Characteristics of Mammographic Density for Women in China

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A thesis submitted in fulfilment of the requirements for the degree of

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Faculty of Health Sciences
University of Sydney

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Candidate's Statement

I, Tong Li, hereby certify that this submission is my own original work and that it contains no material previously published or written by another person or material which has to a substantial extent been accepted for the award of any other degree or diploma at any university or other institute, except where due acknowledgement has been made in the text. I further declare that all sources cited or quoted are indicated and acknowledged by means of a comprehensive list of references.

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Publications and Presentations

The work presented in this thesis has been published and presented in the following forums:

Publications

- Li T, Mello-Thoms C, Brennan PC. *Descriptive epidemiology of breast cancer in China: incidence, mortality, survival and prevalence.* Breast Cancer Research and Treatment. 2016. 159(3): p. 395-406.
- Li T, Li J, Dai M, Ren J, Zhang H, Mi Z, Heard R, Mello-Thoms C, He J, Brennan PC. *Mammographic density and associated predictive factors for Chinese women*. The Breast Journal. 2017 (accepted)
- Li T, Tang L, Gandomkar Z, Heard R, Mello-Thoms C, Shao Z, Brennan PC. *Mammographic density and other risk factors for breast cancer amongst women in China.* The Breast Journal. 2017 (accepted).
- Li T, Tang L, Gandomkar Z, Heard R, Mello-Thoms C, Di G, Gu Y, Xiao Q, Shao Z, Nickson C, Brennan PC. *Using AutoDensity percentage and area measures to characterise mammographic density and associated factors for women in China*. The Oncologist. 2017 (Submitted).

Presentations

Oral

- Li T, Tang L, Gandomkar Z, Heard R, Mello-Thoms C, Di G, Gu Y, Xiao Q, Shao Z, Nickson C, Brennan PC. *Breast density in Chinese women: using percentage and area* *measures from a quantitative technique*. 5th World Congress on Breast Cancer. June 2017. London, U.K.

- Li T, Li J, Dai M, Ren J, Zhang H, Mi Z, Heard R, Mello-Thoms C, He J, Brennan PC. *Mammographic density variations in urban China: associated agents and potential implications*. Sydney Cancer Conference 2016. September 2016. Sydney, Australia.
- Li T, Li J, Dai M, Ren J, Zhang H, Mi Z, Heard R, Mello-Thoms C, Brennan PC, *Variation in mammographic density and associated factors for Chinese women: Results from the National Cancer Screening Program in Urban China.* 4th International "Why Study Mammographic Density?" Meeting: The Measurement Challenge. August 2016. Kingscliff, Australia

- Li T, Li J, Dai M, Ren J, Zhang H, Mi Z, Heard R, Mello-Thoms C, Brennan PC. *Breast density in China.* 2016 Sydney Catalyst Postgraduate and Early Career Researcher Symposium. April 2016. Sydney, Australia.

- Li T, Li J, Dai M, Ren J, Zhang H, Mi Z, Heard R, Mello-Thoms C, He J, Brennan PC. *Mammographic density variations in China: causal agents and potential implications.* Asian Pacific Organisation for Cancer Prevention APOCP 8th General Assembly. April 2016. Brisbane, Australia.

- Li T, Li J, Dai M, Ren J, Zhang H, Mi Z, Heard R, Mello-Thoms C, He J, Brennan PC. *Mammographic density variations in China: causal agents and potential implications*. 2015 Postgraduate Cancer Research Symposium. December 2015. Sydney, Australia.

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- Li T, Mello-Thoms C, Brennan PC. *Comparison of breast density and cancer presentation between women from China and Australia.* 2015 Sydney Catalyst Postgraduate and Early Career Researcher Symposium. April 2015. Sydney, Australia.

- Li T, Mello-Thoms C, Brennan PC. *A New Chinese Journey: breast cancer diagnostics.* 2014 Three Minutes Thesis Competition. June 2014. Sydney, Australia

Poster

- Li T, Tang L, Gandomkar Z, Heard R, Mello-Thoms C, Di G, Gu Y, Xiao Q, Shao Z, Nickson C, Brennan PC. *Determinants of mammographic density in Chinese women: using percentage and area measures from AutoDensity algorithm*. 34th Annual Miami Breast Cancer Conference. March 2017. Miami Beach, the U.S.
- Li T, Tang L, Gandomkar Z, Heard R, Mello-Thoms C, Shao Z, Brennan PC. *Breast density and other factors for breast cancer risk for Chinese women.* 15th St. Gallen International Breast Cancer Conference. March 2017. Vienna, Austria.

- Li T, Mello-Thoms C, Brennan PC. *Comparison of breast density and cancer presentation between women from China and Australia*. Annual Higher Degree Research (HDR) Students Conference. November 2014. Sydney, Australia.

Awards

- Winner, Three Minute Thesis (3MT) Competition, The University of Sydney, 2017

Preface

This thesis explored characteristics of mammographic density for women in China. The work consists of six chapters and includes the candidate's publications, accepted articles and those under consideration for publication along with bridging sections, as stated in the University of Sydney guidelines for thesis containing publications. Each chapter is able to be read independently and the layout of the thesis is shown as follows.

- Chapter one is an introduction to the thesis, providing an overview of background of mammographic density in China, an outline of the deficiencies around the topic and aims and objectives of the thesis in the context of these deficiencies.
- Chapter two is a literature review of the literature on epidemiology of breast cancer in China as well as risk factors. This paper is presented as published in the *Breast Cancer Research and Treatment.*
- Chapter three presents a cross-sectional study which established mammographic density distribution for women without breast cancer and identified factors associated with density using Breast Imaging Reporting and Data System (BI-RADS) breast composition classifications, based on data from a national screening cancer program. This paper is accepted for publication by *The Breast Journal.*
- Chapter four is a study identified prospective factors for mammographic density in Chinese women using a quantitative algorithm named AutoDensity. The study aims to establish statistical models of mammographic density prediction for Chinese females both with and without breast cancer. This work was submitted to *The Oncologist.*
- Chapter five is a cross-sectional study which examined the potential relationship between mammographic density and breast cancer for females in China with density being measured by the AutoDensity algorithm. This study was accepted for publication

in *The Breast Journal*.

- Chapter six is a discussion which described the overview of thesis, implications, limitations, future works and conclusion.

Each chapter contains its own reference list. Ethic approval has been obtained for this work prior to any data collection. The appendices at the end of the thesis contain a copyright permission letter, title slides for conference presentations and ethical approval letters.

Abstract

Objectives

Mammographic density is considered an important risk factor for breast cancer but the characteristics of density for Chinese women are under-studied. The purpose of this study is to understand the characteristics of mammographic density for women in China using both qualitative and quantitative assessment approaches.

