

REVIEW

Breast Cancer in Australian Indigenous Women: Incidence, Mortality, and Risk Factors

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Abstract

The Indigenous people of Australia face significant health gaps compared with the general population, with lower life expectancies, higher rates of death, and chronic illness occurring more often than in non-indigenous Australians. Cancer is the second largest contributor to the burden of disease with breast cancer being the most common invasive cancer diagnosed for females. Despite a lower breast cancer incidence compared with non-indigenous women, fatalities occur at an elevated rate and breast cancers have an earlier age of onset. For indigenous women there are also more advanced and distant tumours at diagnosis, fewer hospitalisations for breast cancer, and lower participation in breast screening. Concomitantly there are demographic, socio-economic and lifestyle factors associated with breast cancer risks that are heavily represented within Indigenous communities. The aim of this two-part narrative review is to examine the available evidence on breast cancer and its risk factors in Australian Indigenous women. Part One presents a summary of the latest incidence, survival and mortality data. Part Two presents the risk factors most strongly associated with breast cancer including age, place of residence, family risk, genetics, reproductive history, tobacco use, alcohol intake, physical activity, participation in screening and breast density. With increasing emphasis on personalized health care, a clear understanding of breast cancer incidence, survival, mortality, and causal agents within the Indigenous population is required if breast cancer prevention and management is to be optimized for Indigenous Australians.

Keywords: Breast cancer- breast neoplasm- Australia- Aboriginal- Indigenous- incidence- mortality- risk factors

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Introduction

Breast cancer is the second most common carcinoma in Australian females with one in eight women developing the disease (Australian Institute of Health and Welfare, 2012a). One-quarter of hospitalizations that occur for Australian women is attributed to breast cancer and it is the second leading cause of cancer-related deaths (Australian Institute of Health and Welfare and National Breast and Ovarian Cancer Centre, 2009). While the number of new cases has almost tripled in the last three decades (there were 5,310 new cases in 1982 and 15,166 in 2012) (Australian Institute of Health and Welfare, 2016), mortality is decreasing and survival is improving. Gains in outcomes which are increasingly evident in most developed countries (Coleman et al., 2011b) are attributed to early detection associated with screening and improvements in the management and treatment of the disease (Australian Institute of Health and Welfare, 2012c). While the recent overall picture of breast cancer survival in Australia is improving, this is not the case for all Australians. Aboriginal and Torres Strait Islander (respectfully referred to hereafter as Indigenous) women

experience significantly poorer breast cancer outcomes than other Australian women (Australian Institute of Health and Welfare and Cancer Australia, 2013).

Indigenous Australians represent around 3% of the total Australian population and are a culturally and linguistically diverse population residing across all Australian states and territories and in urban, regional and remote localities. The greatest absolute numbers of Indigenous Australians reside in NSW and Queensland (208,476 and 188,954 respectively) while the Northern Territory has the largest proportion with around 30% (68,850) identifying as Indigenous (Australian Bureau of Statistics, 2014).

Indigenous Australians experience poorer overall health compared with other Australians. Life expectancy at birth for Indigenous males is estimated to be 67 years and for females it is 73 years, representing gaps of 11.5 and 9.7 years, respectively, compared with other Australians (Australian Bureau of Statistics, 2011). Indigenous people also have a younger age distribution and there is a smaller population of Indigenous people (up to 10% fewer) who are over 50 years old compared with other Australians (Australian Bureau of Statistics, 2011).

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The fertility rate for Indigenous Australians is higher than non-indigenous Australians (Australian Bureau of Statistics, 2011; Australian Bureau of Statistics, 2014). Indigenous mothers have an average of two or more children while non-indigenous mothers have less than two. Cardiovascular disease is the most fatal illness in Indigenous Australians accounting for 25.5% of deaths (Australian Institute of Health and Welfare., 2016). Cancer is ranked second accounting for 19.8% of fatalities making it an important health issue for Australia (Garvey et al., 2011; Australian Institute of Health and Welfare., 2016).

Breast cancer is the most commonly diagnosed carcinoma in Indigenous women. It accounts for 25% of all Indigenous female cancers and one in eleven will develop the disease (Chong and Roder, 2010; Australian Institute of Health and Welfare, 2012a). Whilst Indigenous women are 20% less likely to be diagnosed with breast cancer compared with non-indigenous women (83 and 103 per 100,000 respectively), the mortality rate for this disease is higher (48 compared with 44 per 100,000 women aged 50-69 years, respectively) (Cancer Australia, 2012; Australian Institute of Health and Welfare, 2015a). This scenario is attributed to a combination of factors including socioeconomic disadvantage, lower participation in cancer screening, younger age at diagnosis, geographic remoteness, co-morbidities, and advanced stage of cancer at the time of diagnosis (Cunningham et al., 2008; Chong and Roder, 2010; Australian Institute of Health and Welfare and Cancer Australia, 2013; Australian Institute of Health and Welfare, 2015b; Gibberd et al., 2015).

The aim of this narrative review is to examine the available evidence on breast cancer and its risk factors in Australian Indigenous women. Factors strongly associated with the development of breast cancer such as genetics, hormones and elements of lifestyle have been broadly studied within non-indigenous populations but are yet to be examined to the same degree as Australian Indigenous women. The strategy for this review was to search PubMed, the University of Sydney library catalogue, and grey literature available on the internet for reviews, meta-analyses. In Part One the latest incidence, survival, and mortality data will be summarised. In Part Two the risk factors most strongly associated with breast cancer will be presented including age, place of residence, family risk, genetics, reproductive history, tobacco use, alcohol intake, physical activity, participation in screening and breast density.

