



The association between mammographic density and breast cancer risk in Western Australian Aboriginal women

Ellie Darcey¹ · Rachel Lloyd¹ · Gemma Cadby¹ · Leanne Pilkington² · Andrew Redfern^{3,4} · Sandra C Thompson⁵  · Christobel Saunders^{3,4} · Elizabeth Wylie^{2,3} · Jennifer Stone^{1,6}

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Abstract

Purpose Mammographic density is an established breast cancer risk factor within many ethnically different populations. The distribution of mammographic density has been shown to be significantly lower in Western Australian Aboriginal women compared to age- and screening location-matched non-Aboriginal women. Whether mammographic density is a predictor of breast cancer risk in Aboriginal women is unknown.

Methods We measured mammographic density from 103 Aboriginal breast cancer cases and 327 Aboriginal controls, 341 non-Aboriginal cases, and 333 non-Aboriginal controls selected from the BreastScreen Western Australia database using the Cumulus software program. Logistic regression was used to examine the associations of percentage dense area and absolute dense area with breast cancer risk for Aboriginal and non-Aboriginal women separately, adjusting for covariates.

Results Both percentage density and absolute dense area were strongly predictive of risk in Aboriginal women with odds per adjusted standard deviation (OPERAS) of 1.36 (95% CI 1.09, 1.69) and 1.36 (95% CI 1.08, 1.71), respectively. For non-Aboriginal women, the OPERAS were 1.22 (95% CI 1.03, 1.46) and 1.26 (95% CI 1.05, 1.50), respectively.

Conclusions Whilst mean mammographic density for Aboriginal women is lower than non-Aboriginal women, density measures are still higher in Aboriginal women with breast cancer compared to Aboriginal women without breast cancer. Thus, mammographic density strongly predicts breast cancer risk in Aboriginal women. Future efforts to predict breast cancer risk using mammographic density or standardize risk-associated mammographic density measures should take into account Aboriginal status when applicable.

Keywords Breast cancer risk · Mammographic breast density · Ethnicity · Aboriginal women · Mammographic screening

Abbreviations

ARIA Accessibility/remoteness index of Australia
BMI Body mass index
CI Confidence interval

DA Dense area
FFDM Full-field digital mammogram
HT Hormone therapy
MD Mammographic density
OPERA Odds per adjusted standard deviation
OR Odd ratio
PDA Percent dense area

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✉ Jennifer Stone
jennifer.stone@uwa.edu.au

¹ Centre for Genetic Origins of Health and Disease, Curtin University and The University of Western Australia, 35 Stirling Highway, M409, Perth, WA 6009, Australia

² BreastScreen Western Australia, Women and Newborn Health Service, 9th Floor, Eastpoint Plaza, 233 Adelaide Terrace, Perth, WA 6000, Australia

³ School of Medicine, The University of Western Australia, 35 Stirling Highway, Perth, WA 6009, Australia

⁴ Fiona Stanley Hospital, Robin Warren Drive, Murdoch, WA, Australia

⁵ School of Population and Global Health, Western Australian Centre for Rural Health, The University of Western Australia, 167 Fitzgerald St, Geraldton, WA 6531, Australia

⁶ The RPH Research Foundation, Royal Perth Hospital, 50 Murray Street, Perth, WA 6000, Australia

SD	Standard deviation
SE	Standard error
SEIFA	Socio-economic indexes for areas
SES	Socio-economic status
TA	Total area (of the breast)
WA	Western Australia

Introduction

Breast cancer is the most common cancer and the second leading cause of cancer-related death in Australian women. Population-based mammographic screening provides the best chances of early detection; however, not all women have an equal opportunity to achieve an earlier diagnosis. Women differ both in terms of their underlying risk and also the sensitivity of their mammogram to detect abnormalities. Mammographic density, the white appearance of parenchymal tissue on a mammogram, is one of the strongest predictors of breast cancer risk—on par with carrying a mutation in the *BRCA1* or *BRCA2* genes [1, 2]. The adverse impacts of increased mammographic density are twofold: (i) through increased propensity for tumours to develop and (ii) decreasing sensitivity of mammography by making the detection of tumours more challenging, referred to as “masking”, leading to higher rates of false-positive and false-negative screening outcomes.

Increasing evidence suggests that tailored screening programs—where women at different levels of risk are recommended different screening intervals or supplemental screening modalities—may be a more efficient and cost-effective way of detecting breast cancer [3–5]. Routine measurement of mammographic density at the time of screening could help determine a woman’s risk of disease and her risk of “masking”, the risk of a cancer going undetected. Ethnic differences in the distribution of mammographic density are consistent with breast cancer incidence rates [6]. These differences may impact prediction models to assess individual risk and inform tailored screening recommendations.