Methods

This work consists of three studies. The first one was a cross-sectional study using mammographic cases of 4,867 women without breast cancer and mammographic density was assessed using the BI-RADS density classification (4th edition). Spearman correlations examined the relationship between BI-RADS values and continuous variables, whilst Mann-Whitney Tests and Kruskal-Wallis Tests were conducted to assess categorical variables. The BI-RADS density was then recoded into a dichotomous variable: low density (BI-RADS 1&2) and high density (BI-RADS 3&4). Factors that were found to be statistically significant based on the above tests were entered into binary logistic regression to produce odds ratios for the dichotomous density values. The second study identified factors associated with mammographic density with density being measured by a quantitative algorithm. A total of 1071 (84 with and 987 without breast cancer) women were recruited and density was measured using an automatic algorithm AutoDensity and expressed in both percentage density and area (area of dense tissue) format. Pearson tests were performed to examine relationships between density and continuous variables and t-tests were conducted to compare differences of mean density values between groupings of categorical variables. Multivariate models were built using variables that were found to be statistically significant with the Pearson and t-tests. The third study examined the potential relationship between mammographic density and breast

cancer using the same data from the second study. Baseline differences in the characteristics of the two groups of women with and without breast cancer were examined by using t-tests and chi-square tests, and odds ratios were produced by binary logistic regression. A statistical model was built using multiple logistic regression. These tests were repeated after separating the data sets based on menopause status.

Results

The first (BI-RADS) study showed negative associations ($p < 0.001$) between BI-RADS density and age (rho = -0.23), Body Mass Index (BMI) (rho = -0.18) and weight (rho = -0.16). Density was statistically significantly different ($p < 0.05$) across educational, province of residence and occupation groups. Women with a history of early age of menarche, pre-menopausal status, nulliparity, no breastfeeding and benign breast disease demonstrated increased mammographic density compared with women without such histories ($p < 0.05$). The second (AutoDensity) study found that for women without breast cancer, weight and BMI ($p < 0.01$) were found to be negatively associated ($r = -0.24$, $r = -0.27$) with *percentage density* (PD) whereas positively associated ($r = 0.11$, $r = 0.10$) with *dense area* (DA); lower PD was found within women with secondary education background or below compared to women with tertiary education. There is no associations ($p > 0.05$) for smoking history, alcohol consumption and family history of breast cancer. For women with breast cancer, PD demonstrated similar relationships with those of cancer-free women whilst breast area was the only factor associated with DA ($r = 0.74$, $p < 0.001$). The third study did not find any association between PD or DA and breast cancer amongst all ($p = 0.23$; $p = 0.34$), pre-menopausal ($p = 0.24$; $p = 0.48$) and post-menopausal women ($p = 0.12$; $p = 0.26$).

Conclusions

For the first time in China, this work has shown distribution of Chinese mammographic density and demonstrated important associations between mammographic density and demographic, lifestyle, menstrual, reproductive and familial factors with density being assessed using both qualitative and quantitative methods. Differences between the two quantitative density metrics (PD and DA) emphasise the importance of better understanding what each metric represents for both women with and without breast cancer and ensuring that approaches are standardised for both types of women. The findings should be useful to policy makers responsible for breast cancer preventative strategies so that the impact of this increasingly important health policy issue is minimised.

Chapter One

Introduction

1.1 Breast anatomy and composition

The breast is situated between the superficial and deep layers of the superficial fascia on the anterior chest wall (Figure 1.1). It extends longitudinally over the pectoralis major muscle from the 2nd rib to the 6th intercostal cartilage and is positioned transversely from the edge of the sternum to the anterior axillary line [1]. The axillary tail extends beyond the outer border of the pectoralis major. The breast is firmly attached to the skin by suspensory or Cooper's ligaments, which connect the anterior and posterior fascial plans. These ligaments represent the supporting structurers of the breast and provide the shape of the parenchyma.

The skin of the nipple is pigmented and extended radially 1-2 cm to form the areola, on which small sebaceous glands (named Glands of Montgomery) present. Approximately 15-20 lactiferous ducts open into the epidermis of the nipple, and as they approach the nipple these ducts become wider to form lactiferous sinuses [1]. There is no fat immediately beneath the nipple areola.

The arterial supplies to the breast arise from the internal thoracic, lateral thoracic and intercostal arteries, and the venous drainage is to the axillary, internal thoracic and posterior intercostal veins [1]. The lymphatic drainage of the breast is mostly (>75%) provided by axillary lymph nodes with a relatively less amount provided by internal mammary, pectoral and subcutaneous nodes [2].

Two layers of pectoral fascia present within the breast, superficial and deep layers, which are connected by Cooper's ligaments. Three types of tissue, fibrous, glandular or secretory and adipose or fatty tissue, exist between superficial and deep fascia. The fibrous and glandular (commonly referred to as fibroglandular) tissue contains higher concentration of epithelial cell, stromal cell and collagen than adipose tissue [3, 4].

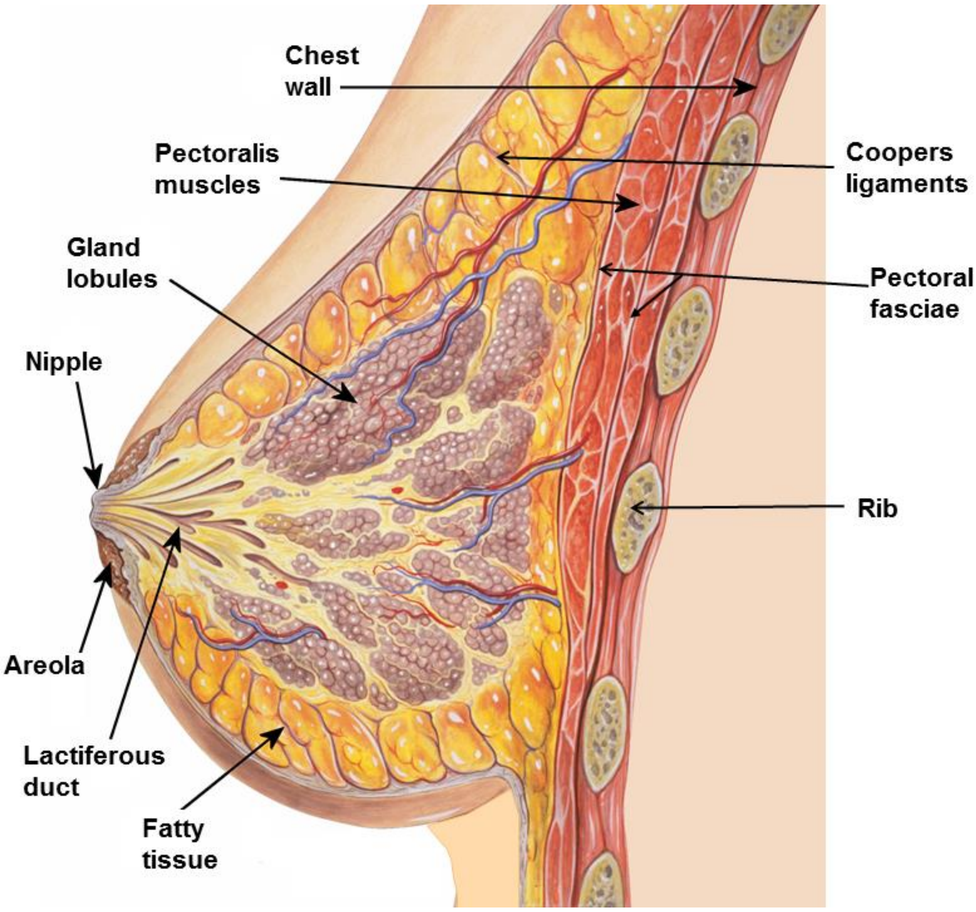

Figure 1.1: Appearance of the breast (reproduced with minor modification with permission from the medical illustrator Patrick J. Lynch (Appendix 1)).