Part One: Breast cancer incidence, mortality, and survival Incidence

Until recently, breast cancer incidence data on Indigenous women were not accurate and experienced inconsistent jurisdiction-specific data collection procedures (Roder et al., 2012b; Australian Institute of Health and Welfare and Cancer Australia, 2013; Moore et al., 2015). The first time that Indigenous breast cancer risk and fatality rates were published in Australia was in 1996 in a document produced by the National Health and Medical Research Council (NHMRC) National Breast Cancer Centre (NBCC) (Carrick, 1996). State and territory based cancer registries and census reports

from 1977 to 1995 were used to calculate the absolute numbers of new cases in Indigenous women. Data were collected from the Northern Territory, South Australia, and Western Australia where 33.1% of the Australian Indigenous population were living (Australian Bureau of Statistics, 1997). The report noted that limitations existed in the data. All Indigenous cases could not be accurately captured because ethnicity was self-reported and collecting this information was neither mandatory nor consistent. Therefore underestimation of incidence in the Indigenous population and overestimation in the non-indigenous population most likely occurred (Condon et al., 2003). Notwithstanding, the NHMRC NBCC report (Carrick, 1996) concluded that the overall incidence for Indigenous women was lower than non-indigenous women based on data from a small representative sample. Condon (2004) (Condon, 2004) reported that the rate ratio of Indigenous to non-indigenous breast cancers in the Northern Territory was 0.3 and in South Australia it was 0.5. The comparatively younger age profile, higher fertility, and multiparity rates of Indigenous women were reported to be associated with lower incidence. However the lack of available information with which to compare risk profiles between populations meant that further conclusions on causal agents could not be reached. The NHMRC NBCC report (Carrick, 1996) recommended that improved collection and linkage of data pertaining to breast cancer and Indigenous Australians was needed nationwide.

Documents published in 2012 (Australian Institute of Health and Welfare, 2012b) and 2013 (Australian Institute of Health and Welfare and Cancer Australia, 2013) reported that Indigenous breast cancer incidence from four states and territories between 2004 and 2008 were of sufficient quality to facilitate the analysis of incidence by Indigenous status. Data was collected from NSW, Queensland, Western Australia and the Northern Territory where 84% of the Indigenous population were residing (Australian Bureau of Statistics, 2014). Data from these jurisdictions continue to be used in current reporting as a surrogate for national data since details remain elusive in some states and territories. Despite improvements in overall data collection (Australian Institute of Health and Welfare, 2010), 12% of the data had no recorded Indigenous or non-indigenous status. This level of data error is tolerable as reporting of ethnicity is voluntary and optional (Australian Institute of Health and Welfare, 2013). Previous findings were confirmed in that the overall incidence of breast cancer was slightly lower in Indigenous compared with non-indigenous women with a rate ratio of 0.8 (Australian Institute of Health and Welfare and Cancer Australia, 2013) (Table 1). While the exact reasons for the disparity in incidence rates between Indigenous and non-indigenous Australians are not entirely clear, differences in the reproductive patterns (such as age at first menarche and age at first childbirth), childbearing practices (such as parity and breastfeeding), younger age structure, and participation in breast screening are considered contributive (Moore et al., 2015). The underscreening of Indigenous women in comparison to their non-indigenous counterparts (35.5% vs. 54.5%

Table 1. Incidence Rates of Breast Cancer in Australian Indigenous Women

Report	Jurisdictions	Reporting period	Indigenous		Non-indigenous		Rate Ratio (e)
			Number(a)	AS Rate(b)	Number(a)	AS Rate(b)	
AIHW 2009 (Australian Institute of Health and Welfare, 2009)	NSW, VIC, NT, QLD, WA (c)	2000-2004	392	84.7	58,742	115	0.7
AIHW 2011 (Australian institute of Health and Welfare, 2011)	QLD, WA, SA, NT (d)	2003-2007	122	171.4	10,417	259.3	0.6
AIHW 2012 (Australian Institute of Health and Welfare, 2012c)	NSW, QLD, WA, NT (c)	2004-2008	438	82.1	35,850	103.6	0.8
AIHW 2014 (Australian Institute of Health and Welfare, 2014b)	NSW, QLD, WA, NT (d)	2005-2009	255	202.9	19,002	270.6	0.7
AIHW 2016 (Australian Institute of Health and Welfare, 2015a)	NSW, QLD, WA, NT (d)	2006-2010	286	213.8	20,173	278.3	0.7

(a), Number of new cases; (b), Direct age standardised (AS) rates were used and are expressed per 100,000 women of the population; (c), Figures for all ages; (d), Figures for women 50-69 years old; (e), Rate ratios were calculated by dividing the Indigenous AS rate by the non-indigenous AS rate

participation rate respectively) (Australian Institute of Health and Welfare, 2015a) could also help explain the lower incidence and is supported by the higher mortality rates and more advanced cancer stage at diagnosis.

