053	5.84	5.56	6.14
1980-1982	1683	275.2643	6.11	5.83	6.41
1983-1985	1824	300.8394	6.06	5.79	6.35
1986-1988	1922	330.4121	5.82	5.56	6.08
1989-1991	1474	296.3217	4.97	4.73	5.23
1992-1994	1548	332.1177	4.66	4.43	4.90
1995-1997	1078	230.4788	4.68	4.41	4.96
1998-2000	454	86.8332	5.23	4.77	5.73
Year of diagnosis of the bilateral breast cancer					
1973-1976	403	64.5361	6.24	5.66	6.89
1977-1979	635	110.3078	5.76	5.33	6.22
1980-1982	889	157.1812	5.66	5.30	6.04
1983-1985	1265	205.5608	6.15	5.82	6.50
1986-1988	1624	261.3966	6.21	5.92	6.52
1989-1991	1897	317.5854	5.97	5.71	6.25
1992-1994	2075	400.8207	5.18	4.96	5.40
1995-1997	2534	491.9542	5.15	4.95	5.36
1998-2000	2247	466.8136	4.81	4.62	5.02

In sub-cohorts of women defined by year of first diagnosis we can see that there is comparatively little difference between the crude and adjusted rate ratios (Table 4-21). In those sub-cohorts diagnosed after 1988 bilateral breast cancer rates are about 20% lower than rates in the earlier sub-cohorts.

In the second analysis where the period-specific rates of bilateral breast cancer were modelled, there was again little difference between crude and adjusted rate ratios (Table 4-21). In this analysis, rates of bilateral breast cancer are lower in later periods after 1991 and approximately 20% lower than rates in the earlier periods.

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.

	Crude estimates			Adjusted estimates †		
	IRR	95% C.I.		IRR	95% C.I.	
Year of diagnosis of first breast cancer						
1973-1976	1.00			1.00		
1977-1979	1.03	0.96	1.10	1.04	0.97	1.11
1980-1982	1.08	1.01	1.16	1.08	1.01	1.16
1983-1985	1.06	0.99	1.13	1.06	0.99	1.13
1986-1988	1.01	0.95	1.08	1.01	0.94	1.08
1989-1991	0.86	0.80	0.92	0.85	0.79	0.91
1992-1994	0.82	0.77	0.88	0.79	0.73	0.85
1995-1997	0.82	0.76	0.88	0.77	0.71	0.84
1998-2000	0.91	0.82	1.01	0.81	0.72	0.90
Year of diagnosis of bilateral breast cancer						
1973-1976	1.00			1.00		
1977-1979	0.94	0.83	1.08	0.96	0.84	1.10
1980-1982	0.92	0.81	1.04	0.93	0.82	1.05
1983-1985	1.01	0.90	1.14	1.02	0.90	1.15
1986-1988	0.99	0.88	1.11	1.00	0.89	1.13
1989-1991	0.97	0.86	1.09	0.97	0.87	1.10
1992-1994	0.83	0.74	0.93	0.84	0.74	0.94
1995-1997	0.83	0.74	0.92	0.83	0.74	0.94
1998-2000	0.77	0.69	0.86	0.78	0.69	0.88

† Adjusted for age at bilateral diagnosis, registry, race, histology, marital status, stage, and radiotherapy.

Explaining these differences is difficult. While screening mammography and tamoxifen use may be playing a role in the effects observed, without any data describing either of these two effects, any discussion of their likely role would be speculative.

4.3.4.4 SEER registry and the incidence of bilateral breast cancer

The SEER data comprise cancer registry data from registries covering eleven regions of the USA (Section 3.3, page 49). The crude incidence of bilateral breast cancer observed in each of these regions is shown below in Table 4-22. There is noticeable variation in bilateral breast cancer rates with the highest incidence occurring in Metropolitan Detroit (6.12 per 1,000 person-years) and the lowest in New Mexico (4.56 per 1,000 person-years), but, in general, there is no evidence of a particular strong association between cancer registry and bilateral breast cancer incidence.

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

SEER Registry	Index Breast Cancers	Metachronous Breast cancers	Person-years (x 1000)	Rate	95% CI	
San Francisco-Oakland SMSA	57,017	2189	412.23467	5.31	5.09	5.54
Connecticut	56,711	2259	390.21158	5.79	5.56	6.03
Metropolitan Detroit	58,765	2443	399.17483	6.12	5.88	6.37
Hawaii	12,982	456	94.07492	4.85	4.42	5.31
Iowa	44,305	1749	314.69008	5.56	5.30	5.82
New Mexico	16,485	503	110.25575	4.56	4.18	4.98
Seattle (Puget Sound)	46,145	1805	312.84775	5.77	5.51	6.04
Utah	16,067	571	111.92600	5.10	4.70	5.54
Metropolitan Atlanta	24,643	730	158.28125	4.61	4.29	4.96
San Jose – Monterey	10,571	192	36.80500	5.22	4.53	6.01
Los Angeles	38,663	671	135.72108	4.94	4.58	5.33

This can be seen more clearly in Table 4-23 where crude and adjusted incidence rate ratios are presented. Using the rates in San Francisco-Oakland as the reference level, the crude rates in Metropolitan Detroit were only 13% higher and those in New Mexico, 15% lower. Multivariate adjustment resulted in little or no change in incidence rate ratios for most cancer registries, with the exception of Hawaii where the IRR increased by 11% (from 0.88 (crude) to 0.98 adjusted), San Jose-Monterey where the IRR increased by 20% (from 0.98 (crude) to 1.18 adjusted), and Los Angeles (from 0.90 (crude) to 1.05 adjusted) a 17% increase.

The San Jose – Monterey and Los Angeles registries are late entries into the SEER program, both entering the program in 1992. Year of diagnosis is the confounder responsible for most of the change in IRR shown in Table 4-23. The change in IRR for Hawaii is principally due to confounding by race. Women in the category ‘other’ were at lower risk of bilateral breast cancer than either white or black women (Table 4-17). Only 5.8% of women in the SEER data were classified in this ‘other’ category, compared to 67% of women in Hawaii.

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

SEER Registry	Crude estimates			Adjusted estimates †		
	IRR	95% C.I.		IRR	95% C.I.	
San Francisco-Oakland SMSA	1.00			1.00		
Connecticut	1.08	1.02	1.15	1.09	1.02	1.16
Metropolitan Detroit	1.13	1.07	1.20	1.12	1.05	1.19
Hawaii	0.88	0.80	0.98	0.98	0.87	1.10
Iowa	1.03	0.97	1.10	1.06	0.99	1.13
New Mexico	0.85	0.76	0.93	0.87	0.79	0.96
Seattle (Puget Sound)	1.08	1.01	1.15	1.10	1.03	1.17
Utah	0.93	0.85	1.03	0.96	0.88	1.06
Metropolitan Atlanta	0.85	0.78	0.92	0.85	0.78	0.92
San Jose – Monterey	0.98	0.84	1.14	1.18	1.01	1.38
Los Angeles	0.90	0.82	0.98	1.05	0.95	1.15

† Adjusted for age at bilateral diagnosis, race, histology, year of diagnosis, marital status, stage, and radiotherapy.

While there is some variation in bilateral breast cancer incidence between cancer registries, the estimated rate ratios are not large and it would appear that registry is only weakly associated with bilateral breast cancer incidence.

4.3.4.5 Radiotherapy use and the incidence of bilateral breast cancer

The incidence of bilateral breast cancer in women who had their first breast cancer treated by radiotherapy was 5.44 per 1,000 person-years and this was comparable to the incidence in women who had not had radiotherapy – 5.50 per 1,000 person-years (Table 4-24).

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

Radiotherapy treatment of first breast cancer	Index Breast Cancers	Metachronous Breast cancers	Person-years (x 1000)	Rate	95% CI	
No	233,399	9572	1740.0164	5.50	5.39	5.61
Yes	119,925	3747	688.7879	5.44	5.27	5.62

This is a crude incidence rate ratio of 0.99 which was altered only marginally after multivariate adjustment (IRR=1.03, Table 4-25). There appears, therefore, to be little evidence that radiotherapy is altering the risk of bilateral breast cancer overall.

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

Radiotherapy treatment of first breast cancer	Crude estimates			Adjusted estimates †		
	IRR	95% C.I.		IRR	95% C.I.	
No	1.00			1.00		
Yes	0.99	0.95	1.02	1.03	0.99	1.07

† Adjusted for age at bilateral diagnosis, registry, race, histology, year of diagnosis, marital status, and stage.

4.4 Survival from First Breast Cancer

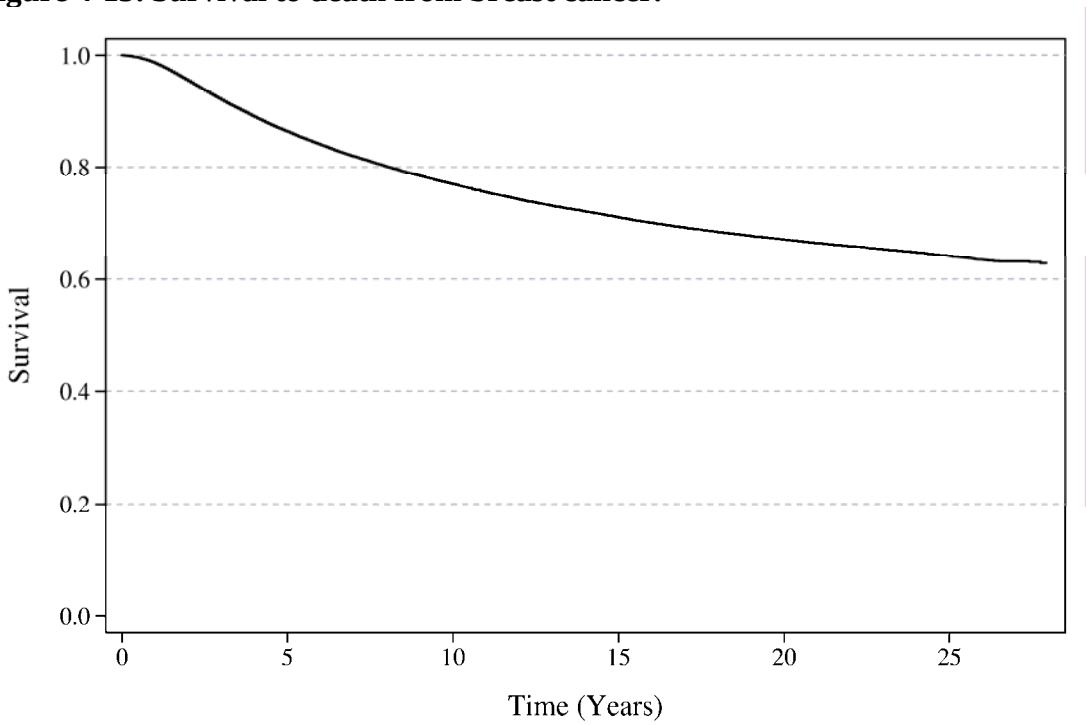
4.4.1 Univariate Analysis

In this section each covariate in the dataset will be examined for its relationship to time to death from breast cancer. Survival will be taken from the date of diagnosis of the first breast cancer and no attempt will be made at this stage to include the second breast primary. The covariates to be considered will be age at diagnosis (in 5 year age groups), year of diagnosis (1973 to 1997 in 4-year groups; 1998-2000), marital status, race, cancer stage (localised or regional), cancer histology, cancer registry, and treatment with radiotherapy. For each of these, Kaplan-Meier survival analysis was used to estimate crude survival.

4.4.1.1 Overall survival

The survival to death from breast cancer for the women in this series is shown in Figure 4-13g. Five-year survival was 86.3% and at 10 years, 76.9%.

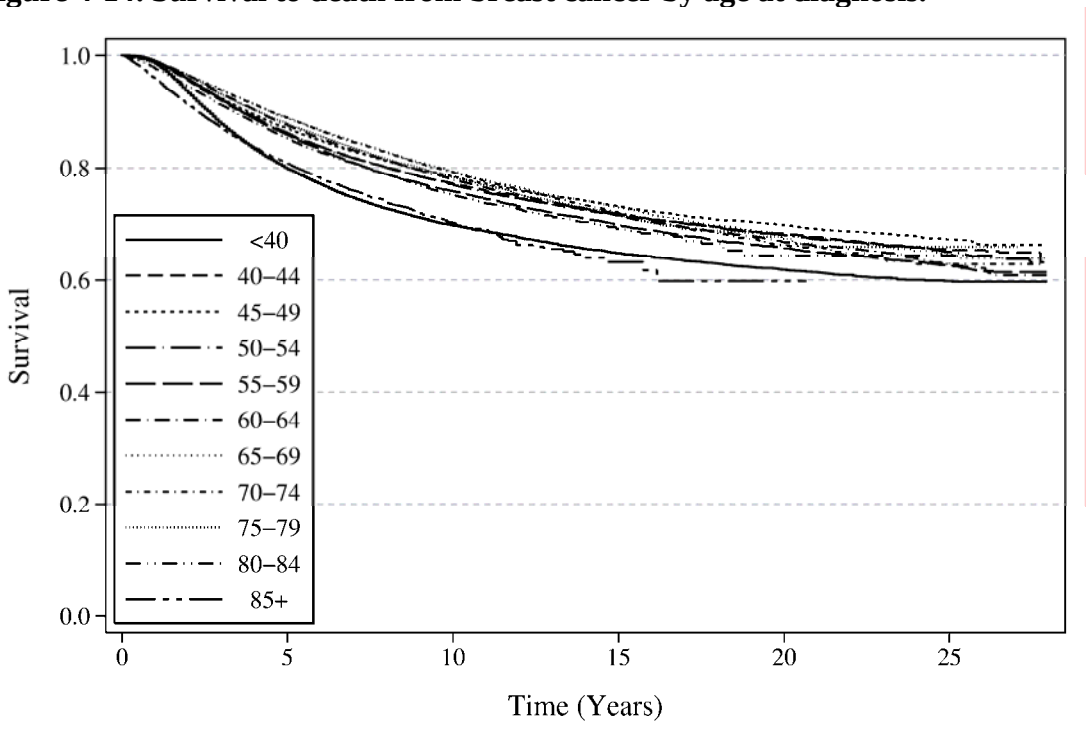
Figure 4-13: Survival to death from breast cancer.



4.4.1.2 Age at diagnosis

Survival by age at diagnosis is shown in Figure 4-14. There are 11 age groups represented and while this does make it difficult to visualize what is happening in each group, it does highlight the two age groups (women age under 40 years and those age 85 or more years) where survival was noticeably worse compared with the remaining age groups. Survival at 5 years was 79.8 % and at 10 years, 69.8%, in women aged less than 40 years, very similar to the survival in women aged 85 years or more: 5-year survival 80.7% and 10-year survival 70.3%.

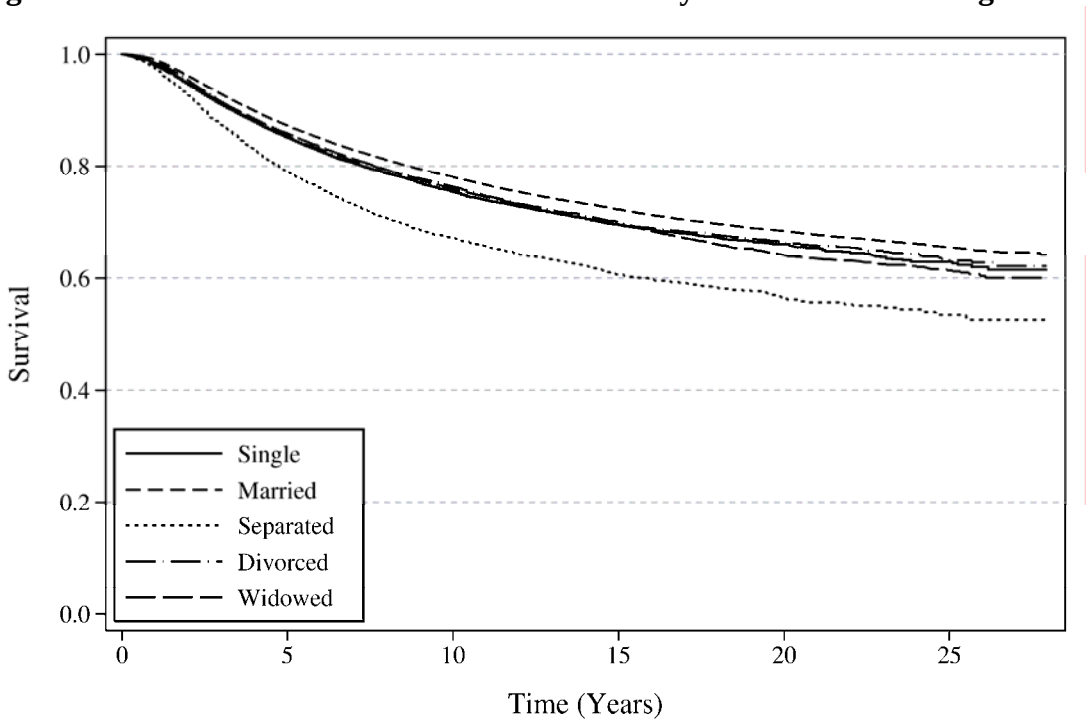
Figure 4-14: Survival to death from breast cancer by age at diagnosis.



4.4.1.3 Marital status

Marital status appears to be associated with survival from breast cancer as can be seen in Figure 4-15 (log-rank = 530.26, 4 df, p<0.0001). Women who were married at the time of their diagnosis of breast cancer had the best survival (5-year survival 87.1% and 78.0% at 10 years) whereas women who are separated from their spouse had the worst survival (77.9% at 5 years and 67.2% at 10 years). The survival for single, married and widowed women was very similar.

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

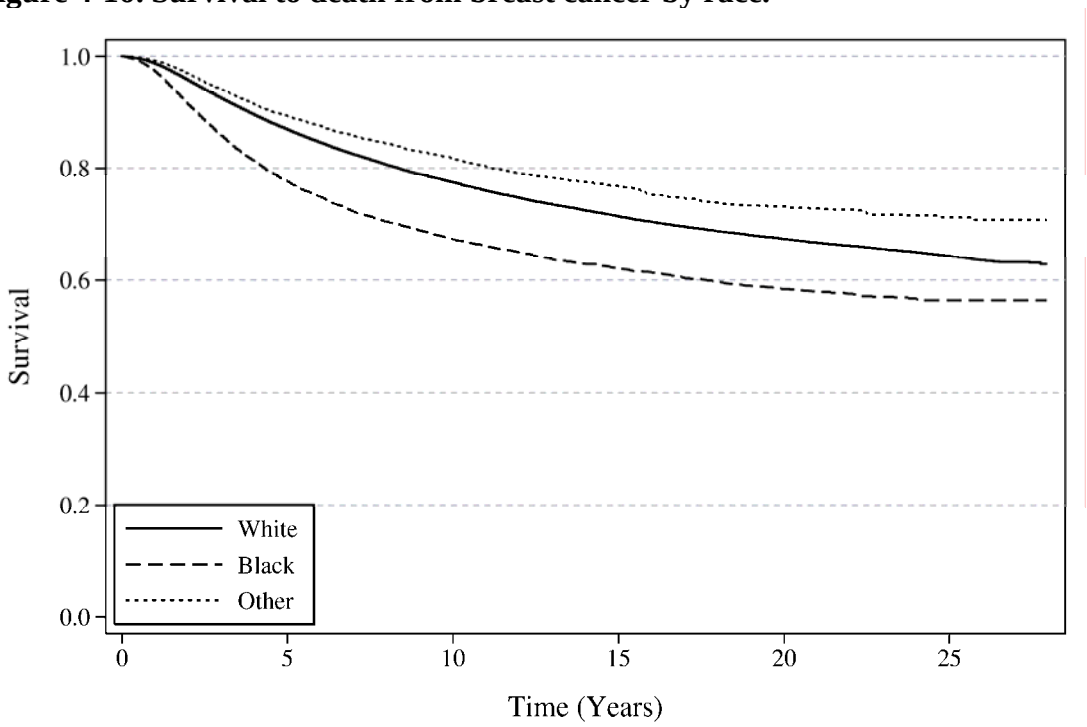


It is difficult to know exactly what is being measured here. It would seem unlikely that marital status *per se* would affect survival from breast cancer, but marital status may be associated with other factors that could affect survival. Alternately, it is also possible that age is confounding the relationship between marital status and survival.

4.4.1.4 Race

The survival from breast cancer of black women in the USA is distinctly worse than for white women (Figure 4-16). While the 5-year survival for white women was over 86.8% in this series, it was only 77.4% for black women. The category 'other' includes, among others, women of Asian or Latino origin and Native Americans. The survival in this group of women was 89.2% at 5 years.

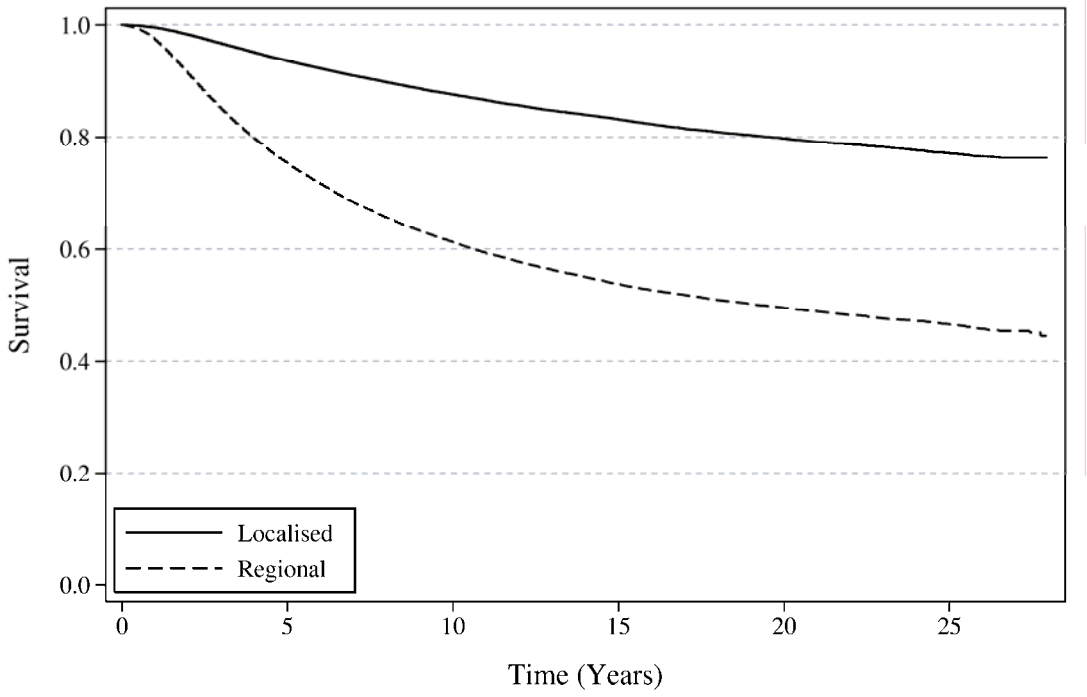
Figure 4-16: Survival to death from breast cancer by race.



4.4.1.5 Cancer stage

The most dramatic differences in survival can be seen in Figure 4-17, where the survival by stage of breast cancer is compared. At 5 years, survival for women diagnosed with a localized Stage 1 tumour was 93.6% and at 10 years, 87.6%, whereas for women who had evidence of metastatic disease in their axillary nodes when diagnosed with breast cancer, survival was notably worse. At 5 years survival was 75.2% in these women and at 10 years, 61.2%.

Figure 4-17: Survival to death from breast cancer by tumour stage.

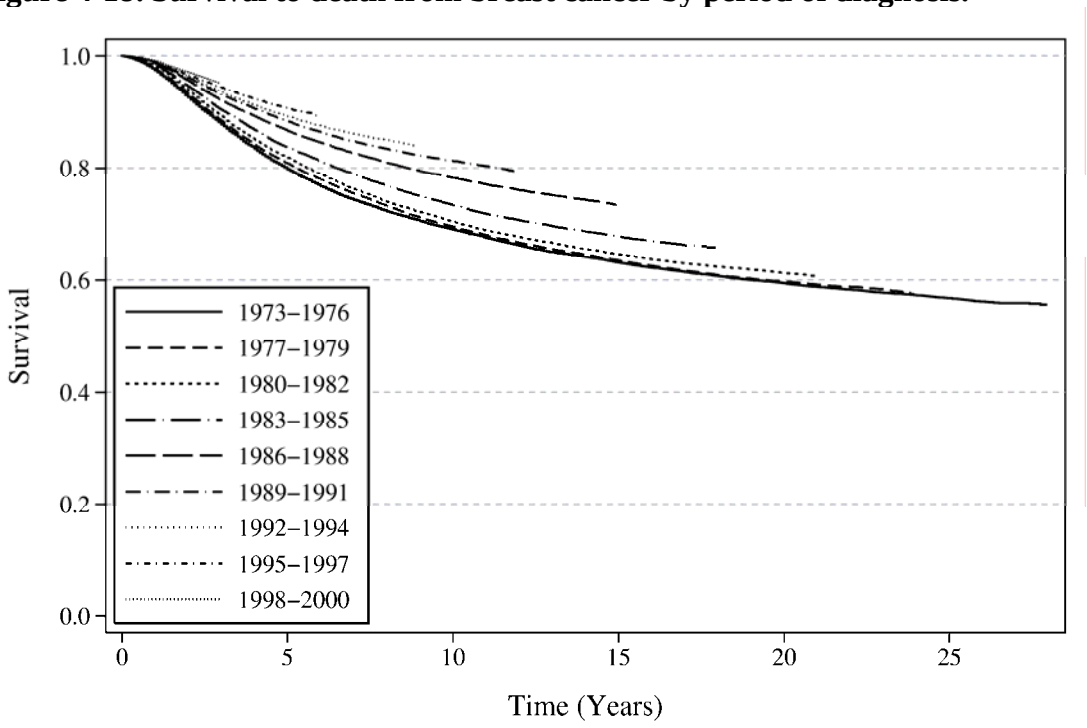


4.4.1.6 Year of diagnosis

When the year of diagnosis is considered (Figure 4-18), there is evidence of a steady improvement in survival from breast cancer over the period 1973 to 2000. Keeping in mind that women with advanced disease have been excluded in this series, we can see that women who were diagnosed with breast cancer between 1973 and 1976 had a 5-year survival of 79.8% and a 10-year survival of 69.0%. Since that time, there has been a steady, incremental improvement in survival to the extent that women diagnosed in 1989-1991 had a 10-year survival of 81.3%, and women diagnosed between 1995 and 1997 had a 5-year survival of 90.6%.

The SEER data contain no information regarding the use of chemotherapeutic agents, so year of diagnosis will play an important role in subsequent multivariate analyses because it will act as a surrogate for improved medical care.

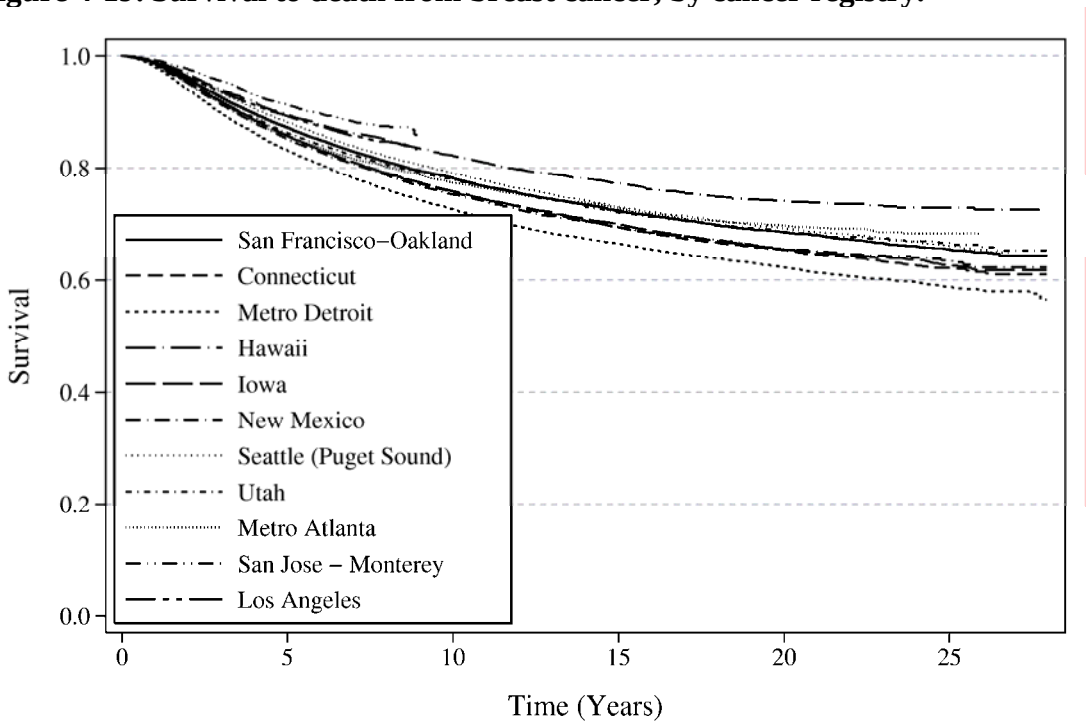
Figure 4-18: Survival to death from breast cancer by period of diagnosis.



4.4.1.7 SEER registry

Overall, there is relatively little meaningful variation in survival between the different cancer registries. While in most registries the 5-year survival was approximately 85%, survival among women diagnosed in Hawaii was slightly higher (89.3% at 5 years) and slightly lower in Detroit (83.0%). Five-year survival was highest in the two most recent registries to be included in the SEER program (San Jose and Los Angeles), but this is to be expected, since survival has improved over time. Among the other registries, some of the variability in survival could possibly be explained by other factors. Similarly, the poorer survival observed in metropolitan Detroit might, in part, be explained by the larger black population residing there since this is a group of women with poorer survival from breast cancer and similarly, the larger Asian and Polynesian populations living in Hawaii could in part explain the better survival observed there.

Figure 4-19: Survival to death from breast cancer, by cancer registry.



4.4.1.8 Histology

A graph of Kaplan-Meier survival by histological type of breast cancer is shown in Figure 4-20 and because this may be somewhat difficult to interpret, estimates of 5-year and 10-years survival by histological type are also presented in Table 4-26. While there is broad disparity in breast cancer survival associated with the histology, there is also evidence of lack of proportionality in breast cancer mortality risks between different histological types.

In terms of long-term survival, histological types appear to fall into one of two groups. The first of these offer comparatively good survival and comprise comedocarcinoma, medullary carcinoma, papillary carcinoma, mucinous carcinoma, tubular carcinoma and sarcoma. These are, however, comparatively rare breast cancer types and in total account for only 8.3% of breast cancers in this series.

The second group contains the remaining histological types which have comparatively poor survival. This includes the most common histological type, infiltrating ductal carcinomas (71.2% of all women in this series), and the second most common, infiltrating lobular carcinoma (11.2%), as well as unspecified carcinomas, and other carcinomas.

Figure 4-20: Survival to death from breast cancer by histology.

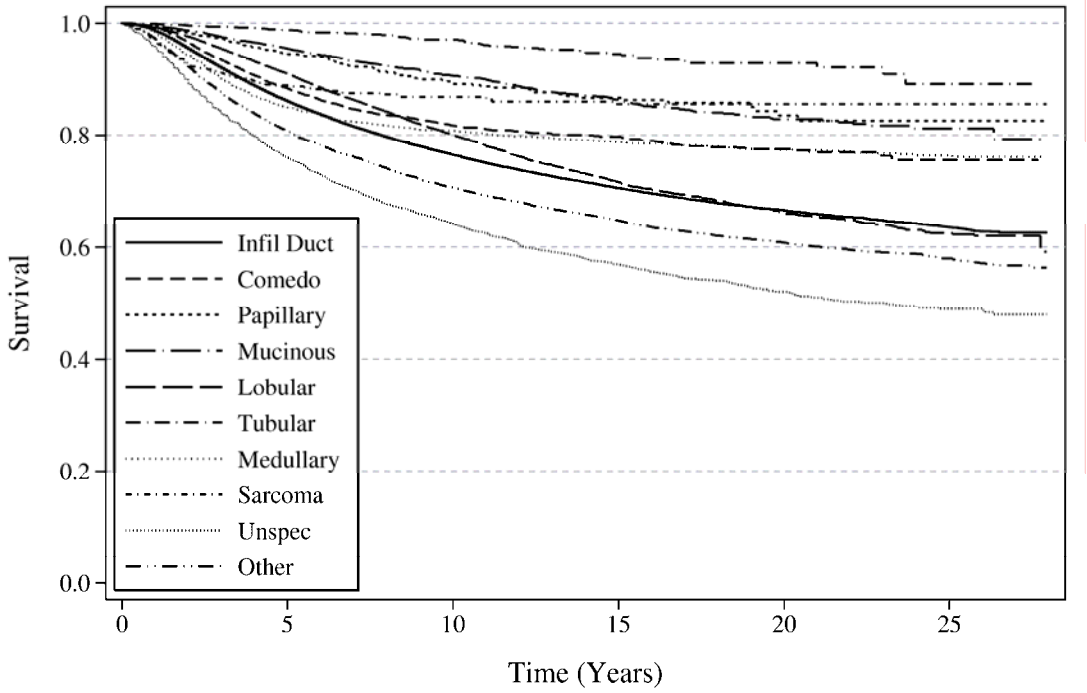


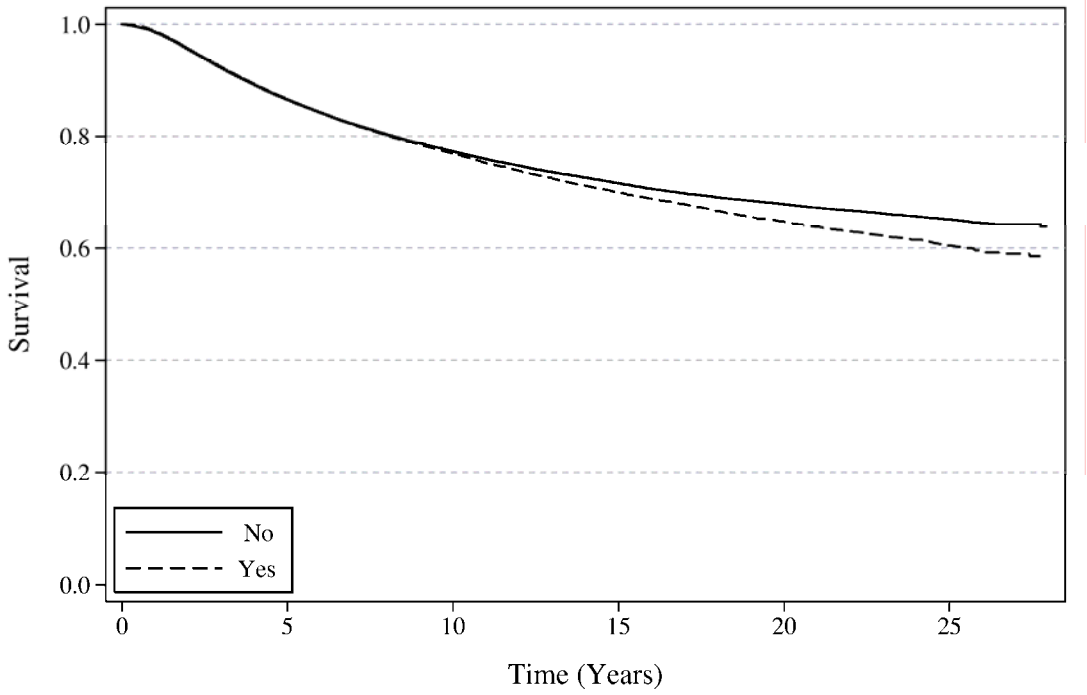
Table 4-26: Survival from breast cancer by histology.

Histological Type	Frequency	5-year survival	10-year survival
Infiltrating Ductal Carcinoma	71.2%	86.0%	76.4%
Comedocarcinoma	1.9%	88.2%	81.7%
Papillary Carcinoma	0.4%	94.5%	89.2%
Mucinous Carcinoma	2.5%	95.4%	90.6%
Lobular Carcinoma	11.2%	90.9%	80.0%
Tubular Carcinoma	1.2%	98.8%	97.1%
Medullary Carcinoma	1.9%	84.9%	80.8%
Sarcoma	0.3%	88.9%	86.8%
Unspecified Carcinoma	2.3%	75.9%	64.1%
Other Carcinoma	7.0%	80.6%	70.6%
	100.0%		

4.4.1.9 Radiotherapy

The use of radiotherapy in the treatment of breast cancer appears, at least at this crude level of comparison, to be unrelated to breast cancer survival (Figure 4-21). In the first 10 years following diagnosis, survival for women who received radiotherapy and for those who did not, is virtually identical (76.8% and 77.2% respectively). There is some divergence in the survival experience of these two groups of women after 10 years, with women who received radiotherapy experiencing worse survival, but the difference is not large. At 20 years, survival in those initially treated with radiotherapy was 64.7% and in those without radiotherapy, 67.8%.

Figure 4-21: Survival to death from breast cancer by treatment with radiotherapy.



4.4.2 Initial Multivariate Analysis

A number of important associations with breast cancer survival have been identified in the previous Section. In particular, the stage of the breast tumour is a particularly

important prognostic factor. Race also appears to be associated with breast cancer survival, as does year of diagnosis.