1.2 Radiographic appearances of breast tissue and mammographic density

The mammographic appearance of the breast is determined by the relative composition of fatty and fibroglandular tissue since fatty tissue is relatively radio-lucent whereas fibroglandular tissue is relatively radio-opaque [6]. Fatty tissue therefore attenuates very little of the X-ray beam (depicts as dark on an image) whilst the fibroglandular tissue attenuates a great amount and allows very little of the X-ray beam to reach the image (shows as white) (Figure 1.2). It is the difference in attenuation between these two types of tissue and all the varying degrees of 'greyness' in between which provides the contrast of mammogram. Therefore, the greater the density of the breast tissue in terms of quantity and extent of the fibroglandular tissue, the greater is the area of radio-opacity demonstrated on the image. Another component of visible mammographic density on an image are ducts, which is commonly seen as white and thin linear structures emanating from the nipple. Mammographic density therefore refers to the proportion of the breast that is composed of radio-opaque (white) area in a mammogram.

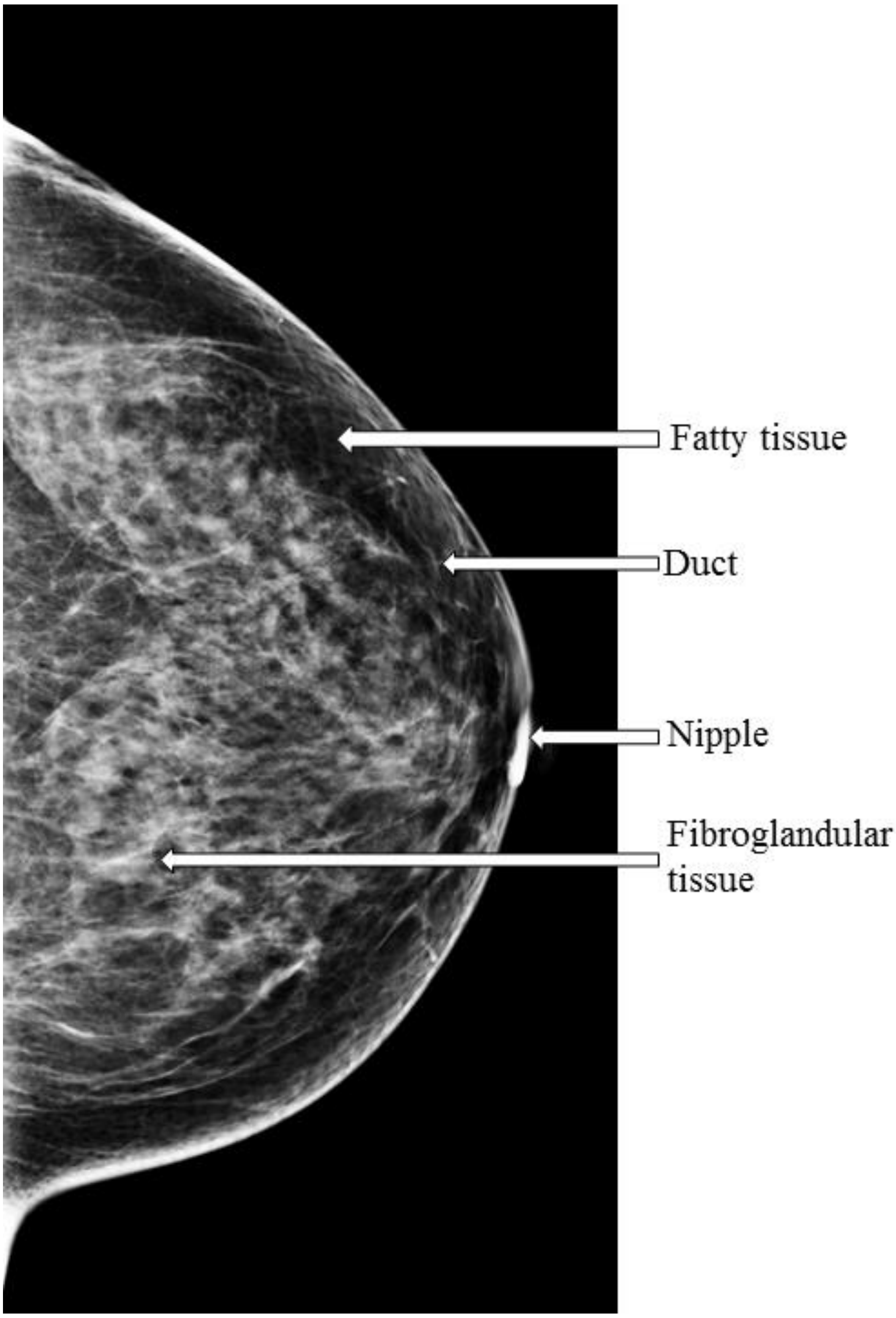

Figure 1.2: Mammographic appearance of the breast (left cranio-caudal view).

1.3 Mammographic density and breast cancer risk in westernised countries

Mammographic density represents the amount of fibroglandular tissue and it is consistently demonstrated as an important risk factor for breast cancer in westernised countries [6-9]. It was suggested that women with highest density were shown to have 2 to 6 times higher risk in developing breast cancer compared to those with the lowest [6, 7, 9-11] and mammographic density is also shown to be associated with approximately 50% of interval breast cancer [6, 11]. The positive association between mammographic density and breast cancer was demonstrated in many epidemiological studies using both qualitative and quantitative methods. The most commonly used qualitative method worldwide in both clinical and screening settings is Breast Imaging Reporting and Data System (BI-RADS) breast composition classifications, which was developed by the American College of Radiology in 2000 [12]. The BI-RADS classifications describes implications of the assigned mammographic density category and areas on the image where cancer is likely to be missed [13]. The association between mammographic density and breast cancer risk was consistently demonstrated by this measure in previous studies, particularly for post-menopausal women [9]. However, the BI-RADS classification has been shown to suffer limited reproducibility with wide inter- (kappa = 0.02-0.77) and intra-reader (kappa = 0.32-0.88) variations largely due to the variations in image appearance/quality and perception of radiographic features [14-19]. This subjectivity has the potential to result in inconsistent breast cancer risk prediction and unnecessary discrepancies in decision-making for density assessment [12].