Aboriginal and Torres Strait Islander people represent ~2.5% of the Australian population and ~2% of women who participate in free mammographic screening provided by BreastScreen Western Australia identify themselves as Aboriginal and Torres Strait Islander. Within this report, Aboriginal and Torres Strait Islander is used in the national context. Within Western Australia (WA), the term Aboriginal is used in preference to Aboriginal and Torres Strait Islander, in recognition that Aboriginal people are the original inhabitants of WA. No disrespect is intended to our Torres Strait Islander colleagues and community.

Previous work has shown that the means and the distributions of mammographic density measures are significantly lower in Western Australian Aboriginal women compared to

age-, screening year-, and screening location-matched non-Aboriginal women [7]. This is consistent with lower breast cancer incidence in Aboriginal and Torres Strait Islander women compared to other Australian women [8]. The association between mammographic density and breast cancer risk in Aboriginal and Torres Strait Islander women has not been studied.

Lower average mammographic density in Western Australian Aboriginal women [7] and lower breast cancer incidence in Aboriginal and Torres Strait Islander women [8] suggests that the sensitivity of mammography would be high and that absolute risk would be relatively low compared to non-Aboriginal women. However, breast cancer mortality rates are twice as high in Aboriginal and Torres Strait Islander women compared to other Australian women due, at least in part, to less screening, later presentation, increased risk factors for more aggressive tumours and, consequently, more advanced disease and higher risk of relapse [8]. There is potential to improve knowledge and awareness about mammographic density within Aboriginal and Torres Strait Islander communities which could help increase screening participation rates by promoting that mammography is a very good test for Aboriginal and Torres Strait Islander women due to lower average mammographic density. Increased understanding of the association between mammographic density and breast cancer risk in Aboriginal and Torres Strait Islander women will be pivotal to disseminating a clear and productive message specific to Aboriginal and Torres Strait Islander women and will also help inform mammographic screening policy in Australia.

We conducted a retrospective “double” case–control study nested within a population-based mammographic screening program. Through identity-protected data linkage, we selected all Aboriginal women diagnosed with breast cancer within the BreastScreen WA program between 1994 and 2015 and three times as many Aboriginal controls, non-Aboriginal cases, and non-Aboriginal controls. The aim was to determine whether absolute and percentage dense area are associated with risk of breast cancer in Aboriginal women and whether the associations differ between Aboriginal and non-Aboriginal women.

Methods

Participants

The participants in this study were selected from BreastScreen WA, a population-based screening program which targets and provides free screening mammograms to women aged 50 to 74 years. Ethical approval was obtained by the WA Department of Health Human Research Ethics

Committee (Project #2014/50) and the WA Aboriginal Health Ethics Committee (Project 581).

We identified 119 self-reported Aboriginal women in the screened population who were diagnosed with breast cancer (Aboriginal cases) between 1994 and 2015. For each Aboriginal case, we attempted to identify (i) three Aboriginal women not diagnosed with breast cancer (Aboriginal controls) and (ii) three non-Aboriginal women with breast cancer (non-Aboriginal cases). For each non-Aboriginal breast cancer case, we then selected one non-Aboriginal not diagnosed with breast cancer (non-Aboriginal controls). We attempted to match on age at screening, screening year and screening location and we selected partial matches using age at screening and screening year when a full match could not be found. Aboriginal status was acquired using both self-reported status at BreastScreen WA and from the Indigenous Status Flag derived by the WA Department of Health [9]. Breast cancer status (invasive and in situ) was taken from information recorded at BreastScreen WA and was later verified using linkage with the WA Cancer Registry (via the Department of Health Data Linkage Branch). The verification resulted in two Aboriginal women originally identified

as cases being reclassified as controls (Aboriginal women without breast cancer) and 17 non-Aboriginal controls being reclassified as women with a history of breast cancer (non-Aboriginal cases). See Fig. 1 for details.

Epidemiological data

Epidemiological data collected by BreastScreen WA included age at screening, family history of breast cancer (first degree relative) and hormone therapy (HT) use in the 12 months before date of mammogram, Socio-Economic Indexes for Areas (SEIFA) [10] and Accessibility/Remoteness Index of Australia (ARIA) [11] scores for each participant. SEIFA is made up of four different indices: Index of Relative Socio-economic Advantage and Disadvantage (henceforth the Advantage and disadvantage index), Index of Relative Socio-economic Disadvantage (henceforth the Disadvantage index), Index of Economic Resources and Index of Education and Occupation. The distribution of scores were divided into deciles with lowest 10% areas having the least advantage, most disadvantage, least economic resource and least education and occupation, respectively.

