UTS UNIVERSITY OF TECHNOLOGY SYDNEY

Gestational breast cancer: maternal and baby outcomes

by Nadom Hikmet Safi

Thesis submitted in fulfilment of the requirements for the degree of

Doctor of Philosophy

under the supervision of Professor Elizabeth Sullivan, Professor Andrew Hayen, Associate Professor Alex Wang, and Doctor Antoinette Anazodo

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Certificate of original authorship

I, Nadom Hikmet Safi, declare that this thesis is submitted in fulfilment of the requirements for the award of Doctor of Philosophy in the Faculty of Health at the University of Technology Sydney.

This thesis is wholly my own work unless otherwise referenced or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

This document has not been submitted for qualifications at any other academic institution.

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To my great family and my parents, I dedicate this thesis.

Format of the thesis

This PhD thesis is in a compilation format. Each of four studies is reported in a thesis chapter. Chapter 4 (study 1) has been published in Plos One. Chapter 5 (study 2) and Chapter 6 (study 3) are currently being prepared for publication, and Chapter 7 (study 4) has been published in the British Journal of Cancer.

Statement of contributions to jointly authored works contained in the thesis

Chapter 4 has been submitted for publication in a peer-reviewed journal. Chapters 5 and 6 are ready for submission, and Chapter 7 is published in a peer-reviewed journal. For each of these manuscripts, I have been responsible for deciding the research question, conducting the statistical analysis and drafting the manuscript.

During this process, I have received support from my principal supervisor Distinguished Professor Elizabeth Sullivan and my co-supervisors Professor Andrew Hayen, Dr Antoinette Anazodo (University of New South Wales) and Associate Professor Alex Wang. Additional assistance in statistical analysis was done by Dr Zhuoyang Li and Dr Marc Remond reviewed the manuscripts.

For Chapters 4 and 6, Professor Christobel Saunders reviewed the manuscripts and added her clinical expertise. Professor Kei Lui provided his clinical opinion on the interpretation of the data for Chapters 4 and 7. For Chapters 6 and 7, Professor Jan E. Dickinson reviewed the manuscripts and added her clinical expertise. Professor Michael Nicholl provided his clinical opinion on the interpretation of the data for Chapters 4 and 5.

I take responsibility for the accuracy of the results presented in these manuscripts.

Abbreviations

ACOG	American College of Obstetricians and Gynecologists
ACR	American College of Radiology
AIHW	Australian Institute of Health and Welfare
AMOSS	Australasian Maternity Outcome Surveillance System
AOR	Adjusted odds ratio
APDC	Admitted Patient Data Collection
BMI	Admitted Patient Data Collection
CHeReL	Centre for Health Record Linkage
CI	Confidence interval
CNB	Core needle biopsy
CS	Caesarean section
CT	Computerised tomography
HER 2	Human epidermal growth factor receptor 2
FNA	Fine needle biopsy
GBC	Gestational breast cancer
ESUR	The European Society of Urogenital Radiology
GC	Gestational cancer
ICU	Intensive care unit
LGA	Large for gestational age
mGy	Milligray
MRI	Magnetic resonance imaging

NICU	Neonatal intensive care unit
NSW	New South Wales
O/E	observed/ estimated
PABC	Pregnancy-associated breast cancer
PAC	Pregnancy-associated cancer
PDC	Perinatal Data Collection
PPH	Post-partum haemorrhage
RDS	Respiratory distress syndrome
SCN	Special care nursery
SGA	Small for gestational age
UTS	University of Technology Sydney
US	United States
WA	Western Australia

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Abstract

Background

The incidence of gestational breast cancer (GBC), also called breast cancer diagnosed during pregnancy, is rising. GBC presents unique challenges in clinical management to optimise outcomes for mothers and their babies.

Aim

To examine the perinatal outcomes of women with GBC to create an evidence-base to assist health care providers in clinical management. The main objectives were:

- to describe the incidence, management, and perinatal outcomes of women with GBC,
- to investigate factors affecting their survival,
- to explore the safety of options available to healthcare providers for diagnosing GBC, and
- to describe the outcomes of babies exposed to GBC systemic treatment.

Methods

Four studies were conducted using population-based data sets. Studies 1 and 2 utilised New South Wales (NSW) data to investigate all women with pregnancies that ended in live birth or stillbirth between 1 January 1994 and 31 December 2013. Studies 3 and 4 utilised data from the Australasian Maternity Outcome Surveillance System GBC study collected in Australia and New Zealand between 1 January 2013 and 30 June 2014.

Results

- Studies 1 and 2: The annual incidence of GBC in NSW was 6.8/100,000 women. Women with GBC were more likely to give birth by labour induction or pre-labour caesarean section (CS) than women with no cancer (adjusted odds ratio (AOR) 4.8, 95%CI: 2.96–7.79). Babies born to women with GBC were more likely to be preterm (AOR 12.93, 95%CI: 8.97–18.64) and low birthweight. Of 122 women identified with GBC, 19.7% died within five years of diagnosis. The mortality rate for women with stage 4 cancer at diagnosis was 1,446/10,000 person-years, which is higher than that for women with stages 2 and 3 (399/10,000 person-years) or stage 1 (222/10,000 person-years).
- Studies 3 and 4: 83% of women with GBC experienced a painless breast lump. Breast ultrasound was the first-line imaging modality in all women. Eighteen babies exposed to breast cancer systemic treatment during pregnancy were born. None had a congenital malformation or major neonatal morbidity .

Conclusion

There was a high rate of preterm birth among women with GBC. Most births followed induction of labour or pre-labour CS. The crude 5-year mortality observed for women with GBC was 19.7%, which is almost double that previously reported for all women diagnosed with breast cancer in Australia. GBC diagnosed during mid-pregnancy and treated with chemotherapy was associated with a high rate of planned preterm birth but no increase in perinatal mortality.

Chapter 1: Introduction to this thesis

1.1 Background

Cancer occurring during pregnancy is rare but highly complex to manage, and it poses unique challenges in optimising outcomes for both the mother and her baby (Amant, Han, et al. 2015; Lee et al. 2012). Cancer is the second-most common cause of death among women of childbearing age, with breast cancer representing over 40% of cancers diagnosed in this age group (Anders et al. 2009; Gardner et al. 2012). The incidence of pregnancy-associated cancer (PAC), which is defined as cancer diagnosed during pregnancy or within one year postpartum, varies from 50 to 200 per 100,000 pregnancies (Alfasi & Ben-Aharon 2019; Amant, Han, et al. 2015; Cottreau et al. 2019; Gardner et al. 2012; Lee et al. 2012; Murgia et al. 2019; Parazzini et al. 2017).

This incidence rose in the state of New South Wales (NSW), Australia, from 112.3 per 100,000 women giving birth in 1994 to 191.5 per 100,000 in 2008 (Lee et al. 2012). The most commonly diagnosed types of PAC are melanoma, breast cancer and cervical cancer (Cottreau et al. 2019; Eibye, Kjaer & Mellemkjaer 2013; Murgia et al. 2019; Parazzini et al. 2017; Stensheim et al. 2009). Other less common types of PAC include ovarian, colon, endocrine and thyroid cancer, as well as Hodgkin's lymphoma and leukaemia (Andersson et al. 2015). Breast cancer is the second-most common cancer diagnosed in women giving birth in NSW after melanoma, representing 33.7% of all cancers (Lee et al. 2012). The incidence of gestational breast cancer (GBC) is rising in high-income countries, in part due to the increasing age of mothers (Andersson et al. 2009; Durrani, Akbar & Heena 2018; Shechter Maor et al. 2019).

Women with GBC are more likely to have inferior birth outcomes, including thromboembolic events, sepsis, induction of labour, and pre-labour caesarean section (Amant, Vandenbroucke, et al. 2015; Lee et al. 2012; Van Calsteren et al. 2010). Preterm birth has been identified as the main adverse neonatal outcome for babies born to women with GBC (Amant, Vandenbroucke, et al. 2015).

There is inconsistency in the literature on whether the mortality rate in women with GBC is higher than in women with breast cancer that is not associated with pregnancy (Albrektsen et al. 2006; Amant et al. 2013; Boudy et al. 2018; Cardonick et al. 2010; Genin et al. 2016; Lyons, Schedin & Borges 2009; Ploquin et al. 2018; Ruiz et al. 2017; Stensheim et al. 2009). However, after adjusting for the age of the woman, the stage of cancer at diagnosis and breast cancer subtype, the survival rates for women are similar in both groups (Amant et al. 2013; Boudy et al. 2018; Cardonick et al. 2010; Genin et al. 2016; Ploquin et al. 2018; Ruiz et al. 2017; Stensheim et al. 2009).

Women who become pregnant after being diagnosed and treated for cancer may have a lower mortality rate than women with no pregnancy after the cancer diagnosis; this is called as the "healthy mother effect" (Azim et al. 2011; Stensheim et al. 2009). Young women treated for breast cancer are willing to conceive, as many of them have yet to complete their family (de Bree et al. 2010; Pagani et al. 2015). However, their chances of conception are low, as some cancer treatment are well known to affect women's fertility (Anderson, Brewster, et al. 2018).

The physiological changes of the breast during pregnancy and concerns regarding the safety of diagnostic procedures during pregnancy can make the diagnosis and staging of breast cancer difficult (de Haan et al. 2016). In addition, the management and treatment of GBC present challenges around weighing up the benefits of cancer treatment against the risks of adverse outcomes for the baby (Pereg, Koren & Lishner 2008).

Existing studies and practice guidelines state that breast surgery can be performed safely in all pregnancy trimesters (Langer et al. 2014; RCOG 2011). In addition, the literature shows that the use of chemotherapeutic agents during the second and third trimesters is not associated with an increase in the incidence of major congenital malformations for babies born to women with cancer (Abdel-Hady el et al. 2012; Loibl et al. 2012; Van Calsteren et al. 2010). However, several studies have demonstrated that antenatal exposure to systemic chemotherapy is associated with high rates of preterm birth, small for gestational age, low birthweight, admission to neonatal intensive care units (NICU) and respiratory distress syndrome (RDS) (Amant, Vandenbroucke, et al. 2015; Loibl et al. 2012; Van Calsteren et al. 2010).

1.2 Objectives

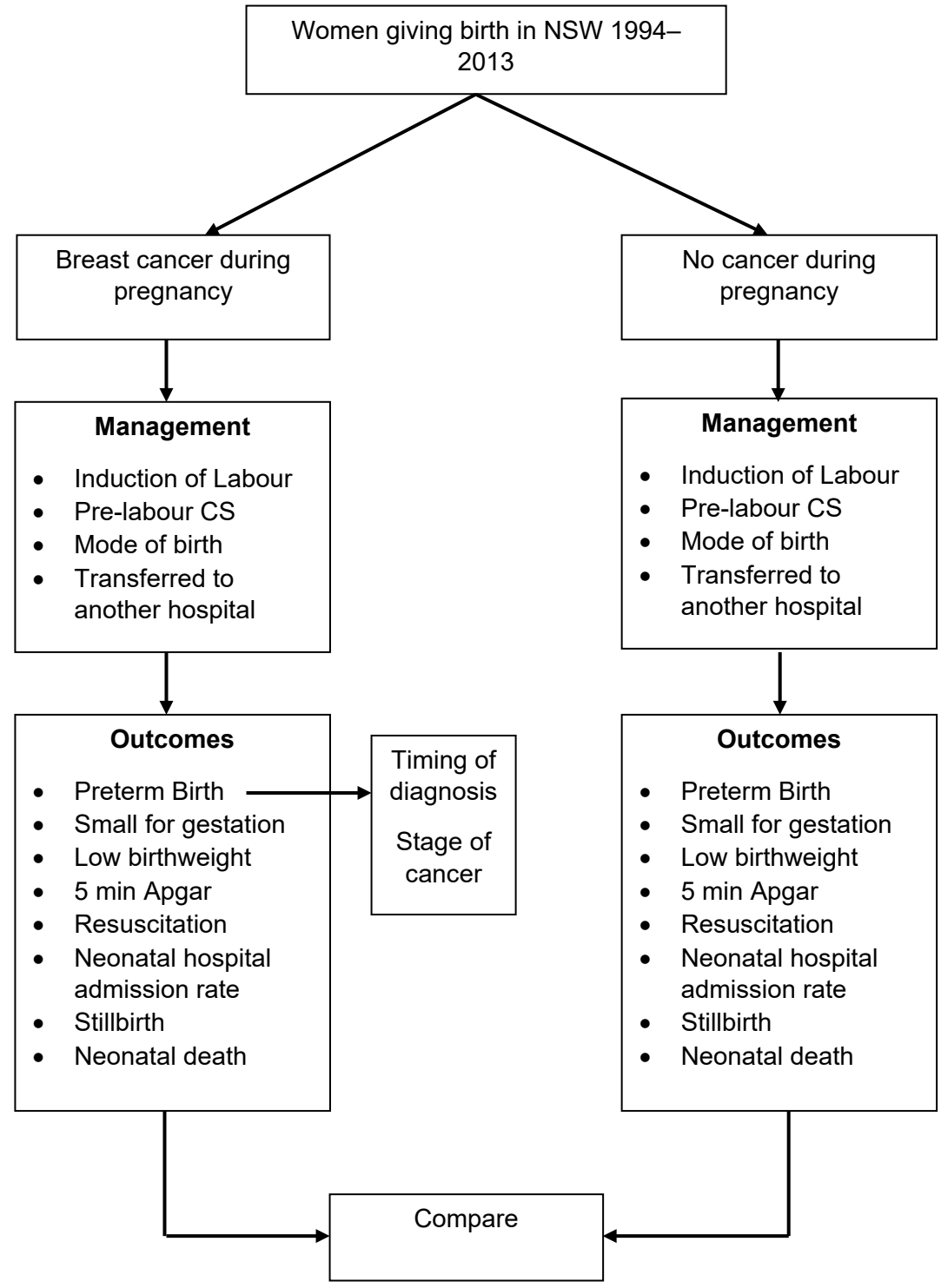
The overarching aim of this research is to inform decision making regarding the clinical management of women with GBC. To meet this aim, this study investigated the effect of GBC on the perinatal outcomes of women from Australia and New Zealand with a first-time diagnosis of breast cancer during

pregnancy, and their babies. It also examined the incidence of GBC and current clinical practices, including methods of diagnosis and treatment options.

Four studies were conducted to achieve this aim:

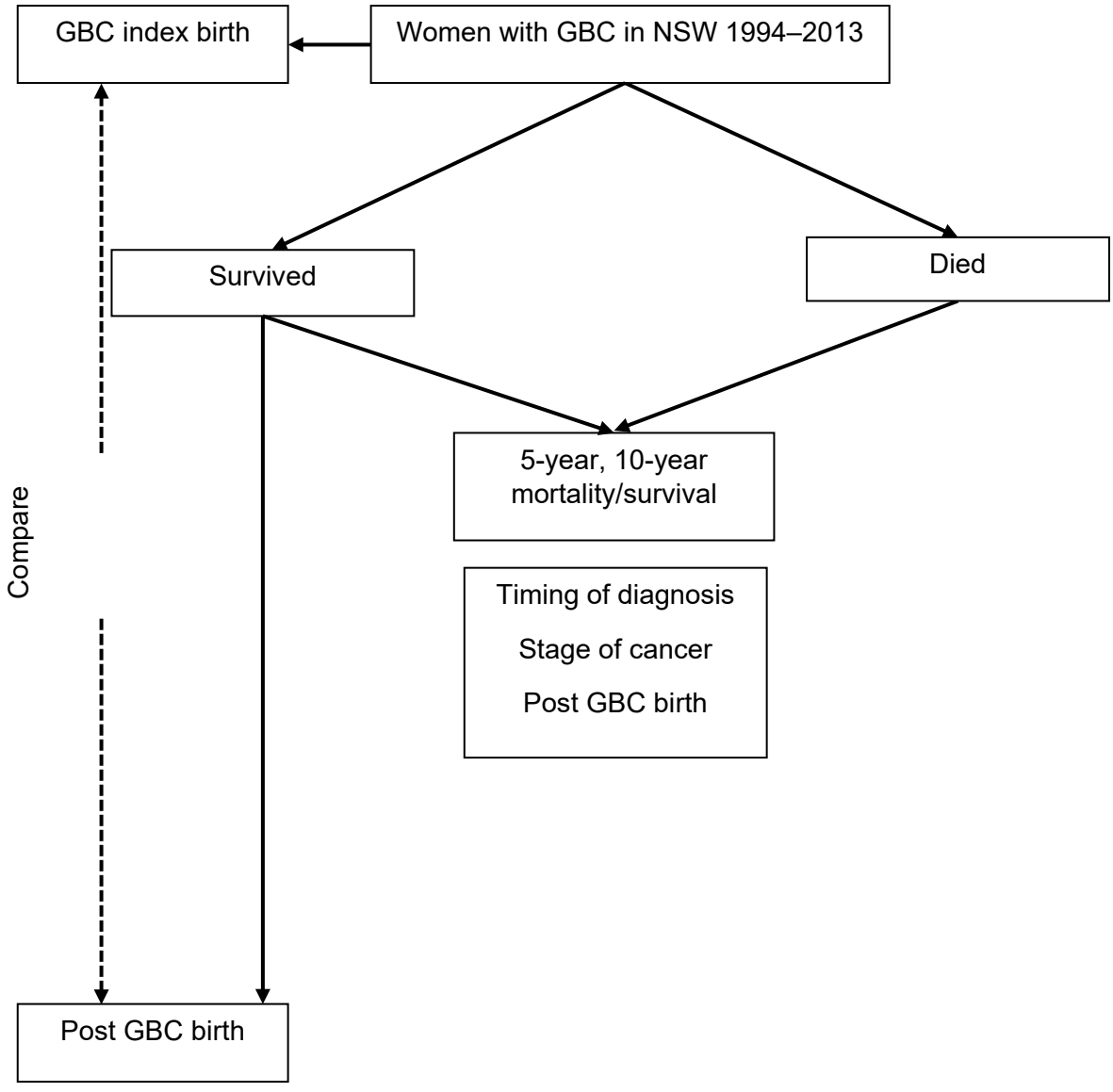
Study one: This is a population-based retrospective cohort study of the incidence, timing of diagnosis, obstetric management and perinatal outcomes of women with GBC and their babies in NSW. It includes all women who gave birth in NSW from 1 January 1994 to 31 December 2013. The study examines how decisions to deliver babies at less than 37 weeks gestation by induction of labour or pre-labour caesarean section (CS) were associated with the timing of breast cancer diagnosis during pregnancy and/or the stage of cancer at diagnosis. Figure 1.1 shows the structure of Study one.

Figure 1.1: Gestational breast cancer in NSW



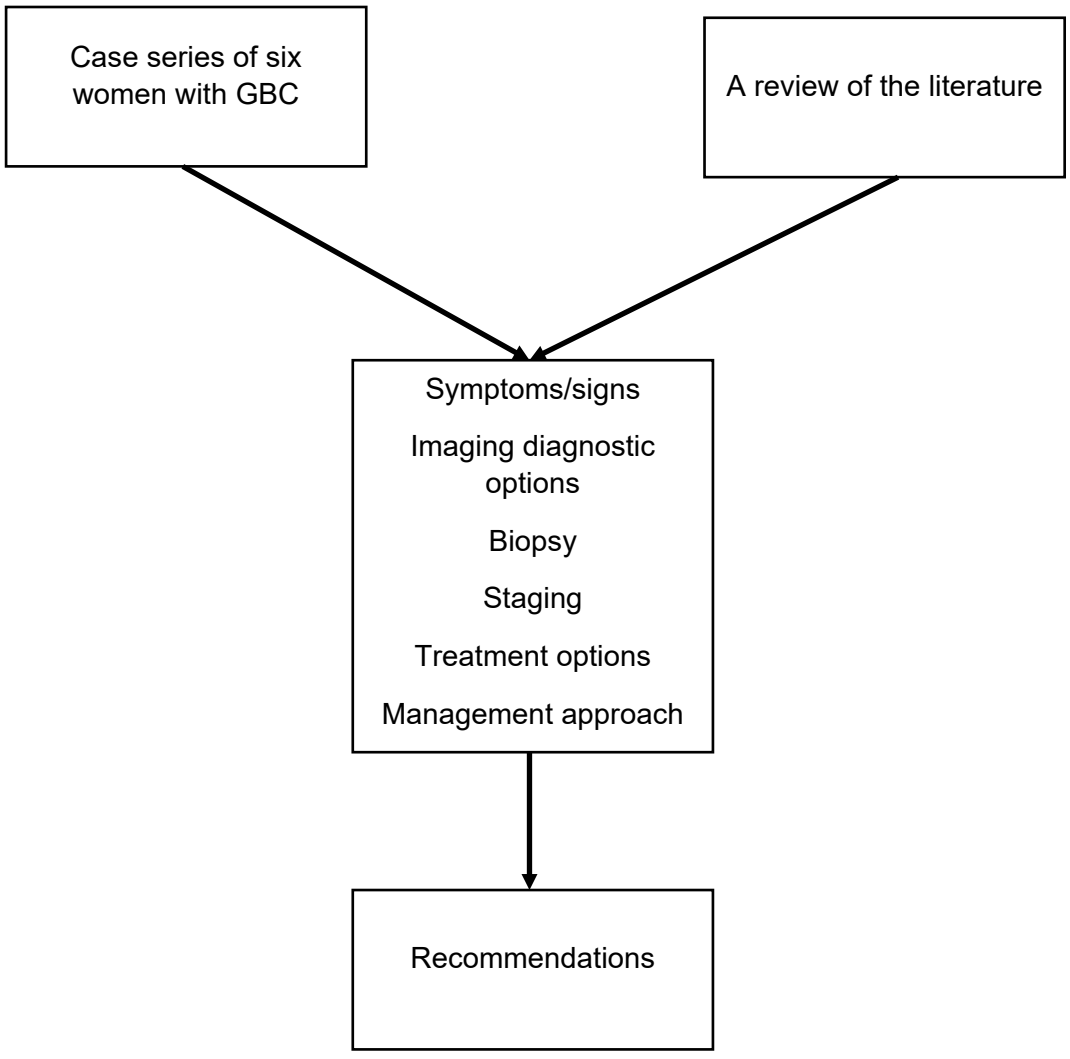
Study two: This is a population-based retrospective cohort study that includes all the women with GBC who were identified in Study one. It examines the survival rates of women with GBC and whether these are associated with the stage of breast cancer at diagnosis or giving birth following GBC index birth. It also examines the rate of giving birth after GBC and describes the perinatal outcomes for the women and their babies of the birth episode subsequent to GBC birth. Figure 1.2 shows the structure of Study two.

Figure 1.2: Survival and giving birth of women with GBC in NSW.



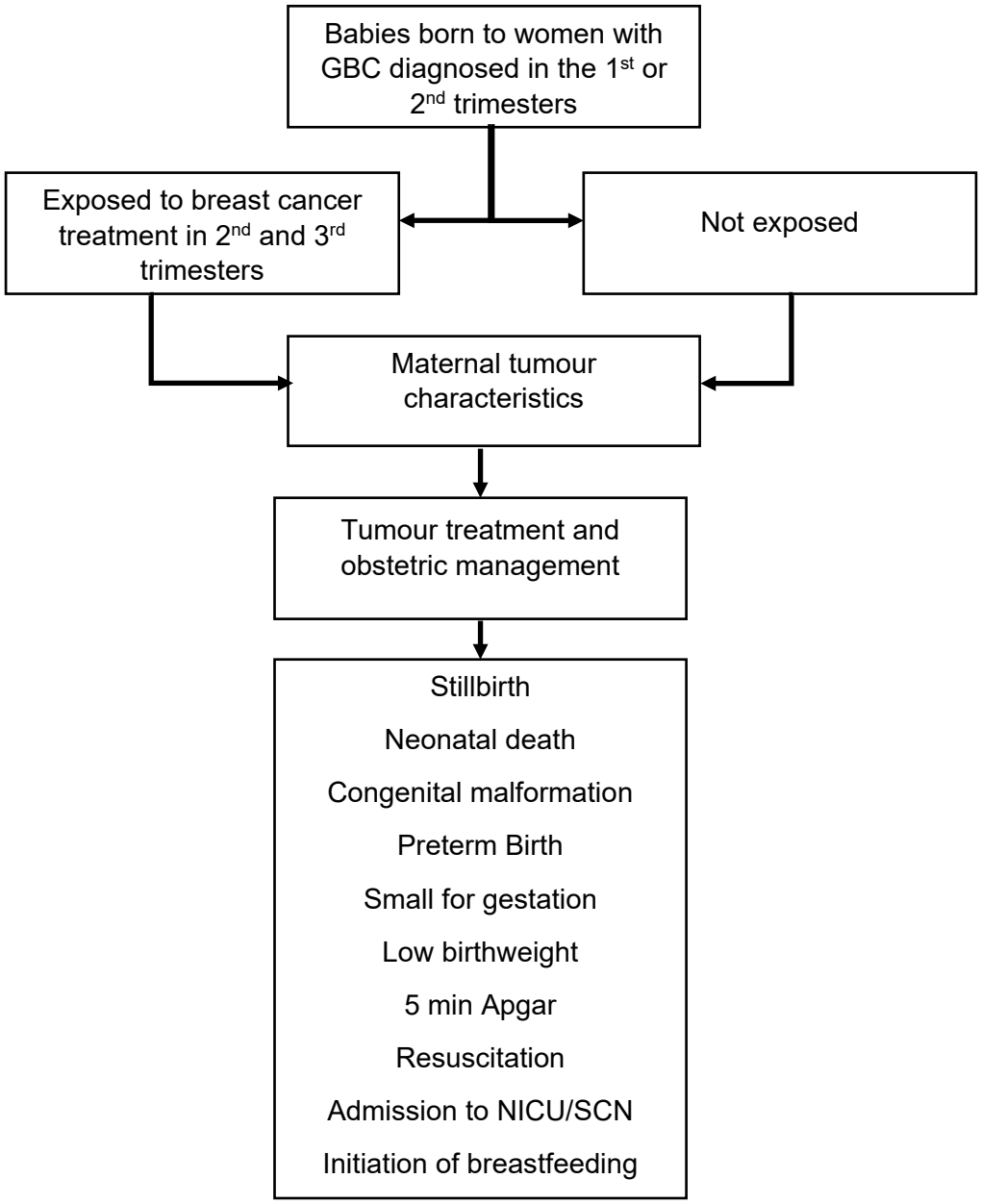
Study three: The aim of this knowledge translation study is to impact the providers of care to women with GBC, such as obstetricians, general practitioners, midwives, and nurses. The study is a case series and a review of the literature describing the diagnosis, management, and outcomes for six women with a first-time diagnosis of breast cancer during pregnancy. These six cases were identified via the Australasian Maternity Outcome Surveillance System (AMOSS) as part of a larger study investigating the epidemiology of GBC in Australia and New Zealand between January 2013 and June 2014. Figure 1.3 shows the structure of Study three.

Figure 1.3: Management of GBC – a management guideline to healthcare providers.



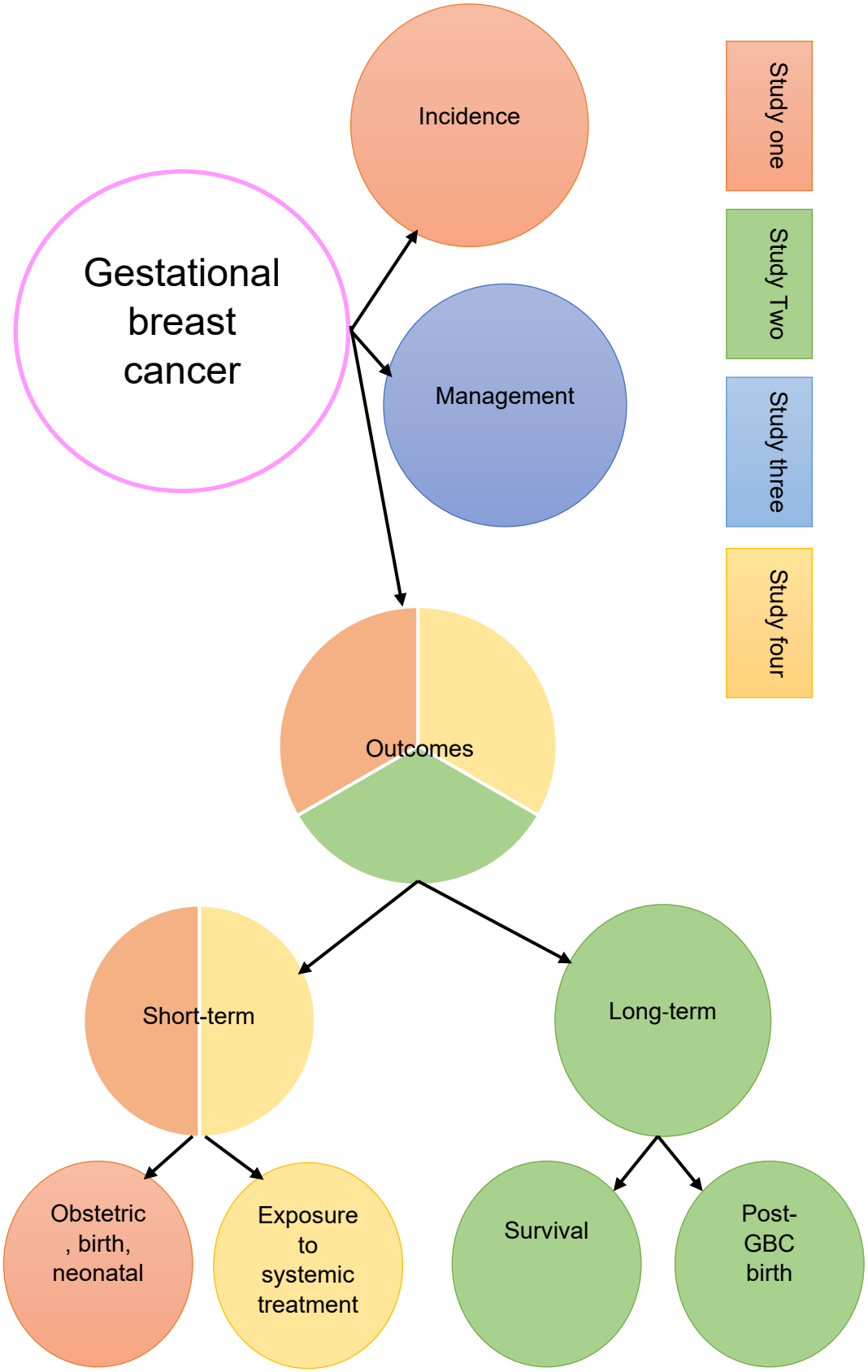
Study four: This population-based prospective cohort study was conducted using the Australasian Maternity Outcomes Surveillance System (AMOSS). Its aim is to provide evidence on the safety of systemic treatment of breast cancer during pregnancy. It examines the effect of in-utero exposure to breast cancer systemic chemotherapy on the perinatal outcomes (including mortality, major morbidity and congenital abnormality) of a cohort of babies born to women with GBC. Figure 1.4 shows the structure of study four.

Figure 1.4: In utero exposure to breast cancer systemic treatment



Each of the four studies mutually contributed to achieving the research aims of this doctoral research. These contributions are shown in Figure 1.5.

Figure 1.5: Overview of the four studies and the primary thesis aims



1.3 Structure of this thesis

This thesis has the following eight chapters.

Chapter 1: Introduction to this PhD thesis

This chapter introduces the thesis and describes the aims and objectives of the research.

Chapter 2: Background and review of the literature

This chapter provides a detailed description of the cancers that are diagnosed around pregnancy. It includes definitions of the main terms used in the literature concerning cancer and pregnancy. This chapter also provides a review of the literature on the management and outcomes for women with cancers diagnosed around pregnancy, focusing on breast cancer diagnosis during pregnancy.

Chapter 3: Methods

This chapter provides a detailed explanation of the methods used in conducting this research.

Chapter 4: Study one

"Gestational Breast Cancer in New South Wales: A population-based linkage study of incidence, management, and outcomes." This study investigates the incidence, management, and outcomes of women with GBC in NSW.

Chapter 5: Study two

" Gestational breast cancer: mortality and giving birth after breast cancer treatment—a New South Wales linkage study." This chapter investigates the long-term outcomes for women with GBC in NSW, including the survival outcome and giving birth subsequent to GBC.

Chapter 6: Study three

"Clinical decision making in the management of breast cancer diagnosed during pregnancy: a review and case series analysis." This chapter provides a guideline to the management of pregnant women with breast cancer. It includes a description of the symptoms, diagnostic procedures and perinatal outcomes of six women with GBC and their babies. It also includes a review of the literature and the current clinical practice guidelines to examine the safety of diagnostic procedures during pregnancy.

Chapter 7: Study four

"In-utero exposure to breast cancer treatment: a population-based perinatal outcome study." This chapter examines the effect of chemotherapy and other systemic breast cancer treatments on neonatal outcomes of babies born to women with GBC. It compares the neonatal outcomes of babies who were exposed antenatally to breast cancer systemic treatment and those who were not.

Chapter 8: Discussion and recommendations

This chapter concludes the thesis by summarising the results of Chapters 4, 5, 6, and 7. It also discusses the results in relation to the literature and gives recommendations for clinical practice and future research.

1.4 The conclusion to the chapter

This chapter has summarised the background and structure of the thesis. The next chapter (Chapter 2) will provide a review of the literature on the coexistence of cancer and pregnancy and on the main issues associated with the diagnosis of cancer in pregnant women. The main focus of the literature review is the diagnosis of breast cancer during pregnancy. Some parts of Chapter 2 may be repeated in the results chapters (4 to 7), which also include literature reviews.

Chapter 2: Background and literature review

2.1 Background

Cancer is the second-most common cause of death among women in their childbearing age after non-intentional injuries (Gardner et al. 2012). The incidence of cancer diagnosed around pregnancy has been increasing in the past few decades as women delay their pregnancies to a later age (Lee et al. 2012). The coexistence of cancer and pregnancy poses a significant challenge to not only the woman, but also healthcare providers (Amant, Han, et al. 2015; Lee et al. 2012). Confronting a diagnosis of cancer during pregnancy is undoubtedly one of the most devastating health events a woman and her family can face (Hammarberg et al. 2018; Henry et al. 2012; Ives, Musiello & Saunders 2012). There is limited research on the association between cancer and reproduction, including on the impact of cancer that is diagnosed during pregnancy, its antenatal management, and subsequent maternal and infant outcomes.

Pregnancy-associated cancer (PAC) or gestational cancer (GC), including gestational breast cancer (GBC), is defined as the diagnosis of cancer during pregnancy or within one year of giving birth (Alfasi & Ben-Aharon 2019; Cottreau et al. 2019; Gooch et al. 2020; Lee et al. 2012; Smith et al. 2003). The rationale behind this definition, including a diagnosis of 1-year postpartum, is that the pathogenic origin of cancer will have started during pregnancy (Smith et al. 2003). However, among the available research studies, variations in the length of the postpartum period range from one to two years (Andersson et al. 2015; Eibye, Kjaer & Mellemkjaer 2013; Hartman & Eslick 2016; Macdonald 2020; Strasser-Weippl et al. 2015). Some studies have included only

pregnancies that ended in a birth (Andersson et al. 2009; Lee et al. 2012; Shechter Maor et al. 2019; Smith et al. 2003; Stensheim et al. 2009), whereas others have included all pregnancies, even those resulting in a miscarriage (Cottreau et al. 2019; de Haan et al. 2018; Ives, Saunders & Semmens 2005; Lataifeh et al. 2011).

2.2 Literature review

The literature reviewed for this research includes studies that either examined all types of PAC (Andersson et al. 2015; Lee et al. 2012; Lee et al. 2013; Lu et al. 2017; Momen et al. 2018; Smith et al. 2001; Smith et al. 2003) or one type of cancer, with most of the latter being GBC. While the majority of the studies examined PAC among women giving birth (Andersson et al. 2015; Lee et al. 2012; Lee et al. 2013; Lu et al. 2017; Momen et al. 2018; Smith et al. 2001; Smith et al. 2003), other studies examined PAC for all pregnancies, including spontaneous miscarriage (Eibye, Kjaer & Mellemkjaer 2013; Murgia et al. 2019; Parazzini et al. 2017). While including only women who gave birth is important for investigating the clinical management and treatment regimens to inform the clinical practice, it can lead to the underestimation of the incidence of cancer during pregnancy and the failure to include early pregnancy loss such as miscarriages or termination of pregnancy.

Study inclusion criteria also varied for the studies that focused on GBC. Most of these studies included women who gave birth (Abenhaim et al. 2012; Andersson et al. 2009; Garcia-Manero et al. 2009; Rodriguez et al. 2008; Shechter Maor et al. 2019) and some included all pregnant women (Genin et al.