1.4 Factors associated with mammographic density in westernised countries

Many epidemiological studies have shown well confirmed associations between mammographic density and causal agents predominantly focusing on demographic and reproductive agents [20-23]. Younger age, lower BMI and reduced weight have been shown to be associated with higher mammographic density for several decades [8, 22, 24, 25]. Younger women and women with high BMI were commonly reported to have almost fatty to scattered fibroglandular breast features on mammography [26, 27]. Education-dependent density differences were also reported with women with higher education experiencing denser breasts compared to individuals with lower level of education [23, 28, 29]. The effect of level of education in the mammographic density was predominately apparent in the highest education category. There was little evidence that reproductive factors explained this association but the area of residence possibly and partially impacted on this association since mammographic density was shown to be greatest among women living in the most affluent areas compared to those living in the deprived regions [28]. Pre-menopausal status, nulliparity, late age at first delivery, a smaller number of live births and family history of breast cancer were also shown to be positively associated with higher mammographic density in studies conducted in North America focusing on Caucasian women [21-23]. These density related factors were reported to link to age and hormonal influences on the epithelial, stromal and adipose tissues in the breast [21, 30].

The relationships between mammographic density and lifestyle factors have not been consistently established and are sometimes contradictory. The available data around associations between density and smoking history and alcohol consumption are inconsistent. Some studies found a positive association with alcohol consumption [31-36] and a negative association with smoking history [37-39], whereas others showed no associations [40-43]. The relationship between physical activity and mammographic density was summarised in a literature review published in Integrative Cancer Therapies in 2016, which found that more than 80% of the studies reported no association, yet other studies found physical activity was negatively associated with mammographic density in peri-menopausal and post-menopausal women [44].

1.5 Mammographic density and associated factors in China

Characteristics of mammographic density have been under-studied in China. From the limited data that are available regarding Chinese mammographic density, the findings are not necessarily consistent. One large observational study (with over 6,000 women) involving 4 large Chinese cities reported that Chinese women predominantly (80%) experienced scattered fibroglandular and heterogeneous mammographic density compared to a minority of women (20%) having almost extremely fatty or extremely dense breasts, however the density values were almost equally distributed between the lower (BI-RADS 1&2) and upper (BI-RADS 3&4) groupings [45], a finding consistent with studies involving Asian women living in western countries [46, 47]. Another single-city based study which recruited more than 3,000 women, in contrast, reported that the number of women with high dense tissue are nearly 10% higher than individuals with low dense breasts [48], which is similar to the distribution of mammographic density in women in North America [49, 50]. The disparity of density distributions might highlight the variation in breast tissue composition due to population difference and geographic locations.

The findings regarding the relationship between mammographic density and breast cancer risk were also inconsistent in these two studies: the former study found no association between density and cancer risk [45] whereas the latter study reported that compared to women without breast cancer, mammographic density was lower and higher for cancer women within the 40-49 and 55-71 age groups, respectively, and there was no association for women aged 50-54 [48].

From the paucity of data that are available, studies examining determinants of mammographic density mainly focused on reproductive and hormonal factors. It appears that women with pre-menopausal status, earlier age at menarche, nulliparity, younger age at first delivery and history of benign breast disease were more likely to have dense breasts [45]. Longer breastfeeding duration and larger breast size were also found to be negatively associated with mammographic density in pre-menopausal women [51].

1.6 Knowledge deficiencies in the literature

These are the deficiencies:

- Factors associated with mammographic density are under-studied for Chinese females. In previous studies which examined determinants of mammographic density in Chinese women, the associations predominantly focused on reproductive agents and these assocations were not consistently demonstrated. Besides, the demographic (e.g. age, BMI and ethnicity) and lifestyle factors (e.g. smoking history, alcohol comsumption and physical activity) are not fully understood, which requires research and will be explored in this thesis.
- All previous studies regarding Chinese mammographic density used the qualitative method of Breast Imaging Reporting and Data System (BI-RADS) breast composition classifications, which is the most commonly used assessment approach of mammographic density in both clinical settings and screening programs in China and many other countries [52, 53]. However, of all the available methods, the BI-RADS classification appears to be the least reliable due to strong subjectivity and limited reproducibility [8]. Therefore the density measurements using quantitative methods is in urgent demand.
- Only two peer-reviewed articles have examined the relationship between mammographic density and breast cancer for women in China. The findings from these two papers are inconsistent: one study which recruited 86 and 28,302 women with and without breast cancer, respectively, from a screening trial across 4 large Chinese cities

showed no association between density and cancer [45]; in contrast another large cross-sectional study, involving 2,527 cancer and 3,394 cancer-free women, reported that, compared to women without breast cancer, mammographic density was lower and higher for cancer women within the 40-49 and 55-71 age groups, respectively, however there was no association for women aged 50-54 [48]. These inconsistent findings therefore require further investigation and refinement.

In view of these deficiencies, the focus of this thesis is to identify the casual agents associated with mammographic density for women in China using both qualitative and quantitative methods and to examine the potential association between mammographic density and breast cancer risk. Without this knowledge, researchers, clinicians and policy makers cannot confidently apply scientific conclusions from westernised countries directly to Chinese women nor can they make appropriate decisions on breast cancer preventative strategies.

1.7 Aims and objectives of this thesis

The aim of this thesis is to investigate mammographic density in women in China.

The objectives are:

- To identify demographic, lifestyle, reproductive and familial factors associated with mammographic density for Chinese women without breast cancer, based on data from a national screening program, using the BI-RADS breast composition classification.
- To identify factors associated with mammographic density using a recently developed algorithm, and based on the data to establish statistical models of mammographic density prediction for Chinese females both with and without breast cancer.

- To initially examine the possibility of mammographic density being a potential risk factor for breast cancer for Chinese females.

1.8 Thesis structure

The scope of this work involves investigating the variations of mammographic density for Chinese females. The thesis is structured in the following manner:

- Chapter two provides a detailed literature review on the descriptive epidemiology of breast cancer in China, in terms of incidence, mortality, survival and prevalence, and explores relevant factors such as age of manifestation, geographic locations and recent and long-term trends. To benchmark the data presented, regular comparisons are made with westernised values, particularly those arising from the United States and Australia, the former being the largest of typical westernised countries and the latter being the closest to China.
- Chapter three determines the distribution of mammographic density in Chinese females using BI-RADS classification and explores the associations with a large number of demographic, environmental, lifestyle, menstrual, reproductive and familial factors.
- Chapter four identified predictors of mammographic density for both Chinese women with and without breast cancer using a quantitative algorithm AutoDensity.
- Chapter five explored the possibility of mammographic density being a potential risk factor for breast cancer for Chinese females.
- Chapter six presents a discussion which describes the overview, implications, limitation and future directions of the thesis.
- A bridging section is inserted at the beginning of each chapter.

- The papers contained within Chapters three and five were contracted to meet the journal requirements. However additional information was contained in the original manuscript and therefore the full manuscript for these chapters are shown in Appendix 2.

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Chapter Two

Descriptive epidemiology of breast cancer in China: Incidence, mortality, survival and prevalence

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Lab meeting, Brain and Mind Centre, Sydney, Australia, April 2015 (Appendix 3.1)

2.1 Bridging section for chapter two

From the Knowledge Deficiencies in the Introduction, it was stated that limited studies are available regarding mammographic density for women in China. Therefore, it was necessary in the first instance to conduct a literature review focusing on the descriptive epidemiology of breast cancer in China, in terms of incidence, mortality, survival and prevalence, including issues around mammographic density wherever possible. Relevant factors of breast cancer epidemiology such as age of manifestation, geographic locations and recent and long-term trends were also explored. The purpose of this literature review was to provide readers with a detailed understanding of the status of breast cancer in China, thus providing a platform and context on which our future investigations could be based.