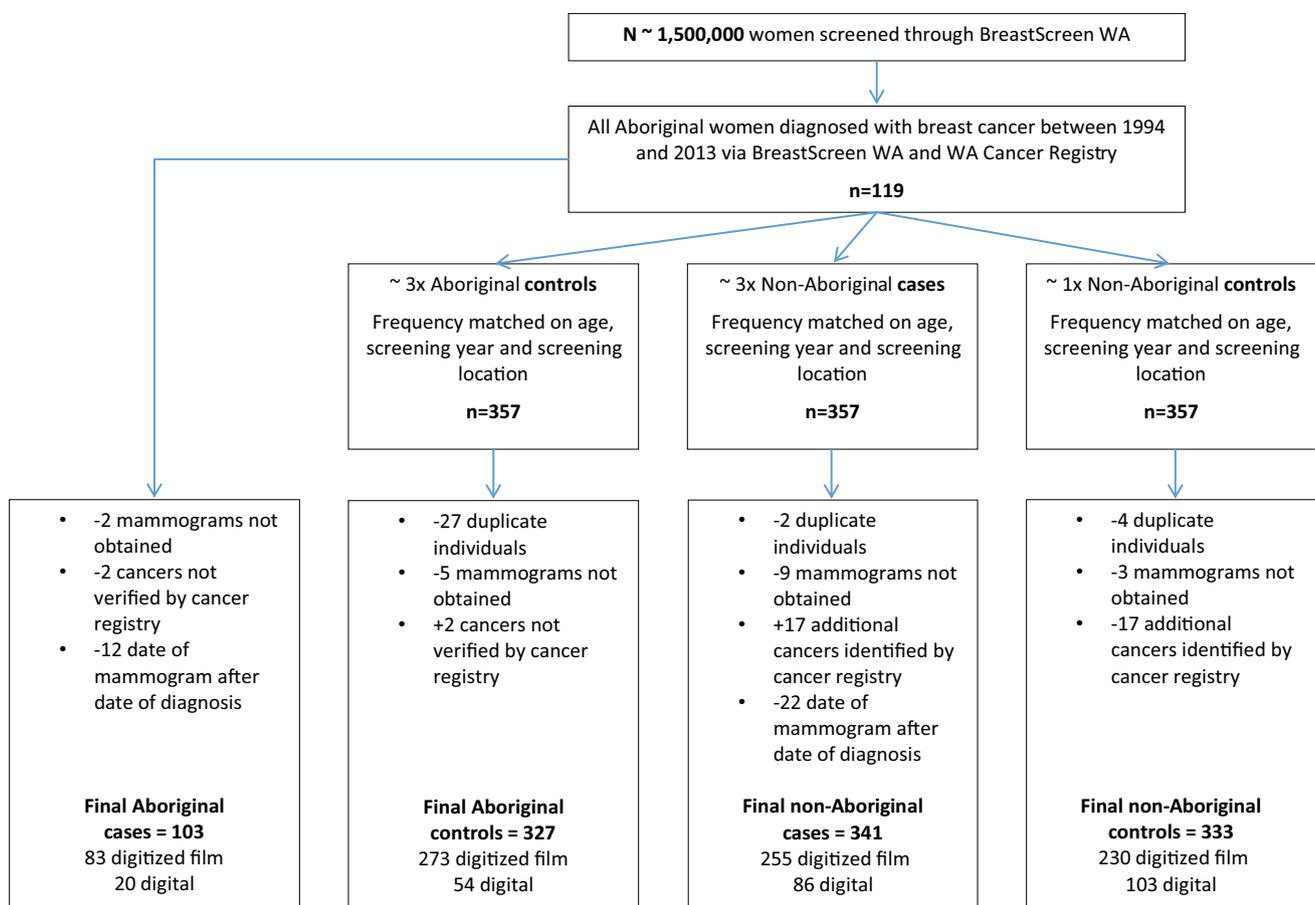


Fig. 1 Study participant selection, participant exclusions and final sample

We classified each index score into four groups: lowest 10%, next 10–40%, next 40–70%, top 70–100%. The ARIA categories were reclassified into four groups as follows: Major city (major city), Regional (inner regional and outer regional), Remote and Very remote.

SEIFA and ARIA rankings were estimated using full residential address. When complete residential information was missing, residential postcode at time of the index mammogram was used to generate SEIFA ($n=324$) and ARIA ($n=307$) scores using data from the Australian Bureau of Statistics [10, 11].

Mammographic data

For each woman, cranio-caudal film mammograms or full-field digital mammograms (FFDM) were extracted from BreastScreen WA with pre-diagnosis mammograms used for women diagnosed with breast cancer. Film mammograms were digitized using a high powered scanner and all FFDM were produced by the same vendor (Siemens). For breast cancer cases, the contralateral breast was measured, and for controls, a randomly selected breast side was measured for each woman. Images were measured by JS using Cumulus software [12] in batches of approximately 100 plus a 10% random repeated sample to check reliability. Measures of percentage dense area, absolute dense area and non-dense area were used in the analysis. Non-dense area was used as a pseudo-measure of body mass index (BMI) in the absence of height and weight data [13]. We excluded duplicates ($n=33$) where the same control was matched to two different cases and participants where either their mammogram could not be obtained ($n=19$) or the date of their mammogram was after their breast cancer diagnosis ($n=34$). A flow diagram outlining the study participant selection, participant exclusions and final sample is presented in Fig. 1.