2016; Gentilini et al. 2005; Halaska et al. 2009; Ives, Saunders & Semmens 2005). Studies that examined PAC included GBC as one of the most common cancers associated with pregnancy. This literature review therefore includes studies that examined PAC in addition to those that examined GBC separately.

2.2.1 Incidence

2.2.1.1 Pregnancy-associated cancer

There is a wide variation in the reported incidence of PAC in the literature. A study using a population health cancer data of New South Wales (NSW), Australia, estimated the incidence of PAC in NSW as 137.3 per 100,000 women giving birth between 1994 and 2008. This was higher than the incidence in Denmark, where it was estimated as 89.6 per 100,000 women giving birth between 1977 and 2006 (Eibye, Kjaer & Mellemkjaer 2013; Lee et al. 2012). In contrast, a recently published US population-based study estimated the incidence of PAC as 109.1 per 100,000 pregnancies in that country (Cottreau et al. 2019). Nevertheless, in studies with similar inclusion criteria, incidence rates differ according to cancer types and geographic areas. The data from NSW show that the most common PAC was malignant melanoma, with the incidence rate representing 45.7 per 100,000 women giving birth, followed by breast cancer at 28.8 per 100,000, thyroid and other endocrine cancers at 17.4 per 100,000 and gynaecological cancers at 14.3 per 100,000 (Lee et al. 2012).

In the US and Italy, breast cancer is the PAC most frequently diagnosed during pregnancy or the postpartum period (Cottreau et al. 2019; Murgia et al. 2019; Parazzini et al. 2017). Murgia and colleagues (2019) analysed Italian data from

2003 to 2015 that included 682,173 pregnancies and found that among the 867 women with PAC, breast cancer was the most common cancer with an incidence of 37.7 per 100,000 pregnancies (Murgia et al. 2019). Similarly, Cottreau et al.'s (2019) population-based study found that the in the US the most common PAC was breast cancer (25%), followed by thyroid (20%) and melanoma (11%) (Cottreau et al. 2019). These statistics confirm the results of a population-based linkage study from Italy that showed that breast cancer is the most common PAC there, with an incidence of 39.9 per100,000 pregnancies (Parazzini et al. 2017). Moreover, a multinational European study found that breast cancer is the most common PAC, representing 39% of all cancers diagnosed during pregnancy (de Haan et al. 2018). The difference in the results regarding the most frequent PAC type might be due to the high incidence of melanoma in Australia compared to the other countries. For example, gestational melanoma incidence in the NSW study was 45.7 per 100,000 women giving birth, yet it was only 6.2 per 100,000 pregnancies in the Italian study (Lee et al. 2012; Murgia et al. 2019).

2.2.1.2 Gestational breast cancer

As with PAC, there is a wide variation in the international reported incidence of GBC, ranging from 6.5 to 37.4 per 100,000 pregnancies or women giving birth (Andersson et al. 2009; Eibye, Kjaer & Mellemkjaer 2013; Ives, Saunders & Semmens 2005; Lee et al. 2012; Shechter Maor et al. 2019). One of the reasons for this variation is the heterogeneity of the studies regarding their inclusion criteria. While some studies included only women who gave birth, others included not only pregnancies that ended in a birth but also those with

early termination. Among the Australian studies, Lee et al. (2012) estimated the overall incidence of GBC (during pregnancy and lactation) in NSW as 28.8 per 100,000 women giving birth, whereas Ives et al.'s (2005) estimation was 23.6 per 100,000 pregnancies (Ives, Saunders & Semmens 2005; Lee et al. 2012). These two studies, however, had different inclusion criteria; Lee et al. (2012) included only women who gave birth and excluded those with miscarriage, while Ives et al. (2005) included all pregnancies. Anderson and colleagues conducted a population-based study in Sweden that was similar to the NSW study; they included only women who gave birth and estimated the incidence as 27.9 per 100,000 women giving birth (Andersson et al. 2009). Shechter et al. (2019) reported a lower rate of GBC (6.5 per 100,000 pregnancies) but they included only women with breast cancer diagnosed during pregnancy (Shechter Maor et al. 2019). The rate of diagnosis of breast cancer during pregnancy has been shown to be lower than that in the postpartum period. Lee et al (2012) estimated the rate of GBC during pregnancy as 7.3 per 100,000 compared to the rate for postpartum GBC of 21.5 per 100,000 women giving birth (Lee et al. 2012).

2.2.1.3 Incidence during pregnancy vs postpartum

The literature shows that the rate of diagnosis of cancer during pregnancy is lower than that in the postpartum. Smith et al. (2003) found that almost two thirds (64%) of PAC were diagnosed in the 12 months postpartum (Smith et al. 2003). Similarly, Lee et al.'s (2012) results show that 72.2% of PAC cases were diagnosed within one year postpartum, with only 27.8% of cases diagnosed during pregnancy (Lee et al. 2012). Similarly, Ives et al. (2005) found that two

thirds of women with GBC were diagnosed postpartum, and only one third diagnosed during pregnancy (Ives, Saunders & Semmens 2005). Possible reasons for the higher rate of diagnosis in the postpartum period may be the inherent difficulties in cancer detection during pregnancy or, alternatively, changes in cancer progression during pregnancy (Andersson et al. 2015; Smith et al. 2003). Purported lower rates of cancer diagnosis during pregnancy may be due to many factors, including the physiological changes during pregnancy masking the clinical signs and symptoms of cancer, as both patients and their physicians relate cancer signs and symptoms (such as darkening mole or hyperpigmentation or the development of benign transient lumps in the breast) to pregnancy; and physicians' reluctance to request radiologic or invasive investigations during pregnancy (Amant, Loibl, et al. 2012; Salani, Billingsley & Crafton 2014; Smith et al. 2003; Stensheim et al. 2009). These suggestions are supported by evidence from a population-based study that included more than 4.5 million women who gave birth in Sweden from 1963 to 2007 (Andersson et al. 2015). That study found that for all types of cancer, the ratio of observed versus expected cases (O/E) for cancers diagnosed during pregnancy was 0.46 (95% CI; 0.43-0.49), while the same ratio for the first six months postpartum was 0.93 (95%CI; 0.88 – 0.98) and for the 7 – 12 months postpartum was 0.96 (95% CI; 0.91 – 1.01), the postpartum ratio twice that of those diagnosed during pregnancy (Andersson et al. 2015). These results reflect a diagnostic delay in 54% of the cases during pregnancy compared to only 4% – 7% within the first year postpartum. Interestingly, an earlier study that used population data from 1970 to 1979 found similar results with (O/E) ratio was 0.64 (95% CI; 0.57-0.76) (Haas 1984).

2.2.1.4 The incidence differs by the pregnancy trimesters

The literature indicates that higher rates of diagnosis occur in the third trimester and, conversely, lower rates of diagnosis occurs in the first trimester. Andersson and colleagues found that for all types of cancers combined, the observed/ estimated (O/E) ratios were 0.66 (95%CI; 0.60 – 0.72) for the cases diagnosed in the third trimester, higher than 0.41 (95%CI; 0.37 – 0.47) in the second trimester, and 0.29 (95%CI; 0.25 – 0.34) in the first trimester (Andersson et al. 2015). The high O/E ratio in the third trimester is most likely due to a higher rate of diagnoses in this trimester. Similar to all types of cancers, the highest rate of breast cancer diagnosed during pregnancy was observed in the third trimester and the lowest rate in the first trimester (Andersson et al. 2015). Smith and colleagues found that the rate of cancer diagnosis increased steadily over the nine months of pregnancy, and over 40% were diagnosed within three months of giving birth (Smith et al. 2003). However, these findings may differ with some types of cancers. For example, colon and endocrine malignancies are more likely to be diagnosed in the second trimester, as the highest O/E ratio occurs between the fourth and the sixth months of pregnancy, while thyroid malignancy diagnosis is more likely in the first trimester, as highest (O/E) ratio occur between the first and the third months (Andersson et al. 2015).

2.2.1.5 The incidence is on the rise

The incidence of PAC has increased in recent years. Stensheim et al. (2009) analysed Norwegian national data from 1967 to 2002 and found an annual increase of 2.5% in the rate of cancer diagnosed during pregnancy and an increase of 1.6% in the rate of cancer diagnosed within six months postpartum

(Stensheim et al. 2009). Similarly, Ebye and colleagues who analysed the Danish national data from 1977-2006, found a 2.9% increase in the PAC rate each year (Eibye, Kjaer & Mellemkjaer 2013). Lee, et al. (2012), who studied 1798 PAC cases in NSW from 1994 to 2008 found that the rate of PAC increased from 112.3 per 100,000 women giving birth in 1994 to 191.5 per 100,000 women giving birth in 2007. However, two recent population-based studies were not able to confirm the increasing incidence over time (Murgia et al. 2019; Parazzini et al. 2017). Parazzini and colleagues (2017) who analysed population-based linked data from Lombardy, Italy, were not able to show the incidence increase over the time, as the trend of risk increase per calendar year was not significant (Parazzini et al. 2017). Similarly, Murgia et al.'s (2019) population-based study conducted in Apulia, Italy, analysed data from 2003 to 2015 and found an increasing incidence trend for the period from 2006 to 2009 only, with a peak in 2009 and unexplained spikes in 2006 and 2011 (Murgia et al. 2019).

2.2.1.6 The incidence and the increase in maternal age

The literature suggests that increasing maternal age can explain the increase in the incidence of PAC (Andersson et al. 2009; Cordeiro & Gemignani 2017; Gooch et al. 2020; Rubach et al. 2018; Stensheim et al. 2009). However, maternal age only partially contributes to this increase (Andersson et al. 2009; Eibye, Kjaer & Mellemkjaer 2013; Lee et al. 2012). Lee et al. (2012) estimated the PAC age-standardised rate in 2007 as 164 per 100,000 pregnancies, which is 14.4% lower than the crude incidence rate for the same year (191.5 per 100 000) (Lee et al. 2012). Therefore, maternal age at conception attributed only

14% of the increase in the incidence rate. These authors suggested that advanced diagnostic procedures, the increase in detection rate, and improved both antenatal and postnatal health care are possible factors responsible for the increase in the PAC rate (Lee et al. 2012). This conclusion is supported by Eibye et al. (2013), who found, after adjusting for women's age that the annual increase in PAC rate was decreased by 44.8% from 2.9 to 1.6% (Eibye, Kjaer & Mellemkjaer 2013). They found the highest proportion of cancers occur in the 25 – 29-year age group and also concluded that age could only partially explain the increase in PAC incidence rate and factors such as improved antenatal care and increase detection rate are other possible explanatory factors (Eibye, Kjaer & Mellemkjaer 2013).

2.2.2 Maternal and neonatal outcomes

2.2.2.1 Maternal pregnancy and birth outcomes

Available evidence suggests that women with PAC have inferior obstetric outcomes compared to women giving birth without a history of cancer. Lee et al. (2012) found that compared to women giving birth without cancer, women diagnosed with cancer during pregnancy have significantly higher risks of thromboembolic events, sepsis and severe maternal morbidities (Lee et al. 2012). In addition, they were more likely to be hospitalised in the antenatal period and to have planned preterm birth, induction of labour, CS delivery, hysterectomy and more extended hospital stays (Lee et al. 2012; Smith et al. 2001). Thromboembolic events, sepsis and other severe maternal morbidities are more likely to affect women who had their cancer diagnosed during

pregnancy than women who were diagnosed postpartum (Lee et al. 2012). Eibye et al. (2013) examined the outcomes for all pregnancies and found that nearly one third of the women with PAC had miscarriage and two thirds of those were induced (Eibye, Kjaer & Mellemkjaer 2013).

Women with GBC are more likely to give birth by labour induction or pre-labour leading to higher rates of iatrogenic preterm birth (Abenhaim et al. 2012; Gomez-Hidalgo et al. 2019). Abenhaim and colleagues (2012) found that women with GBC are more likely to have their labour induced (AOR = 2.25, 95% CI 1.9 – 2.7) and give birth by CS (AOR = 1.16, 95% CI 0.9 – 1.4) (Abenhaim et al. 2012).

2.2.2.2 Neonatal outcomes

Babies born to women with PAC are more likely to be preterm, be at higher risk of neonatal death, have low birthweight, be small for gestational age (SGA), and have more extended neonatal hospital stays (Dalrymple et al. 2005; Lu et al. 2017; Momen et al. 2018; Smith et al. 2001).

Preterm birth

The literature shows that preterm birth is the most common adverse neonatal outcomes for women with cancer diagnosed during pregnancy (de Haan et al. 2018; Loibl et al. 2012; Shechter Maor et al. 2019). Shechter and colleagues (2019) found that the risk of preterm birth among babies born to women with GBC is five times the risk for babies born to women with no cancer (Shechter Maor et al. 2019). de Haan et al. (2018) found a high proportion (48%) of preterm birth among women with any type of cancer diagnosed during pregnancy (de Haan et al. 2018). Similarly, Simoes et al. (2018) found that 53%

of babies of women with GBC were preterm (Simoes et al. 2018). Sun and colleagues (2018) conducted a meta-analysis including seven studies for women with GBC and concluded that babies born to women with GBC are more likely to be born preterm (Sun et al. 2018).

Preterm birth is associated with adverse short and long term outcomes for babies (Melamed et al. 2009; Moster, Lie & Markestad 2008). The literature shows that the leading cause of preterm birth among the babies born to women is iatrogenic to facilitate maternal systemic chemotherapy postpartum (Amant, Van Calsteren, et al. 2012; Loibl et al. 2012).

Preparing and then caring for a preterm baby is demanding and places the mother at increased risk of anxiety and stress (Ionio et al. 2016). Women with GBC already experience high levels of fatigue and sleep disturbance underpinned by both the side effects of chemotherapy and psychological and biological factors (Ancoli-Israel et al. 2014; Bardwell & Ancoli-Israel 2008; Goldstein et al. 2012). Thus, a preterm baby may present unique challenges to a mother coping with cancer symptoms, treatment side effects and providing care for a baby with increased needs.

Loibl et al. (2012), in a multinational population-based cohort study, suggested that a decision to planned preterm birth is "often taken without medical indication" and concluded that delaying systemic chemotherapy for women with early breast cancer until term did not significantly affect their survival rate (Loibl et al. 2012). It is therefore important to consider the long-term impact on the fetus of preterm birth.

Other adverse neonatal outcomes

Momen et al. (2018), a binational population-based register study, found that babies born to women with cancer diagnosed during pregnancy have a higher risk of low birthweight and low Apgar score and they are more likely to be born preterm (Momen et al. 2018). The literature is not consistent regarding the risk of stillbirth or neonatal death for women with PAC. For example, Lu et al. (2017) found a higher risk of stillbirth among women with any type of cancer diagnosed during pregnancy while Dalrymple et al. (2005) found higher odds of stillbirth for women with pregnancy-associated cervical cancer (Dalrymple et al. 2005; Lu et al. 2017). However, Shechter Maor et al. (2019), who examined the outcomes for women with GBC, did not find any difference (Dalrymple et al. 2005; Shechter Maor et al. 2019). Lu et al. (2017) found that the risk of neonatal death for babies born to women with cancer diagnosed during pregnancy was almost three times the risk for babies born to women with no cancer (Lu et al. 2017). Similarly, Lataifeh et al. (2011) found a high proportion (13%) of neonatal mortality for women with cancer diagnosed during pregnancy (Lataifeh et al. 2011); however, Lee et al. (2012) did not find any significant association between PAC and the increased odds of perinatal death (Lee et al. 2012).

2.2.3 The association between breast cancer treatment and birth outcome

There is limited evidence on the impact of maternal systemic chemotherapy to the fetus. International regulations typically exclude pregnant women from randomised trials as they are considered a "vulnerable population" requiring protection for themselves and their fetuses (Blehar et al. 2013; Liu & Mager

2016). Therefore, the impact of in-utero exposure of systemic chemotherapy on fetuses and their perinatal outcomes can only be assessed via observational studies. Furthermore, chemotherapy is often reserved for more invasive disease or breast cancer at a more advanced stage, while breast cancer surgery and radiotherapy are the mainstays of early breast cancer treatment (Bergh et al. 2012; Curigliano et al. 2017). In clinical practice, the timing of when to initiate breast cancer systemic treatment is challenging, especially if breast cancer is diagnosed early in the first trimester, as fetal exposure to chemotherapy during the period of organogenesis (third – eighth weeks of gestation) has been associated with an increased risk of congenital malformations (Albright & Wenstrom 2016; Sadler 2012). Several observational studies have demonstrated that fetal exposure to chemotherapeutic agents during the second and third trimesters does not increase the incidence of major congenital malformations for babies born to women with cancer diagnosed during pregnancy (Abdel-Hady el et al. 2012; Amant, Han, et al. 2015; Hahn et al. 2006; Loibl et al. 2012; Van Calsteren et al. 2010). Hahn et al. (2006) conducted a retrospective cohort study to examine the short-term effect of breast cancer treatment on babies born to women treated for breast cancer during pregnancy (Hahn et al. 2006). They reported that exposure to the chemotherapeutic regimen (5-fluorouracil, doxorubicin, cyclophosphamide) was not associated with major neonatal morbidities or congenital malformation in the short term (Hahn et al. 2006).

However, the literature also shows that exposure to systemic chemotherapy during pregnancy is associated with high rates of preterm birth, small for gestational age, low birthweight, admission to neonatal intensive care units

(NICU), and respiratory distress syndrome (RDS) (Amant, Vandenbroucke, et al. 2015; Loibl et al. 2012; Peres et al. 2001; Van Calsteren et al. 2010).

Amant et al. (2012) found a high rate of preterm birth among babies exposed to chemotherapy (47 out of 70) (Amant, Van Calsteren, et al. 2012). Similarly, Peres et al. (2001) found significantly higher rates of preterm birth among babies exposed to chemotherapy (6 out of 8) compared with non-exposed babies (2 out of 10) (Peres et al. 2001). The high rate of preterm birth is due to the clinical decision to induce labour or to deliver by planned CS to facilitate further treatment in the postpartum period rather than the effect of chemotherapy (Amant, Van Calsteren, et al. 2012; Loibl et al. 2012).

2.2.3.1 Type of therapeutic agents

2.2.3.1.1 Chemotherapy

The literature shows that the most common chemotherapeutic agents used to treat breast cancer in pregnancy are doxorubicin and cyclophosphamide (Cardonick et al. 2010; Loibl et al. 2012). Cardonick et al. (2010) reported that over two thirds of women with GBC received doxorubicin and cyclophosphamide in the second and third trimesters (Cardonick et al. 2010). Loibl and colleagues (2012) conducted a multinational population-based study and found that the most common chemotherapeutic regimens used was the combination of an anthracyline (doxorubicin or epirubicin) and cyclophosphamide, the second-most common regimen was an anthracycline, cyclophosphamide and a taxane, the third-most common regimen included 5-fluorouracil, an anthracycline and cyclophosphamide (Loibl et al. 2012). Both

studies did not find any significant difference in the neonatal outcomes between babies who were exposed to chemotherapy after the first trimester compared to those who were not (Cardonick et al. 2010; Loibl et al. 2012).

2.2.3.1.2 Tamoxifen

Tamoxifen, a selective oestrogen receptor modulator, is used commonly as adjuvant therapy for the treatment of estrogen-positive receptor (ER +ve) breast cancer (Daurio et al. 2016). However, it is contraindicated during pregnancy, as it has been associated with congenital malformations, including ambiguous genitalia and craniofacial malformations (Braems et al. 2011; Peccatori et al. 2018; Zagouri, Psaltopoulou, et al. 2013). Guidelines by the Royal College of Obstetricians and Gynaecologists (RCOG) (2011) on the management of breast cancer during pregnancy recommend that tamoxifen should be delayed until after giving birth (RCOG 2011). These recommendations were based on level-3 evidence (case reports and case series). However, there are some case reports that show the delivery of healthy neonates after exposure to tamoxifen during pregnancy (Oksuzoglu & Guler 2002).

2.2.3.1.3 Trastuzumab

Trastuzumab, a monoclonal antibody that antagonises human epidermal growth factor receptor 2 (HER2), has been associated with oligohydramnios, pulmonary hypoplasia, renal impairment in the fetus and neonatal death; therefore, it's use is contraindicated during pregnancy (Bader et al. 2007; Beale, Tuohy & McDowell 2009; Gottschalk et al. 2011; Shachar et al. 2017). Previous case reports showed that oligohydramnios and renal impairment are reversible

and suggested ceasing the trastuzumab therapy and instituting close monitoring of amniotic fluid and the fetal bladder volume as surrogates for fetal renal function (Bader et al. 2007; Gottschalk et al. 2011; Mandrawa et al. 2011; Rasenack et al. 2016). However, other studies revealed that exposure to trastuzumab during pregnancy does not affect neonatal outcomes (Azim, Metzger-Filho, et al. 2012; Lambertini et al. 2019). Azim et al. (2012) examined the effect of trastuzumab on women who become pregnant while on trastuzumab or within three months of stopping treatment (Azim, Metzger-Filho, et al. 2012). The study concluded that trastuzumab has no adverse effect on fetal development among women who continued their pregnancy, although 25% of the women who were exposed to trastuzumab experienced spontaneous abortion (Azim, Metzger-Filho, et al. 2012). Lambertini et al. (2019) examined the effect of unintentional exposure to trastuzumab during pregnancy on the birth outcomes and reported no congenital malformations or other adverse neonatal outcomes for women who chose to continue their pregnancy (Lambertini et al. 2019). Nonetheless, no reliable conclusion can be drawn from these two studies as both have a small sample size, and trastuzumab was discontinued when pregnancy was confirmed. In addition, the exposure group in both studies also included women who become pregnant within three months or over from the exposure to trastuzumab (Azim, Metzger-Filho, et al. 2012; Lambertini et al. 2019).

2.2.4 Long-term children's outcomes

The information on long-term cognitive, developmental and other outcomes for children born to mothers with PAC is limited. The available data from three

recent studies are reassuring. Passera et al. (2019) examined the effect of in-utero exposure to the chemotherapeutic regimen that includes anthracycline and cyclophosphamide on brain growth and the neurodevelopmental outcome for children born to women with breast cancer and concluded that in-utero exposure to chemotherapy does not affect fetal brain growth (Passera et al. 2019). Amant et al. (2015) found that children born to mothers with PAC did not differ significantly from children in the comparison group in cognitive development at 18 and 36 months using Bayley Scales of Infant Development (Amant, Vandenbroucke, et al. 2015). Similarly, Cardonick et al. (2015) did not find any significant difference between children exposed to chemotherapy during pregnancy and non-exposed children in cognitive function and school performance (Cardonick et al. 2015). Moreover, Hahn et al. (2006) found that of 18 children at school age, 16 have normal development compared to their peers, with only two needing special attention, one with attention deficit syndrome and the other with Downs syndrome(Hahn et al. 2006).

The literature shows that exposure to anthracyclines at a young age is associated with an increased risk of developing cardiovascular disease later in life (Maggen et al. 2020; Mulrooney et al. 2009). Mulrooney et al. (2009) studied the effect of exposure to anthracycline among pediatric cancer survivors and reported that anthracycline exposure (250 mg/m^2 or over) in childhood could result in a significantly increased risk of congestive cardiac failure, and pericardial and valvular diseases up to 30 years after exposure (Mulrooney et al. 2009). Fortunately, studies on babies exposed to anthracyclines during pregnancy do not show the adverse effect on cardiac function (Amant, Vandenbroucke, et al. 2015; Aviles, Neri & Nambo 2006; Murthy et al. 2014).

An earlier study, led by Aviles et al. (2006) examined (clinically and by echocardiogram) participants aged 9 – 29 years who were exposed to in-utero anthracyclines and found no evidence of cardiac dysfunction (Aviles, Neri & Nambo 2006). Similarly, Murthy et al. (2014) assessed the cardiac function at a median age of 7 years for children exposed in-utero to anthracycline, and found no significant cardiotoxic effects (Murthy et al. 2014). In addition, Amant et al. (2015), who analysed data for 26 children exposed in-utero to an anthracycline agent did not find any signs of cardiac dysfunction; however, the cardiac evaluation was performed at an earlier age (36 months) (Amant, Vandenbroucke, et al. 2015).

2.2.5 The psychological impact of PAC

A cancer diagnosis is a stressful event that imposes burdens on women and their families (Kyriakides 2008). The literature shows that women diagnosed with breast cancer are more likely to undergo one or more of the long-term complications such as anxiety, depression, sleep disturbance, fatigue, forgetfulness, loss of sexual interest, cognitive dysfunction, concentration and word-finding disorders, and worry about the future (Burgess et al. 2005; Conner-Spady et al. 2005; de Jong et al. 2005; Fan et al. 2005; Feiten et al. 2014). In addition, 20% – 50% of patients with cancer have anxiety or depression (Singh et al. 2015; Thalen-Lindstrom et al. 2013). Major depressive disorder was found in 34% of cancer patients in a single centre study (Sharpe et al. 2004).

Women in the postpartum period can undergo transient mild psychological changes called postpartum blues that last for several days (Harrison 2013; O'Hara & McCabe 2013). However, they may undergo more severe psychological illnesses, including postpartum depression and, rarely, postpartum psychosis (Harrison 2013; O'Hara & McCabe 2013). The occurrence of pregnancy and cancer at the same time would likely amplify the psychological impacts of these two stressful events on women giving birth (Harrison 2013; Ives, Musiello & Saunders 2012).

Only a small number of studies have been conducted to explore the psychological impact of the diagnosis of cancer on pregnant women (Harrison 2013). Evidence from quantitative studies on the psychological burden of PAC on women is limited. Most studies are qualitative case reports. Henry et al. (2012), in a prospective study, provided valuable quantitative evidence on the psychological impact of cancer diagnosed during pregnancy; they investigated the risk factors for long-term stressors by using two self-administered questionnaires: the Impact of Event Scale (IES) and the Brief Symptom Inventory-18 (BSI-18), both being valid and reliable measures for post-traumatic stressors (Beck et al. 2008; Meachen et al. 2008). Henry et al. (2012) reported a high level of distress among women with PAC regarding intrusive thoughts, anxiety and somatisation (Henry et al. 2012). In addition, they suggested that the proportion of women with distress in the PAC cohort (51%) was higher than in non-pregnant women (30%) in the same cancer registry (Henry et al. 2012). They also suggested that non-ART conception, termination of pregnancy, preterm birth, caesarean delivery, surgery in the postpartum period, insufficient milk for breastfeeding, and cancer recurrence are factors associated with high

levels of long-term distress (Henry et al. 2012). A recent study by Vandenbroucke et al. (2017), which aimed to examine risks for high levels of distress among women with GBC and their partners revealed that women are more willing to continue pregnancy than their partners (Vandenbroucke et al. 2017). However, the study did not show any significant differences between women with PAC and their partners on distress regarding cancer, pregnancy outcome and the health of their child (Vandenbroucke et al. 2017).

2.2.6 Long-term maternal outcomes

2.2.6.1 Survival rate

The effect of pregnancy on the spread of breast cancer has not been adequately studied (Lee et al. 2012; Stensheim et al. 2009). It has been suggested that the increased levels of progesteron, estrogen and insulin-like growth factor-1 during pregnancy may be associated with an increase in the proliferation of tumour cells for women with breast cancer, leading to impact survival for those women in whom breast cancer is diagnosed during pregnancy (Albrektsen et al. 2006; Lyons, Schedin & Borges 2009; Stensheim et al. 2009). It has also been suggested that the increase in breast tissue vascularisation during pregnancy might enhance the development of breast tumours (Albrektsen et al. 2006). In addition, tumour molecular subtypes is another important risk factor associated with the poor survival outcome of women with breast cancer (de Lemos et al. 2019). Nonetheless, the literature reveals that breast cancer in young women, whether pregnant or not, is associated with adverse prognostic factors that lead to poorer survival outcomes, including the

late stage at diagnosis and more aggressive tumours (Assi et al. 2013; Paluch-Shimon et al. 2020). In summary, the potential reasons for the poor survival outcome for women with GBC may include their younger age, the effect of hormonal changes during pregnancy on the growth and metastasis of cancer, the tumour subtype and the stage of cancer at diagnosis (Albrektsen et al. 2006; Amant et al. 2013; Boudy et al. 2018; Cardonick et al. 2010; Genin et al. 2016; Johansson et al. 2018; Ploquin et al. 2018; Ruiz et al. 2017; Stensheim et al. 2009).

2.2.6.1.1 Younger age/tumour subtype

Australian statistics reveal that young women diagnosed with breast cancer have a lower 5-year survival rate than other women diagnosed with breast cancer; the lowest survival rate was among women aged 20 – 24 years (84.7%) and the highest was among women aged 65 – 69 years (93.7%) (Australian Institute of Health and Welfare 2015b, 2019). These findings are supported by studies which report that the mortality rate among premenopausal women with breast cancer is higher than among postmenopausal women (Paluch-Shimon et al. 2020; Partridge et al. 2016). On the other hand, the literature shows that breast cancer in young women is associated with more aggressive molecular tumour subtypes, including the triple-negative and luminal b and HER2- positive tumours (Partridge et al. 2016; Slepicka, Cyrill & dos Santos 2019). It has been suggested that younger age is an independent risk factor for an adverse survival outcome in women with breast cancer (Anders et al. 2009). However, a recent study reported that the effects of age on survival vary with the pathological subtypes of breast cancer; while younger age was an independent

predictor of poor outcome in the luminal tumour, it had a marginal effect on triple-negative subtypes and no effect on HER2–positive subtypes (Partridge et al. 2016).

2.2.6.1.2 The effect of pregnancy

The published literature is inconsistent on whether women with GBC may have a poorer survival outcome than those with breast cancer not associated with pregnancy. Some studies report that the prognosis of women with GBC does not differ from that of young women with breast cancer not associated with pregnancy (Amant et al. 2013; Azim, Santoro, et al. 2012; Boudy et al. 2018; Cardonick et al. 2010; Genin et al. 2016; Murphy et al. 2012; Ploquin et al. 2018; Ruiz et al. 2017; Stensheim et al. 2009), while other studies report poorer survival outcomes for women with GBC (Bae et al. 2018; Gooch et al. 2020; Johansson et al. 2018; Rodriguez et al. 2008). It is worth noting that those studies reporting poorer survival outcome in women with GBC have utilised broader inclusion criteria that include women with breast cancer diagnosed up to 1-year postpartum rather than just women diagnosed during pregnancy. It has been reported that breast cancer diagnosed postpartum is more likely to have metastasised and have a poorer outcome compared to breast cancer diagnosed during pregnancy (Callihan et al. 2013; Ruiz et al. 2017; Stensheim et al. 2009; Van den Rul et al. 2011). This factor may have resulted in confounding in the studies reporting poorer survival in women with GBC that included women diagnosed up to 1-year postpartum; perhaps leading to an erroneous conclusion that a diagnosis of breast cancer during pregnancy may affect the survival outcome.

2.2.6.1.3 The stage of cancer at diagnosis

For women with breast cancer, whether diagnosed during pregnancy or not, the stage at diagnosis is the major contributor to survival rates (de Lemos et al. 2019; Hunter 2000; Ibrahim et al. 2000; Johansson et al. 2018; Stensheim et al. 2009). Johansson and colleagues (2018) who analysed data from Swedish registries between 1992 – 2009 for women aged 15 – 44 years with a diagnosis of breast cancer, reported that the stage of cancer at diagnosis and the progesterone and estrogen receptor status could explain the high mortality rate among women with GBC (Johansson et al. 2018). Similarly, Baulies et al. (2015) found that women with GBC have a significantly poorer survival rate compared with women with breast cancer not associated with pregnancy (Baulies et al. 2015). They also found that this association became non-significant after controlling for women's age and cancer stage at diagnosis and concluded that the delay in breast cancer diagnosis and the advanced stage of cancer is responsible for the high mortality rate rather than the effect of pregnancy (Baulies et al. 2015). Stensheim et al. (2009) reported similar results for women diagnosed with breast cancer during pregnancy, however, for women diagnosed postpartum the poor survival outcome remains significant even after controlling for age and stage of cancer at diagnosis, concluding that the stage of cancer is not an independent risk factor for the adverse survival outcome in this group of women (Stensheim et al. 2009).

2.2.6.2 Post-cancer birth

Advances in cancer diagnosis and treatment have led to substantial improvements in cancer survival rates (Dickman & Adami 2006). In Australia,

approximately 9,000 new cases of cancer are diagnosed annually in women aged 25 – 49 years, with the 5-year relative survival (across all cancers) being over 85% (Australian Institute of Health and Welfare 2014). In addition to dealing with the risks of long-term physical and psychological morbidity that are common to all cancer survivors (Bleyer et al. 2008), female survivors considering pregnancy are also faced with concerns about the impact of cancer therapy on fertility, the ability to maintain a normal pregnancy, and the possibility of adverse outcomes for the baby (Haggar et al. 2014; Schover 2005). There is a lack of epidemiological data on the reproductive potential and successful birthing in women with or following cancer in general. Most of the published research have been either small, institution-based studies or studies that focussed on one specific type of cancer (Bath, Wallace & Critchley 2002; Dalrymple et al. 2005; Gnaneswaran, Deans & Cohn 2012; Langagergaard 2011; Langagergaard et al. 2008; Langagergaard et al. 2007).

Cancer survivors tend to experience more complications in pregnancy, placing them at a higher risk for adverse pregnancy and birth outcomes compared with the general population (Clark et al. 2007; Haggar et al. 2014; Hudson 2010; Madanat-Harjuoja et al. 2010; Madanat et al. 2008; Stensheim et al. 2011; Stensheim et al. 2013; Syse, Kravdal & Tretli 2007). A recent population-based cohort study by Haggar et al. (2014) examined the adverse obstetric, and perinatal outcomes following treatment of young women with cancer (Haggar et al. 2014). They found an increased risk of obstetric complications such as pre-eclampsia and gestational diabetes among women treated for cancer, compared with women with no history of cancer (Haggar et al. 2014). Babies born to cancer survivors experience significantly elevated risks of preterm

delivery, low birthweight and neonatal morbidities (including admission to a special care unit) compared with those born to mothers without a history of cancer (Clark et al. 2007; Haggar et al. 2014; Madanat-Harjuoja et al. 2010; Stensheim et al. 2013).

Previous studies have reported radiation-induced damage to the pelvis as being associated with fetal growth restriction, resulting in excess morbidity compared with the general reproductive population (Green, Hall & Zevon 1989; Green et al. 2010; Green et al. 2002; Heffner 2004). Also, uterine fibrosis has been reported to be associated with cervical incompetence or placentation abnormalities, both of which are related to preterm delivery (Ananth et al. 1999; Ananth & Wilcox 2001; Byrne et al. 1988; Lee et al. 2006; Lumley 2003).

Young women with breast cancer are potentially more willing to conceive after being treated, as many of them will not yet have completed their family at the time of being diagnosed and treated (de Bree et al. 2010; Pagani et al. 2015). Nonetheless, their chances of becoming pregnant are lower than those of other women of similar ages, as some cancer treatments are well known to affect women's fertility (Anderson, Brewster, et al. 2018).

It has been suggested that women who become pregnant after being diagnosed and treated for cancer have better survival rates than women who do not become pregnant after their cancer diagnosis – the so-called "healthy mother effect" (Azim et al. 2011; Stensheim et al. 2009). However, studies reporting this "healthy mother effect" may be flawed in that they did not control for the potential confounding factor that only healthier women may be willing to conceive after treatment for breast cancer, and some of the studies did not

adjust for the immortal time in their analysis (Giobbie-Hurder, Gelber & Regan 2013; Hanley & Foster 2014; Lévesque et al. 2010; Rippy, Karat & Kissin 2009; Valachis et al. 2010).

2.2.7 Diagnosis of breast cancer during pregnancy

Breast lump is the most common presenting symptom of breast cancer in women, representing over 80% of the first presentation, followed by nipple changes and breast pain (Koo et al. 2017). For women with breast cancer diagnosed during pregnancy, a painless breast lump is the most common presenting symptom (Amant, Loibl, et al. 2012; Langer et al. 2014). Lumpiness in the breast of a pregnant woman is not uncommon, as the breasts undergo physiological changes during pregnancy (Amant, Loibl, et al. 2012; Vashi et al. 2013). For these reasons, the diagnosis of breast cancer during pregnancy can present difficulties to women and their health care providers as pregnancy-associated physiological changes may mask breast cancer symptoms (Salani, Billingsley & Crafton 2014). In addition, during pregnancy, many physicians are reluctant to request imaging studies using ionising radiation such as mammography to avoid harm to the conceptus (Langer et al. 2014).

2.2.7.1 Primary diagnostic imaging modalities

2.2.7.1.1 Ultrasonography

Breast ultrasonography is a valuable first-line diagnostic procedure for detecting breast cancer during pregnancy as it is relatively safe and reasonably sensitive (American College of Obstetricians and Gynecologists 2017; Johansson et al.