2.2 Statement from author confirming authorship contribution of the PhD candidate

As a co-author of the paper "Descriptive epidemiology of breast cancer in China: incidence, mortality, survival and prevalence", we confirm that Tong Li has made the following contributions:

- Conception and design of the literature review
- Guarantor of the integrity of the entire study
- Literature search
- Manuscript preparation
- Manuscript editing and critical appraisal of content

Claudia Mello-Thoms …………………………………… Date: 8/5/2017

Patrick C. Brennan …………………………………… Date: 8/5/17

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REVIEW

Descriptive epidemiology of breast cancer in China: incidence, mortality, survival and prevalence

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Abstract Breast cancer is the most common neoplasm diagnosed amongst women worldwide and is the leading cause of female cancer death. However, breast cancer in China is not comprehensively understood compared with Westernised countries, although the 5-year prevalence statistics indicate that approximately 11 % of worldwide breast cancer occurs in China and that the incidence has increased rapidly in recent decades. This paper reviews the descriptive epidemiology of Chinese breast cancer in terms of incidence, mortality, survival and prevalence, and explores relevant factors such as age of manifestation and geographic locations. The statistics are compared with data from the Westernised world with particular emphasis on the United States and Australia. Potential causal agents responsible for differences in breast cancer epidemiology between Chinese and other populations are also explored. The need to minimise variability and discrepancies in methods of data acquisition, analysis and presentation is highlighted.

Keywords Breast cancer · China · Incidence · Mortality · Survival · Prevalence

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Introduction

Breast cancer is the most common neoplasm diagnosed amongst women worldwide and is the leading cause of female cancer death [1]. It is globally estimated that over one million people are diagnosed with breast cancer annually and at least 400,000 females will die from the disease every year, accounting for 14 % of total cancer deaths [2–4]. The highest incidence and prevalence rates of breast cancer are recorded in North America, Australia and New Zealand as well as Northern and Western Europe, and lowest in Eastern Asia [5]. In China, much less is known; however, from the limited data that are available, features such as prevalence and age of manifestation appear to be quite different compared to Westernised populations.

China has a relatively low incidence of breast cancer compared with other countries. The China National Cancer Centre (2011) reported 248,620 new breast cancer cases in females, corresponding to an age-standardised incidence rate of 29 per 100,000 Chinese women, which favourably compares with approximately 120 per 100,000 in Westernised population [6]. The incidence, however, has increased by 20–30 % over the past three decades and annually grows by 3–5 % according to Chinese urban cancer registries [3, 7, 8], this increase being substantially higher than the worldwide average increase of 1.5 % [9, 10]. It has been predicted that by 2021, the cases of breast cancer in China will reach 2.2 million amongst women aged 35–49 years in 2001, corresponding to more than 100 new cases per 100,000 women [11]. In China, breast cancer is most frequently diagnosed in the 40–50 year age group with a mean age of 48–49, which is more than 10 years younger than that reported in Westernised countries [12–14].

Even though the breast cancer incidence rate is low, the absolute number of deaths tends to be high in China because of the large population. Consequently even small increases in the incidence of breast cancer will result in a substantial loss of life. During the last two decades (1990–2010), the number of deaths from breast cancer increased 78 % from 29,200 to 52,500 across all age categories [15].

This review will provide an overview of recent breast cancer statistics in China and long-term trends in terms of incidence, mortality, survival and prevalence. Also, possible explanations for the unique nature of Chinese breast cancer will be explored. To benchmark the data presented, regular comparisons will be made with Westernised data, particularly those arising from the United States and Australia, the former being the biggest typical Westernised country and the latter being the closest to China. The data discussed should be of value to policy makers in China and elsewhere who are considering the implementation and implications of population-based breast cancer screening programs.

Incidence

Breast cancer is the most commonly diagnosed neoplasm in Chinese females, with an age-standardised rate (ASR) of 29 per 100,000 in 2011, being accountable for 17 % of total reported cancers in women [6]. Between 2003 and 2011,[1] the ASR of breast cancer increased from 21 to 29 per 100,000 women, whereas the proportion of breast cancer within total reported cancer cases in females fluctuated slightly over the same time period (Fig. 1a) [16–24].

For comparison purposes, the age-standardised incidence rates of Australia and the United States from 2003 to 2011 are presented in Fig. 1b along with that of China [16–26]. During this time period, the incidence rate of female breast cancer in China was approximately one-fifth of that within the two other countries. However, despite a relatively lower incidence and due to the large Chinese population of 1.31 billion residents, the observed number of new cases (248,620 cases in 2011) is higher than that reported in the same year for either Australia (14,290 cases) or the U.S. (194,860 cases) [6, 26, 27]. Nonetheless these inter-country ratios are dynamic, and one year later, in 2012, 11.2 % of all newly diagnosed breast cancer across the world was estimated to occur in China, which was second to the U.S. at 13.9 % [28]. Whichever numbers are accepted, published values for China most likely under-represent the true figures since the estimate is derived from recorded data involving approximately 10 % of the total population [28–31]. On the other hand, the American estimate is based on national data covering 95 % of the U.S. population [26].

The reasons for the noticeable differences in incidence rates in China compared with typical Westernised states are most likely multi-factorial, including unavailability of early detection through comprehensive population-based screening, exclusion of unsuspected asymptomatic breast cancers and variations in lifestyle and reproductive activity [1, 12, 32–35].

Incidence by age

In China, female breast cancer is strongly related to age, with the incidence rate being fairly low in women up to 30-year old and increasing quickly until peaking at start of the fifth decade [29–31, 36]. Amongst breast cancer admissions in China, approximately two in three are diagnosed amongst women aged 40–59, whilst relatively very few (roughly 6 %) are diagnosed in those aged 70 and over [12, 13, 37–40]. The China National Cancer Centre reports demonstrated that between 2005 and 2009 the incidence rate was highest in females aged 50–54 being 92–108 per 100,000 Chinese women (Fig. 1c, Supplementary Table A) [21, 29, 30, 41, 42]. However, an earlier report (2004) showed the rate peaked between the age of 45–49 (89 per 100,000), marginally ahead of the 50–54 age category (88 per 100,000) [22]. It is likely that this discrepancy is due to the timing of the reports since in the 1980s in Shanghai the incidence peaked within 40–44-year old but peaked in the 50–54-year old a decade later [37].

Although this shifting of incidence peaks to older age groups during the last three decades, the peak age is still substantially younger than that in Westernised populations, where the highest incidence occurs within the 65- to 69- and 75- to 79-year old in Australia and the United States, respectively (Fig. 1d) [25, 30, 43]. This substantial dissimilarity is also demonstrated with mean age values. The mean age at diagnosis of Chinese breast cancer is 49, which is conspicuously different from the Westernised world where the mean age values are 60 (Australia) and 61 (the U.S.), respectively [14, 27, 43]. This demonstrates that breast cancer in China affects women at least a decade earlier when compared with women from Australia and the U.S. It is likely that the differences in life expectancy (75, 83 and 81 years in China, Australia and the U.S. respectively), age structure of populations and environmental risk factors are at least partly responsible for the variations seen [30, 37, 39, 44–47].