Similar trends have been reported for some indigenous populations internationally. A lower breast cancer rate was also observed within the Native American and Sami women in Norway (Coleman et al., 2011a) and indigenous women in Ecuador, Brazil, and Chile (Moore et al., 2014). However discrepancies with this pattern have been seen elsewhere. Indigenous women of Alberta, Canada demonstrate an incidence similar to that of non-indigenous women (Coleman et al., 2011a). Indigenous women of Alaska and New Zealand have elevated breast cancer rates compared with their non-indigenous counterparts (Moore et al., 2015).

Mortality and survival

Despite lower incidence, breast cancer-related deaths occur at a higher rate for Indigenous women compared with other Australian women thus reflecting lower survival rates. This was not always the case. Records from the Northern Territory and Western Australia between 1988 and 1993 suggest that mortality rates were similar between the two groups of women (Kricke, 1996). However in the last 20 years, reports from five states and territories where the majority of the Indigenous populations reside indicate that while overall mortality for the disease is decreasing in Australia, the rate for Indigenous women increased and surpassed that of non-indigenous women (Table 2). This finding was particularly pronounced in the 50 to 69 year age group (48 per 100,000 for Indigenous and 44 per 100,000 for non-indigenous women) but was consistent across all ages (24 per 100,000 and 22 per

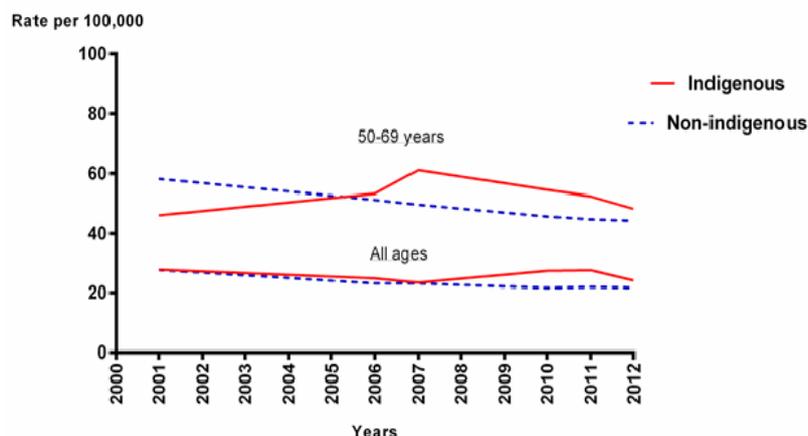


Figure 1. Chart of the Mortality Rate of Indigenous Women with Breast Cancer of All Ages and Indigenous Women 50-69 Years Old between 2001 and 2012.

a, Rates are expressed per 100,000 women of the population; b, 2001-2006 rates of all ages and 50-69 years were for Qld WA, NT and SA; c, 2007-2012 rates of all ages and 50-69 years were for NSW, Qld WA, NT and SA. Sources: 2001-2006 data AIHW 2009 (Australian Institute of Health and Welfare, 2009); 2003-2007 data, AIHW 2011(Australian institute of Health and Welfare, 2011); 2006-2010 data, AIHW 2012(Australian Institute of Health and Welfare, 2012b); 2007-2010 data, AIHW 2014 (Australian Institute of Health and Welfare, 2014b); and 2008-2012 data, AIHW 2015 (Australian Institute of Health and Welfare, 2015a).

Table 2. Mortality Rates of Indigenous Women with Breast Cancer for 50-69 Year Olds and All Ages

Report	Jurisdictions	Reporting period	Age groups	Indigenous		Non-indigenous		Rate Ratio (d)
				Number(a)	AS Rate(b)	Number (a)	AS Rate (b)	
AIHW 2009 (Australian Institute of Health and Welfare, 2009)	QLD, WA,NT,SA	1997-2001	50-69	- (c)	45.8	-(c)	58.2	0.8
			All	-(c)	27.8	-(c)	27.7	1
AIHW 2009 (Australian Institute of Health and Welfare, 2009)	QLD, WA,NT,SA	2002-2006	50-69	-(c)	53.2	-(c)	51.1	1
			All	-(c)	24.8	-(c)	23.1	1
AIHW 2011 (Australian institute of Health and Welfare, 2011)	NSW, NT, QLD, WA, SA	2003-2007	50-69	64	61.2	3,743	49.9	1.2
			All	113	23.4	9,176	23.1	1
AIHW 2012 (Australian Institute of Health and Welfare, 2012c)	NSW, NT, QLD, WA, SA	2006-2010	50-69	69	54.5	3,784	45.5	1.1
			All	137	27.4	9,407	21.6	1.2
AIHW 2014 (Australian Institute of Health and Welfare, 2014b)	NSW, NT, QLD, WA, SA	2007-2010	50-69	69	52.3	3,827	44.4	1.1
			All	140	27.6	9,586	21.9	1.2
AIHW 2015 (Australian Institute of Health and Welfare, 2015a)	NSW, NT, QLD, WA, SA	2008-2012	50-69	75	48.1	3,847	43.9	1
			All	149	24.1	9,582	21.7	1.1

(a), Number of new cases; (b), Direct age standardised (AS) rates were used and are expressed per 100,000 women of the population; (c), Figures were not reported for this period; (d), Rate ratios were calculated by dividing the Indigenous AS rate by the non-indigenous AS rate.

100,000 respectively) (Figure1). Whilst the changes in the reporting of Indigenous status in medical records most likely contributed to the sudden increase in the breast cancer mortality count, the comparatively poorer outcomes experienced by Indigenous women with breast cancer could be explained by a combination of other factors described below.