Statistical methods

Correlation coefficients were used to estimate the reliability of the repeated mammographic measurements. Reliability was found to be high (intraclass correlation > 97%) for both dense area and percentage dense area. Descriptive data were generated for all variables by Aboriginal status and case–control status. *T* tests and χ^2 tests were used to identify differences between characteristics of cases and controls separately for Aboriginal and non-Aboriginal women. Logistic regression was used to examine the associations between mammographic density measures and breast cancer risk. Additionally, we calculated the odds per adjusted standard deviation (OPERAS) for the investigation of mammographic density measures associated with breast cancer risk [1]. We analysed Aboriginal and non-Aboriginal women separately for all regressions except for models investigating

interactions. All multivariate analyses were adjusted for age at screening and non-dense area (as surrogate for BMI; scaled to 10 cm²) as they are important predictors for both mammographic density and breast cancer risk. The effects of other potentially important factors (e.g. family history, HT use, ARIA and SEIFA) were examined in multivariate regression models and were included in the model if the factors had large effects on model coefficients. To determine whether there are differences in the strength of associations of mammographic density measures with breast cancer risk between Aboriginal and non-Aboriginal women, a combined analysis was undertaken which included an interaction between Aboriginal status and density measures. All data management and analysis were carried out using Stata, version 14.2. Model testing using residuals and link function testing on multivariate logistic regression models were undertaken to ensure model assumptions were upheld.

The results presented below are for participants with digitized film mammograms only; results for analysis with all participants (both FFDM and digitized film mammograms) can be found in Supplementary Material.

Results

The characteristics of the study participants with digitized film mammograms are presented in Table 1. The study participants consisted of 356 Aboriginal women (83 cases and 273 controls) and 485 non-Aboriginal women (255 cases and 230 controls). Among Aboriginal women, cases and controls were similar in terms of age at mammogram, HT use in the last 12 months, family history of breast cancer, ARIA and all SEIFA indices. Among non-Aboriginal women, cases were more advantaged and less disadvantaged than controls but were similar in terms of age at mammogram, HT use in the last 12 months, family history of breast cancer, ARIA and other SEIFA indices. In terms of mammogram measurements, Aboriginal women without breast cancer had similar non-dense breast area compared with Aboriginal women with breast cancer. However, percentage density and absolute dense area were higher in the breast cancer cases (percentage density mean = 13.7%, absolute density mean = 19.2 cm²) than the controls (percentage density mean = 9.1%, absolute density mean = 12.0 cm²). Non-dense area was similar between cases and controls among non-Aboriginal women but there was no evidence of differences between percentage dense area and absolute dense area (percentage dense area: $P=0.559$; absolute dense area: $P=0.278$).

The logistic regression results for breast cancer for absolute and percentage density among Aboriginal and non-Aboriginal women are presented in Table 2. For each 10 cm² increase in absolute dense area, odds of breast cancer

Table 1 Characteristics of the Aboriginal ($n=356$) and non-Aboriginal ($n=485$) women with digitized film images by case–control status