Age appears to be important only in that younger and older women are at increased risk of breast cancer death, but at the crude level of comparison, these effects were not large. There appears to be little variation in the risk of dying from breast cancer for women aged between 40 and 79 years.

These are, however, all crude associations and we might expect confounding by other factors to be biasing these effects to some extent. In the following section I will fit an initial multivariate proportional hazards model to examine this further.

4.4.2.1 Initial model

Cox proportional hazards models were fitted for each of the covariates separately, to estimate crude relative risks (RR), and then with all covariates entered, to estimate adjusted RR. These estimates are shown in Table 4-27.

In the Kaplan-Meier analyses, older and younger age groups were at increased risk of breast cancer death. Geographically, metropolitan Detroit had the worst survival and Hawaii the best. Married women had the best survival and women who had been married but were separated at the time of the breast cancer diagnosis had the worst survival. Black women had a higher risk of dying from breast cancer than white women. Cancer stage showed the greatest variation in the risk of death from breast cancer. Over time there has been a steady improvement in breast cancer survival since 1973.

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

Covariate		Unadjusted RR	Adjusted RR	95% confidence interval		p value
Stage	Local	1.00	1.00			<0.001
	Regional	3.68	3.39	3.33	3.45	
Age group	< 40	1.00	1.00			<0.001
	40 – 44	0.73	0.77	0.74	0.80	
	45 – 49	0.69	0.73	0.70	0.76	
	50 – 54	0.73	0.78	0.75	0.81	
	55 – 59	0.78	0.82	0.79	0.85	
	60 – 64	0.71	0.77	0.75	0.80	
	65 – 69	0.65	0.75	0.72	0.78	
	70 – 74	0.65	0.78	0.75	0.81	
	75 – 79	0.68	0.83	0.80	0.87	
	80 – 84	0.81	0.99	0.94	1.04	
	85 +	1.10	1.35	1.28	1.42	
Race	White	1.00	1.00			<0.001
	Black	1.58	1.48	1.44	1.53	
	Other	0.79	0.98	0.94	1.03	
Marital Status	Single	1.00	1.00			<0.001
	Married	0.88	0.90	0.87	0.92	
	Separated	1.41	1.03	0.97	1.09	
	Divorced	0.97	0.99	0.95	1.03	
	Widowed	0.98	0.97	0.94	1.01	
Year	1973-1976	1.00	1.00			<0.001
	1977-1979	0.98	0.99	0.96	1.02	
	1980-1982	0.93	0.93	0.90	0.96	
	1983-1985	0.82	0.85	0.83	0.88	
	1986-1988	0.65	0.72	0.70	0.74	
	1989-1991	0.55	0.63	0.61	0.65	
	1992-1994	0.50	0.58	0.56	0.60	
	1995-1997	0.44	0.52	0.50	0.54	
	1998-2000	0.41	0.48	0.45	0.51	
Registry	San Francisco-Oakland	1.00	1.00			<0.001
	Connecticut	1.13	1.11	1.07	1.14	
	Metropolitan Detroit	1.27	1.23	1.19	1.26	
	Hawaii	0.79	0.94	0.88	1.00	
	Iowa	1.13	1.19	1.16	1.23	
	New Mexico	1.15	1.23	1.17	1.28	
	Seattle (Puget Sound)	0.96	1.05	1.01	1.08	
	Utah	1.04	1.10	1.05	1.15	
	Metropolitan Atlanta	1.03	1.06	1.02	1.10	
	San Jose – Monterey	0.65	1.02	0.94	1.12	
	Los Angeles	0.80	1.17	1.12	1.23	

Table (Cont.)

Covariate		Unadjusted RR	Adjusted RR	95% confidence interval		p value
Morphology	Infiltrating Ductal Carcinoma	1.00	1.00			<0.001
	Comedocarcinoma	0.74	0.94	0.88	1.00	
	Papillary Carcinoma	0.42	0.49	0.41	0.59	
	Mucinous Carcinoma	0.37	0.49	0.45	0.53	
	Lobular Carcinoma	0.80	0.86	0.84	0.89	
	Tubular Carcinoma	0.13	0.21	0.17	0.26	
	Medullary Carcinoma	0.78	0.71	0.66	0.75	
	Sarcoma	0.62	0.91	0.76	1.10	
	Unspecified Carcinoma	1.40	1.20	1.14	1.27	
	Other Carcinoma	1.25	1.05	1.02	1.08	
Radiotherapy	No	1.00	1.00			<0.001
	Yes	1.03	1.10	1.08	1.12	

If we compare the relative risks obtained from the full multivariate model to the unadjusted relative risks we can see that the seemingly protective effect associated with diagnosis in the San Jose-Monterey area and in the Los Angeles area has largely disappeared in the multivariate model. This is not surprising since these are the two most recent registries in the SEER data set, and, given the overall improvement in survival over time, one would expect that in a crude comparison to the other registries, the more recent registries would appear to have a better survival. Adjusted, these effects disappear. There is now very little variation in the risk of death from breast cancer between the various registries. Hawaii still remains comparatively lower however (RR = 0.949), but this amounts to only a 5% reduction in risk.

The relative risks associated with the various categories of marital status have all been attenuated after multivariate adjustment. Married women still have the lowest risk of death from breast cancer relative to single women – RR = 0.90, a 10% reduction in risk compared with single women.

While multivariate adjustment has reduced the magnitude of the relative risk associated with black women to some extent, their risk of dying from breast cancer is still 48% greater than the risk experienced by white women. The lower risk for breast cancer death that was initially seen in the remaining women, those in the 'other' category, has, however, largely disappeared after multivariate adjustment.

We can also see that while the crude comparison between women treated with or without radiotherapy had not indicated any significant difference in risk of breast cancer death, after multivariate adjustment the risk in women treated with radiotherapy is 10% greater than the risk in women who did not receive radiotherapy.

4.4.2.2 Proportional hazards assumption

Taking the previous model, we can test the proportional hazards assumption using the method of Therneau et al. (1990). The results of this are shown below in Table 4-28. The *rho* is the correlation coefficient of the Schoenfeld residuals against the log of time.

If we consider only the p-values associated with this correlation coefficient, then it would appear for many of the covariates the proportionality assumption is problematic. Significant p-values can be seen for almost all age groups, for black women, for married women (the majority in this dataset), for almost all time periods, and for cancer stage, and this would suggest that all contradict the proportional hazards assumption. In fact every covariate in the model appears problematic with the exception of radiotherapy use.

While this may appear to indicate significant problems with the multivariate model shown in Table 4-27, this is not necessarily the case.

P-values are sensitive to sample size and in this set of data there were over 300,000 women with breast cancer of whom more 65,000 died from breast cancer in the period 1973 to 2000. The test of proportionality is based on residuals calculated at the time of each death. Consequently there is sufficient statistical power to detect quite small effects and this is what is being detected. If we look at the values of *rho* that are statistically significant in Table 4-28 they are, in most cases, extremely small – less than 0.1 for all covariates with the exception of cancer stage, where the *rho* for regional Stage is –0.106.

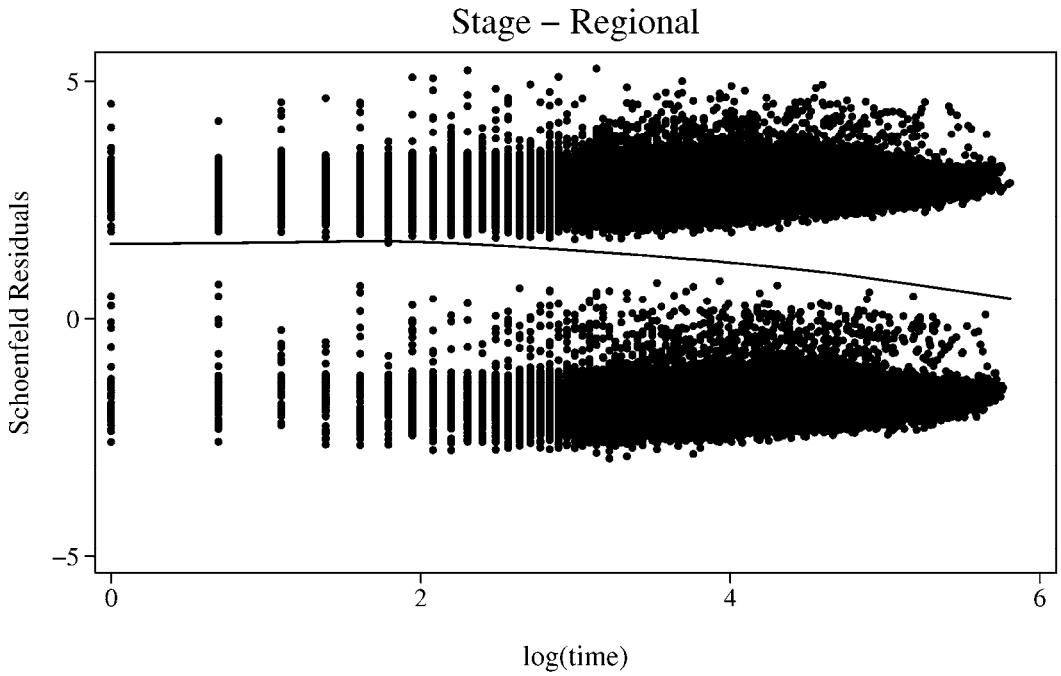
Table 4-28: Tests for proportional hazards assumption.

Covariate		Rho	χ^2	p value
Stage	Regional	-0.106	639.10	<0.001
Age group	40 – 44	0.011	6.76	0.009
	45 – 49	0.008	3.68	0.055
	50 – 54	0.010	5.51	0.019
	55 – 59	0.022	27.18	<0.001
	60 – 64	0.032	59.44	<0.001
	65 – 69	0.029	48.20	<0.001
	70 – 74	0.025	34.27	<0.001
	75 – 79	0.003	0.69	0.407
	80 – 84	-0.016	13.96	<0.001
	85 +	-0.048	130.15	<0.001
Race	Black	-0.047	121.72	<0.001
	Other	0.005	1.52	0.218
Marital Status	Married	0.015	12.35	<0.001
	Separated	0.005	1.26	0.261
	Divorced	0.005	1.31	0.252
	Widowed	0.002	0.15	0.700
Year	1977-1979	0.008	3.33	0.068
	1980-1982	0.010	5.56	0.018
	1983-1985	0.014	10.69	0.001
	1986-1988	0.004	0.97	0.324
	1989-1991	-0.005	1.31	0.253
	1992-1994	-0.012	8.69	0.003
	1995-1997	-0.016	15.18	<0.001
	1998-2000	-0.011	6.63	0.010
Registry	Connecticut	0.002	0.28	0.598
	Metropolitan Detroit	-0.011	6.84	0.009
	Hawaii	-0.011	6.34	0.012
	Iowa	-0.001	0.03	0.870
	New Mexico	-0.018	18.10	0.000
	Seattle (Puget Sound)	0.006	1.86	0.173
	Utah	-0.017	17.10	<0.001
	Metropolitan Atlanta	-0.016	14.05	<0.001
	San Jose – Monterey	0.005	1.54	0.215
	Los Angeles	-0.001	0.03	0.872
Morphology	Comedocarcinoma	-0.014	11.59	0.001
	Papillary Carcinoma	0.002	0.23	0.634
	Mucinous Carcinoma	0.012	7.74	0.005
	Lobular Carcinoma	0.077	331.21	<0.001
	Tubular Carcinoma	0.006	2.16	0.142
	Medullary Carcinoma	-0.065	240.14	<0.001
	Sarcoma	-0.053	161.15	<0.001
	Unspecified Carcinoma	-0.052	151.73	<0.001
	Other Carcinoma	-0.040	89.96	<0.001
Radiotherapy	Yes	0.005	1.66	0.198

We can ignore most of these statistically significant results since the differences detected are not large enough to create significant problems with interpretation of the model. We will, however, examine the proportionality assumption more carefully for cancer stage.

A plot of the Schoenfeld residuals against log(time) for regional staged cancers is shown in Figure 4-22. A LOWESS smoother has been run over this to fit a curve to these points and it is evident from this that there is a lack of proportionality over time.

Figure 4-22: Schoenfeld residuals for stage of first breast cancer.



For the remaining variables in the multivariate Cox model, the Schoenfeld residuals showed little evidence of lack of proportionality. These can be found in Appendix Q.

If we fail to account for the lack of proportionality associated with cancer stage, this could lead to misspecification of the effect associated with stage. More importantly, however, since stage is strongly associated with breast cancer survival and is therefore

an important potential confounding factor, any misspecification of the effect of stage would also result in misspecification of any confounding effect.

We can accommodate the lack of proportionality of stage by either stratifying on the stage variable, or by modelling survival for localised (Stage 1) and regional (Stage 2) breast cancers separately.

In the following table (Table 4-29) are the results obtained from each of these approaches. First are the adjusted relative risks obtained from the full model with stage as a covariate (these are the same as presented earlier in Table 4-27), followed by the full model with stage as a stratification variable, and then from the two stage-specific models.

There is little difference in the estimated effects produced by the first model with stage as a covariate and the second model which is stratified on stage. This would tend to indicate that if there is a problem with proportionality associated with stage, it is not occurring to such an extent that the confounding effect of stage is being mis-specified.

The last two models – the stage-specific models – do, however, produce slightly different estimates of the relative effect of some covariates. There are differences, for example, in the age effects and the year of diagnosis effects depending on whether the breast cancer was localised or regional.

Table 4-29: Comparison of results from full model, stage-stratified model, and stage-specific models.

		Full model			Stratified Model			Localised Stage Model			Regional Stage Model		
		RR	95% CI		RR	95% CI		RR	95% CI		RR	95% CI	
Age group	< 40	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
	40 – 44	0.77	*0.74*	*0.80*	0.77	*0.74*	*0.81*	0.76	*0.71*	*0.81*	0.78	*0.75*	*0.82*
	45 – 49	0.73	*0.70*	*0.76*	0.73	*0.70*	*0.76*	0.67	*0.63*	*0.71*	0.77	*0.73*	*0.80*
	50 – 54	0.78	*0.75*	*0.81*	0.78	*0.75*	*0.81*	0.69	*0.65*	*0.73*	0.84	*0.80*	*0.88*
	55 – 59	0.82	*0.79*	*0.85*	0.82	*0.79*	*0.85*	0.73	*0.68*	*0.77*	0.88	*0.84*	*0.92*
	60 – 64	0.77	*0.75*	*0.80*	0.77	*0.75*	*0.80*	0.70	*0.66*	*0.74*	0.82	*0.79*	*0.86*
	65 – 69	0.75	*0.72*	*0.78*	0.75	*0.73*	*0.78*	0.66	*0.62*	*0.71*	0.81	*0.78*	*0.85*
	70 – 74	0.78	*0.75*	*0.81*	0.78	*0.75*	*0.81*	0.70	*0.65*	*0.75*	0.84	*0.80*	*0.88*
	75 – 79	0.83	*0.80*	*0.87*	0.84	*0.80*	*0.88*	0.77	*0.72*	*0.82*	0.89	*0.84*	*0.94*
	80 – 84	0.99	*0.94*	*1.04*	0.99	*0.95*	*1.04*	0.97	*0.89*	*1.05*	1.01	*0.95*	*1.07*
	85 +	1.35	*1.28*	*1.42*	1.36	*1.29*	*1.44*	1.45	*1.33*	*1.58*	1.30	*1.21*	*1.39*
Year	1973-1976	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
	1977-1979	0.99	*0.96*	*1.02*	0.99	*0.96*	*1.02*	1.01	*0.96*	*1.06*	0.98	*0.94*	*1.02*
	1980-1982	0.93	*0.90*	*0.96*	0.93	*0.90*	*0.96*	0.93	*0.88*	*0.98*	0.95	*0.91*	*0.99*
	1983-1985	0.85	*0.83*	*0.88*	0.85	*0.83*	*0.88*	0.85	*0.80*	*0.89*	0.87	*0.83*	*0.90*
	1986-1988	0.72	*0.70*	*0.74*	0.72	*0.70*	*0.74*	0.67	*0.64*	*0.71*	0.76	*0.73*	*0.79*
	1989-1991	0.63	*0.61*	*0.65*	0.63	*0.61*	*0.66*	0.54	*0.51*	*0.58*	0.70	*0.67*	*0.73*
	1992-1994	0.58	*0.56*	*0.60*	0.59	*0.57*	*0.61*	0.48	*0.45*	*0.51*	0.66	*0.63*	*0.69*
	1995-1997	0.52	*0.50*	*0.54*	0.53	*0.50*	*0.55*	0.44	*0.41*	*0.47*	0.58	*0.56*	*0.61*
	1998-2000	0.48	*0.44*	*0.51*	0.49	*0.45*	*0.52*	0.46	*0.41*	*0.52*	0.50	*0.46*	*0.55*
Race	White	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
	Black	1.48	*1.44*	*1.53*	1.48	*1.44*	*1.53*	1.47	*1.40*	*1.55*	1.48	*1.43*	*1.53*
	Other	0.98	*0.94*	*1.03*	0.98	*0.93*	*1.03*	0.81	*0.74*	*0.89*	1.07	*1.01*	*1.14*
Radiotherapy	No	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
	Yes	1.10	*1.08*	*1.12*	1.11	*1.09*	*1.13*	1.01	*0.97*	*1.04*	1.16	*1.14*	*1.19*

Table 4-29: (cont.)

		Full model			Stratified Model			Localised Stage Model			Regional Stage Model		
		RR	95% CI		RR	95% CI		RR	95% CI		RR	95% CI	
Marital Status	Single	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
	Married	0.89	*0.87*	*0.92*	0.90	*0.87*	*0.92*	0.91	*0.87*	*0.96*	0.89	*0.86*	*0.92*
	Separated	1.03	*0.97*	*1.09*	1.02	*0.97*	*1.09*	1.04	*0.94*	*1.15*	1.02	*0.95*	*1.10*
	Divorced	0.99	*0.95*	*1.03*	0.99	*0.95*	*1.03*	1.01	*0.94*	*1.08*	0.98	*0.94*	*1.03*
	Widowed	0.97	*0.94*	*1.01*	0.97	*0.94*	*1.01*	0.99	*0.94*	*1.06*	0.96	*0.92*	*1.01*
Registry	San Francisco-Oakland SMSA	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
	Connecticut	1.11	*1.07*	*1.14*	1.11	*1.08*	*1.14*	1.18	*1.12*	*1.24*	1.08	*1.04*	*1.12*
	Metropolitan Detroit	1.23	*1.19*	*1.26*	1.23	*1.19*	*1.26*	1.25	*1.19*	*1.32*	1.22	*1.17*	*1.26*
	Hawaii	0.94	*0.88*	*1.00*	0.94	*0.88*	*1.00*	0.92	*0.83*	*1.02*	0.96	*0.89*	*1.03*
	Iowa	1.19	*1.16*	*1.23*	1.19	*1.16*	*1.23*	1.23	*1.16*	*1.29*	1.17	*1.13*	*1.22*
	New Mexico	1.23	*1.17*	*1.28*	1.22	*1.17*	*1.28*	1.25	*1.16*	*1.35*	1.21	*1.15*	*1.28*
	Seattle (Puget Sound)	1.04	*1.01*	*1.08*	1.04	*1.01*	*1.08*	1.07	*1.01*	*1.13*	1.03	*0.99*	*1.08*
	Utah	1.10	*1.05*	*1.15*	1.10	*1.05*	*1.15*	1.16	*1.08*	*1.25*	1.07	*1.01*	*1.13*
	Metropolitan Atlanta	1.06	*1.02*	*1.10*	1.06	*1.02*	*1.10*	1.05	*0.98*	*1.12*	1.06	*1.01*	*1.11*
	San Jose – Monterey	1.02	*0.93*	*1.11*	1.02	*0.93*	*1.11*	1.02	*0.88*	*1.19*	1.01	*0.91*	*1.12*
	Los Angeles	1.17	*1.12*	*1.23*	1.17	*1.11*	*1.22*	1.28	*1.18*	*1.39*	1.11	*1.04*	*1.18*
Histology	Ductal Carcinoma	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
	Comedocarcinoma	0.94	*0.88*	*1.00*	0.94	*0.88*	*1.00*	0.75	*0.68*	*0.83*	1.12	*1.03*	*1.22*
	Papillary Carcinoma	0.49	*0.41*	*0.59*	0.49	*0.41*	*0.59*	0.43	*0.33*	*0.55*	0.56	*0.43*	*0.72*
	Mucinous Carcinoma	0.49	*0.45*	*0.53*	0.49	*0.45*	*0.54*	0.43	*0.39*	*0.48*	0.58	*0.51*	*0.66*
	Lobular Carcinoma	0.86	*0.84*	*0.89*	0.86	*0.83*	*0.89*	0.79	*0.75*	*0.83*	0.89	*0.86*	*0.93*
	Tubular Carcinoma	0.22	*0.18*	*0.27*	0.22	*0.18*	*0.27*	0.23	*0.18*	*0.29*	0.21	*0.14*	*0.30*
	Medullary Carcinoma	0.71	*0.67*	*0.75*	0.71	*0.67*	*0.75*	0.75	*0.69*	*0.82*	0.66	*0.61*	*0.72*
	Sarcoma	0.91	*0.76*	*1.10*	0.91	*0.75*	*1.09*	0.79	*0.63*	*0.99*	1.14	*0.81*	*1.60*
	Unspecified Carcinoma	1.20	*1.14*	*1.27*	1.20	*1.14*	*1.27*	1.14	*1.04*	*1.25*	1.23	*1.15*	*1.31*
	Other Carcinoma	1.05	*1.02*	*1.08*	1.05	*1.02*	*1.08*	0.91	*0.87*	*0.96*	1.13	*1.09*	*1.17*
Stage	Localised	1.00	-	-									
	Regional	3.39	*3.33*	*3.45*									

4.4.3 Implications for the following Analysis

The most important factor in explaining survival from breast cancer is the stage of the breast cancer at diagnosis. Unfortunately, stage is not producing hazards that can be assumed to be proportional over time and this complicates the analysis. While the lack of proportionality can be handled by stratification on the stage variable, stage is not a nuisance variable and ultimately I would wish to examine the effect of a diagnosis of a bilateral breast cancer separately for breast cancers stage as localised or regional.

Because the sample size is so large, I can deal with cancer stage in future models by fitting models separately for women diagnosed with Stage 1 (localised) breast cancer and for women diagnosed with Stage 2 (regional) breast cancer and estimate the effect of bilateral breast cancer on survival separately in each of these. I can then fit a model using the whole cohort and estimate in this the stage-specific effects of bilateral breast cancer on survival. Comparing the results from this model to those obtained in the Stage 1 and Stage 2 models, will allow me to gauge to what extent this proportionality problem is affecting the results.

4.5 Survival – Synchronous Bilateral Breast Cancer

Up until now, I have not dealt with synchronous bilateral breast cancers, preferring instead to concentrate on the incidence of metachronous bilateral breast cancers. In my analysis, I defined bilateral breast cancers diagnosed after the first breast cancer as metachronous and those diagnosed at the same time as the first breast cancer as synchronous.

When considering survival, however, women with synchronous bilateral breast cancers need to be considered because they are a clinical entity and it is reasonable to determine

if women with two breast cancers diagnosed at the same time are at greater risk of breast cancer death than women with only one diagnosis.

4.5.1 Coding Stage for Synchronous Bilateral Breast Cancer

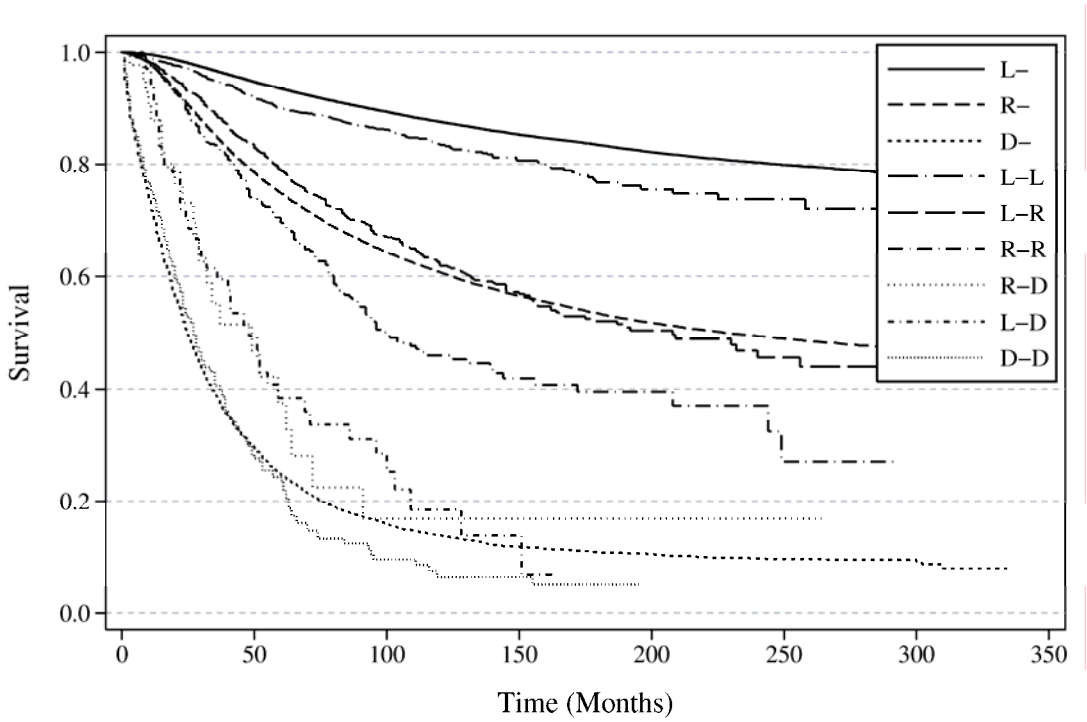
In the previous section, I had excluded Stage 4 (Distant) breast cancers because I felt that there was a reasonable suspicion of misclassification bias in the early bilateral breast cancer diagnoses. Similarly, when developing a model for breast cancer survival to estimate the effect of a metachronous breast cancer diagnosis on survival, I excluded women with Stage 4 (Distant) breast cancers for the same reason. Should these breast cancers be excluded when examining the survival of women with synchronous breast cancers?

In Figure 4-23, I have estimate the crude survival by cancer stage for women with unilateral breast cancer and for women with synchronous bilateral breast cancer. For women with unilateral disease there is, of course, only one cancer stage, but for women with bilateral disease there are two cancer stages.

In this figure I have represented each combination of cancer stage for the women with bilateral breast cancer. L represents localised (Stage 1) breast cancers, R represents regional (Stage 2) breast cancers and D, distant (Stage 4) breast cancers. Thus L-L represents women with bilateral breast cancer where both cancers were staged as localised, L-R women with one localised and the one regional breast cancer, etc.

Three distinct groups are apparent in this figure. Women with unilateral localised breast cancer (L-) and those with bilateral localised breast cancer (L-L) form one group. Women with at least one breast cancer stage as regional (R- , L-R, and R-R) form another and women with at least one breast cancer stage as distant (D- , D-L, D-R, and D-D) form the last group.

Figure 4-23: Survival by stage for unilateral and synchronous bilateral breast cancers.



It would appear that survival in women with synchronous bilateral breast cancer was determined to a large extent by the stage of the more advanced of the two tumours. However, there was a problem with the staging of synchronous bilateral breast cancers when distant metastatic disease was present.

Between 1973 and 2000 there were 4,278 women diagnosed with synchronous bilateral breast cancers and the stage distributions for the left and right breast for these women are shown below in Table 4-30.

We can see in this table that while there is little difference in the marginal stage distributions of left and right breast cancers, there is a strong association between Stage 4 primaries in the left and right breast. Most Stage 4 cancers were diagnosed together as synchronous pairs with Stage 1/Stage 4 or Stage 2/Stage 4 pairs observed far less frequently than the marginal distributions would lead one to expect. This association is, I believe, likely to be an artefact of the criteria used to stage cancers.

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

Right Breast	Left Breast			All
	Stage 1 Localised	Stage 2 Regional	Stage 4 Distant	
Stage 1 – Localised	1,923	688	40	2,651
	72.54	*25.95*	*1.51*	*100*
	71.78	*56.58*	*10.44*	*61.97*
Stage 2 – Regional	721	504	21	1,246
	57.87	*40.45*	*1.69*	*100*
	26.91	*41.45*	*5.48*	*29.13*
Stage 4 – Distant	35	24	322	381
	9.19	*6.3*	*84.51*	*100*
	1.31	*1.97*	*84.07*	*8.91*
All	2,679	1,216	383	4,278
	62.62	*28.42*	*8.95*	*100*
	100	*100*	*100*	*100*

Staging criteria are designed to stage single tumours and breast cancers are classified as Stage 4 if distant metastases are present, regardless of tumour size or presence or absence of metastatic disease in the axillary nodes. If breast cancers are diagnosed synchronously and distant metastatic disease is present, then both tumours should be, by definition, Stage 4 since there will often be no way of determining which breast cancer was responsible for this metastatic disease.

If this is indeed what is happening, then the staging of each synchronous bilateral breast cancer may not be reliable when distant metastatic disease is present. Consequently, I have excluded from further analysis any synchronous pair where one or both primaries were Stage 4.

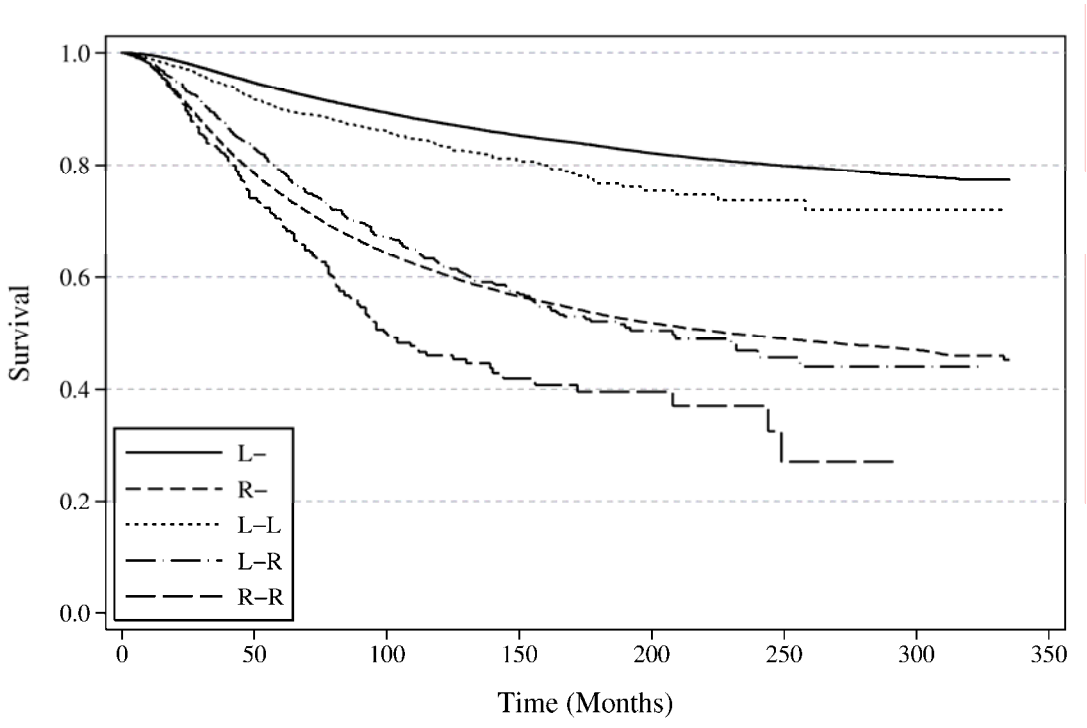
4.5.2 Survival by Stage of Synchronous Bilateral Breast Cancers

Before determining the best way of dealing with stage in this analysis, we should examine the crude survival associated with stage both for the unilateral breast cancers

and both synchronous breast cancers (Figure 4-24). The survival by stage for each unilateral breast cancer is presented together with the survival by each combination of stage for women with synchronous bilateral breast cancers. Women with localised breast cancers (Stage 1), either synchronous or bilateral, have similar survivals, albeit somewhat worse for women with synchronous bilateral Stage 1 cancers.

There is little difference in survival between women with unilateral regional breast cancers (Stage 2) and synchronous bilateral breast cancers where one was regional and the other localised (Stage 2/Stage1). For women with synchronous bilateral breast cancer where both were regional (Stage 2/Stage 2), survival appears to be worse than for other groups.

Figure 4-24: Survival by stage for unilateral and synchronous bilateral breast cancers.



I have fitted a proportional hazards model using this classification of stage of synchronous bilateral breast cancers (Table 4-31) and tested the proportional hazards assumption (Table 4-32).

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

Stage		Crude			Adjusted†		
		RR	95% confidence interval		RR	95% confidence interval	
Unilateral	Stage 1	1.00			1.00		
	Stage 2	3.79	3.72	3.85	3.45	3.38	3.51
Bilateral	Both Stage 1	1.44	1.27	1.64	1.45	1.27	1.66
	Stage 1 and Stage 2	3.49	3.15	3.85	3.35	3.02	3.27
	Both Stage 2	5.34	4.63	6.16	5.04	4.36	5.84

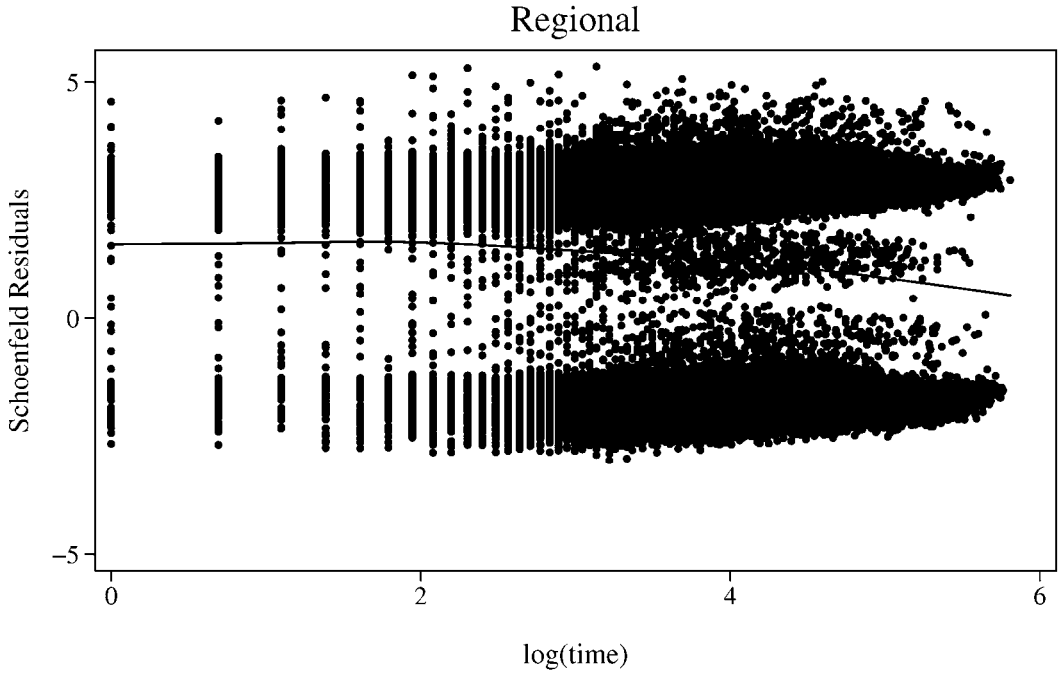
† Adjusted for age, registry, race, year of diagnosis, marital status, histology and radiotherapy.

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

Covariate		Rho	χ^2	p value
Stage	Stage 2	-0.096	493.93	0.000
	Stages 1 & 1	-0.008	3.50	0.061
	Stages 1 & 2	-0.008	3.13	0.077
	Stages 2 & 2	-0.002	0.18	0.674

As we might expect, the effect of stage of the unilateral primaries is not conforming to the proportional hazards assumption as we saw previously (Table 4-28). A plot of the Schoenfeld residuals versus log(time) is shown in Figure 4-25.

Figure 4-25: Schoenfeld residuals for unilateral Stage 2 (regional) breast cancers.



Given the problem with lack of proportionality associated with the variable stage, I conducted stage-specific analyses. I suspected that the most advanced tumour in a synchronous pair would, to a large extent, determine the type of treatment provided, and, ultimately, have the strongest influence on breast cancer survival. I therefore grouped synchronous pairs on the basis of the stage of the most advanced tumour in the pair. This would create two stage groupings and hence two analyses.

The first analysis compared the survival in women with synchronous Stage 1 (localised) bilateral breast cancers to women with unilateral Stage 1 (localised) tumours. Both the crude effects and the effects after adjustment for other covariates are shown in Table 4-33.

In the second analysis, I compared the survival of women with synchronous Stage 2 (regional) bilateral breast cancers; women with synchronous bilateral breast cancers, one Stage 2 (regional) and the other Stage 1 (localised); and women with unilateral,

Stage 2 (regional) breast cancer. The crude and adjusted effects from this analysis are shown in Table 4-34.

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

Covariate		RR	95% confidence interval		p value
Crude effect					
Stage	Unilateral: localised	1.00	-	-	<0.001
	Bilateral: localised – localised	1.41	1.24	1.61	
Adjusted effect†					
Stage	Unilateral: localised	1.00	-	-	<0.001
	Bilateral: localised – localised	1.46	1.28	1.67	

† Adjusted for age, registry, race, year of diagnosis, marital status, histology and radiotherapy.

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†.