2019; Langer et al. 2014; Robbins et al. 2011; Taylor et al. 2011). The American College of Obstetricians and Gynecologists (ACOG) recommends that breast ultrasound at lowest possible acoustic output level should be used as the primary diagnostic procedure as it carries a low risk to the fetus (American College of Obstetricians and Gynecologists 2017). Robbins et al. (2011) reported breast ultrasound to be highly sensitive in detecting a malignant breast mass during pregnancy and lactation, with a 100% sensitivity and 86% specificity (Robbins et al. 2011). However, in a recently conducted meta-analysis, Sood et al. (2019) analysed results from 26 studies that examined the effectiveness of using ultrasonography in breast cancer detection and found that the pooled sensitivity was 80.1%, 95% CI: 72.2% to 86.3% and the specificity was 88.4%, 95% CI: 79.5% to 93.6% (Sood et al. 2019).

2.2.7.1.2 Mammography

Health care providers are reluctant to use mammography during pregnancy due to the concerns regarding the safety of ionising radiation on the growing fetus (Langer et al. 2014). It has been reported that the effects of ionising radiation on the fetus can be either deterministic or stochastic (American College of Radiology 2018; Tremblay et al. 2012). Deterministic effects are dose-dependent and associated with damage to a number of cells (cause organ failure), whereas stochastic effects are random (not dose-dependent) and associated with damage to a single cell which can cause carcinogenesis (American College of Radiology 2018; Tremblay et al. 2012). Clinically significant deterministic effects are not expected to occur at a dose lower than 100 mGy (Tremblay et al. 2012). Therefore, the risk of ionising radiation to the

fetus from mammography is low (0.001 – 0.01mGy), and with lead apron shielding this risk can be reduced by half (American College of Obstetricians and Gynecologists 2017; Arasu et al. 2018). Nonetheless, the use of mammography during pregnancy and lactation is controversial. It has been suggested that due to the physiological breast changes in pregnancy, the breast parenchymal tissue become more dense, compromising the sensitivity of mammography in detecting breast tumours in pregnant and lactating women (Arasu et al. 2018; Obenauer & Dammert 2007; Sabate et al. 2007). The sensitivity of mammography during pregnancy has been shown to vary between 78% and 90% (Ahn et al. 2003; de Haan et al. 2016; Langer et al. 2014). This variability in diagnostic sensitivity may reflect the difficulties in image interpretation of breast with high parenchymal tissue density (de Haan et al. 2016).

2.2.7.1.3 Breast magnetic resonance imaging (MRI)

The ACOG has stated that MRI is one of the best diagnostic models to use during pregnancy as it is not associated with adverse outcomes to the mother and the fetus; however, it should only be used when results from other diagnostic models are inconclusive (American College of Obstetricians and Gynecologists 2017). The reported sensitivity of MRI in detecting breast cancer in pregnancy and lactation is 98% (Myers et al. 2017). MRI is superior to ultrasound in detecting deeper soft tissue lesions and similar to ultrasound in safety as it is free of any ionising radiation (American College of Obstetricians and Gynecologists 2017). Gadolinium-enhanced breast MRI has a higher sensitivity in detecting invasive breast cancer, and it accurately measures

tumour size and the extent of disease in the breast and the surrounding tissue (Monticciolo 2011). However, the use of gadolinium-enhanced MRI during pregnancy is controversial. The European Society of Urogenital Radiology (ESUR) has updated their recommendations for the use of gadolinium during pregnancy, stating that in pregnant women gadolinium-based contrast media should only use the low or intermediate risk agents in a low dose and be given only when it provides crucial diagnostic information (Thomsen et al. 2013). A recent Canadian population-based study found that the use of gadolinium-enhanced MRI at any time during pregnancy increased the risk of stillbirth or neonatal death (Ray et al. 2016).

2.2.7.2 Cancer staging

2.2.7.2.1 Computerised tomography (CT)

The ACOG has stated that the CT scan could be used during pregnancy (American College of Obstetricians and Gynecologists 2017). While the use of a CT scan during pregnancy has been increasing annually, its use carries an increased risk of exposure to a high dose of radiation (American College of Obstetricians and Gynecologists 2017; American College of Radiology 2018). However, its use during pregnancy should be limited to the low-exposure technique which can reduce the fetal exposure dose to less than 35 mGy for a single-phase scan of the pelvis (American College of Obstetricians and Gynecologists 2017; American College of Radiology 2018; de Haan et al. 2016). However, while pelvic CT would generally be part of staging for breast cancer, it is not recommended to include the pelvis in CT scanning during any

stage of pregnancy in which ultrasound can be used as an alternative (Peccatori et al. 2018).

2.2.7.2.2 Nuclear medicine

Although the literature on nuclear medicine imaging during pregnancy is sparse, its use is possible when other diagnostic modalities are inconclusive (de Haan et al. 2016). The ACOG (2017) concluded that the use of technetium^{99m} (Tc^{99m}) is considered safe during pregnancy as conceptus exposure resulted from this procedure is low (<5 mGy), and the half-life of this isotope is short (6 hours) (American College of Obstetricians and Gynecologists 2017). However, MRI without gadolinium may be a better alternative to bone scan in cancer staging in cases where metastases are suspected (Zagouri et al. 2016).

2.2.7.3 Breast biopsy

Core needle biopsy (CNB) is considered the standard method to obtain a pathological diagnosis of breast lesion and it continues to replace Fine Needle Biopsy (FNA) in the diagnosis of breast cancer (Brancato et al. 2012). Wang et al. (2017) conducted a meta-analysis that included 12 studies and showed that the pooled sensitivity of CNB is better than that of FNA (87% vs. 74%) and the specificity is nearly similar (98% vs. 96%) (Wang et al. 2017).

2.2.8 Management of breast cancer during pregnancy

2.2.8.1 Approach to management

The management of GBC requires a multidisciplinary team approach, which is essential for the best outcomes for mother and child (Amant et al. 2010). Clinical practice guidelines recommend that the multidisciplinary team may include an obstetrician, surgeon, oncologist, radiation oncologist, and neonatologist, as well as support from specialist nurses and allied health (Peccatori et al. 2013; RCOG 2011).

2.2.8.2 Termination of pregnancy

The literature shows that there is no evidence that pregnancy termination can improve the long-term outcome for women with GBC (Amant et al. 2013; Beadle et al. 2009; RCOG 2011; Yu et al. 2017). Amant et al. (2013) did not find any significant difference in overall survival among women with GBC and non-pregnant women with breast cancer (Amant et al. 2013). Similarly, Beadle et al. (2009) found no significant difference between women with GBC and women with breast cancer not associated with pregnancy in regard to overall survival, local recurrence, and metastasis (Beadle et al. 2009). However, pregnancy termination may be considered if the women is diagnosed with advanced cancer in the early first trimester that requires chemotherapy or with accidental pregnancy while the woman is on tamoxifen or chemotherapy (Peccatori et al. 2013; Zagouri, Psaltopoulou, et al. 2013). Therefore, it is recommended that the decision to terminate a pregnancy should be individually tailored for each

patient, as the survival rate depends on the type and stage of cancer (Shim et al. 2016).

2.2.9 Gaps in the literature

The literature includes clinical practice guidelines in the broader field of cancer; however, there is limited research specific to PAC and its management. Pregnant women are commonly excluded from clinical trials, whether therapeutic or preventive (Blehar et al. 2013). This exclusion has unintended consequences on the women with PAC and has contributed to a paucity of evidence regarding the safety of surgical procedures, chemotherapy and radiotherapy on the women and their offspring (Blehar et al. 2013).

The majority of available evidence regarding the clinical management of women with PAC is low-level evidence based on expert opinion and non-analytical studies (case-control or cohort studies) with a high risk of confounding (RCOG 2011). A recent systematic review found that population-based studies on PAC are limited as it identified only 24 studies, 11 of those on any type of PAC and 13 on a specific type of cancer; of these 13 studies, five were on breast cancer (Dalmartello et al. 2020).

Moreover, evidence from population-based studies on the long-term neurodevelopmental and cognitive outcomes of children born to women with PAC is limited (Amant, Vandenbroucke, et al. 2015; Cardonick et al. 2015).

There is enormous gap of knowledge regarding the impact of PAC on the woman's psychological and mental health, as there are no population-based studies on it and the majority of the existing studies are qualitative involving

women's experiences, case reports or single centre studies (Hammarberg et al. 2018; Henry et al. 2012; Ives, Musiello & Saunders 2012).

2.3 Significance of this thesis

This thesis is a population-based study using two population datasets: a dataset composed of NSW population health and mortality datasets, and the binational prospective AMOSS GBC dataset. It provides evidence-based data to contribute to the epidemiology, outcomes and patterns of care of women with GBC who gave birth in NSW and their babies. It also contributes to the national and international literature on the association between the stage of GBC and timing of diagnosis and the maternal mortality and morbidity. It will provide clinicians and patients with information for use in counselling and planning service needs and provide baseline information on the maternal and neonatal outcomes of women with GBC.

The strength of this thesis is that it uses two types of population-based data; population-linked health, and mortality datasets, both of which allow for women to be followed beyond the neonatal period and also provide information regarding hospital admission for both the mother and the baby. In addition, the prospective population-based AMOSS GBC dataset, which provides details on cancer treatment and diagnostic procedures, has enabled the study to investigate the effects of these interventions on perinatal outcomes.

Chapter 3 Methods

This chapter provides information on the designs, study populations and data sources for the results chapters (Chapters 4, 5, 6 and 7) of this thesis. It also explains the data analysis used in each chapter and the respective ethics approvals.

3.1 Study designs

This thesis includes four observational studies (Chapters 4, 5, 6 and 7). A population-based retrospective cohort study design was used in Chapters 4 (study 1) and Chapter 5 (study 2). A case series analysis with a narrative literature review was the design of Chapter 6 (study 3), and a population-based prospective cohort study design was used in Chapter 7 (study 4).

3.2 Study populations and sources of data

3.2.1 Studies utilising NSW linked population datasets

3.2.1.1 Chapter 4 (study 1): Gestational breast cancer in New South Wales: A population-based linkage study of incidence, management, and outcomes

The population for this study included all women who gave birth in NSW and their babies between 1 January 1994 and 31 December 2013. The datasets used included three linked NSW health datasets: The Perinatal Data Collection (PDC), the NSW Cancer Registry (NSWCR) and the Admitted Patient Data Collection (APDC).

The PDC is a state-wide surveillance system that captures data relating to patterns of pregnancy care, services and outcomes for all births in NSW (whether in public or private hospitals or home births) (CHeReL 2019a). The PDC provides data on pregnancies and births, including demographic characteristics and factors relating to the pregnancy, labour and birth, and perinatal outcomes. The PDC was used as the primary dataset to identify all women who gave birth in NSW between 1 January 1994 and 31 December 2013 and their babies.

The NSWCR is a population-based cancer registry that captures demographic, incidence, cancer stage and death information of all people diagnosed with cancer (excluding non-melanoma skin cancers) in NSW (CHeReL 2019a). The NSWCR was linked to the PDC to identify women with gestational breast cancer (GBC).

The APDC provides information on discharges, transfers or deaths on all patients admitted to all hospitals in NSW (public, private, repatriation and psychiatric hospitals). APDC data were only available from July 2001(CHeReL 2019a).

3.2.1.2 Chapter 5 (study 2): Gestational breast cancer: mortality and giving birth after breast cancer treatment – a New South Wales linkage study

This study used records of all women who gave birth with a first-time diagnosis of breast cancer during pregnancy in NSW and their babies between 1 January 1994 and 31 December 2013. Data were extracted from linked NSW health and mortality datasets. These include the PDC, NSWCR Cause of Death Unit

Record File (COD URF) and the NSW Registry of Births, Deaths and Marriages (RBDM).

Similar to study 1, the PDC was used as the primary dataset to identify all women who gave birth in and their babies during the study period, and the NSWCR was linked to the PDC to identify all women with breast cancer diagnosed during pregnancy.

The NSW RBDM and COD URF were used to obtain maternal and infant mortality information for at least four years from the date of diagnosis of GBC. Data from RBDM were available up to 31 December 2017 (the end of follow up period) and from COD URF up to December 2015.

3.2.1.3 Outcome measures from the data sources of the linked dataset by for Chapter 4 (study 1) and Chapter 5 (study 2)

The PDC contains the maternal outcomes of the women, including the pregnancy and birth outcomes and maternal medical and obstetric history. It also provided information on the perinatal outcomes for the babies and the subsequent births for the women. The APDC contains data on the neonatal outcomes, including the major neonatal morbidities and frequency of hospital admissions. NSWCR contains information on the date of breast cancer diagnosis and the stage of cancer. It also provided information on the date of death, which is used for validation. The mortality data provided information on date and cause of death. Table 3.1 shows the linked data outcome measures with the corresponding data sources.

Table 3.1: Outcome measures from the linked data

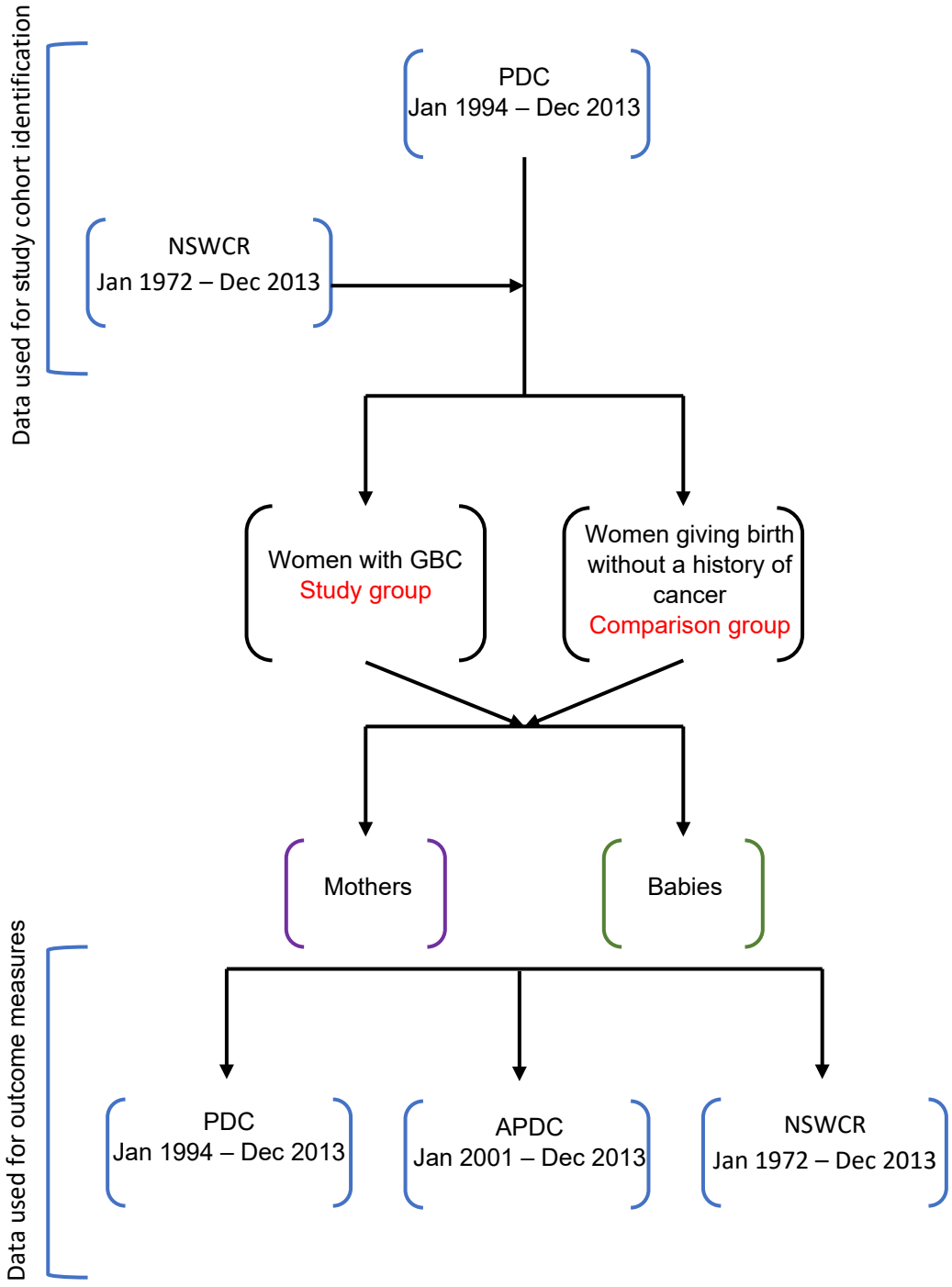
Outcome		**Data source**
Mortalities	Maternal mortality, stillbirth, neonatal mortality	PDC, NSWCR, RBDM, COD URF
Morbidities – pregnancy and birth	Induction of labour, caesarean section, preterm labour (spontaneous and induced), gestational diabetes, preeclampsia, duration of hospital stay, subsequent births	PDC, APDC
Morbidities – Perinatal and infant outcomes	Preterm birth, congenital malformation, small for gestational age, low birthweight, Apgar score, the need for resuscitation, admission to a neonatal intensive, care unit, admission to special care nursery unit, neonatal hospital stay.	PDC, APDC

3.2.1.4 Method of data linkage

The Centre for Health Record Linkage (CHeReL), the NSW data linkage facility established in 2006 (Boyd et al. 2012), linked all perinatal, cancer registry, hospital admission and mortality records. The steps describe in the linkage process are as follows:

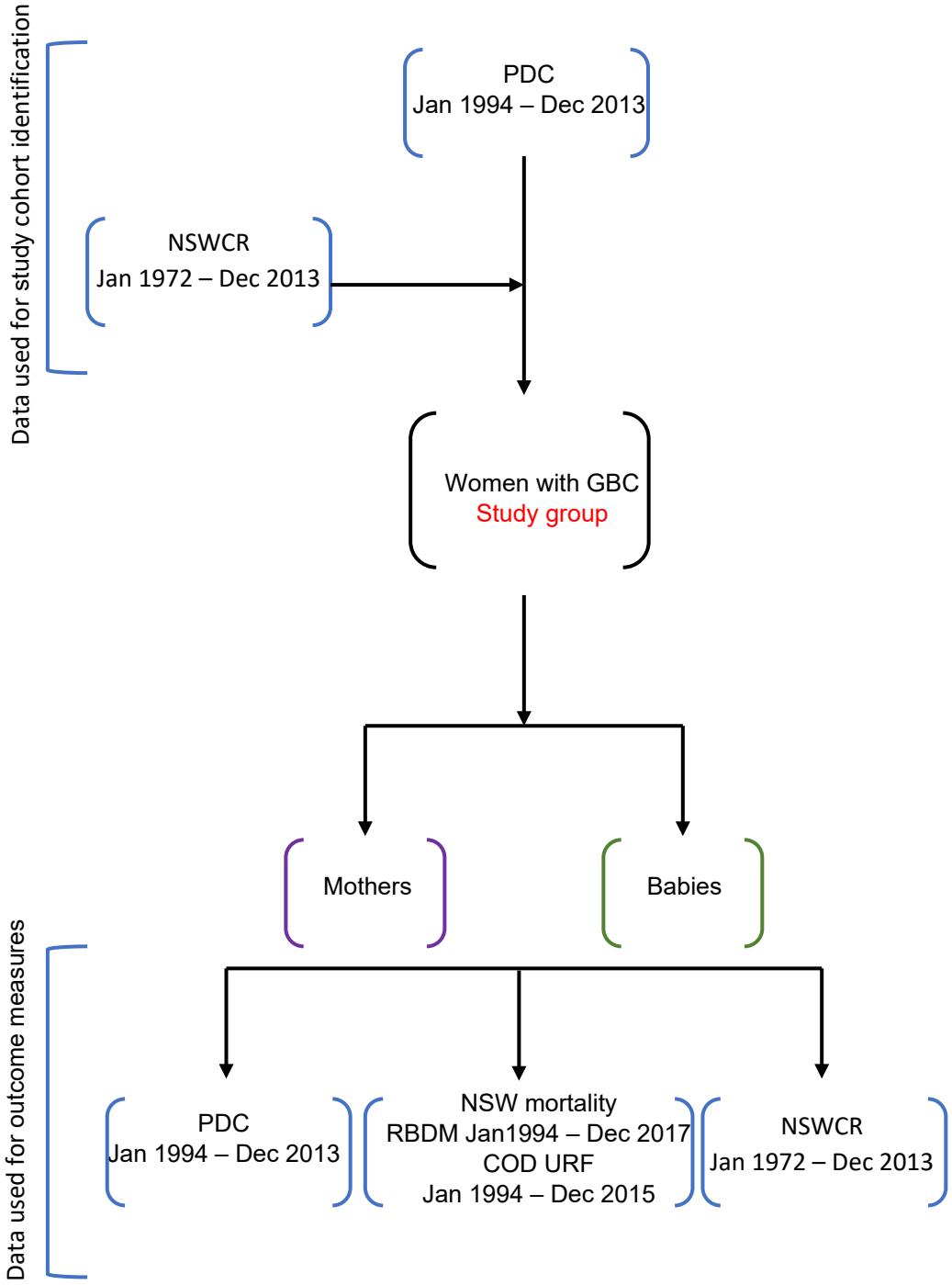
The data custodians provide CHeReL with an encrypted source record number and demographic details for each record in their dataset. Then CHeReL uses probabilistic matching of the demographic details and assigns a CHeReL person number for records that belong to the same person. Once linked, personal identifiers (such as the mother's name and address) are removed, and a unique project person number (PPN) assigned to each mother and baby for this project. The data custodian decrypts the source record number and merges the project person number with the clinical variables that have been approved for use in the project. The researcher is then able to combine the records for the same person from the different datasets using the PPN (Boyd et al. 2012; CHeReL 2019b; Emery & Boyle 2017; Moore et al. 2016). Details on NSW health data sets and the linkage process are available from The NSW Centre for Health Record Linkage (CHeReL), which performed the data linkage (CHeReL 2019a, 2019b). Figures 3.1 and 3.2 show the linked datasets for Chapter 4 (study 1) and Chapter 5 (study 2), respectively.

Figure 3.1: Linked datasets for study 1



APDC: Admitted Patient Data Collection
GBC: gestational breast cancer
NSWCR: NSW Cancer Registry
PDC: Perinatal Data Collection

Figure 3.2: Linked datasets for study 2



COD URF: Cause of Death Unit Record File
GBC: gestational breast cancer
NSWCR: NSW Cancer Registry
PDC: Perinatal Data Collection
RBDM: Registry of Births, Deaths and Marriages

3.2.2 Studies utilised AMOSS GBC dataset

3.2.2.1 Chapter 6 (study 3): Clinical decision making in the management of breast cancer diagnosed during pregnancy: a review and case series analysis.

The study population included women who gave birth with a first-time diagnosis of breast cancer during pregnancy in Australia and New Zealand between 1 January 2013 and 30 June 2014.

Data of this study are a subset of the AMOSS GBC study, which included details on the diagnosis, treatment and outcomes. Data description and method of collection are shown in Section 3.2.2.3 and Section 3.2.2.4.

3.2.2.2 Chapter 7(study 4): In-utero exposure to breast cancer treatment: a population-based perinatal outcome study

The study population in this chapter included babies born to women with a first-time diagnosis of breast cancer during pregnancy through monthly surveillance between January 2013 and June 2014.

The data of this study were extracted from the AMOSS GBC study. Details of this dataset are shown in the next sub-section.

3.2.2.3 AMOSS GBC data description

AMOSS (the Australasian Maternity Outcomes Surveillance System) prospectively collects data from 300 hospitals with eligible maternity units across Australia and New Zealand (Halliday et al. 2013). Eligible maternity units are those with a birth rate of over 50 births per year (Halliday et al. 2013; Safi et al. 2019). AMOSS is a surveillance and research system that monitors rare and serious events in pregnancy such as vasa praevia, eclampsia, amniotic fluid

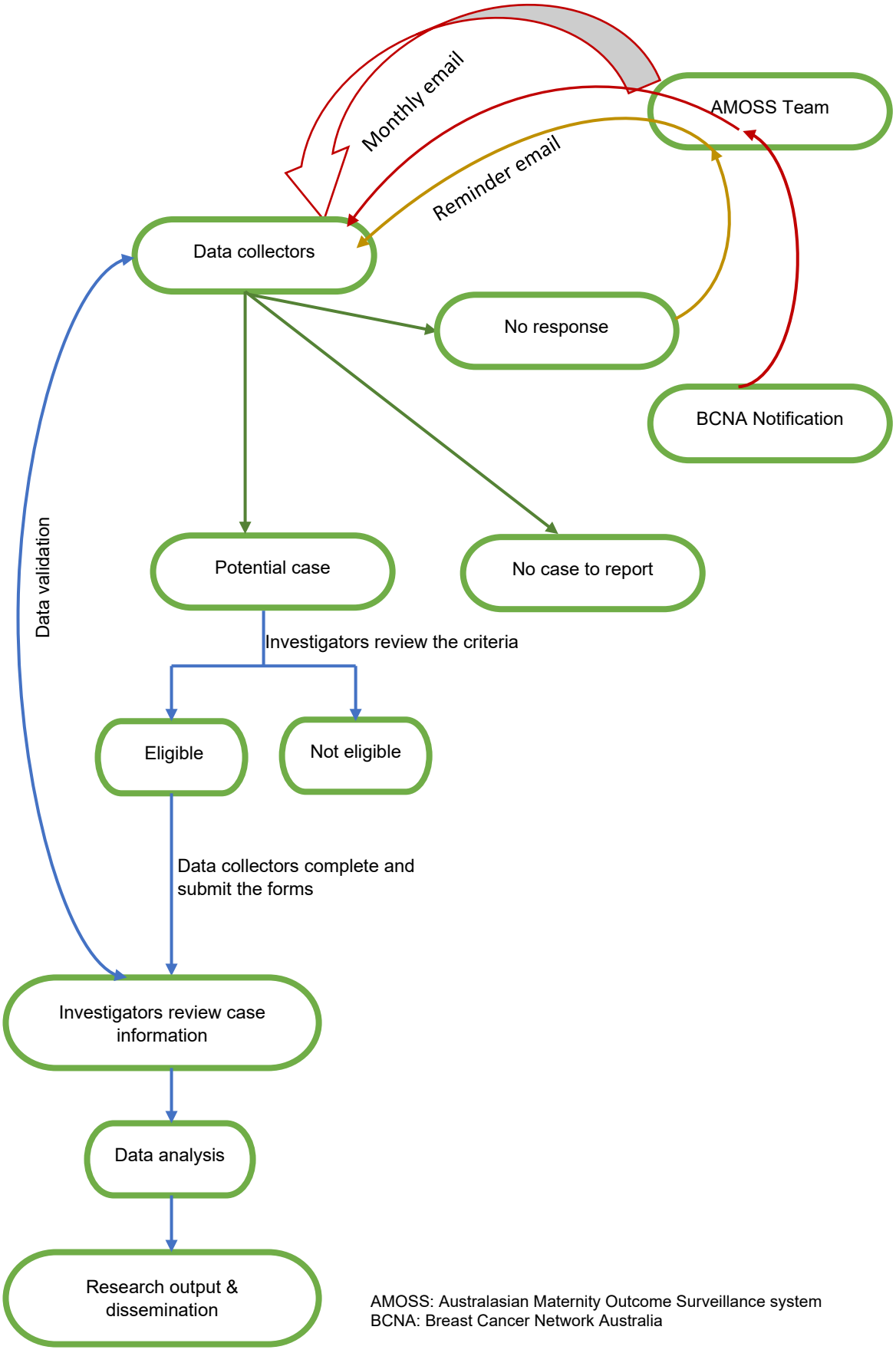
embolism, massive obstetric haemorrhage placenta accrete, and renal disease (Safi et al. 2019; Sullivan et al. 2017).

3.2.2.4 AMOSS case identification and data collection for GBC study

The process of case identification included sending monthly emails via the AMOSS system to the data collectors, asking them whether they had identified a case of a woman with a diagnosis of breast cancer during pregnancy in their hospitals. The email we sent contained a link to an encrypted electronic web-based survey. When data collectors did not complete the survey, we sent them a reminder email asking them to do so. Data collectors from the eligible hospitals identified women with GBC using different sources, including maternity records within the hospital, notifications from clinicians, and audit committees. The AMOSS team also contacted clinicians to ask them to inform data collectors if they cared for a woman with a diagnosis of breast cancer during pregnancy. When they identified an eligible case, the data collectors completed two electronic forms; a general maternity form, and case-specific report form. The general form included data on the obstetric history of the woman and the current pregnancy and birth information. The case-specific report form included data on breast cancer diagnosis (pathology and imaging) and treatment. After completing the two electronic forms, the data collectors then submitted them to AMOSS system. In some instances, when data collectors were not able to complete the electronic forms, they completed the paper version of the forms and sent them to the AMOSS team to enter the data electronically on their behalf. During the period of data collection, data collectors received support and education regarding the study's aims, and inclusion

criteria from AMOSS team. Figure 3.3 summarises the data collection and notification AMOSS GBC study.

Figure 3.3: Data collection and notification AMOSS GBC study



AMOSS: Australasian Maternity Outcome Surveillance system
BCNA: Breast Cancer Network Australia

3.2.2.5 Outcome measures for studies 3 and 4

The AMOSS GBC dataset provided detailed information on pregnancy and birth outcomes. Table 3.2 shows the outcome measures from the AMOSS GBC dataset.

Table 3.2: Outcome measures from the linked data

Outcome	
Maternal – pregnancy and birth	Induction of labour, caesarean section, preterm labour (spontaneous and induced), preeclampsia, duration of hospital stay
Perinatal outcomes	Preterm birth, stillbirth, neonatal death, congenital malformation, small for gestational age, low birthweight, Apgar score, respiratory support, the need for resuscitation, admission to a neonatal intensive, care unit, admission to special care nursery unit, neonatal hospital stay
Breast cancer diagnosis and treatment	Presenting symptom/signs, type of imaging modality used, type biopsy, cancer grade, spread of cancer (lympho-vascular invasion, distant metastasis), type of systemic breast cancer treatment, the multidisciplinary team involved in the management.

3.3 Statistical analysis

In study 1, the chi-squared test, independent samples t-test and Mann–Whitney U test were used to compare the maternal and baby outcomes for women with

GBC and their babies and the women with no cancer and their babies. Binary logistic regression models were used to examine maternal characteristics and outcomes for the women and their babies in the study and comparison groups. Odds ratio (OR) adjusted odds ratio (AOR), and 95% confidence interval (CI) were calculated. A (P-value) of <0.05 was considered as the statistical level of significance.

In study 2, the Kaplan – Meier curve and Logrank test were used to examine the survival rate for women with GBC factored by the stage of cancer at the time of diagnosis. In addition, descriptive statistics were used to report continuous variables, and the paired t-test was used to examine the difference in the outcomes between the birth associated with the diagnosis of GBC (GBC birth) and any subsequent birth by the same women (post-GBC birth).

Study 3 is a case series, which is a descriptive report of six cases with no statistical analysis conducted. In study 4, a chi-squared test, independent samples t-test, and Fisher's exact test were used to examine the difference in the baby outcomes between those exposed to chemotherapy during pregnancy and those who were not.

Details of the statistical analysis section are found in each corresponding study. Statistical Package for Social Sciences (SPSS) version 25.0 were used for data analysis (IBM Corp, New York, United States).

3.4 Ethical considerations

3.4.1 NSW Health and mortality datasets

3.4.1.1 Ethics approval

For the studies that used the NSW linked health data sets (studies 1 and 2), ethical approval was obtained from the NSW Population and Health Services Research Ethics Committee (reference HREC/17/CIPHS/11) and the University of Technology Sydney (UTS) Human Research Ethics Committee (UTS HREC REF NO. ETH18-2362).

3.4.1.2 Informed consent

Studies 1 and 2 are retrospective population-based linkage studies using pre-collected administrative data collections. A waiver of consent was approved to conduct these studies. The justification for the waiver of consent is that participants' involvement in the research carries a negligible risk as the research events have already occurred and the information about women and their cancer diagnosis and birth outcomes have been already collected. The participants had not received any kind of intervention. In addition, no named data would be used, and only aggregate data would be published to minimise any potential breach of participant privacy.

3.4.1.3 Confidentiality, data storage and record retention

All data transferred to the UTS are non-identifiable; all study information was maintained in the strictest confidence following the NHMRC National Statement on Ethical Conduct in Research Involving Humans (The National Health and Medical Research Council. The Australian Research Council and the Australian

Vice-Chancellors' Committee 2007 (Updated May 2015)). The data files are stored on secure network servers at the UTS. Access to the data files is password-protected and restricted to users specified by the UTS Human Research Ethics Committee. The UTS storage system is managed by the eResearch Support Group in the Information Technology Department (ITD) with its physical location held across two UTS data centres. Physical access to data centre sites is controlled by secured doors with limited access for UTS security and IT staff requiring access to the data centre. The storage network is protected by firewalls and intrusion prevention systems managed centrally by the ITD security team. The storage system snapshots the archive regularly to prevent against accidental deletion, and backups may be located on a third-party site in a secured physical cabinet or other security mechanisms. In accordance with the National Statement on Ethical Conduct in Research Involving Humans, the data will be stored on the server mentioned above for seven years after completion of the project (The National Health and Medical Research Council. The Australian Research Council and the Australian Vice-Chancellors' Committee 2007 (Updated May 2015)). Information will be disposed of not before seven years after completion of the project. All electronic files will then be permanently deleted from the computer server, and the research data management systems at the UTS will ensure correct retention and disposal in a timely fashion. All paper documents will be shredded or disposed of in a locked security bin.

3.6.2 AMOSS GBC dataset

3.4.2.1 Ethics approval

Studies that used the AMOSS GBC dataset (studies 3 and 4) received ethics approval from the NSW Population and Health Services Research Ethics Committee (HREC/09/CIPHS/21), multiple Human Research Ethics Committees across Australia. In New Zealand, ethics approval was granted by Multi-Regional Ethics Committee (MEC/09/73/EXP). Ethics approvals were ratified by the UTS Human Research Ethics Committee (HREC Ref No. 2014000417).

3.4.2.2 Confidentiality, data storage and record retention

The raw research data for AMOSS are entered by designated AMOSS data collectors via a web-based data management system. These data are encrypted and secured in a stand-alone research directory on an off-site SQL server. Research dataset files for analysis of AMOSS studies may only be downloaded from the secured SQL server by authorised AMOSS research staff. These datasets are stored and secured with the use of password protected files on a UTS server. Security measures applied to GBC are similar to those applied for the linked health datasets and follow the National Statement on Ethical Conduct in Research Involving Humans (The National Health and Medical Research Council. The Australian Research Council and the Australian Vice-Chancellors' Committee 2007 (Updated May 2015)).

Chapter 4

Study 1 Gestational breast cancer in New South Wales: A population-based linkage study of incidence, management, and outcomes

4.1 Introduction

The incidence of breast cancer diagnosed during pregnancy is increasing and its management is complicated because it requires careful weighing of the potential benefit of breast cancer treatment on maternal survival against risks of such treatment to the developing fetus. This study aimed to examine the incidence, timing of diagnosis, obstetric management, and perinatal outcomes of women with a first-time diagnosis of breast cancer during pregnancy (GBC) and their babies in New South Wales (NSW), Australia. The study also examined whether decisions to deliver preterm babies by labour induction or pre-labour caesarean section (CS) were associated with the timing of diagnosis of breast cancer during pregnancy or the stage of cancer at diagnosis.

This study is currently under review in *PlosOne Journal*:

Nadom Safi, Christobel Saunders, Andrew Hayen, Antoinette Anazodo, Kei Lui, Zhuoyang Li, Marc Remond, Michael Nicholl, Alex Wang, Elizabeth Sullivan. “Gestational Breast Cancer in New South Wales: A population-based linkage study of incidence, management, and outcomes.” *Plos One*.

4.2 Abstract

4.2.1 Background

The incidence of gestational breast cancer (GBC) is increasing in developed countries. Our study aimed to examine the epidemiology, management, and outcomes of women with GBC in New South Wales (NSW), Australia.

4.2.2 Methods

A retrospective cohort study using linked data from three NSW datasets. The study group comprised women giving birth with a first-time diagnosis of GBC, while the comparison group comprised women giving birth without any type of cancer. Outcome measures included incidence of GBC, maternal morbidities, obstetric management, neonatal mortality, and preterm birth.

4.2.3 Results

Between 1994 and 2013, 122 women with GBC gave birth in NSW (crude incidence 6.8/ 100,000, 95%CI: 5.6 – 8.0). Women aged ≥35 years had higher odds of GBC (adjusted odds ratio (AOR) 6.09, 95%CI: 4.02 – 9.2) than younger women. Women with GBC were more likely to give birth by labour induction or pre-labour CS compared to women with no cancer (AOR 4.8, 95%CI: 2.96 – 7.79). Among women who gave birth by labour induction or pre-labour CS, the preterm birth rate was higher for women with GBC than for women with no cancer (52% vs 7%; AOR 17.5, 95%CI: 11.3 – 27.3). However, among women with GBC, preterm birth rate did not differ significantly by timing of diagnosis or cancer stage.