In addition, unlike Australia and the United States, in China the slope of the incidence-age group curve after menopause becomes flat specifically for the group

[1] The population-based data regarding specific cancer from China National Cancer Centre is available since 2003.

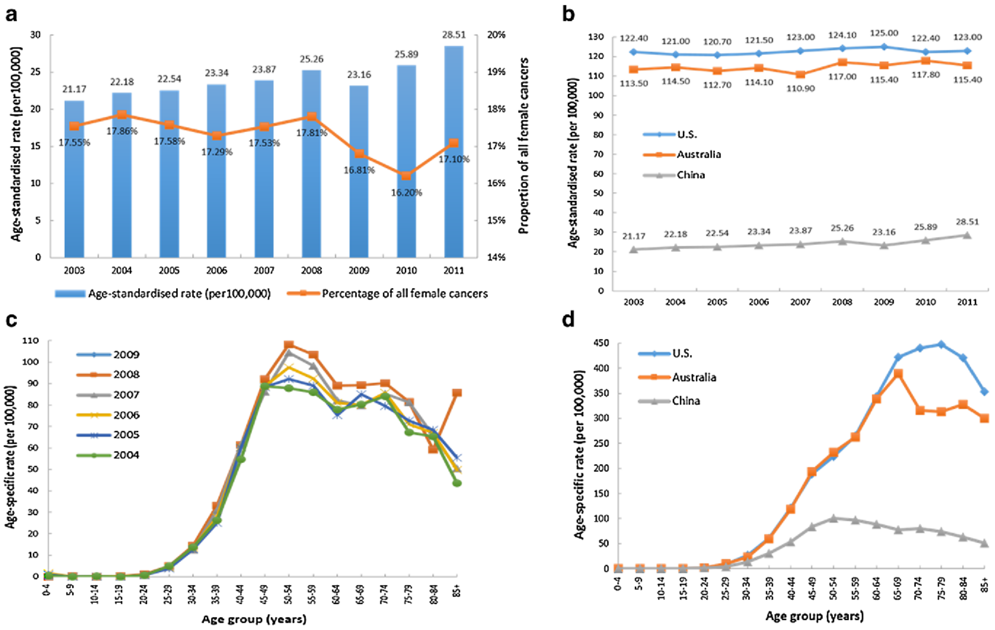

Fig. 1 **a** Incidence rates of female breast cancer in China from 2003 to 2011. Percentage amongst total reported female cancers in 2003 refers to the average percentage amongst total reported female cancers from 2003 to 2007. **b** Incidence rates of female breast cancer in China, Australia and the United States from 2003 to 2011. **c** Age-specific incidence rates of female breast cancer in China from 2004 to 2009. **d** Age-specific incidence rates of female breast cancer in China, Australia and the United States. The age-specific incidence rate in the United States refers to the average rate of 2008–2012; the age-specific incidence rates in China and Australia refer to the rates of 2009

60–69 years and then shows a downward trend from the age of 70 (Fig. 1c, d) [36]. This unique Sino-dependent pattern is a possible reflection of an increasing incidence within earlier generations of the female population rather than a real absolute decrease in risk with age [48]. Again, the reasons for the age-specific incidence rate in China are partly attributed to reproductive and environmental factors [11, 37, 49, 50].

Geographical distribution of incidence

The incidence of female breast cancer varies by geographic regions in China. Breast cancer is more commonly diagnosed in women within regions close to the East coast (25.5 per 100,000) compared with women from Central and Western China (18.9 per 100,000) [51]. This is partly due to socioeconomic variations, inequality of accessibility to health services and varying levels of diagnostic accuracy [8, 52].

In urban areas, breast cancer is the most common cancer diagnosed amongst women, a factor of two higher than the incidence rate in rural locations [52]. During the period from 1998 to 2007, the average urban ASR was 31.3 compared with 12.1 per 100,000[2] in rural regions with an average annual increase of 3 and 5 %, respectively [36]. These significant differences between cities and rural locations probably result from varying levels of exposure to Westernised lifestyles and associated environmental risk factors [30, 53]. Such Westernised influences may also explain the older median age (50.2 ± 11.6 years old) of urban females with breast cancer compared with their rural counterparts (48.5 ± 10.5) [54, 55].

Whilst the incidence rate remained higher in urban locations between 2003 and 2011, the ASR of breast cancer increased almost 1.4 times as rapidly in rural (13 per 100,000) than in urban locations (9 per 100,000), resulting in a reduction of regional disparities (Table 1) [16–24]. This quick growth in rural breast cancer is unlikely to be fully explained by the availability of a free breast cancer screening program in rural areas commencing from 2009 [56–58]. It is also worth noting that concomitantly, the incidence curves by age were similar in direction for both

[2] Average ASR has been standardised to world Segi's population.

Table 1 Incidence and mortality of female breast cancer by remoteness area, China, 2003–2011

Year	Incidence									Mortality								
	All areas			Urban			Rural			All areas			Urban			Rural		
	ASR[a]	Prop[b]	Ranking[c]	ASR[a]	Prop[b]	Ranking[c]	ASR[a]	Prop[b]	Ranking[c]	ASR[a]	Prop[b]	Ranking[c]	ASR[a]	Prop[b]	Ranking[c]	ASR[a]	Prop[b]	Ranking[c]
2011	28.51	17.10	1st	33.66	19.47	1st	22.59	14.11	2nd	6.57	7.88	6th	6.95	8.67	5th	6.17	7.04	5th
2010	25.89	16.20	1st	30.50	17.64	1st	20.78	14.34	1st	6.56	7.90	5th	7.19	8.59	5th	5.78	7.09	5th
2009	23.16	16.81	1st	27.32	18.80	1st	13.69	11.27	4th	4.94	7.54	5th	5.41	8.55	5th	3.80	5.24	6th
2008	25.26	17.81	1st	28.35	19.43	1st	12.48	9.84	4th	4.90	7.41	5th	5.20	8.20	5th	3.59	4.50	6th
2007	23.87	17.53	1st	27.14	19.47	1st	12.60	9.93	4th	4.61	6.95	6th	4.85	7.72	5th	3.74	4.68	6th
2006	23.34	17.29	1st	26.42	19.18	1st	10.64	8.55	5th	4.71	6.86	6th	4.89	7.62	5th	3.52	4.24	6th
2005	22.54	17.58	1st	26.42	20.00	1st	9.88	8.43	5th	5.00	7.47	6th	5.35	8.48	5th	3.84	4.70	6th
2004	22.18	17.86	1st	25.96	20.14	1st	9.84	8.97	5th	4.80	7.28	5th	5.24	8.28	4th	3.46	4.55	5th
2003	21.17	17.55	1st	24.61	19.62	1st	9.22	8.42	5th	4.87	7.31	6th	5.42	8.30	5th	2.93	4.13	6th

Percentage of all female cancers in 2003 refers to the average percentage of all female cancers from 2003 to 2007

[a] Age-standardised rate (per 100,000) of female breast cancer within corresponding areas

[b] Proportion of female breast cancer cases amongst all reported cancer cases in female within corresponding areas

[c] Ranking of female breast cancer amongst all reported female cancers within corresponding areas

locations [29, 30]. However, the age-specific incidence rate in cities remained at a peak between the ages of 50–54 (Supplementary Table B), whilst in rural regions, initially the peak age was 5 years older at 55–59 but became identical to that of urban locations (ages of 50–54) in 2009 (Supplementary Table C) [21, 22, 29, 30, 41, 42].