Covariate		RR	95% confidence interval		p value
Crude effect					
Stage	Unilateral: regional	1.00	-	-	<0.001
	Bilateral: localised – regional	0.92	0.83	1.01	
	Bilateral: regional – regional	1.39	1.21	1.61	
Adjusted effect†					
Stage	Unilateral: regional	1.00	-	-	<0.001
	Bilateral: localised – regional	0.96	0.87	1.07	
	Bilateral: regional – regional	1.45	1.25	1.68	

† Adjusted for age, registry, race, year of diagnosis, marital status, histology and radiotherapy.

Adjustment for other covariates produced only small changes in the estimated relative risks in both models. The risk of breast cancer death in women with bilateral Stage 1 (localised) tumours was increased by 46% (95% C.I.: 25% – 68%) compared to the risk for women with only one Stage 1 tumour (Adjusted effect, Table 4-33).

In the second model (Table 4-34), there was little difference in risk of breast cancer death between women with a single Stage 2 (regional) tumour and those with bilateral breast cancer where one tumour was Stage 2 and the other Stage 1. For women with bilateral breast cancer where both were Stage 2, however, the risk of breast cancer death was increased by 45% (95% C.I.: 25% – 68%).

If we refer back to Table 4-31, where the results from the combined analysis were presented, we can see that these are essentially the same as those obtained in the stratified analysis above (Table 4-33 and Table 4-34).

In Table 4-35 below are the results of the combined model with Unilateral Stage 1 breast cancer as the reference level (as in Table 4-31) and then the results from the same model, but with unilateral Stage 2 taken as the reference level.

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

Stage		Adjusted† (Ref. – Unilateral Stage 1)			Adjusted† (Ref. – Unilateral Stage 2)		
		RR	95% confidence interval		RR	95% confidence interval	
Unilateral	Stage 1	1.00			0.29	0.28	0.30
	Stage 2	3.45	3.38	3.51	1.00		
Bilateral	Both Stage 1	1.45	1.27	1.66	0.42	0.37	0.48
	Stage 1 and Stage 2	3.35	3.02	3.27	0.97	0.88	1.08
	Both Stage 2	5.04	4.36	5.84	1.46	1.26	1.69

† Adjusted for age, registry, race, year of diagnosis, marital status, histology and radiotherapy.

We can see that using this model the risks for synchronous Stage 2 bilateral breast cancer and for synchronous bilateral breast cancer (one at Stage 1 and the other at Stage 2) relative to the risk for unilateral Stage 2 breast cancer are virtually the same as those obtained in Table 4-34.

Similarly, the risk of breast cancer death for women with bilateral Stage 1 breast cancers relative to women with unilateral Stage 1 breast cancer in the overall analysis (Table 4-35) and is essentially the same as obtained in the stratified analysis (Table 4-33).

It would appear that if there is any problem with proportionality associated with tumour stage, it is exerting relatively little influence on risk estimates.

4.6 Survival – Metachronous Bilateral Breast Cancer

4.6.1 Introduction

In the analysis of overall breast cancer survival (Section 4.4.2) and with the analysis of survival in women with synchronous bilateral breast cancer (Section 4.5), the effects associated with tumour stage did not appear to conform to the proportional hazards assumptions. This lack of proportionality did not, however, appear to be sufficient to bias relative risk estimates in the analysis of survival from synchronous bilateral breast cancer, but this may not be the case for survival from metachronous bilateral breast cancer.

The analysis of synchronous bilateral breast cancer survival did, however, illustrate that the survival for women with bilateral breast cancer where one was Stage 1 and the other was Stage 2 was little different from the survival for women with unilateral Stage 2 breast cancer. The additional Stage 1 breast cancer therefore contributed little additional risk. This may or may not be the case for metachronous bilateral breast cancer where the interval of time between the two primaries may be expected to be important.

In addition, previous studies of survival from metachronous bilateral breast cancer have produced single time-dependent estimates of the effect of the diagnosis of the second

primary, ignoring the stage of the first and second primary and ignoring the effect of the interval of time between the two.

In the following analysis, the effect of bilateral breast cancer on survival was first estimated using a single time-dependent effect. A single time-dependent effect was also estimated separately depending on the stage of the first breast cancer. Following this, models employing multiple time-dependent effects were fitted. These were constructed by partitioning the time since the first diagnosis into 1-year intervals and capturing the survival effect of bilateral breast cancers occurring within these intervals by fitting a separate time-dependent effect within each of the intervals. This allowed the effect of a bilateral breast cancer diagnosis to vary with time since the first breast cancer diagnosis. These models were also fitted for all women and then separately by stage of the first breast cancer.

Finally, these analyses were repeated with the stage of the bilateral breast cancer modelled as a time-dependent effect.

By incrementally increasing the complexity of the survival models in this way, the level of complexity actually required to describe the effect of metachronous bilateral breast cancer on survival could be determined.

4.6.2 A single Time-Dependent effect

Estimating the effect of a metachronous bilateral breast cancer on survival with a single time-dependent covariate replicates the approach taken in previous studies (Section 2.6.3, page 43). Relative risks for the crude effect, the effect adjusted for stage of the first breast cancer only, and the effect adjusted for stage and other covariates are shown in Table 4-36. Stratified proportional hazards models were also fitted, stratifying on stage of the first breast cancer.

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

Model		RR	95% Conf. Interval	
	Second Primary			
Crude effect	No	1.00		
	Yes	2.21	2.14	2.38
Adjusted for Stage	No	1.00		
	Yes	2.30	2.22	2.38
Adjusted for Stage†	No	1.00		
	Yes	2.25	2.17	2.34
Stratified on Stage	No	1.00		
	Yes	2.29	2.21	2.37
Stratified on Stage†	No	1.00		
	Yes	2.25	2.16	2.33

† Adjusted for age, registry, race, year of diagnosis, marital status, histology and radiotherapy

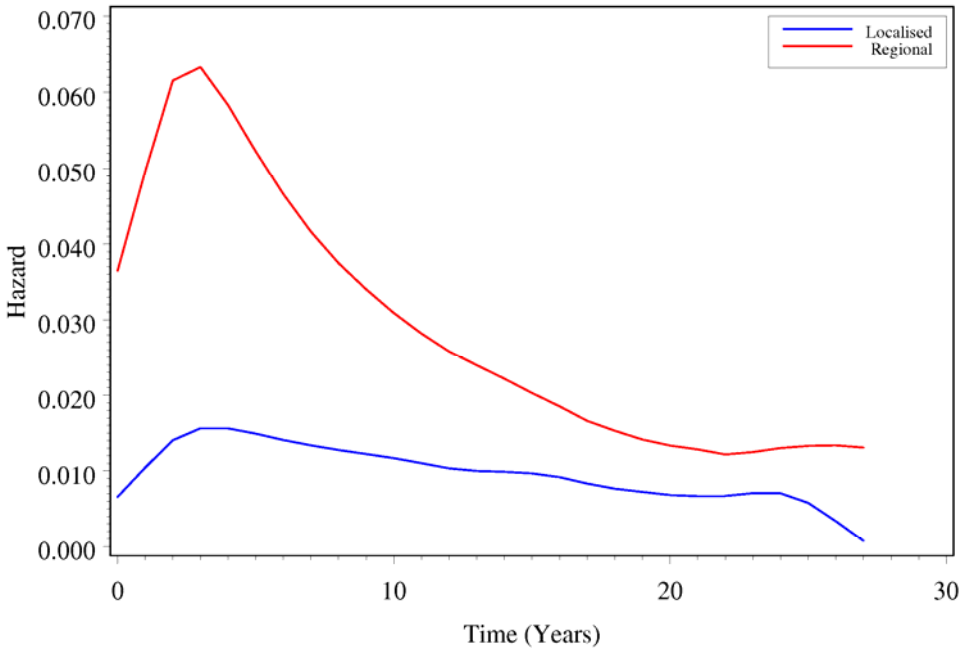
A model containing only the single time-dependent variable – the diagnosis of a metachronous bilateral breast cancer – resulted in a crude estimated relative risk of 2.21. After adjusting for stage of the first breast cancer, this effect was modified only slightly (RR = 2.30) and further adjustment for other covariates also produced only slight modification (RR = 2.25). Using stratified proportional hazards models and stratifying on stage produced similar effect estimates – RR = 2.29 stratifying on stage alone and RR = 2.25 stratifying on stage and adjusting for other covariates.

These relative risks indicate the change in risk associated with the diagnosis of a metachronous bilateral breast cancer. After adjustment for other factors, the risk of dying from breast cancer is increased by 125% relative to the risk faced by women who have survived up until that time, but have not had a bilateral breast cancer.

Crude hazard curves for women with Stage 1 and Stage 2 breast cancer are shown in Figure 4-26. This underlying risk for women without bilateral breast cancer is not

constant over time nor is it the same for women who had an initial breast cancer that was localised (Stage 1) as compared to women who had an initial breast cancer that was regional (Stage 2).

Figure 4-26: Hazard associated with stage of first breast cancer.



The risk for both groups increased early (Figure 4-26), but more markedly in women with Stage 2 breast cancers. These women have been diagnosed with evidence of regional spread – metastatic disease in the axillary nodes – and are consequently at greater risk of dying because of this. After this initial period, the risk declined in both groups, but the rate of decline was greater in women who were originally diagnosed with regional disease.

Fitting separate proportional hazards models, one for women with an initial breast cancer that was localised (Stage 1) and the other for women with regional disease (Stage 2), produced the following results (Table 4-37).

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†.

Stage of first breast cancer		RR	95% Conf. Interval	
	Second Primary			
Localized	No	1.00		
	Yes	2.57	2.43	2.71
Localized†	No	1.00		
	Yes	2.55	2.41	2.69
Regional	No	1.00		
	Yes	2.11	2.01	2.21
Regional†	No	1.00		
	Yes	2.03	1.94	2.14

† Adjusted for age, registry, race, year of diagnosis, marital status, histology and radiotherapy

A metachronous bilateral breast cancer increases the risk of death from breast cancer to a greater extent in women with localised breast cancer than it does in women who initially had regional disease. This seems paradoxical, but, as can be seen in Figure 4-26, women with localised disease are always at lower risk than women with regional disease. A new primary, therefore, has greater impact on those at lower risk.

Given this, we might expect to find that the diagnosis of a metachronous bilateral breast cancer would have a greater impact on survival the more distant in time it occurred after the first breast cancer and therefore less impact if it occurred soon after the first breast cancer, when the risk associated with the first breast cancer is still comparatively high.

In the following sections I will explore this in more detail by fitting multiple time-dependent variables, each estimating the effect of a metachronous bilateral breast cancer diagnosed within a one-year interval.

4.6.3 Multiple Time-Dependent Effects

In following analysis, the follow-up period – the time since diagnosis of the first breast cancer – was partitioned into 20 intervals, the first 19 being 1-year intervals after diagnosis and the last being 20 or more years. Within each of these, a time-dependent covariate was fitted to estimate the effect of a diagnosis of a metachronous bilateral breast cancer within that time interval (Table 4-38).

The first adjusted results contain the relative risk estimates from a model after adjustment for other covariates including stage and the second set of adjusted results are from a stratified proportional hazards model with stratification by stage and adjustment for other covariates.

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.

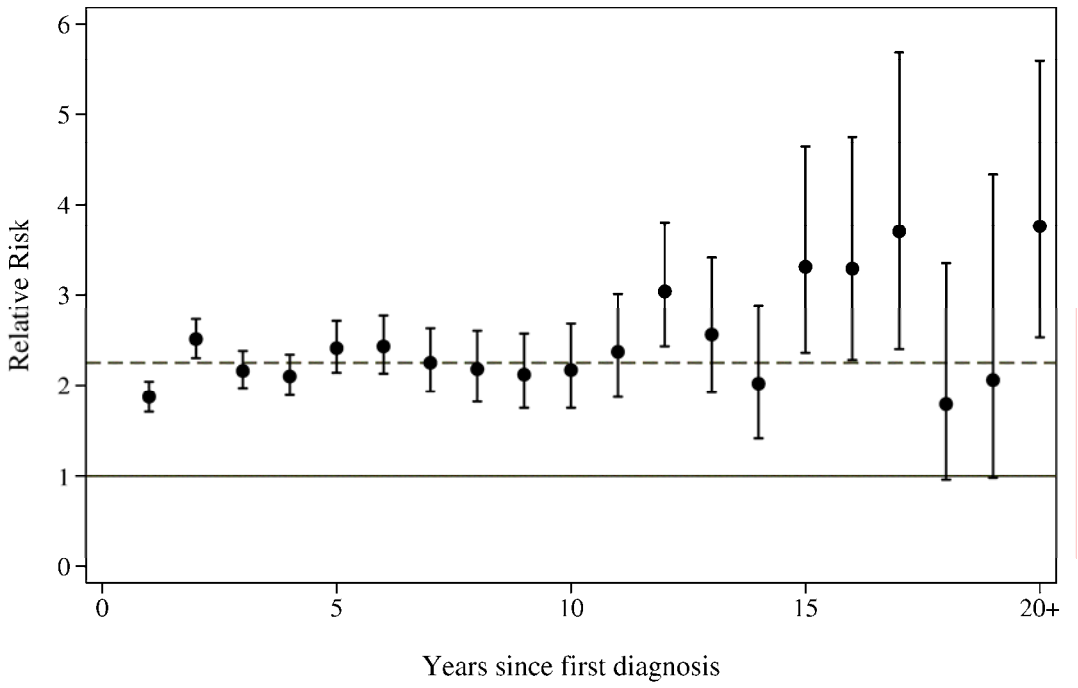
Year since first breast cancer diagnosis	Unadjusted			Adjusted†			Adjusted‡		
	RR	95% CI		RR	95% CI		RR	95% CI	
1	1.71	1.56	1.86	1.88	1.71	2.05	1.87	1.71	2.04
2	2.48	2.29	2.68	2.53	2.32	2.75	2.51	2.30	2.73
3	2.24	2.04	2.45	2.16	1.97	2.38	2.16	1.97	2.38
4	2.10	1.89	2.33	2.11	1.89	2.35	2.10	1.89	2.34
5	2.37	2.11	2.66	2.40	2.13	2.70	2.41	2.14	2.71
6	2.42	2.13	2.74	2.45	2.15	2.79	2.43	2.13	2.77
7	2.27	1.96	2.62	2.28	1.95	2.66	2.25	1.93	2.63
8	2.11	1.78	2.51	2.20	1.84	2.63	2.18	1.82	2.60
9	2.16	1.80	2.59	2.14	1.77	2.59	2.12	1.75	2.57
10	2.30	1.88	2.82	2.16	1.75	2.66	2.17	1.75	2.68
11	2.33	1.85	2.93	2.35	1.85	2.98	2.37	1.87	3.01
12	3.05	2.45	3.79	2.97	2.38	3.72	3.04	2.43	3.80
13	2.49	1.88	3.28	2.58	1.93	3.43	2.56	1.92	3.41
14	2.21	1.58	3.10	1.91	1.34	2.72	2.02	1.42	2.88
15	3.14	2.28	4.33	3.52	2.51	4.94	3.31	2.36	4.64
16	3.08	2.15	4.42	3.21	2.22	4.63	3.29	2.28	4.75
17	3.63	2.43	5.44	3.77	2.45	5.81	3.70	2.40	5.69
18	2.18	1.26	3.76	1.80	0.96	3.35	1.79	0.96	3.35
19	2.48	1.29	4.78	2.03	0.96	4.27	2.06	0.98	4.33
20+	3.83	2.63	5.58	3.61	2.43	5.37	3.76	2.53	5.59

† Adjusted for age, registry, race, year of diagnosis, marital status, histology, radiotherapy and stage

‡ Adjusted for age, registry, race, year of diagnosis, marital status, histology, radiotherapy and stage by stratification

There are comparatively small differences between all three models. The relative risks from the third model are shown in Figure 4-27, with the horizontal line indicating the effect (RR = 2.25) obtained from Table 4-36 using a single time-dependent covariate.

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†.



† Adjusted for age, registry, race, year of diagnosis, marital status, histology, radiotherapy and stage by stratification

One can see that when the effect of the metachronous bilateral breast cancer is allowed to vary over time, there is more variability in the relative risk estimates than is captured by the use of only a single time-dependent covariate.

A diagnosis of a metachronous bilateral breast cancer in the first year increases the risk of breast cancer death by 87% and a diagnosis in the second year increases the risk by 151%. The increase in the risk of breast cancer death associated with a diagnosis of a metachronous bilateral breast cancer between 3 and 10 years after the first breast cancer is comparatively constant and similar to the increase estimated from the single time-dependent model – a 125% increase. When metachronous bilateral breast cancers are

diagnosed more than ten years after the first breast cancer, the relative risk estimates are less precise, but suggest an increase in the risk of breast cancer that is greater than estimated in the single time-dependent model. Finally, the estimate associated with a diagnosis more than 20 years after the first breast cancer (the final estimate in Figure 4-27) is clearly greater than the estimate from the single time-dependent model.

These relative risks estimate the relative increase in the risk of breast cancer death associated with the diagnosis of a bilateral breast cancer at different times following the diagnosis of the first breast cancer. They are relative to the risk of breast cancer death in women without bilateral breast cancer who have survived the same length of time without a diagnosis of metachronous bilateral breast cancer. They suggest that as the risk of breast cancer death associated with the first breast cancer declines, as it will with time since diagnosis, the greater the impact on risk of breast cancer death that will result from the diagnosis of a bilateral breast cancer.

4.6.4 Stage-Specific Models

The results in Table 4-38, however, assume that the increase in risk associated with a bilateral breast cancer diagnosis is the same regardless of the stage of the first breast cancer. This may not be so.

To investigate this further, the analysis above was repeated separately for women with initial localised disease (Stage 1) and initial regional disease (Stage 2). These results are in Table 4-39. For comparison, the results for all stages combined from Table 4-38 above are repeated in this table.

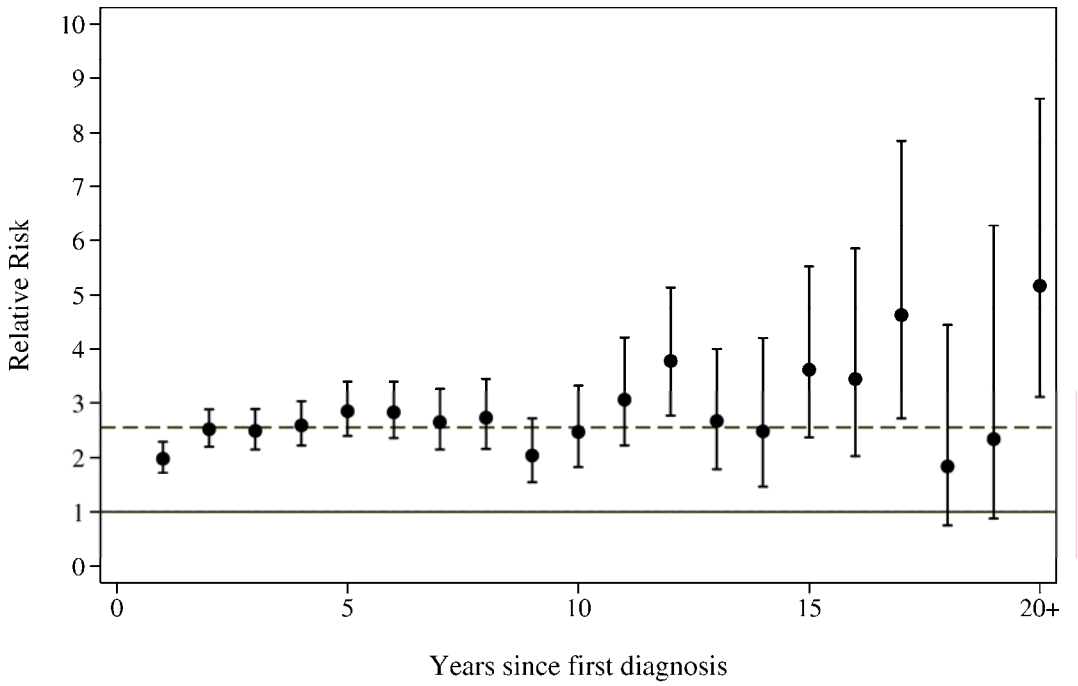
Table 4-39: Effect of a metachronous bilateral breast cancer on risk of death from breast cancer by time since diagnosis of first breast cancer and stage of first breast cancer.

Year since first breast cancer diagnosis	All Stages Strata(Stage)			First Primary Stage 1 Adjusted†			First Primary Stage 2 Adjusted†		
	RR	95% CI		RR	95% CI		RR	95% CI	
1	1.87	1.71	2.04	1.98	1.72	2.29	1.76	1.57	1.98
2	2.51	2.30	2.73	2.52	2.20	2.88	2.49	2.24	2.78
3	2.16	1.97	2.38	2.49	2.15	2.89	1.98	1.75	2.24
4	2.10	1.89	2.34	2.59	2.22	3.03	1.77	1.52	2.06
5	2.41	2.14	2.71	2.85	2.40	3.40	2.12	1.80	2.50
6	2.43	2.13	2.77	2.83	2.36	3.40	2.11	1.75	2.54
7	2.25	1.93	2.63	2.65	2.15	3.27	1.92	1.53	2.42
8	2.18	1.82	2.60	2.73	2.16	3.45	1.73	1.32	2.27
9	2.12	1.75	2.57	2.04	1.54	2.72	2.18	1.68	2.83
10	2.17	1.75	2.68	2.47	1.83	3.33	1.94	1.44	2.62
11	2.37	1.87	3.01	3.06	2.22	4.21	1.86	1.31	2.66
12	3.04	2.43	3.80	3.78	2.77	5.14	2.48	1.79	3.43
13	2.56	1.92	3.41	2.67	1.79	4.00	2.45	1.63	3.70
14	2.02	1.42	2.88	2.48	1.46	4.20	1.74	1.08	2.80
15	3.31	2.36	4.64	3.62	2.37	5.52	3.01	1.70	5.32
16	3.29	2.28	4.75	3.45	2.03	5.85	3.13	1.88	5.22
17	3.70	2.40	5.69	4.62	2.72	7.85	2.68	1.27	5.64
18	1.79	0.96	3.35	1.84	0.76	4.44	1.83	0.76	4.43
19	2.06	0.98	4.33	2.34	0.88	6.28	1.75	0.56	5.46
20+	3.76	2.53	5.59	5.17	3.11	8.62	2.63	1.39	4.97

†Adjusted for age, registry, race, year of diagnosis, marital status, histology and radiotherapy.

If we look at women who were initially diagnosed with a Stage 1 (localised) breast cancer (Figure 4-28), there is a 98% increase in the risk of breast cancer death associated with the diagnosis of a metachronous bilateral breast cancer in the first year. After this, there is comparatively little difference between the time interval-specific relative risk estimates and the overall relative risk estimate of 2.55 obtained in Table 4-37 at least for the first 10 years after the initial diagnosis. After 10 years, the relative risk estimates become more variable, but the 95% confidence intervals for most of these still enclose the value of 2.55. The overall estimate for 20 or more years is, however, significantly higher than 2.55 (RR = 5.17, 95% C.I.: 3.11 – 8.62).

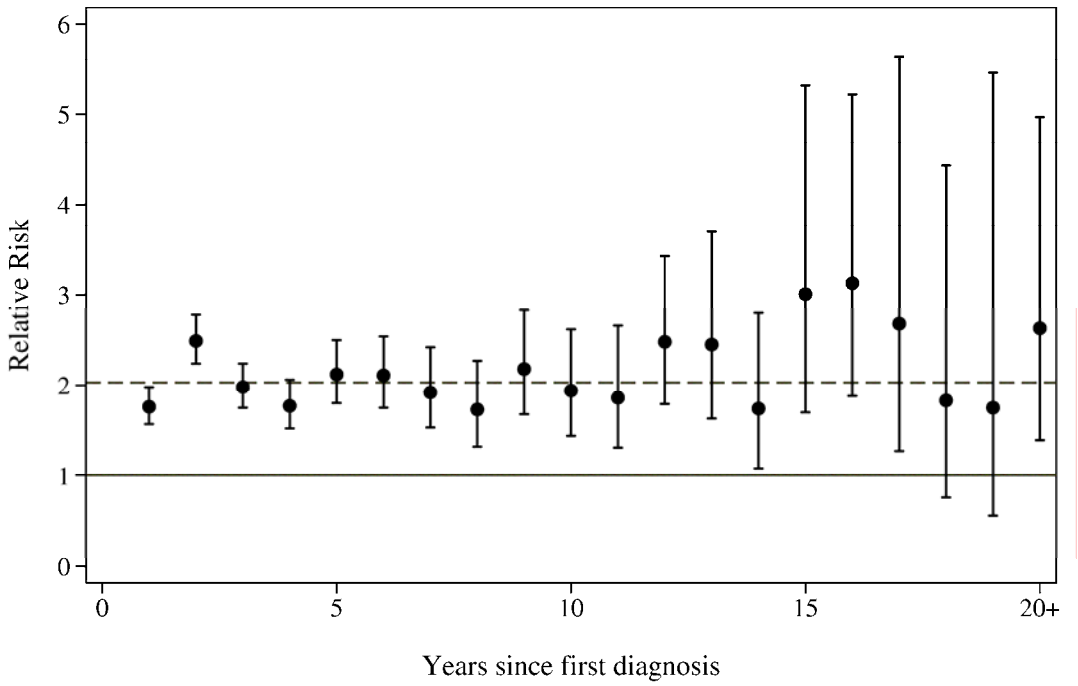
Figure 4-28: Effect of a metachronous bilateral breast cancer on risk of death from breast cancer by time since diagnosis of Stage 1 (localised) first breast cancers†.



† Adjusted for age, registry, race, year of diagnosis, marital status, histology, and radiotherapy.

For metachronous bilateral breast cancers occurring after the diagnosis of a Stage 2 (regional) breast cancer, the relationship with time since first breast cancer is similar (Figure 4-29). The horizontal line indicates the overall relative risk estimate obtained in Table 4-37 (RR = 2.03). The relative risk in the first year is significantly lower than this and in the second year it is significantly higher. In all subsequent years, however, there is no significant difference between the time interval-specific estimates and the overall estimate of 2.03.

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†.



† Adjusted for age, registry, race, year of diagnosis, marital status, histology, and radiotherapy.

4.6.5 Incorporating the Stage of the Bilateral Breast Cancer

The analyses above have shown differences in the estimated effects of a metachronous primary diagnosis, but they ignore the stage of the second primary. If the stage of the first breast cancer can influence the effect of the diagnosis of a metachronous primary, then one would expect that the stage of the metachronous primary itself would also be important.

To incorporate the stage of the second primary, separate models were fitted for stage of the first breast cancer. While the initial breast cancer was restricted to being either Stage 1 or Stage 2, there was no restriction placed on the stage of the bilateral breast cancer which could be Stage 1, Stage 2 or Stage 4 (distant). Stage of second primary was fitted as three dummy or indicator variables, one for each stage of the second

primary, with the reference level being no second primary. This enabled the effect of the diagnosis of a bilateral breast cancer of a given stage, at a given time since diagnosis from the first primary, to be estimated.

Before presenting the results of this model, I first fitted stage of the metachronous bilateral breast cancer as a single time-dependent covariate to estimate the overall 'average' effect. The results from this model are shown in Table 4-40 and indicate that the stage of the bilateral breast cancer has an important influence on the risk of death from breast cancer.

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.

Stage of second breast cancer	Stage of first breast cancer					
	Stage 1			Stage 2		
	RR	95% CI		RR	95% CI	
Crude effects:						
No BBC	1.00			1.00		
Stage 1	1.59	1.48	1.72	1.22	1.13	1.32
Stage 2	4.88	4.47	5.33	2.96	2.74	3.20
Stage 4	20.28	17.56	23.43	8.60	7.72	9.60
Adjusted† effects:						
No BBC	1.00			1.00		
Stage 1	1.60	1.48	1.73	1.19	1.10	1.29
Stage 2	4.67	4.28	5.11	2.80	2.59	3.03
Stage 4	17.21	14.87	19.92	8.03	7.17	8.98

†Adjusted for age, registry, race, year of diagnosis, marital status, histology and radiotherapy.

I will use the relative risk estimates from these models as a point of comparison in the subsequent models where the follow-up time is partitioned.

4.6.5.1 Stage 1 breast cancer cohort

For women whose first breast cancer was Stage 1 (localised), the estimates of the effect of a diagnosis of a bilateral breast cancer, by stage of this cancer are shown in Table 4-41.

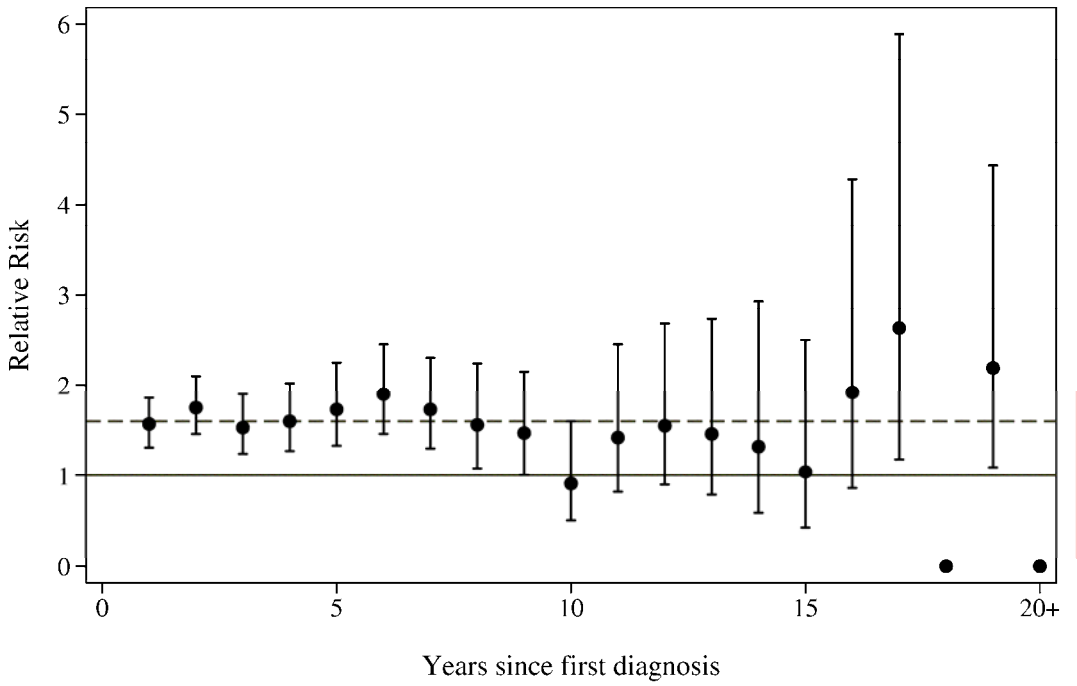
Table 4-41: Effect of stage of metachronous bilateral breast cancer on risk of death from breast cancer by time since diagnosis of Stage 1 (localised) first breast cancers.

Year since first breast cancer diagnosis	Stage of second breast cancer								
	Stage 1 Localised			Stage 2 Regional			Stage 4 Distant		
	RR	95% CI		RR	95% CI		RR	95% CI	
1	1.57	1.31	1.86	4.16	3.21	5.38	8.25	3.09	22.00
2	1.75	1.46	2.10	4.76	3.75	6.03	12.37	8.06	19.00
3	1.53	1.24	1.90	4.88	3.80	6.28	13.07	8.89	19.21
4	1.60	1.27	2.02	4.10	3.20	5.25	15.26	10.13	22.99
5	1.73	1.33	2.25	4.28	3.20	5.72	20.51	13.35	31.50
6	1.90	1.46	2.45	4.14	3.01	5.69	27.51	17.08	44.30
7	1.73	1.30	2.30	4.41	2.90	6.70	20.29	12.60	32.69
8	1.56	1.08	2.24	4.66	3.23	6.71	16.20	8.70	30.15
9	1.47	1.01	2.15	3.93	2.47	6.25	5.34	1.72	16.58
10	0.91	0.51	1.60	6.07	4.03	9.14	19.00	8.51	42.41
11	1.42	0.82	2.45	6.38	4.11	9.91	24.90	10.34	59.94
12	1.55	0.90	2.68	7.29	4.53	11.76	51.61	25.74	103.49
13	1.46	0.79	2.73	4.61	2.39	8.87	28.77	10.77	76.83
14	1.32	0.59	2.93	3.07	0.99	9.54	34.90	13.06	93.29
15	1.04	0.43	2.50	9.81	5.67	16.95	74.91	27.99	200.42
16	1.92	0.86	4.28	5.85	2.43	14.10	51.17	12.74	205.53
17	2.63	1.18	5.89	8.58	4.07	18.08	261.65	36.39	1881.60
18	0.00	.	.	4.24	1.36	13.21	9.74	1.37	69.33
19	2.19	1.09	4.43	5.96	2.65	13.41	30.04	12.39	72.79
20+	0.00	.	.	0.00	.	.	0.00	.	.

† Adjusted for age, registry, race, year of diagnosis, marital status, histology and radiotherapy.

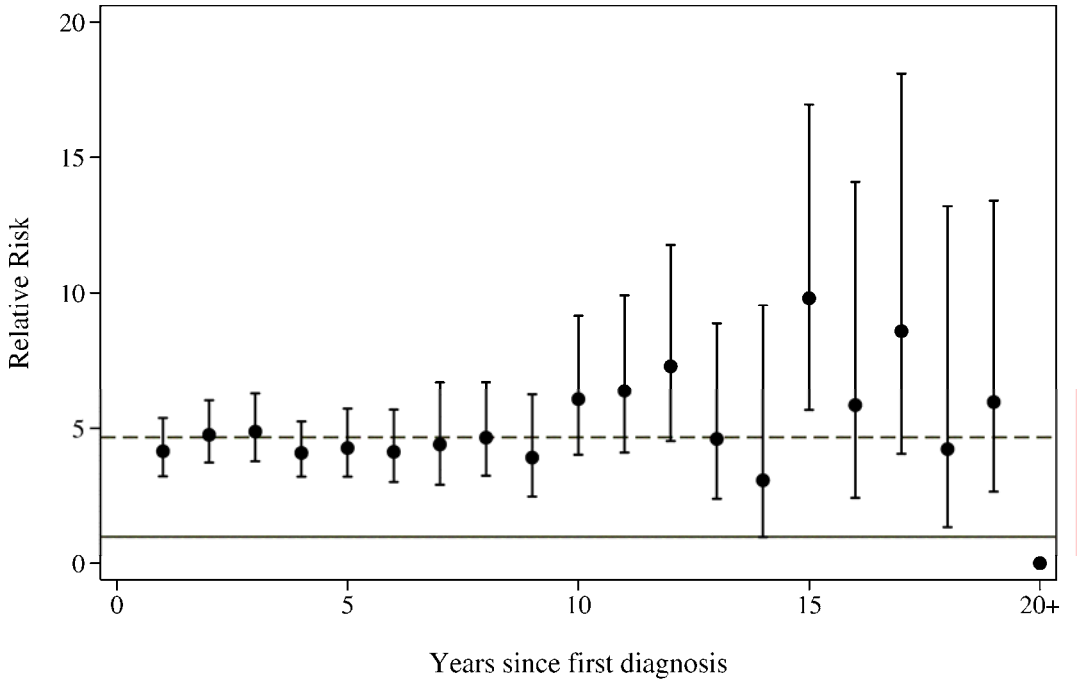
These results have been graphed below. For women with a bilateral breast cancer that was Stage 1 (localised), there is little evidence of any major differences between the time-dependent relative risk estimates (Figure 4-30) and the overall relative risk estimate of 1.60 in Table 4-40. Similarly, when the bilateral breast cancer was Stage 2 (regional) there was little difference between interval-specific relative risk estimates (Figure 4-31) and the overall time-dependent estimate of 4.67 (Table 4-40).

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†.



† Adjusted for age, registry, race, year of diagnosis, marital status, histology, and radiotherapy.

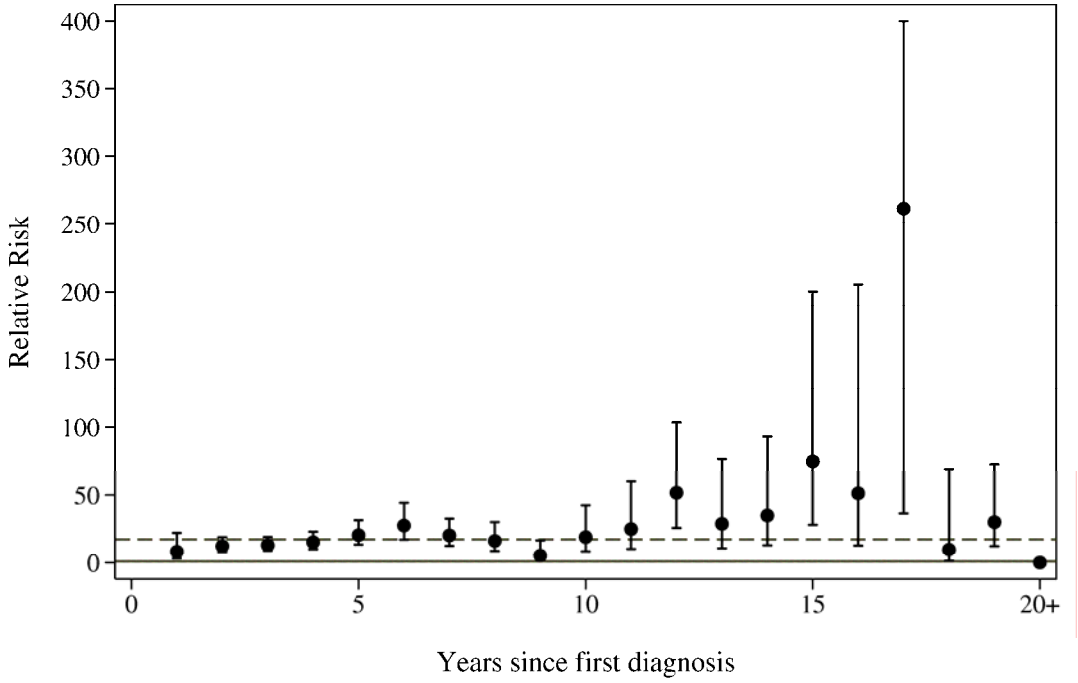
Figure 4-31: Effect of a metachronous Stage 2 (regional) bilateral breast cancer on risk of death from breast cancer by time since diagnosis of Stage 1 (localised) first breast cancers†.