At the time of diagnosis, Indigenous women are likely to be younger (Cancer Australia, 2012). Younger women diagnosed with breast cancer face a lower survival rate with more aggressive tumours that may be less responsive to treatment (Rosenberg and Partridge, 2015). One study (Roder et al., 2012a) of women screened between 1991 and 2006 found that 20.6% of Indigenous women with breast cancer were under 50 years of age compared with 11.7% for non-indigenous women. Indigenous women are also more likely to be diagnosed with more advanced disease (Gibberd et al., 2015) and have larger tumours or tumours with distant spread (Moore et al., 2015) compared with non-indigenous women. This could explain the higher rate of mastectomy at first surgery as opposed to breast conserving surgery for Indigenous women (Roder et al., 2014; Supramaniam et al., 2014). This advanced stage of disease can be linked to poorer attendance at screening programs, and would help explain the different mortality patterns between Indigenous and non-indigenous women. In addition, increased co-morbidities, limited access to radiotherapies due to

geographic remoteness and other cultural factors could also be contributive (Cancer Australia, 2012). Overall, hospitalisations for breast cancer for Indigenous women are lower compared with other Australians (Australian Institute of Health and Welfare and Cancer Australia, 2013) and the former are less likely to receive surgical treatment or complete the full course of treatment for breast cancer (Cancer Australia, 2012; Australian Institute of Health and Welfare and Cancer Australia, 2013). Evidence suggest that Indigenous women face a significantly lower chance of surviving five years after a breast cancer diagnosis compared with other Australian women regardless of age or place of residence (Cancer Australia, 2012).

The Indigenous population is growing at a faster annual rate compared with the general Australian population with numbers expected to reach over 900,000 by the year 2026. Although life expectancy is improving, poorer health outcomes continue to be experienced by Indigenous women. Despite lower breast cancer incidence, fatalities from the disease occur at an elevated rate compared with non-indigenous women. While Australia as a whole is moving towards improvements in breast cancer outcomes with better diagnostic, treatment, and management strategies, there is a need to extend these benefits to all segments of the population.

PART TWO: Risk factors

The causes of breast cancer are complex and are often interrelated with socio-economic, demographic, and environmental factors that co-function with biomedical causes. As Indigenous Australians experience greater socio-economic disadvantage compared with other Australians, the social determinants of health bear a heavy influence upon the overall picture of breast cancer in Indigenous women (Australian Institute of Health and Welfare, 2014a). Social determinants are estimated to explain up to 46% of the health gap that exists between Indigenous and non-Indigenous Australians (Australian Bureau of Statistics, 2013). It was indicated (Australian Institute of Health and Welfare and Cancer Australia, 2013) that pertinent to the risk profile of Indigenous women are age, place of residence, familial risks, genetic factors, reproductive history, lifestyle factors such as nutrition and alcohol intake, participation in screening, and mammographic density, each of which will be considered below.

Age

A woman's risk of developing breast cancer increases with increasing age. Seventy-seven percent of all breast cancer diagnoses in Australia are in women aged 50 years and over (Australian Institute of Health and Welfare, 2015a). While there is a smaller population of Indigenous people (up to 10% fewer) in this age group compared with other Australians, the number of at risk Indigenous women is still substantial at 46,650 (Australian Institute of Health and Welfare, 2015b). It was reported (Australian Institute of Health and Welfare, 2014a) that the lifespan of Indigenous women improved by 6 months between the periods 2005-2007 and 2010-2012 and it is estimated that this trend will continue. As Indigenous women's life expectancy increases over time, the age related risk for breast cancer will also increase.

Place of residence

In Australia, remoteness is measured by the Accessibility/Remoteness Index of Australia (ARIA) and refers to the physical distances people must travel to reach facilities such as health services (Australian Government, 2001). According to census data (Australian Bureau of Statistics, 2011) 79% of Indigenous Australians live in metropolitan areas, 7% live in remote locations, and 14% in very remote regions. While more Indigenous people live in and around urban centres, 61% of people in remote to very remote locations are Indigenous.

Poorer overall health has been observed with increasing geographic remoteness in Australia (Australian Institute of Health and Welfare, 2014a). Geographic remoteness is reported to be associated with poorer nutrition and higher obesity rates, socio-economic disadvantage, the prevalence of unhealthy behaviors such as alcohol abuse and smoking, and lower access to health care services (Australian Institute of Health and Welfare, 2008; Australian Institute of Health and Welfare., 2016).

While the lowest rates of new breast cancer cases are found in women living in very remote areas (Australian Institute of Health and Welfare, 2015a) the mortality rate is similar to that in major cities (Australian Institute of

Health and Welfare, 2007). A number of studies specific to individual jurisdictions have reported breast cancer incidence and mortality for Indigenous women and these are described below.

It has been reported (Roder et al., 2014) that Australians living in remote areas are more often from lower socio-economic standing ($p < 0.001$) and have differential experiences of cancer treatments. Remote breast cancer patients compared with metropolitan breast cancer patients have a higher rate of mastectomy than breast conservation surgery, and are more likely to undergo adjuvant chemotherapy. This research also suggested that people living remotely have limited access to specialised treatment services thus leading to poorer survival outcomes. As Indigenous Australians are disproportionately represented in rural and remote areas they are more likely to have these experiences.