As reported above, between 2003 and 2011, the breast cancer rate continued to increase in China regardless of location. It is expected that this increase was at least in part due to the increasing number and effectiveness of national cancer registries, which experienced a sevenfold growth during this time from 35 to 243, with the population being covered by the registries almost tripling from 4.34 to 13.01 % [6, 23, 59]. At the same time, there was also a notable improvement in the quality of the data collected [6, 60, 61].

It is also important to note that the breast cancer incidence rate has been growing relatively steadily over the last three decades in Hong Kong, a well-developed region in China, and the incidence rate was 1-3 times higher than that in other parts in China between the 1970s and 1990s [62–64]. The ASR was 27.7 per 100,000 women in 1973–1999 and increased to 45.9 in 1999–2003 with an average annual increase rate of 1.2 % during the time period, at least in part influenced by socioeconomic developmental and continued adoption of Westernisation lifestyles [62, 64, 65]. The incidence rate is predicted to increase by approximately 1.7 % per year over the next 10 years, from 56.7 per 100,000 in 2011–2015 to 63.5 in 2021–2025 [66].

Incidence trends over the last 50 years

The incidence rate of female breast cancer has been increasing since the late 1960s, with this upward trend occurring more rapidly from the late 1980s [67–69]. In terms of the urban–rural disparities, breast cancer rose quinquennially by nearly 20 and 40 % in urban and rural regions, respectively, since the early 1990s [7, 37, 52, 70, 71]. Overall this means that the incidence rate of breast cancer rose by 68 and 166 % in urban and rural locations, respectively, from the period 1989–1993 to 2004–2008 [70].

Recently, the incidence of breast cancer in China has been maintained at a fairly steady rate of 3–5 % every year in contrast to the annual increase of 0.2 % in Australia and 0.5 % in the U.S. [3, 9, 10, 43, 72, 73]. At this rate of growth, a proliferation of Chinese breast cancer cases is expected over the next decade. For example, it was estimated that by 2021, 2.5 million cases of breast cancer would be reported amongst Chinese women who were aged between 35 and 49 years in 2011, even though the predicted cases could be restricted to 2.2 million if recent

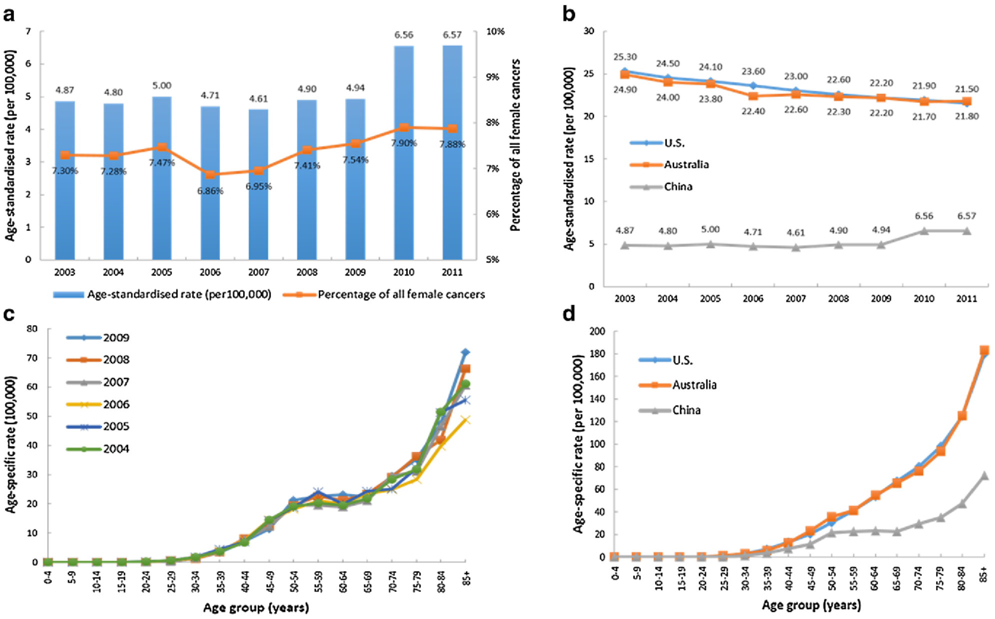

Fig. 2 **a** Mortality rates of female breast cancer in China from 2003 to 2011. Percentage of death number amongst total reported female cancer cases in 2003 refers to the average percentage of death number amongst total reported female cancer cases from 2003 to 2007. **b** Mortality rates of female breast cancer in China, Australia and the United States from 2003 to 2011. **c** Age-specific mortality rates of female breast cancer in China from 2004 to 2009. **d** Age-specific mortality rates of female breast cancer in China, Australia and the United States. The age-specific mortality rate in the United States refers the average rate of 2008–2012; the age-specific mortality rates in China and Australia refer to the rates of 2009

campaigns around reduced alcohol consumption, less use of postmenopausal hormone and limited adult obesity are effective [11]. Taking age structure and population size into account, it is anticipated that the age-standardised incidence rate will increase to 85 per 100,000 women aged 35–69 by 2021—a tripling of currently reported levels [74].

For all these estimates, the number of breast cancer cases might be exaggerated since the modelling approaches employed were based on Westernised females and validated by samples from the urban environment of Shanghai. Specifically, the breast cancer predictive model has not yet been validated by or applied to a wider population and its relevance across China has not been demonstrated although it appears to be relevant to the sampled data following a downward calibration correction of 43 % [74]. Nevertheless, the current estimates do not factor in that more than half of Chinese residents live in remote regions rather than in metropolitan locations such as Shanghai, therefore all estimates of incidence, even after calibration, may need revisiting [75].

Mortality

Breast cancer is the 6th leading cause of cancer-related mortality amongst Chinese females, with an age-standardised mortality rate of 6.6 per 100,000 in 2011 compared with 21.8 and 21.5 per 100,000 in Australia and the U.S., respectively [6, 25, 26]. Despite the lower mortality rate compared with Westernised countries, the absolute number of women in China dying from this cancer-type appears to be increasing rapidly and reached 60,473 in 2011, surpassing those reported for Australia (2901 cases) and the U.S. (40,931) combined [6, 25, 26].