† Adjusted for age, registry, race, year of diagnosis, marital status, histology, and radiotherapy.

Finally, the estimates of relative risk associated with the diagnosis of a bilateral breast cancer that was Stage 4 (distant) are shown. The overall time-dependent relative risk estimate obtained in Table 4-40 was 17.21 and only three of the interval-specific estimates are significantly different from this (the estimates for 12, 15 and 17 years) (Figure 4-32). (note: the upper confidence interval for the 17th year estimate has been truncated at 400).

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†.



† Adjusted for age, registry, race, year of diagnosis, marital status, histology, and radiotherapy.

4.6.5.2 Stage 2 breast cancer cohort

For women who had an initial Stage 2 (regional) breast cancer, the relative risk of death from breast cancer by time since the first breast cancer and stage of the bilateral breast cancer is shown in Table 4-42.

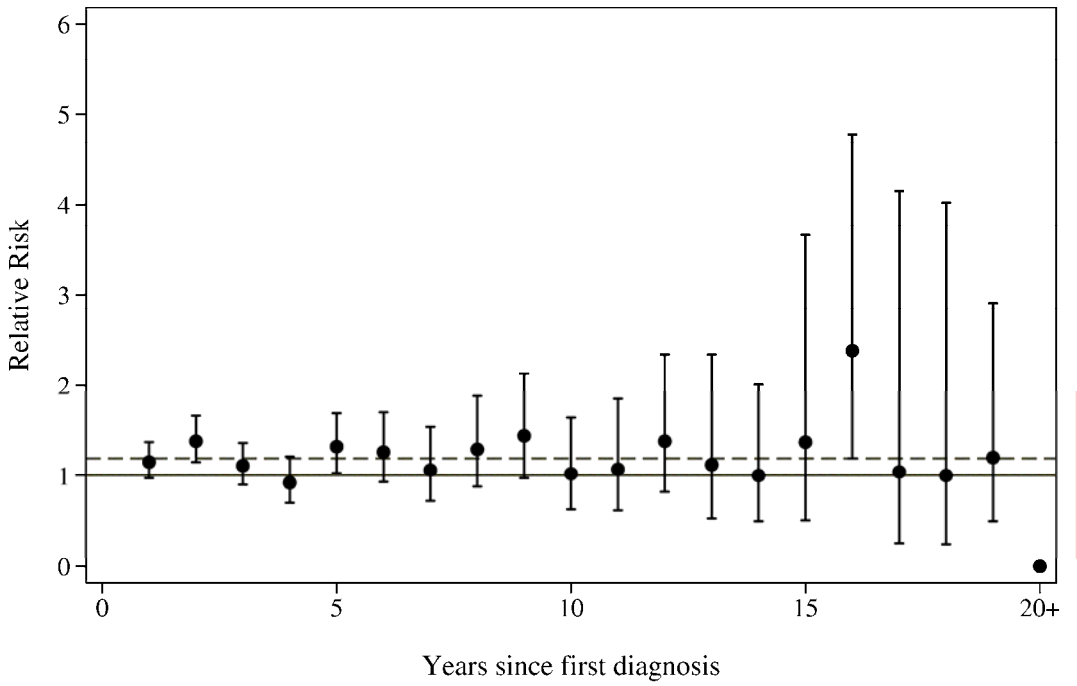
Table 4-42: Effect of stage of metachronous bilateral breast cancer on risk of death from breast cancer by time since diagnosis of Stage 2 (regional) first breast cancers†.

Year since first breast cancer diagnosis	Stage of second breast cancer								
	Stage 1 Localised			Stage 2 Regional			Stage 4 Distant		
	RR	95% CI		RR	95% CI		RR	95% CI	
1	1.15	0.97	1.37	2.55	2.10	3.09	10.32	7.33	14.53
2	1.38	1.15	1.66	3.25	2.73	3.87	8.83	7.09	11.00
3	1.11	0.90	1.36	2.79	2.30	3.39	6.10	4.58	8.12
4	0.92	0.70	1.21	2.29	1.80	2.91	5.89	4.26	8.13
5	1.32	1.03	1.69	2.96	2.23	3.92	7.90	5.34	11.71
6	1.26	0.93	1.70	2.89	2.15	3.87	7.78	4.83	12.52
7	1.06	0.72	1.54	2.78	1.96	3.93	8.69	4.93	15.32
8	1.29	0.88	1.88	2.13	1.33	3.44	5.49	2.62	11.53
9	1.44	0.97	2.13	2.79	1.80	4.34	9.83	5.28	18.28
10	1.02	0.63	1.64	2.58	1.53	4.36	15.14	8.13	28.18
11	1.07	0.62	1.85	2.34	1.22	4.50	9.71	4.85	19.44
12	1.38	0.82	2.34	3.78	2.24	6.39	8.44	3.79	18.82
13	1.12	0.53	2.34	3.44	1.78	6.62	13.36	6.36	28.07
14	1.00	0.50	2.01	2.81	1.17	6.76	11.47	2.86	45.94
15	1.37	0.51	3.66	5.80	2.60	12.93	14.12	3.52	56.61
16	2.38	1.19	4.78	3.77	1.57	9.09	5.11	0.72	36.37
17	1.04	0.26	4.15	7.79	2.92	20.84	119.99	16.66	864.26
18	1.00	0.25	4.02	4.02	1.29	12.52			
19	1.20	0.50	2.91	3.73	1.39	10.00	34.81	11.09	109.26
20+	0.00	.	.	0.00	.	.	0.00	.	.

† adjusted for age, registry, race, year of diagnosis, marital status, histology, and radiotherapy.

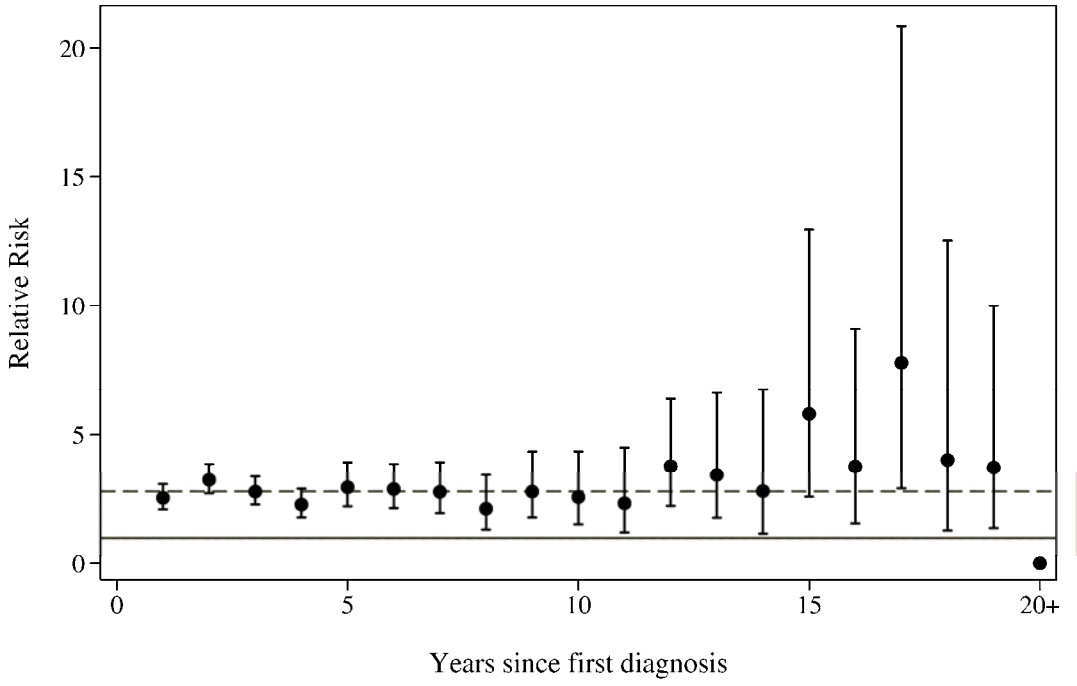
For these women, the relative risk of breast cancer death associated with a diagnosis of a Stage 1 (localised) bilateral breast cancer was 1.19 overall (from Table 4-40) and the interval-specific estimates in Figure 4-33 are in general quite similar to this. Similarly there is comparatively little difference between the overall time-dependent relative risk estimate associated with a Stage 2 (regional) bilateral breast cancer diagnosis (RR = 2.80) in Table 4-40 and the interval-specific estimates in Figure 4-34.

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†.



† Adjusted for age, registry, race, year of diagnosis, marital status, histology, and radiotherapy.

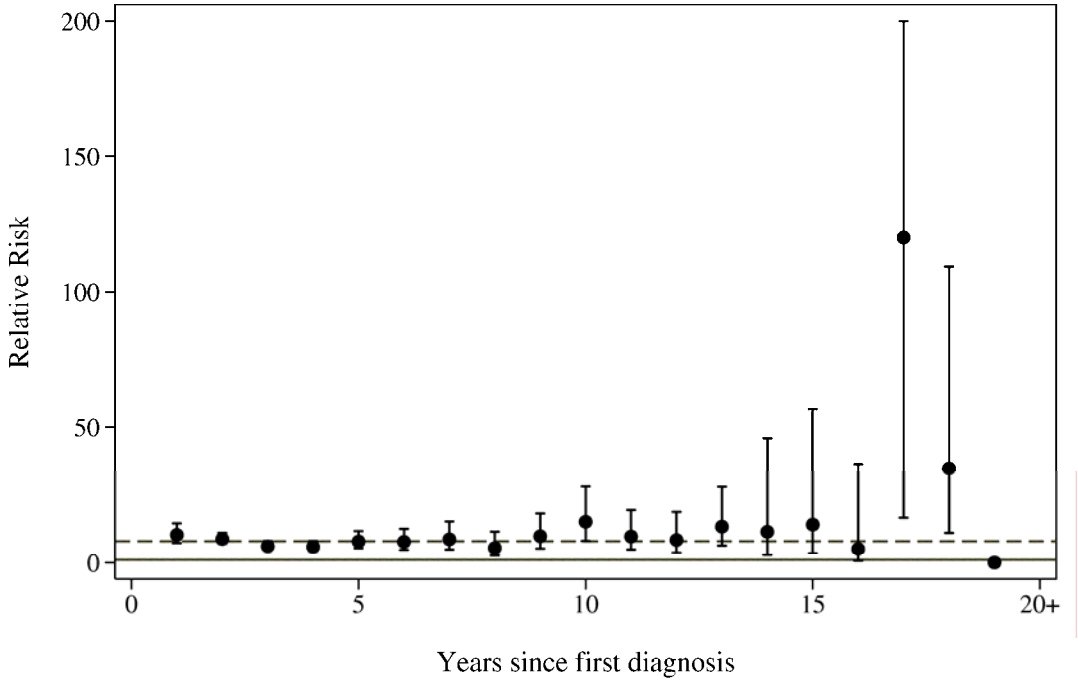
Figure 4-34: Effect of a metachronous Stage 2 (regional) bilateral breast cancer on risk of death from breast cancer by time since diagnosis of Stage 2 (regional) first breast cancers†.



† Adjusted for age, registry, race, year of diagnosis, marital status, histology, and radiotherapy.

Finally, the overall time-dependent effect and the interval-specific effects when the bilateral breast cancer was Stage 4 (distant) are compared in Figure 4-35. The overall time-dependent relative risk was 8.03 in Table 4-40 and this is within the confidence intervals of all but one of the interval-specific estimates (year 17).

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†.



† Adjusted for age, registry, race, year of diagnosis, marital status, histology, and radiotherapy.

4.6.6 Summary

Breast cancer stage is an important predictor of breast cancer survival. In terms of bilateral breast cancer, stage of the first breast cancer is also an important determinant of the baseline risk against which the risk associated with a bilateral breast cancer diagnosis is compared. While an initial Stage 1 breast cancer carries a risk of death from breast cancer, it is smaller than the risk for women with an initial Stage 2 breast cancer and much smaller again than the risk that would be experienced by women with an initial Stage 4 breast cancer.

The relative risks associated with a diagnosis of bilateral breast cancer presented Table 4-40 are relative to this baseline level of risk, but averaged across the time since the first diagnosis. The impact of a diagnosis of a bilateral breast cancer is more noticeable in women whose baseline risk is low – women with an initial Stage 1 breast cancer. The effect for women with a high baseline risk – those with an initial Stage 2 breast cancer – is less dramatic.

Partitioning the time since the first breast cancer into one-year intervals and estimating the effect of a bilateral breast cancer diagnosis separately within each of these, did not however produce convincing evidence that the effect of a bilateral breast cancer diagnosis changed over time at least for the first 15 years after diagnosis of the first breast cancer. After 15 years, the incidence rate estimates were too imprecise for any definitive comparison of risk to be made.

By fitting the occurrence of a bilateral breast cancer as a time-dependent effect and adjusting for stage of the first breast cancer, age at diagnosis of the first breast cancer, registry, race, year of first diagnosis, marital status, histology of the first breast cancer and use of radiotherapy to treat the first breast cancer (Table 4-36) the effect of a diagnosis of metachronous bilateral breast cancer on survival from breast cancer was estimated to be 2.25 (95% CI: 2.17 – 2.34). If stage was used as a stratification variable in the proportional hazards model, the effect was similar: 2.25 (95% CI: 2.16 – 2.33). Both results therefore indicate that the risk of death from breast was increased by the diagnosis of bilateral breast cancer.

Subsequent analyses indicated that this effect was slightly different in cohorts of women first diagnosed with localised (Stage 1) breast cancer and with regional (Stage 2) breast cancer (Table 4-37). In women with Stage 1 breast cancer, the adjusted effect of a

bilateral breast cancer diagnosis was 2.55 (95% CI: 2.41 – 2.69) and in women with Stage 2 breast cancer it was 2.03 (95% CI: 1.94 – 2.14).

4.7 Modelling the whole cohort

The relative risks above are not directly comparable because they have been estimated in different cohorts of women and from prior analysis we know that the risk of death from breast cancer for women with Stage 2 breast cancer was over three times higher (RR = 3.39, 95% CI: 3.33 – 3.45) than for women with Stage 1 breast cancer (Table 4-29).

If we now combine the Stage 1 and Stage 2 cohorts and re-fit the proportional hazards model, we can incorporate an interaction between the stage of the first breast cancer and the stage of the bilateral breast cancer. Both the crude and adjusted hazard ratios and interaction multipliers obtained are shown in Table 4-43 and there is comparatively little difference between these.

Table 4-43: Crude and adjusted estimates of relative risk of death from breast cancer.

Covariate		Unadjusted RR	Adjusted † RR	95% confidence interval	
Stage					
First breast cancer	Local	1.00			
	Regional	3.79	3.47	3.41	3.54
Bilateral breast cancer	None	1.00			
	Local	1.81	1.80	1.67	1.94
	Regional	5.56	5.33	4.88	5.82
	Distant	22.30	19.32	16.67	22.40
Interaction §					
	Regional × Local	0.64	0.63	0.57	0.71
	Regional × Regional	0.52	0.51	0.45	0.58
	Regional × Distant	0.39	0.42	0.35	0.51

† Adjusted for age, registry, race, year of diagnosis, marital status, histology and radiotherapy.
§ The interaction term was the stage of the first breast cancer × the stage of the second breast cancer

The interaction multipliers can be used in two ways to estimate the increase in risk associated with a diagnosis of bilateral breast cancer. The effect of the stage of the bilateral breast cancer can be estimated separately for women whose first breast cancer was Stage 1 and for those women whose first breast cancer was Stage 2 – this should produce results similar to those obtained from the earlier analyses in Table 4-40.

In Table 4-44 I have presented the results previously obtained from the two stage-specific models that were reported in Table 4-40 and the results obtained from the current model.

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.

Stage of second breast cancer	Stage of first breast cancer					
	Stage 1			Stage 2		
	RR	95% CI		RR	95% CI	
Results of stage-specific models reported in Table 4-40						
Adjusted† effects:						
No BBC	1.00			1.00		
Stage 1	1.60	1.48	1.73	1.19	1.10	1.29
Stage 2	4.67	4.28	5.11	2.80	2.59	3.03
Stage 4	17.21	14.87	19.92	8.03	7.17	8.98
Results from current model						
Adjusted† effects:						
No BBC	1.00			1.00		
Stage 1	1.80	1.67	1.94	1.14	1.05	1.23
Stage 2	5.33	4.88	5.82	2.73	2.52	2.95
Stage 4	19.32	16.67	22.40	8.14	7.27	9.11

†Adjusted for age, registry, race, year of diagnosis, marital status, histology and radiotherapy.

There is virtually no difference between the effects estimated for women who were first diagnosed with Stage 2 (regional) breast cancer, while for women first diagnosed with Stage 1 (localised) breast cancer the effects estimated in the current model are between 12 and 14% larger than those obtained from the earlier stage-specific model. If there is a problem with proportionality associated with the effects of stage of the first breast

cancer, it seems to be exerting a comparatively small effect on the risk ratios in women with Stage 1 breast cancer only.

The current model (Table 4-43) can also be used to estimate the relative risk of breast cancer death associated with stage of the bilateral breast cancer relative to the risk of breast cancer death in women with an initial Stage 1 breast cancer and no subsequent diagnosis of bilateral breast cancer (Table 4-45).

Since the interaction multipliers in Table 4-43 are all less than one, the effect of a bilateral breast cancer diagnosis on survival in women first diagnosed with Stage 2 breast cancer are all less than would be expected if there were no multiplicative interaction.

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.

Stage of second breast cancer	Stage of first breast cancer					
	Stage 1			Stage 2		
	RR	95% CI		RR	95% CI	
Adjusted† effects:						
No BBC	1.00			3.47	3.41	3.54
Stage 1	1.80	1.67	1.94	3.95	3.65	4.27
Stage 2	5.33	4.88	5.82	9.46	8.74	10.24
Stage 4	19.32	16.67	22.40	28.25	25.23	31.64

†Adjusted for age, registry, race, year of diagnosis, marital status, histology and radiotherapy.

For example, women with Stage 2 breast cancer and no subsequent bilateral breast cancer diagnosis are 3.47 times more likely to die of breast cancer than women with Stage 1 breast cancer. Women with an initial Stage 1 breast cancer subsequently diagnosed with a bilateral Stage 1 breast cancer are 1.8 times more likely to die of breast cancer than women with Stage 1 breast cancer and no subsequent diagnosis of bilateral breast cancer.

If there were no multiplicative interaction we would expect that the diagnosis of a bilateral Stage 1 breast cancer in women initial diagnosed with Stage 2 breast cancer would increase their risk of dying from breast cancer by 3.47 × 1.80 = 6.25 times.

4.7.1 Summary of Results of Survival Analysis

The risk of breast cancer death in women with synchronous bilateral Stage 1 breast cancer is 45% higher than the risk in women with unilateral Stage 1 breast cancer. Similarly, women with synchronous bilateral Stage 2 breast cancer have a 46% higher risk of breast cancer mortality than women with unilateral Stage 2 breast cancer. Synchronous bilateral breast cancers where one is Stage 1 and the other Stage 2 seems to confer no extra risk compared to women with unilateral Stage 2 breast cancer.

In women with unilateral breast cancer, the diagnosis of a metachronous bilateral breast cancer increases the risk of breast cancer death. This increase in risk is not dependent on the interval of time between the first and second diagnosis.

The increase in risk is dependent on the stage of the bilateral breast cancer.

In women first diagnosed with Stage 1 breast cancer, diagnosis of metachronous Stage 1 bilateral breast cancer increases the risk of breast cancer death by 80%. The diagnosis of a metachronous bilateral breast cancer that is Stage 2 is associated with a more than 5-fold increase in risk (RR = 5.33) and diagnosis of metachronous Stage 4 bilateral breast cancer with almost a 20-fold increase (RR = 19.32).

In women first diagnosed with Stage 2 breast cancer, diagnosis of metachronous Stage 1 bilateral breast cancer results in only a modest increase in risk of 14%. If the metachronous bilateral breast cancer is Stage 2, however, the risk increases nearly 3-fold (RR = 2.73) and if it is Stage 4 the risk increases more than 8-fold (RR = 8.14).

5 DISCUSSION

5.1 Introduction

In the next Section I will discuss the relationship between Stage of the first breast cancer and the incidence of bilateral breast cancer. In Section 5.2.2 (page 171) I will discuss findings concerning age and the incidence of bilateral breast cancer and then breast cancer histology and its relationship with bilateral breast cancer incidence in Section 5.2.3 (page 176).

Following this in Sections 5.2.4 and 5.2.5, I will discuss the results of the analyses examining the effect of synchronous bilateral breast cancer and metachronous bilateral breast cancer on survival from breast cancer.

I will then briefly describe various models of multistage carcinogenesis (Section 5.3, page 187) and use these to interpret the incidence of bilateral breast cancer.

I will then discuss how this would affect our understanding of how breast cancer occurs in the population (Section 5.4, page 198).

5.2 Summary of Main Findings

5.2.1 Stage and the Incidence of Bilateral Breast Cancer

A number of previous studies have found an association between stage of the first breast cancer and the subsequent incidence of bilateral breast cancer and these are listed in Appendix G.

In my analysis, I found that in women whose first breast cancer was Stage 1 (localised) the overall incidence of bilateral breast cancer was 5.38 per 1,000 person-years, very similar to the incidence of 5.68 per 1,000 person-years in women whose first breast

cancer was Stage 2 (regional). In women whose first breast cancer was Stage 4 (distant), however, the overall incidence was much higher: 7.39 per 1,000 person-years.

It is difficult to compare these results directly to those of previous studies because of the different staging criteria that were used and different summary measures reported. Slack et al. (1973), Hankey et al. (1983) and Storm and Jensen (1986) all found a positive relationship between Stage of the first breast cancer and the incidence of bilateral breast cancer, whereas Haagensen (1971) found an inverse relationship and Horn and Thompson (1988) no relationship. Among these studies, however, only those of Hankey et al. (1983) and Storm and Jensen (1986) were based on analysis of large population-based cancer registries. All of these studies reported overall crude bilateral breast cancer incidence, whereas I have concentrated on the annual incidence of bilateral breast cancer.

Overall, the annual incidence is comparatively constant, apart from the incidence in the first year which is elevated. This elevation in the incidence of bilateral breast cancer in the first year was first described by Robbins and Berg (1964) and has been found in subsequent studies (Hankey et al., 1983; Prior and Waterhouse, 1978; Horn et al., 1987) and is generally interpreted as being caused by increased medical surveillance following the diagnosis of the first breast cancer.

This elevated incidence of bilateral breast cancer in the first year was apparent in the Stage 1 and Stage 2 sub-cohorts (Figure 4-2 and Figure 4-3). In the sub-cohort of women with Stage 4 breast cancer, however, bilateral breast cancer incidence was elevated in the first three years (Figure 4-4) and was largely responsible for the higher overall incidence of bilateral breast cancer observed in this sub-cohort.

Given that these early elevations in incidence seem to be capable of distorting comparisons of overall incidence, we need to be able to explain why they are occurring. These effects could be produced by one of two mechanisms. They could be evidence of metastases from the first breast cancer occurring in the contralateral breast and being misclassified as a new bilateral primary breast cancer. Alternately, the early elevations in incidence could simply be an effect of increased surveillance in women newly diagnosed with breast cancer. In other words, these early elevations in incidence could be the result of either misclassification bias or ascertainment bias.

Misclassification of metastatic disease arising from the first breast cancer was an on-going concern in early studies of bilateral breast cancer and this led to the development of various criteria for discerning true bilateral breast cancer from metastatic disease (Section 2.3). Most of these criteria had the net effect of introducing more bias than reducing any bias that might have been occurring due to misclassification of metastatic disease. In addition, there was no evidence that demonstrated that misclassification was occurring to an extent that would cause significant bias. Prima facie evidence of misclassification bias would, however, be provided if an association between the incidence of bilateral breast cancer and stage of the first breast cancer were demonstrated.

From my analysis I find it difficult to attribute the early elevations in incidence to misclassification of metastatic disease.

First, I found an elevated in incidence in the first year in women diagnosed with Stage 1 breast cancer. These are women whose first breast cancer was localised and who had no evidence of metastases in their axillary nodes. They are therefore a group of women who would be least likely to develop metastatic disease at any site, including the contralateral breast. Given this, it seems unlikely that in these women a) metastatic

disease arising in contralateral breast in the first year after diagnosis would be occurring to a significant extent and b) that it would then be misclassified to an extent to cause a noticeable increase in the incidence of bilateral breast cancer in the first year.

Second, while the incidence was elevated in the first year following diagnosis of Stage 1 breast cancers, the incidence in the four years after this are all lower than the overall average incidence (Figure 4-2). It is difficult to explain why this would occur if misclassification was producing the elevation in the first year since we would expect misclassification to simply add to the incidence.

Third, while the pattern of annual incidence following Stage 2 breast cancers is less clear than for Stage 1 breast cancers, there is nevertheless a general decline in incidence after the elevation in the first year and a period of lower than average incidence observed some four to seven years after the first breast cancer diagnosis.

The pattern of incidence in women diagnosed with Stage 4 breast cancers is perhaps what we might expect to see if misclassification were occurring. The incidence is elevated substantially above the average in the first three years. While metastatic disease can occur at any time, the risk of recurrence of breast cancer is highest within the first five years following diagnosis (Saphner et al., 1996; Karrison et al., 1999), with the peak risk being in the second or third years. Thus if misclassification were to have an observable effect on the incidence of bilateral breast cancer one would expect to observe this in the first few years following diagnosis of the first breast cancer as is seen in the incidence of bilateral breast cancer in women with Stage 4 breast cancer. Yet there is still a period of lower than average incidence that can be observed five to seven years after first diagnosis of breast cancer in these women.

These patterns of annual incidence of bilateral breast cancer observed following Stage 1, 2 and 4 breast cancers are consistent with an effect of heightened surveillance (i.e. ascertainment bias).

Any bilateral breast cancer detected within five to eight years of the first breast cancer is likely to have been present at the time of diagnosis of the first breast cancer. Any cancer diagnosed within one year of the first breast cancer is almost certain to have been present when the first breast cancer was diagnosed. We would expect that women with breast cancer would experience some level of surveillance following their first diagnosis and it would not be unexpected that this surveillance might be more intense for a period of time immediately following this diagnosis. It would also not be unexpected to find that a period of more intense surveillance would be longer for women diagnosed with Stage 4 breast cancer who had distant metastatic disease present when they were diagnosed, than for women diagnosed with Stage 2 breast cancer, who had positive axillary nodes at diagnosis. Similarly, for women with Stage 1 breast cancer and therefore with no sign of metastatic disease, any period of intense surveillance would likely be less than that experienced by women with Stage 2 or Stage 4 breast cancer.

In a period of intense surveillance following breast cancer diagnosis we would expect some elevation in bilateral breast cancer incidence because there would be a greater likelihood of detection of latent disease in the contralateral breast. We would also expect to see, following this period of intense surveillance, a period of lower incidence since bilateral breast cancers that would have been detected during this period have been detected earlier.

The conclusion from this is that there was evidence of bias in the bilateral breast cancer incidence rates, but this was confined to the first year in women with Stage 1 and Stage 2 breast cancer, but extended over the first three years in women with Stage 4 breast

cancer. Regardless of what was actually causing this bias, since it was confined to the first year in women with Stage 1 and 2 breast cancer, it could be isolated and accounted for in any analysis. Because it was spread over three years in women with Stage 4 breast cancer it was more difficult to deal with, and it was easier to simply exclude these women from further analysis.

5.2.2 Age and the Incidence of Bilateral Breast Cancer

In previous studies, women who were aged younger than 45 years when first diagnosed with breast cancer have been identified as a group at increased risk of bilateral breast cancer (Robbins and Berg, 1964; Hankey et al., 1983; Chaudary et al., 1984; Bernstein et al., 2003) and as a high-risk group in others (Prior and Waterhouse, 1978; Storm and Jensen, 1986).

These studies have investigated the relationship between age and bilateral breast cancer incidence using a number of different analytic approaches. The main approach was to calculate the expected number of bilateral breast cancers using population rates of breast cancer and then calculate indirect standardized incidence rate ratios. Studies adopting this approach have all found that the O/E to be higher in young women than in older women.

In addition, a number of studies (Haagensen, 1971; McCredie et al., 1975; Bailey et al., 1980; Adami et al., 1981; Rosselli Del Turco et al., 1982; Brenner et al., 1993; Healey et al., 1993; Abdalla et al., 2000) reported a younger average age at first diagnosis of breast cancer among women with bilateral breast cancer compared to women with unilateral breast cancer.

5.2.2.1 The average age at first diagnosis

A feature of the epidemiology of bilateral breast cancer that has often been interpreted as supporting the susceptibility hypothesis concerns the average age at diagnosis of the first breast cancer in women (Chen et al., 1999; Bernstein et al., 2003). Women with metachronous bilateral breast cancer have been consistently found to have had their first breast cancer at a younger age on average than women who have not developed bilateral breast cancer.

I have shown that these findings are simply artefacts of failing to take into account mortality effects. In my analysis, annual incidence of bilateral breast cancer was essentially constant and hence the annual risk is constant. The lifetime risk of bilateral breast cancer, however, is dependent on the age that a woman is first diagnosed with breast cancer. Women diagnosed in their 40's or 50's have a greater overall life expectancy than women first diagnosed in their 60's or 70's and therefore over any period of follow-up we would expect proportionally more younger women to be diagnosed with a bilateral breast cancer. This is because younger women are exposed to this risk for a longer period of time. It should not be surprising that a crude comparison of average age-at-first-diagnosis for women with and without bilateral breast cancer would indicate that women with bilateral breast cancer were first diagnosed with breast cancer at younger ages. This comparison ignores their extended time at risk due to their greater life expectancy. When the comparison is restricted to those still alive at various times after diagnosis of the first breast cancer, there is no indication of any difference in average age at first diagnosis (Table 4-6).

5.2.2.2 The age-specific incidence of bilateral breast cancer

In my analysis I made an explicit distinction between incidence rates determined by the age-at-first diagnosis of breast cancer and incidence rates determined by age-at-diagnosis of the bilateral breast cancer. Age-at-first diagnosis is simply a characteristic of women in my cohort and the rates of bilateral breast cancer by age-at-first diagnosis shown in Table 4-3 are simply crude rates of bilateral breast cancer for sub-cohorts of women in my analysis. Age-at-second diagnosis, however, is the age when the bilateral breast cancer was diagnosed and incidence rates calculated using this age are true age-specific rates of women at risk of bilateral breast cancer.

Very few studies have considered the age at diagnosis of the bilateral breast cancer. Haagensen et al., (1981), reported age-specific rates of bilateral breast cancer in groups of women defined by their age at first diagnosis of breast cancer. They found that in young women, aged less than 40 years when first diagnosed with breast cancer, the incidence of bilateral breast cancer declined as they aged. They discounted this finding, however, assuming that it occurred in all age cohorts and was being obscured by the inclusion of private patients in their analysis, this group having a higher incidence of bilateral breast cancer.

Prior and Waterhouse (1978) and more recently Bernstein et al., (2003) graphed the overall age-specific rates of bilateral breast cancer and obtained results similar to those I found (Figure 4-9), but both studies focussed on comparing these to the age-specific incidence of first primary breast cancer.

What is novel in my analysis is that age-specific rates were calculated within different sub-cohorts of women defined by their age-at-first diagnosis.

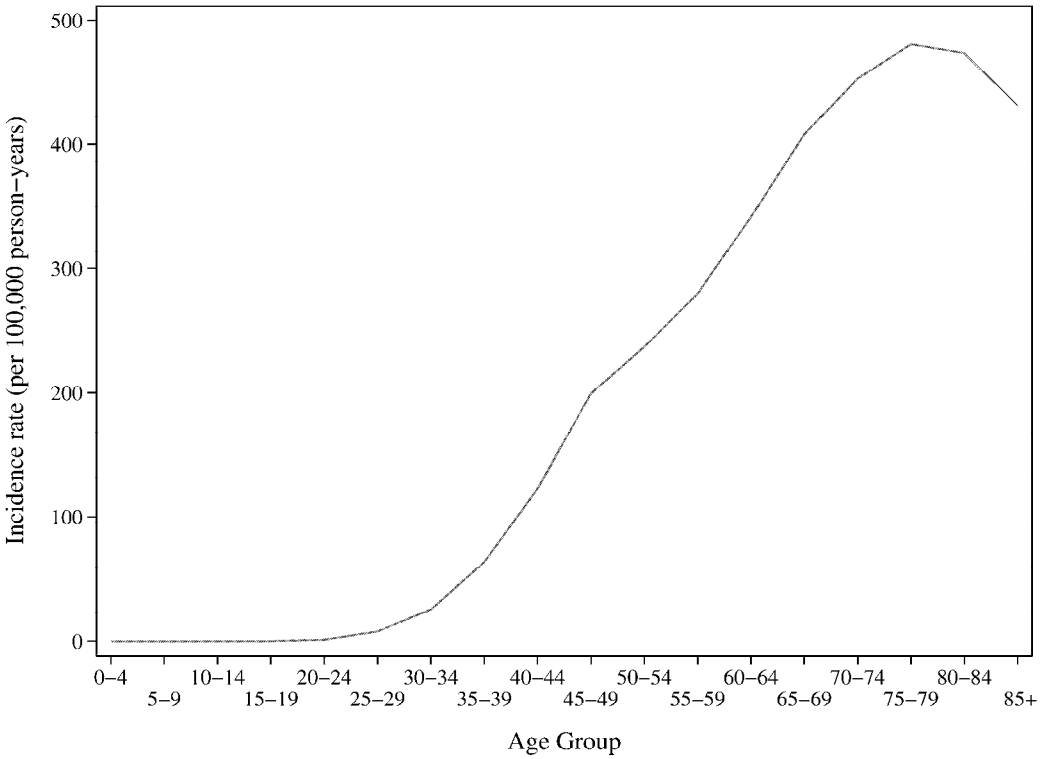
By doing so, I was able to more clearly observe the age effects on the incidence of bilateral breast cancer. I found that young women with breast cancer did indeed have a higher incidence of bilateral breast cancer, but this higher incidence was confined to that period of time when they were young. As they aged, the incidence of bilateral breast cancer declined and began to level out at age 50 to 54.

The higher risk of bilateral breast cancer for young women was not, therefore, a level of risk that they maintained for the remainder of their lifetime, but a transient increase in risk. Once they passed through the pre-menopausal period, their risk was little different from that of women first diagnosed at older ages.

There was little difference in age-specific rates in cohorts of women first diagnosed with breast cancer when aged over 50 years, but for women first diagnosed at ages less than 50 years the age-specific rates appeared to be associated with age at first diagnosis (Table 4-4 , page 83). I chose to ignore this and combine all age-specific rates of bilateral breast cancer (Figure 4-9). If we are prepared to accept for the moment that these overall age-specific rates of bilateral breast cancer are indicative of what a large cohort of women would experience if diagnosed with breast cancer at a young age, then the pattern of age-specific rates in Figure 4-9 has features that are similar to what is observed in the age-specific rates of first primary breast cancer.

The age-specific incidence of first primary breast cancer in the geographic regions of the USA covered by the SEER program are shown below (Figure 5-1). These data are from published annual cancer statistics (SEER, 1993) and are for period 1989 to 1993. These rates are less likely to be distorted by effects of population screening than rates from later periods.

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



The incidence of first primary breast cancer increases from ages 20-24 to 45-49. After this, however, the rate of increase diminishes slightly before increasing again after ages 55-59. This is well-described pre-menopausal feature of breast cancer incidence (Kelsey and Bernstein, 1996) sometimes referred to as Clemmesen's hook (Clemmesen, 1948). The incidence of breast cancer continues to increase until age 75-79, after which it declines. Various explanations have been offered for this decline in incidence, but under-ascertainment seems most likely although age-specific heterogeneity of risk factor exposures can not be ruled out (see Hertz-Picciotto and Sonnenfeld (2001) for a discussion of these).

My thesis is that bilateral breast cancer is not a sign of susceptibility, but simply a second occurrence of breast cancer. If this is so, we would expect that the factors responsible for these features of breast cancer incidence would also have effects on the incidence of bilateral breast cancer. We would expect elevated rates in younger women,

lower rates in the age range from 50 to 59 years, and declining rates in older age groups. When we look at the age-specific rates of bilateral breast cancer in Figure 4-9 this is what we observe.