Babies born to women with GBC were more likely to be preterm (AOR 12.93, 95%CI 8.97 – 18.64), low birthweight (AOR 8.88, 95%CI 5.87 – 13.43) or admitted to higher care (AOR 3.99, 95%CI 2.76 – 5.76) than babies born to women with no cancer.

4.2.4 Conclusion

Women aged ≥35 years are at increased risk of GBC. There is a high rate of preterm birth among women with GBC that is not associated with timing of diagnosis or cancer stage. Most births followed induction of labour or pre-labour CS, with no major short-term neonatal morbidity.

Keywords: Breast cancer, pregnancy, incidence, perinatal outcomes.

4.3 Introduction

In 2018, breast cancer was the most commonly diagnosed cancer in women, globally representing 24.2% of all cancers in women and the most common cause of cancer-related mortality in women (Ferlay et al. 2019). In Australia, breast cancer is the second-most common cancer diagnosed during pregnancy, with an incidence of 7.3 per 100,000 women giving birth (Lee et al. 2012) The incidence of GBC, defined as a first-time diagnosis of breast cancer during pregnancy, is increasing in high-income countries in part due to the increasing age of mothers (Andersson et al. 2009; Durrani, Akbar & Heena 2018; Shechter Maor et al. 2019).

Women with GBC have higher rates of adverse obstetric outcomes, including thromboembolic events, sepsis, induction of labour and pre-labour CS (Amant, Vandenbroucke, et al. 2015; Lee et al. 2012; Van Calsteren et al. 2010). Preterm birth has been identified as the main adverse neonatal outcome for babies born to women with GBC (Amant, Vandenbroucke, et al. 2015). Decisions around preterm delivery in the majority of cases of GBC are taken

without any obvious clinical indication (Loibl et al. 2012). This is concerning, as it has been suggested that preterm birth is the main risk factor for developmental problems in babies born to women with GBC, irrespective of whether or not they were exposed to chemotherapy during pregnancy (Amant, Vandenbroucke, et al. 2015).

Our study aimed to examine the incidence, timing of diagnosis, obstetric management and perinatal outcomes of women with a first-time diagnosis of GBC and their babies in New South Wales (NSW), Australia. We also examined whether decisions to deliver preterm babies iatrogenically by labour induction or pre-labour CS were associated with the timing of breast cancer diagnosis during pregnancy and/or the stage of cancer at diagnosis.

4.4 Methods

We conducted a population-based cohort study using linked NSW Health data. The study population included all women with pregnancies that ended in live birth or stillbirth in NSW between 1 January 1994 and 31 December 2013. Birth was defined as the delivery of an infant of at least 400 grams birthweight or at least 20 weeks' gestation, whether live or stillborn (Centre for Epidemiology and Evidence 2018). For this study, GBC was defined as a first-time diagnosis of primary breast cancer during pregnancy.

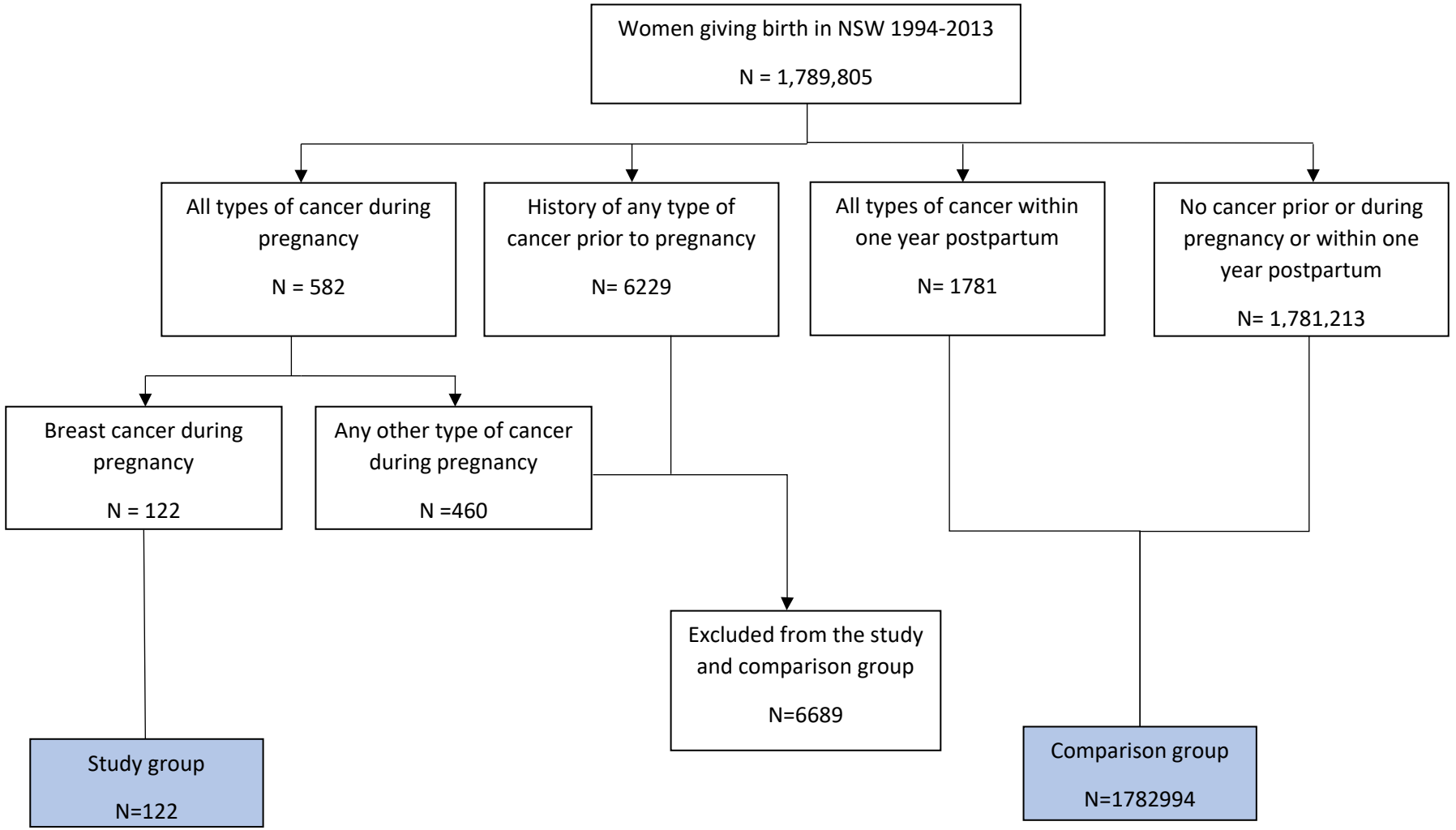
The study group comprised all eligible pregnancies with GBC. The comparison group comprised women who delivered with no history of cancer before or during pregnancy (Figure 4.1). The rationale for using a population-based comparison group is that: 1) a large sample size increases the statistical

precision of analyses (i.e. with a large comparison group, we can obtain a more precise estimate of the true difference between groups compared with using a small comparison group), 2) increases the representativeness of the target population, and 3) minimises any potential selection bias (Hemkens, Contopoulos-Ioannidis & Ioannidis 2016; Riniolo 1999; Thygesen & Ersbøll 2014).

We used three linked datasets: Perinatal Data Collection (PDC), the NSW Cancer Registry (NSWCR) and the Admitted Patient Data Collection (APDC). The NSW Centre for Health Record Linkage (CHeReL) performed the data linkage and details of the data linkage process are available on the CHeReL website (CHeReL 2019b). The PDC is a state-wide surveillance system that captures data relating to patterns of pregnancy care, services and outcomes for all births in NSW (whether in public or private hospitals or home births) (CHeReL 2019a). The NSWCR is a population-based cancer registry that captures demographic, incidence, cancer stage and death information of all people diagnosed with cancer (excluding non-melanoma skin cancers) in NSW (CHeReL 2019a). The APDC provides information on discharges, transfers or deaths on all patients admitted to all hospitals in NSW (public, private, repatriation and psychiatric hospitals). APDC data were only available from July 2001 (CHeReL 2019a). The PDC was used as the primary dataset to identify the study cohort (NSW pregnancies from 1994 to 2013) and the NSWCR was used to identify the group of women with GBC in the study cohort. The APDC was merged based on the babies' Project-specific Person Numbers (PPN) (CHeReL 2019b) and was used to determine the frequency of hospital

admissions and any diagnoses during the neonatal period for babies born to women with GBC.

Figure 4.1: Selecting the study and comparison groups



The degree of spread of cancer is categorised as follows: stage 1 is defined as cancer localised to the tissue of origin; stages 2-3 are defined as cancer that has spread to the regional lymph nodes and/or adjacent organs (the chest wall and/or the skin); stage 4 involves distant metastasis (CHeReL 2019a; Royal College of Pathologists of Australasia 2012). Our dataset did not include information on stage 0 cancer, carcinoma in situ (CIS).

We classified women giving birth in NSW into three groups:

1. The study group (GBC group) comprised women with a first-time diagnosis of breast cancer during pregnancy;
2. The comparison group comprised women without a history of cancer before or during pregnancy: and
3. An excluded group that comprised women with any type of cancer (including breast cancer) diagnosed prior to pregnancy (as prior cancer and its treatment may affect pregnancy outcomes (Dalberg, Eriksson & Holmberg 2006; Momen et al. 2018)) and women with cancer other than breast cancer diagnosed during pregnancy (as any decisions on their pregnancy management may not have differed from those for women with GBC).

4.4.1 Main outcome measures

Maternal outcomes included pregnancy and birth management and complications (induction of labour, CS), pregnancy complications (gestational diabetes and gestational hypertension) and maternal mortality. Neonatal outcomes included perinatal death (stillbirth or neonatal death), preterm birth (<37 weeks gestation), low birthweight (<2500 gm), small for gestational age

(SGA) (birthweight below the 10th percentile for the age and sex (Li et al. 2015)), intraventricular haemorrhage, and respiratory distress syndrome of newborn.

4.4.2 Statistical analysis

The chi-squared test was used to compare the prevalence of SGA between preterm and term babies born to women with GBC. Mann–Whitney U test was used to examine the difference in median gestational age at birth between women with GBC and women with no cancer. Independent samples t-test was used to compare the mean difference in maternal age and baby birthweight between the study and comparison groups.

A Poisson regression model was used to examine the estimated increase in the incidence of GBC each year. The indirect age-standardised rate was used to account for the increasing maternal age during the study period when examining the incidence of GBC. As our data comprised population data, we used all women giving birth during the study period as a standard population for the calculation of the indirect age-standardised rate.

Binary logistic regression models were used to identify independent factors associated with dichotomous outcomes. Analysis of neonatal outcomes was limited to singleton births due to the small number of multiple pregnancies (1.6%), the lack of data on the second baby in twin pregnancies, and to avoid the confounding effect of multiple pregnancies (Papiernik et al. 2010). These models incorporated all factors associated with each outcome in univariable analyses ($p<0.20$). Potential confounders including maternal age, parity, plurality, pre-existing chronic conditions such as diabetes and hypertension,

previous CS, smoking during pregnancy, hospital sector (public or private) and remoteness of residence were also included. Odds ratio (OR), adjusted odds ratio (AOR), and 95% confidence interval (CI) were calculated and variables with a statistical level of significance (P-value) of <0.05. Clinicians in the research team determined which interactions were plausible and we limited our investigations to these. All variables in a regression models were assessed for collinearity with the variance inflation factor (VIF) threshold is <3. We tested the interaction term between pre-existing hypertension and smoking during pregnancy, and there is no evidence of interactions (Wald-test p>0.05). Statistical Package for Social Sciences (SPSS) version 25.0 was used for data analysis (IBM Corp, New York, United States).

4.4.3 Ethics approval

NSW Population & Health Services Research Ethics Committee provided the ethical approval for the project (reference HREC/17/CIPHS/11) and the University of Technology Sydney (UTS) Human Research Ethics Committee (UTS HREC REF NO. ETH18-2362).

4.5 Results

There were 122 women with a first-time diagnosis of breast cancer during pregnancy (GBC group) and 1,782,994 women who gave birth without a history of any type of cancer before or during pregnancy (Figure 4.1).

4.5.1 Incidence of GBC

The crude incidence rate of GBC in NSW from 1994 to 2013 was 6.8 diagnoses of GBC per 100,000 women giving birth (Figure 4.2). The incidence of GBC increased from 5.8 per 100,000 women giving birth in 1994 to 7.3 per 100,000 women giving birth in 2013, reaching a peak of 13.6 per 100,000 women giving birth in 2011. This represents an average annual increase of 2.8% (95%CI: 0.3% – 5.9%) per year. However, this increasing trend in incidence was not significant (p=0.075).

4.5.2 Maternal characteristics

4.5.2.1 Age

The mean (SD) age of women with GBC was significantly higher than that of women giving birth with no cancer (34.8 $\pm$ 4.4 years vs 29.6 $\pm$ 5.6 years, p<0.001; mean difference 5.27 years (95%CI 4.48 – 6.1)). The odds of GBC among women aged ≥35 years was six times the odds for those aged <35 years (AOR 6.09, 95%CI 4.02 – 9.20) (Table 4.1). Among women with GBC, there were 16 (13%) aged less than 30 years, 33 (27%) aged between 30 to 34 years, 54 (44%) between 35 to 39 years, and 19 (16%) aged 40 years or over.

4.5.2.2 Timing of diagnosis and stage of cancer

Of the 122 women with GBC, 25 (20.5%) were diagnosed in the first trimester, 39 (32.0%) in the second trimester, and 58 (47.0%) in the third trimester. Data on cancer stage were available for 113 women (92.6%) and missing for nine (7.4%). Of the 113 women with a known cancer stage, 42 (37.2%) were stage 1, 64 (56.6%) were stages 2-3, and seven (6.2%) were stage 4 cancer.

4.5.2.3 First-time mothers

Women with GBC were less likely to be first-time mothers (nullipara) than women in the comparison group (32% vs 41.8%). However, when adjusting for age and other maternal characteristics, the association was not significant (AOR 1.09, 95%CI: 0.70 – 1.68) (Table 4.1).

Figure 4.2: Crude, indirect age-standardised incidence rate with upper and lower limits for 95%CI of the indirect age-standardised incidence rate of breast cancer diagnosis during pregnancy in NSW 1994–2013 per 100,000 women giving birth

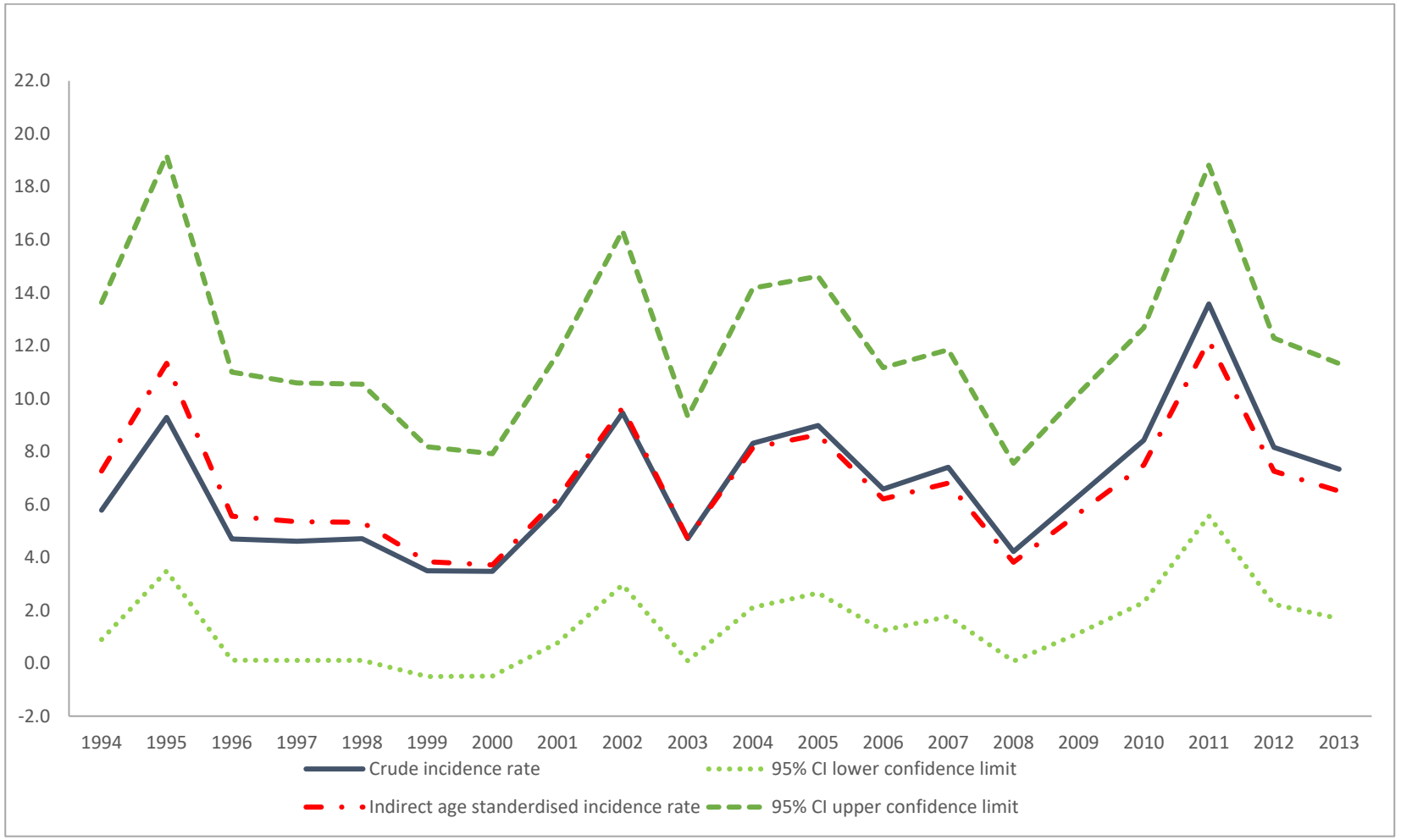


Table 4.1 Maternal characteristics and pre-existing conditions

	Breast Cancer N=122	No cancer (N=1,782,994)	OR (95% CI)	AOR (95% CI)
Country of birth				
Other countries	40(32.8)	517504(29.0)		Reference
Australia	82(67.2)	1260229(70.7)	0.84(0.58-1.23)	1.17 (0.76-1.79)
Not stated*	0(0.0)	5261(0.3)		
Maternal age				
<35	49(40.2)	1431525(80.3)		Reference
=>35	73(59.8)	350771(19.7)	6.08(4.23-8.73)	6.16 (4.09-9.27)
Not stated*	0(0.0)	698(0.0)		
Parity				
Nullipara	39(32)	744494(41.8)	Reference	Reference
Para 1+	83(68)	1036047(58.1)	1.53(1.05-2.24)	1.08 (0.7-1.67)
Not stated*	0(0.0)	2453(0.1)		
Plurality				
Singleton	120(98.4)	1756474(98.5)	Reference	Reference
Multiple pregnancy	2(1.6)	26520(1.5)	1.1(0.27-4.47)	0.52 (0.07-3.73)
Previous CS				
No previous CS	86(70.5)	1369535(76.8)	Reference	Reference
CS 1+	18(14.8)	193811(10.9)	1.48(0.89-2.46)	0.97 (0.57-1.68)
Not stated*	18(14.8)	219648(12.3)		
Smoking during pregnancy				
No	118(96.7)	1502063(84.2)	Reference	Reference
Yes	4(3.3)	275928(15.5)	0.18(0.07-0.50)	0.29 (0.11-0.79)
Not stated*	0(0.0)	5003(0.3)		
Pre-existing hypertension				
No	118(96.7)	1767310(99.1)	Reference	Reference
Yes	4(3.3)	15684(0.9)	3.82(1.41-0.35)	2.43 (0.77-7.69)
Pre-existing diabetes				
No	122(100)	1772966(99.4)	NA	NA
Yes	0(0.0)	10028(0.6)	NA	NA
Remoteness				
Major Cities	101(82.8)	1354589(76.0)	Reference	Reference
Inner Regional	17(13.9)	308563(17.3)	0.74(0.44-1.24)	0.99 (0.57-1.75)
Outer Regional	3(2.5)	88797(5.0)	0.45(0.14-1.43)	0.74 (0.23-2.35)

	Breast Cancer N=122	No cancer (N=1,782,994)	OR (95% CI)	AOR (95% CI)
Remote/very remote	1(0.8)	12583(0.7)	1.07(0.15-7.64)	2.14 (0.3-15.47)
Not stated*	0(0.0)	18462(1.0)		

*OR: crude odds ratio, AOR: adjusted odds ratio *Not included in the analysis, #No previous birth.*

4.5.2.4 Pregnancy complications and obstetric management (mode and timing of birth)

There were no significant differences in the rates of gestational diabetes, gestational hypertension or hospital transfer for women with or without GBC (Table 4.2).

Table 4.2 Obstetric management and pregnancy complications by cancer status

Outcome	Breast cancer	No cancer (reference)	OR(95% CI)	AOR(95% CI)*
Induction of labour				
No	29(23.8)	1087440(61.0)		
Yes	51(41.8)	438172(24.6)	4.36(2.77-6.89)	4.40 (2.63-7.38)
Not applicable (Pre-labour CS)**	42(34.4)	256929(14.4)		
Not stated*	0(0.0)	453(0.0)		
Induction of labour or pre-labour CS				
No	29(23.8)	1087440(61.0)		
Yes	93(76.2)	695101(39.0)	5.02(3.31-7.61)	4.96 (3.06-8.05)
Not stated	0(0.0)	453(0.0)		
Mode of birth				
Vaginal birth***	67(54.9)	1330464(74.6)		
Birth By CS	55(45.1)	451638(25.3)	2.42 (1.69-3.46)	2.46 (1.57-3.86)
Not stated	0(0.0)	892(0.1)		
Gestational diabetes				
No	117(95.9)	1701488(95.4)		
Yes	5(4.1)	81506(4.6)	0.89 (0.36-2.18)	0.57 (0.21-1.56)
Gestational Hypertension				
No	118(96.7)	1674225(93.9)		
Yes	4(3.3)	108769(6.1)	0.52 (0.19-1.41)	0.55 (0.20-1.51)
Hospital sector				
Public	86(70.5)	1395153(78.2)		
Private	36(29.5)	387799(21.7)	1.51 (1.02-2.22)	1.11 (0.72-1.73)
Not stated**	0(0.0)	42(0.0)		
Transferred to another hospital				
No	118(96.7)	1723181(96.6)		

Yes	4(3.3)	59053(3.3)	0.99 (0.37-2.68)	1.40 (0.50-3.92)
Not stated**	0(0.0)	760(0.0)		

*OR: crude odds ratio, AOR: adjusted odds ratio *All variables are adjusted for maternal characteristics **Not included in the analysis, ***Including breech and instrumental birth.*

4.5.2.5 Birth intervention

Among women with GBC, 51 (41.8%) had labour induction; of these, 41 (80.4%) had a vaginal birth and 10 (19.6%) gave birth by CS (Table 4.2). After adjusting for maternal characteristic, pre-existing conditions and hospital sector (public or private), women with GBC had significantly higher odds of labour induction (AOR 4.40, 95% CI: 2.63 – 7.38) and CS (AOR 2.46, 95% CI: 1.57 – 3.86) than women without cancer (Table 4.2).

4.5.2.6 Labour induction and pre-labour CS

Ninety-three (76.2%) women with GBC gave birth either by labour induction or pre-labour CS compared to 695,101 (39%) in the control group. After adjusting for maternal characteristics, pre-existing conditions and hospital sector, the odds of labour induction or pre-labour CS were significantly higher in the GBC group (AOR 4.96, 95% CI 3.06 – 7.79) (Table 4.2).

Among women who gave birth by labour induction or pre-labour CS, there was a higher rate of preterm birth in women with GBC (n=48, 51.6%) compared to women with no cancer (n=46,855, 6.7%) p<0.001.

4.5.2.7 Timing of diagnosis, stage of cancer and birth by labour induction or pre-labour CS

Among the 93 women with GBC who gave birth by labour induction or pre-labour CS, 10 (10.8%) were diagnosed in the first trimester, 32 (34.4%) in the second trimester, and 51 (54.8%) in the third trimester. Of those

women diagnosed in the third trimester, 39 (76.5%) were diagnosed before 37 weeks gestation. Seven (70%) of the women diagnosed in the first trimester gave birth prematurely compared to 19 (59%) of the women diagnosed in the second trimester and 22 (56%) of the women diagnosed in the third trimester before 37 weeks gestation. However, the rate of preterm birth among women diagnosed in the second and third trimester (<37 weeks) was not significantly different from that in women diagnosed in the first trimester (OR 0.63, 95%CI: 0.14 – 2.88 and OR 0.55, 95%CI: 0.12 – 2.47 respectively) (Table 4.3).

Table 4.3: Timing of diagnosis and stage of cancer by gestational age at birth for the 93 women who gave birth by induction of labour or pre-labour CS.

	Preterm<37 weeks N (%)*	**Term =>37 weeks N (%)***	**OR (95% CI)**
Timing of diagnosis			
1st trimester	7(70.0)	3(30.0)	Reference
2nd trimester	19(59.4)	13(40.6)	0.63 (0.14-2.88)
3rd trimester*	22(56.4)	17(43.6)	0.55 (0.12-2.47)
Cancer stage			
Stage 1	14(51.9)	13(48.1)	Reference
Stages 2-3	31(57.4)	23(42.6)	1.25 (0.49-3.17)
Stages 4	1(16.7)	5(83.3)	0.19 (0.02-1.81)
Not stated**	2(33.3)	4(66.7)	

**For women who were diagnosed before 37 weeks only, **Not included in the analysis*

Among the 93 women with GBC who gave birth by labour induction or pre-labour CS, there were 27 (29.0%) with cancer stage 1, 54 (58.1%) with stages 2-3, and six (6.5%) with stage 4. Cancer stage was not known for six (6.5%) women. Fourteen (52%) of the women with stage 1 delivered prematurely compared to 31 (57%) of the women with stages 2-3 and one (17%) of the women with stage 4. The rate of preterm delivery among women with cancer stages 2-3 or stage 4 was not significantly different

from that in women with cancer stage 1 (OR 1.25, 95%CI: 0.49 – 3.17 and OR 0.19 95%CI: 0.02 – 1.81 respectively) (Table 4.3).

4.5.2.8 Neonatal outcomes

Table 4.4 describes the neonatal outcomes for 120 singleton babies born to women with GBC and 902,653 singleton babies born to women with no cancer. There were no stillbirths or neonatal deaths among babies born to women with GBC. Among singleton babies born to women with GBC, 53 (44.2%) were born preterm; 8 (15.1%) of these babies were delivered at 29 - 32 weeks' gestation while 45 (84.9%) were delivered at 33 - <37 weeks' gestation. Babies born to women with GBC were more likely to require a high level of resuscitation, including intermittent positive pressure respiration and external cardiac massage (11% vs 5%, AOR 2.01, 95%CI: 1.12 – 3.62). They are also more likely to be admitted to special care nursery (SCN) or neonatal intensive care unit (NICU) (42% vs 15% AOR, 3.74, 95%CI: 2.58 – 5.43) than babies born to women with no cancer. Four neonates had major neonatal morbidities; one baby had congenital cardiomyopathy and three (34-, 34- and 33-weeks' gestation) had respiratory distress syndrome of newborn, two of whom required prolonged ventilatory support. Two of those with respiratory distress syndrome were born at 34 weeks gestation and one at 33 weeks gestation.

Table 4.4: Neonatal outcomes for singleton babies by maternal cancer status.

Outcome	Breast cancer	No cancer (reference)	OR (95% CI)	AOR (95% CI)*
Sex of baby				
Male	59(49.2)	903557(51.4)		
Female	61(50.8)	851876(48.5)	1.10 (0.77-1.57)	1.10 (0.77-1.57)
Indeterminate**	0(0.0)	222(0.0)		
Not stated**	0(0.0)	819(0.0)		
Preterm birth				
No	67(55.8)	1654251(94.2)		
Yes	53(44.2)	101834(5.8)	12.85(8.96-18.43)	13.17(9.14-18.96)
Not stated	0(0.0)	389(0.0)		
Small for gestation* **				
No	108(90.0)	1568077(89.8)		
Yes	12(10.0)	178297(10.2)	0.98 (0.54-1.78)	1.18 (0.65-2.16)
Birthweight<2500 g**				
No	88(73.3)	1668218(95.5)		
Yes	32(26.7)	77482(4.4)	7.85 (5.24-11.77)	9.1 (6.02-13.77)
Not stated**	0(0.0)	674(0.0)		
5 min Apgar* **				
>7	115(95.8)	1686705(96.6)		
7 or less	5(5.8)	54000(4.1)	1.36 (0.56-3.33)	1.32 (0.54-3.24)
Not stated	0(0.0)	5669(6.2)		
High resuscitation*#				
No	86(71.7)	1305741(74.8)		
Yes	13(10.8)	91537(5.2)	2.16 (1.20-3.87)	2.01 (1.12-3.62)
Not stated**	21(17.5)	349096(20.0)		
Admitted to SCN/NICU for 4 hours or more* **				
No	70(58.3)	1480563(84.8)		
Yes	50(41.7)	264646(15.2)	4.00 (2.78-5.75)	3.74 (2.58-5.43)
Not stated**	0(0.0)	1165(0.1)		
Discharge status				
Discharged	113(94.2)	1664307(94.8)	NA	NA
Stillborn	0(0.0)	10100(0.6)		
Neonatal death	0(0.0)	3965(0.2)		
Transferred	7(5.8)	77088(4.4)		
Not stated	0(0.0)	1014(0.1)		

*OR: crude odds ratio, AOR: adjusted odds ratio *All variables are adjusted for maternal characteristics (5 min Apgar, High resuscitation and Admitted to SCN/NICU are also adjusted to the method of birth), **Not included in the analysis, ***live birth only, # intermittent positive pressure respiration and external cardiac massage*

The median gestational age at birth for babies born to women with GBC was lower than babes born to women with no cancer (37 weeks (IQR 35 – 38) vs 39 weeks (IQR 38 - 40), $p < 0.001$). The odds of preterm birth were

higher in babies born to women with GBC (AOR 12.93, 95% CI 8.97 – 18.64).

The mean birthweight for live-born singletons to women with GBC was significantly lower than that for those born to women with no cancer (2,905 ± 634 g vs 3,409 ± 546 g, p<0.001). The birthweight distribution for preterm babies in both groups is shown in Table 4.5.

4.5.2.9 Preterm birth in babies born to women with GBC

There were 53 (44.2%) preterm births among the 120 singletons born to women with GBC. Of these, 22 (42%) were born by induction of labour and 26 (49%) were born by pre-labour CS. Thirty-five (66%) of the preterm births were late preterm born between 34 and 36 weeks' gestation, 17 (32.1%) were moderately preterm (32-33 weeks' gestation), and one (1.9%) was early preterm (<32 weeks' gestation) (Table 4.5).

The mean birthweight of preterm babies born to women with GBC (2,469 ± 453 g) was significantly lower than term babies (3,250 ± 539 g) (p<0.001). Among the preterm babies of women with GBC, there were 29 (54.7%) babies with birthweight <2500 grams, compared to three (4.5%) among term babies (p<0.001). However, among babies of women with GBC, the prevalence of SGA was lower for preterm compared to term babies (1.9% vs 18.8%, p=0.004).

Table 4.5 Characteristics of singleton preterm babies by cancer status

Outcome	Breast cancer	No cancer
Gender of baby		
Male	29(54.7)	55779(54.8)
Female	24(45.3)	45889(45.1)
Indeterminate	0(0.0)	117(0.1)
Not stated	0(0.0)	49(0.0)
Gestational age		
≤33 weeks	18(34.0)	30854(30.3)
34-36 weeks	35(66.0)	70980(69.7)
Birthweight*		
<2000	7(13.2)	23289(24.7)
2000 to <2500	22(41.5)	25206(26.7)
2500 to <3000	20(37.7)	29512(31.3)
3000 or over	4(7.5)	16120(17.1)
Not stated	0(0.0)	120(0.1)
Discharge status		
Discharged	47(88.7)	72942(71.6)
Stillborn	0(0.0)	7587(7.5)
Neonatal death	0(0.0)	3161(3.1)
Transferred	6(11.3)	17862(17.5)
Not stated	0(0.0)	282(0.3)
Timing of maternal cancer diagnosis		
1st trimester	10(18.9)	NA
2nd trimester	20(37.7)	NA
3rd trimester	23(43.4)	NA
Stage of maternal cancer		
Stage 1	17(32.1)	NA
Stages 2-3	32(60.4)	NA
Stages 4	2(3.8)	NA

**Excluding stillbirth*

4.5.2.10 Hospital admissions during the neonatal period

Of the 120 singletons born to women with GBC, hospitalisation data were available for 102 (85%). Of these, 53 (52%) had at least one hospital admission within 28 days of birth (44 had one admission, six had two admissions, and three had three admissions).

4.6 Discussion

We found an overall incidence of GBC in NSW between 1994 and 2013 of 6.8 per 100,000 women giving birth and that women with GBC had higher rates of planned preterm birth either by induction of labour or a pre-labour CS compared to women with no cancer. Surprisingly, the rate of planned preterm birth for women with GBC was not impacted by the timing of diagnosis or stage of cancer. Babies born to women with GBC were more likely to be preterm, require a high level of resuscitation, and be admitted to SCN or NICU. In contrast, the proportion of SGA for preterm babies was very low at 1.9%, suggesting planned preterm birth for maternal management. There were no stillbirths or neonatal deaths among these babies, and the prevalence of major neonatal morbidities was relatively low.

Our results revealed a 20-year trend of increasing GBC incidence but that this trend was not statistically significant. These findings are similar to results from two recently published studies that reported that there has been no significant increase in the incidence of PAC over the last decade (Murgia et al. 2019; Parazzini et al. 2020). Nonetheless, increased awareness of gestational breast cancer is indicated to address the demographic shift of increasing maternal age at first pregnancy consistent with national trends (Australian Institute of Health and Welfare 2021) to mitigate increasing age as a risk factor for breast cancer diagnosis. However, this trend does not translate into an overall increase in the number of women diagnosed with gestational breast cancer (Murgia et al. 2019).

The odds of GBC were six times higher among women aged ≥35 years compared to those <35 years of age. Furthermore, women with GBC were significantly older than women with no cancer. Women aged ≥35 years comprised 59.8% of the GBC group compared to only 19.7% of the no-cancer group.

In agreement with previous studies (Maxwell et al. 2019; Shechter Maor et al. 2019; Simoes et al. 2018), our results show that women with GBC have higher rates of labour induction and/or delivery by CS than women with no cancer. It has been argued that these higher rates are due to management decisions relating to the stage of cancer at diagnosis (Kuo & Caughey 2019). However, our results showed no differences in the odds of preterm labour induction or pre-labour CS among women diagnosed at different trimesters or with different stages of cancer at diagnosis. Nonetheless, these results should be interpreted with caution owing to the relatively low incidence rate of GBC and the small number of cases of GBC in this study.

There was a high rate of preterm birth among women with GBC. The majority of these births were planned and considered iatrogenic from a neonatal perspective. This is consistent with the high rate of preterm labour among women with GBC previously reported by Loibl et al. (2012), who argued that decisions to initiate early iatrogenic birth are often taken in the absence of a clear clinical indication (Loibl et al. 2012). In our study, we were unable to show any association between the high rate of iatrogenic preterm birth and any specific cancer stage or timing of diagnosis. This finding supports the views of Loibl et al. (2012). However,

owing to the small number of cases in our study, this finding should be treated with caution.

Preterm babies, whether born to women with GBC or to women with no cancer, had higher rates of adverse neonatal outcomes than babies born at ≥ 37 weeks (Platt 2014). Preterm babies of women with GBC had lower birthweights and increased rates of resuscitation and admission to SCN/NICU than term babies of women with GBC. Preparing and then caring for a preterm baby is demanding and inevitably places the mother at increased risk of anxiety and stress (Ionio et al. 2016). Women with GBC already experience high levels of fatigue and sleep disturbance underpinned by both the side effects of chemotherapy (whether given during pregnancy or after birth) and psychological and biological factors (Ancoli-Israel et al. 2014; Bardwell & Ancoli-Israel 2008; Goldstein et al. 2012). Caring for a preterm baby who has increased needs is likely to present unique challenges to mothers coping with cancer symptoms in parallel with treatment side effects.

Although our data show a low prevalence of major neonatal morbidities in our preterm babies, we did not have data to examine the long-term developmental effect of these infants. Amant et al. (2015) found that preterm babies born to women with a diagnosis of cancer during pregnancy are more likely to have long-term developmental problems whether or not they were exposed to chemotherapy while in utero (Amant, Vandenbroucke, et al. 2015). Given this, it is important to promote a term birth whenever clinically possible in order to avoid the potential negative effects of preterm birth on both the mother and her baby.