A study in the Northern Territory (Condon et al., 2016) where approximately one-quarter of the population are Indigenous and two-thirds of the overall population live remotely, found that Indigenous breast cancer incidence between 1991-1996 and 2007-2012 increased by 274% while for non-Indigenous women the increase was 9%. Improved access to breast screening with the introduction of mobile screening vans that travel to remote communities was reported to only marginally account for the increase as Indigenous participation in screening in the Northern Territory was low at a level between 18%-24% in those years. Condon and colleagues proposes that changes to the way Indigenous people live and lifetime cumulative exposure to cancer risk factors related to behaviour, specifically smoking, have driven the increase in cancer rates.

A study in South Australia (Chong and Roder, 2010) reported that Indigenous people with remote residence had a higher relative risk of death (RR 3.73) from all types of cancers compared with their non-Indigenous counterparts. Although the study categorised breast cancer as a low frequency cancer with low case fatalities, survival was significantly lower for Indigenous female population compared with non-Indigenous women. This was linked to poorer access to specialised treatment services.

A study in Queensland (Diaz et al., 2015) found that Indigenous cancer patients living in rural and remote areas had lower survival rates than Indigenous urban dwellers and were 30% less likely to access cancer treatment services compared with urban patients. The study identified remoteness and the associated physical, financial and emotional stresses of travelling away from home and community as barriers facing Indigenous people living remotely.

Family History and Genetics

Women with breast cancer have a 20-30% chance of having at least one family member with the disease, and the gene mutations BRCA1 and BRCA2 are found to have the strongest association with risk (Edlich et al., 2005). The cumulative risk of developing breast cancer by age 70 is 65% within carriers of an inherited BRCA1 variant, and 45% within carriers of the inherited BRCA2 variant. (Cancer Australia and National Breast and Ovarian Cancer

Centre, 2009). For women who have inherited both the BRCA1 and BRCA2 gene mutations the risk of breast cancer is 10-30 times higher than that for women without the inherited gene mutation. While family history plays an important role in determining risk, the relative risk to the overall female population due to known BRCA1 and BRCA2 inherited gene mutation is less than 5% in Australia (Cancer Australia and National Breast and Ovarian Cancer Centre, 2009), and between 5-10% in the US (Edlich et al., 2005).

The level of risk increases with the number of first degree-relatives with the disease, especially for women with a high risk gene mutation and first degree relatives with breast cancer diagnosed before the age of 40. In Australia however, less than 1% of the female population falls within this very specific category (Cancer Australia and National Breast and Ovarian Cancer Centre, 2009). While genetic testing will determine inherited biological susceptibility and give an estimation of risk and potential treatment options, shared environments and behaviours within a family should also be taken into account when assessing familial risk. As genetic testing is by nature invasive and personal, concomitant genetic counseling with psychosocial support is recommended (Riley et al., 2012).

There is limited information on familial and genetic breast cancer risk for Indigenous Australians. Indeed genetic research has proven controversial with Indigenous communities raising ethical concerns around the consent to genetic research, privacy and storage of genetic samples, ownership and use of genetic information, and potential risks to the community (Kowal et al., 2012). However, with increasing information around the benefits of genetic research particularly its implications on personalised medicine, discussions around genetic services involving Indigenous Australians have been revisited (Kowal et al., 2012). A study conducted across four large public hospitals in Queensland (Bernardes et al., 2014) surveyed 252 Indigenous cancer patients' beliefs and attitudes around genetic counseling and familial risk assessment. Twenty five percent (n=63) of the cohort were Indigenous breast cancer patients, and of these 38% (n=24) had a family history of the disease and 22% (n=14) had a first degree relative with the disease. This study suggested that Indigenous breast cancer patients have family history of the disease, were concerned about a family member getting cancer, and expressed a willingness to participate in genetic services. The study found a significant relationship between having concerns about cancer and willingness to participate in genetic counseling and/or testing. Furthermore genetic services need to be accessible and culturally appropriate for Indigenous Australians.

Reproductive history and hormones

The differences in breast cancer incidence rates between Indigenous and non-Indigenous women may be explained to some extent by reproductive events and child-bearing practices. Some factors related to reproduction are linked to increased breast cancer risk such as nulliparity or low parity, first childbirth after the age of 30, menopause occurring after the age of 55, and the

onset of menarche before 12 years old (Cancer Australia and National Breast and Ovarian Cancer Centre, 2009). One known protective practice is breastfeeding for longer periods particularly in multiparous women and those who were younger at first childbirth (Zhou et al., 2015). The levels and interactions of endogenous and exogenous estrogens within a woman's body in relation to these events are fundamentally important to the influence of reproductive agents on breast cancer risk.

Indigenous mothers are likely to have more children and have their first child at younger ages than non-Indigenous mothers (Australian Bureau of Statistics, 2011). Indigenous mothers on average have 2 or more children compared with all mothers who tend to have less than 2 children and the median age at first childbirth is 25.1 years and 30.9 years respectively (Australian Bureau of Statistics, 2011). While the Indigenous fertility rate is higher than the nation's average, rates for both Indigenous and non-Indigenous birth have been steadily declining since 2009 (Australian Bureau of Statistics, 2014).