Characteristics	Aboriginal ($n=356$)			Non-Aboriginal ($n=485$)		
	Case ($n=83$)	Control ($n=273$)	P value ^a	Case ($n=255$)	Control ($n=230$)	P value ^a
Mean age at mammogram (SD)	58.1 (8.9)	58.0 (9.3)	0.933	58.6 (9.4)	56.9 (9.7)	0.057
HT use in the last 12 months ^b (%)	6 (7.2)	19 (7.0)	0.933	62 (24.4)	51 (22.3)	0.579
Family history of breast cancer (%)	5 (6.0)	16 (5.9)	0.956	30 (11.8)	23 (10.0)	0.534
ARIA ^c (%)			0.970			0.611
Major city	17 (20.5)	56 (20.5)		186 (72.9)	166 (72.2)	
Inner and outer regional	15 (18.1)	44 (16.1)		51 (20.0)	43 (18.7)	
Remote	15 (18.1)	54 (19.8)		16 (6.3)	16 (7.0)	
Very remote	36 (43.4)	119 (43.6)		2 (0.8)	5 (2.2)	
Advantage and disadvantage index ^{d,e} (%)			0.689			0.001
1 (lowest)	34 (50.0)	123 (45.0)		46 (18.0)	15 (6.5)	
2	32 (38.6)	87 (31.9)		84 (32.9)	93 (40.4)	
3	11 (13.2)	37 (13.6)		71 (27.8)	58 (25.2)	
4 (highest)	6 (7.2)	26 (9.5)		54 (21.2)	64 (27.8)	
Disadvantage index ^{d,f} (%)			0.212			0.002
1 (lowest)	38 (45.8)	127 (46.5)		48 (18.8)	22 (9.6)	
2	32 (38.6)	79 (28.9)		80 (31.4)	93 (40.4)	
3	6 (7.2)	38 (13.9)		74 (29.0)	51 (22.2)	
4 (highest)	7 (8.4)	29 (10.6)		53 (20.8)	64 (27.8)	
Economic resources index ^{d,g} (%)			0.656			0.233
1 (lowest)	35 (42.2)	133 (48.7)		27 (10.6)	15 (6.5)	
2	32 (38.6)	88 (32.2)		80 (31.4)	87 (37.8)	
3	13 (15.7)	39 (14.3)		83 (32.5)	67 (29.1)	
4 (highest)	3 (3.6)	13 (4.8)		65 (25.5)	61 (26.5)	
Education and occupation index ^{d,h} (%)			0.686			0.803
1 (lowest)	21 (25.3)	77 (28.2)		30 (11.8)	22 (9.6)	
2	41 (49.4)	118 (43.2)		85 (33.3)	81 (35.2)	
3	15 (18.1)	49 (18.0)		61 (23.9)	51 (22.2)	
4 (highest)	6 (7.2)	29 (10.6)		79 (31.0)	76 (33.0)	
Mean total area in cm ² (SD)	152.9 (49.0)	153.7 (49.5)	0.896	132.0 (47.7)	123.8 (43.7)	0.048
Mean absolute dense area in cm ² (SD)	19.2 (20.8)	12.0 (18.9)	0.003	21.6 (20.3)	19.6 (19.4)	0.278
Mean non-dense area in cm ² (SD)	133.7 (49.4)	141.7 (54.0)	0.228	110.5 (52.1)	104.2 (48.5)	0.170
Mean percentage dense area in % (SD)	13.7 (14.0)	9.1 (13.3)	0.007	19.0 (17.9)	18.1 (16.9)	0.559

SD standard deviation, HT hormone therapy

^a P value for t test when mean and standard deviation is presented or Chi-squared test when percentage is presented

^bTwo individuals missing information on HT use. One in each of cases and controls for non-Aboriginal women

^cAccessibility/Remoteness Index of Australia (ARIA) scores

^dSEIFA scores are on a scale from 1 to 4, where 1 indicates the lowest 10% of the population in the state (least advantaged and most disadvantaged, most disadvantaged, least economic resources and least education and occupation opportunities) and 4 indicates the highest 30% of the population in the state (most advantage and least disadvantaged, least disadvantaged, most economic resources and most education/occupation opportunities)

^eIndex of Relative Socio-Economic Advantage and Disadvantage based on Western Australian state rankings

^fIndex of Relative Socio-Economic Disadvantage based on Western Australian state rankings

^gIndex of Economic Resources based on Western Australian state rankings

^hIndex of Education and Occupation based on Western Australian state rankings

increased by 19% (OR 1.19, 95% CI 1.05, 1.36) among Aboriginal women (adjusted for age at mammogram and non-dense area) and by 14% (OR 1.14, 95% CI 1.02, 1.27) among

non-Aboriginal women (adjusted for age at mammogram, non-dense area and advantage and disadvantage index). For each 10% increase in percentage density, odds of developing

Table 2 Odds ratios (95% confidence interval) for the association between breast cancer risk and absolute and percentage dense area among Aboriginal ($n=356$) and non-Aboriginal ($n=485$) women with digitized film mammograms

Characteristics	Univariate		Multivariable	
	Odds ratio (95% CI)	<i>P</i> value	Odds ratio (95% CI)	<i>P</i> value
Absolute dense area (per 10 cm ²)				
Aboriginal ($n=356$)	1.18 (1.05, 1.33)	0.006	1.19 (1.05, 1.36)	0.009 ^a
Non-Aboriginal ($n=485$)	1.05 (0.960, 1.15)	0.278	1.14 (1.02, 1.27)	0.018 ^b
Percentage dense area (per 10%)				
Aboriginal ($n=356$)	1.25 (1.06, 1.48)	0.009	1.32 (1.06, 1.66)	0.014 ^a
Non-Aboriginal ($n=485$)	1.03 (0.931, 1.14)	0.558	1.24 (1.06, 1.44)	0.006 ^b

^aAdjusted for age and non-dense area^bAdjusted for age, non-dense area and advantage and disadvantage index**Table 3** OPERAS (95% confidence interval) for the association between breast cancer risk and absolute and percentage dense area among Aboriginal ($n=356$) and non-Aboriginal ($n=485$) women with digitized film mammograms