The age-specific rates in young women of both first primary breast cancer and bilateral breast cancer are not inconsistent with hormonal effects on tumour latency. Studies of breast cancer doubling times have found that faster growing breast tumours are more characteristic of younger women (Peer et al., 1993; Brekelmans et al., 1996). This would imply that younger women would have a shorter latency period on average than older, post-menopausal women. A shorter latency period would manifest itself as an elevation in the incidence of first primary breast cancer and, in women already diagnosed with breast cancer, an elevation in the incidence of bilateral breast cancer.

In the immediate post-menopausal period, latency times would lengthen and this would manifest itself as a reduction in the rate of increase of age-specific rates of first primary breast cancer. In bilateral breast cancer, however, where the underlying rate is constant, this would appear as a reduction in the age-specific rates.

5.2.3 Histology and the Incidence of Bilateral Breast Cancer

A higher incidence of bilateral breast cancer in women first diagnosed with a lobular carcinoma of the breast was first reported by Robbins and Berg (1964) and has been found in a number of subsequent studies (Appendix H). This association with bilateral breast cancer is now viewed as an established characteristic of lobular carcinoma and many breast pathology textbooks contain some discussion of this (For example, Rosen's Breast Pathology, pages 627-628 (Rosen, 2001)).

More recently, Bernstein et al. (2003) reported elevated rates of bilateral breast cancer in women initially diagnosed with medullary carcinoma.

In those studies that found a higher incidence of bilateral breast cancer following a lobular carcinoma, none presented any adequate explanation for why this would occur. Invariably, the authors of these studies hypothesised that the elevated incidence indicated some difference in genetic susceptibility.

In my analysis, by concentrating on the annual incidence of bilateral breast cancer it was possible to examine in more detail the association between histology of the first breast cancer and incidence of bilateral breast cancer. More importantly, it was possible to examine associations between the histology of the first breast cancer and histology of the bilateral breast cancer.

My initial analysis found that the crude incidence of bilateral breast cancer was associated with the histology of the first breast cancer (Table 4-7). While the overall incidence in women with infiltrating ductal carcinomas was 5.31 per 1,000 person-years, for women with lobular carcinoma, it was 6.56 per 1,000 person-years and for women with medullary carcinoma, 6.67 per 1,000 person-years.

However, when I examined the annual incidence of bilateral breast cancer by histology of the first breast cancer, there were clearly differences in incidence in the first year. This suggested that the association between histology and bilateral breast cancer could in part be explained by the presence of a differential surveillance effect. This effect was most noticeable in women with lobular carcinoma and absent in women with medullary carcinoma.

If the first three years of annual incidence were ignored, however, differences in the incidence of bilateral breast cancer by the histology of the first breast cancer still remained. The incidence four or more years after diagnosis in women with infiltrating

ductal carcinoma was 5.35 per 1,000 person-years compared to 5.89 per 1,000 person-years in women with lobular carcinoma and 6.91 in women with medullary carcinoma.

This raised a number of questions. If the incidence of bilateral breast cancer was elevated in the first year because of a surveillance effect, why would this effect be different depending on the histology of the first breast cancer? More fundamentally, however, why should the incidence of bilateral breast cancer be associated with histology of the first breast cancer at all?

An answer to both of these questions was provided when the annual incidence of bilateral breast cancer by the histology of both the first and the bilateral breast cancer was calculated (Figure 4-11 and Figure 4-12).

There was a much larger surveillance effect observed when both the first and bilateral breast cancers were lobular and this contributed to a large extent to the effect observed in Figure 4-10 when only the histology of the first breast cancer was considered. This is not unexpected because, in general, lobular carcinomas are more difficult to detect than ductal carcinomas. They are more difficult to detect by mammography (Ma et al., 1992; Porter et al., 1999) and more likely to be detected by physical examination than infiltrating ductal carcinomas (Newcomer et al., 2002).

Three or more years after diagnosis, there remains an association between histology and incidence of bilateral breast cancer, but this is because the mix of histological types in the bilateral breast cancers is associated with the histology of the first breast cancers.

In the cohort of women with infiltrating ductal carcinomas, the incidence of bilateral lobular carcinoma is very low in comparison to the incidence in the cohort of women with lobular carcinoma. Similarly, bilateral medullary carcinoma is much more likely

in the cohort of women with medullary carcinoma than in the cohort of women with infiltrating ductal carcinoma.

If there are factors are that are causally related to the development of either lobular carcinomas or medullary carcinomas, then this association between histology of the first breast cancer and the bilateral breast cancer is not surprising since in any woman exposed to such factors, it would be reasonable to expect that both breasts would be exposed.

The epidemiology of breast cancers of particular histological types has only become the subject of research relatively recently. Established risk factors for breast cancer appear to have different effects on the risk of lobular carcinoma compared to their effect on the risk of infiltrating ductal carcinoma. For example, use of oral contraceptives appears to be associated with an elevated risk of lobular carcinoma, but not ductal carcinoma (Li et al. 2003; Newcomer et al. 2003). Li et al. (2003) also found differential, but not statistically significant, effects associated with age at menarche and age at menopause that suggested that these factors where more strongly associated with ductal carcinoma rather than lobular carcinoma. Li et al. have also reported that alcohol use appeared to be associated with lobular carcinoma rather than ductal carcinoma (Li et al., 2003).

Medullary breast cancer has been observed to occur more frequently than expected in families with a strong history of breast cancer (Rosen et al., 1982; Clause et al., 1993). It is also associated with early-onset breast cancer (Armes et al., 1998). More significantly, it has been associated with the breast cancer gene BRCA-1 to such an extent that it has been suggested as a marker for this gene (Eisinger et al., 1998; Anonymous, 1997).

5.2.4 Survival from Synchronous Bilateral Breast Cancer

A number of previous studies have estimated survival from synchronous bilateral breast cancer (Section 2.6, page 38 and Appendix L).

Most of these studies provided crude survival estimates and few have used multivariate methods – Holmberg et al. (Holmberg, 1988 #1376}) is the first I can find that used proportional hazards regression. Consequently, there was little statistical testing conducted of the results from most of these studies, many of which were comparatively small hospital-based samples of women with breast cancer.

In addition, most early hospital-based studies suffered to some degree through the application of "criteria" for the definition of bilateral breast cancers and later studies, conducted after 1971, were affected by the variety of definitions of "synchronous". The degree to which estimates were affected by these is difficult to specify with any confidence.

5.2.4.1 Cancer stage and synchronous bilateral breast cancer

When I examined the stage distributions of left and right synchronous bilateral breast cancers, I found that there were comparatively few Stage 1 or Stage 2 breast cancers diagnosed synchronously with a Stage 4 breast cancer (Table 4-30, page 137). If a woman presented with synchronous bilateral breast cancers and with distant metastatic disease evident, both breast cancers would have to be Stage 4 unless a pathologist could unequivocally determine which breast cancer was responsible for producing the metastases. My results (Table 4-30) would suggest that this is what is occurring.

5.2.4.2 The effect of synchronous bilateral breast cancer on breast cancer survival

The proportional hazards assumption was tested prior to modelling the data and showed some evidence of lack of proportionality associated with stage. To deal with this, the approach followed was to first ignore this and fit a model that would allow the estimation of hazard ratios associated with various staged-defined groups of synchronous bilateral breast cancers (both Stage 1, both Stage 2, or one Stage 1 and the other Stage 2) compared with the survival in women with unilateral Stage 1 breast cancer.

Following this, two distinct models were fitted. The first compared the survival in women with bilateral Stage 1 breast cancer to the survival in women with unilateral Stage 1 breast cancer. The second compared the survival in women with bilateral breast cancer where both were Stage 2 or where one was Stage 1 and the other Stage 2 to the survival in women with unilateral Stage 2 breast cancer.

From the first of these models (after adjustment for age at first diagnosis, year of first diagnosis, registry, race, marital status, use of radiotherapy, and histology), the risk of breast cancer death in women with bilateral Stage 1 breast cancer was 46% (95% C.I.: 28% – 67%) higher than in women with unilateral Stage 1 breast cancer.

From the second model, after adjustment for the same factors as noted above, survival in women with bilateral breast cancer where one tumour was Stage 1 and the other Stage 2 was little different from the survival in women with unilateral Stage 2 breast cancer (HR = 0.96, 95% C.I.: 0.87 – 1.07), implying that the additional Stage 1 breast cancer did not affect significantly alter the risk of breast cancer death. In women with bilateral Stage 2 breast cancer, however, the risk of breast cancer death was increased by 45% (95% C.I.: 25% – 68%) relative to the risk in women with unilateral Stage 2 breast cancer.

I then returned to the initial combined model and showed that virtually the same results could be obtained from this model, indicating that any problems that may have been caused by lack of proportionality were minimal.

Perhaps the most interesting and puzzling result is that the relative effect of synchronous bilateral breast cancer Stage 2 breast cancers compared to unilateral Stage 2 breast cancer is essentially the same as the relative effect of synchronous bilateral breast cancer Stage 1 breast cancers compared to unilateral Stage 1 breast cancer. I would have expected to see a greater relative risk for women with synchronous bilateral breast cancer Stage 1 breast cancers compared to unilateral Stage 1 breast cancer. The following, somewhat crude calculations will illustrate why this would have been expected.

A woman with breast cancer has a risk, *R*, of dying from breast cancer in an interval of time and therefore her probability of surviving that period of time is 1-*R*. A woman with bilateral breast cancer is exposed to two risks, R_1 and R_2, and her probability of surviving a period of time is therefore:

$$\begin{aligned}(1-R_1)\times(1-R_2) &= 1-R_1-R_2+(R_1\times R_2)\\ &= 1-(R_1+R_2-(R_1\times R_2))\end{aligned}$$

Therefore her risk of dying in this interval of time is: $R_1+R_2-(R_1\times R_2)$.

Now, if we consider women with synchronous bilateral breast cancer where both tumours are the same Stage and we assume the same risk is attached to both, then their risk of dying from breast cancer in an interval of time would be: $2R-R^2$.

Given these assumptions, the expected relative risk comparing women with synchronous bilateral breast cancer both at the same Stage to women with unilateral breast cancer at the same Stage would be:

$$RR = \frac{2R - R^2}{R}$$

The crude 5-year survival for women with Stage 1 breast cancer was 93.6% and for women with Stage 2 breast cancer, 75.2% (Section 4.4.1.5). These can be used to obtain crude estimates of the 5-year risk of breast cancer death: 6.4% and 24.8% respectively.

Therefore, comparing the survival in women with synchronous Stage 1 bilateral breast cancer to women with unilateral breast cancer we would expect:

$$RR = \frac{2R - R^2}{R} = \frac{2 \times 0.064 - 0.064^2}{0.064} = 1.94$$

For women with synchronous Stage 2 bilateral breast cancer to women with unilateral breast cancer we would expect:

$$RR = \frac{2R - R^2}{R} = \frac{2 \times 0.248 - 0.248^2}{0.248} = 1.75$$

These calculations are made using the crude survival of all women in the cohort whereas the relative risks obtained from the proportional hazards model are adjusted for other covariates. However, even after adjustment, we would not have expected to see equivalent relative effects. Instead we see lower, and equivalent, relative risks for the two scenarios.

The calculations of expected relative risks above assume that the risks are independent and the risk attached to each breast cancer in women with synchronous bilateral breast cancer is the same as the risk in women with unilateral breast cancer. The results from my survival analysis would suggest that this is not the case.

One possible reason for this may be that women with synchronous bilateral breast cancer are being treated more aggressively than women with unilateral disease. Unfortunately data describing treatment are limited in the SEER database. There is some description of surgical procedures performed, but this is simply coded as surgery, yes or no, for women treated between 1973 and 1988. Regardless of this, it is unlikely that differences in surgical intervention would be significant since the outcomes in women treated by lumpectomy or mastectomy are similar (Fisher at al., 1989; Fisher et al., 1985). It is more likely that if treatment differences exist, they are to be found in the use of adjuvant chemotherapy. Unfortunately there are no data describing the use of chemotherapy in the SEER database.

5.2.5 Survival from Metachronous Bilateral Breast Cancer

There are numerous studies that have attempted to determine the effect of a metachronous bilateral breast cancer on survival from breast cancer. The approaches taken to determine this effect can be broadly classified in three ways.

First, there are those studies that have estimated survival from diagnosis of the first breast cancer. These studies produced biased estimates of survival from metachronous bilateral breast cancer because the time from diagnosis of the first breast cancer to the diagnosis of the bilateral breast cancer was incorrectly assigned to the survival time from the metachronous bilateral breast cancer. The bias introduced by this method led to optimistic estimates of metachronous bilateral breast cancer survival (Section 2.6.2.1, page 40).

Second, there are those that estimated survival from the date of diagnosis of the metachronous bilateral breast cancer and compared this to the survival in women with unilateral breast cancer. In general, these studies found either no difference in survival following unilateral or metachronous bilateral breast cancer (Robbins and Berg, 1964;

Khafagy et al., 1975; Carmichael et al., 2002) or a lower survival in those with metachronous bilateral breast cancer (Fracchia et al., 1985; Robinson et al., 1993). This method ignores the period of time between diagnosis of the first breast cancer and diagnosis of the bilateral breast cancer. While this makes it difficult to estimate the effect that this interval may have on survival, it also biases survival estimates of women with unilateral breast cancer since the time between first and second diagnosis is removed from the survival estimates of these women.

Third, there are those studies that have used Cox proportional hazards regression to model the time-dependent effect of a diagnosis of a metachronous bilateral breast cancer on breast cancer survival (Appendix M). There are comparatively few studies that have used this method (Healey et al., 1993; Black et al., 1996; Abdalla et al., 2000; Heron et al., 2000; Kollias et al., 2001). All of these found that the diagnosis of a metachronous bilateral breast cancer was associated with an increase in the risk of breast cancer death.

The hospital-based studies reported by Healey et al. (1993) and Heron et al. (2000) were small and the effects found were not statistically significant. The larger hospital-based studies conducted by Abdalla et al. (2000) and Kollias et al. (2001) estimated relative risks associated with bilateral breast cancer diagnosis of 1.46 and 1.67 respectively.

Only the study by Black et al. (1996), based on the SEER data for 1973 to 1990, was large enough to estimate effects quite precisely (RR=1.56), but the primary focus of their study was to test for a hypothesised protective effect of in situ carcinoma. Their analysis was of survival to death from any cause and while they estimated the effect associated with a metachronous bilateral breast cancer, their model also included the time-dependent effects associated metachronous in situ bilateral breast cancers, with subsequent in situ cancers diagnosed at other sites, and with subsequent malignant cancers diagnosed at other sites.

In my analysis, stage of the first breast cancer was found to be problematic with regard to the proportional hazards assumption. The strategy followed to deal with this was similar to that adopted in the analysis of survival from synchronous bilateral breast cancer. The results from overall analyses were compared to the results from stage-specific analyses to determine the extent that lack of proportionality associated with stage might be affecting these results.

To determine if the time between diagnosis of the first breast cancer and the bilateral breast cancer was an important determinant of the effect of the bilateral breast cancer on survival, models with a single time-dependent effect were compared with models employing multiple time-dependent effects.

Overall, estimates derived from models fitting multiple time-dependent effects did not differ significantly from corresponding models fitting only a single time-dependent effect.

The estimates of effect by stage of bilateral breast cancer derived separately from models for women first diagnosed with Stage 1 and first diagnosed with Stage 2 breast cancer did not differ markedly from estimates derived from a model where both these groups were combined. This indicated that if there were problems associated with stage of the first breast cancer and the proportional hazards assumption, these were exerting comparatively little influence on the overall results.

If a bilateral breast cancer was diagnosed early (Stage 1) its effect on survival in women with a history of Stage 2 breast cancer was minimal. In women with a history of Stage 1 breast cancer, the risk of breast cancer death was increased by 80% (Table 4-44).

If a bilateral breast cancer was diagnosed as Stage 2, however, its effect was more pronounced (Table 4-44). In women with a history of Stage 1 breast cancer the risk of

breast cancer death was increased more than 5 times (RR=5.33, 95% C.I.: 4.88 – 5.82). In women with a history of Stage 2 breast cancer, their risk more than doubled (RR=2.73, 95% C.I.: 2.52 – 2.95).

If bilateral breast cancers were diagnosed at Stage 4 their effects on breast cancer survival were large regardless of the stage of the first breast cancer, increasing the risk in women with a history of Stage 1 breast cancer by over 19 times and the risk in women with a history of Stage 2 breast cancer by over 8 times (Table 4-44).

If relative risk estimates are made using a common reference – women with unilateral Stage 1 breast cancer (Table 4-45) – the increases in risk for women with a history of Stage 2 breast cancer are always much larger than the corresponding increase in women with a history of Stage 1 breast cancer.

These results underline the importance of continued surveillance of the contralateral breast in women with a history of breast cancer.

5.3 Multistage Models of Carcinogenesis

Bilateral breast cancer has come to be regarded as a marker of increased susceptibility to breast cancer (Prior and Waterhouse, 1978; Chaudary et al., 1984; Sterns et al. (1991); Bernstein et al., 1992; Greene, (1997); Carmichael et al., 2002). This stems from early interpretations of the occurrence of multiple primary cancer (for example, Ewing, 1928), from early studies of multiple primary cancers (Warren and Gates, 1932; Lund, 1933; Warren and Ehrenreich, 1944; Thomas et al., 1948).

While one might logically infer that women who were highly susceptible to breast cancer would also be highly susceptible to bilateral breast cancer, this does not make bilateral breast cancer a marker of susceptibility. Even in a group of women with no

variation in susceptibility to breast cancer, we would still expect to see the occurrence of bilateral breast cancer in some of these women. This is because carcinogenesis, whether it be in the breast or any other site, develops in a multi-stage process (Knudson, 2001) and the first stage in this process – the initiation of carcinogenesis – is a stochastic event. With a large number of cells exposed to the of risk of this first event, the possibility of carcinogenesis initiating in one, two, or more cells would be expected (Moolgavkar, 2003). Thus there is no need to invoke susceptibility to explain the occurrence of multiple cancers in the same organ: under multistage carcinogenesis they would be expected to occur.

It is my thesis that if we eschew notions of susceptibility and instead interpret bilateral breast cancer as simply an outcome of multistage carcinogenesis we will arrive at a better understanding, not only of the incidence of bilateral breast cancer, but also the incidence of first primary breast cancer in the population. In other words, the incidence of bilateral breast cancer tells us something about the incidence of breast cancer itself.

Various mathematical models of carcinogenesis have been developed and evaluated by assessing their ability to fit the age distribution of cancer in populations (Armitage and Doll, 1954; Armitage and Doll, 1957; Moolgavkar, 1978; Moolgavkar et al., 1980), yet none of these have considered the incidence of subsequent primary cancers in the same organ.

If bilateral breast cancer is not a sign of increased susceptibility and if instead the occurrence of bilateral breast cancer is an expected outcome of multistage carcinogenesis, then a model of multistage carcinogenesis applied to breast cancer should be able to fit not only the age distribution of breast cancer incidence in the population, but should also the incidence of subsequent bilateral breast cancer.

To do this, models of multistage carcinogenesis will have to be very different from those currently proposed, because while these can fit the incidence of breast cancer in the population which increases with age, the incidence of bilateral breast cancer is comparatively constant, with little age variation.

A constant incidence of cancer over time is rarely observed. Retinoblastoma, for example, is observed in children where there is a family history of the disease and in children without any family history – in hereditary and non-hereditary forms. In the hereditary form, the incidence of retinoblastoma is constant over time, an observation that led Knudson to postulate that retinoblastoma was caused by deletion of both copies of one gene and that children with the hereditary form were born with one copy of this gene already deleted. The initiation of retinoblastoma in these children therefore required only one mutational event, the deletion of this remaining copy. This led to Knudson's "one-hit" hypothesis of retinoblastoma (Knudson, 1971).

By observing the difference in incidence of the hereditary and non-hereditary forms of retinoblastoma and interpreting these differences in terms of multistage carcinogenesis theory, Knudson was able to draw an inference concerning the aetiology of retinoblastoma.

This is the approach that I intend to take to explain the incidence of bilateral breast cancer because if we can understand why the annual incidence is constant then this will tell us something about the aetiology of breast cancer.

5.3.1 Nordling's Multistage Model

To consider why the incidence of bilateral breast cancer would be constant, we could begin by considering one of the first models of multistage carcinogenesis – the

Armitage-Doll Model (Armitage and Doll, 1954) which was directly inspired by the work of Nordling (1953).

Bauer (1949) had suggested that cancer occurred because of some cellular mutation, but this would not explain the age distribution of cancer incidence. Nordling (1953) realised that if cancer was caused by a single mutation, then this would largely result in a constant age-specific incidence of cancer after the age corresponding to the latency period for cancer. He also realised that, from evidence available at the time, that the latency period of cancer was likely to be of the order of years rather than decades, so variation in tumour latency would not explain the age distribution of cancer incidence in the population. Further to this, he argued that if two mutations were required, then the resulting incidence would increase linearly with age. Three mutations would result in cancer incidence that increased in proportion to the second power of age. With four mutations, cancer incidence would increase in proportion to the third power of age. Thus if I were the observed age-specific incidence, t the age, and k the number of mutations required for a tumour to develop:

$$I \approx t^{k-1}$$
$$\therefore \ln(I) \approx k - 1\ln(t)$$

Following this line of thought, he plotted the log of age-specific incidence (actually the log of age-specific mortality, since at that time reliable incidence data were not available) against the log of age for all cancers in males using data from the United States, the United Kingdom, France and Norway. In each population he observed a linear relationship with a slope (k-1) equal to 6 and concluded that 7 mutations were required for cancer to occur.

5.3.2 The Armitage-Doll Multistage Model

Nordling's model had a number of limitations. The model explicitly assumed that the probability of mutation was constant and the fit to age-specific cancer incidence that he obtained was based on all cancer mortality in men only. Armitage and Doll (1954) used cancer-specific mortality rates for men and women in England and Wales in 1950-51 to test Nordling's hypothesized model in more detail.

They found that age-specific rates for cancer of the oesophagus in men and stomach, colon, rectum and pancreas in both men and women were in accord with Nordling's model. In other words, the probability of transition from one stage to the next remained constant throughout life. These cancers, they noted, were independent of any hormonal influence or any known external environmental factors with the exception of cancer of the oesophagus.

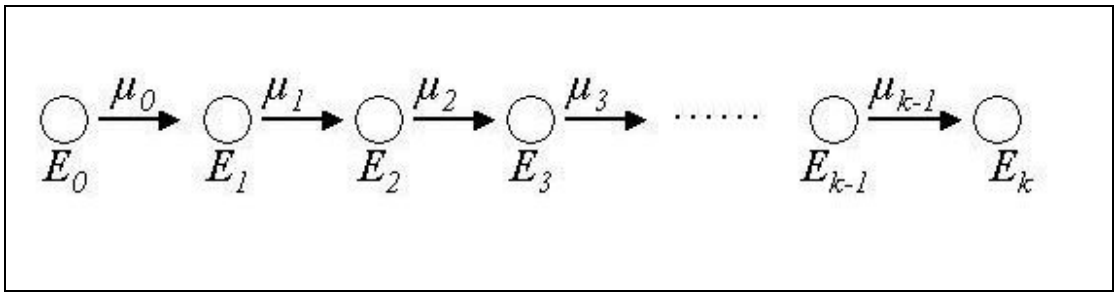
When they examined the age-specific rates of cancer of the lung, bladder, and prostate in men and lung, breast, ovary, cervix and corpus uteri in women, however, they found that cancers at these sites did not fit Nordling's model particularly well.

Cancers of the prostate, breast, ovary, cervix, and corpus uteri were known to be affected by hormonal exposures that could vary between individuals and at different ages. Bladder cancer was known at that time to be mainly influenced by occupational exposures which could vary during different calendar periods and at different ages.

They reasoned that these cancers could not be expected to fit Nordling's model because the probabilities of transition from one stage to the next would be affected by the strength of exposures acting at different times.

Armitage and Doll proposed a model of multi-stage carcinogenesis similar to Nordling's model, where normal cells progressed towards malignancy in a series of specific and discrete stages (Figure 5-2).

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



In Nordling's model there were 6 stages and 7 transition probabilities with the rate at some age, *t*, being:

$$\text{rate} = k \times \mu_1 \times \mu_2 \times \mu_3 \times \mu_4 \times \mu_5 \times \mu_6 \times \mu_7 \times t^6$$

and where the transition probabilities, μ_i, were all equal.

Since this model did not fit cancers known to be affected by carcinogenic exposures that could vary at different ages, Armitage and Doll reasoned that these transition probabilities were being affected by these exposures and could no longer be considered to be constant.

In their model, the incidence at a particular age, *t*, would now be a weighted mean of the probabilities of transition from age 0 to age *t*. The weight that they constructed was influenced by the time that the exposure occurred, t_0, and the stage in the multi-stage process that it affected. This weight was proportional to:

$$t_0^{s-1}(t-t_0)^{6-s}$$

where *s* was the affected stage.

This approach produced a multistage model with some interesting attributes. Exposures that affected early stages had relatively little effect on age-specific rates in later life, whereas exposures that effected later stages had a more direct impact on age-specific rates. If exposures affected the final stage, then age-specific rates would be directly proportional to this exposure and the longer the period of exposure the higher the rate.

This model, however, made a number of assumptions that were no less restrictive than the model proposed by Nordling. While Nordling had required all the transition probabilities to be the same, in order to derive weighted averages of the transition probabilities, Armitage and Doll required that all the stages of carcinogenesis had to occur in a particular order.

5.3.3 Armitage and Doll's Two Stage Model of Carcinogenesis

While Nordling's model had suggested a multistage carcinogenesis process involving seven stages, there was no direct experimental evidence that carcinogenesis involved any more than two stages (Armitage and Doll, 1957). In a letter to the Lancet, Platt (1955) suggested that cancer could develop in two stages, the first, which produced a growth advantage in the affected cells so that they multiplied at a faster rate than normal cells, and the second, which produced a malignant cell. The increase in age-specific incidence would then be driven by the increase over time in the number of affected cells produced by the first stage exposure.

Armitage and Doll (1957) were able to derive a mathematical model that involved only two stages where the probability of transition in the first stage, p_1, was dependent on the strength or concentration, d_1, of some exposure. Affected cells then experience exponential growth so that at any age, t, the probability of malignancy occurring was:

$$p_2 e^{kt}$$

where p_2 was the transition probability of a single cell and this was proportional to the strength or concentration, d_2, of some exposure, and k was a constant.

Using this model, Armitage and Doll were able to obtain a good fit to the age-specific rates of a number of cancers. They did not, however, present results for cancer of the breast, cervix or corpus uteri in women because for these cancers the relationship between age and incidence was more complex.

For these cancers, age-specific rates in older age groups were lower than expected. For cancer of the cervix, for example, rates did not rise noticeably over age 60. Armitage and Doll suggested that the two-stage model would still fit these rates if it were assumed that the growth advantage experienced by cells produced by the first stage was hormone-dependent and was subsequently lost in older age.

5.3.4 Moolgavkar's Two-Stage Model of Carcinogenesis

Following Armitage and Doll's proposed two-stage model, other two-stage models were developed by Kendall (1960) and Neyman and Scott (1967).

Evidence had begun to emerge, however, that suggested that comparatively few cells had the ability to self-replicate and that most cells lacked this ability and had only limited lifetimes (Till et al., 1964). These self-replicating cells, referred to as stem cells, maintained the viability of an organ by replenishing normal cells via a process of differentiation (Reya et al.; 2001).

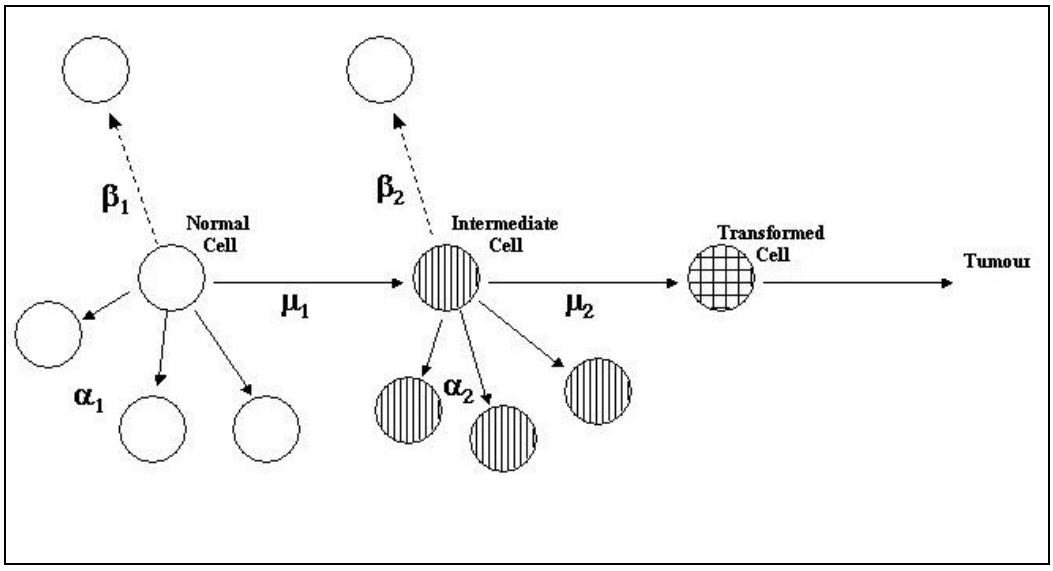
Moolgavkar and others (Moolgavkar and Venzon, 1979; Moolgavkar et al., 1980; Moolgavkar and Knudson, 1981) approached the modelling of carcinogenesis by reasoning that if carcinogenesis was the result of an accumulation of mutations within a cell, then this could only occur in cells that had the ability to self-replicate. Any mutation in a stem cell would be passed on to daughter stems cells thus leading over

time to a clone of stem cells with an acquired mutation. Differentiation, on the other hand, would remove stem cells from this clone. Thus the processes of replication and differentiation would have opposite effects on the number of intermediate cells in a two-stage model of carcinogenesis.

This aspect of tumour growth was added to the two-stage model by Moolgavkar (1978). In this model, illustrated in Figure 5-3, a normal stem cell could divide into two normal stem cells at some rate α_1 or differentiate (or die) at some rate β_1. Alternatively, the normal stem cell could divide and experience some mutational 'hit', producing an intermediate cell at some rate μ_1. This intermediate cell could in turn produce two daughter cells at some rate α_2 or differentiate at some rate β_2.

The growth of the intermediate cells over time was therefore dependent on the parameters α_2 and β_2 and a proliferative advantage was apparent if $\alpha_2 - \beta_2 > 0$, resulting in the growth of a clone of intermediate cells. This clone of intermediate cells was then susceptible to the second mutational 'hit' which occurred at some rate μ_2, resulting in a malignant cell.

Figure 5-3: Schematic representation of Moolgavkar's two-stage carcinogenesis model.



In this two stage model it is cellular kinetics – the growth of the pre-malignant clone of intermediate cells – that drives the observed increase in age-specific rates of breast cancer. While μ_2, the rate that intermediate cells become malignant, may remain constant, the risk of this event occurring will increase with time as the number of intermediate cells increases, placing greater numbers of cells at risk.

Moolgavkar et al. were able to fit this model to breast cancer incidence data by altering the cellular kinetics – the growth of the clone of intermediate cells. In doing so they were able to provided an explanation of how age at menarche, age at first pregnancy, and age at menopause could act as risk factors for breast cancer (Moolgavkar et al., 1980).

A first full-term pregnancy would cause a woman's breast to undergo extensive re-modelling resulting in an increase in differentiation of both normal and intermediate cells. This would result in a decrease in the number of intermediate cells and, in terms of their model, a decrease in the growth advantage specified by $\alpha_2 - \beta_2$. The younger a women was at first full-term pregnancy, the smaller the clone of intermediate cells experiencing differentiation and hence a greater the protective effect produced.

Subsequent full-term pregnancies induce less remodelling of breast tissue and hence less cellular differentiation of normal or intermediate cells and hence any protective effect is less than that experienced from the first full-term pregnancy.

Early age at menarche would cause an increase in the risk of breast cancer because this would cause development of the breast to occur at an earlier age and hence the development and growth of any intermediate clone of cell would begin at an earlier age. Similarly, menopause would result in loss of breast tissue and a net loss of normal and

intermediate cells, leading to a reduction in the size of any clone of intermediate cells. The later in life this occurred, the smaller would be the reduction in risk.

All of these changes were modelled by Moolgavkar et al. by altering the growth determining parameters of their model – α_2 and β_2. In their model, the rate of transition, μ_1, from normal cell to intermediate cell and μ_2, from intermediate cell to malignant cell determines the overall incidence of breast cancer, but the age-specific incidence is determined by the normal growth of the breast and its physiological response to puberty, pregnancy, and menopause, and by the cellular kinetics of the intermediate clone produced by these same responses.

Another aspect of this model is that it allows exposures to act in two different ways. An exposure that increased the transition rates, either μ_1 or μ_2, to new constant levels would result in an increase in risk for the exposed individuals that was constant with time. This is because the ratio of the number of cells in the intermediate clone in exposed and unexposed individuals would remain constant over time.

If, however, an exposure increased the proliferative advantage of the intermediate clone, α_2-β_2, by a constant amount without altering the transition probabilities, μ_1 and μ_2, this would result in an increase in risk for exposed individuals that increased with time. This is because the ratio of the number of cells in the intermediate clone in exposed and unexposed individuals would increase over time.

In subsequent work, Moolgavkar and Knudson (1981) used this model to examine the effect of smoking and, in particular, cessation of smoking, on lung cancer incidence rates, the occurrence of childhood cancers such as retinoblastoma, and to model adult cancers that reach a peak incidence at a certain age and then decline (for example, testicular cancer).

5.4 Bilateral Breast Cancer and Multistage Carcinogenesis

The incidence of bilateral breast cancer is constant over time. To understand what this implies it will be instructive to consider how this could occur under the multi-stage model originally proposed by Armitage and Doll (1954) and the two-stage model proposed by Moolgavkar et al. (1980).

5.4.1 The Armitage-Doll Model and Bilateral Breast Cancer

In the original model developed by Armitage and Doll (1954) carcinogenesis progressed in a series of stages and the probability of transition from one stage to the next was constant. One implication of this is that if we could identify women in the final stage (E_{k-1} in Figure 5-2), the observed incidence of breast cancer in these women would be constant. This is because in these women only one more mutational event – one 'hit' – would be required to produce a malignant cell and the probability of this occurring is constant.

The constant incidence of bilateral breast cancer implies that when women are diagnosed with breast cancer, if carcinogenesis is also developing in the other breast it has reached this final stage and only one mutational 'hit' is required for cancer to occur.

This also implies that carcinogenesis must develop in both breasts over the same period of time. If carcinogenesis reaches the final stage in one breast, it must also reach this same stage in the other breast. This would seem unlikely if the Armitage and Doll (1954) model were correct. With a large number of stages and with transition from one stage to the next being determined by fixed probabilities, if carcinogenesis were developing in both breasts it seems unlikely that both would arrive at the final stage at the same time.

For the incidence of bilateral breast cancer to be constant would therefore require a carcinogenesis model that involved relatively few stages.

5.4.2 The Two-Stage Model and Bilateral Breast Cancer

This requirement would appear to be satisfied by Moolgavkar's two-stage model (Moolgavkar et al., 1980). In this model, the incidence of breast cancer is determined by the number of cells in the intermediate stage of carcinogenesis. Furthermore, while the size of this intermediate clone of cells may be affected by exposures, either exogenous or endogenous, it would not be unreasonable to expect that if carcinogenesis were developing in both breasts, that these exposures would have similar effects.

The two-stage model, however, does not lead to a constant incidence of bilateral breast cancer. If carcinogenesis is developing in both breasts, when breast cancer occurs in one breast, the intermediate clone of cells in the other breast would continue to increase in size. This model would therefore predict that the incidence of bilateral breast cancer would increase over time.

These models of carcinogenesis will therefore not explain the constant incidence of bilateral breast cancer. For a model of carcinogenesis to adequately explain the incidence of breast cancer and the constant incidence of bilateral breast cancer it would have to have a distinct final stage, but comparatively few stages overall.

5.4.3 The Proportion of Women at Risk of Breast Cancer

While the constant incidence of bilateral breast cancer has implications for how we conceptualise the process of carcinogenesis, the incidence rate itself also has implications when we consider what proportion of women in the population will be at risk of breast cancer in their lifetime.

If carcinogenesis never initiates in some women, then clearly these women are at no risk of breast cancer in their lifetime. Similarly, if carcinogenesis does initiate in some women, but progresses so slowly that it never reaches the final stage within their lifetime, then these women could also be regarded as having no risk of breast cancer.

The only women at risk of breast cancer are those in whom carcinogenesis initiates and progresses to the final stage within their lifetime. We can use the incidence of bilateral breast cancer to infer what the proportion of these 'at-risk' women is likely to be.

In my analysis I found the incidence of bilateral breast cancer to be 5.5 per 1,000 person-years and constant over time. In the argument presented above, I concluded that this was consistent with what would be expected if carcinogenesis in the contralateral breast was in the final stage when the first breast cancer was diagnosed. This does not imply, however, that carcinogenesis is occurring in the contralateral breast of all women first diagnosed with breast cancer, simply this if it is, it is in the final stage.

To infer what proportion of women in the population will be at risk of breast cancer in their lifetime, I need to determine what the incidence of bilateral breast cancer would be in those women with breast cancer where carcinogenesis is actually occurring in the contralateral breast.

If we assume that all women with breast cancer also have carcinogenesis developing in the contralateral breast, then the observed incidence of 5.5 per 1,000 person-years is the rate of breast cancer in one breast that is in the final stage of carcinogenesis. From the argument presented above, I concluded that the constant incidence of bilateral breast cancer implied that if carcinogenesis was occurring in both breasts, then it would progress to the final stage in both breasts at the same time.