4.6.1 Strengths and limitations

An important strength of our study was the population-based design that included all births in NSW over a 20-year period from which we identified all women with invasive breast cancer during pregnancy. Limitations include the lack of information in respect to breast cancer treatment.

4.6.2 Conclusions

The odds of GBC were six times higher among women aged ≥35 years compared to those <35 years of age. There was a high rate of preterm birth among women with GBC, which could not be explained by the timing of breast cancer diagnosis or stage of cancer at diagnosis. Spontaneous onset of labour of preterm birth was uncommon, with most births following induction of labour or pre-labour CS. The high rate of preterm birth had a minimal impact in the short term, as major neonatal morbidity was uncommon.

4.6.3 Acknowledgement

This research is supported by an Australian Government Research Training Program.

4.7 Chapter summary

This chapter investigated the incidence of invasive GBC in NSW, Australia. It also examined timing of diagnosis of GBC and stage of breast cancer at diagnosis and investigated their association with the obstetric management and perinatal outcomes of women with GBC. Results from

this chapter will provide clinicians delivering health care to women with GBC with important prognostic guidance that will be useful for counselling women with GBC and for informing discussions about treatment options.

The most important findings described in this chapter are:

- The incidence of GBC in NSW from 1994 – 2013 was 6.8 per 100,000 women giving birth.
- Higher odds of GBC were noted among women aged ≥35 years compared to those <35 years of age.
- A high incidence of birth by induced labour or pre-labour CS was noted among women with GBC.
- There was a high rate of preterm birth among women with GBC. This increase in preterm deliveries was not associated with cancer stage at diagnosis or the timing of diagnosis during pregnancy.
- There were few adverse short-term neonatal outcomes in babies born to women with GBC, and those that did occur were associated preterm birth.

This chapter examined the short-term outcomes for women with GBC and their babies. The following chapter will investigate the 5- and 10-year survival rates of women diagnosed with GBC.

Chapter 5

Study 2: Gestational breast cancer: mortality and giving birth after breast cancer treatment—a New South Wales linkage study.

5.1 Introduction to this chapter

The literature is inconsistent on whether women with GBC have poorer survival outcomes than women with breast cancer not associated with pregnancy. In addition, there is uncertainty on the effects of pregnancy on breast cancer survivors' long-term survival outcomes. This study analyses the survival rates of women with GBC.

The format of this chapter is based on the British Jornal of cancer guidelines.

5.2 Abstract

5.2.1 Background

We aimed to describe the survival rate of women diagnosed with gestational breast cancer (GBC) and to explore whether survival was associated with stage of cancer at diagnosis and a subsequent birth after the GBC index birth.

5.2.2 Methods

We conducted a retrospective cohort study of women with GBC who gave birth in New South Wales, Australia, between 1994 and 2013. Data was collected from jurisdictional health and mortality datasets. Survival outcomes were examined using Kaplan-Meier curves.

5.2.3 Results

Of 122 women identified with GBC, 24 (19.7%) died within five years of diagnosis. The mortality rate for women with stage 4 cancer at diagnosis

was 1446 per 10,000 person-years, higher than that for women with stages 2 and 3 (399 per 10,000 person years) and women with stage 1 (222 per 10,000 person-years). Thirteen women (10.7%) had a subsequent birth, and all survived at 10-year follow-up.

5.2.4 Conclusion

The crude 5-year mortality observed for women with GBC (19.7%) is almost double that previously reported for all women diagnosed with breast cancer in Australia (10.2%). A subsequent uncomplicated birth after GBC can be achieved and does not appear to impact a woman's overall survival or that of her neonate.

5.3 Background

Over recent decades, there has been a well-documented increase in the incidence of breast cancer diagnosed during pregnancy (also known as gestational breast cancer or GBC) (Andersson et al. 2009; Durrani, Akbar & Heena 2018; Shechter Maor et al. 2019). Despite this increase, the effects of pregnancy on the spread of breast cancer have not been adequately studied (Lee et al. 2012; Stensheim et al. 2009). It has been suggested that high levels of progesterone, estrogen, and insulin-like growth factor-1 during pregnancy may be associated with an increase of the "aggressiveness" of breast cancer, leading to decreased survival for patients in whom breast cancer is diagnosed during pregnancy (Albrektsen et al. 2006; Lyons, Schedin & Borges 2009; Stensheim et al. 2009). It has also been postulated that the increase in breast tissue

vascularisation during pregnancy might enhance the development of breast tumours (Albrektsen et al. 2006). Nonetheless, the published literature does not support these hypotheses, leading to the conclusion that the prognosis of breast cancer diagnosed during pregnancy might not differ from the prognosis of breast cancer not associated with pregnancy when controlling for age of woman, stage of cancer at diagnosis and other risk factors (Amant et al. 2013; Boudy et al. 2018; Cardonick et al. 2010; Genin et al. 2016; Ploquin et al. 2018; Ruiz et al. 2017; Stensheim et al. 2009). These studies are supported by findings that breast cancer in young women, regardless of pregnancy status, is associated with adverse prognostic factors that lead to poorer survival outcomes, including the late stage at diagnosis and the high prevalence of more aggressive tumour pathological subtypes (Assi et al. 2013; de Lemos et al. 2019; Paluch-Shimon et al. 2020; Partridge et al. 2016; Slepicka, Cyrill & dos Santos 2019).

Apart from the uncertainty of the impact of pregnancy on outcomes for women with GBC, it has been suggested that women who become pregnant after being diagnosed and treated for cancer have better survival rates than women who do not become pregnant after their cancer diagnosis – the so-called “healthy mother effect” (Azim et al. 2011; Stensheim et al. 2009). However, studies reporting this “healthy mother effect” may be flawed either because of immortal-time bias or because only healthier surviving women may be willing to conceive (Giobbie-Hurder, Gelber & Regan 2013; Hanley & Foster 2014; Lévesque et al. 2010; Rippy, Karat & Kissin 2009; Valachis et al. 2010).

Young women with breast cancer are potentially more willing to consider family formation post-treatment, as many will not have completed their family at the time of being diagnosed and treated (de Bree et al. 2010; Pagani et al. 2015). Nonetheless, their ability to conceive is lower than for other women of similar ages, as some cancer treatments are well known to affect women's fertility, although little is known about the perinatal outcomes of women who gave birth after their cancer treatment (Anderson, Brewster, et al. 2018).

The aim of this study is (1) to describe the survival rates of women with GBC; (2) to determine whether survival is associated with cancer stage at diagnosis; (3) to examine the rate of giving birth after a previously confirmed diagnosis of GBC; and (4) to describe the perinatal outcomes for the women and their babies.

5.4 Methods

We conducted a population-based retrospective cohort study using linked New South Wales (NSW) health data sets. The study population included 122 women who gave birth in NSW between January 1994 and December 2013 with a first-time diagnosis of GBC (breast cancer diagnosed during pregnancy) and their babies. Birth was defined as the delivery of a live or stillborn baby of at least 20 weeks' gestation or 400 grams birthweight or more (Centre for Epidemiology and Evidence 2018).

The linked data set used for this analysis was obtained by merging four NSW health data sets: the Perinatal Data Collection (PDC), the NSW Cancer Registry (NSWCR), Cause of Death Unit Record File (COD URF),

and the NSW Registry of Births, Deaths and Marriages (RBDM). The PDC was used as the primary data set to identify all women giving birth in NSW public and private hospitals and their babies during the study period and up to one year after (December 2014) in order to identify women who survived GBC and gave birth subsequently (post-GBC births). The NSWCR was used to identify women with a first-time diagnosis of breast cancer during the study period. The NSW RBDM and COD URF were used to obtain maternal and infant mortality information for a minimum of four years from the date of diagnosis of GBC. Data from RBDM were available up to 31 December 2017 (the end of follow-up period) and from COD URF up to December 2015. Details on these health data sets and the linkage process are available from The NSW Centre for Health Record Linkage (CHeReL) who performed the data linkage (CHeReL 2019a, 2019b).

The primary outcome measures include overall mortality (all, 5-year, and 10-year mortality) and subsequent birth following GBC. Secondary outcomes include birth by caesarean section (CS), and neonatal morbidity including preterm birth, small for gestational age (SGA), low birthweight, the need for resuscitation, and admission to neonatal intensive care unit (NICU) or special care nursery (SCN).

The NSWCR categorises the extent of spread of cancer into four stages: stage 1 comprises cancer that is localised to the breast tissue; stages 2 -3 comprise cancers that involve the regional lymph nodes, the adjacent organs (chest wall, skin) or both; stage 4 comprises cancers with distant metastases. The NSWCR also includes stage 0 cancers, comprising carcinoma in situ (CIS) (CHeReL 2019a; Royal College of Pathologists of

Australasia 2012). Information relating to women with CIS was not available in our dataset.

Statistical analysis

Continuous variables were reported as mean (standard deviation) or median (range and interquartile range (IQR)) as appropriate. The paired t-test was used to examine the mean difference in baby gestational age and birthweight between the birth associated with the diagnosis of GBC (GBC birth) and any subsequent birth by the same women (post-GBC birth). Kaplan-Meier curve and Log-rank test used to examine the survival rate for women with GBC factored by the stage of cancer at the time of diagnosis. SPSS version 26.0 was used for data analysis (IBM Corp, New York, United States).

Ethical approval

Ethics approval was obtained from NSW Population & Health Services Research Ethics Committee provided (reference HREC/17/CIPHS/11) and the UTS Human Research Ethics Committee (UTS HREC REF NO. ETH18-2362).

5.5 Results

Mortality

Between January 1994 and December 2013, we identified 122 women with GBC who gave birth in NSW. By the end of the follow-up period (31 December 2017), 39 (32%) women had died while 83 (68%) survived. Of those who died, 24 (62%) died within five years, nine (23%) died between

over five to 10 years and six (15%) died between over 10 years to 21 years following diagnosis.

Overall mortality

The overall mortality incidence rate was 328 per 10,000 person-years follow-up time. The mean survival time was 16.3 years (95% CI: 14.6 to 18.0 years). The median age at the time of breast cancer diagnosis for those women who survived (median 35 years; IQR 31 – 38 years) was similar to women who died (median 35 years; IQR 32 – 39 years). Table 5.1 reports the stage of GBC at the time of diagnosis and maternal characteristics by 5-year survival status.

Table 5.1: Women obstetric and cancer characteristics by 5-year survival status

	Survival status		P value
	Died N(%)*	Survived N(%)*	
Stage of cancer			
Stage 1	5(12.8)	34(87.2)	0.158
Stage 2 - 3	17(27)	46(73)	
Stage 4	2(33.3)	4(66.7)	
Not stated	0(0.0)	9(100.0)	
Country of birth			
Others	16(20.3)	63(79.7)	0.920
Australia	8(21.1)	30(78.9)	
Maternal age			
<35	12(25.0)	36(75.0)	0.316
=>35	12(17.4)	57(82.6)	
Parity			
Nullipara	7(18.4)	31(81.6)	0.698
Para 1+	17(21.5)	62(78.5)	
Plurality			
Singleton	23(20.0)	92(80.0)	0.370
Multiple pregnancy	1(50.0)	1(50.0)	
Previous CS			
No previous CS	12(27.9)	31(72.1)	0.518
One or more CS	3(16.7)	15(83.3)	
Not applicable	7(18.4)	31(81.6)	
Not stated	2(11.1)	16(88.9)	
Smoking while pregnant			
Yes	2(50.0)	2(50.0)	0.186
No	22(19.5)	91(80.5)	
Pre-existing hypertension			
Yes	0(0.0)	4(100.0)	0.580
No	24(21.2)	89(78.8)	

*Row percentage

Five-year mortality rate

Within five years of follow-up, 93 (76.2%) women had survived and 24 (19.7%) died. The 5-year follow up was not available for five (4.1%) women. The 5-year mortality incidence rate was 202 per 10,000 person-years follow-up time. The mean survival time was 4.6 years (95% CI:4.2 to 4.7 years).

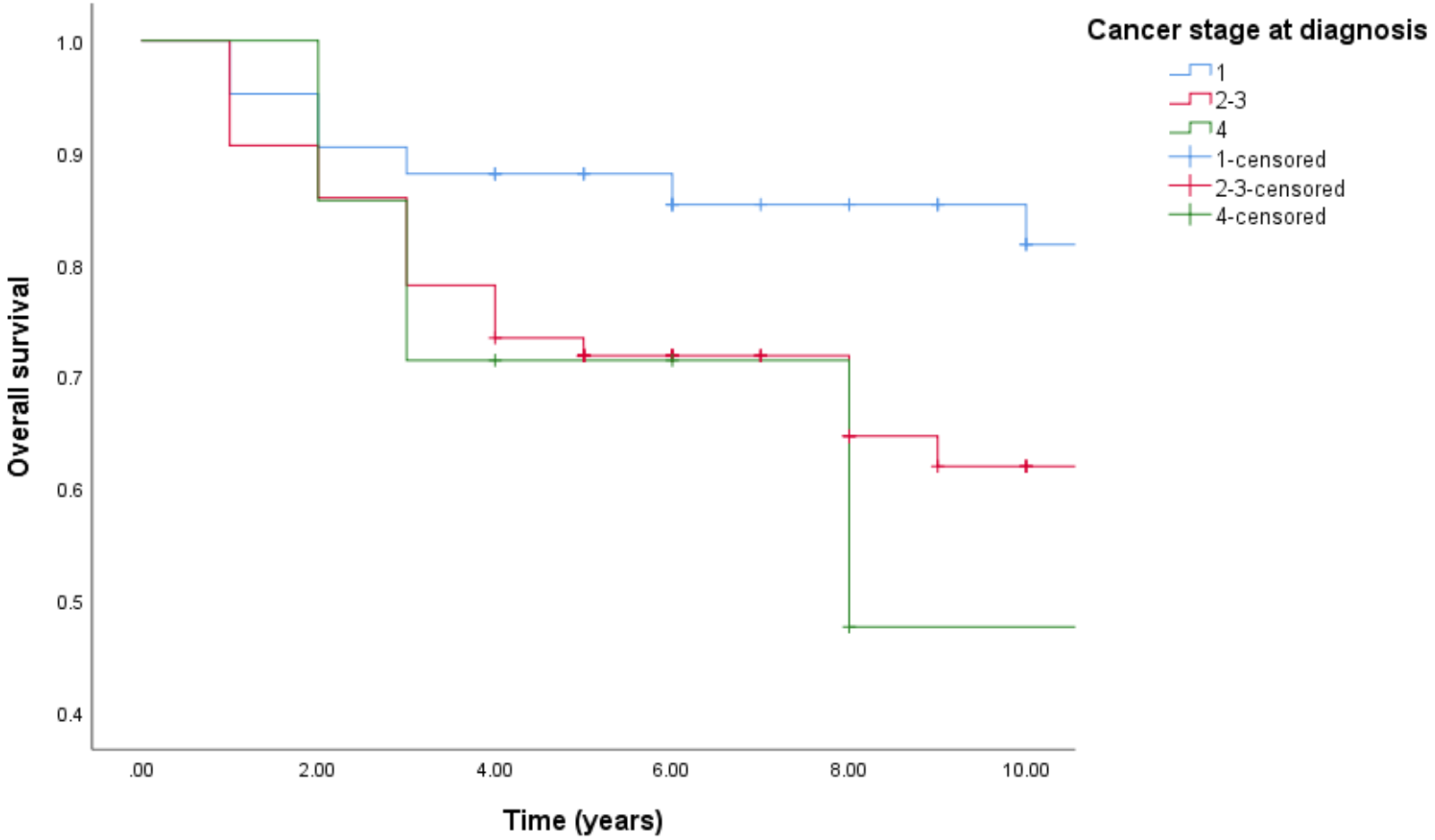
Ten-year mortality rate

Within ten years of follow-up 52 (42.7%) women had survived and 33 (27.0%) died. The 10-year follow up was not available for 37 (30.3%) women. The 10-year mortality incidence rate was 278 per 10,000 person-years. The mean survival time was 8.2 years (95% CI: 7.6 to 8.8 years).

Mortality by stage of cancer at diagnosis

The stage of GBC at the time diagnosis was known for 113 women (Table 5.1). The mortality incidence rate for women initially diagnosed with stage 4 was 1446 per 10,000 person-year, which is higher than the mortality incidence rate among women with stages 2-3 (399 per 10,000 person-year) and women with stage 1 (222 per 10,0007 person-year). Figure 5.1 shows the survival of women with GBC by cancer stage.

Figure 5.1: Survival of women with GBC by cancer stage



Women giving birth following GBC (post-GBC birth)

Of the 122 women who gave birth with GBC, 13 (10.7%) women had at least one subsequent post-GBC birth. The median interval between the GBC birth and the post-GBC birth was 41 months (minimum 15, maximum 92, IQR 33.5 75.0 months) and the interval to post-GBC birth was at least two years for 12 (92%) women (Table 5.2). Within 10 years of follow-up, none of the women with a post-GBC birth died. In those women with a post-GBC birth, 10 (77%) had cancer stage 1 at time of diagnosis, three (23%) had stage 2-3 cancer, and none had stage 4 cancer (Table 5.2).

Table 5.2: Characteristics of the 13 women with at least one post-GBC birth

Maternal Characteristics	n (%)
Stage of cancer at diagnosis	
Stage 1	10
Stage 2-3	3
Country of birth	
Others	8
Australia	5
Maternal age	
<35	4
=>35	9
Parity	
Para 1	10
Para 2	2
Para 4	1
Previous CS	
No previous CS	7
One or more CS	6
Interval between births	
<24 months	1
24-47 months	6
48-71 months	2
72-95 months	4

Obstetric management and complications of the 1st post-GBC birth

Of the 13 women with post-GBC birth, seven (54%) had a normal vaginal birth (five spontaneous and two induced) and six (46%) gave birth by pre-labour caesarean section (CS). The indication for CS in five cases was previous CS, and one was recorded as having an elective CS for no clinical indication. With the exception of two women who developed gestational diabetes, none had any pregnancy or birth complications.

Neonatal outcomes of the post-GBC birth

Thirteen women who had at least one subsequent birth after giving birth with GBC gave birth to singleton babies. The mean gestational age was 39 (95%CI: 38 – 39) weeks, which is significantly higher than the mean gestational age for babies born to the same women in the previous birth with GBC (37 (95%CI: 36 – 38) weeks, P-value = 0.015). The mean birthweight of babies born in the first post-GBC birth was significantly higher than the mean birthweight of babies born to the same women in the previous birth with GBC (3428 (95% CI: 3,164 – 3,692) vs. 2839 (95% CI: 2560 – 3118) grams, P-value = 0.004). Table 5.3 shows the neonatal outcomes for the GBC birth and the first subsequent post-GBC birth for the same group of women.

Table 5.3 Neonatal outcomes for babies conceived and born after their mothers were previously treated for GBC compared to their older siblings who were born while their mothers were under treatment for GBC.

	Post – GBC birth	GBC birth
Preterm birth		
Yes	0(0.0)	4(30.8)
No	13(100.0)	9(69.2)
Small for gestation		
Yes	0(0.0)	1(7.7)
No	13(100.0)	12(92.3)
Birthweight<2500 g		
Yes	0(0.0)	4(30.8)
No	13(100.0)	9(69.2)
5 min Apgar		
>7	13(100.0)	12(92.3)
7 or less	0(0.0)	1(7.7)
High Resuscitation		
Yes	0(0.0)	1(7.7)
No	13(100.0)	10(76.9)
Not stated	0(0.0)	2(15.4)
Admitted to SCN/NICU for 4 hours or more		
Yes	2(15.4)	5(38.5)
No	11(84.6)	8(61.5)
Discharge status		
Discharged	13(100.0)	12(92.3)
Transferred	0(0.0)	1(7.7)

5.6 Discussion

Our results show that these 122 women in NSW with a first-time diagnosis of GBC had an overall mortality incidence rate of 328 per 10,000 person-years follow-up time. The 5-year crude mortality was 19.7%, and 10-year crude mortality was 38.8%. The observed mortality rate was higher among women with stage 4 cancer and stage 2-3 compared to those with stage 1 cancer. Ten percent of the women had a second birth following the GBC index birth, and none of these had any major maternal or neonatal adverse outcomes.

5.6.1 High mortality rate

The 5-year crude mortality rate of women with GBC in our cohort was almost twice the Australian national 5-year crude mortality rate for all women with breast cancer (19.7% vs. 10.2%) (Australian Institute of Health and Welfare 2012). Explanations for the increased mortality rate in women diagnosed during pregnancy are not known but may include their younger age and the effects of pregnancy (particularly hormonal changes) on cancer growth and metastasis, and may be associated with the pathological subtype of the tumour and the stage of cancer at diagnosis (Albrektsen et al. 2006; Amant et al. 2013; Boudy et al. 2018; Cardonick et al. 2010; Genin et al. 2016; Johansson et al. 2018; Ploquin et al. 2018; Ruiz et al. 2017; Slepicka, Cyrill & dos Santos 2019; Stensheim et al. 2009). However, our study provided only indirect evidence of increased mortality for women with GBC as we did not have access to data for a comparison group of women with breast cancer who were not pregnant. In addition, other confounding factors such as the distribution of stage of cancer and the type of treatment received during and after pregnancy may have impacted the results.

Younger age

Australian statistics reveal that young women diagnosed with breast cancer have a lower 5-year survival rate than other women diagnosed with breast cancer (Australian Institute of Health and Welfare 2019). The lowest survival rate was among women aged 20 – 24 years (84.7%) and the highest was among women aged 65 – 69 years (93.7%) (Australian Institute of Health and Welfare 2019). These findings are supported by studies which report that the

mortality rate among premenopausal women with breast cancer is higher than among postmenopausal women (Paluch-Shimon et al. 2020; Partridge et al. 2016). It has been suggested that younger age is an independent risk factor for an adverse survival outcome in women with breast cancer (Anders et al. 2009). However, a recent study reported that the effects of age on survival vary with the pathological subtypes of breast cancer – while younger age was an independent predictor of poor outcome in the luminal tumour, it had a marginal effect on triple-negative subtypes and no effect on HER2–positive subtypes (Partridge et al. 2016). Thus, while the age of women in our cohort may be younger than the median age of women diagnosed with breast cancer in Australia, this factor alone is unlikely to explain their increased risk of mortality.

The effect of pregnancy

There is conflicting information in the published literature regarding whether GBC may have a poorer survival outcome than breast cancer not associated with pregnancy. Some studies report that the prognosis of GBC patients does not differ from that of young patients with breast cancer not associated with pregnancy (Amant et al. 2013; Azim, Santoro, et al. 2012; Boudy et al. 2018; Cardonick et al. 2010; Genin et al. 2016; Murphy et al. 2012; Ploquin et al. 2018; Ruiz et al. 2017; Stensheim et al. 2009), while other studies report poorer survival outcomes for women with GBC (Bae et al. 2018; Gooch et al. 2020; Johansson et al. 2018; Rodriguez et al. 2008). It should be noted, however, that those studies reporting poorer survival outcomes in women with GBC used broader inclusion criteria that include women with breast cancer diagnosed up to one year postpartum rather than just women diagnosed during pregnancy. It has been reported that breast cancers diagnosed postpartum are more likely to

have metastasised and have poorer outcomes compared to breast cancer diagnosed during pregnancy (Callihan et al. 2013; Ruiz et al. 2017; Stensheim et al. 2009; Van den Rul et al. 2011). This is because of the highly aggressive tumour subtypes (luminal B and triple-negative tumours) associated with breast cancer diagnosed within five years postpartum (Collins et al. 2015; Slepicka, Cyrill & dos Santos 2019). This factor may have resulted in confounding in the studies reporting poorer survival in women with GBC that included women diagnosed up to one year postpartum or over, and perhaps have led to an erroneous conclusion that a diagnosis of GBC may affect the survival outcome.

The stage of cancer at diagnosis

For women with breast cancer, whether diagnosed during pregnancy or not, stage at diagnosis is the major contributor to survival rates (de Lemos et al. 2019; Hunter 2000; Johansson et al. 2018). Our results show that women with cancer stage 4 and stage 2-3 had poorer survival outcomes than women with stage 1. These findings are consistent with those of Johansson and colleagues (2018), who reported that the high mortality rate among women with GBC can be explained by the stage of cancer at diagnosis and the progesterone and estrogen receptor status (Johansson et al. 2018). It is important to note that while analysis of our data indicates that the highest mortality occurred in women with higher stages of cancer, other confounding factors, including breast cancer histological subgroup and the type and timing of breast cancer treatment, may have impacted the results. Hence, it was not possible to conclude that higher staging was a causal factor in mortality for this cohort.

5.6.2 Post- GBC birth

The healthy mother effect

Previous studies report that women who give birth after breast cancer are more likely to survive than women with no subsequent birth, known as “the healthy mother effect” (Valachis et al. 2010). The women in our study who had a post-GBC birth had no deaths within 10 years from the date of the diagnosis of breast cancer. The majority of those women initially presented with early-stage (stage 1) cancer at the time of diagnosis, and none had metastases. Due to the factor above (early-stage cancer at diagnosis) and the small number of women with post-GBC birth, we are not able to confirm ‘the healthy mother effect”. In addition, the previous studies that confirmed “the healthy mother effect” were likely biased as they did not control for the immortal time or the initial breast cancer stage and breast cancer subtype (Newman et al. 2020; Rippy, Karat & Kissin 2009; Stensheim et al. 2009; Valachis et al. 2010). Importantly, our results are reassuring because they show that subsequent uncomplicated births after GBC can be achieved and do not appear to impact overall survival of the woman or her neonate. These findings are supported by recent studies which reported that pregnancy in women with a previous diagnosis of breast cancer is safe and it is not associated with increased risk of recurrence of breast cancer (Lambertini et al. 2020; Lambertini, Kroman, et al. 2018; Lambertini et al. 2019). However, this result should be interpreted with caution due to the small sample size.

Maternal and neonatal outcomes

Our results suggest that post-GBC birth is not associated with increased adverse maternal or neonatal outcomes compared to the GBC birth outcomes for the same women. In another population-based study, Dalberg and colleagues reported that women previously treated for breast cancer have a high rate of birth by CS (Dalberg, Eriksson & Holmberg 2006). Those findings are consistent with the high rate of CS birth among the women with post-GBC birth in our study.

It has previously been suggested that while the overall neonatal outcomes for babies born to women previously treated for breast cancer are not different from those for babies born to women without a history of cancer; women with ER-negative breast cancer are more likely to give birth to a preterm baby (Anderson, Engel, et al. 2018; Dalberg, Eriksson & Holmberg 2006). In our study, none of the 13 women with post-GBC birth had a preterm birth. However, we did not have access to data relating to cancer subtype and hence we could not test these previous findings.

5.6.3 Strengths and limitations

A strength of our study is the population-based design with the ability to follow-up the majority of women with GBC for at least five years to examine survival rates. However, the lack of data regarding the type of breast cancer treatment and breast cancer subtypes limited our ability to examine survival outcome by these factors. In addition, our data contain information on women who gave birth only and lack information on early pregnancy loss, which limited our ability to estimate the rate of post-GBC pregnancy.

5.6.4 Conclusion

The crude 5-year mortality observed for women with GBC (19.7%) is almost double that previously reported for all women diagnosed with breast cancer in Australia (10.2%). The poor survival outcome is associated with the stage of breast cancer at diagnosis. Subsequent uncomplicated birth after GBC can be achieved and does not appear to impact a woman's overall survival or that of her neonate.

5.7 Chapter summary

This chapter examined the long-term outcomes for women with GBC, including the overall survival and birth subsequent to GBC index birth.

The main points of this chapter are:

- The overall mortality incidence rate was 328 per 10,000, person-years follow-up time.
- The crude 5-year mortality rate for women with GBC was 19.7%, representing almost double the crude 5-year mortality rate for women with breast cancer not associated with pregnancy in Australia (10.2%).
- Stage of breast cancer at diagnosis was associated with the survival rate of women with GBC. Women initially diagnosed with stage 4 have poorer survival outcomes than women with stages 1 to 3.
- Subsequent uncomplicated birth after GBC can be achieved and does not appear to impact a woman's overall survival or that of her neonate.

While this chapter and Chapter Four used the NSW linked health data to examine the short- and the long-term outcomes for the 122 women with GBC and their babies, Chapter Six will use data with details on investigations, treatment and outcomes for women with GBC. It will examine the short-term outcomes in relation to the imaging and modalities used in the diagnosis and staging of breast cancer during pregnancy.

Chapter 6

Study 3 Clinical decision making in the management of breast cancer diagnosed during pregnancy: a review and case series analysis

6.1 Introduction to this chapter

Owing to potential safety issues for fetuses with respect to diagnostic procedures and breast cancer treatment during pregnancy, the diagnosis and management of GBC is challenging to healthcare providers. This study aimed to elucidate the difficulties involved in the management of GBC and to provide healthcare providers with an evidence-base to help inform their decision making regarding diagnostic methods and treatment for GBC. To achieve this aim, the study described the management and outcomes of a series of six cases with breast cancer diagnosed during pregnancy and presented these alongside a review of recent studies and guidelines relating to the diagnosis and management of cancer during pregnancy. More specifically, it investigated the safe use of available diagnostic methods during pregnancy by comparing the management and outcomes of those six cases with recent published evidence. Data for the six cases were extracted from the AMOSS GBC dataset (The Australasian Maternity Outcomes Surveillance System (AMOSS) 2015).

6.2 Abstract

6.2.1 Aim

To highlight the various options available for the management of breast cancer diagnosed during pregnancy by describing the investigations, treatments, and outcomes in relation to women with GBC.

6.2.2 Method

This is a narrative review of the literature and of a series of descriptive case of six women with a first-time diagnosis of breast cancer during pregnancy. These six cases were identified via the Australasian Maternity Outcome Surveillance System (AMOSS) as part of a larger study investigating the epidemiology of GBC in Australia and New Zealand.

6.2.3 Results

Of the six cases, two were diagnosed in each pregnancy trimester. A painless breast mass was the presenting symptom in five cases (83%). In all cases, breast ultrasound was the primary diagnostic imaging procedure. Chest x-ray was performed in three cases (50%) and computed tomography in two cases (33%). A core needle biopsy was performed in all cases, and sentinel lymph node biopsy in three cases (50%). Four women had grade 3 tumors, and five had estrogen receptor-positive tumors. Four women had breast surgery during pregnancy. Five women gave birth following induction of labour and/or Cesarean Section (CS). In all six cases, a multidisciplinary team was involved in delivery of health care.

6.2.4 Conclusion

Regular breast examinations are needed for all pregnant woman during prenatal visits. Breast ultrasonography should be offered if a breast lump is detected or other symptoms elicited. Breast surgery can be safely performed during all pregnancy trimesters, and some systemic therapeutic agents can be administered safely in the second and third trimesters.

Keywords: Breast cancer, clinical decision making, management, pregnancy.

6.3 Introduction

Breast cancer is one of the most common malignancies diagnosed in women during pregnancy, with an incidence in Australia of 23 per 100,000 pregnancies (Ives, Saunders & Semmens 2005). The most common presenting symptom is a painless breast lump (Amant, Loibl, et al. 2012). This can present diagnostic difficulties, as normal physiological changes during pregnancy can lead to the development of benign transient lumps in the breast of a pregnant woman, thereby masking breast cancer symptoms (Amant, Loibl, et al. 2012; Salani, Billingsley & Crafton 2014; Vashi et al. 2013). This problem is compounded by physician reluctance to request imaging studies using ionising radiation such as mammography, in order to avoid potential harm to the conceptus (Langer et al. 2014). This is despite published evidence that mammography is relatively safe during pregnancy and that with proper shielding the fetus is exposed to a negligible radiation dose (American College of Radiology 2018; Vashi et al. 2013). Together, these factors can lead to delays, resulting in breast cancer diagnosis in pregnant women at a more advanced stage compared with non-pregnant women (Amant, Loibl, et al. 2012).

Despite concerns about the adverse effects of chemotherapeutic agents on fetal well-being, in many cases of cancer in pregnancy, use of these agents cannot be delayed until the postpartum period (Cardonick & Iacobucci 2004). Recent studies demonstrate that a cancer diagnosis during pregnancy is not an absolute indication for termination of pregnancy and that fetal exposure to chemotherapy after the first trimester is not associated with major complications

or congenital anomalies (Abdel-Hady el et al. 2012; Amant, Han, et al. 2015; de Haan et al. 2018).

Preterm birth is a significant adverse outcome associated with breast cancer diagnosed during pregnancy. A recent European population-based study found that the preterm birth rate among women with any type of cancer was 48%, with the majority of preterm birth (88%) being iatrogenic. For women in the study diagnosed with breast cancer, 50% delivered preterm (de Haan et al. 2018).

This study utilised the Australasian Maternity Surveillance System (AMOSS) GBC dataset. AMOSS is a hospital-based surveillance and research system of serious and rare conditions in pregnancy, with data coordinators in nearly 300 Australian and New Zealand maternity units. It undertook a population-wide epidemiological study of all women diagnosed with GBC in Australia and New Zealand between January 2013 and June 2014. Ethics approval was granted by multiple ethics committees across Australia, including the New South Wales Population and Health Services Research Ethics Committee (HREC/09/CIPHS/21) (Vaughan et al. 2012). The process of data collection for AMOSS has been described by (Safi et al. 2019). We describe six case reports to illustrate the current management of GBC in Australia and New Zealand.

6.4 Case Reports:

We report six cases of women diagnosed with GBC. Their median age was 34.5 (29–39) years. Two women were diagnosed in each pregnancy trimester. A painless breast mass was the presenting symptom in five cases (83%). In all cases, breast ultrasound was the primary diagnostic imaging procedure

followed by mammogram in three cases (50%) (Table 6.1). Chest x-ray was performed in three cases (50%) and computed tomography (CT) in two cases (33%). Core needle biopsy (CNB) was performed in all cases and sentinel lymph node biopsy (SLNB) in three cases (50%). Four women had grade 3 (high) tumor, five had estrogen receptor positive tumors (Table 6.2). Four women had breast surgery during pregnancy. Five women gave birth following induction of labor and/or CS (Table 6.3). Three babies were born preterm and none of the six babies had congenital malformations or experienced major complications at birth (Table 6.4). In all our cases a multidisciplinary team was involved in the care of the women with teams' members, including an obstetrician, maternal-fetal medicine specialist, breast cancer surgeon, medical oncologist, radiation oncologist, anesthetist, and a breast care nurse.

Table 6.1: diagnostic procedures

Case	Age group (years)	Gestation at diagnosis (weeks)	CXR	Breast US	Mammogram	Nuclear Medicine	CT Chest /Abdomen	Histological Diagnosis	Lymph node biopsy procedures
1	30-34	4	No	Yes	Yes	Bone scan	Yes	CNB	SLNB and AC
2	35-39	8	No	Yes	No	No	No	CNB	SLNB and AC
3	35-39	15	Yes	Yes	Yes	No	No	CNB	AC
4	30-34	17	Yes	Yes	Yes	VQ scan	No	CNB	AC
5	25-29	33	No	Yes	No	No	No	CNB	Not known
6	35-39	38	Yes	Yes	No	Bone scan	Yes	CNB	SLNB

CXR chest x-ray, US Ultrasound, AC axillary clearance, SLNB sentinel lymph node biopsy, CNB core needle biopsy, VQ ventilation perfusion lung scan,

Table 6.2: Tumor characteristics

Case	Maximum tumor diameter (mm)	Tumor grade	Lymphovascular Invasion	Estrogen Receptor Status	Progesterone Receptor Status	Her2 Status	Lymph nodes with cancer
1	40	High	No	Positive	Positive	Negative	15
2	9	Low	No	Positive	Positive	Negative	0
3	35	High	Not known	Positive	Positive	Positive	10
4	40	High	Yes	Positive	Negative	Negative	2
5	Not known	High	Not known	Negative	Positive	Positive	-
6	8	Intermediate	No	Positive	Positive	Negative	15

Table 6.3*:* Obstetric and cancer management during pregnancy

Case	Labor induction/reason	CS /Indication	Breast surgery	Chemotherapy	Prenatal Corticosteroids	Lactation suppression
1	No	No	Breast conservation	Yes	No	No
2	Yes/ postdate	Yes/Poor progress in labor and non-reassuring FHR trace	Mastectomy	No	No	No
3	No	Yes/Maternal request	Mastectomy	Yes	Yes	No
4	No	Yes/Previous cesarean section and maternal request	Breast conservation	Yes	Yes	Yes
5	Yes/ Breast cancer management	No	Delayed until end of pregnancy	No	Yes	Yes
6	No	Yes/Breast cancer management	Delayed until end of pregnancy	No	No	No

CS Cesarean Section, FHR fetal heart rate

Table 6.4: Perinatal outcomes

Case	Preterm or term baby	Gender	Birthweight (gm)	5 min Apgar score	Major infant complications	Congenital malformations	Resuscitation	Respiratory support	Admission to NICU/SCN
1	Preterm	Female	2801	9	No	No	No	No	No
2	Term	Female	3225	9	No	No	No	No	No
3	Preterm	Female	2315	9	No	No	No	No	Yes
4	Term	Female	2750	9	No	No	No	No	No
5	Preterm	Female	2578	9	No	No	No	No	No
6	Term	Male	3540	9	No	No	No	No	No

NICU neonatal intensive care unit, SCN special care nursery

6.4.1 Trimester 1

Case 1

A gravida 3, para 2 woman was diagnosed with grade 3, hormone receptor-positive breast cancer at four weeks gestation. Bone scan and CT showed no distant metastases. Breast conservation surgery and axillary lymph node clearance were performed at five weeks gestation. Adjuvant systemic therapy (doxorubicin, cyclophosphamide followed by paclitaxel) commenced at 13 weeks gestation. The last dose was given at 36 weeks gestation, and spontaneous rupture of membranes occurred shortly after.