Rates of breastfeeding by Indigenous and non-Indigenous mothers are similar at 87% and 90% respectively (Australian Indigenous HealthInfoNet, 2015). However, only 11% of 5-month old Indigenous infants were being exclusively breastfed compared with 27% of non-Indigenous babies (Australian Indigenous HealthInfoNet, 2015). While the period of breastfeeding individual children may be less for Indigenous mothers, multiparity suggests a longer overall breastfeeding duration over the lifetime of an Indigenous mother compared with a non-Indigenous mother. This is important since studies have shown that the protective effect of breastfeeding in relation to breast cancer risk increases with overall periods of breastfeeding (Collaborative Group on Hormonal Factors in Breast Cancer, 2002; Zhou et al., 2015).

The link between the late onset of menopause and the associated exposure to hormones namely estrogen and progesterone and breast cancer is well established (Reeves et al., 2006). However research into the menopausal experience for Indigenous women globally is scarce. This is particularly so for Indigenous Australians with only two small scale studies available on the subject (Jones et al., 2012; Chadha et al., 2016). Therefore it is difficult to make extensive comparisons between the average onset age of menopause between Indigenous and non-Indigenous women in Australia (for whom menopausal data is substantial). A study (McKenna, 2001) with a population-based sample of 313 participants in Far North Queensland reported the mean age of menopause for Indigenous women at 46.9 years, 1.4 years younger than non-Indigenous women (48.3 years). Rurally located Indigenous women were reported to experience menopausal symptoms even earlier at 45.9 years of age. Similarly studies into hormone replacement therapy (HRT) and oral contraceptive (OC) use within Australian Indigenous women are scarce, despite the well recognised association between HRT and OC current and recent use and breast cancer risk (Reeves et al., 2006; Jordan et al., 2015). Nonetheless a small Western Australia community-based study (Davis et al., 2003), demonstrated that 100%

of perimenopausal and postmenopausal Indigenous women (n=17) reported never having been prescribed or used HRT.

Lifestyle factors

Among the factors related to behaviours such as alcohol consumption, cigarette smoking, physical activity and body size are widely reported to have the strongest association with breast cancer incidence, recurrence, and mortality. Indigenous compared with non-indigenous Australians had a higher prevalence of behavior-related risk factors for cancer as they are reported to be one-and-a-half times more likely to drink alcohol at dangerous levels than non-indigenous Australians, are more than twice as likely to be daily smokers, one-and-a-half times more likely to be sedentary, and 1.6 times more likely to be obese (Castles et al., 2016).

Alcohol

Epidemiological studies have consistently reported the association between alcohol consumption and breast cancer risk (Ferrini et al., 2015; Mourouti et al., 2015). A reanalysis of 53 epidemiological studies (Hamajima et al., 2002) reported that for each 10g per day of alcohol consumed (equating to one 175ml glass of red wine) the relative risk of developing breast cancer increases by 7.1%. Furthermore risk increases concomitantly with increased alcohol intake so that heavy drinkers or individuals consuming ≥ 30 g of alcohol per day, have up to 20% increased breast cancer risk (Key et al., 2003). In the 2012 to 2013 Australian Aboriginal and Torres Strait Islander Health Survey (Australian Bureau of Statistics, 2013) 68% of Indigenous female respondents over 15 years old reported consuming alcohol in the past year. Ten percent of these women reported to exceed drinking more than two standard drinks on any day, a level that is reportedly linked to increased lifetime risk of alcohol-related diseases in females by the NHMRC (National Health and Medical Research Council, 2009). However, this rate is not dissimilar to the drinking habits of non-indigenous females over 15 years old in Australia (rate ratio of 1.0). Indeed, Indigenous women over 55 years old were 3% less likely than their non-indigenous counterparts to exceed the lifetime risk guidelines for alcohol consumption.

Smoking

The American Cancer Society (Gaudet et al., 2013) supports the hypothesis that active smoking is linked to the development of breast cancer with a 24% and 13% higher incidence found within current and former smokers compared with never smokers. Women who started smoking before their first menarche had a 61% increased risk than never smokers, and those that started after first menarche but eleven or more years before first child birth had a 45% increased risk. The effect of passive smoking on breast cancer remains controversial. A laboratory study (Di Cello et al., 2013) demonstrated passive and active exposure to tobacco smoke over long periods lead to more aggressive breast cancers and metastasis. However an updated review of epidemiological data (Lee and Hamling,

2016) found methodological weaknesses in the previous studies suggesting further epidemiological evidence is needed to convincingly link passive smoking and breast cancer risk.

In Australia, tobacco smoking is reported to be responsible for 12.3% of the total burden of disease and injury within Indigenous peoples (Australian Institute of Health and Welfare., 2016). According to the 2012-2013 Australian Aboriginal and Torres Strait Islander Health Survey (Australian Bureau of Statistics, 2013), Indigenous Australians compared with non-indigenous are 2.6 times more likely to have a daily smoking habit with two in five Indigenous people being current smokers and similar proportions evident in males (43%) and females (39%). The prevalence of smoking was higher for remote-living Indigenous people than non-remote, with significantly higher rates in ages 34 years and younger in remote locations compared with their counterparts in non-remote areas. There is however limited information on breast cancer risk and cigarette smoking within Indigenous Australians.