It therefore follows that if we have women with carcinogenesis in the final stage in both breasts, the annual incidence in the left breast, I_L, would be 5.5 per 1,000 person-years and the annual incidence in the right breast, I_R, would be 5.5 per 1,000 person-years.

The overall annual incidence, I, that we would observe would therefore be:

$$\begin{aligned} I &= I_L + I_R - (I_L \times I_R) \\ &= 0.0055 + 0.0055 - (0.00003025) \\ &= 0.01097 \\ &\simeq 11 \text{ per } 1{,}000 \text{ person-years} \end{aligned}$$

This will be the breast cancer rate in the final stage of carcinogenesis regardless of the age at which this final stage was reached. The age-specific incidence of breast cancer will be observed to increase with age because more and more women will reach this final stage of carcinogenesis as they age.

This implies that if carcinogenesis initiated in both breasts in all women in the population and it progressed to the final stage of carcinogenesis within the lifetime of all of these women, then the age-specific incidence of breast cancer would ultimately reach 11 per 1,000 person-years or 1,100 per 100,000 person-years.

The age-specific incidence of breast cancer observed in Western populations never reaches a rate of this magnitude at any age. The maximum rate observed in Figure 5-1, for example, was 470 per 100,000 person-years in women age 75 to 79 years. This would imply that when calculating age-specific incidence in the population we are including in the denominator of the rate the person-years of women who are not in the final stage of carcinogenesis. Using the maximum age-specific rate in Figure 5-1, for example, the 100,000 person-years in the denominator includes 57,265 person-years from women not yet at the final stage of carcinogenesis. In other words, approximately

57% of women in the population have not reached the final stage of carcinogenesis by age 75 to 79 years.

This calculation is derived by assuming that when carcinogenesis initiates it does so in both breasts. While this may seem to be a very strong assumption, it is actually conservative.

Suppose instead we assume that when breast carcinogenesis initiates it does so bilaterally in 80% of women and in only one breast in the remaining 20% of women. The observed incidence of bilateral breast cancer (5.5 per 1,000 person-years) is now no longer an estimate of the incidence of breast cancer in the final stage in one breast. The denominator of this rate now includes 20% of women at no risk of bilateral breast cancer. The incidence in one breast in the final stage of carcinogenesis is now 5.5 per 800 person-years or 6.9 per 1,000 person-years.

Therefore if carcinogenesis progresses to the final stage within the lifetime of all of these women, the rate in the final stage for the 80% of women with bilateral carcinogenesis would be 13.8 per 1,000 person-years and in the 20% with carcinogenesis in only one breast, 6.9 per 1,000 person-years. The overall rate of breast cancer in women reaching the final stage of carcinogenesis would be a weighted average of these: 12.4 per 1,000 person-years.

Using a similar argument, it can be shown that if carcinogenesis initiated bilaterally in only 20% of women and in only one breast in the remaining 80% of women, the incidence of breast cancer in women who reach the final stage of carcinogenesis would be 33 per 1,000 person-years.

So, the conclusion drawn above that the incidence of bilateral breast cancer implied that by age 75 to 79 year, 57% of women in the population have not yet reached the final stage of carcinogenesis is a conservative estimate.

A similar conclusion was reached by Peto and Mack (2000) in a study of breast cancer incidence in twins and in women with a family history of breast cancer. In this study, when one twin was diagnosed with breast cancer, follow-up of the unaffected twin began. In monozygotic twins, the incidence of breast cancer in the unaffected twin was found to be 13.1 per 1,000 person-years and constant. In dizygotic twins, the incidence in the unaffected twin was 5 per 1,000 person-years and constant.

In women with a family history, the incidence of breast cancer was determined for ages older than the age at diagnosis of their affected relative. This was found to be 3.6 per 1,000 person-years and constant.

Peto and Mack (2000) concluded that these temporal patterns in the incidence of breast cancer could be accounted for if many breast cancers arose in a susceptible minority of women whose incidence, on average, increased to a high constant level at a predetermined age that varied between families. They hypothesized that breast cancer incidence was constant after predetermined ages in families and suggested that heterochronic genes – timing genes – may play a role in breast cancer incidence.

These results were controversial. Hemminki and Granstrom (2002) using data from Swedish Family-Cancer Database, found that the age-specific incidence of breast cancer continued to increase at ages older than the age at diagnosis of the affected relative. In a study of twins, however, Hemminki and Li (2002) observed patterns of breast cancer incidence that they concluded were not inconsistent with those observed by Peto and

Mack (2000). Unlike Peto and Mack (2000), however, they concluded that these had no obvious biologic explanation.

The problem with these studies is that they have not considered that multistage carcinogenesis when interpreting their findings. Peto and Mack (2000) interpreted the high constant incidence they observed in twins as evidence of genetic susceptibility and, citing earlier studies of bilateral breast cancer (Robbins and Berg, 1964; Harvey and Brinton, 1985), interpreted the high constant incidence of bilateral breast cancer in the same way.

The constant incidence of bilateral breast cancer observed in women after their first diagnosis of breast cancer implies that carcinogenesis in the contralateral breast is in the final stage of a multistage process. The high incidence rate observed is therefore not unexpected and is entirely consistent with multistage carcinogenesis and there is no need to invoke genetic susceptibility to explain this (Moolgavkar and Luebeck, 2003).

What will vary between women is the time required to transition through all the stages of carcinogenesis. For some women this will occur relatively quickly, whereas for others, longer periods of time are required. This is, after all, how the original Armitage and Doll model (Armitage and Doll, 1954) explained the age distribution of cancer.

Transition through all stages of carcinogenesis in the Armitage and Doll model was entirely probabilistic, however. If genetic characteristics are playing a role in carcinogenesis, then it is likely that they are affecting the time required to make a complete transition through all stages of carcinogenesis. This is entirely plausible since women with a family history have a higher incidence of breast cancer at younger ages than women without a family history (Bernstein et al., 1992). Given this, the observed constant of incidence of breast cancer in unaffected twins from the date of diagnosis of

their affected twin could be explained without invoking a role for heterochronic genes as suggested by Peto and Mack (2000) nor would the observation be biologically implausible as suggested by Hemminki and Li (2002).

5.5 Conclusions

The incidence of metachronous bilateral breast cancer is constant following the diagnosis of the first breast cancer.

This study has found that the pattern of age-specific incidence of bilateral breast cancer is consistent with effects already well established in the literature describing the incidence of first primary breast cancer. Women who are younger than 50 years when first diagnosed with breast cancer are at increased risk of bilateral breast cancer, but this is only transient, as they age, the risk declines. This is more consistent with a pre-menopausal effect. Older women appear to have a lower risk of bilateral breast cancer, but this is more consistent with an effect of under-ascertainment after age 75 years.

This study has found that estimates of the incidence of bilateral breast cancer are subject to bias caused by an elevation in the incidence in the first year following diagnosis of the first breast cancer. This is most likely an effect of increased surveillance.

In this study, associations between the histology of the first breast cancer and the incidence of metachronous bilateral breast cancer were largely explained by differential surveillance effects. More importantly, when these surveillance effects were isolated, any remaining association between histology and bilateral breast cancer incidence could be explained by the different mixture of bilateral breast cancer histology. This suggests that there are likely to be different exposures responsible for infiltrating ductal carcinoma, lobular carcinoma, and medullary carcinoma.

In this study, bilateral breast cancer was found to increase the risk of breast cancer mortality.

Finally, the constant incidence of bilateral breast cancer suggests a final, discrete stage in breast carcinogenesis. If we assume that all women are at risk of breast cancer, then this study suggests that by age 75 to 79 years only half the women in the population have reached this final stage.

APPENDICES

Appendix A. Estimates of synchronous and metachronous bilateral breast cancer "incidence".

Author	Sample size	Synchronous Bilateral	Metachronous Bilateral	Comments
Kilgore (1921)	659	2.0%	3.6%	At least 3 years follow-up
McWilliams (1925)	3132	0.2%	4.7%	This study is a compilation of a large number of patients treated by a number of surgeons. The data were obtained via a questionnaire, but there is no description of average length of follow-up.
Harrington (1946)	6,318	1.0%	3.4%	At least 3 years follow-up. Among this group were 57, some of whom had their first operation performed elsewhere
Smithers et al. (1952)	1777	0.6%	2.4%	All new cases of breast cancer treated between 1937 and 1948.
Hubbard (1953)	264	1.1%	3.4%	The original series had 17 metachronous primaries recorded, 8 had had their first breast cancer treated elsewhere. Person-years were also calculated.
Guiss (1954)	1521	0.1%	1.0%	Appears also to have included in this series, patients treated for their second primary and having a "history of prior mastectomy".
Fitts and Patterson (1955)	724	1.8%	5.7%	Follow-up ranged from 1 to 13 years. The case series is described as consecutive, but does not specify that only women having a first breast cancer were included.
Kilgore et al. (1956)	1,200	-	2.6%	The cases series is poorly described. Patients with a second primary whose first was treated elsewhere were removed however.
Farrow (1956)	5,576	0.4%	3.2%	Included patients who had had their first breast cancer treated elsewhere.
Moertel and Soule (1957)	2,945	0.3%	3.7%	All patients treated by mastectomy between 1944 and 1953. Excluded some, but not all patients where the second breast cancer was treated elsewhere.
Treves and Holleb (1958)	549	0.4%	3.9%	The women in this study were all 35 years or younger at the time of their first breast cancer. Minimum follow-up was five years.

Appendix B. Estimates of proportion of synchronous bilateral breast cancer and incidence of metachronous bilateral breast cancer in the literature.

Author(s)	Location	Period	Number of women	Second primaries		Total Person-years	Incidence per 1000 person-years	Comments
				Synchronous	Metachronous			
Midler et al. (1952)	Strong Memorial and Rochester Municipal Hospitals	1926-52	941	-	25	4,645	5.4	Person-years were calculated from diagnosis of first cancer to death or loss to follow-up. Included some patients from outside the cohort. Excluded more than 50% of bilateral patients because of their diagnostic criteria.
Hubbard (1953)	Surgical Pathology Dept, University of Minnesota Hospitals	1932-39	267	3 (1.1%)	9	1,540.5	5.8	Person-years were calculated from diagnosis of first cancer to death, bilateral breast cancer diagnosis, or end of follow-up
Robbins and Berg (1964)	Memorial Hospital, New York	1940-43	1,458	4 (0.3%)	87	12,818	6.8	Person-years calculated at total persons in the series alive at the end of an interval plus one half of those leaving the series during the interval.
Haagensen (1971)	Columbia-Presbyterian Medical Center	1935-57	626	4 (0.6%)	36	6200.25	5.8	No mention of exactly how person-years were calculated, but they appear correct.
Schottenfeld and Berg (1971)	Memorial Sloan-Kettering Cancer Center, New York	1949-62	9,792	58 (0.6%)	248	40676.3	6.1	Person-years calculated from date of diagnosis, although no specific mention is made what person-years were calculated too.

Appendix B (cont.)

Author(s)	Location	Period	Number of women	Second primaries		Total Person-years	Incidence per 1000 person-years	Comments
				Synchronous	Metachronous			
Slack et al. (1973)	National Surgical Adjuvant Breast Project	1961-68	2,734	-	52	12,217	4.3	Person-years calculated as the number entering a particular follow-up interval. Stage I or II breast cancer, no evidence of distant metastases, aged 30 – 75 years.
McCredie et al. (1975)	London Clinic of the Ontario Cancer Treatment and Research Foundation	1953-71	1,489	-	88	Not provided	10.0	Synchronous bilateral breast cancers (within 6 months) excluded. Those developing local recurrence or distant metastases excluded. Person-years calculated as number entering the interval less half those lost to follow-up in that interval.
Schoenberg (1977)	Connecticut Cancer Registry	1935-64	18,010	0.6%	596	96,934.9	6.1	A large general study of multiple primary cancers, so the person-years may be slightly truncated as a result of this.
Mueller and Ames (1978)	Upstate Medical Center Cancer Registry, Syracuse, NY	1956-74	3,558	33 (0.9%)	96	Not provided	8-10	Very crude attempt at estimating incidence by comparing annual numbers of bilateral breast cancers with the survival curve of all breast cancer cases.
Sakamoto et al. (1978)	Cancer Institute Hospital, Tokyo	1946-75	3,365	12 (0.4%)	80	23,406	3.89	Person-years calculated using the method of 1964, but it is not clear that this was done. The rate calculated also incorrectly incorporated the simultaneous primaries into the calculation.

Appendix B (cont.)

Author(s)	Location	Period	Number of women	Second primaries		Total Person-years	Incidence per 1000 person-years	Comments
				Synchronous	Metachronous			
Prior and Waterhouse (1978)	Birmingham Regional Cancer Registry	1936-64	21,967	89 (0.4%)	310	91,233	3.4	Excluded second primaries were distant metastases were present at the time of diagnosis. It appears that the person-years were calculated as the number alive at the beginning of an interval of follow-up.
Donegan and Spratt (1979)	Ellis Fischel State Cancer Hospital	1940-58	704	-	15	4663	3.2	Some errors evident in this calculation. The person-years should be 3,307.5 and the number of second breast cancers, 14. Results in an incidence of 4.2 per 1000 person-years.
Bailey et al. (1980)	Royal Marsden Hospital	1969-80	911	17 (1.9%)	22	Not provided	8.2	No mention was made of how person-years were calculated, but the authors do mention that the overall percentage was often confused with incidence.
Rosselli Del Turco et al. (1982)	Florence	1969-80	2311	28 (1.2%)	40	9141	4.4	No definition of how person-years was calculated
Hankey et al. (1983)	Connecticut Tumor Registry	1935-75	27,175	excluded	1,544	Not provided	7.1	Person-years calculated from diagnosis of first breast cancer to the date of bilateral breast cancer, death, or date of last follow-up. I can estimate the person-years to be 217,158.9.
Burns et al. (1984)	Breast Cancer Registry, Alberta.	1971-79	2,231	48 (2.2%)	39	6,013	6.4	Appears that person-years were calculated as the number alive at the beginning of an interval of time.

Appendix B (cont.)

Author(s)	Location	Period	Number of women	Second primaries		Total Person-years	Incidence per 1000 person-years	Comments
				Synchronous	Metachronous			
Schenker et al. (1984)	Israel Cancer Registry	1960-77	12,302	?	246	?	1.1	No information on how person-years were calculated and in one graph is described as per 1000 breast cancer patients
Fisher et al. (1984)	NSABP Trial	1971-74	1,578	excluded	66	Not provided.	5-10	Stage I and Stage II invasive breast cancer cases. Incidence calculated as the average number diagnosed per year.
Chaudary et al. (1984)	Breast Cancer Unit, Guy's Hospital, London	1950-82	2,453	14 (0.3%)	40	5,241	7.6	4,656 women originally treated between 1950 and 1982, of whom 2,453 were observed in the interval 1980 to March 1982. 513 diagnosed in 1980 to March 1982. Included *in situ* lesions in the contralateral breast. Person-years calculated as the number alive at the beginning of an interval of time.
Hislop et al. (1984)	A Maxwell Evans Clinic, Vancouver, BC	1946-76	Over 9,000	100 (?%)	235	Over 45,000	3.8	A difficult paper to follow. Incidence appears to be calculated from a 5% sample of the original cohort. Unclear exactly how this was done.
Harvey and Brinton (1985)	Connecticut Tumor Registry	1935-82	41,109		1,927	271,524	7.1	This study was examining the occurrence of any second cancer not just breast, so the accumulation of person-years will not have terminated with the diagnosis of a second breast cancer.

Appendix B (cont.)

Author(s)	Location	Period	Number of women	Second primaries		Total Person-years	Incidence per 1000 person-years	Comments
				Synchronous	Metachronous			
Storm and Jensen (1986)	Danish Cancer Registry, Denmark	1943-80	56,237	-	1,840	345,573.5	5.3	The calculation of the person-years was well described.
Murakami et al. (1987)	Osaka Cancer Registry	1965-82	9,503	-	90	53,738	1.7	Another study looking at the occurrence of any cancer after diagnosis of breast cancer. Excluded 1,778 who died within 3 months and 150 who developed a second cancer within 3 months.
Robinson et al. (1993)	SEER database	1973-86	139,935	2454	3431	598,631	5.73	Cancers coded first or second in order of appearance in the database, this may mean that second breast cancers in the ipsilateral breast were classified as bilateral. No mention of exclusion of in situ breast cancers. Synchronous defined as within 6 months.
Healey et al. (1993)	Joint Center for Radiation Therapy, Harvard Medical School, Boston	1968-85	1,624	-	77	Not reported	6.8	Bilateral breast cancer defined as occurring 1 month or more after first breast cancer and before development of recurrence or distant metastases.
Gajalakshmi et al. (1998)	Cancer Institute, Chennai, India	1960-89	2,665	-	39	17,317	2.25	Only women who had survived at least one year after their first breast cancer were included. Person-years were calculated (correctly) from this time.

Appendix B (cont.)

Author(s)	Location	Period	Number of women	Second primaries		Total Person-years	Incidence per 1000 person-years	Comments
				Synchronous	Metachronous			
Vaittinen and Hemminki (2000)	Swedish Family-Cancer Database, Sweden	1970-96	72,096+ 1443 +2529	1056 (1.5%)	2,529	491,665	5.12	Synchronous defined as within 6 months. Person-years calculated correctly.
Chen et al. (2001)	Provincial Cancer Registry, Manitoba, Canada	1970-97	14,220	-	628	109,628.5	5.73	Women considered at risk of second primary 6 months after diagnosis of first breast cancer, therefore no synchronous bilateral breast cancers reported.

Appendix C. Age and Bilateral Breast Cancer – summary of results from previous studies

Author	Design	Sample size	Results	Comments
Robbins and Berg (1964)	Cohort study Recruited 1940-43	1,458 women with breast cancer	Incidence per 1000 person-years Age 20-29 8.06 30-39 8.69 40-49 8.33 50-59 6.30 60-69 4.33 70+ 4.97	Concluded that women who are pre-menopausal at the time of their first cancer are at greatest risk of a bilateral breast cancer and that it was reasonable to suspect that the second cancer had its origin in the pre-menopausal period.
Haagensen (1971)		622 women with breast cancer	Incidence per 1000 person-years Age <35 0.00 35-45 3.31 45-55 7.79 55-65 6.27 65+ 4.58 Average age Whole cohort 51.9 years MBBC 41.7 years	Concluded that there was no evidence of a relationship with age at first diagnosis. Suggestive of a peak incidence in the 45-55 age group. .
McCredie et al. (1975)	Cohort study, London Clinic of the Ontario Cancer Treatment and Research Foundation	1,489 women with breast cancer	Average age UBC 58 years MBBC 52 years	

Appendix C (Cont.)

Author	Design	Sample size	Results	Comments
Prior and Waterhouse (1978)	Cohort study Birmingham Regional Cancer Registry 1936-64	21,967 women with breast cancer	Plotted the age-specific incidence rates, but actual rates not provided elsewhere. Presented Observed / Expected Age O/E 15-44 5.3 45-59 3.0 60+ 1.0	Used age-specific rates of breast cancer to compute expected number. Concluded that maximum incidence of bilateral breast occurred in the youngest age group. There was an exponential decrease in risk with age. Possible explanations: exhaustion of a genetically susceptible population or previous exposure to a carcinogen on a single occasion or over a brief period. .
Bailey et al. (1980)	Royal Marsden Hospital	911 women with breast cancer, 39 of these with BBC	Mean Age at first diagnosis UBC 59 years SBBC 53 years MBBC 56 years	Concluded that there was no statistically significant difference in average age.
Adami et al. (1981)	Three northern regions of Sweden, Sept 1977 to Nov 1978	1351 consecutive cases of breast cancer, 67 with a prior breast cancer diagnosis	Mean age at first diagnosis UBC 63.5 years BBC 55.2 years	Concluded that bilateral breast cancer cases were younger than unilateral controls at the time of their first diagnosis and this could be explained simply because they live long enough for a second breast cancer to develop.
Rosselli Del Turco et al. (1982)	Institute of Radiology, Florence University Centre for Oncologic Study and Prevention, Florence	2,311 women with Breast cancer 1969-80	Mean age at first diagnosis All BC 57.3 years BBC 50.7 years	Concluded that lower average age of women who developed bilateral breast cancer could indicate a different biological behaviour in younger women.

Appendix C (Cont.)

Author	Design	Sample size	Results	Comments
Hankey et al. (1983)	Connecticut Tumor Registry	27,175 women with breast cancer 1935-75	Incidence per 1000 person-years Period 1935-59 Age at diagnosis of first breast cancer <45 6.96 45-54 6.09 55+ 5.30 Period 1960-75 Age at diagnosis of first breast cancer <45 10.05 45-54 8.11 55+ 7.58	Observed that risk of bilateral breast cancer was inversely related to age, but this was only apparent in the first 10 years after diagnosis of the first breast cancer. After 10 years there was no trend with age. For all ages, the risk of bilateral breast cancer was higher in the second period (1960-75) than in the first (1935-59).
Chaudary et al. (1984)	Cohort study Guys Hospital Jan 1980 – Mar 1982	4656 women with breast cancer treated since 1950	Incidence per 1000 person-years Age <30 0 30-39 29.76 40-49 12.18 50-59 5.95 60-69 7.71 70+ 4.03	Concluded that there was a definite correlation between age at first primary and risk of developing a second breast cancer. Argued that this was not an artefact of better survival. No inferences as to the cause of this increase in risk.
Storm and Jensen (1986)	Cohort study. Danish Cancer Registry	56,237 women with breast cancer, 1943-1980	Observed / expected <45 5.5 45-54 3.4 >55 2.1 Incidence per 1000 person-years <45 6.46 45-54 5.35 55+ 4.97	Concluded that relative risk was high at all ages but decreased with age. Examining this relative risk for the two younger age groups by time since diagnosis of the first primary, they found the difference in relative risk was maintained. Discussed implications of this. They considered genetic predisposition, but on the basis of earlier work examining family history, thought this unlikely. Considered exposure to exogenous risk factors in the younger age groups a possible explanation.

Appendix C (Cont.)

Author	Design	Sample size	Results	Comments
Horn and Thompson (1988)	Case-control Cases – bilateral breast cancers Controls – unilateral breast cancers	292 cases 264 controls	Age at first diagnosis, adjusted nulliparity, menopausal status, smoking, histology, radiotherapy, chemotherapy, time since diagnosis: ≤ 54 1.10 ≥ 55 1.00	No difference found and the authors concluded that age at initial cancer does not strongly influence risk of contralateral breast cancer
Bernstein et al. (1992)	Cohort study Women with breast cancer previously recruited into a case-control study.	4,660 women with a first breast cancer	Incidence rates /1000 py Age Group 20-24 0.00 25-29 7.04 30-34 12.02 35-39 6.94 40-44 6.08 45-49 6.70 50-54 5.83 55-54 9.36	Included *in situ* carcinomas in the contralateral breast. Analysis was conducted by comparing rate ratios. Three age groups used and rate ratios were larger in younger age groups than in older. Found an elevated risk in peri-menopausal women. Not statistically significant however Problems with limited follow-up – only between 4 and 6 years. Also a narrower age range of patients originally included
Brenner et al. (1993)	Cohort study Cancer Registry, Saarland, Germany	9,585 women with a first breast cancer	Compared percentages Bilateral Age All First Second ≤49 23.1 33.1 20.3 50-64 36.1 40.2 34.7 ≥65 40.6 26.7 45.0 Average Age at first diagnosis All BC 60.5 BBC 55.7	Concluded that the age distribution of bilateral breast cancer patients at the time of their second cancer was the same as the age distribution for all cancers. Bilateral breast cancer patients had their first cancer at younger ages on average than women with unilateral breast cancer. Concluded that younger women may differ from other women with breast cancer with regard to risk factors such as family disposition.

Appendix C (Cont.)

Author	Design	Sample size	Results	Comments
Robinson et al. (1993)	SEER database 1973-1986	139,932 women with breast cancer of whom 3431 had a metachronous breast cancer	A graph of the 'age-specific' incidence rates for metachronous bilateral breast cancer was presented, but the actual numbers not provided.	The authors concluded that the incidence was increased in younger women. These are not, I believe, age-specific incidence rates, however. They are the incidence rates by age of diagnosis of the first breast cancer – they are therefore crude incidence rates.
Healey et al. (1993)	Joint Center for Radiation Therapy, Harvard Medical Center, Boston	1,624 women treated for breast cancer between 1968-85	Cox proportional hazards regression to investigate time to development of metachronous bilateral breast cancer for AGE in decades RR 0.79 (0.62 – 1.01) Average Age at first diagnosis UBC 53 BBC 51	Concluded that younger age placed women at greater risk of developing bilateral breast cancer.
Broët et al. (1995)	Institut Curie, Paris	4748 women with breast cancer in whom 282 developed metachronous bilateral breast cancer	Kaplan-Meier survival analysis and Cox proportional hazards regression to investigate time to development of metachronous bilateral breast cancer. RR <55 1.36 (1.10 – 1.73) 55+ 1.00 Adjusted for lobular histology, chemotherapy, metastases, local recurrence.	Concluded that their estimate of the risk associated with younger age was in accordance with previous findings.

Appendix C (Cont.)

Author	Design	Sample size	Results	Comments
Gajalakshmi et al. (1998)	Cohort study Madras India 1960-89	2704 women	Relative rate ratios reported <45 years 20.2 45-54 years 9.8 55+ years 9.0 From data in paper, incidence rates can be determined <45 years 1.49 45-54 years 2.29 55+ years 2.55	Large number of exclusions, including those with cancers at other sites, those with bilateral breast cancer within one years of first, those who had not completed one modality of treatment for fist breast cancer, those who did not survive one year. Age specific rates were age-standardized to world pop. No explanation as to why this was done. Rate ratios were doubled to reflect only one breast at risk. Concluded that younger age group is at higher risk, but did not calculate the incidence rates themselves. These show lower incidence in the youngest age group. Their incidence data for breast cancer overall, also show a lower risk for youngest age group.
Abdalla et al. (2000)	Cohort Study University of Chicago Hospitals	2136 women with breast cancer 1927-87	Mean Age at first diagnosis UBC 54.7 BBC 51.7	Age was the only major difference between UBC and BBC patients found in this study. Concluded that the greater risk experienced by younger women was due to their greater cumulative incidence rather than any inherent tendency to develop breast cancer.
Chen et al. (2001)	Cohort Study Manitoba Cancer Registry	14,220 women with breast cancer 1970-1997	Incidence per 1000 person-years Age <40 6.47 40-49 5.77 50-59 4.96 60-69 6.58 70-79 5.53 80+ 4.79	While incidence rate in younger age groups was not elevated, the rate relative to the rate of first breast cancers was. Discussed genetic predisposition as possible reason for this. Possible greater prevalence of BRAC1 in younger women (1995) and higher associated risk of contralateral breast cancer in women with BRCA1 (2000). Also considered effect of radiation with larger risk associated with exposure in younger women (1992).

Appendix C (Cont.)

Author	Design	Sample size	Results		Comments
Bernstein et al. (2003)	Cohort study	352,413 women with breast cancer registered in the SEER database, 1973 to 1998	Age specific incidence rates per 1,000 person-years of bilateral breast cancer by (age at second primary) Age 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80-84 85+	 8.3 8.7 9.2 8.1 7.0 6.9 6.0 6.0 6.3 7.1 7.2 7.2 6.4 5.0	Incidence rates higher in younger women. This observation, together with other age related differences in incidence by tumour characteristics and other risk factors, led the authors to conclude that younger women were more likely than older patients to represent gene carriers especially predisposed to second primary breast cancer.

Appendix D. Age at Menarche, Parity, Age at Menopause and Bilateral Breast Cancer – summary of results from previous studies.

Author	Design	Sample size	Results		Comments
Adami et al. (1981)	Case-control Cases diagnosed bilateral breast cancers; controls unilateral breast cancers	66 cases women with a history of prior breast cancer 1285 controls, (no history) No matching of cases and controls.	Parity 0 1 2 3+ Age at first birth Nulliparous <20 20-29 30+	 1.00 1.06 0.47 0.82 1.00 0.43 0.72 1.01	No odds ratios were calculated, so I computed those shown to the left. For parity there was no statistically significant association with parity or with age at first birth.
Hislop et al. (1984)	Matched Case-Control study	275 cases of bilateral breast cancer matched to unilateral cases by age, year of diagnosis and alive at time of diagnosis of the matched case	Age at first birth Metachronous <25 25+ Synchronous <25 25+	 1.0 1.5 1.0 2.7	Neither result was statistically significant. Nulliparous women were excluded from the comparison. The authors provided no comment on the results.
Kato et al. (1986)	Matched Case-Control study	61 pairs matched on age, time of diagnosis, and survival	Age at first birth Nulliparous, or 26+ <26	 0.60 1.00	A protective effect, but not statistically significant.

Appendix D (Cont.)

Author	Design	Sample size	Results	Comments
Horn and Thompson (1988)	Case-control Cases – bilateral breast cancers Controls – unilateral breast cancers	292 cases diagnosed with BBC between 1975 and 1983 264 controls diagnosed with breast cancer after 1935, but alive at recruitment. No matching	Adjusted age, family history, nulliparity, menopausal status, smoking, histology, radiotherapy, chemotherapy, time since diagnosis appropriate Age at menarche ≤ 12 0.9 ≥ 13r 1.0 Age at first birth ≤ 24 1.0 25-29 1.1 ≥ 30 0.5 Menopausal status Pre 0.7 Post 1.0 Parity Nulliparous 1.1 Parous 1.0	None of these results are statistically significant. There is weak support for the decrease in risk for older age at first birth in the literature (1981; 1986). The authors did not discuss the other results. The authors concluded that because the confidence interval around the nulliparous effect (0.6 – 1.7) did not exclude the 50% increase in risk that this exposure has on the development of an initial breast cancer, they could not draw firm conclusion about its effect on development on a bilateral breast cancer was different from its effect of development of a first breast cancer.
Bernstein et al. (1992)	Cohort study Women with breast cancer previously recruited into a case-control study.	4,660 women with a first breast cancer	Parity Nulliparous 1.12 Parous 1.00 Oral contraception use Yes 0.91 No 1.00	The authors concluded that while parity may be associated with risk of first breast cancer, it did not appear to be related to the incidence of bilateral breast cancer. While at the time of this study oral contraception use was suspected to be associated with breast cancer incidence, the authors could find no significant association with bilateral cancer risk.

Appendix D (Cont.)

Author	Design	Sample size	Results	Comments
Ursin et al. (1992)	Matched Case-control pre-menopausal bilateral breast cancer Controls – unaffected sisters	149 cases 243 controls	Oral contraception use Yes 1.7 No 1.0	After adjustment for age the use of oral contraception was found to be associated with bilateral breast cancer. Women taking oral contraception were 70% more likely to have bilateral breast cancer than women without breast cancer. This study is different from other case-control studies reviewed here because it compares cases to unaffected controls. Thus it could find risk factors for breast cancer rather than risk factors for bilateral breast cancer *per se*. This paper and those by 1996 and by 1997 all come from the same study.
Cook et al. (1996)	Case-control Cases diagnosed bilateral breast cancer Controls unilateral breast cancers matched on age and stage	211 cases 416 controls who were alive at the time of the case diagnosis and matched on year, age and stage of first breast cancer	Parous – pre-menopausal Yes 0.96 No 1.00 Parous – post-menopausal Yes 0.85 No 1.00 Parous – overall Yes 0.89 No 1.00	No significant effect. Authors concluded that there was a suggestion of a protective effect in post-menopausal women.
Haile et al. (1996)	Matched Case-control Cases – pre-menopausal bilateral breast cancer Controls – unaffected sisters	144 cases 232 controls	Age at first birth Nulliparous 1.6 <20 1.0 (ref) 20-25 1.2 25+ 1.8	Concluded that, apart from the imprecision of their estimates, reproductive factors associated with breast cancer also appeared to be risk factors for pre-menopausal bilateral breast cancer.

Appendix E. Family History and Bilateral Breast Cancer – summary of results from previous studies

Author	Design	Sample size	Results	Comments
Harris et al. (1978)	Cohort Study	198 familial breast cancer patients from 75 breast cancer-prone pedigrees	Life-tables were used to determine the cumulative risk of bilateral breast cancer, which was then modelled using curvilinear regression. Found an annual increase in risk of bilateral breast cancer of 1.6% per year for the first 6 years, a period of no increase for 7 years, followed by a period where the risk began to increase again by 5.9% per year.	They concluded that carcinogenesis did occur independently in both breasts and that the disease free period implied a host response. A more likely explanation is that the effect is a chance observation and that the decision to use a curvilinear model was data driven. There is no evidence that this model improved fit over a simple linear model or indeed if such a test was done. The cumulative risk observations to which the model was fitted are not independent, but correlated, and the patients used to derive these cumulative risk estimates are not independent, but related.
Hislop et al. (1984)	Matched Case-Control study	275 cases of bilateral breast cancer matched to unilateral cases by age, year of diagnosis and alive at time of diagnosis of the matched case	Family History in mother or sister Metachronous Yes 3.1 No 1.00 Synchronous Yes 1.6 No 1.00	The authors found a family history of breast cancer was related to metachronous bilateral breast cancer, but not synchronous bilateral breast cancer. They offered no interpretation for this difference.
Kato et al. (1986)	Matched Case-Control study	61 pairs matched on age, time of diagnosis, and alive at time of diagnosis of the matched case	Sibling history of breast cancer Yes 2.57 No 1.00	While not statistically significant, it was suggestive of an effect.

Appendix E (Cont.)

Author	Design	Sample size	Results	Comments
Adami et al. (1981)	See above	See above	Family history Yes 1.29 No 1.00	Family history defined as breast cancer in any first degree relative. The observed association was not statistically significant.
Anderson and Badzioch (1985)	Cohort Study	566 patients with breast cancer	Cumulative Risk of bilateral breast cancer Pre-menopausal (<50) Family History Mother At 5 years 13.0% At 10 years 26.5% Sister At 5 years 13.3% At 10 years 33.2% 2nd Degree relative At 5 years 9.1% At 10 years 24.8% Post-menopausal (50+) Mother At 5 years 12.2% At 10 years 18.2% Sister At 5 years 5.6% At 10 years 7.7% 2nd Degree relative At 5 years 8.3% At 10 years 8.5%	Concluded that a family history together with an early, pre-menopausal diagnosis increased the risk of a subsequent diagnosis of bilateral breast cancer. They discussed Harris's assertion that host defence mechanisms had an inhibitory effect on development of bilateral breast cancer in pre-menopausal women (1978). They found no support for this. They also thought that such mechanisms were unlikely given current theories for explaining the difference between hereditary and non-hereditary cancers such as Knudson's two-stage model (1971).
Horn and Thompson (1988)	Case-control Cases – bilateral breast cancers Controls – unilateral breast cancers	292 cases 264 controls	Family history – adjusted for age, nulliparity, menopausal status, smoking, histology, radiotherapy, chemotherapy, time since diagnosis: None 1.0 Mother 1.7 Sister 3.2 Both 2.5	Family history defined as breast cancer in any first degree or second degree relative. The authors concluded that there was a strong association with risk of bilateral breast cancer Concluded that the greater risk associated with having an affected sister rather than an affected mother could indicate genetic risk passed through the paternal line; a genetic susceptibility to breast cancer characterized by an earlier age at onset.

Appendix E (Cont.)

Author	Design	Sample size	Results	Comments
Bernstein et al. (1992)	Cohort study – women recruited into the Cancer and Steroid Hormone Study	4,660 women with breast cancer diagnosed between 1980-82	Family history – adjusted for age, age at first birth, nulliparity, age at menarche, menopausal status, stage and lobular histology of first primary, BMI: RR 95%C.I. None 1.00 (ref) Mother 1.35 0.76-2.41 Sister 2.91 1.51-5.62 Both 2.36 0.58-9.63 Aunt 1.68 1.11-2.55 Grandmother 0.43 0.14-1.36 Age at onset Mother None 1.00 (ref) ≤ 45 2.35 1.02-5.43 > 45 1.04 0.53-2.04 Sister None 1.00 (ref) ≤ 45 3.36 1.62-6.98 > 45 2.01 0.75-5.77 Laterality Mother None 1.00 (ref) Unilateral 1.07 0.56-2.07 Bilateral 2.55 1.02-6.35 Sister None 1.00 (ref) Unilateral 3.35 1.74-6.49 Bilateral 0.93 0.13-6.69	This study demonstrated strong patterns of association between various measures of family history of breast cancer and risk of bilateral breast cancer. One of the most interesting findings was the age-related risk of bilateral breast cancer compared to the age-related risk of unilateral breast cancer. In women with a first degree relative with breast cancer, the risk of first breast cancer declined with age. The risk of bilateral breast cancer did not, however, alter with age and was approximately double the risk of women with no exposed first degree relative at all ages.

Appendix E (Cont.)

Author	Design	Sample size	Results	Comments
Cook et al. (1996)	Case-control Cases diagnosed bilateral breast cancer Controls unilateral breast cancers matched on age and stage	211 cases 416 controls who were alive at the time of the case diagnosis and matched on year, age and stage of first breast cancer	Family history – pre-menopausal Yes 1.88 No 1.00 Family history – post-menopausal Yes 1.85 No 1.00 Family history – overall Yes 1.86 No 1.00	Family history defined as breast cancer in any first degree relative (mother or sister). Statistically significant for post-menopausal effect and for overall effect. With affect mother: OR = 1.29 (0.66 – 2.52) With affected sister: OR = 2.56 (1.29 – 5.05) With both: OR = 5.27 (0.97 – 28.8) Concluded that effect was consistent with results from studies of first breast cancer.