Case 2

A primigravid woman presented with a painless mass discovered on examination at eight weeks gestation. This grade 1 cancer was confirmed by breast ultrasound, and CNB. She underwent a mastectomy and SLNB six weeks after diagnosis. Chemotherapy and radiotherapy were not recommended. Labour was induced at 40 weeks' gestation. Due to the slow progress of labour and a non-reassuring fetal heart rate (FHR) trace, the baby was delivered by CS.

6.4.2 Trimester Two

Case 3

A gravida 2, para 0 woman reported a unilateral breast lump associated with breast erythema two weeks before CNB confirmed an inflammatory

malignancy at 15 weeks' gestation. Neo-adjuvant chemotherapy (Doxorubicin and Cyclophosphamide) was initiated at 18 weeks' gestation, with the last dose administered at 26 weeks' gestation. Mastectomy and axillary clearance were performed at 29 weeks' gestation and pathology confirmed residual 35 mm of grade 3 tumor with 10 out of 20 lymph nodes involved. A CS was scheduled at 35 weeks' gestation at maternal request. Radiotherapy was delayed until after birth, and chemotherapy continued postpartum. The baby was born preterm and admitted to the special care nursery due to the preterm birth and low birthweight.

Case 4

A gravida 3, para 2 woman with one prior CS presented with a non-tender breast lump. Diagnostic procedures and tumor characteristics are shown in Tables 6.2 and 6.4. Wide local excision and axillary node dissection were performed eight days after diagnosis with two of the 25 removed lymph nodes containing tumor deposits. Adjuvant chemotherapy was initiated at 23 weeks' gestation (Doxorubicin, Cyclophosphamide). The last dose of chemotherapy was administered at 31 weeks' gestation. The woman received Paclitaxel postpartum and the treatment ended 13 weeks after giving birth. Radiotherapy to the breast was then performed.

6.4.3 Trimester Three

Case 5

A primigravid woman presented with a breast lump and nipple retraction for five weeks. Surgery, systemic therapy, and radiotherapy were delayed until the end of pregnancy. Labour was induced two weeks after diagnosis,

at 35 weeks' gestation to initiate breast cancer management. The woman delivered a healthy infant by an unassisted vaginal birth. The total hospital stay for the woman was six days, following which she was transferred to another hospital to commence neo-adjuvant chemotherapy.

Case 6

A gravida 4, para 1 woman experienced a painless breast lump for eight weeks. The CNB confirmed a unilateral grade 2 tumor at 38 weeks' gestation. Two days after the pathological diagnosis, the woman delivered a healthy infant by planned CS. Four cycles of neo-adjuvant chemotherapy commenced four days after delivery.

6.5 Discussion

These six cases highlight the complexity and differences in the management of GBC based on gestational age and cancer stage. In keeping with the literature, the main presenting sign/symptom in cases 2 to 6 was a painless breast lump (Amant, Loibl, et al. 2012; Basaran et al. 2014). Detecting breast lump during pregnancy may be difficult due to the physiological changes (Amant, Loibl, et al. 2012; Vashi et al. 2013). Therefore, there is a need to examine every pregnant woman for breast lumps during the antenatal visits.

Ultrasonography

Irrespective of the timing of diagnosis, breast ultrasonography represented the primary diagnostic imaging modality in all cases (Table 6.1). This result is reassuring, as data from recent studies reinforce the effectiveness of

breast ultrasonography in detecting GBC (Johansson et al. 2019). The literature shows breast ultrasound to be highly sensitive in detecting a malignant breast mass during pregnancy and lactation, with sensitivity varying from 74 – 100% (Langer et al. 2014; Robbins et al. 2011; Taylor et al. 2011). Furthermore, current guidelines of the ACOG (2017) recommend the use of ultrasound as the primary breast imaging modality during pregnancy as it carries a low fetal risk; however, it is recommended that ultrasound be used with the lowest possible acoustic output level (American College of Obstetricians and Gynecologists 2017).

Imaging utilising ionising radiation

Ionising radiation can affect the fetus in two ways. “Deterministic effects” are dosedependent and associated with damage to a number of cells, potentially leading to organ failure. Clinically significant deterministic effects are not expected to occur at a dose lower than 100 mGy (Tremblay et al. 2012). In contrast, “stochastic effects” are random (not dose dependent) and associated with damage to a single cell which can cause carcinogenesis (American College of Radiology 2018; Tremblay et al. 2012).

Four of our cases were exposed to at least one ionising radiation imaging technique (mammography, chest X-Ray, CT scan) at varying stages of pregnancy. These women all delivered babies without major complications or congenital malformations. Mammography was used in three cases (50%): in one case it was used in the first trimester, and in the two other cases it was used in the second trimester (Table 6.1). While some women and health care providers hold concerns about the use of mammography

during pregnancy, it carries a low risk to the fetus (Langer et al. 2014). Previous studies report that mammography appears safe at any time during pregnancy and lactation (American College of Radiology 2018; Vashi et al. 2013). The published data show that exposure of the fetus to ionising radiation from mammography is 0.001 – 0.01mGy, and with lead shielding this exposure can be reduced by half (American College of Obstetricians and Gynecologists 2017; Arasu et al. 2018). However, the sensitivity of mammography in detecting breast cancer during pregnancy varies, with studies reporting a sensitivity of 78 – 90% (Langer et al. 2014; Vashi et al. 2013). This variability in diagnostic sensitivity is probably due to the high breast tissue density during pregnancy and lactation, which may affect image interpretation (de Haan et al. 2016).

Apart from CT scans of the pelvis, the dosages used in all imaging with ionising radiation techniques fall well below the deterministic effects threshold; therefore, they can be considered safe during pregnancy (de Haan et al. 2016). Two of our cases underwent CT scans. One woman was diagnosed in the first trimester and the other in the third trimester, but the actual date of the scan is unknown in either case. Nonetheless, ACOG (2017) recommendations concerning the use of diagnostic imaging do permit CT scans during pregnancy (American College of Obstetricians and Gynecologists 2017). CT scans do entail high radiation exposure yet their use as an imaging procedure during pregnancy increased annually by 25% between 1997 and 2006 (American College of Obstetricians and Gynecologists 2017; American College of Radiology 2018). This increase is underpinned by the use of a low-exposure technique that can reduce the fetal exposure dose to less than 35 mGy for a single-phase scan of the

pelvis (American College of Obstetricians and Gynecologists 2017; American College of Radiology 2018; de Haan et al. 2016). However, while pelvic CT would normally be part of staging for breast cancer, it is not recommended to include the pelvis in staging CT scanning during any stage of pregnancy. Ultrasound can be used as an alternative to CT scanning for abdominal and pelvic staging (Peccatori et al. 2018). In addition, diffusion-weighted MRI can be considered as a potential alternative to a CT scan during pregnancy (Loibl et al. 2015; Peccatori et al. 2017). The advantage of using diffusion-weighted MRI examination is that it does not require the injection of gadolinium as a contrast agent nor does it expose the women or fetus to ionising radiation (Peccatori et al. 2017).

Nuclear medicine

Although the literature on nuclear medicine imaging during pregnancy is sparse, its use is not recommended, and it may only be considered when other diagnostic modalities are inconclusive (de Haan et al. 2016; Loibl et al. 2015; Peccatori et al. 2013). In our series, it was used in three cases (two had a bone scan and one had a Ventilation-Perfusion lung scan (VQ scan)). However, MRI without gadolinium may be a better alternative to bone scan in cancer staging in cases where metastases are suspected (Zagouri et al. 2016).

Biopsy

All of our cases underwent CNB for pathological diagnosis. These results reflect the decline in the use of fine-needle aspiration (FNA) in favour of CNB, which is now considered the standard pathology diagnostic method

for breast lesions (Amant, Loibl, et al. 2012; Brancato et al. 2012; Wang et al. 2017). Results from a recent meta-analysis show the pooled sensitivity of CNB is superior to that of FNA (87% vs. 74%) and that the specificity is similar (98% vs. 96%) (Wang et al. 2017).

Surgery

In our cohort, the four women diagnosed with breast cancer in the first and second trimesters underwent breast surgery during pregnancy. The existing literature and practice guidelines state that breast surgery can be performed safely in all pregnancy trimesters (Langer et al. 2014; RCOG 2011).

Axillary clearance and/or SLNB procedures were offered to five of our cases (Table 6.1). SLNB is used to assess lymph node involvement in patients diagnosed with breast cancer (de Haan et al. 2016). The standard SLNB procedure involves the injection of a ^{99m}technetium – sulfur colloid (^{99m}Tc – TSC) and blue dye (isosulfan blue) interstitially into the breast (Peccatori et al. 2018). Performing SLNB during pregnancy is controversial due to the potential for radiation exposure to the conceptus and anaphylactic reaction to the blue dye. ACOG concluded that the use of technetium^{99m} (Tc^{99m}) for sentinel node mapping during pregnancy is considered safe as conceptus exposure to radiation is low (<5 mGy) and the half-life of the isotope is short (6 hours) (American College of Obstetricians and Gynecologists 2017). Similarly, the Royal College of Obstetricians and Gynaecologists (RCOG) stated that uterine radiation from radioisotope scintigraphy is minimal (RCOG 2011). In contrast, the American Society of Clinical Oncology (ASCO) clinical practice guideline

update in 2016 recommended that SLNB should not be performed during pregnancy due to insufficient evidence relating to its impact on the fetus (Lyman, Somerfield & Giuliano 2017). This is despite recent studies suggesting that the use of ^{99m}Tc or patente blue SLNB during pregnancy appears safe (Gropper et al. 2014; Han et al. 2018). SLNB was performed in three of our cases; two in the first trimester and one in the third trimester, with no significant complications or congenital malformations. However, our data does not include information about whether Tc^{99m} or blue dye or both was used.

Chemotherapy

Three cases received chemotherapy during pregnancy. In one case, the diagnosis was confirmed at <5 weeks' gestation but chemotherapy was delayed until the end of the first trimester. In the two other cases, the diagnosis was confirmed during the second trimester. These practices are consistent with the literature and RCOG (2011) guidelines that indicate that the use of chemotherapeutic agents (anthracycline and taxane) in the second and third trimesters is not associated with significant adverse perinatal outcomes such as perinatal deaths and major congenital malformations (Abdel-Hady el et al. 2012; Loibl et al. 2012; RCOG 2011; Van Calsteren et al. 2010). We noted that if the diagnosis was confirmed in the first and second trimester rather than the third trimester, the women were more likely to receive chemotherapy during pregnancy, depending on the tumor grade.

Tamoxifen and Trastuzumab

Five women had estrogen-receptor-positive tumors (Table 6. 2). For one of these women, systemic therapy was not recommended during pregnancy, while for another woman, the decision was made to delay all therapy until after the birth as she had been diagnosed in the third trimester. The other three women received chemotherapy without Tamoxifen while pregnant. Tamoxifen is linked to congenital malformations in the fetus and is not recommended for use during pregnancy (Peccatori et al. 2018). Therefore, women in the second or third trimester for whom Tamoxifen is indicated should be counselled about the potential adverse baby outcomes associated with such treatment so that they can make an informed decision regarding their clinical management (Buonomo et al. 2020; Schuurman et al. 2019).

Two women had HER2-positive tumors (Table 6.2). One of these women was diagnosed in the third trimester, and so systemic therapy was delayed until after birth. The other received Doxorubicin and Cyclophosphamide without Trastuzumab. Trastuzumab, a monoclonal antibody that antagonises HER2 receptors, is of a large molecular size and hence requires active transport to cross the placental barrier. Active transport across the placental barrier only occurs from 14 weeks gestation onward (Lambertini, Peccatori & Azim 2015). Therefore, any accidental exposure during the first trimester does not appear to impact perinatal outcomes (Lambertini, Di Maio, et al. 2018; Lambertini et al. 2019). However, Trastuzumab is associated with perinatal morbidity, e.g. pulmonary hypoplasia and renal impairment when exposure occurs in the second and third trimester (Bader et al. 2007; Gottschalk et al. 2011; Lambertini et al.

2019; Shachar et al. 2017; Zagouri, Sergentanis, et al. 2013). As with Tamoxifen, Trastuzumab treatment should be delayed until after delivery.

Challenges in the management of breast cancer in women

All women in our series were younger than 40 years, with the median age 34.5 years. Management of breast cancer in young women is challenging as the diagnosis is difficult and prognosis may be poorer than in older women (Anwar et al. 2019; Desreux 2018).

Four (67%) of the women in our series were diagnosed with grade 3 (high) tumors, which is consistent with an observational study that found breast cancer is more likely to be aggressive in younger women (Anwar et al. 2019).

Management approach

A multidisciplinary management approach was utilised in all cases. A multidisciplinary team, which may include an obstetrician, a surgeon, an oncologist, a radiation oncologist and a neonatologist, as well as support from specialist nurses and allied health practitioners, is essential for the management of women diagnosed GBC and for the safety of the fetus (Zagouri et al. 2016; Zagouri, Psaltopoulou, et al. 2013).

Perinatal outcomes

Preterm birth is the main adverse perinatal outcome in women diagnosed with GBC with most births being planned preterm births. In our series, three women were delivered preterm. Of those, two were delivered by induction of labour/CS without an obstetric indication. When planning an early induction of labour or CS, the maternal risk of postponing

chemotherapy versus the risk of preterm birth should be considered, given the risks associated with preterm delivery, this should be avoided whenever possible (Amant, Han, et al. 2015; Amant, Vandenbroucke, et al. 2015).

Women who are expected to deliver preterm are given corticosteroids prenatally to stimulate fetal lung maturation and thus reduce the risk of respiratory distress syndrome (RDS) (Roberts et al. 2017; Sweet et al. 2017). Prenatal corticosteroids were administered in three cases, of which two were preterm births at 34 weeks and 35 weeks' gestation. The optimal timing for antenatal corticosteroid administration is 24 hours to seven days before the predicted delivery (Sweet et al. 2017). Prenatal corticosteroids administration in women with predicted birth before 34 weeks can reduce the RDS risk (Roberts et al. 2017).

6.5.1 Conclusion

The management of GBC requires a multidisciplinary team who have expertise in oncology, breast surgery, maternal-fetal medicine, and neonatology to provide optimal care and support from diagnosis to birth and subsequent treatment. This approach can optimise outcomes for mother and child. For every pregnant woman, breast examination should regularly be performed at her prenatal visits, and breast ultrasonography should be offered if a breast lump or other symptom is detected. Breast surgery can be performed during all pregnancy trimesters, and chemotherapy can be administered in the second and third trimesters.

6.6 Chapter summary

This chapter provides details on the management and outcomes of six women with a diagnosis of GBC. Data for this study were extracted from the AMOSS GBC dataset from Australia and New Zealand. The diagnostic methods used and management of the six women were compared with the most recent available evidence and guidelines regarding the diagnosis and management of cancer in pregnancy. The study aims to provide healthcare providers with information regarding best-practice diagnostic and management options for women diagnosed with GBC.

The most important findings of this chapter are:

- A painless breast lump was the most common sign of GBC in our sample of women; therefore, breast examination may be considered for every pregnant woman.
- Breast ultrasonography is the first-line diagnostic imaging modality during all pregnancy trimesters and it should be offered to every woman with a suspected breast lump.
- Imaging with ionising radiation techniques such as mammography and chest x-ray can be considered safe during pregnancy with the proviso that protective shielding must be used to ensure that the radiation dose is reduced to the bare minimum. Note, however, that this finding cannot be applied to a CT of the pelvis.
- Some types of chemotherapy can be given during pregnancy in the second and third trimesters, but all chemotherapy should be avoided during the first trimester.

- Breast surgery can usually be performed safely throughout pregnancy.
- Collaboration between oncology, obstetric and neonatal staff is essential to optimise outcomes for mother and child.

This chapter examined the management of GBC, including diagnostic procedures and surgical and oncological treatment. The following chapter will examine the short-term effects of breast cancer systemic treatment on the neonatal outcomes of babies born to women with GBC.

Chapter 7

Study Four: In-utero exposure to breast cancer treatment: a population-based perinatal outcome study

7.1 Introduction to this chapter

Data on the effects of fetal exposure to chemotherapy are limited, as pregnant women are excluded from randomised trials because they are considered a “vulnerable population” requiring protection for themselves and their fetuses (Blehar et al. 2013; Liu & Mager 2016). The use of breast cancer systemic treatment during the second and third trimesters may be associated with adverse perinatal outcomes, and this effect can only be investigated by conducting observational studies. Chapter four of this thesis (Study One) examined the short-term outcomes for babies born to women with GBC. However, the population data used in Study One lacked information on breast cancer treatment, and therefore the study was not able to analyse the perinatal outcomes on the basis of exposure to systemic treatment. Study Four fills this gap by using the AMOSS GBC dataset, which includes information on the systemic treatment of breast cancer and the timing of treatment administration during pregnancy (The Australasian Maternity Outcomes Surveillance System (AMOSS) 2015). Study Four examines the effect of breast cancer systemic therapy on the perinatal outcomes of babies born to women with GBC and exposed to systemic treatment during the second and third trimesters.

A shorter version of this chapter was published in the *British Journal of Cancer*:

Safi, N., Anazodo, A., Dickinson, J.E., Lui, K., Wang, A.Y., Li, Z. & Sullivan, E.A. 2019, 'In utero exposure to breast cancer treatment: a population-based perinatal outcome study', *Br J Cancer,* vol. 121, no. 8, pp. 719-21.

This chapter is written and formatted according to the *British Journal of Cancer* guidelines.

7.2 Abstract

7.2.1 Background Chemotherapy during a viable pregnancy may be associated with adverse perinatal outcomes. We examined the perinatal outcomes of babies born to women with breast cancer detected during pregnancy.

7.2.2 Methods An Australian and New Zealand prospective case-cohort population study was conducted between January 2013 and June 2014. Eligible births of >400g or > 20 weeks of gestation born to women with breast cancer detected during pregnancy were identified using the Australasian Maternity Outcomes Surveillance System.

7.2.3 Results Among the 24 births identified, all the mothers had been diagnosed with breast cancer in the first or second trimesters, and 18 had chemotherapy. Chemotherapy commenced at a median of 20 (range 13 to 30) weeks of gestation, with combination drugs for a mean duration of 10 weeks. Twelve (66.7%) exposed infants were born preterm (31 to 36 weeks of gestation) with 11 by induced labour or elective caesarean section. Overall, 20 babies were exposed to maternal breast cancer surgery during pregnancy, with four surgeries delayed until postpartum. None had exposure to radiotherapy during pregnancy. There were no perinatal deaths or congenital malformations.

7.2.4 Conclusion Breast cancer diagnosed during mid-pregnancy is often treated with chemotherapy. Other than induced preterm births, there were no serious adverse perinatal outcomes.

7.3 Background

The management of cancer diagnosed during pregnancy poses unique challenges in optimising maternal and infant outcomes (Amant, Han, et al. 2015; Lee et al. 2012). One of these challenges is choosing the optimal treatment regimen to balance the benefit to the woman and the potential risks of adverse outcomes for the fetus (Morice, Uzan & Uzan 2012). Timing to initiate treatment is also challenging, especially if the cancer diagnosis is early in the first trimester, as fetal exposure to chemotherapy during the period of organogenesis (weeks three to eight of gestation) has been associated with an increased risk of congenital malformations (Albright & Wenstrom 2016; Sadler 2012).

Several observational studies have demonstrated that fetal exposure to chemotherapeutic agents during the second and third trimesters does not increase the incidence of major congenital malformations for babies born to women with cancer diagnosed during pregnancy (Abdel-Hady el et al. 2012; Loibl et al. 2012; Van Calsteren et al. 2010). However, the literature also shows that exposure to systemic chemotherapy during pregnancy is associated with high rates of preterm birth, small for gestational age, low birthweight, admission to neonatal intensive care units (NICU), and respiratory distress syndrome (RDS) (Amant, Vandenbroucke, et al. 2015; Loibl et al. 2012; Van Calsteren et al. 2010).

There is limited evidence on the impact of maternal systemic chemotherapy to the fetus, as international regulations typically exclude pregnant women from randomised trials (Liu & Mager 2016) because they are considered a “vulnerable population” requiring protection for

themselves and their fetuses (Blehar et al. 2013). Therefore, the impact of in-utero exposure of systemic chemotherapy on fetuses and their perinatal outcomes can only be assessed via observational studies. Furthermore, chemotherapy is often reserved for more invasive disease or more advanced stages of breast cancer, with surgery and radiotherapy are the mainstays of early breast cancer treatment (Bergh et al. 2012; Curigliano et al. 2017).

This study examines the effect of in-utero exposure to breast cancer systemic chemotherapy on the perinatal outcomes (including mortality, major morbidity and congenital abnormality) of a cohort of babies born to women with breast cancer diagnosed during pregnancy.

7.4 Methods

We conducted an Australia and New Zealand population-based prospective cohort study design using the Australasian Maternity Outcomes Surveillance System (AMOSS). The AMOSS is a bi-national surveillance and research system that studies and records rare conditions during pregnancy and the postpartum period. Babies born to women with a confirmed diagnosis of breast cancer during pregnancy were identified by participating AMOSS sites through monthly surveillance between 1 January 2013 and 30 June 2014. Participating AMOSS sites include more than 96% of the hospitals in Australia and New Zealand with maternity units of more than 50 births annually. Australia and New Zealand combined had 369,528 births above 20 weeks of gestation during 2013 (Australian Institute of Health and Welfare 2015a; Perinatal and Maternal

Mortality Review Committee 2015). It was our expectation that any woman with breast cancer diagnosed during pregnancy would be referred to a tertiary obstetric institution for pregnancy management. To meet our study's inclusion criteria, live or stillborn babies born to women with breast cancer diagnosed during pregnancy must have weighed at least 400 grams or had a gestational age not less than 20 weeks.

Web-based data-collection forms were completed by data collectors at AMOSS participating sites for all eligible women and their babies. Data were collected on baseline demographic and pregnancy factors, breast cancer diagnosis, management and interventions, and outcomes of the women and their babies.

The study group included all the eligible births born to women with breast cancer diagnosed during the first and second pregnancy trimesters, whether exposed to systemic chemotherapy or not. The primary perinatal outcomes for this study included stillbirths, neonatal deaths, major congenital malformations, preterm births (defined as birth of a baby before 37 completed weeks of gestation), low birthweight (defined as birthweight < 2,500 grams) and small for gestational age (birthweight < 10^{th} percentile for gestational age and gender) (Australian Institute of Health and Welfare 2017).

Chi-square, Fisher's exact test, and an independent-sample t-test were used to investigate the difference in outcomes between babies born to women with breast cancer diagnosed during pregnancy and exposed to systemic therapy during pregnancy and those who were not exposed to

systemic therapy. SPSS, version 24.0 (IBM Corporation, Somers, NY, USA) was used for data analysis.

Ethics approval was granted by the NSW Population and Health Services Research Ethics Committee (HREC/09/CIPHS/21), multiple Human Research Ethics Committees across Australia. Multi-Regional Ethics Committee approval (MEC/09/73/EXP) was granted in New Zealand and the UTS Human Research Ethics Committee (HREC Ref No. 2014000417).

7.5 Results

Twenty-four babies born to women with breast cancer diagnosed in the first and second trimesters of pregnancy were eligible to be included in the study. Of these, 18 babies had been exposed to breast cancer systemic chemotherapy and six had not.

The demographic characteristics of the 24 women with breast cancer diagnosed during pregnancy are shown in Table 7.1. Women who had received systemic therapy during pregnancy did not differ in their characteristics from those who had not. Table 7.2 compares maternal breast cancer characteristics and management for the exposed and non-exposed babies. Of the 18 women who had chemotherapy-exposed pregnancies, one third had metastatic disease; all had surgery, 15 of them during pregnancy and three post-delivery; and 12 had their radiotherapy delayed to post-delivery.

Table 7.1: Maternal demographics

	Exposed (n=18)	Non-exposed (n=6)
Country		
Australia	15(83.3)	5(83.3)
New Zealand	3(16.7)	1(16.7)
Age (years)		
<35	9(50.0)	3(50.0)
≥35	9(50.0)	3(50.0)
BMI (kg/m^2)		
18.50 - 24.99	12(66.7)	4(66.7)
≥25.00	5(27.8)	2(33.3)
Unknown	1(5.6)	0(0.0)
Hospital Sector		
Public	11(61.1)	5(83.3)
Private	7(38.9)	1(16.7)
Parity		
0	7(38.9)	4(66.7)
≥1	11(61.1)	2(33.3)
Smoking status		
Never smoked	9(50.0)	5(83.3)
Quit smoking before becoming pregnant	4(22.2)	0(0.0)
Smoking during pregnancy	1(5.6)	1(16.7)
Not known	4(22.2)	0(0.0)
ART*		
Yes	0(0.0)	0(0.0)
No	18(100.0)	5(83.3)
Not known	0(0.0)	1(16.7)

*ART = assisted reproductive technology

Antenatal care and obstetric management were compared based on exposure to systemic chemotherapy. The rate of antenatal corticosteroid use for fetal lung maturation was higher in the exposed group (Table 7.2).

Table 7.2: Maternal cancer characteristics, tumour treatment and obstetric management

	Exposed (n=18)	Non-exposed (n=6)
Tumour grade		
Low	0(0.0)	3(50.0)
Intermediate	3(16.7)	0(0.0)
High	12(66.7)	3(50.0)
Not known	3(16.7)	0(0.0)
Lymphovascular Involvement		
Yes	7(38.9)	0(0.0)
No	9(50)	5(83.3)
Not known	2(11.1)	1(16.7)
Estrogen receptor status		
Positive	12(66.7)	4(66.7)
Negative	5(27.8)	1(16.7)
Not known	1(5.6)	1(16.7)
Progestrone receptor status		
Positive	9(50.0)	4(66.7)
Negative	8(44.4)	1(16.7)
Not known	1(5.6)	1(16.7)
HER 2 status		
Positive	4(22.2)	0(0.0)
Negative	13(72.2)	4(66.7)
Not known	1(5.6)	2(33.3)
Metastatic Disease		
Yes	6(33.3)	0(0.0)
No	11(61.1)	6(100.0)
Not known	1(5.6)	0(0.0)
Surgery During Pregnancy		
Yes	15(83.3)	5(83.3)
No, delayed until end of pregnancy	3(16.7)	1(16.7)
Radiotherapy During Pregnancy		
No, not recommended	6(33.3)	3(50.0)
No, delayed until end of pregnancy	12(66.7)	3(50.0)
Postpartum Systemic Therapy		
Yes	17(94.4)	2(33.3)
No	1(5.6)	3(50.0)
Not known	0(0.0)	1(16.7)
Corticosteroid for fetal lung maturity		
Yes	10(55.6)	0(0.0)
No	6(33.3)	6(100.0)
Not known	2(11.1)	0(0.0)
Induction of labour		
Yes	10(55.6)	5(83.3)
No/not applicable	8(44.4)	1(16.7)
Method of birth		
Vaginal birth	11(61.1)	4(66.6)
Caesarean section	7(38.9)	2(33.3)

Table 7.3 shows the perinatal outcomes for the 24 babies. There were no stillbirths or neonatal deaths in any of the groups. No baby was diagnosed with a congenital malformation, and there were no severe neonatal complications. The mean gestational age at birth for the 18 chemotherapy-exposed babies was 35.7 ± 2 weeks, which was significantly lower than for the six non-exposed babies (mean 38.8 ± 1.5 weeks) (P =0.002). Compared with no small for gestational age babies in the non-exposed babies, there were two in the exposed group, one delivered preterm at 32 weeks of gestation and the other by pre-labour caesarean section (CS) at 38 weeks of gestation.

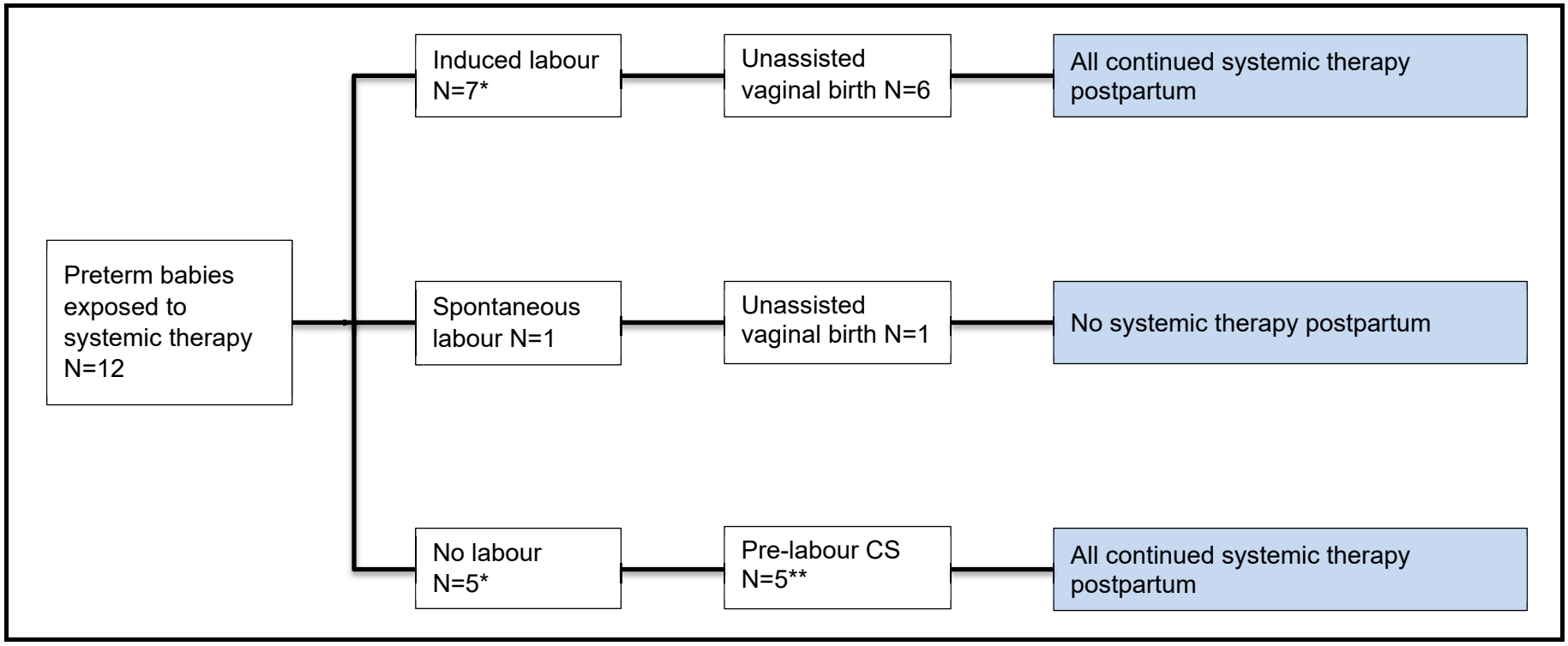
Among the 12 preterm babies who had been exposed to chemotherapy, seven were delivered by unassisted vaginal birth (six with labour induction and one spontaneous), and five by pre-labour CS. The reasons for the six inductions were breast cancer management in five cases and premature rupture of membranes in the sixth. The reasons for five CS included: two cases of maternal disease/surgery related to the breast cancer (RANZCOG category 4), one case of maternal request (RANZCOG category 4), one case of maternal hypertension (RANZCOG category 2), and one case of preeclampsia with intrauterine growth restriction (RANZCOG category 2) (RANZCOG 2015). The 11 women with preterm births following planned induction of labour or pre-labour CS continued their chemotherapy postpartum (Figure 7.1).

Table 7.3: Perinatal outcomes among the 24 babies

	Exposed (n=18)	Non-exposed (n=6)	P-value
Live births	18(100.0)	6(100.0)	NA
Neonatal deaths*	0(0.0)	0(0.0)	NA
Preterm (<37 weeks)			
Yes	12(66.7)	0(0.0)	
<32 weeks	*1(5.6)*	*0(0.0)*	0.014
33-<37 weeks	*11(61.1)*	*0(0.0)*	
No	6(33.3)	6(100.0)	
Small for gestational age	2(11.1)	0(0.0)	1.000
Low birthweight (<2500 g)	9(50.0)	0(0.0)	0.052
Resuscitation			
Yes	6(33.3)	0(0.0)	
Neopuff or CPAP mask only	*3(16.7)*	*0(0.0)*	
Oxygen	*1(5.6)*	*0(0.0)*	0.277
Neopuff or CPAP mask + Suction + Oxygen	*2(11.1)*	*0(0.0)*	
No	12(66.7)	6(100.0)	
Respiratory support			
Yes**	1(5.6)	0(0.0)	1.000
No	16(88.9)	6(100.0)	
Not known	1(5.6)	0(0.0)	
Apgar score (5 minutes)			
8	5(27.8)	0(0.0)	
9	10(55.6)	5(83.3)	0.348
10	3(16.7)	1(16.7)	
Admission to NICU/SCN	9(50.0)	1(16.7)	0.341
Breastfeeding initiated			
Yes	6(33.3)	5(83.3)	0.061
No	12(66.7)	1(16.7)	

*During hospital stay only, **CPAP mask only

Figure 7.1: Mode of birth and postpartum maternal treatment for preterm babies exposed to systemic therapy



*One case with the failure of induction also included in no labour category and was delivered by RANZCOG Cat. 2 CS

**In three cases the CS was RANZCOG category 4 and in the two other cases RANZCOG category 2.

The types of systemic chemotherapeutic agents used during the pregnancies are listed in Table 7.4.

Table 7.4: Systemic therapeutic agents during pregnancy.

	Timing of therapy		
	2nd Trimester (13-27 weeks) (n=14) n* (%)	3rd Trimester (28-40) weeks (n=4) n* (%)	Total (n=18) n* (%)
Cyclophosphamide			
Yes	13(92.9)	4(100.0)	17(94.4)
No	1(7.1)	0(0.0)	1(5.6)
Carboplatin			
Yes	1(7.1)	0(0.0)	1(5.6)
No	13(92.9)	4(100.0)	17(94.4)
Docetaxel			
Yes	2(14.3)	1(25.0)	3(16.7)
No	12(85.7)	2(50.0)	14(77.8)
Not stated	0(0.0)	1(25.0)	1(5.6)
Doxorubicin			
Yes	12(85.7)	3(75)	15(83.3)
No	2(14.3)	0(0.0)	2(11.1)
Not stated	0(0.0)	1(25.0)	1(5.6)
Epirubicin			
Yes	1(7.1)	0(0.0)	1(5.6)
No	13(92.9)	2(50.0)	15(83.3)
Not stated	0(0.0)	2(50.0)	2(11.1)
Fluorouracil			
Yes	1(7.1)	0(0.0)	1(5.6)
No	13(92.9)	2(50.0)	15(83.3)
Not stated	0(0.0)	2(50.0)	2(11.1)
Paclitaxel			
Yes	6(42.9)	1(25.0)	7(38.9)
No	8(57.1)	2(50.0)	10(55.6)
Not stated	0(0.0)	1(25.0)	1(5.6)
Tamoxifen			
Yes	2(14.3)	0(0.0)	2(11.1)
No	12(85.7)	2(50.0)	14(77.8)
Not stated	0(0)	2(50.0)	2(11.1)
Trastuzumab			
Yes	0(0.0)	1(25.0)	1(5.6)
No	14(100.0)	2(50.0)	16(88.9)
Not stated	0(0.0)	1(25.0)	1(5.6)

*Babies may have been exposed to more than one therapeutic agent.

Table 7.4 shows that the median gestational age at the time of first chemotherapeutic exposure was 20 weeks (range 13 to 31 weeks).

Fourteen (77.8%) had their first exposure in the second trimester and four (22.2%) in the third trimester. All had been exposed to a minimum of two therapeutic agents in fetal life, with a mean duration of exposure of 10.4 ± 5.8 weeks.