Physical Activity and Body Size

There is strong epidemiological evidence that physical activity is inversely associated with breast cancer risk. A meta-analysis (Loprinzi et al., 2012) reported a statistically significant protective effect for physical activity on breast cancer risk in most studies, with a mean reduction of risk of up to 36% for individuals who exercised compared with those who did not. People who engaged in vigorously intense exercise and those who were regularly physically active over their lifetime experienced the most benefit with 26% and 30% risk reduction respectively. However, even moderately intense exercise produced a 13% reduction in risk. While regular exercise during adolescence was associated with the highest mean reduction in breast cancer risk than at other times in a person's life, physical activity in women who are postmenopausal, not overweight and no family history showed the greatest reduction of breast cancer risk (Loprinzi et al., 2012). Furthermore several studies have demonstrated that the timing of physical activity in relation to a breast cancer diagnosis impacted upon the risk of recurrence and death. A systematic review (Chlebowski, 2013) found that cancer patients with stages 1-3 disease who were physically active at a level of 2.5 hours of moderate exercise or 1.5 hours of vigorous exercise per week before diagnosis, had a lower risk recurrence in 2 years. Also that post-diagnosis physical activity was associated with 34% fewer breast cancer deaths and 41% fewer deaths from all causes.

Engaging in physical activity is known to improve metabolic health, decrease weight gain and prevent obesity (World Health Organization, 2010). There is convincing evidence that postmenopausal women who are at a healthy weight and have low body mass index (BMI) are at a lower risk for developing breast cancer (Cancer Australia and National Breast and Ovarian Cancer Centre, 2009). In premenopausal women on the other hand the opposite has been observed in that greater weight is associated with lower breast cancer risk; however breast cancers are rare in younger women and the risk of developing the disease

significantly rises if obesity continues into menopause and beyond. The Australian Institute of Health and Welfare reported that Indigenous females are 1.7 times more likely to be obese (BMI >30.00) than non-indigenous women (Australian Institute of Health and Welfare, 2015b).

Within the Indigenous population, it was estimated that physical inactivity is responsible for around 8% of the total burden of disease and injury, and it is also associated with obesity which accounts for 11% of the total burden of disease (Australian Institute of Health and Welfare., 2016). In the 2012-2013 health survey (Australian Bureau of Statistics, 2013), Indigenous women were less likely to meet the national physical activity target of 2.5 hours of moderate exercise per week compared with Indigenous men (40% vs. 49.2%) and with non-indigenous females (40% vs 48.2%). Furthermore Indigenous women had the highest obesity rate between the ages of 45-54 years (50%), and this rate was higher than the obesity rates of Indigenous men (35%), non-indigenous males (34.2%) and females (31.1%) of the same age group (Australian Bureau of Statistics, 2013). A study (Stewart et al., 2012) which surveyed 385 Indigenous females who attended a health service in Western Australia found that 27% of the respondents reported to be overweight and 53% were obese. There are similar reports within Indigenous populations internationally. Canada's First Nation and Metis populations (Withrow et al., 2014) and New Zealand's Maori women (Lawrenson et al., 2016) are significantly less likely to be physically active and more likely to be obese than their non-native counterparts.

Breast Screening

The early detection of breast cancers precedes timely access to effective diagnostic and treatment services that lead to more positive outcomes for women (Lauby-Secretan et al., 2015). It can achieve a nine year survival rate of 97% compared with 41% with late detection and distant spread of disease (Commonwealth of Australia, 2009). BreastScreen Australia is the national population-based mammography screening program that aims to reduce mortality and burden of disease by inviting 50 to 74 year old women to participate in free biennial mammograms. According to the BreastScreen (Commonwealth of Australia, 2009), the program's sensitivity is high. Within first-screened 50 to 69 year-old women between 2000 to 2003, sensitivity was 78.5% (95% CI: 74.8-82.2), and for women who underwent subsequent screening in the same years sensitivity was 70.3% (95% CI: 68.8-71.8). There is broad acceptance of the program with a steady national participation rate of around 55%. However only 35.5% of eligible Indigenous women participated which is 19% lower than the rate for non-indigenous women (54.5%) (Australian Institute of Health and Welfare, 2015a). Indigenous women are also less likely to participate in re-screening within the recommended 27 months and attend post-screening assessment within the recommended 28 days if recalled (Cancer Australia, 2012). To address these attendance issues, concerted national efforts to improve access via mobile screening units that travel to communities and targeted culturally-attuned health promotion campaigns have been implemented (Australian

Health Ministers' Advisory Council, 2015; Australian Indigenous HealthInfoNet, 2015).

The underutilisation of cancer screening services is not uncommon amongst Indigenous populations and ethnic minorities internationally as shown in the USA, Canada, Alaska, Pacific Islands, and New Zealand with concomitant higher prevalence, more advanced tumours at diagnosis and increased fatality (Martins et al., 2013; Moore et al., 2015; Seneviratne et al., 2015). A systematic review of the knowledge, attitudes and behaviours towards Indigenous cancer screening (Kolahdooz et al., 2014) reported that while the factors that affect screening attendance for non-indigenous and indigenous populations were very similar, the indigenous peoples reported traditional cultural beliefs and practices as having a significant influence on screening behaviors. The review identified one West Australian study (Shahid et al., 2009) of 29 urban and regionally located Indigenous women that reported limited and vague understanding of screening for any type of cancer. For some women, cancer was associated with spirituality and fatalism, and a positive diagnosis brought about pain, fear, and shame thereby leading to delays in screening. Kolahdooz and colleagues concluded that greater understanding of indigenous groups' specific systems of beliefs and knowledge, including the clinical implementation of culturally appropriate strategies are needed to optimise cancer detection in diverse populations.