Appendix F. Obesity and Bilateral Breast Cancer – summary of results from previous studies

Author	Design	Sample size	Results	Comments
Kato et al. (1986)	Matched Case-Control study	61 pairs matched on age, time of diagnosis, and survival	Weight <60kg 1.00 60+kg 3.01	Weight was associated with the risk of bilateral breast cancer and after stratification by menopausal status, the effect was more pronounced in post-menopausal women and only a weak association in pre-menopausal women.
Horn and Thompson (1988)	Case-control Cases – bilateral breast cancers Controls – unilateral breast cancers	292 cases 264 controls	Quetelet index <34 1.0 35+ 1.2	Not significant. The authors concluded that while body build is associated with the risk of an initial breast cancer it was not associated with the risk of a bilateral breast cancer.
Bernstein et al. (1992)	Cohort study Women with breast cancer previously recruited into a case-control study.	4,660 women with a first breast cancer	Relative risks Quetelet index <1.86 1.00 1.86-2.15 0.77 >2.15 0.91	Not significant association.
Cook et al. (1996)	Case-control Cases diagnosed bilateral breast cancer Controls unilateral breast cancers matched on age and stage	211 cases 416 controls who were alive at the time of the case diagnosis and matched on year, age and stage of first breast cancer	Body Mass Index (BMI) Menopausal Status Age / Pre / Post / All <22 1.00 1.00 1.00 22-24 0.81 1.25 1.19 25-29 1.15 0.76 0.96 30+ 2.25 0.61 0.98	Nothing statistically significant. A suggestion of a trend in pre-menopausal women.

Appendix G. Stage of First Breast Cancer and Bilateral Breast Cancer: summary of results from previous studies

Author	Design	Sample size	Results	Comments
Haagensen (1971)		622 women with breast cancer of whom 36 developed bilateral breast cancer.	Incidence rates per 1000 person-years by stage A 6.23 B 5.23 C 3.07 D 0.00	Bilateral breast cancers in first 6 months regarded as synchronous. Concluded that incidence was directly related to stage of the first primary. Interpreted this as women with early stage breast cancers lived longer, therefore had greater chance of getting a second primary and therefore higher incidence rate.
Slack et al. (1973)	Cohort study of patients recruited into the National Surgical Adjuvant Breast Project.	2,734 women with breast cancer of whom 52 subsequently developed bilateral breast cancer.	Incidence rates (per 1000 person-years) Tumour size (cm) 0.1-1.9 2.51 2.0-2.9 4.67 3.0-3.9 3.04 4.0-4.9 6.10 5.0-5.9 6.29 6.0-6.9 13.18 7.0+ 12.32 Nodal involvement (number of positive nodes) 0 5.32 1-3 4.26 4+ 6.23	Women with Stage 1 or Stage 2 breast cancer aged between 30 and 75 years. Concluded that incidence was much greater in women with initial large tumours (>6cm). If metastases were being misclassified as second primaries, then it would be expected that the incidence would be higher for node positive initial tumours. This did not appear to be the case as the differences by nodal status were small.
Hankey et al. (1983)	Cohort Study Connecticut Tumor Registry 1935 to 1975	27,175 women diagnosed with a breast cancer. Excluded those with metastatic disease.	Incidence rates (per 1000 person-years) Node Negative 6.37 Node Positive 8.43	Excluded women with distant metastatic disease at first diagnosis. The authors noted that the relationship with stage would be expected if metastatic disease were being misclassified, but differential effects with age were difficult to explain. They thought these effects were unlikely to be due to differences in intensity of follow-up or problems with diagnosis. Concluded that node involvement in younger women could possibly indicate genetic predisposition.

Appendix G (Cont.)

Author	Design	Sample size	Results	Comments
Storm and Jensen (1986)	Cohort study Danish Cancer Registry	56,237 women with breast cancer, 1943-80. 1840 bilateral breast cancers.	Observed/Expected by age group for women having radiotherapy (R) or no radiotherapy (NR) (first 5 years excluded) Local stage R NR <45y 5.1 3.8 45-54y 3.5 2.1 55+y 2.3 1.0 Regional stage <45y 6.0 0.0 45-54y 4.2 4.3 55+y 2.3 0.9 Distant stage <45y 20.0 0.0 45-54y 5.0 10.0 55+y 5.8 2.9	Concluded that stage was a weak risk factor for bilateral breast cancer and a significant factor in young women who had received radiotherapy for their first breast cancer.
Horn and Thompson (1988)	Case-control Cases – bilateral breast cancers Controls – unilateral breast cancers	292 cases 264 controls	Stage of first breast cancer, adjusted for age, family history, histology, radiotherapy, chemotherapy and time since diagnosis. 0 1.83 I 1.0 II 0.8 III 1.0	Included in situ breast cancers. Excluded cases (bilateral breast cancers) if ipsilateral chest wall recurrence or distant metastatic disease present at time of diagnosis. Controls were not matched but time since first diagnosis was used in analysis. Cases diagnosed between July 75 and Dec 1983. This period divided into 6 intervals and controls picked from within these. The mid-point of each interval was used to calculate time since first diagnosis for controls. No relationship with stage of the first breast cancer was found.

Appendix H. Histology and Bilateral Breast Cancer – summary of results from previous studies

Author	Design	Sample size	Results	Comments
Robbins and Berg (1964)	Cohort study Recruited 1940-43	1,458 women with breast cancer	Incidence per 1000 person-years Medullary Carcinoma 7.67 Colloid Carcinoma 8.96 Lobular Carcinoma 9.79 Comedocarcinoma 10.13	These rates were based on small numbers of bilateral cases: Medullary (5 cases); Colloid (4 cases); Lobular (10 cases); and Comedocarcinoma (8 cases). While acknowledging their lack of statistical significance, the authors suggested that the increased rates associated with lobular and comedocarcinomas might be real.
Lewison and Neto (1971)	Cohort study Recruited between 1964 and 1968	490 women with breast cancer in whom 42 cases of bilateral breast cancer developed.	Proportion developing bilateral breast cancer during follow-up. All patients 8.6% Excluding lobular carcinoma 7.3%	This is a quite small study reporting prevalent proportions of patients who developed bilateral breast cancer during an unspecified period of follow-up. Very little can be drawn from this.
Lagios et al. (1980)	Histology study	211 mastectomy samples from 204 patients 7 SBBC 20 MBBC	Tubular carcinoma associated with bilateral carcinoma Tubular Total BBC 6 (22%) 27 UBC 10 (5.4%) 184 Total 16 (7.6%) 211	This is a confusing study. There are 204 patients and 211 mastectomy samples, yet 27 patients apparently had bilateral breast cancer. This should give 231 mastectomy samples. It also appear that all the mastectomy samples were analysed as if they were independent and those identified as BBC are the second breast cancers.
Hislop et al. (1984)	Matched Case-Control study	275 cases of bilateral breast cancer matched to unilateral cases by age, year of diagnosis and alive at time of diagnosis of the matched case	First primary lobular MBBC Yes 1.00 No 1.00 SBBC Yes 4.3 No 1.00	No association found for metachronous bilateral breast cancer, but a strong association with synchronous bilateral breast cancer, defined in this study as within 1 year of the first breast cancer.

Appendix H (Cont.)

Author	Design	Sample size	Results	Comments
Horn et al. (1987)	Case-control study	338 cases of bilateral breast cancer; 338 random controls with breast cancer; 336 controls frequency matched on age at first diagnosis and time since first diagnosis.	First primary lobular Crude odds ratios Random controls No 1.0 Yes 2.4 (1.3 – 4.5) Matched controls No 1.0 Yes 3.4 (1.7 – 7.1) Adjusted for age, time since diagnosis, stage, race, marital status, radiotherapy, chemotherapy Random controls No 1.0 Yes 2.2 (1.2 – 4.2) Matched controls No 1.0 Yes 3.4 (1.7 – 6.9)	Concluded that lobular histology was associated with a statistically significant increase in the risk of bilateral breast cancer. An increase in risk that remained after adjustment for other factors. They hypothesized that this risk might reflect differences in the biology or aetiology of lobular carcinoma. No apparent time-interval for synchronous bilateral breast cancer used.
Horn and Thompson (1988)	Case-Control study Cases – bilateral breast cancers Controls – unilateral breast cancers	292 cases 264 controls	First primary lobular Adjusted for age, family history, stage, radiotherapy, chemotherapy, time since diagnosis No 1.0 Yes 1.8 (1.0 – 3.5)	The authors concluded that lobular carcinoma was associated with an increased risk of bilateral breast cancer, the effect remained after adjustment for other risk factors, and it did not seem to alter with time since first breast cancer. They tested this by fitting an interaction between lobular histology (Y/N) and time since first cancer diagnosis. They reported the interaction multiplier (0.7) which was not statistically significant, hence their conclusion of no change in the effect of lobular histology over time.

Appendix H (Cont.)

Author	Design	Sample size	Results	Comments
Bernstein et al. (1992)	Cohort study	4,660 women with a first breast cancer	First primary lobular Rate ratios Yes 1.96 No 1.00	The authors concluded that the risk associated with lobular histology of the first breast cancer was consistent with findings from previous studies.
de la Rochefordiere et al. (1994)	Descriptive study of synchronous bilateral breast cancers	149 women with synchronous bilateral breast cancer	5 women with lobular carcinoma in both breasts compared to 1 expected.	While this excess of bilateral lobular carcinomas was not statistically significant (p=0.06), it was very close. The authors concluded that lobular carcinoma in both breast of the same women occurred slightly more frequently than one would expect by chance alone.
Broët et al. (1995)	Cohort study	4,748 women with breast cancer, 282 with metachronous bilateral breast cancer	Lobular Carcinoma Relative risk Yes 1.50 (1.05 – 2.18) No 1.00 Adjusted for age (<50;50+) and chemotherapy	Used Cox proportional hazards regression to estimate increase in risk associated with lobular histology.
Cook et al. (1996)	Nested case-control study Cases diagnosed bilateral breast cancer Controls unilateral breast cancers matched on age and stage	211 cases 416 controls who were alive at the time of the case diagnosis and matched on year, age and stage of first breast cancer	Initial breast cancer histology Lobular Pre-menopausal 95% CI Yes 2.15 (0.58 – 7.88) No 1.00 Post-menopausal Yes 1.32 (0.65 – 2.67) No 1.00 Overall Yes 1.47 (0.79 – 2.74) No 1.00	Bilateral breast cancers selected if diagnosed more than 6 months after the first breast cancer. No statistically significant effects. Suggestion of effect in pre-menopausal women but not post-menopausal.

Appendix H (Cont.)

Author	Design	Sample size	Results	Comments
Newman et al. (2001)	Case-control study	70 cases of bilateral breast cancer and 70 controls (unilateral breast cancer) matched on age and survival interval	Found no difference between unilateral and bilateral cases with regard to histology. No odds ratios presented, only percentages.	This study was quite small and, while matching was used in the design, no method was used to take this into account during the analysis. Synchronous (within 6 months) and metachronous were combined.
Li et al. (2003)	Cohort study	1,285 pre-menopausal women (aged < 45) previously recruited in two case-control studies.	Relative risk of bilateral breast cancer estimated by proportional hazards model. Ductal 1.0 Medullary 0.9 (0.2-3.6) Lobular 0.7 (0.2-2.3) Other 0.9 (0.5-1.6)	Bilateral breast cancers were defined as occurring more than 6 months after initial breast cancer. No effect for lobular carcinomas was found.
Bernstein et al. (2003)	Cohort study	352,413 women with breast cancer registered in the SEER database, 1973 to 1998	Age specific incidence rates per 1,000 person-years of bilateral breast cancer by histology of first breast cancer. Age of bilateral breast cancer Age 20-44 45-59 60+ Ductal 7.3 6.1 6.6 DCIS 5.3 6.6 7.6 Medullary 11.7 6.6 6.7 Lobular 9.8 7.1 7.1 Other 8.1 6.1 6.6	Bilateral breast cancers were defined as occurring after 6 month from diagnosis of the first breast cancer. Higher rates for lobular carcinoma were observed in each age-group, but also for medullary carcinoma in the youngest age group.

Appendix I. Hormone Receptors and Bilateral Breast Cancer – summary of results from previous studies

Author	Design	Sample size	Results	Comments
Horn and Thompson (1988)	Case-control study		Adjusted for age, exogenous oestrogen exposure, family history, histology, stage, radiotherapy, chemotherapy, time since diagnosis. Oestrogen Receptors Positive 0.8 (0.3 – 2.0) Borderline 0.7 (0.1 – 2.9) Negative 1.0 Progesterone Receptors Positive 3.2 (1.0 – 9.5) Borderline - Negative 1.0	While no effect was found for ER positive first breast cancers, an elevated risk was associated with positive PR. This was however only evident in the first year after diagnosis (OR=7.8) and not for bilateral breast cancers diagnosed after one year (OR=0.4).
Mariani et al. (1997)	Cohort study	1,763 women with node-negative breast cancer	Relative risk of bilateral breast cancer using Cox proportional hazards regression. Log(ER) * Age <45 0.54 46-55 1.27 55+ 1.10 Log(PR) * Histology Ductal 1.64 Lobular 0.58 Intraductal 2.25 Other 1.00	The results in this paper were presented in a rather confusing manner. The logged values of ER and PR were modelled. Interactions between ER and age group were found and between PR and Histology. It would appear that ER+ tumours are protective for bilateral breast cancer in younger women and only slightly associated with bilateral breast cancer in older women. PR+ lobular tumours appear protective for bilateral breast cancer.

Appendix I (Cont.)

Author	Design	Sample size	Results	Comments
Li et al. (2003)	Cohort Study	1,488 women with breast cancer previously recruited into two prior case-control studies. Only 907 had tumour marker data recorded.	Cox proportional hazards regression used to estimate risk of BBC diagnosis ER + 1.0 - 0.8 (0.5-1.5) PR + 1.0 - 1.0 (0.6-1.8) adjusted for age and year at diagnosis, AJCC stage, chemotherapy	Found no association between ER and PR levels and risk of bilateral breast cancer. Concluded that this could be due to small size of the study and hence lack of power.

Appendix J. Chemotherapy and Bilateral Breast Cancer – summary of results from previous studies

Author	Design	Sample size	Results	Comments
Bernstein et al (1992)	Cohort study	4,660 women with a first breast cancer	Chemotherapy For first breast cancer Yes 0.56 No 1.00	Found a protective effect for chemotherapeutic treatment of the first breast cancer.
Early Breast Cancer Trialists' Collaborative Group (1998)	Meta-analysis of 55 randomised controlled trials	36,689 women with breast cancer	Relative risk of bilateral breast cancer for tamoxifen use by years since first breast cancer 1 year 0.87 2 years 0.74 5 years 0.53	The authors concluded that 5 years use of tamoxifen almost halves the incidence of bilateral breast cancer. The reduction in risk was apparently independent of age (<50 years, 50+ years) and also independent of the ER status of the first primary. The authors also reported in passing the bilateral breast cancer incidence in Japan, since one quarter of the women analysed were in Japanese trials. The rate was 2 per 1,000 person-years.
Horn and Thompson (1988)	Case-control Cases – bilateral breast cancers Controls – unilateral breast cancers	292 cases 264 controls	Chemotherapy For first breast cancer Yes 0.3 No 1.0 Ever Yes 0.4 No 1.0	Both effects statistically significant
Cook et al. (1996)	Case-control Cases diagnosed bilateral breast cancer Controls unilateral breast cancers matched on age and stage	211 cases 416 controls who were alive at the time of the case diagnosis and matched on year, age and stage of first breast cancer	Chemotherapy for initial breast cancer Overall Yes 0.84 No 1.00 Pre-menopausal / Post-menopausal Yes 0.84 / 0.84 No 1.00 / 1.00	While there is some suggestion of a protective effect, the confidence intervals are very wide and nothing is statistically significant. Authors concluded that there was a suggestion of reduced risk particularly in the first few years following the initial breast cancer diagnosis

Appendix J (Cont.)

Author	Design	Sample size	Results	Comments
Gajalakshmi et al. (1998)	Cohort study Madras India	2704 women 1960-89	Relative rate, adjusted for reproductive factors, age at and stage of first breast cancer, family history, education, income, religion, radiotherapy, surgery, time since diagnosis. Chemotherapy for first breast cancer, Yes 0.5 No 1.0 Hormone therapy None 1.0 Oophorectomy or radio-castration 0.5 Oophorectomy or radio-castration plus hormone 0.2 Tamoxifen 0.2	The authors concluded that the reduction in incidence was in line with similar effects reported in other studies.

Appendix K. Radiotherapy and bilateral Breast Cancer – summary of results from previous studies

Author	Design	Sample size	Results	Comments
McCredie et al. (1975)	Cohort study, London Clinic of the Ontario Cancer Treatment and Research Foundation	1,489 women with breast cancer	Cumulative risk of bilateral breast cancer Interval: No Radiotherapy / Radiotherapy 1: 0 / .01 ±.1 2: .02 ±.1 / .02 ±.1 5: .04 ±.1 / .04 ±.1 10: .11 ±.4 / .08 ±.1 15: .17 ±.1 / .11 ±.2 20: .17 ±.1 / .23 ±.6	Concluded that there was no difference in cumulative risk of bilateral breast cancer between women treated with radiotherapy and those treated by surgery alone.
Storm and Jensen (1986)	Cohort study Danish Cancer Registry	56,237 women with breast cancer, 1943-1980	Observed/Expected number of bilateral breast cancers Radiotherapy for first breast cancer Yes 2.5 No 3.6	Women with missing information on radiotherapy were included in the no radiotherapy group. The authors concluded that the results supported the hypothesis that radiotherapy of the first breast cancer increased the risk of contralateral breast cancer in long term survivors.
Hankey et al. (1983)	Connecticut Tumor Registry	27,175 women with breast cancer 1935-75	Relative risk of bilateral breast cancer (Radiotherapy versus surgery only) Period 1935-59 Follow up (yrs): Node - / Node + 0-4: 1.4 / 1.3 5-9: 1.0 / 0.7 10-14: 0.9 / 1.2 15+: 0.8 / 0.9 Period 1960-75 0-4: 1.2 / 1.3 5-9: 1.2 / 1.0 10-14: 0.3 / 1.6 15+: – / –	Relative risks were calculated in intervals of time following the first breast cancer, but the authors no consistent pattern between the two cohorts in terms of the risk associated with radiotherapy treatment for the first breast cancer. They concluded that there was a marginal increase in long-term risk after 10 years for women in the latter cohort, but this based only very small numbers of bilateral breast cancers.

Appendix K (Cont.)

Author	Design	Sample size	Results	Comments
Basco et al. (1985)	Case-control study matched on age, year of diagnosis	194 women with contralateral breast cancer and 194 controls and survival time	Relative risk per 100cGy dose of radiotherapy Overall 0.99 Diagnosed < 5 y 0.94 Diagnosed 10+ y 0.83	The authors concluded that there was no evidence of a dose response overall nor was there any evidence after stratifying on the interval between the first and second breast cancer.
Horn and Thompson (1988)	Case-control Cases – bilateral breast cancers Controls – unilateral breast cancers	292 cases 264 controls	Radiotherapy for first breast cancer, adjusted for age, family history, histology, stage, chemotherapy, and time since diagnosis. Yes 1.3 No 1.0	No measurement of radiation dose was available for analysis, so radiotherapy was assessed simply as a binary variable. The results were not statistically significant. Controls were selected at random. Adjusting for time since diagnosis does not get around possible mortality effects that may be present.
Bernstein et al. (1992)	Cohort study Women with breast cancer previously recruited into a case-control study.	4,660 women with a first breast cancer	Relative risks (Cox model), adjusted for age, age at first birth, age at menarche, age at menopause, stage of first cancer, family history, nulliparity, menopausal status, lobular histology, Radiotherapy for first breast cancer Yes 1.19 (0.78 – 1.80) No 1.00	The authors concluded that there was no evidence of an increase in risk.
Boice et al. (1992)	Case-control study matched on age and year at first diagnosis, and survival	Cases were women who had a bilateral breast cancer more than 5 years after their first cancer. Controls.	Odds ratios Radiotherapy Yes 1.19 (0.94 – 1.50) No 1.00 By time after treatment No radiotherapy 1.00 5 – 9y 0.99 10-14y 1.98 ≥ 15y 0.93	An overall effect for radiotherapy was found, although not statistically significant. A dose-response was found for women first diagnosed at age < 45, but not for women first diagnosed at ages 45 and over. This interaction was not tested, however, so the results are suggestive rather than conclusive. The authors also considered that women who had already had a breast cancer may undergo greater surveillance, leading to earlier detection of radiation induced bilateral breast cancers.

Appendix K (Cont.)

Author	Design	Sample size	Results	Comments
Storm et al. (1992)	Case-control study matched on age, year of diagnosis and survival time	529 women cases (bilateral breast cancer) 8 or more years after their first breast cancer 529 controls	Radiotherapy for first breast cancer Odds ratio Yes 1.04 No 1.00 Time since radiotherapy treatment No radiotherapy 1.00 < 10 y 0.83 10 – 14 y 0.93 ≥ 15 y 1.23	The authors obtained radiation dosage information from patient case-notes and so were able to estimate dose-response estimates of relative risk. These showed no discernable trend with dose. They concluded that there was little or no effect of radiotherapy associated with contralateral breast cancer risk. Radiation dose was missing for a large portion of cases (25.3%) and controls (21.9%), but these were included in the modelling as a separate category (unknown).
Cook et al. (1996)	Case-control Cases diagnosed bilateral breast cancer Controls unilateral breast cancers matched on age and stage	211 cases 416 controls who were alive at the time of the case diagnosis and matched on year, age and stage of first breast cancer	Radiotherapy for initial breast cancer Pre-menopausal Yes 1.24 No 1.00 Post-menopausal Yes 1.36 No 1.00 Overall Yes 1.31 No 1.00	A suggestion of an effect, but once again, the confidence intervals are very wide and nothing is statistically significant. The authors concluded that while an elevated risk was apparent, the study was small, and the effect was limited to the first few years after diagnosis of the initial breast cancer.
Gajalakshmi et al. (1998)	Cohort study Madras India	2704 women 1960-89	Relative rate. Radiotherapy for first breast cancer, Yes 1.1 No 1.0	After adjustment for reproductive factors, age at and stage of first breast cancer, family history, education, income, religion, chemotherapy, surgery, time since diagnosis. No significant effect found, but radiation was only assessed as a binary variable. No dose data were available.

Appendix K (Cont.)

Author	Design	Sample size	Results			Comments
Gao et al. (2003)	Cohort Study. SEER data, 1973 to 1996	134,502 women with local invasive breast cancer and 18,895 women with ductal in situ carcinoma	Relative risk Radiotherapy vs. no radiotherapy By interval between 1st and second breast cancer			Women were excluded if they survived less than 3 months. Bilateral breast cancers diagnosed at autopsy or on a death certificate were included. Survival times were censored at occurrence of a second primary at another site.
			Overall	<5y 0.96 (0.88–1.04)	5+y 1.14 (1.03–1.26)	
			Age (y)	<5y	5+y	
			<45	0.98 (0.81–1.19)	1.32 (1.06–1.64)	
			45–55	0.94 (0.79–1.12)	1.02 (0.83–1.24)	
			>55	0.97 (0.87–1.08)	1.15 (1.01–1.32)	

Appendix L. Survival and Bilateral Breast Cancer – summary of results from previous studies

Author	Location Period	Sample size	Survival Method	Results	Comments
Harrington (1946)	Mayo Clinic 1910-40	6,318 women with breast cancer, 212 with metachronous BBC, and 62 with simultaneous BBC	All-cause mortality. Survival methods unclear. Survival calculated from date of diagnosis of the first primary.	5-year survival UBC 48% SBBC 29% MBBC 65%	Commenting on the better survival of women with metachronous BBC, the author noted that fewer women with metachronous BBC had metastases at diagnosis of their first breast cancer. He also indicated that the difference in survival could result from women with metachronous BBC having a period of survival before the second breast cancer developed.
Cliffton and Young (1951)	Tumor Registry, Yale University 1922-48	468 women with breast cancer, 5 with SBBC and 10 with MBBC	Five years follow-up on all patients Survival is the proportion alive at 5 years. Calculated from date of diagnosis of the first primary	5-year survival UBC 55% MBBC 70%	Concluded that metachronous bilateral breast cancer patients had a survival as least as good or better than unilateral breast cancer cases.
Guiss (1954)	Los Angeles County Hospital 1942-49	611 women treated for breast cancer plus an additional 314 private cases. 115 developed lesions in the second breast; all but 21 of these were excluded because they were considered metastatic disease.	Survival from all causes and estimated from the first breast cancer diagnosis	Survival 5 years 89% 5-10 years 69%	Considered the possibility that a second primary re-immunized the body or remobilised a control mechanism that enhanced control over disseminated cancer cells. Guiss, however, also thought it more likely that better survival was due to a selection process – women had to survival a period of time to get a metachronous BBC. Nevertheless, he concluded that women with metachronous BBC had a better survival than women with unilateral BC.

Appendix L (Cont.)

Author	Location Period	Sample size	Survival Method	Results	Comments
Farrow (1956)	Memorial Center for Cancer and Allied Diseases, 1940-1949	5,576 women with operable breast cancer, 93% followed up for at least 5 years. 21 synchronous BBC and 181 metachronous BBC	Survival from all causes and estimated from the date of the second breast cancer diagnosis.	5-year survival SBBC 14.0% 5 year survival MBBC Interval between 1st and 2nd breast cancer (years) 0-1 16.1% 1-2 11.1% 2-3 27.3% 3-4 31.3% 4-5 31.6% 5-10 65.4%	Included patients who had their first breast cancer treated elsewhere, but the second treated at Memorial Center. After computing survival on the basis of the interval between the two metachronous bilateral breast cancers, Farrow concluded that survival was considerably worse when the interval between the two cancers was less than 2 years and were considerably better when the interval was greater than 5 years.
Moertel and Soule (1957)	Mayo Clinic, 1944 – 54	2945 cases of breast cancer, 118 with synchronous BBC and 110 with metachronous BBC	Survival from all causes and estimated from the date of the second breast cancer diagnosis.	5-year survival UBC 60% MBBC 56%	Concluded that there was little difference in survival outcomes between those with or without bilateral breast cancer.
Robbins and Berg (1964)	Memorial Hospital, New York	1,458 women with breast cancer in whom 4 had synchronous BBC and 87 metachronous BBC	Actuarial survival analysis was used.	5-year survival UBC 62% MBBC 54% from date of second primary	The authors matched the bilateral with the unilateral group to obtain expected survival from the first cancer and expected survival from the second cancer. They found little difference. They then combined these to obtain expected survival overall. From this they concluded that the second cancer posed a significant and independent risk. They also noted that second cancers were usually found earlier and less aggressive which would improve survival.

Appendix L (Cont.)

Author	Location Period	Sample size	Survival Method	Results	Comments
Slack et al. (1973)	NSABP	2374 women with unilateral stage I or II breast cancer; 52 with metachronous BBC	Described a conventional life tables. Survival was calculated from date of diagnosis of the first primary.	I have estimated the following from a survival graph, since percentages not explicitly stated in the text. 5-year survival Node-negative UBC 82% BBC 88% Node positive UBC 52% BBC 48%	The authors discuss previous work that has shown that by taking survival from the first diagnosis, apparent differences in survival can be found that are not apparent when survival is taken from date of diagnosis of the second primary. Having acknowledged this, they still calculated survival from the first diagnosis because, they state, the follow-up period was short and the degree of bias will therefore be small. They concluded that in their series bilateral breast cancer did not pose an added risk.
Wilson and Alberty (1973)	Four teaching hospitals, Oregon, USA	119 cases of bilateral breast cancer; 39 synchronous and 80 metachronous	No description of survival methods provided, however, it is clear that survival was calculated from date of diagnosis of the first primary.	5-year survival Overall 73% SBBC 44% MBBC 98%	The authors noted that the metachronous groups had much better survival than expected given published survival estimates for unilateral breast cancer. They concluded that no single factor could account for this anomaly. They described as simplistic the notion that women with less aggressive tumours lived long enough to develop a second primary. They concluded, giving reference to a previous theory of 1954, that women who developed metachronous BBC were women with good host resistance.

Appendix L (Cont.)

Author	Location Period	Sample size	Survival Method	Results	Comments
Khafagy et al. (1975)	1949-59	4955 women with breast cancer, of whom 82 had bilateral breast cancer, the second cancer being diagnosis more than 5 years after the first.	Survival in the metachronous group was taken from diagnosis of the second primary. Survival; estimates are simply the proportion alive at 5-years and do not account for non-cancer deaths.	5-year survival by stage All stages All women 64% BBC 70% Localized All women 82% BBC 79% Regional All women 50% BBC 41%	This study was motivated by previous theories of host immunity or the possibility of mammary tumour viruses. Statistical significance of the survival differences were tested using χ^2 tests. No differences in survival were found and the authors concluded that any inference concerning immune response or a tumour antigen could only be regarded as conjectural.
Bailey et al. (1980)	Royal Marsden Hospital	911 with breast cancer of whom 36 had bilateral breast cancer, 17 of these SBBC	Actuarial survival estimates obtained, apparently of overall survival – this is not made explicit. For the metachronous group, survival was calculated from the first diagnosis and also the second.	Survival estimates were graphed but not explicitly stated in the text. I have taken the following from the graph, UBC 75% SBBC 60% MBBC 95%	The small numbers of second primary tumours make these somewhat inconclusive. Statistical testing was performed using χ^2 tests for trend which would be inappropriate. The authors concluded that any adverse effect of the first primary was offset by the earlier stage at diagnosis of the second primary.

Appendix L (Cont.)

Author	Location Period	Sample size	Survival Method	Results	Comments
Al-Jurf et al. (1981)	University of Iowa hospitals; 1931-77	5608 BC 104 BBC	5- and 10-year survivals were presented, the only reference to the method used was in a table footnote that stated 'actuarial survival'. Excluded women lost to follow-up.	5-year survival UBC 78% SBBC 38% MBBC 92% from diagnosis of first primary	Mean survival was presented as one main outcome – no indication as to how this was calculated. Censoring not explicitly described. End-point not explicitly stated, presumably death from any cause. Concluded that favourable outcome of metachronous group was due to less aggressive first primaries, allowing longer survival and greater risk of developing a second primary.
Schell et al. (1982)	MD Anderson Hospital 1947-76	126 bilateral breast cancers, of which 39 were synchronous.	Reference is made to the work of Berkson and Gage (for example: 1950; 1952), but how the survival analyses were performed is not clear.	5-year survival Unilateral 76% Synchronous 74% Metachronous 82% from diagnosis of first primary 20-year survival UBC 61% SBBC 60% MBBC 55% from diagnosis of first primary	The authors concluded that there was no change in survival rate associated with a second breast cancer.
Rosselli Del Turco et al. (1982)	Florence	2311 women with breast cancer, 68 with bilateral breast cancer (28 synchronous)	Survival analysis was conducted using actuarial methods.	5-year survival UBC 83% SBBC 81% MBBC 71%	In this study, although survival was taken from treatment of the first cancer, the metachronous group had poorer survival. The authors do not address this adequately. They suggest that a similar effect was found by Robbins and Berg (which is not the case).

Appendix L (Cont.)

Author	Location Period	Sample size	Survival Method	Results	Comments
Burns et al. (1984)	Alberta cancer registry; 1971-79	2231 women with breast cancer of whom 106 had bilateral breast cancer, 48 of these being synchronous.	Used censored survival curves used to determine survival (presumably from all causes) and disease free survival.	Survival was graphed, but no actual survival estimates were quoted in the text. These are derived from the graph. 5-year survival UBC 72% SBBC 70% MBBC 75% From date of second diagnosis	For synchronous primaries survival was calculated from the date of the second primary diagnosis. They found no significant difference in survival between synchronous, metachronous and unilateral cases. The authors, while comparing their results to those of others, drew no specific conclusions from their study.
Michowitz et al. (1985)	Tel-Aviv Medical Center	1215 women with breast cancer; in whom 66 developed a bilateral breast cancer, 6 of these were synchronous	Survival estimated crudely at 5 and 10 years as the proportion alive out of the number 'followed up'. This was only done for the bilateral cancers and 20 of these were apparently not in this analysis.	5-year survival MBBC 48% from first diagnosis 10-year survival MBBC 23% from first diagnosis	A very small and ultimately not very informative. The authors concluded that metachronous bilateral breast cancer patients had better survival because the longer a woman survived the more likely she was to develop a metachronous breast cancer.

Appendix L (Cont.)

Author	Location Period	Sample size	Survival Method	Results	Comments
Wanebo et al. (1985)	University of Virginia Medical Center, Charlottesville, Virginia	100 women with unilateral breast cancer compare to 37 with bilateral breast cancer	Survival taken from date of diagnosis of first breast cancer. Calculated by method of 1958.	5-year survival UBC 68% MBBC 89% from first diagnosis MBBC 61% from second diagnosis 10-year survival UBC 54% MBBC 63% from first diagnosis MBBC 23% from second diagnosis	The main aim of this paper was to advocate contralateral biopsy as an investigative means of detecting lesions in the opposite breast. Apart from comparing their survival estimates to those of others, the authors offered no new insights.
Fracchia et al. (1985)	Memorial Sloane-Kettering 1962-72	403 women with bilateral breast cancer of whom 129 of these synchronous. However of these only 246 were invasive bilateral cancers and 78 of these were synchronous.	Disease-free survival was calculated using the method of 1958 and statistical significance was assessed using the log rank test (1966). For metachronous cases, survival was taken from diagnosis of BBC.	Node Negative 5-year survival SBBC 79% MBBC 65% 10-year survival SBBC 67% MBBC 52% Node Positive SBBC 65% MBBC 33% 10-year survival SBBC 52% MBBC 28%	This study was conducted of a comparably small sample of patients. Most of the discussion of the results centred on the use of contralateral biopsy at the time of diagnosis of the first breast cancer.

Appendix L (Cont.)

Author	Location Period	Sample size	Survival Method	Results	Comments
Holmberg et al. (1988)	Cases originally recruited in a case-control study; Sweden 1977-78	1423 women with breast cancer.	Actuarial method used to calculate survival curves. Relative survival determined using the method of 1985. Proportional hazards regression (1972) used to investigate time interval between 1st and 2nd primary.	8-year survival UBC 54.4% MBBC 40.9% Relative survival 8-year survival UBC 69.4% MBBC 52.6% Time-dependent effect, adjusting for age, histopathology, axillary nodes RR 0.98 95% CI: 0.94 -1.00	This is the first study to make use of multivariate methods to infer the effect of the time interval between the two bilateral breast cancers on survival. The results imply that for metachronous bilateral breast cancers, the effect of the first primary on survival from the second primary diminishes as the interval between the two increases.
Pomerantz et al. (1989)	Northwestern Memorial Hospital, Chicago	187 women with breast cancer with at least two years follow-up; of whom 22 developed bilateral breast cancer.	Survival analysis was conducted using the 'standard life-table method'	The authors found 5-year survival in women with metachronous bilateral breast cancer to be approximately 60%.	Unclear how the data was set up for survival analysis since there is no explicit statement of how survival was calculated, but it appears that survival was calculated from diagnosis of the second primary. Similarly, there is no discussion of censoring so one is left to assume that it is survival to death from all causes that is being estimated.
Péloquin et al. (1992)	Nötre Dame Hospital; Montreal 1960-80	1510 BC 157 women who had had a previous cancer.	Survival analysis was done using the Lee-Dezu non-parametric test	5-year survival death from breast cancer history of BC Yes 87% No 68%	They found a better survival among women with a history of other cancers than those with breast cancer only.

Appendix L (Cont.)

Author	Location Period	Sample size	Survival Method	Results	Comments
Arriagada et al. (1992)	Institut Gustave-Roussy, France	2,850 women with early stage breast cancer recruited into two randomised controlled trials	Cumulative incidence rates estimated using method described in 1980, pp 168-171.	10-year cumulative incidence rates of contralateral breast cancer high risk pre-menopausal 4.2% high risk post-menopausal 4.5% low risk post-menopausal 5.6%	More an illustration of a method for including competing risks (multiple end-points) in the analysis than an analysis of bilateral breast cancer *per se*.
Robinson et al. (1993)	SEER database 1973-86	139,932 women with breast cancer of whom 2454 had a synchronous bilateral breast cancer and 3431 a metachronous breast cancer	For metachronous cases, survival was calculated from date of the second primary. Survival was estimated as the ratio of the observed survival to the expected derived from survival of the unilateral group. Multivariate analysis was conduced using Cox proportional hazards regression.	13-year survival Localized first primary BC 58.1% BBC 55.2% Regionally advanced first primary BC 32.5% BBC 9.5%	The authors found that in stage-specific analyses, survival from diagnosis of the second primary was shorter than for single tumours. This finding persisted after adjustment for age. No results from the Cox modelling were provided. The authors stated that the interval between primaries was not significant, but no details were provided as to how this was modelled. They concluded that survival differences were not due to the interval between primaries, but could be due to a more aggressive malignant potential, a possible effect of chemotherapy of radiotherapy of the first primary, or a genetic effect.

Appendix L (Cont.)