Characteristics	Multivariable ^a	
	OPERA (95% CI)	<i>P</i> value
Absolute dense area (per adjusted SD)		
Aboriginal ($n=356$)	1.36 (1.09, 1.69)	0.007
Non-Aboriginal ($n=485$)	1.22 (1.03, 1.46)	0.024
Percentage Dense area (per adjusted SD)		
Aboriginal ($n=356$)	1.36 (1.08, 1.71)	0.010
Non-Aboriginal ($n=485$)	1.26 (1.05, 1.50)	0.011

OPERAS odds PER adjusted standard deviation

^aAdjusted for age and non-dense area

breast cancer increased by 32% and 24% for Aboriginal (OR 1.32, 95% CI 1.06, 1.66) and non-Aboriginal (OR 1.24, 95% CI 1.06, 1.44) women, respectively.

Calculated odds per adjusted standard deviation (OPERAS) for both absolute dense area and percentage dense area are found in Table 3. For absolute dense area, there was an 36% and 22% increase in odds per adjusted standard deviation for developing breast cancer for Aboriginal (OPERAS = 1.36, 95% CI 1.09, 1.69) and non-Aboriginal women (OPERAS = 1.22, 95% CI 1.03, 1.46), respectively. Similar results were observed for increases in percentage density, with the OPERAS for Aboriginal women and non-Aboriginal women 1.36 (95% CI 1.08, 1.71) and 1.26 (95% CI 1.05, 1.50), respectively.

Results from the combined analysis found for each 10 cm² increase in absolute dense area, Aboriginal women had a 23% increase in odds of breast cancer (OR 1.23, 95% CI 1.09, 1.39) compared with an 10% increase for non-Aboriginal women (OR 1.10, 95% CI 0.998, 1.22). However, there was no evidence to suggest a difference between odds of developing breast cancer between Aboriginal and non-Aboriginal women with differences in absolute dense area ($p_{\text{interaction}}=0.15$). There was marginal evidence suggesting

differences in odds for developing breast cancer for increases in percentage dense area between Aboriginal and non-Aboriginal women ($p_{\text{interaction}}=0.04$). Aboriginal women were found to have a 43% increase in odds of breast cancer (OR 1.43, 95% CI 1.18, 1.73) for each 10% increase in percentage dense area compared to non-Aboriginal who had an 16% increase (OR 1.16, 95% CI 1.02, 1.33).

Model testing revealed data collected on two Aboriginal women and three non-Aboriginal women had undue influence on the model resulting in violations to model assumptions. The analysis was repeated without these influential observations, resulting in increases in estimates for odds ratios and OPERAS for absolute dense area on odds of developing breast cancer among Aboriginal women (OR 1.31, 95% CI 1.12, 1.52; OPERAS = 1.46, 95% CI 1.19, 1.80) and non-Aboriginal women (OR 1.17, 95% CI 1.04, 1.31; OPERAS = 1.24, 95% CI 1.05, 1.48), as well as increases to odds ratios and OPERAS for percentage dense area on odds of developing breast cancer among Aboriginal (OR 1.44, 95% CI 1.13, 1.83; OPERAS = 1.43, 95% CI 1.14, 1.80) and non-Aboriginal women (OR 1.26, 95% CI 1.08, 1.48; OPERAS = 1.27, 95% CI 1.06, 1.52). In the combined analysis, after the exclusion of the influential observations, there was evidence of a difference in the odds of developing breast cancer between Aboriginal and non-Aboriginal women for increases in absolute dense area ($p_{\text{interaction}}=0.034$) and percentage dense area ($p_{\text{interaction}}=0.012$).

Discussion

This study was the first to show that Aboriginal women with increased mammographic density are at higher risk of developing breast cancer relative to other Aboriginal women of similar age and non-dense area (a pseudo-measure of BMI). We found evidence that the magnitude and the strength of the associations between the mammographic measures and breast cancer risk were stronger in Aboriginal women compared to non-Aboriginal women. Based on these findings and given the lower mean mammographic density in

Aboriginal women compared to non-Aboriginal women, we recommend taking Aboriginal status into account when predicting breast cancer risk using mammographic density or standardizing risk-associated mammographic density measures (if applicable).

Mammographic breast cancer screening is free for women over the age of 40 years in Australia and is largely accessible. Participation rates within Aboriginal communities are substantially lower compared to non-Aboriginal women (33.44 vs. 54.89%). Knowledge that Aboriginal women have, on average, less mammographic density but that Aboriginal women who have increased mammographic density *relative to other Aboriginal women* are at higher risk of breast cancer has important clinical implications. Aboriginal women with dense breasts could potentially benefit from supplemental screening using a modality other than mammography. Unfortunately, due to the case–control study design (and therefore the absence of a baseline Aboriginal-associated risk of breast cancer), it is impossible to determine if an Aboriginal woman with a given mammographic density measure is at higher risk of breast cancer compared to a non-Aboriginal woman with the same mammographic density (adjusted for other risk factors).