Exposure to chemotherapy: Eighteen (100%) babies had been exposed to alkylating agents – either nitrogen mustard (Cyclophosphamide) or platinum compounds (Carboplatin), 16 (88.9%) to anthracyclines (Doxorubicin or Epirubicin), 10 (55.6%) to taxanes (Paclitaxel or Docetaxel) and 1 (5.6%) to Fluorouracil. All 18 babies had been exposed to at least two chemotherapeutic agents.

Exposure to Tamoxifen: Two babies had been exposed to the anti-oestrogenic agent Tamoxifen in combination with other systemic therapy. One had been exposed to Cyclophosphamide, Doxorubicin and Docetaxel in addition to Tamoxifen, with the treatment starting in the 23rd week of gestation and concluding at the 32nd week of gestation. Delivery occurred at 36 weeks of gestation by induced normal vaginal birth, with a birthweight of 2480 grams and an Apgar score at 5 minutes of 8. The reason for the induction of labour was to continue maternal breast cancer systemic therapy and commence radiation therapy. The baby was discharged home without the need for admission to NICU or Special Care Nursery (SCN).

One baby had been exposed to Paclitaxel and Carboplatin in addition to Tamoxifen, with the treatment starting in the 21st week of gestation and the last dose given in the 32nd week of gestation. Delivery occurred at 34 weeks of gestation by CS after the failure of induced labour, with a

birthweight of 2240 grams and an Apgar score at 5 minutes of 8. The reason for the early induction and CS was thrombocytopenia secondary to preeclampsia. This baby was resuscitated at birth with a continuous positive airway pressure (CPAP) mask and admitted to the SCN.

Exposure to Trastuzumab: Only one baby had been exposed to the monoclonal antibody Trastuzumab, in combination with Docetaxel and Cyclophosphamide. The treatment started in the 28th week of gestation and the last dose was given in the 31st week of gestation. This baby was delivered preterm at 36 weeks of gestation by induced normal vaginal birth, with a birthweight of 2380 grams and Apgar score of 10. It was admitted to SCN for low birthweight and mild respiratory distress, but did not require ventilation support and was discharged home on day 4.

Ten of the babies had been exposed to Taxanes in addition to other chemotherapeutic agents. However, their perinatal outcomes did not significantly differ from those who had been exposed to non-Taxanes chemotherapy (Table 7.5).

Table 7.5: Perinatal outcomes amongst the 18 babies exposed to chemotherapy based on their exposure to Taxanes.

	Taxanes yes (n=10)	Taxanes no (n=8)	P-value
Live births	10(100.0)	8(100.0)	NA
Neonatal deaths	0(0.0)	0(0.0)	NA
Preterm (<37 weeks)			
Yes	7(70.0)	5(62.5)	
<32 weeks	*0(0.0)*	*1(12.5)*	1.000
33-<37 weeks	*7(70.0)*	*4(50)*	
No	3(30.0)	3(37.5)	
Small for gestational age	1(10.0)	1(12.5)	1.000
Low birthweight (<2500 g)	(0.0)	(0.0)	1.000
Resuscitation			
Yes	4(40.0)	2(25.0)	
Neopuff or CPAP mask only	*2(20.0)*	*1(12.5)*	
Oxygen	*1(10.0)*	*0(0.0)*	1.000
Neopuff or CPAP mask + Suction + Oxygen	*1(10.0)*	*1(12.5)*	
No	6(60.0)	6(75.0)	
Respiratory support			
Yes	1(10.0)	0(0.0)	1.000
No	9(90.0)	7(87.5)	
Not known	0(0.0)	1(12.5)	
Apgar score (5 minutes)			
8	3(30.0)	2(25.0)	
9	4(40.0)	6(75.0)	0.241
10	3(30.0)	0(0.0)	
Admission to NICU/SCN	5(50.0)	4(50.0)	1.000
Breastfeeding initiated			
Yes	3(30.0)	3(37.5)	1.000
No	7(70.0)	5(62.5)	

7.6 Discussion

We examined the effect of fetal exposure to maternal breast cancer chemotherapy on perinatal outcomes. As expected, the gestation at diagnosis influenced the decision on the timing of chemotherapy and the non-use of radiotherapy during pregnancy. All cases in our study, whether exposed to chemotherapy or not, were diagnosed in the first or second trimesters. Other factors influencing management decisions were the

grading and the staging of the breast cancer. Of note, none of the non-exposed babies' mothers had distant metastasis, and none had a preterm birth.

It is recognised that management decisions are often a delicate balance in considering the treatment impacts on both maternal and fetal health during pregnancy. In this population study in Australia and New Zealand, other than preterm birth, we did not find serious adverse perinatal outcomes in the 18 babies exposed to chemotherapy or in the six not exposed. There were no perinatal deaths or congenital malformations.

Exposure to systemic therapy for all babies in the study group occurred in the second and third trimesters. The majority of babies had been exposed to Cyclophosphamide and Doxorubicin, with one exposed to Trastuzumab and two to Tamoxifen. This is consistent with other studies in which the babies were mainly exposed to a combination of Cyclophosphamide and Doxorubicin (Amant, Vandenbroucke, et al. 2015; Cardonick et al. 2015; Hahn et al. 2006; Loibl et al. 2012). All babies in our study had been exposed to at least two chemotherapeutic agents and for a mean duration of 10 weeks. In our analysis, there was no congenital malformation in any of the 24 babies, whether exposed or not exposed, and only two infants had been born small for gestation. The results of a study published by Hahn et al. (2006) are similar to ours and show no perinatal deaths among babies exposed to a combination of 5-Fluorouracil, Doxorubicin, and Cyclophosphamide.

In comparison to other recent studies, however, the babies in our study had better outcomes. For example, Loibl et al. (2012) found significantly

higher rates of events (congenital malformations or newborn complications) among the infants who were exposed to systemic treatment than among those who were not exposed, but they concluded that these adverse outcomes were related to preterm birth; they also reported two neonatal deaths among the 203 exposed infants. Amant et al. (2015) reported six minor congenital abnormalities and 28 small for gestation infants among 127 infants born to women who had received breast cancer diagnoses during pregnancy, whether they were exposed to chemotherapy or not. However, these authors did not find a significant difference compared to the control group of infants who were born to women without a diagnosis of cancer.

Tamoxifen, a selective oestrogen receptor modulator, is contraindicated during pregnancy, as it has been associated with congenital malformations including ambiguous genitalia and craniofacial malformations (Braems et al. 2011; Peccatori et al. 2018; Zagouri, Psaltopoulou, et al. 2013). Guidelines by the Royal College of Obstetricians and Gynaecologists (RCOG 2011) on the management of breast cancer during pregnancy recommend that Tamoxifen should be delayed until after giving birth. These recommendations were based on level 3 evidence (case reports and case series). In our study, the two babies who had been exposed to Tamoxifen for 9 and 11 weeks were born without congenital malformations. These results are consistent with a previous case report of a healthy neonate delivered after exposure to Tamoxifen (Oksuzoglu & Guler 2002). However, due to the small number of babies exposed to Tamoxifen in our study, we are unable to recommend the use of

Tamoxifen during pregnancy. Larger observational studies would be required to assess the fetal effects of Tamoxifen.

Trastuzumab, a monoclonal antibody that antagonises HER2 receptors, is contraindicated during pregnancy, as it has been associated with oligohydramnios, pulmonary hypoplasia and renal impairment in the fetus (Bader et al. 2007; Gottschalk et al. 2011; Shachar et al. 2017). We were unable to confirm this association because in our study only one baby had been exposed to Trastuzumab in the third trimester. This baby was admitted to SCN for low birthweight and mild respiratory distress. Previous case reports show that oligohydramnios and renal impairment are reversible and suggest ceasing the Trastuzumab therapy and instituting close monitoring of amniotic fluid and fetal bladder volume as surrogates for fetal renal function (Bader et al. 2007; Gottschalk et al. 2011; Mandrawa et al. 2011; Rasenack et al. 2016).

In agreement with other studies, our results show a significantly higher rate of preterm births among babies exposed to systemic therapy during pregnancy compared to non-exposed babies (12 out of 18 vs none out of six). Amant et al. (2012) found a high rate of preterm birth among babies exposed to chemotherapy (47 out of 70) (Amant, Van Calsteren, et al. 2012). Similarly, Peres et al. (2001) found significantly higher rates of preterm birth among babies exposed to chemotherapy (six out of eight) compared with non-exposed babies (two out of 10) (Peres et al. 2001).

Preterm birth is associated with adverse short- and long-term outcomes for babies (Melamed et al. 2009). Morbidities in neonates (low birthweight and admission to NICU/SCN) in our study were directly linked to preterm

birth. Similar to previous studies (Amant, Van Calsteren, et al. 2012; Loibl et al. 2012), the leading cause of preterm birth among the exposed group in our study was iatrogenic to facilitate maternal systemic chemotherapy postpartum.

Loibl et al. (2012), in a multinational population-based cohort study, suggested that a decision to planned preterm birth is “often taken without medical indication” and concluded that delaying systemic chemotherapy for women with early breast cancer until term did not significantly affect their survival rates (Loibl et al. 2012). It is therefore important to consider providing the fetus with the opportunity, if possible, to reach term in order to avoid the deleterious effects of a preterm birth.

Although studies have shown that the use of Cyclophosphamide and Doxorubicin during the second and third trimesters is relatively safe, they are inconsistent regarding the rates of perinatal deaths and congenital malformations (Amant, Van Calsteren, et al. 2012; Loibl et al. 2012). In addition, there is inconsistency regarding the adverse perinatal outcomes after exposure to Tamoxifen and Trastuzumab. There is growing evidence on the safety of exposure to anthracyclines containing regimens after the first trimester (Germann, Goffinet & Goldwasser 2004; Gziri et al. 2012); however, the evidence is limited for the other chemotherapeutic agents and for non-chemotherapy systemic treatment. There is a need for standardised information onthe effects of maternal-fetal exposure to chemotherapy and the other systemic anticancer agents used in pregnancy. This information should be collated internationally into a database to inform clinical practice and research worldwide

7.6.1 Strengths and limitations of the study

One of the strengths of this study is its prospective population study design that included all cases occurring in both Australia and New Zealand during the study period. The study's generalisability is limited by the rarity of the condition, the low uptake of chemotherapy during pregnancy and the follow-up period being restricted to the perinatal period.

7.6.2 Conclusion

Few studies on the use of chemotherapy in the second and third trimesters of pregnancy include maternal and fetal outcomes. Our study found no congenital abnormalities or perinatal deaths among the 18 babies exposed to at least two different chemotherapy agents during pregnancy. The directionality of our findings is consistent with the two largest studies in the international literature, particularly regarding preterm birth (Amant, Vandenbroucke, et al. 2015; Cardonick et al. 2015). There is an urgent need for larger observational studies to provide better information on fetal exposure to chemotherapy and outcomes to inform gestational breast cancer management.

Additional Information:

- Ethics approval and consent to participate:

Ethics approval for our study was granted by the NSW Population and Health Services Research Ethics Committee (HREC/09/CIPHS/21), multiple Human Research Ethics Committees across Australia and the UTS Human Research Ethics Committee (HREC Ref No. 2014000417).

Multi-Regional Ethics Committee approval (MEC/09/73/EXP) was granted in New Zealand.

- Consent for publication: NA
- Availability of data and material: data will be available from the corresponding author on reasonable request.
- Conflict of interest: the authors declare no conflict of interest.
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- Authors' contributions: All authors were involved in the conception and design of the study and data interpretation. NS drafted the manuscript and performed data analysis. AW and ZL were involved in the data analysis. All authors critically revised the manuscript and approved it for submission.

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7.7 Chapter summary

This chapter provides information on the impact of exposure to breast cancer systemic treatment during the second and third pregnancy trimesters on the perinatal outcomes of babies born to women with GBC. The source of data for this study was the AMOSS GBC dataset (The

Australasian Maternity Outcomes Surveillance System (AMOSS) 2015). The study group of 24 babies included 18 babies exposed to breast cancer systemic treatment, including chemotherapy with or without Tamoxifen or Trastuzumab. The comparison group consisted of the six babies born to women with GBC who had not been exposed to systemic treatment. All women in this study were diagnosed in the first or second trimester, and none of them received radiotherapy.

The main points of this chapter:

- Eighteen babies in the study group had been exposed to at least two chemotherapeutic agents.
- There were no congenital abnormalities or perinatal deaths among the 18 babies exposed to chemotherapy during pregnancy.
- The results of this study suggest that the use of chemotherapy during the second and third trimesters has minimal impact on the short-term outcomes of the babies born to women with GBC. However, the sample size is small and, therefore, there is a need for larger observational studies to provide more information on the impact of antenatal exposure to chemotherapy on neonatal outcomes to inform gestational breast cancer management.

Chapter 8: Discussion

8.1 Introduction to this chapter

For this thesis two sources of data, the NSW linked health data sets and the AMOSS GBC data set, were used to answer the research questions of Chapters 4, 5, 6 and 7. In this concluding chapter I discuss the main results of this research and consider the implications of this thesis for clinical practice.

8.2 The rationale for conducting this research

Research on the associations between breast cancer and pregnancy is limited. There is a gap in the literature on the impact of GBC on cancer treatment, antenatal management, and maternal and infant outcomes. There is limited evidence on the survival rate for women with GBC, and the subsequent perinatal outcomes of GBC survivors. This research examined the impact of the GBC on the short-term outcomes for the women and their babies, including their obstetric and cancer management. It also examined their 5- and 10-year survival rates. These aims were achieved through:

1. an examination of the incidence, obstetric and cancer management and birth outcomes of women with GBC,
2. an investigation of the factors affecting the overall survival of women with GBC,
3. a description of the outcomes of subsequent birth for GBC survivors,

4. an exploration of the options available to healthcare providers to early diagnose breast cancer in pregnant women by reviewing the safety of diagnostic procedures; and
5. an investigation of the effect of treatment for breast cancer of the babies born to women treated for breast cancer during pregnancy.

This thesis describes four studies that address the gap in the literature on GBC management and outcomes in Australia.

8.3 Main findings

The findings of this research highlight the challenges in providing optimal management for women with GBC, especially the balancing of clinical options for the woman with perinatal outcomes for the baby.

Women with GBC are more likely to give birth prematurely. The mode of delivery is by induction of labour or pre-labour CS. Decisions regarding induction at a preterm birth were not associated with the cancer stage at diagnosis or with the timing of diagnosis during pregnancy. Babies born to women with GBC were more likely to require resuscitation and admission to NICU or SCN. However, these outcomes were associated with prematurity, and the requisite associated epigenetic risk. Babies exposed to systemic breast cancer treatment during the second and third pregnancy trimesters were born with no congenital malformations, and their neonatal outcomes were comparable to babies born to women with GBC without being exposed to chemotherapy during pregnancy.

Painless breast lumps discovered by routine examination were the main sign of GBC, and breast ultrasound could be used safely as a first-line imaging technique when a breast lump is suspected. Treatment with selected breast cancer therapy in the second and third trimesters appeared to be safe. Breast surgery was safe throughout pregnancy. The findings of this research show that the crude 5-year mortality observed for women with GBC is almost double that previously reported for all women diagnosed with breast cancer in Australia.

8.4 Implications for clinical practice

A diagnosis of breast cancer during pregnancy puts a burden on the woman and her healthcare providers. The findings of the four studies in this thesis inform counselling and education for women and provide evidence for multidisciplinary teams involved in GBC management. This thesis contributes evidence-based data to describe the epidemiology, patterns of care and outcomes of women with GBC and their babies. By using population-based data, it assists healthcare providers' decision making in regard to the management of GBC by providing them with information on the available options to treat women with GBC.

8.5 Discussion based on the results of Chapters 4 (study 1), 5 (study 2), 6 (study 3) and 7 (study 4)

8.5.1 Study 1: Gestational breast cancer in New South Wales: A population-based linkage study of incidence, management, and outcomes.

In study 1, NSW linked health datasets (PDC, NSWCR, APDC) were used to estimate the incidence of GBC and to examine the obstetric management ad birth outcomes for women with GBC and their babies. The study population included all women who gave birth in NSW from 1 January 1994 to 31 December 2013 and their babies. The study compared the management and outcomes for women with GBC to those for women who gave birth in NSW without cancer during the study period.

The study estimated the incidence of GBC in NSW during the 20-year study period as 6.8 per 100,000 women giving birth. While the results show an increase in the incidence from 5.8 in 1994 to 7.3 per 100,000 women giving birth, the trend over time was not significant (p=0.075). The study shows that women with GBC tend to be older than women with no cancer, and are more likely to give birth by induction of labour or pre-labour CS. Women with GBC have a higher rate of preterm birth than women with no cancer. The study also shows that babies born to women with GBC had lower birthweights and higher rates of resuscitation and admission to SCN/NICU. There were no stillbirths or neonatal deaths among these babies, and the prevalence of major neonatal morbidities was relatively low.

Previous studies have shown that the incidence of PAC is increasing (Eibye, Kjaer & Mellemkjaer 2013; Lee et al. 2012; Stensheim et al. 2009). While this increase is consistent with the results of this study, the trend of the increase in the incidence of GBC over 20 years (1994 – 2013) in study 1 was not significant. This largely reflects the different inclusion criteria. This study included women who were diagnosed with breast cancer during pregnancy, whereas the other studies included women with any type of cancer diagnosed during pregnancy or within one year of giving birth (Eibye, Kjaer & Mellemkjaer 2013; Lee et al. 2012; Stensheim et al. 2009). However, similar to the results of study 1, another recent study was not able to show a significant increase in the incidence over time (Parazzini et al. 2017).

The results of study 1 show that women with GBC have higher rates of labour induction and/or delivery by CS than women with no cancer. These results are consistent with results from previous research (Maxwell et al. 2019; Shechter Maor et al. 2019; Simoes et al. 2018). It has been suggested that the higher rates of labour induction and pre-labour CS in GBC are due to management decisions relating to the stage of cancer at diagnosis (Kuo & Caughey 2019).

Study 1 showed a high rate of planned preterm birth among women with GBC, which was not associated with any specific cancer stage or timing of diagnosis. The directionality of this finding of iatrogenic preterm birth supports the results from a previous study that concluded that decisions to initiate early iatrogenic birth are often taken in the absence of a clear clinical indication (Loibl et al. 2012). Notwithstanding, this finding of study

1should be treated with caution due to the small number of cases analysed.

Study 1 shows that among women with GBC, preterm babies have an increased rate of low birthweight and the need for resuscitation and admission to SCN/NICU compared to term babies. The literature shows that preterm babies have higher rates of adverse neonatal outcomes than babies born at ≥ 37 weeks (Platt 2014). Caring for a preterm baby who has increased needs is likely to present unique challenges to a mother coping with cancer symptoms and probably treatment side effects. Therefore, it is essential to support a term birth where clinically possible in order to avoid the potential negative effects of preterm birth on both the mother and her baby.

It is evident from study 1 that women with GBC are more likely to have a planned preterm birth with induction of labour or pre-labour CS. This high rate of iatrogenic preterm birth cannot be explained by the stage of cancer at diagnosis or the timing of diagnosis during pregnancy.

8.5.2 Study 2: Gestational breast cancer: mortality and giving birth after breast cancer treatment – a New South Wales linkage study.

In this study, NSW linked health and mortality datasets (PDC, NSWCR, COD URF, RBDM) were used to examine the survival outcomes for women with GBC. The study also examined the subsequent birth following the index GBC birth (the birth of the pregnancy at which breast cancer is diagnosed).

Study 2 found that the 5-year crude mortality rate of women with GBC in our cohort was almost double the Australian national 5-year crude mortality rate for all women with breast cancer (19.7% vs. 10.2%) (Australian Institute of Health and Welfare 2012). The explanation for the increased mortality rate in women diagnosed during pregnancy is not known but may include their younger age; the effects of pregnancy (particularly hormonal changes) on cancer growth and metastasis; and be associated with the pathological subtype of the tumour and the stage of cancer at diagnosis (Albrektsen et al. 2006; Amant et al. 2013; Boudy et al. 2018; Cardonick et al. 2010; Genin et al. 2016; Johansson et al. 2018; Ploquin et al. 2018; Ruiz et al. 2017; Slepicka, Cyrill & dos Santos 2019; Stensheim et al. 2009). Results from this study provide further evidence of the role of the stage of breast cancer at diagnosis on the survival outcome. Women with GBC who were initially diagnosed with cancer stages 2–4 had poorer survival outcomes compared to those with stage 1, while women with stage 4 had lower rates of survival.

This study also found that 10 percent of women had a second birth following the GBC index birth, and none of these pregnancies was associated with major adverse maternal or neonatal outcomes. Previous studies report that women who give birth after breast cancer are more likely to survive than women with no subsequent birth; this is known as “the healthy mother effect” (Valachis et al. 2010). Among the women in our study who had a post-GBC birth, there were no deaths within 10 years from the date of the diagnosis of breast cancer. However, this study is not able to confirm the “healthy mother effect” for two main reasons: first, the small number of women in the cohort with post-GBC birth, and second, the

majority of the women who initially presented with stage 1 had the best survival outcome. Nonetheless, this study shows that subsequent uncomplicated birth after GBC can be achieved and does not appear to impact either a woman's overall survival or the perinatal outcomes of her baby.

8.5.3 Study 3: Clinical decision making in the management of breast cancer diagnosed during pregnancy: a review and case series analysis

This study provides details on GBC management during pregnancy, including signs, methods of investigation, treatment and outcomes. It explored six cases of GBC, underpinned by a review of recent studies and guidelines on GBC. Data for the six cases were compiled from the AMOSS GBC dataset. Of the six cases, two were diagnosed in each pregnancy trimester. A painless breast mass was the presenting sing in five cases (83%), which is consistent with the literature (Amant, Loibl, et al. 2012; Basaran et al. 2014). Breast ultrasonography represented the primary diagnostic imaging modality in all cases. This practice is consistent with the current guidelines of the ACOG, which recommends the use of ultrasonography as the primary breast imaging modality during pregnancy, as it carries a low fetal risk (American College of Obstetricians and Gynecologists 2017; Robbins et al. 2011). However, ACOG (2017) also recommends that ultrasonography be used with the lowest possible acoustic output level (American College of Obstetricians and Gynecologists 2017). In contrast to physicians who are reluctant to request imaging studies during pregnancy using ionising radiation (e.g. mammography) in order to avoid potential harm to the conceptus (Langer

et al. 2014), four women in the study were exposed to at least one ionising radiation imaging technique (mammography, chest X-Ray, CT scan) at varying stages of pregnancy. These women all delivered babies without major complications or congenital malformations. Other studies have shown that mammography appears safe at any time during pregnancy and that exposure of the fetus to ionising radiation from mammography is minimal (0.001 – 0.01 mGy) and, with lead shielding, this exposure can be reduced by half (American College of Obstetricians and Gynecologists 2017; American College of Radiology 2018; Arasu et al. 2018; Vashi et al. 2013). In addition, it has been reported that the dosages used in all imaging with ionising radiation techniques (except CT scans of the pelvis) fall well below the deterministic effects threshold, and therefore can be considered safe during pregnancy (de Haan et al. 2016).

Nuclear medicine was used in four cases in study 3 in the form of SLNB, bone scan, and Ventilation-Perfusion lung scan (VQ scan), and all these women gave birth to babies without congenital malformations or significant complications. However, data on the use of these procedures in pregnancy are limited, and their use may only be considered when other diagnostic modalities are inconclusive (de Haan et al. 2016). All cases in study 3 had CNB for pathological diagnosis. These results reflect the decline in the use of fine-needle aspiration (FNA) in favour of CNB, which is now considered the standard pathological diagnostic method for breast lesions (Amant, Loibl, et al. 2012; Brancato et al. 2012; Wang et al. 2017).

The six cases in this study received care from a multidisciplinary team that included an obstetrician, a surgeon, an oncologist, a radiation oncologist, and a neonatologist, as well as support from specialist nurses and allied

health practitioners. The literature shows that the multidisciplinary approach is essential for the management of women diagnosed with GBC and for the safety of the fetus (Zagouri et al. 2016; Zagouri, Psaltopoulou, et al. 2013). Similar to the results of study 1, the main adverse perinatal outcome was preterm birth, with most being planned to facilitate the management of breast cancer.

Study 3 highlights the need for a multidisciplinary approach to the management of GBC. As the majority of the women had a painless breast lump, which may not always be recognised by patients, breast examination should be regularly performed at prenatal visits, and breast ultrasonography should be offered if a breast lump or other symptom is detected.

8.5.4 Study 4: In-utero exposure to breast cancer treatment: a population-based perinatal outcome study

Following from the findings of the previous three studies, which provided information on the outcomes for the women with GBC and their babies, study 4 examined the effect of antenatal exposure to chemotherapy and other breast cancer systemic treatment on the perinatal outcomes of babies born to women with GBC. The data source for this study is the AMOSS GBC study, which collected data from all eligible birthing units in Australia and New Zealand. In this study, 24 babies born to women with GBC in the first and second trimesters were eligible to be included. Of these, 18 babies were exposed to breast cancer systemic chemotherapy, and six were not. This study shows that the gestational age at diagnosis

influenced the decision on the timing of chemotherapy administration and the non-use of radiotherapy during pregnancy. The other factors influencing management decisions are the grading and staging of breast cancer. None of the non-exposed babies' mothers had local lymphovascular involvement or metastatic disease, and none had a preterm birth. Similar to study 1, preterm birth was the main adverse perinatal outcome in this population study and there were no serious adverse perinatal outcomes in the 18 babies who were exposed to chemotherapy or in those who were not exposed. Nor were there perinatal death or congenital malformations. The majority of babies were exposed to cyclophosphamide and doxorubicin, and the exposure was in the second and third trimesters. The results study 4 are consistent with other research in which the babies were mainly exposed to a combination of cyclophosphamide and doxorubicin (Amant, Vandenbroucke, et al. 2015; Cardonick et al. 2015; Hahn et al. 2006; Loibl et al. 2012). The babies in study 4 had better outcomes than babies in other studies that found significantly higher rates of events (congenital malformations, or newborn complications) among the infants who were exposed to systemic treatment than among those who were not exposed (Loibl et al. 2012). In study 4 there were no congenital malformations in all 24 babies, whether exposed or not exposed. However, the neonatal complications in Loibl et al.'s (2012) study were associated with preterm birth (Loibl et al. 2012). Similar to Amant et al. (2012) and Loibl et al. (2012), The main perinatal adverse outcome is preterm birth, which was in the majority of the cases, planned to facilitate the management of GBC postpartum (Amant, Van Calsteren, et al. 2012; Loibl et al. 2012). There are few studies on the use of

chemotherapy in the second and third trimesters of pregnancy and the consequent maternal and fetal outcomes.

Study 4 provides assurance that the use of chemotherapy in the second and third trimesters of pregnancy is less likely to impact the baby's outcome in the short term. However, the small sample size and the short follow-up period of the study necessitates larger observational studies to provide better information on the effect of antenatal exposure to chemotherapy on the short-and long-term outcomes of babies born to women with GBC.

8.6 Research strengths and limitations

This research drew on four observational studies and two different population datasets. One of the strengths of this thesis is the use of population datasets. Studies 1 and 2 used linked population health and mortality datasets from NSW, Australia, over a 20-year period from 1994 to 2013 that included almost 1.8 million women giving birth. The population-based designs and large sample sizes enabled these studies to identify all women who gave birth and had a diagnosis of breast cancer during pregnancy, estimate the incidence of GBC accurately, and examine the obstetric management and the outcomes for the women and their babies. Study 2 was able to follow up the majority of the women with GBC for at least five years after the date of breast cancer diagnosis to investigate their survival outcomes.

Furthermore, the prospective collection of data in the AMOSS GBC dataset enabled studies 3 and 4 to provide details on the methods of

diagnosis, types of treatment and outcomes for the women and their babies. A limitation of the NSW health datasets is the lack of information on breast cancer treatment and breast cancer molecular subtypes, which limits the ability to examine the outcomes by those two factors. However, the AMOSS GBC dataset covers this gap by providing details on breast cancer treatment during pregnancy.

8.7 Recommendations for future research

This thesis provides information on the incidence and perinatal outcomes for women with GBC and their babies, and on the survival outcome of women with GBC. Results from this thesis show both a high rate of mortality among women with GBC and reassurance of no adverse neonatal effects for babies exposed to systemic treatment during the second and third trimesters of pregnancy. These results demonstrate the need for further studies that overcome the limitations identified in this thesis. These could include the linking of additional Australian datasets, including the Medicare Benefits Schedule (MBS) and the Pharmaceutical Benefits Scheme (PBS), to the datasets used in studies 1 and study 2 in order to:

- examine whether early treatment in pregnancy is associated with higher rate of survival, and
- conduct longitudinal studies of the long-term outcomes for children born to women with GBC and exposed to systemic treatment or to ionising radiation used in diagnostic procedures. Example of long

term outcomes are cardiac function for children exposed to in-utero anthracyclines and the neurodevelopmental outcomes.

8.8 Overall conclusion

The management of GBC is complicated. It puts a burden on the women and their health care providers. A multidisciplinary approach that aims to balance the outcomes for the women and their babies is indicated.

This research found that the incidence of GBC in NSW was 6.8 per 100,000 women who gave birth. It also showed the high uptake of planned birth by induction of labour or pre-labour caesarean section among women with GBC. The main adverse outcome was the high rate preterm birth, but this is not associated with stage of cancer at diagnosis or the timing of diagnosis during pregnancy.

The results of this research reveal that the 5-year crude mortality rate of women with GBC is almost double the crude mortality rate for women with breast cancer in Australia. The stage of breast cancer at diagnosis is associated with women's overall mortality. This research shows that women who were initially diagnosed with breast cancer stages 2–4 have higher rates of mortality than women who were initially diagnosed with stage 1. The most inferior survival outcome was noticed among women with stage 4 breast cancer at the time of diagnosis.

This research also shows that subsequent uncomplicated birth after GBC can be achieved and does not appear to impact a woman's overall survival or the perinatal outcomes of her baby.

This research found that the painless breast mass is the most common presenting sign for women with GBC, and its detection by the women is difficult due to the physiological changes involving the breast during pregnancy. Therefore, it is recommended that breast examination should be performed for every pregnant woman, and if breast mass is suspected, breast ultrasound should be offered as a first-line diagnostic imaging procedure. The research also showed that breast surgery is safe and can be performed in all pregnancy trimesters.

This research did not find any congenital abnormalities or perinatal deaths at birth among a cohort of babies exposed to breast cancer systemic treatment during the second and third trimesters.

This research recommends that the fetus should be given a chance to grow to at least 37 weeks gestation to avoid the deleterious effect of preterm birth on the health of the neonates and to minimise the risk of women with cancer needing to care of a premature baby. This recommendation is supported by results that show that some breast cancer systemic treatments after the first trimester and breast surgery during pregnancy are not associated with adverse perinatal outcomes. In addition, the high mortality rate among women with GBC is of great concern. Therefore, this research recommends further investigation of the risk factors associated with the high mortality rate among women with GBC, as detected in this research.

Appendices

Appendix 1: Glossary of terms

Apgar score: is a scoring system used to assess the condition of the baby at one and five minutes after birth. The system assesses the following physical signs: heart rate, muscle tone, respiration, reflexes and colours. The lowest score is zero, and the highest score is 10 (10 means the baby is in a perfect condition).

Birthweight: is the first bare weight of the newborn baby in grams.

- Birthweight of less than 1,000 grams is considered as extremely low birthweight.
- Birthweight of less than 1,500 grams is considered as very low birthweight.
- Birthweight of less than 2,500 grams is considered as low birthweight.

Caesarean section: Birth of the fetus through an abdominal incision. Pre-labour caesarean section: a caesarean section performed before the onset of labour.

Gestational age: represent the duration of pregnancy from the first day of the last normal menstrual period and measured in completed weeks.

Induction of labour: is the initiation of labour by one of the following methods:

- Surgical: artificial rupture of membranes (ARM).
- Medical: the use of prostaglandins or oxytocic agents.
- Combined surgical and medical induction.

Live birth: the delivery of a baby that able to breathe or show any signs of life.

Parity: refers to the total number of previous births, including both live and stillbirths.

Perinatal death: refers to stillbirth or death in the neonatal period (neonatal death).

Plurality: represents the total number of fetuses in utero at 20 weeks gestation that are subsequently born separately.

Preterm birth: is the birth of an infant before 37 completed week gestation.

Stillbirth: the delivery of the conceptus of at least 400 grams birthweight or 20 at least 20 weeks gestation that is not able to breathe or show any signs of life.

GBC index birth: is the birth resulted from the pregnancy during which the woman was diagnosed with breast cancer.

Post-GBC birth: is the birth following the GBC index birth.

Appendix 2: Published articles

Safi, N., Saunders, C., Hayen, A., Anazodo, A., Lui, K., Li, Z., Remond, M., Nicholl, M., Wang, A.Y. & Sullivan, E. 2021, 'Gestational breast cancer in New South Wales: A population-based linkage study of incidence, management, and outcomes', PLoS One, vol. 16, no. 1, p. e0245493.

PLOS ONE

RESEARCH ARTICLE

Gestational breast cancer in New South Wales: A population-based linkage study of incidence, management, and outcomes

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Data Availability Statement: Primary data cannot be shared publicly because they are confidential health data held by the New South Wales Ministry of Health and subject to Australian privacy

Abstract

Background

The incidence of gestational breast cancer (GBC) is increasing in high-income countries. Our study aimed to examine the epidemiology, management and outcomes of women with GBC in New South Wales (NSW), Australia.

Methods

A retrospective cohort study using linked data from three NSW datasets. The study group comprised women giving birth with a first-time diagnosis of GBC while the comparison group comprised women giving birth without any type of cancer. Outcome measures included incidence of GBC, maternal morbidities, obstetric management, neonatal mortality, and preterm birth.

Results

Between 1994 and 2013, 122 women with GBC gave birth in NSW (crude incidence 6.8/100,000, 95%CI: 5.6–8.0). Women aged ≥35 years had higher odds of GBC (adjusted odds ratio (AOR) 6.09, 95%CI 4.02–9.2) than younger women. Women with GBC were more likely to give birth by labour induction or pre-labour CS compared to women with no cancer (AOR 4.8, 95%CI: 2.96–7.79). Among women who gave birth by labour induction or pre-labour CS, the preterm birth rate was higher for women with GBC than for women with no cancer (52% vs 7%; AOR 17.5, 95%CI: 11.3–27.3). However, among women with GBC, preterm birth rate did not differ significantly by timing of diagnosis or cancer stage. Babies born to women with GBC were more likely to be preterm (AOR 12.93, 95%CI 8.97–18.64), low birthweight (AOR 8.88, 95%CI 5.87–13.43) or admitted to higher care (AOR 3.99, 95% CI 2.76–5.76) than babies born to women with no cancer.

regulations. Ethics approval for this project only authorizes specific researchers named in the original ethics application access to the de-identified linked data derived from the primary health data sets held by New South Wales Health. Data inquiries can be directed to: NSW Population & Health Services Research Ethics Committee. CINSW-Ethics@health.nsw.gov.au Phone Phone: 02 8374 5689 (Ethics Officer) or 02 8374 3610 (Executive Officer, Manager Research Ethics).

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Competing interests: The authors have declared that no competing interests exist.

Conclusion

Women aged ≥35 years are at increased risk of GBC. There is a high rate of preterm birth among women with GBC, which is not associated with timing of diagnosis or cancer stage. Most births followed induction of labour or pre-labour CS, with no major short term neonatal morbidity.

Introduction

In 2018, breast cancer was the most commonly diagnosed cancer in women, globally representing 24.2% of all cancers in women, and the most common cause of cancer-related mortality in women [1]. In Australia, breast cancer is the second most common cancer diagnosed during pregnancy after melanoma, with an incidence of 7.3 per 100,000 women giving birth [2]. The incidence of gestational breast cancer (GBC), defined as a first-time diagnosis of breast cancer during pregnancy, is increasing in high-income countries, in part due to the increasing age of mothers [3–5].

Women with GBC have higher rates of adverse obstetric outcomes, including thromboembolic events, sepsis, induction of labour and pre-labour cesarean section [2, 6, 7]. Preterm birth has been identified as the main adverse neonatal outcome for babies born to women with GBC [7]. It has been reported that preterm birth is a risk factor for developmental problems, irrespective of whether or not a baby is born to a women with GBC [8, 9]. Decisions around preterm delivery in the majority of cases of GBC are taken without any obvious clinical indication [10]. This is concerning as it has been suggested that preterm birth is the main risk factor for developmental problems in babies born to women with GBC irrespective of whether or not they were exposed to chemotherapy during pregnancy [7].

Our study aimed to examine the incidence, timing of diagnosis, obstetric management and perinatal outcomes of women with a first-time diagnosis of breast cancer during pregnancy (GBC) and their babies in New South Wales (NSW), Australia. We also examined whether decisions to deliver preterm babies iatrogenically by labour induction or pre-labour caesarean section (CS) were associated with the timing of breast cancer diagnosis during pregnancy and/or the stage of cancer at diagnosis.