Author	Location Period	Sample size	Survival Method	Results	Comments
Mose et al. (1997)	Department of Radiotherapy and Radiooncology Westfälischee Wilhelms-Universität, 1977-82	498 women with breast cancer in whom 36 developed a metachronous bilateral breast cancer	Kaplan-Meier survival analyses were conducted using date of diagnosis of the first breast tumour	5-year survival BC 73% BBC 83%	The authors found no difference in survival between the two groups. They found considerable variance in results from previously published survival studies. They discussed their results in comparison to these and suggested that varying eligibility criteria could be responsible. They justifies measuring survival from the first diagnosis by quoting opinion that all metachronous bilateral breast cancers were really synchronous but not detectable tumours (1984).
Gajalakshmi et al. (1999)	Cancer Institute, Chennai, India, 1960-89	UBC 3163 women with unilateral breast cancer and 67 with metachronous breast cancer	Relative survival	5-year survival BC 51% BBC 47% 10-year survival BC 41% BBC 30%	Used relative survival (Hakulinen and Abeywickrama, 1985) taking survival from the date of diagnosis of the second primary for women with bilateral breast cancer. Multivariate analysis conducted using proportional hazards regression method for relative survival (Hakulinen and Tenkanen, 1987). The authors modelled the time interval between first and second primaries but gave no details as to how this was done. They found no effect.
Skowronek and Piotrowski (2002)	Greatpoland Cancer Center 1983-95	36 women with bilateral breast cancer	Kaplan-Meier survival taking survival from the date of diagnosis of the second primary for women with BBC.	5-year survival BBC 55.6% Time interval effect < 2y 0.00% 2 – 5y 42.9% > 5y 73.9%	The authors found that longer intervals between metachronous primaries were correlated with longer survival. However, this conclusion was drawn from an analysis that divided the time interval into 3 groups – the estimate in the first group is based on 6 women and on the second group, 7 women.

Appendix L (Cont.)

Author	Location Period	Sample size	Survival Method	Results	Comments
Bernstein et al. (2002)	All recruited from the Cancer and Steroid (CASH) Hormone case-control study	369 women with bilateral breast cancer	Cox proportional hazards regression was used for survival analysis. When data describing a factor (present or absent) was missing, the data were recoded to absent. Survival was estimated from diagnosis of the second breast cancer.	Relative risks: Age <35 1.59 35-44 1.07 45+ 1.00 Time interval (months) <6 1.19 6-11 2.25 12-59 1.92 60+ 1.00	The authors found: Young age at diagnosis of second primary was associated with higher risk of mortality. Shorter interval between primaries was associated with higher risk of mortality Late stage of either tumour was associate with poor survival. The study had a very small sample size for the number of variables that were examined. The fitting of an interaction term between race and income may possibly have been misinterpreted. Statistical significance was incorrectly reported – the significance of categories was reported rather than the significance of the whole factor.
Carmichael et al. (2002)	A district general hospital in UK 1963-99	1945 women with breast cancer in whom 92 had a bilateral breast cancer, 43 of these synchronous.	Kaplan-Meier survival taking survival from the date of diagnosis of the second primary for women with BBC. Cox proportional hazards regression was also used, but no results reported.	5-year survival UBC 88.7% SBBC 70.0% MBBC 76.7%	The authors found a that synchronous bilateral breast cancer patients were at greatest risk of mortality, but after adjustment for age, nodal status, grade and tumour size, the differences were no longer significant. They compared their results to those of other studies and conclude that in part, differences in results could be due to differences in definition of synchronous. Concluded that synchronous bilateral breast cancer was not an independent predictor of survival.

Appendix M. Survival studies of Bilateral Breast Cancer that employed time-dependent Cox proportional hazards regression.

Author	Location, Period	Sample Size	Results	Comments
Healey et al. (1993)	Joint Center for Radiation Therapy, Harvard Medical School	1,624 women with breast cancer in whom 77 developed metachronous bilateral breast cancer.	Relative risk of breast cancer death Unadjusted RR 1.20 (0.61 – 2.36) Adjusted RR for age, nodes, stage and adjuvant therapy 1.16 (0.59 – 2.28)	The authors did not find a statistically significant association with the occurrence of bilateral breast cancer and breast cancer death. They did, however, acknowledge that they may not have had the power to do so because of the relatively short overall length of follow-up in their cohort (5 years).
Black et al. (1996)	SEER database 1973 – 1990	138,962 women with breast cancer, *in situ* or malignant, diagnosed between 1973 and 1986	Survival to death from any cause Effect of bilateral breast cancer diagnosis adjusted for stage and age (fitted as a linear effect) Overall 1.56 Age<50 / Age 50+ Localised 2.53 / 1.35 Regional 2.64 / 1.41	Also modelled the time-dependent effects of second primary non-breast cancers. While presenting results for the effect of a diagnosis of a metachronous primary on death from all causes, the authors were principally concerned with the effect of in situ tumours. Consequently they did not discuss these results explicitly.
Heron et al. (2000)	Kimmel Cancer Center of Jefferson Medical College and the Thomas Jefferson University Hospital; 1960-95.	1465 women with breast cancer, of whom 47 had synchronous bilateral breast cancer, and 103 had metachronous bilateral breast cancer.	Survival to breast cancer death. Estimated the effect of synchronous occurrence (within 1 year) and metachronous occurrence (after one year). RR synchronous 1.32 (95%CI: 0.57 – 3.05) RR metachronous 1.33 (95% CI: 0.57 – 3.20) adjusted for age (<=65 and >65) and for stage Interval between primaries (years).	This analysis appears to have treated death from breast cancer as the end-point, but it is not clearly stated. Kaplan-Meier survival estimates are, however, what one would expect for breast cancer survival rather than all-cause survival. The authors excluded women who developed metastatic disease between the first and second breast cancer. This will bias survival estimates since it is a time-dependent exclusion and applies to only one group.

Appendix M (Cont.)

Author	Location, Period	Sample Size	Results	Comments
Abdalla et al. (2000)	University of Chicago hospitals, 1927-87	2136 with breast cancer, 23 with synchronous bilateral breast cancer and 109 with metachronous bilateral breast cancer	Relative risk of breast cancer death, RR = 1.46 (95% CI: 1.09 – 1.95) adjusted for age, tumour size, and nodal status.	Concluded that the occurrence of a bilateral breast cancer increased the risk of breast cancer death by 50% (RR=1.46). Attempted to estimate the effect associated with the interval between first and second breast cancer, but this is poorly described and may be erroneous. The results do not appear to have been derived from a time-dependent model. They found no effect.
Kollias et al. (2001)	Nottingham City Hospital; 1975 to 1995	3,210 women with breast cancer, 26 of whom had synchronous bilateral breast cancer and a further 80 developed metachronous bilateral breast cancer	Overall effect of a metachronous bilateral breast cancer diagnosis Relative risk 1.67 (1.08 – 2.56) By time to second primary 1-24 months 1.62 (0.84-3.17) 25-60 months 1.57 (0.74-3.32) > 60 months 1.85 (0.81-4.19)	These time-interval effects were obtained from a Cox model were they were modelled as time-dependent effects. The authors do not describe exactly how they did this, however. They concluded that the interval between primaries was not prognostic.

Appendix N. Morphology codes used to create broad histological grouping of malignant breast cancers.

Group	M-Code	ICD-O-2 Morphology Term
Infiltrating Ductal Carcinoma	8500	Infiltrating duct carcinoma Infiltrating duct adenocarcinoma Duct adenocarcinoma, NOS Duct carcinoma, NOS Duct cell carcinoma Ductal carcinoma
Comedocarcinoma	8501	Comedocarcinoma, NOS
Papillary Carcinoma	8260	Papillary Adenocarcinoma, NOS
	8503	Intraductal papillary adenocarcinoma with invasion Infiltrating and papillary adenocarcinoma
	8504	Intracystic carcinoma, NOS Intracystic papillary adenocarcinoma
Mucinous Carcinoma	8480	Mucinous adenocarcinoma Mucinous carcinoma Colloid adenocarcinoma Colloid carcinoma Gelatinous adenocarcinoma Gelatinous carcinoma Mucoid adenocarcinoma Mucoid carcinoma Mucous adenocarcinoma Mucous carcinoma
	8481	Mucin-producing adenocarcinoma Mucin-producing carcinoma Mucin-secreting adenocarcinoma Mucin-secreting carcinoma
Lobular Carcinoma	8520	Lobular carcinoma, NOS Lobular adenocarcinoma Infiltrating lobular carcinoma
	8522	Infiltrating duct and lobular carcinoma Infiltrating duct and lobular carcinoma in situ Lobular and ductal carcinoma Intraductal and lobular carcinoma
Tubular Carcinoma	8211	Tubular adenocarcinoma Tubular carcinoma
Medullary Carcinoma	8510	Medullary carcinoma, NOS Medullary adenocarcinoma
	8512	Medullary carcinoma with lymphoid stroma

Appendix N (Cont.)

Group	M-Code	ICD-O-2 Morphology Term
Sarcoma	8800	Sarcoma, NOS Soft tissue sarcoma Soft tissue tumour, malignant Mesenchymal tumour, malignant
	8801	Spindle cell sarcoma
	8802	Giant cell sarcoma (except of Bone M-9250/3) Pleomorphic cell sarcoma
	8803	Small cell sarcoma Round cell sarcoma
	8804	Epithelioid sarcoma Epithelioid cell sarcoma
	8810	Fibrosarcoma, NOS
	8811	Fibromyxosarcoma
	8830	Fibrous histiocytoma, malignant Fibroxanthoma, malignant
	8850	Liposarcoma, NOS Fibroliposarcoma
	8851	Liposarcoma, well differentiated Liposarcoma, differentiated
	8852	Myxoid liposarcoma Myxoliposarcoma
	8854	Pleomorphic liposarcoma
	8890	Leiomyosarcoma, NOS
	8894	Angiomyosarcoma
	8895	Myosarcoma
	8900	Rhabdomyosarcoma, NOS Rhabdosarcoma
	8920	Alveolar rhabdomyosarcoma
	8990	Mesenchymoma, malignant Mixed mesenchymal sarcoma
	9020	Phyllodes tumour, malignant (C50._) Cystosarcoma phyllodes, malignant (C50._)
	9120	Hemangiosarcoma Angiosarcoma
	9130	Hemangioendothelioma, malignant Hemangioendothelial sarcoma
	9150	Hemangiopericytoma, malignant
	9580	Granular cell tumour, malignant Granular cell myoblastoma, malignant

Appendix O. Incidence of bilateral breast cancer in the first three years and subsequent years following diagnosis of the first breast cancer for sub-cohorts defined by other histological types.

	Time (years)	Metachronous breast cancers	Person-years (×1000)	Rate	95% CI	
Comedocarcinoma	0-1	37	6.6567	5.56	4.03	7.67
	1-2	28	6.2022	4.51	3.12	6.54
	2-3	19	5.6526	3.36	2.14	5.27
	3+	177	36.5410	5.27	4.55	6.11
Papillary Carcinoma	0-1	15	1.4923	10.05	6.06	16.67
	1-2	6	1.3761	4.36	1.96	9.71
	2-3	6	1.2413	4.83	2.17	10.76
	3+	42	7.6370	5.50	4.06	7.44
Mucinous Carcinoma	0-1	55	8.4561	6.50	4.99	8.47
	1-2	37	7.4833	4.94	3.58	6.82
	2-3	23	6.5833	3.49	2.32	5.26
	3+	213	38.2869	5.56	4.86	6.36
Tubular Carcinoma	0-1	23	4.1234	5.58	3.71	8.39
	1-2	18	3.6288	4.96	3.13	7.87
	2-3	14	3.1499	4.44	2.63	7.50
	3+	90	17.0882	5.27	4.28	6.48
Sarcoma	0-1	5	1.0471	4.78	1.99	11.47
	1-2	4	0.8883	4.50	1.69	12.00
	2-3	6	0.7530	7.97	3.58	17.74
	3+	14	5.5232	2.54	1.50	4.28
Unspecified Carcinoma	0-1	39	7.6128	5.12	3.74	7.01
	1-2	34	6.7273	5.05	3.61	7.07
	2-3	24	5.9131	4.06	2.72	6.06
	3+	250	41.2251	6.06	5.36	6.86
Other Carcinoma	0-1	142	23.9000	5.94	5.04	7.00
	1-2	120	21.5280	5.57	4.66	6.67
	2-3	109	19.1129	5.70	4.72	6.88
	3+	775	143.5714	5.40	5.03	5.79

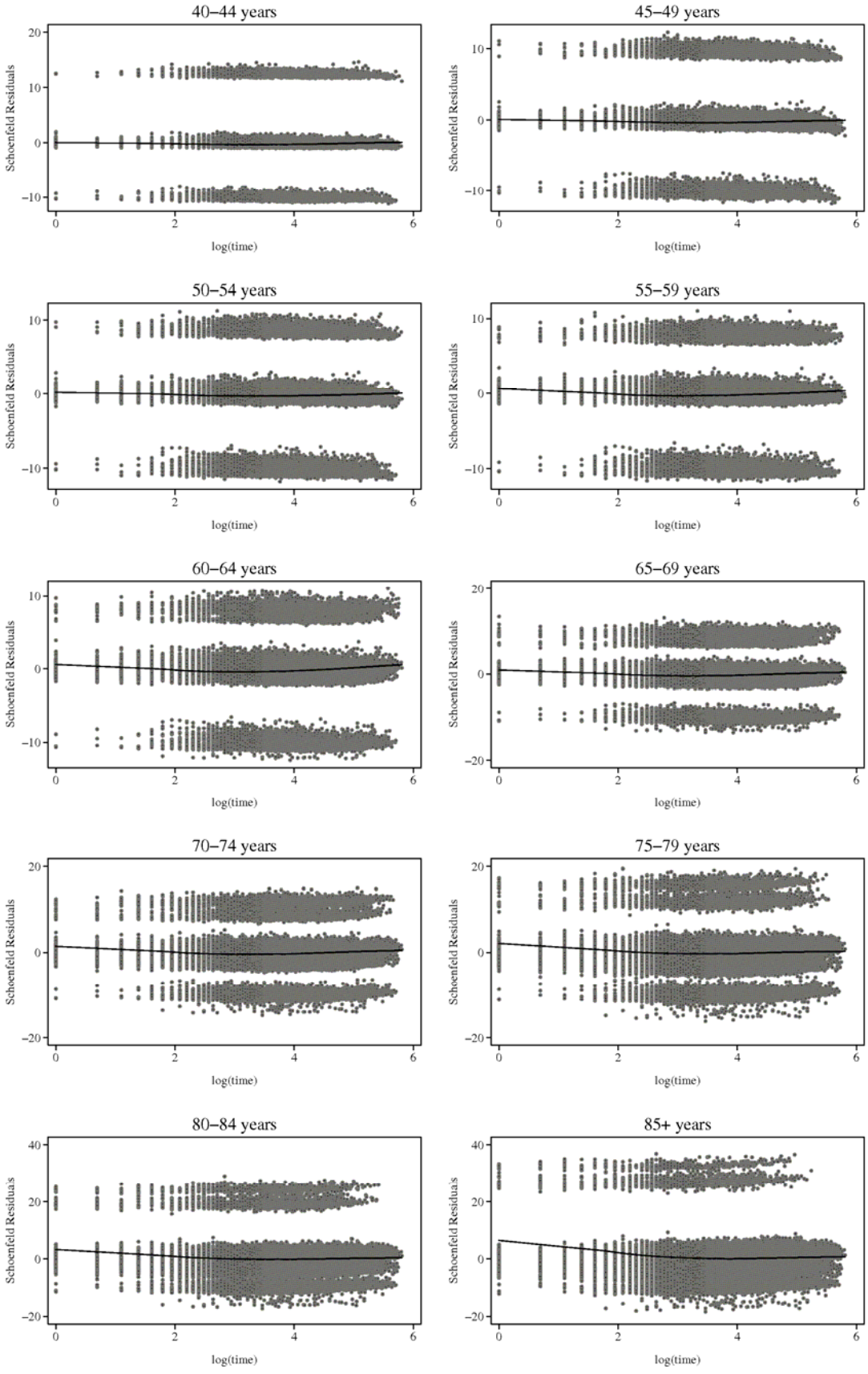
Appendix P. Crude and adjusted† incidence rate ratios of bilateral breast cancer in the first three years and in subsequent years by histology of the first breast cancer.

Histology	Interval	Crude Estimates IRR	95% C.I.		Adjusted Estimates IRR	95% C.I.	
Infiltrating Ductal Carcinoma	0-1	1.03	0.97	1.10	1.05	0.94	1.18
	1-2	0.96	0.90	1.02	0.98	0.89	1.08
	2-3	0.94	0.87	1.00	0.96	0.88	1.05
(ref)	3+	1.00			1.00		
Comedocarcinoma	0-1	1.00	0.72	1.41	1.03	0.72	1.46
	1-2	0.85	0.59	1.25	0.88	0.60	1.30
	2-3	0.66	0.42	1.03	0.69	0.44	1.09
	3+	0.97	0.83	1.13	0.99	0.84	1.15
Papillary Carcinoma	0-1	1.87	1.10	3.15	1.91	1.12	3.26
	1-2	0.87	0.39	1.94	0.90	0.40	2.00
	2-3	0.96	0.43	2.14	0.99	0.45	2.22
	3+	1.07	0.78	1.45	1.06	0.78	1.44
Mucinous Carcinoma	0-1	1.16	0.87	1.54	1.21	0.90	1.62
	1-2	0.99	0.71	1.36	1.03	0.74	1.43
	2-3	0.66	0.44	1.01	0.69	0.46	1.06
	3+	1.05	0.92	1.21	1.05	0.92	1.21
Tubular Carcinoma	0-1	1.05	0.69	1.59	1.11	0.72	1.71
	1-2	0.97	0.61	1.54	1.05	0.65	1.67
	2-3	0.87	0.52	1.47	0.95	0.56	1.60
	3+	0.99	0.80	1.23	1.03	0.83	1.27
Sarcoma	0-1	0.81	0.30	2.16	0.82	0.31	2.20
	1-2	0.95	0.36	2.54	0.96	0.36	2.57
	2-3	1.41	0.58	3.38	1.41	0.59	3.41
	3+	0.50	0.29	0.86	0.48	0.28	0.83
Unspecified Carcinoma	0-1	0.99	0.68	1.44	0.93	0.63	1.38
	1-2	0.99	0.66	1.48	0.93	0.62	1.40
	2-3	0.88	0.56	1.39	0.83	0.53	1.31
	3+	1.17	1.01	1.35	1.11	0.96	1.28
Other Carcinoma	0-1	1.12	0.94	1.33	1.06	0.87	1.30
	1-2	1.06	0.88	1.28	1.01	0.83	1.24
	2-3	1.04	0.85	1.27	0.99	0.81	1.22
	3+	1.02	0.94	1.10	0.97	0.90	1.05

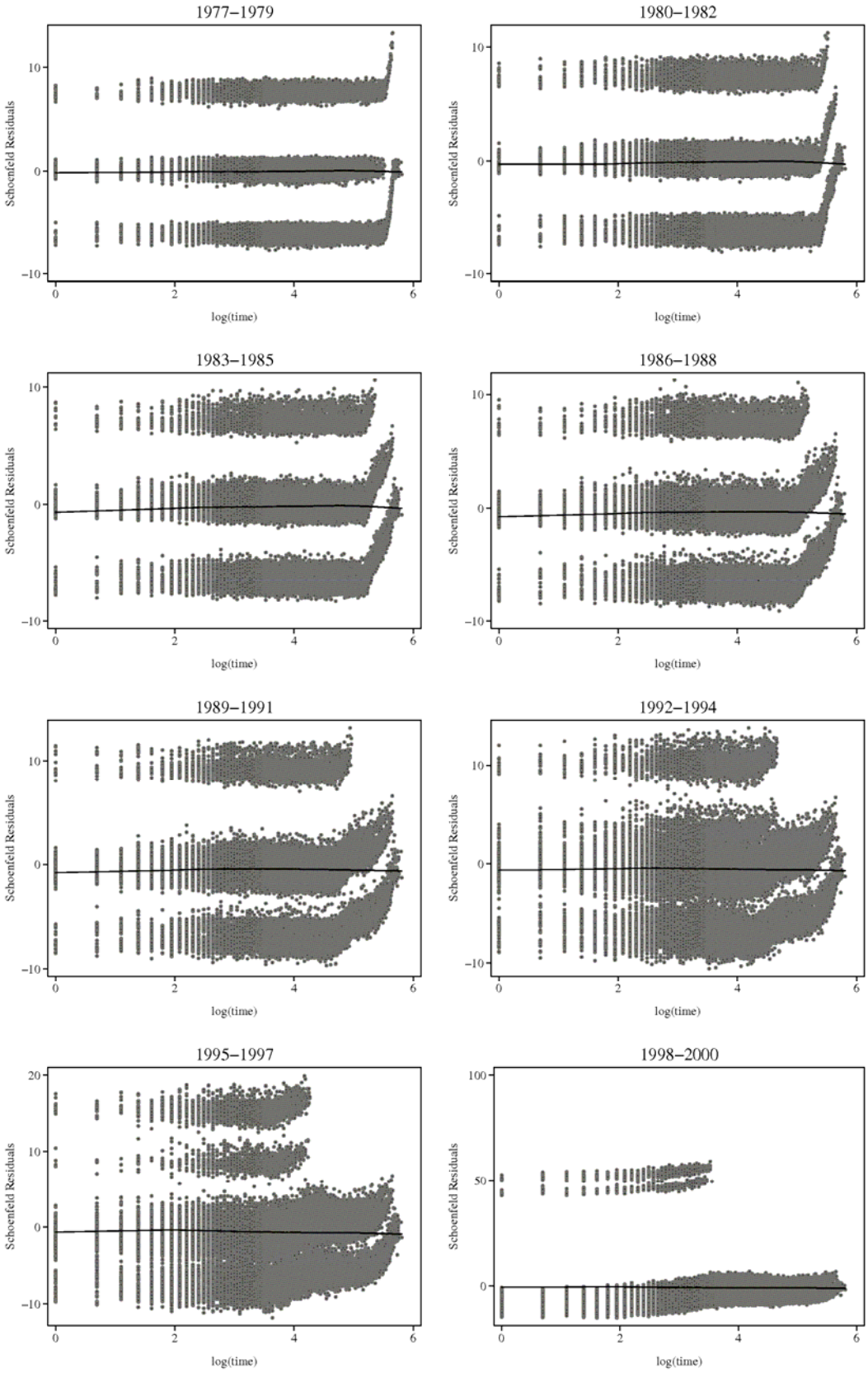
† Adjusted for age at bilateral diagnosis, registry, race, year of diagnosis, marital status, stage, and radiotherapy.

Appendix Q. Schoenfeld Residuals

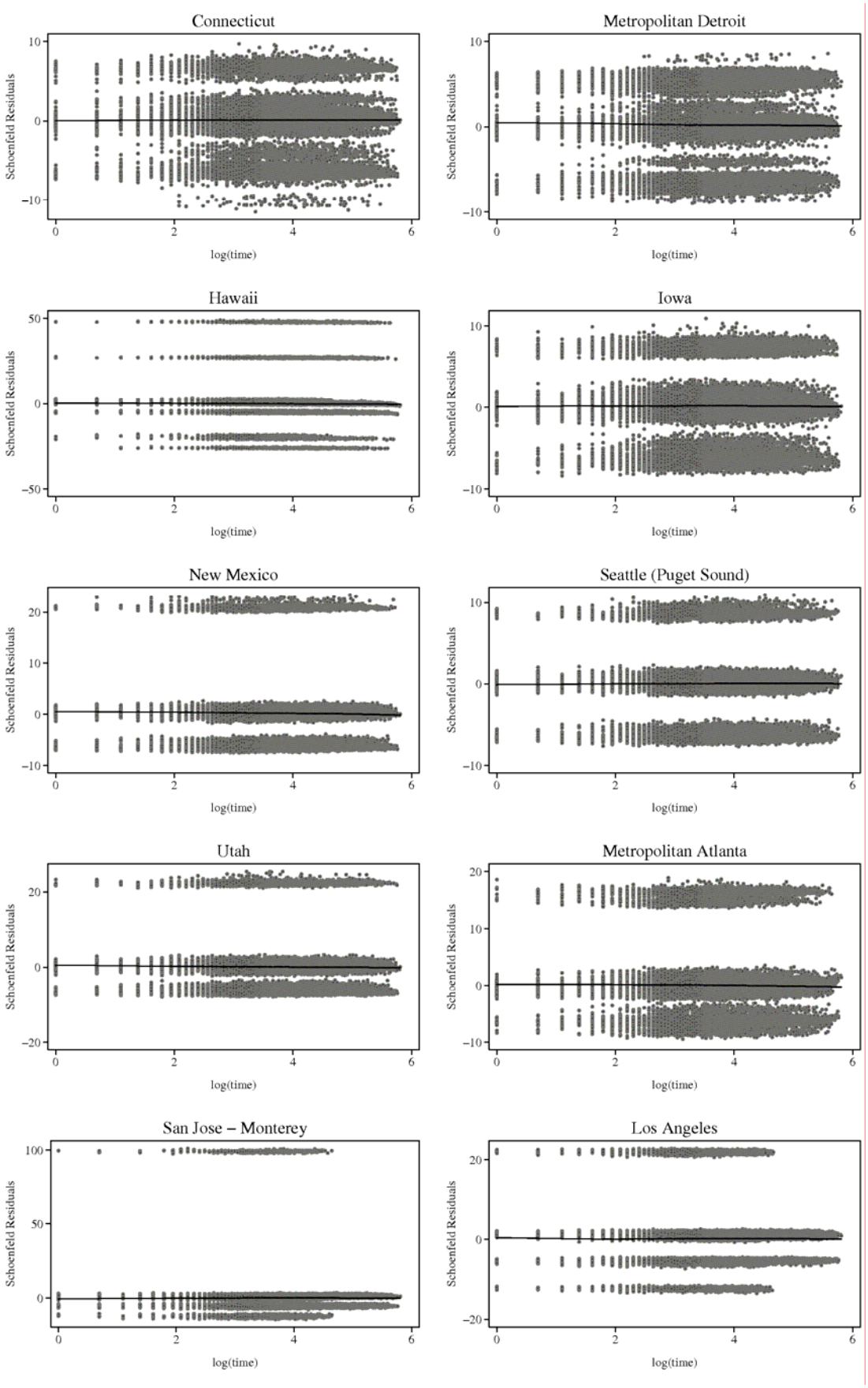
Schoenfeld residuals for age at first breast cancer diagnosis for proportional hazards model presented in Table 4-27, page 125.



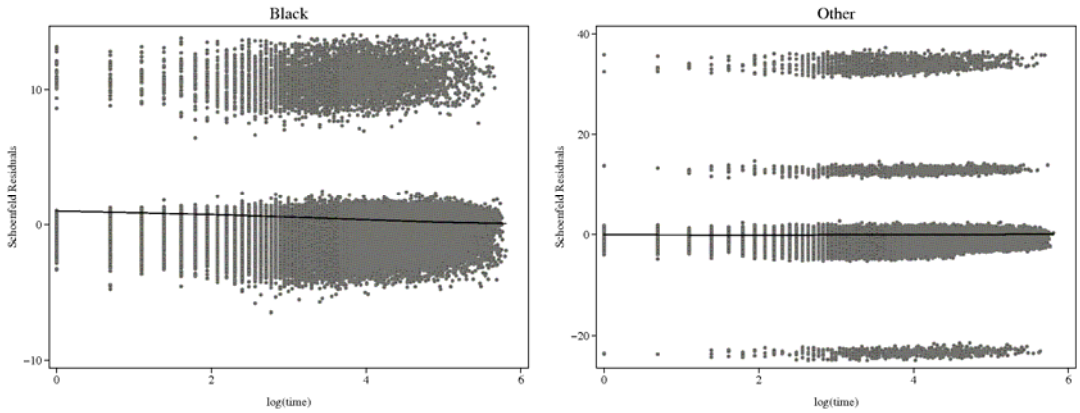
Schoenfeld residuals for year of first diagnosis for proportional hazards model presented in Table 4-27, page 125.



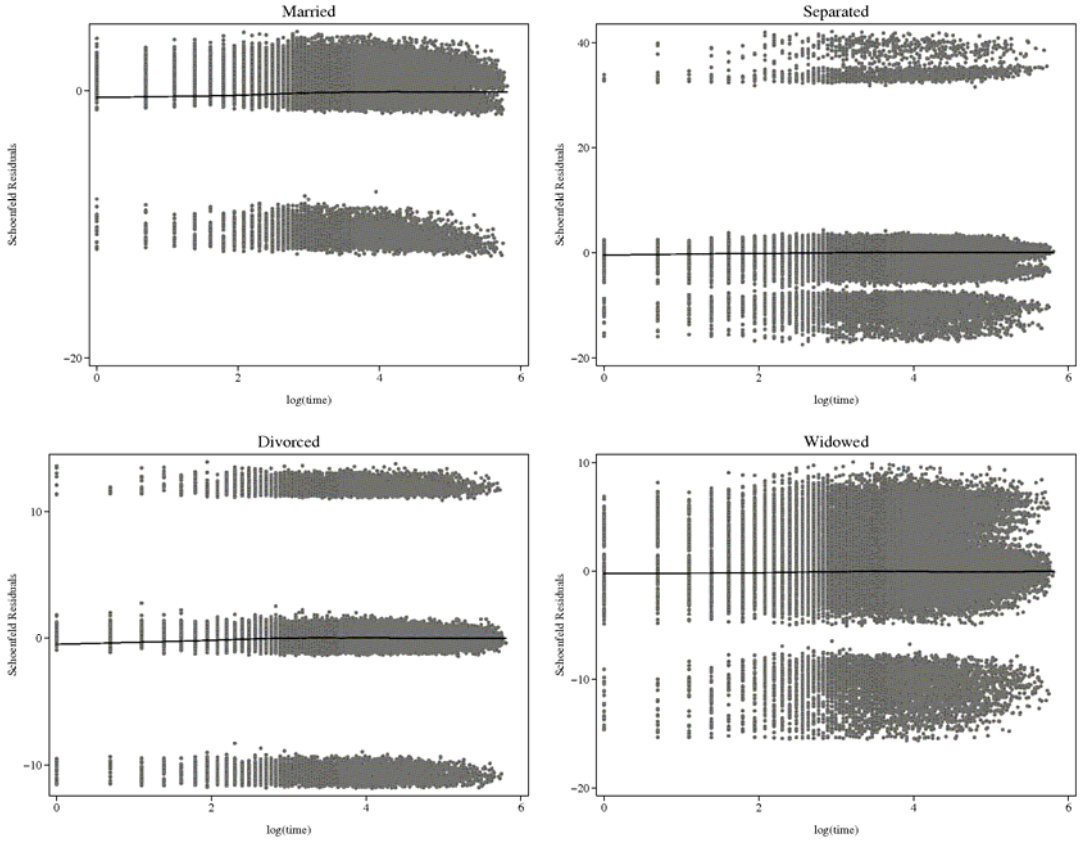
Schoenfeld residuals for registry for proportional hazards model presented in Table 4-27, page 125.



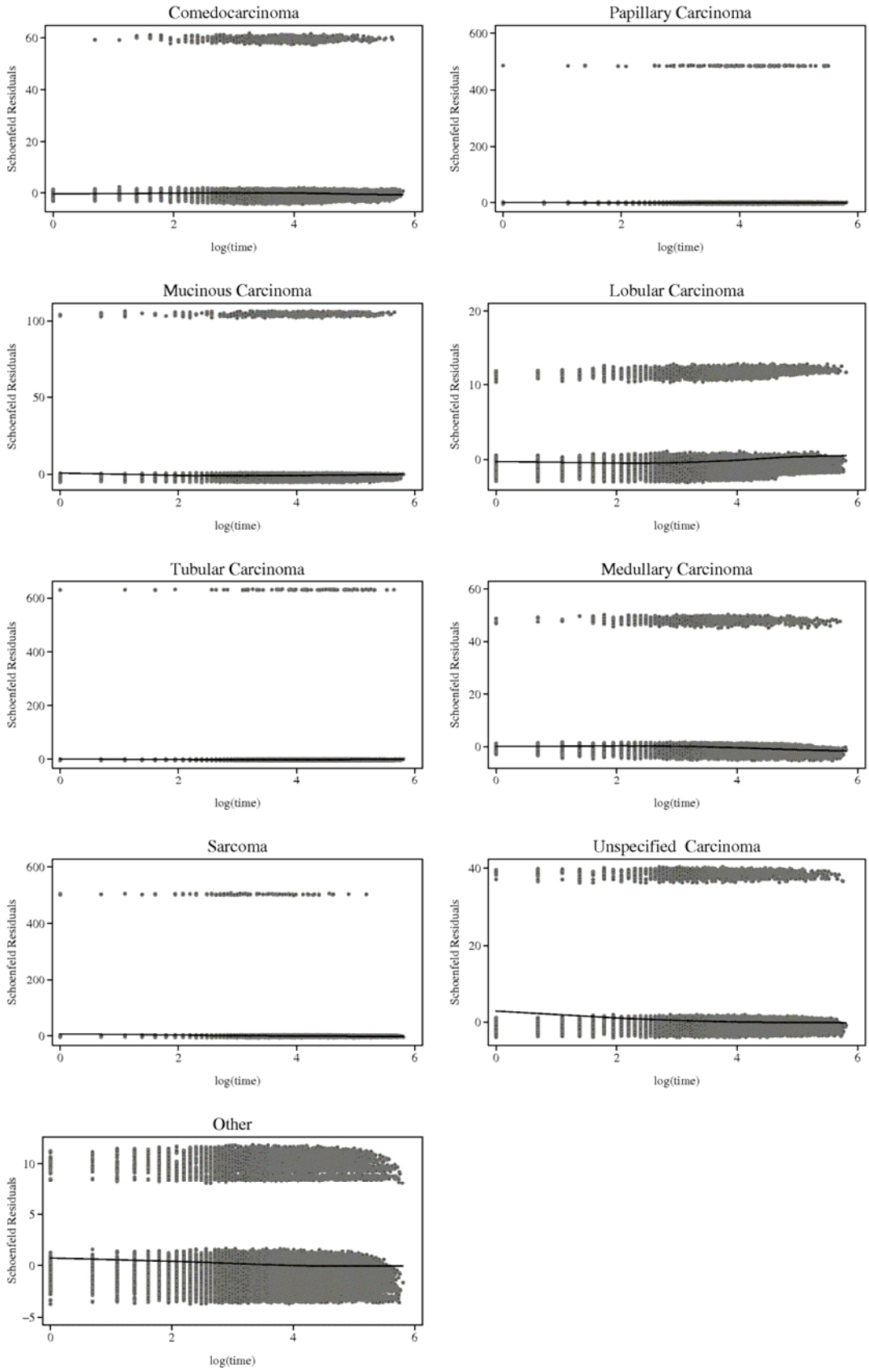
Schoenfeld residuals for race for proportional hazards model presented in Table 4-27, page 125.



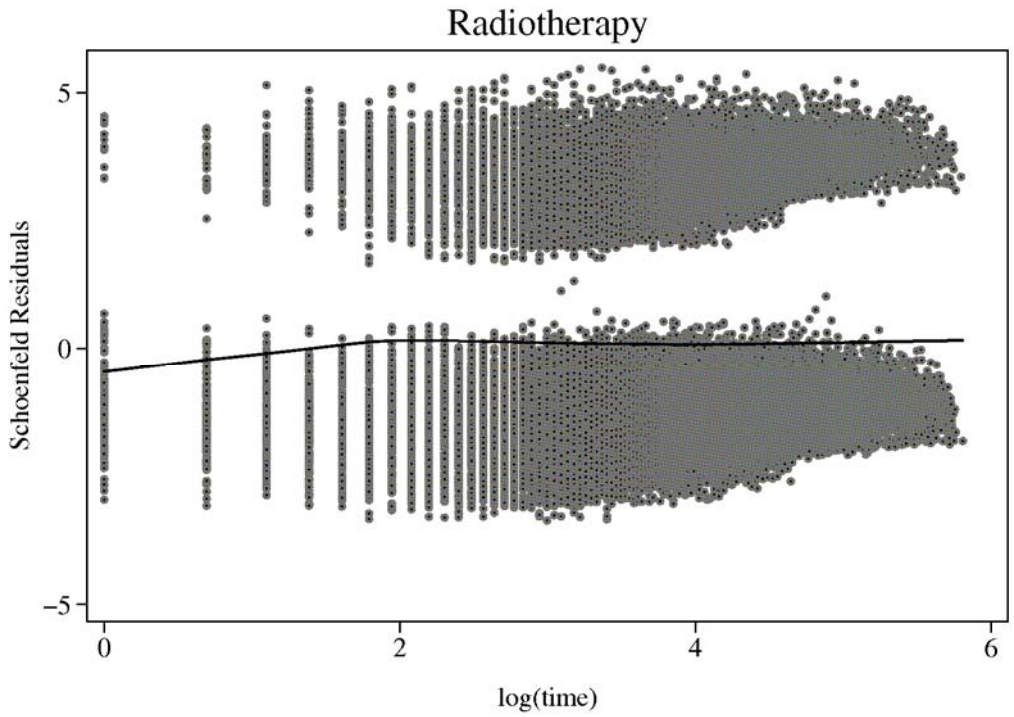
Schoenfeld residuals for marital status for proportional hazards model presented in Table 4-27, page 125.



Schoenfeld residuals for histology for proportional hazards model presented in Table 4-27, page 125.



Schoenfeld residuals for radiotherapy for proportional hazards model presented in Table 4-27, page 125.



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