For the main analysis, we presented results from digitized film mammograms only and excluded subjects with FFDM images. Mammography machine manufacturers apply processing algorithms to digital images to improve detection which systematically affects density measurement [14]. Results from the combined film and FFDMs, provided in Supplementary Material, showed very similar OR estimates with increased strength of association (likely due to increased sample size); however, there was evidence of interaction between absolute dense area and mammogram type (film vs FFDM) for both Aboriginal and non-Aboriginal women (see Supplementary Table 3). The strength of association between mammographic measures from FFDM images and breast cancer risk appears to be stronger than that from digitized film mammograms, which is encouraging for future studies as screening programs in Australia have transitioned completely to FFDM. However, due to the systematic differences in mammographic measures from film and FFDM images and the small number of cases/controls with FFDMs, women with FFDM images were excluded from the main results.

There was no evidence of association of remoteness of residence or any of the sociodemographic variables with breast cancer risk in Aboriginal women, likely due to the frequency matching of Aboriginal controls to Aboriginal cases by screening location. However, the attempted matching of non-Aboriginal cases to Aboriginal cases by screening location did not result in similar ARIA and SEIFA distributions, with very few non-Aboriginal women residing in remote or very remote regions and much higher proportions

of non-Aboriginal women with higher SEIFA indices. Non-Aboriginal controls were frequency matched to non-Aboriginal cases (not Aboriginal cases) and the resulting ARIA distributions were very similar between non-Aboriginal cases and controls. Despite the matching, there was evidence that being more socially advantaged was associated with higher breast cancer risk in non-Aboriginal women, consistent with the literature [15–17].

In summary, even with a relatively small number of Aboriginal breast cancer cases ($n = 83$), this study showed strong evidence of association between mammographic density measures and breast cancer risk in Western Australian Aboriginal women. Aboriginal women with increased mammographic density are at increased risk of breast cancer relative to other Aboriginal women of similar age and non-dense breast area (pseudo-BMI). Breast cancer risk prediction models that incorporate mammographic density or efforts to standardize risk-associated mammographic density measures should take Aboriginal status into account where applicable.

Conclusion

BreastScreen WA is currently the only state-run BreastScreen program that notifies women if they have mammographically dense breasts. We have filled significant gaps in knowledge regarding the distribution and determinants of mammographic density in Aboriginal women and now its association with breast cancer risk. How this information will be used and its impact is currently under consideration in collaboration with the Aboriginal Women's Reference Group of BreastScreen WA. It is hoped that these study results can be utilized to provide better information to Aboriginal women and to inform mammographic screening approaches and policy in Australia.

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Data availability The datasets generated and analysed during the current study are not publically available but can be made available upon request (and pending approval) from Western Australia's Department of Health Data Linkage Branch and BreastScreen Western Australia.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Western Australian Department of Health Human Research Ethics Committee (Project #2014/50) and the Western Australian Aboriginal Health Ethics Committee (Project 581)) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent A waiver of informed consent was received to obtain access to de-identified linked data.