Strategies can be implemented to transform participation rates within under-served populations. For example in 2003 at BreastScreen Midland, a rural practice in New Zealand with a predominantly Maori population implemented a strategy called, 'Encouraging Participation' (Thomson et al., 2009). The program comprised of local advocacy and community-based education and health promotion that saw the Maori women's participation rate increase from 45% to 98% in 2005 and 2007. In 2013 in Australia, the Closing the Gap initiative in BreastScreen Queensland saw a 7% increase in the participation of 50-69 year old Indigenous women from 49% in 2010-2011 to 56% in 2012-2013 (The Australian, 2014). The program involved the development of culturally appropriate resources, partnerships with local Indigenous groups, and Indigenous health workers to educate, recruit, and support women being screened for the first time or rescreened. The involvement of Indigenous Australians in all aspects of health research and service delivery where Indigenous peoples are concerned is critically important to establish maximum efficacy and value (Garvey et al., 2011).

Breast Density

Breast density refers to the amount of fibroglandular tissue in the breast. A breast with higher amounts of fibroglandular tissue and lower amounts of fat would be referred to as a dense breast, whereas a breast with more fat and less fibro-glandular tissue would be referred to as a fatty breast. Mammographic breast density refers to the radiographic appearance of fibroglandular and fat tissues visible on a mammogram. Epithelium and stromal cells within dense fibroglandular tissue attenuate x-rays more than fat and therefore appear white on mammograms whilst non-dense fatty tissue appears dark. Density can

be measured by both qualitative and quantitative methods, via automated tools and manual means using area and volume percentages or specific classification techniques (Kerlikowske and Vachon, 2016). It is well documented that breast density is strongly associated with breast cancer risk with a four to six-fold increase in risk for women with highly dense breasts (50% to >75% density) (McCormack and Silva, 2006; Boyd et al., 2007; Checka et al., 2012; Al Mousa et al., 2014). The mechanism by which breast density affects risk is not fully understood however, it is well known that tumorigenesis occurs within epithelial cells (McCormack and Silva, 2006). Separately the masking effect of dense tissue on the visibility of tumours may lead to some cancers being missed on a mammogram (Boyd et al., 2007).

Breast density, while largely genetically determined, is observed to be alterable by factors such as age, hormones, menopausal status, body weight and size (Aitken et al., 2010; Kerlikowske et al., 2010; Ekpo et al., 2016; Kerlikowske and Vachon, 2016). For instance, older women who are multiparous and have a higher body weight were reported to have lower breast density measures (Boyd et al., 2005). This may seem contradictory to its relationship with breast cancer risk as we know that older age and increased body weight is associated with elevated breast cancer risk. It is thus suggested that cumulative lifetime exposure to high breast density as an effect of age and exogenous and endogenous hormones underlies the connection between breast density and breast cancer risk (McCormack and Silva, 2006; Martin and Boyd, 2008). In addition, variations in breast density have been observed with components of nutrition, parity, level of education and socioeconomic standing. In a United Kingdom study (Aitken et al., 2010), highly educated women and those living in the most affluent areas were found to have around 6% (95% CI 1.6%, 10.5%) higher mammographic density measures than women with lower education attainment and living in less affluent areas.

Little is known about the mammographic density profile of Australian Indigenous women. A study (Pape et al., 2016) categorised the mammographic parenchymal patterns (MPP) of 502 Indigenous women attending a regional Australian breast screening service using the Tabár method of classification. The researchers found most women in the study (42.1%) were categorised under 'Pattern II: predominance of fat tissue', or low breast density, but there were no identifiable and unique MPP to support increased breast cancer risk within this cohort. The MPP of non-Indigenous women were not analysed and therefore comparative information was not available. Studies in other parts of the world have shown diverse results. In the USA an older study (del Carmen et al., 2007) found that there were no significant differences in breast densities across racial groups when controlling for age, BMI and breast size in an analysis of qualitative density measures. However a recent study (McCarthy et al., 2016) found that African American women had higher quantitative density than Caucasian women after accounting for age, BMI, HRT use, reproductive history, and family history of breast or ovarian cancer. In Alaska, variations in breast densities were found within different

ethnic groups of native Alaskan women that were inconsistent with breast cancer incidences (Roubidoux et al., 2003). In the United Kingdom (McCormack et al., 2008) and also in New Zealand (Ellison-Loschmann et al., 2013) differences in breast densities were observed between ethnic groups that were consistent with breast cancer risk. Further studies into the breast density profiles of Australian Indigenous women are warranted to achieve a comprehensive understanding of breast density in relation to ethnicity and breast cancer risk, and may help inform personalised screening methods for all Australian women. As Australian Indigenous populations are diverse, comprehensive studies that look at differences in breast density, to establish if variations do exist between Indigenous groups and the general population, would also be useful.

With concomitant declining fertility and increasing life expectancy in the Indigenous population, breast cancer will continue to be an important health issue for Australia. If health outcomes for Indigenous women are to be improved there is a need for targeted research so that the level of evidence around breast cancer is comparable between these women and their non-Indigenous counterparts. For instance breast density, one of the most established independent risk factors for breast cancer, warrants further investigation within Indigenous women particularly as density has implications on early detection, pathways to better care, and is potentially modifiable.

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