Methods

We conducted a population-based cohort study using linked NSW Health data. The study population included all women with pregnancies that ended in live birth or stillbirth in NSW between 1 January 1994 and 31 December 2013. Birth was defined as the delivery of an infant of at least 400 grams birthweight or at least 20 weeks gestation whether live or stillborn [11]. For this study, gestational breast cancer (GBC) was defined as a first-time diagnosis of primary breast cancer during pregnancy.

The study group comprised all eligible pregnancies with GBC. The comparison group comprised women who delivered with no history of cancer before or during pregnancy (Fig 1).

We used three linked datasets: Perinatal Data Collection (PDC), the NSW Cancer Registry (NSWCR) and the Admitted Patient Data Collection (APDC). The PDC is a state-wide surveillance system that captures data relating to patterns of pregnancy care, services and outcomes for all births in NSW (whether in public or private hospitals or home births) [12]. The NSWCR is a population-based cancer registry that captures demographic, incidence, cancer stage and death information of all people diagnosed with cancer (excluding non-melanoma

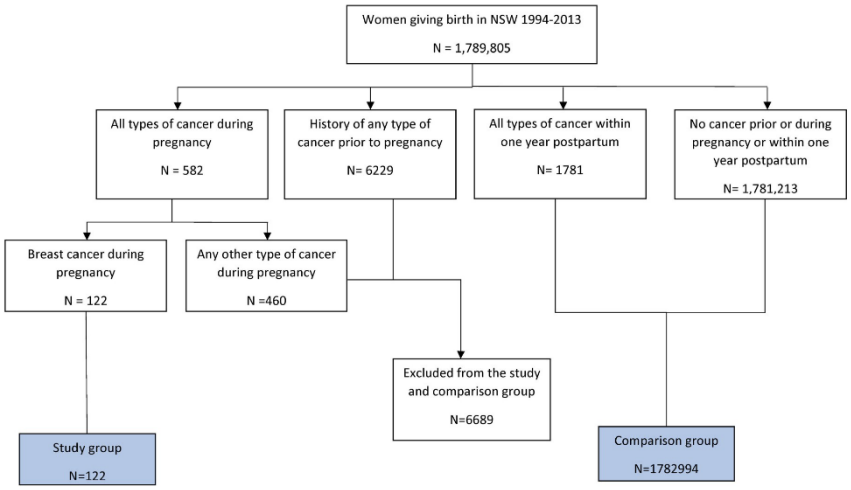

Fig 1. Selecting the study and comparison groups.

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skin cancers) in NSW [12]. The APDC provides information on discharges, transfers or deaths on all patients admitted to all hospitals in NSW (public, private, repatriation and psychiatric hospitals). APDC data were only available from July 2001 [12]. The NSW Centre for Health Record Linkage (CHeReL) performed the data linkage. Details of the data linkage process are available on the CHeReL website [13]. The PDC was used as the primary dataset to identify the study cohort (NSW pregnancies from 1994 to 2013) while the NSWCR was used to identify the group of women with GBC in the study cohort. The APDC was merged based on the babies' Project-specific Person Numbers (PPN) [13] and was used to determine the frequency of hospital admissions and any diagnoses during the neonatal period for babies born to women with GBC.

Data relating to the degree of spread of cancer was obtained from NSWCR and was categorized as follows: stage 0—carcinoma in situ; stage 1—cancer localized to the tissue of origin; stage 2—cancer that has spread to the regional lymph nodes and/or adjacent organs; and stage 3—distant metastasis. We modified these data staging categories so as to reconcile them with the Royal College of Pathologists of Australasia cancer staging classification system. That is, final cancer staging was determined as follows: stage 1 cancer localized to the tissue of origin; stages 2–3 cancer that has spread to the regional lymph nodes and/or adjacent organs (the chest wall and/or the skin); stage 4 involves distant metastasis [12, 14]. Our dataset did not include information on stage 0 cancer, carcinoma in situ (CIS).

We classified women giving birth in NSW into three groups:

i. The study group (GBC group) comprised women with a first-time diagnosis of breast cancer during pregnancy;

ii. The comparison group comprised women without a history of cancer before or during pregnancy;

iii. An excluded group that comprised women with any type of cancer (including breast cancer) diagnosed prior to pregnancy (as prior cancer and its treatment may affect pregnancy outcomes [15, 16]) and women with cancer other than breast cancer diagnosed during pregnancy (as any decisions on their pregnancy management may not have differed from those for women with GBC).

Main outcome measures

Maternal outcomes included pregnancy and birth management and complications (induction of labour, caesarean section (CS)), pregnancy complications (gestational diabetes and gestational hypertension) and maternal mortality. Neonatal outcomes included perinatal death (stillbirth or neonatal death), preterm birth (<37 weeks gestation), low birthweight (<2500 gm), small for gestational age (SGA) (birthweight below the 10th percentile for the age and sex [17]), intraventricular haemorrhage, and respiratory distress syndrome of newborn.

Statistical analysis

The chi-squared test was used to compare the prevalence of SGA between preterm and term babies born to women with GBC. Mann–Whitney U test was used to examine the difference in median gestational age at birth between women with GBC and women with no cancer. Independent samples t-test was used to compare the mean difference in maternal age and baby birthweight between the study and comparison groups.

A Poisson regression model was used to examine the estimated increase in the incidence of GBC each year. The indirect age-standardized rate was used to account for the increasing maternal age during the study period when examining the incidence of GBC. As our data comprised population data, we used all women giving birth during the study period as a standard population for the calculation of the indirect age-standardized rate.

Binary logistic regression models were used to identify independent factors associated with dichotomous outcomes. Analysis of neonatal outcomes was limited to singleton births due to the small number of multiple pregnancies (1.6%), the lack of data on the second baby in twin pregnancies and to avoid the confounding effect of multiple pregnancies [18]. These models incorporated all factors associated with each outcome in univariable analyses ($p<0.20$). Potential confounders including maternal age, parity, plurality, pre-existing chronic conditions such as diabetes and hypertension, previous CS, smoking during pregnancy, hospital sector (public or private) and remoteness of residence were also included. Odds ratio (OR), adjusted odds ratio (AOR), and 95% confidence interval (CI) were calculated and variables with a statistical level of significance (P-value) of <0.05 were considered significant. We consulted with clinicians in the research team, including an obstetrician, a breast surgeon, a neonatologist and an oncologist, to determine which interactions were plausible and limited our investigations to these. All variables in a regression models were assessed for collinearity with a variance inflation factor (VIF) threshold of <3. We tested the interaction term between pre-existing hypertension and smoking during pregnancy, and there was no evidence of interactions (Wald-test $p>0.05$). Data analysis was undertaken using Statistical Package for Social Sciences (SPSS) version 25.0 (IBM Corp, New York, United States).

Ethics approval

NSW Population & Health Services Research Ethics Committee provided the ethical approval for the project (reference HREC/17/CIPHS/11).

Fig 2. Crude, indirect age-standardized incidence rate with upper and lower limits for 95%CI of the indirect age-standardized incidence rate of breast cancer diagnosis during pregnancy in NSW 1994–2013 per 100,000 women giving birth.

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Results

There were 122 women with a first-time diagnosis of breast cancer during pregnancy (GBC group) and 1,782,994 women who gave birth without a history of any type of cancer before or during pregnancy (Fig 1).

Incidence of GBC

The crude incidence rate of GBC in NSW from 1994 to 2013 was 6.8 diagnoses of GBC per 100,000 women giving birth (Fig 2). The incidence of GBC increased from 5.8 per 100,000 women giving birth in 1994 to 7.3 per 100,000 women giving birth in 2013, reaching a peak of 13.6 per 100,000 women giving birth in 2011. This represents an average annual increase of 2.8% (95%CI: -0.3%– 5.9%) per year. However, this increasing trend in incidence was not significant (p = 0.075).

Maternal characteristics

Age. The mean (SD) age of women with GBC was significantly higher than that of women giving birth with no cancer (34.8 ± 4.4 years vs 29.6 ± 5.6 years, p<0.001; mean difference 5.27 years (95%CI 4.48–6.1)). The odds of GBC among women aged ≥35 years was six times the odds for those aged <35 years (AOR 6.09, 95%CI 4.02–9.20) (Table 1). Among women with GBC, there were 16 (13%) aged less than 30 years, 33 (27%) aged between 30 to 34 years, 54 (44%) between 35 to 39 and 19 (16%) aged 40 years or over.

Timing of diagnosis and stage of cancer. Of the 122 women with GBC, 25 (20.5%) were diagnosed in the first trimester, 39 (32.0%) in the second and 58 (47.0%) in the third trimester. Data on cancer stage were available for 113 (92.6%) and missing for 9 (7.4%). Of the 113 women with a known cancer stage, 42 (37.2%) were stage 1, 64 (56.6%) stages 2–3, and 7 (6.2%) stages 4 cancer.

First-time mothers. Women with GBC were less likely to be first-time mothers (nulliparа) than women in the comparison group (32% vs 41.8%). However, when adjusting for age

Table 1. Maternal characteristics and pre-existing conditions.

	Breast Cancer N = 122	No cancer (N = 1,782,994)	OR (95% CI)	AOR (95% CI)
Country of birth				
Other countries	40(32.8)	517504(29)		Reference
Australia	82(67.2)	1260229(70.7)	0.84 (0.58–1.23)	1.17 (0.76–1.79)
Not stated*	0(0)	5261(0.3)		
Maternal age				
<35	49(40.2)	1431525(80.3)		Reference
= >35	73(59.8)	350771(19.7)	6.08 (4.23–8.73)	6.16 (4.09–9.27)
Not stated*	0(0)	698(0)		
Parity				
Nullipara	39(32)	744494(41.8)	Reference	Reference
Para 1+	83(68)	1036047(58.1)	1.53 (1.05–2.24)	1.08 (0.7–1.67)
Not stated*	0(0)	2453(0.1)		
Plurality				
Singleton	120(98.4)	1756474(98.5)	Reference	Reference
Multiple pregnancy	2(1.6)	26520(1.5)	1.1 (0.27–4.47)	0.52 (0.07–3.73)
Previous CS				
No previous CS	86(70.5)	1369535(76.8)	Reference	Reference
CS 1+	18(14.8)	193811(10.9)	1.48 (0.89–2.46)	0.97 (0.57–1.68)
Not stated*	18(14.8)	219648(12.3)		
Smoking during pregnancy				
No	118(96.7)	1502063(84.2)	Reference	Reference
Yes	4(3.3)	275928(15.5)	0.18 (0.07–0.50)	0.29 (0.11–0.79)
stated*	0(0)	5003(0.3)		
Pre-existing hypertension				
No	118(96.7)	1767310(99.1)	Reference	Reference
Yes	4(3.3)	15684(0.9)	3.82 (1.41–10.35)	2.43 (0.77–7.69)
Pre-existing diabetes				
No	122(100)	1772966(99.4)	NA	NA
Yes	0(0)	10028(0.6)	NA	NA
Remoteness				
Major Cities	101(82.8)	1354589(76)	Reference	Reference
Inner Regional	17(13.9)	308563(17.3)	0.74 (0.44–1.24)	0.99 (0.57–1.75)
Outer Regional	3(2.5)	88797(5)	0.45 (0.14–1.43)	0.74 (0.23–2.35)
Remote/very remote	1(0.8)	12583(0.7)	1.07 (0.15–7.64)	2.14 (0.3–15.47)
Not stated*	0(0)	18462(1)		

OR: crude odds ratio, AOR: adjusted odds ratio

*Not included in the analysis

#No previous birth.

https://doi.org/10.1371/journal.pone.0245493.t001

and other maternal characteristics, the association was not significant (AOR 1.09, 95%CI: 0.70–1.68) (Table 1).

Pregnancy complications and obstetric management (mode and timing of birth)

There were no significant differences in the rates of gestational diabetes, gestational hypertension or hospital transfer for women with or without GBC (Table 2).

Table 2. Obstetric management and pregnancy complications by cancer status.

Outcome	Breast cancer	No cancer (reference)	OR(95% CI)	AOR(95% CI)*
Induction of labour				
No	29(23.8)	1087440(61)		
Yes	51(41.8)	438172(24.6)	4.36 (2.77–6.89)	4.40 (2.63–7.38)
Not applicable (Pre-labour CS)**	42(34.4)	256929(14.4)		
Not stated*	0(0)	453(0)		
Induction of labour or pre-labour CS				
No	29(23.8)	1087440(61)		
Yes	93(76.2)	695101(39)	5.02 (3.31–7.61)	4.96 (3.06–8.05)
Preterm	*48(51.6)*	*46855(6.7)*		
Term	*45(48.4)*	*648116(93.2)*		
Not stated	*0(0.0)*	*130(0.0)*		
Not stated	0(0)	453(0)		
Mode of birth				
Vaginal birth***	67(54.9)	1330464(74.6)		
Birth By CS	55(45.1)	451638(25.3)	2.42 (1.69–3.46)	2.46 (1.57–3.86)
Not stated	0(0)	892(0.1)		
Gestational diabetes				
No	117(95.9)	1701488(95.4)		
Yes	5(4.1)	81506(4.6)	0.89 (0.36–2.18)	0.57 (0.21–1.56)
Gestational Hypertension				
No	118(96.7)	1674225(93.9)		
Yes	4(3.3)	108769(6.1)	0.52 (0.19–1.41)	0.55 (0.20–1.51)
Hospital sector				
Public	86(70.5)	1395153(78.2)		
Private	36(29.5)	387799(21.7)	1.51 (1.02–2.22)	1.11 (0.72–1.73)
Not stated**	0(0)	42(0)		
Transferred to another hospital				
No	118(96.7)	1723181(96.6)		
Yes	4(3.3)	59053(3.3)	0.99 (0.37–2.68)	1.40 (0.50–3.92)
Not stated**	0(0)	760(0)		

OR: crude odds ratio, AOR: adjusted odds ratio

*All variables are adjusted for maternal characteristics

**Not included in the analysis

***Including breech and instrumental birth.

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Birth intervention. Among women with GBC, 51 (41.8%) had labour induction; of these, 41 (80.4%) had a vaginal birth and 10 (19.6%) gave birth by CS (Table 2). After adjusting for maternal characteristic, pre-existing conditions and hospital sector (public or private), women with GBC had significantly higher odds of labour induction (AOR 4.40, 95%CI 2.63–7.38) and CS (AOR 2.46, 95% CI 1.57–3.86) than women without cancer (Table 2).

Labour induction and pre-labour CS. Ninety-three (76.2%) women with GBC gave birth either by labour induction or pre-labour CS compared to 695,101 (39%) in the control group. After adjusting for maternal characteristics, pre-existing conditions and hospital sector, the odds of labour induction or pre-labour CS were significantly higher in the GBC group (AOR 4.96, 95% CI 3.06–7.79) (Table 2).

Among women who gave birth by labour induction or pre-labour CS, there was a higher rate of preterm birth in women with GBC (n = 48, 51.6%) compared to women with no cancer (n = 46,855, 6.7%) p<0.001.

Timing of diagnosis, stage of cancer and birth by labour induction or pre-labour CS. Among the 93 women with GBC who gave birth by labour induction or pre-labour CS, 10 (10.8%) were diagnosed in the first trimester, 32 (34.4%) in the second trimester, and 51 (54.8%) in the third trimester. Of those women diagnosed in the third trimester, 39 (76.5%) were diagnosed before 37 weeks gestation. Seven (70%) of the women diagnosed in the first trimester gave birth prematurely compared to 19 (59%) of the women diagnosed in the second trimester and 22 (56%) of the women diagnosed in the third trimester before 37 weeks gestation. However, the rate of preterm birth among women diagnosed in the second and third trimester (<37 weeks) was not significantly different from that in women diagnosed in the first trimester (OR 0.63, 95%CI: 0.14–2.88 and OR 0.55, 95%CI: 0.12–2.47 respectively) (S1 Table).

Among the 93 women with GBC who gave birth by labour induction or pre-labour CS, there were 27 (29.0%) with cancer stage 1, 54 (58.1%) with stages 2–3, and 6 (6.5%) with stages 4. Cancer stage was not known for 6 (6.5%). Fourteen (52%) of the women with stage 1 delivered prematurely compared to 31 (57%) of the women with stages 2–3 and 1 (17%) of the women with stages 4. The rate of preterm delivery among women with cancer stages 2–3 or stages 4 was not significantly different from that in women with cancer stage 1 (OR 1.25, 95% CI: 0.49–3.17 and OR 0.19 95%CI: 0.02–1.81 respectively) (S1 Table).

Neonatal outcomes

The 122 pregnancies resulted in the birth of 120 singletons and two sets of twins. Table 3 describes the neonatal outcomes for 120 singleton babies born to women with GBC and 902,653 singleton babies born to women with no cancer. There were no stillbirths or neonatal deaths among babies born to women with GBC. Babies born to women with GBC were more likely to, require a high level of resuscitation including intermittent positive pressure respiration and external cardiac massage (11% vs 5%, AOR 2.01, 95%CI: 1.12–3.62). They are also more likely to be admitted to special care nursery (SCN) or neonatal intensive care unit (NICU) (42% vs 15% AOR, 3.74, 95%CI: 2.58–5.43) than babies born to women with no cancer. However, after adjusting for preterm birth, there is no significant difference in the odds of the need for a high level of resuscitation or admission to NICU/SCN between babies born to women with GBC versus those who were born to women with no cancer (AOR, 0.98 (95%CI: 0.54–1.81) and AOR,1.28 (95%CI: 0.81–2.02) respectively). Four neonates had major neonatal morbidities; one baby had congenital cardiomyopathy and three (34, 34 and 33 weeks' gestation) had respiratory distress syndrome of newborn, two of whom required prolonged ventilatory support.

The median gestational age at birth for babies born to women with GBC was lower than that for babies born to women with no cancer (37 weeks (IQR 35–38) vs 39 weeks (IQR 38–40), p < 0.001). The odds of preterm birth were higher in babies born to women with GBC (AOR 12.93, 95% CI 8.97–18.64).

The mean birthweight for live-born singletons to women with GBC was significantly lower than that for those born to women with no cancer (2,905 ± 634 g vs 3,409 ± 546 g, p<0.001). The birthweight distribution for preterm babies in both groups is shown in S2 Table.

Preterm birth in babies born to women with GBC. There were 53 (44.2%) preterm births among the 120 singletons born to women with GBC. Of these, 22 (42%) were born by induction of labour and 26 (49%) were born by pre-labour CS. Thirty-five (66%) of the preterm births were late preterm born between 34 and 36 weeks gestation, 17 (32.1%) were

Table 3. Neonatal outcomes for singleton babies by maternal cancer status.

Outcome	Breast cancer	No cancer (reference)	OR(95% CI)	AOR(95% CI)*
Sex of baby				
Male	59(49.2)	903557(51.4)		
Female	61(50.8)	851876(48.5)	1.10 (0.77–1.57)	1.10 (0.77–1.57)
Indeterminate**	0(0)	222(0)		
Not stated**	0(0)	819(0)		
Preterm birth				
No	67(55.8)	1654251(94.2)		
Yes	53(44.2)	101834(5.8)	12.85 (8.96–18.43)	13.17 (9.14–18.96)
Not stated	0(0)	389(0)		
Small for gestation***				
No	108(90)	1568077(89.8)		
Yes	12(10)	178297(10.2)	0.98 (0.54–1.78)	1.18 (0.65–2.16)
Birthweight< 2500 g**				
No	88(73.3)	1668218(95.5)		
Yes	32(26.7)	77482(4.4)	7.85 (5.24–11.77)	9.1 (6.02–13.77)
Not stated**	0(0)	674(0)		
5 min Apgar***				
>7	115(95.8)	1686705(96.6)		
7 or less	5(5.8)	54000(4.1)	1.36 (0.56–3.33)	1.32 (0.54–3.24)
Not stated	0(0)	5669(6.2)		
High resuscitation*#				
No	86(71.7)	1305741(74.8)		
Yes	13(10.8)	91537(5.2)	2.16 (1.20–3.87)	2.01 (1.12–3.62)
Not stated**	21(17.5)	349096(20)		
Admitted to SCN/NICU for 4 hours or more***				
No	70(58.3)	1480563(84.8)		
Yes	50(41.7)	264646(15.2)	4.00 (2.78–5.75)	3.74 (2.58–5.43)
Not stated**	0(0)	1165(0.1)		
Discharge status				
Discharged	113(94.2)	1664307(94.8)	NA	NA
Stillborn	0(0)	10100(0.6)		
Neonatal death	0(0)	3965(0.2)		
Transferred	7(5.8)	77088(4.4)		
Not stated	0(0)	1014(0.1)		

OR: crude odds ratio, AOR: adjusted odds ratio

*All variables are adjusted for maternal characteristics (5 min Apgar, High resuscitation and Admitted to SCN/NICU are also adjusted to the method of birth)

**Not included in the analysis

***live birth only

intermittent positive pressure respiration and external cardiac massage

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moderately preterm (32–33 weeks gestation), and 1 (1.9%) was early preterm (<32 weeks gestation) (S2 Table).

The mean birthweight of preterm babies born to women with GBC (2,469 ± 453 g) was significantly lower than term babies (3,250 ± 539 g) ($p<0.001$). Among the preterm babies of women with GBC, there were 29 (54.7%) babies with birthweight <2500 grams compared to 3 (4.5%) among term babies ($p<0.001$). However, among babies of women with GBC, the prevalence of SGA was lower for preterm compared with term babies (1.9% vs 18.8%, $p = 0.004$).

has increased needs is likely to present unique challenges to mothers coping with cancer symptoms in parallel with treatment side effects. These factors, together with the potential longer-term impacts of low birthweight and neonatal complications associated with premature birth, suggest that decisions regarding pre-term induction of labour or pre-labour CS in women with GBC needs to be carefully considered. A delicate balance is required to be drawn between any potential benefits to the mother of commencing early cancer treatment and the potential adverse effects of preterm birth both to the mother and her child.

Current literature suggests that having gestational cancer or cancer treatment during pregnancy may be associated with a higher risk of SGA [6, 10]. However, our results do not support this, possibly due to the small sample size of women with GBC which may have impacted the power of the study to detect any such difference.

Although our data show a low prevalence of major neonatal morbidities in our preterm babies, we did not have data to examine the long-term developmental effect of these infants. Amant and colleagues (2015) previously found that preterm babies born to women with a diagnosis of cancer during pregnancy are more likely to have long term developmental problems whether or not they were exposed to chemotherapy while in utero [7]. Given this, it is important to promote a term birth where clinically possible in order to avoid the potential negative effects of preterm birth on both the mother and her baby.

Strengths and limitations

An important strength of our study was the population-based design that included all births in NSW over a 20-year period from which we identified all women with invasive breast cancer during pregnancy. Limitations include the lack of information on Indigenous status, and breast cancer treatment. The latter has limited our ability to examine the maternal and perinatal outcomes by exposure to treatment. The third limitation was resultant from the fact that, early pregnancy loss before 20 weeks' gestation is out of the scope of the perinatal data collection.

Conclusions

The odds of GBC were six times higher among women aged ≥35 years compared to those <35 years of age. There was a high rate of preterm birth among women with GBC, which could not be explained by the timing of breast cancer diagnosis or stage of cancer at diagnosis. Spontaneous onset of labour of preterm birth was uncommon with most births following induction of labour or pre-labour CS. This had a minimal impact in the short-term as major neonatal morbidity was uncommon.

Supporting information

S1 Table. Timing of diagnosis and stage of cancer by gestational age at birth for the 93 women who gave birth by induction of labour or pre-labour CS.
(DOCX)

S2 Table. Characteristics of singleton preterm babies by cancer status.
(DOCX)

S3 Table. Regression model of Table 1.
(DOCX)

S4 Table. Regression models of Table 2.
(DOCX)

Hospital admissions during the neonatal period. Of the 120 singletons born to women with GBC, hospitalization data were available for 102 (85%). Of these, 53 (52%) had at least one hospital admission within 28 days of birth (44 had one admission, 6 had two admissions, and 3 had three admissions).

Discussion

We found an overall incidence of GBC in NSW between 1994 and 2013 of 6.8 per 100,000 women giving birth and that women with GBC had higher rates of planned preterm birth either by induction of labour or a pre-labour CS compared to women with no cancer. Surprisingly, the rate of planned preterm birth for women with GBC was not impacted by the timing of diagnosis or stage of cancer. Babies born to women with GBC were more likely to be preterm, require a high level of resuscitation and be admitted to SCN or NICU. In contrast, the proportion of SGA for preterm babies was very low at 1.9%, suggesting planned preterm birth for maternal management. There were no stillbirths or neonatal deaths among these babies, and the prevalence of major neonatal morbidities was relatively low.

Our results revealed a 20-year trend of increasing GBC incidence but that this trend was not statistically significant.

The odds of GBC were six times higher among women aged ≥35 years compared to those <35 years of age. Furthermore, women with GBC were significantly older than women with no cancer—women aged ≥35 years, comprised 59.8% of the GBC group compared to only 19.7% of the no cancer group.

In agreement with previous studies [3, 19, 20], our results show that women with GBC have higher rates of labour induction and/or delivery by CS than women with no cancer. It has been argued that the higher rates of labour induction and pre-labour CS in GBC are due to management decisions relating to the stage of cancer at diagnosis [21]. However, our results showed no differences in the odds of preterm labour induction or pre-labour CS among women diagnosed at different trimesters or with different stages of cancer at diagnosis. Nonetheless, these results should be interpreted with caution owing to the relatively low incidence rate of GBC and the small number of cases of GBC in this study. Additionally, as we were not able to obtain data relating to cancer treatment, we could not determine whether management decisions relating to treatment were associated with increased rates of labour induction and pre-labour CS.

There was a high rate of preterm birth among women with GBC. The majority of these births were planned and considered iatrogenic from a neonatal perspective. This is consistent with the high rate of preterm labour among women with GBC previously reported by Loibl and colleagues in 2012 where they argued that decisions to initiate early iatrogenic birth are often taken in the absence of a clear clinical indication [10]. In our study, we were unable to show any association between the high rate of iatrogenic preterm birth and any specific cancer stage or timing of diagnosis. This finding supports the views of Loibl and colleagues. However, owing to the small number of cases in our study, this finding should be treated with caution.

Preterm babies, whether born to women with GBC or to women with no cancer, have higher rates of adverse neonatal outcomes than babies born at ≥ 37 weeks [22]. Thus, in our cohort preterm babies of women with GBC had lower birthweights and increased rates of resuscitation and admission to SCN/NICU than term babies. Preparing, and then caring, for a preterm baby is demanding and inevitably places any mother at increased risk of anxiety and stress [23]. Women with GBC already experience high levels of fatigue and sleep disturbance underpinned by both the side effects of chemotherapy (whether given during pregnancy or after birth) and psychological and biological factors [24–26]. Caring for a preterm baby who

S5 Table. Regression models of Table 3.
(DOCX)

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BRIEF COMMUNICATION

Epidemiology

In utero exposure to breast cancer treatment: a population-based perinatal outcome study

Nadom Safi[1], Antoinette Anazodo[2,3], Jan E. Dickinson[4], Kei Lui[5,6], Alex Y. Wang[1], Zhuoyang Li[1] and Elizabeth A. Sullivan[1,7]

Chemotherapy during a viable pregnancy may be associated with adverse perinatal outcomes. We conducted a prospective cohort study to examine the perinatal outcomes of babies born following in utero exposure to chemotherapy in Australia and New Zealand. Over 18 months we identified 24 births, of >400 g and/or >20-weeks' gestation, to women diagnosed with breast cancer in the first or second trimesters. Eighteen babies were exposed in utero to chemotherapy. Chemotherapy commenced at a median of 20 weeks gestation, for a mean duration of 10 weeks. Twelve exposed infants were born preterm with 11 by induced labour or pre-labour caesarean section. There were no perinatal deaths or congenital malformations. Our findings show that breast cancer diagnosed during mid-pregnancy is often treated with chemotherapy. Other than induced preterm births, there were no serious adverse perinatal outcomes.

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BACKGROUND

The management of cancer diagnosed during pregnancy poses unique challenges in optimising maternal and infant outcomes. One of these challenges is choosing the optimal treatment regimen to balance the benefit to the women and the potential risks of adverse outcomes for the foetus.[1] Timing of treatment initiation is also challenging, especially if cancer diagnosis is early in the first trimester as foetal exposure to chemotherapy during the period of organogenesis has been associated with an increased risk of congenital malformations.[2,3]

This study describes the perinatal outcomes of babies of women diagnosed with breast cancer during the first or second trimesters of pregnancy by whether exposed to in utero systemic chemotherapy or not.

METHODS

A population-based prospective cohort study design was conducted in Australia and New Zealand using the Australasian Maternity Outcomes Surveillance System (AMOSS).[4] We identified babies born to women with a confirmed diagnosis of breast cancer during pregnancy through monthly surveillance between January 2013 and June 2014. Eligible births included live or stillborn babies of at least 400 g or 20 weeks gestation whether exposed to chemotherapy or not. Data were collected on maternal and cancer care, and perinatal outcomes.

Perinatal outcomes included: stillbirth, neonatal death, major congenital malformations, preterm birth (<37 completed weeks of gestation), low birthweight (<2,500 grams) and small for gestational age (birthweight <10th percentile for gestational age).[5]

Chi-square, Fisher's exact test, Fisher-Freeman-Halton test, and independent sample *t*-test were used to investigate the difference in outcomes of babies stratified by in utero exposure to chemotherapy.

RESULTS

Of the 24 babies born to women diagnosed with breast cancer during the first and second trimesters of pregnancy, 18 (75%) were exposed to chemotherapy, and six were not (detailed in Supplementary Table 1). Demographic and treatment characteristics of the 24 women are shown in Supplementary Tables 1 and 2.

The types of systemic chemotherapeutic agents used during the pregnancies are listed in Supplementary Table 3. The median gestational age at first in utero exposure was 20 weeks (range 13–31). Fourteen (77.8%) of the 18 babies had their first exposure in the second trimester and four (22.2%) in the third trimester. All 18 babies were exposed to a minimum of two therapeutic agents with a mean duration of exposure of 10.4 ± 5.8 weeks. All babies were exposed to alkylating agents; either nitrogen mustard (Cyclophosphamide) or platinum compounds (Carboplatin), 16 (88.9%) were exposed to anthracyclines (Doxorubicin or Epirubicin), 10 (55.6%) to taxanes (Paclitaxel or Docetaxel) and 1 (5.6%) to Fluorouracil.

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Table 1. Perinatal outcomes amongst the 24 babies

	Exposed (*n* = 18)	Non-exposed (*n* = 6)	*P* value
Live births	18 (100)	6 (100)	NA
Neonatal deaths[a]	0 (0)	0 (0)	NA
Preterm (<37 weeks)			
Yes	12 (66.7)	0 (0)	0.014
<32 weeks	*1 (5.6)*	*0 (0)*	
33– < 37 weeks	*11 (61.1)*	*0 (0)*	
No	6 (33.3)	6 (100)	
Small for gestational age	2 (11.1)	0 (0)	1.000
Low birthweight (<2500 g)	9 (50)	0 (0)	0.052
Resuscitation			
Yes	6 (33.3)	0 (0)	0.277
Neopuff or CPAP mask only	*3 (16.7)*	*0 (0)*	
Oxygen	*1 (5.6)*	*0 (0)*	
Neopuff or CPAP mask + Suction + Oxygen	*2 (11.1)*	*0 (0)*	
No	12 (66.7)	6 (100)	
Respiratory support			
Yes[b]	1 (5.6)	0 (0)	1.000
No	16 (88.9)	6 (100)	
Not known	1 (5.6)	0 (0)	
Apgar score (5 min)			
8	5 (27.8)	0 (0)	0.348
9	10 (55.6)	5 (83.3)	
10	3 (16.7)	1 (16.7)	
Admission to NICU/SCN	9 (50)	1 (16.7)	0.341
Breastfeeding initiated			
Yes	6 (33.3)	5 (83.3)	0.061
No	12 (66.7)	1 (16.7)	

[a]During hospital stay only
[b]CPAP mask only
Neopuff Infant T-Piece Resuscitator
CPAP Continuous Positive Airways Pressure

The mean gestational age at birth for the 18 chemotherapy exposed babies was 35.7 ± 2 weeks, significantly lower than that for the six non-exposed babies (mean 38.8 ± 1.5 weeks) ($P = 0.002$) (Table 1). There were no stillbirths, diagnosed congenital malformations or neonatal deaths in any of the 24 babies. The need for resuscitation was seen in the two babies exposed to Tamoxifen combined systemic therapy (Cyclophosphamide, Doxorubicin and Docetaxel and Tamoxifen; and Paclitaxel, Carboplatin and Tamoxifen). The former was female born following induction at 36 weeks, birthweight 2480 g Apgar score at 5 min of 8 and resuscitated with a continuous positive airway pressure (CPAP) mask, however, discharged home without the need for admission to neonatal intensive care (NICU) or Special Care Nursery (SCN). The latter was a boy delivered at 34 weeks by CS (birthweight 2240 g, Apgar score at 5 min of 8) and required resuscitation with a continuous positive airway pressure (CPAP) mask and admission to the SCN.

A third baby exposed to Trastuzumab, Docetaxel and Cyclophosphamide was born vaginally following induction at 36 weeks (birthweight 2380 g; Apgar score of 10) and was admitted to SCN with mild respiratory distress before being discharged home on day 4.

Ten of the babies were exposed to Taxanes in addition to other chemotherapeutic agents. However, their perinatal outcomes did not significantly differ from those who had exposed to non-Taxane chemotherapy (Supplementary Table 4).

DISCUSSION

In this analysis, we examined the effect of in utero exposure to chemotherapy on perinatal outcomes. As expected, the gestation at diagnosis influenced the decision on the timing of chemotherapy and the non-use of radiotherapy during pregnancy. All cases in our study whether exposed to chemotherapy or not were diagnosed in the first or second trimesters. The other factors influencing management decisions are the grading and staging of breast cancer. Of note, none of the non-exposed babies' mothers had distant metastasis and none had a preterm birth.

It is recognised that management decisions are often a delicate balance in considering the treatment impacts on both the maternal and foetal health during the pregnancy. In this study, apart from preterm birth, there were no serious adverse perinatal outcomes in the 18 babies exposed to chemotherapy nor in the six non-exposed babies. There was no perinatal death or congenital malformations.

The majority of exposed babies were exposed to cyclophosphamide and doxorubicin, with one baby exposed to trastuzumab and two others to tamoxifen. This is consistent with the other studies in which the babies were mainly exposed to a combination of cyclophosphamide and doxorubicin.[6–9]

Tamoxifen is contraindicated during pregnancy.[10] The two babies who were exposed to tamoxifen in our study were born without congenital malformations. However, due to the small number of babies exposed to tamoxifen in our study, we were unable to recommend the use of tamoxifen during pregnancy.

Trastuzumab is contraindicated during pregnancy, as it has been associated with oligohydramnios and renal impairment in the foetus.[11] We were unable to confirm this association as in our study only one baby was exposed to trastuzumab in the third trimester.

In agreement with other studies,[2] our results show a significantly higher rate of preterm births among babies exposed to systemic therapy during pregnancy compared to the non-exposed babies (12 out of 18 vs 0 out of 6).

Morbidities in neonates (low birthweight and admission to NICU/SCN) in our study were directly linked to preterm birth. Similar to the previous studies,[2,9] the leading cause of preterm birth amongst the exposed group in our study is iatrogenic to facilitate maternal systemic chemotherapy postpartum (supplementary fig. 1).

There is a growing evidence on the safety of exposure to anthracyclines containing regimens after the first trimester; however, it is limited for the other chemotherapeutic agents and the non-chemotherapy systemic treatment. There is a need for standardised information on the maternal-foetal exposure and outcomes of chemotherapy and other systemic anticancer agents use in pregnancy that is collated internationally into a database for use in informing clinical practice and research worldwide.

A major strength of this cohort study is its population-design of all cases in Australia and New Zealand during the study period. Limitations include the rarity of the condition, the low uptake of chemotherapy during pregnancy and the follow-up period being restricted to the perinatal period.

CONCLUSION

Our study provides assurance that there were no congenital abnormalities or perinatal deaths among the 18 babies exposed to at least two different chemotherapy agents during pregnancy. The directionality of our findings is consistent with the two largest studies in the international literature, particularly regarding preterm birth.[6,7] Larger observational studies are needed to provide better information on in utero exposure and outcomes following chemotherapy to inform gestational breast cancer management.

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AUTHOR CONTRIBUTIONS

All authors were involved in the conception and design of the study and data interpretation. N.S. drafted the paper and performed data analysis. A.W., Z.L. were involved in the data analysis and N.S., A.W., Z.L. and E.A.S. in data interpretation. All authors critically revised the paper and approved it for submission.

ADDITIONAL INFORMATION

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