References

- Hopper JL (2015) Odds per adjusted standard deviation: comparing strengths of associations for risk factors measured on different scales and across diseases and populations. *Am J Epidemiol* 182(10):863–867. <https://doi.org/10.1093/aje/kwv193>
- McCormack VA, dos Santos Silva I (2006) Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiol Biomark Prev* 15(6):1159–1169. <https://doi.org/10.1158/1055-9965.EPI-06-0034>
- Evans DG, Astley S, Stavrinou P, Harkness E, Donnelly LS, Dawe S, Jacob I, Harvie M, Cuzick J, Brentnall A, Wilson M, Harrison F, Payne K, Howell A (2016) In: Improvement in risk prediction, early detection and prevention of breast cancer in the NHS Breast Screening Programme and family history clinics: a dual cohort study. Programme Grants for Applied Research. Southampton (UK). <https://doi.org/10.3310/pgfar04110>
- Evans DG, Donnelly LS, Harkness EF, Astley SM, Stavrinou P, Dawe S, Watterson D, Fox L, Sergeant JC, Ingham S, Harvie MN, Wilson M, Beetles U, Buchan I, Brentnall AR, French DP, Cuzick J, Howell A (2016) Breast cancer risk feedback to women in the UK NHS breast screening population. *Br J Cancer* 114(9):1045–1052. <https://doi.org/10.1038/bjc.2016.56>
- Stone J (2018) Should breast cancer screening programs routinely measure mammographic density? *J Med Imaging Radiat Oncol* 62(2):151–158. <https://doi.org/10.1111/1754-9485.12652>
- Burton A, Maskarinec G, Perez-Gomez B, Vachon C, Miao H, Lajous M, Lopez-Ridaura R, Rice M, Pereira A, Garmendia ML, Tamimi RM, Bertrand K, Kwong A, Ursin G, Lee E, Qureshi SA, Ma H, Vinnicombe S, Moss S, Allen S, Ndumia R, Vinayak S, Teo SH, Mariapun S, Fadzli F, Peplonska B, Bukowska A, Nagata C, Stone J, Hopper J, Giles G, Ozmen V, Aribal ME, Schuz J, Van Gils CH, Wanders JOP, Sirous R, Sirous M, Hipwell J, Kim J, Lee JW, Dickens C, Hartman M, Chia KS, Scott C, Chiarelli AM, Linton L, Pollan M, Flugelman AA, Salem D, Kamal R, Boyd N, Dos-Santos-Silva I, McCormack V (2017) Mammographic density and ageing: a collaborative pooled analysis of cross-sectional data from 22 countries worldwide. *PLoS Med* 14(6):e1002335. <https://doi.org/10.1371/journal.pmed.1002335>
- McLean K, Darcey E, Cadby G, Lund H, Pilkington L, Redfern A, Thompson S, Saunders C, Wylie E, Stone J (2019) The distribution and determinants of mammographic density measures in Western Australian aboriginal women. *Breast Cancer Res* 21(1):33. <https://doi.org/10.1186/s13058-019-1113-4>
- Roder D, Webster F, Zorbas H, Sinclair S (2012) Breast screening and breast cancer survival in aboriginal and Torres Strait Islander women of Australia. *Asian Pacific J Cancer Prev* 13(1):147–155
- Christensen D, Davis G, Draper G, Mitrou F, McKeown S, Lawrence D, McAullay D, Pearson G, Rikkers W, Zubrick SR (2016) Evidence for the use of an algorithm in resolving inconsistent and missing indigenous status in administrative data collections. *Aust J Soc Issues* 49(4):423–443
- Statistics ABo (2018). <http://www.abs.gov.au/websitedbs/census/home.nsf/home/seifa>
- Statistics ABo (2018). <http://www.abs.gov.au/websitedbs/d3310114.nsf/home/remoteness+structure>
- Byng JW, Boyd NF, Fishell E, Jong RA, Yaffe MJ (1994) The quantitative analysis of mammographic densities. *Phys Med Biol* 39(10):1629–1638
- Stone J, Ding J, Warren RM, Duffy SW, Hopper JL (2010) Using mammographic density to predict breast cancer risk: dense area or percentage dense area. *Breast Cancer Res* 12(6):R97. <https://doi.org/10.1186/bcr2778>
- Burton A, Byrnes G, Stone J, Tamimi RM, Heine J, Vachon C, Ozmen V, Pereira A, Garmendia ML, Scott C, Hipwell JH, Dickens C, Schuz J, Aribal ME, Bertrand K, Kwong A, Giles GG, Hopper J, Perez Gomez B, Pollan M, Teo SH, Mariapun S, Taib NA, Lajous M, Lopez-Ridaura R, Rice M, Romieu I, Flugelman AA, Ursin G, Qureshi S, Ma H, Lee E, Sirous R, Sirous M, Lee JW, Kim J, Salem D, Kamal R, Hartman M, Miao H, Chia KS, Nagata C, Vinayak S, Ndumia R, van Gils CH, Wanders JO, Peplonska B, Bukowska A, Allen S, Vinnicombe S, Moss S, Chiarelli AM, Linton L, Maskarinec G, Yaffe MJ, Boyd NF, Dos-Santos-Silva I, McCormack VA (2016) Mammographic density assessed on paired raw and processed digital images and on paired screen-film and digital images across three mammography systems. *Breast Cancer Res* 18(1):130. <https://doi.org/10.1186/s13058-016-0787-0>
- Meijer M, Bloomfield K, Engholm G (2013) Neighbourhoods matter too: the association between neighbourhood socioeconomic position, population density and breast, prostate and lung cancer incidence in Denmark between 2004 and 2008. *J Epidemiol Community Health* 67(1):6–13. <https://doi.org/10.1136/jech-2011-200192>
- Robert SA, Strombom I, Trentham-Dietz A, Hampton JM, McElroy JA, Newcomb PA, Remington PL (2004) Socioeconomic risk factors for breast cancer: distinguishing individual- and community-level effects. *Epidemiology* 15(4):442–450
- Webster TF, Hoffman K, Weinberg J, Vieira V, Aschengrau A (2008) Community- and individual-level socioeconomic status and breast cancer risk: multilevel modeling on Cape Cod, Massachusetts. *Environ Health Perspect* 116(8):1125–1129. <https://doi.org/10.1289/ehp.10818>

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