Temporal changes in age-standardised mortality rate are evident and appear to follow a similar pattern to incidence rates (Fig. 2a) [16–24]. It is interesting to note that a steep increase of 1.6 per 100,000 of mortality rate was reported from 2009 to 2011 without a concomitant equivalent increase (0.4 %) in the percentage of all cancer deaths from females. The reason for this increase is currently unclear, but it should be monitored over subsequent years to establish whether a disproportional increase in mortality rate from breast cancer is occurring.

Mortality rates of breast cancer in Australia and the U.S. have been decreasing since the mid-1990s in part due to both the increased availability and quality of mammographic screening and improved treatments [27, 43, 76–78]. Without population-based cancer screening or other effective interventions, a continuing growth of mortality will reduce the differences in death rates from breast cancer between China and the occident, with a possible intersection of the rates within the next two to three decades (Fig. 2b) [16–26].

Recent age-specific mortality rate

Whilst the incidence rate of breast cancer for women aged 60 and over was lower than that for women aged 45–59, mortality rates did not reflect this pattern. Instead, the rate increased with age, with the sharpest increase observed for women aged 85 and over (Fig. 2c, Supplementary Table D)) [21, 22, 29, 30, 41, 42]. For example in 2009, the mortality rate from breast cancer was 47 per 100,000 for 80-to 84-year old and increased to 72 per 100,000 at the age of 85 and over [30].

Age-mortality curves are similar in trajectory between China and both Australia and the U.S. with the sharpest rise in those over 85-year old in all countries (Fig. 2d) [25, 30, 43]. However, there may be a subtle difference: the mortality curve of China appears to stabilise between ages 50 and 69, whereas the linear relationship between mortality and age is more consistent in Australia and the United States. Unfortunately the underlying reasons generating this difference are yet unclear.

Recent geographic distribution of mortality

Aligning strongly with the geographic distribution of incidence, breast cancer is the leading cause of deaths in locations close to the East coast of China (ASR at 6.33–12.18/100,000 women), which is not the case in other parts of the country (5.32/100,000 women) [79]. In terms of the temporal differences reported recently over the period 2003–2011, whilst the mortality rates of breast cancer in both regions increased, the greater change was observed in rural (111 %) compared with urban locations (28 %) (Table 1) [16–24]. The data, however, are not always consistent with a separate study indicating over a corresponding time period (2002–2008), a tripling of mortality rate in urban locations compared with an increase of only 16 % in rural regions [80]. This type of discrepancy is most likely due to the inconsistency of study samples and the very limited availability of population-based statistics. Therefore, to ensure the most effective allocation of resources, further data are required.

Unlike the remaining parts of China, the mortality trends in Hong Kong appeared to be relatively stagnant over the last three decades, with an average decrease rate of 0.02 % per annum between 1976 and 2010, which is closer to the pattern in Westernised states [1, 32, 66, 81]. Given that a population-based screening program is unavailable in Hong Kong, this stagnation or reduction was more likely due to improvement in survival from advanced treatment care [66].

Mortality trends over the last 50 years

Chinese breast cancer mortality rates across the whole country have been rising for successive generations of women since the early 1970s, but this is not consistent for all regions. According to the three national death surveys from the 1970s to 2000s (Table 2), the mortality rate increased by 16 % in urban regions but decreased by 4 % in rural areas during the first two decades; however, from 1990–1992 to 2004–2005, the rate increased rapidly in rural locations by 32 %, with urban regions maintaining a steady increase of 23 % [82]. For this later period, these death survey numbers are consistent with other studies (1987–1999), indicating that the mortality rate increased more rapidly amongst rural compared with urban females, although in absolute terms the rural values remained lower [48, 83, 84]. Even though a fast growth was witnessed in rural areas since 1990s, the mortality rate over the last four decades still increased more rapidly in urban locations

Table 2 Mortality from female breast cancer by national deaths surveys (1st–3rd) and remoteness areas, China, 1973–2005

	1st (1973-1975)			2nd (1990-1992)			3rd (2004-2005)		
	ASR[a]	Prop[b]	Ranking[c]	ASR[a]	Prop[b]	Ranking[c]	ASR[a]	Prop[b]	Ranking[c]
All areas	2.88	4.65	7th	2.99	4.41	7th	3.97	5.9	6th
Urban	3.42	5.11	7th	3.98	6.38	6th	4.91	7.18	5th
Rural	2.69	4.46	7th	2.59	3.69	8th	3.42	5.12	6th

[a] Age-standardised rate (per 100,000) of female breast cancer within corresponding areas

[b] Proportion of female breast cancer deaths amongst all reported cancer deaths in female within corresponding areas

[c] Ranking of female breast cancer amongst all reported female cancers within corresponding areas

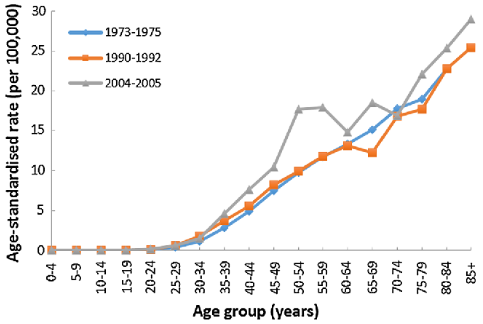

Fig. 3 Age-specific mortality rates of female breast cancer by national death surveys in China from 1973 to 2005

(44 %) compared with rural regions (27 %), possibly as a result of higher intake of dietary fat, greater levels of obesity and limited physical activity in cities [85–88]. Overall, however, the absolute number of deaths from breast cancer in China increased by 155 % by the end of 2005 compared to that in 1991 [84].

A further important mortality-based consideration is the age-dependent variations over time. From 1973–1975 to 2004–2005, the age-specific mortality rate of female breast cancer nearly doubled for 50- to 54-year old and became 1.5 times higher for the 65–69 age group (Fig. 3, Supplementary Table E) [82]. A rapid rise was also witnessed in women younger than 40 [82]. Again urban–rural discrepancies are manifest, with one study indicating that, between 1991 and 2005, the highest increase in mortality rate was amongst 45- to 54-year old in rural regions and 35–44 in urban locations with annual increases of 7.3 % and 3.3 %, respectively [84]. For younger women aged 15–34, an increase in the mortality rate of 4.8 % and a decrease of 2.2 % per year were noted for rural and urban locations, respectively [61, 83].

Survival

The data for survival from breast cancer are updated very slowly in China and nationwide statistics are often not available for external access. In addition, the comprehensiveness, quality, accuracy and validity of survival data from different regions are highly variable. The most recent (between 1990 and 2000) age-standardised data for 0- to 74-year old across available cancer registries demonstrate that the 5-year relative survival varied from 58 to 90 % with a median value of 88 % [73, 89–94]. This large range in breast cancer survival is most likely in part due to the inclusion of all women regardless of whether the cancer was detected at an early or late stage, and in part because of the varying level of health services across China. For example, a greater level of accessibility to diagnosis and treatment services in urban areas, such as Shanghai (5-year relative survival at 79 %) and Tianjing (85 %), has yielded a substantially higher survival rate compared with rural locations, such as Qidong (60 %) (Table 3) [9, 89, 95–98]. During a similar time period in Australia (1995–1999) and the U.S. (1990–1999), the 5-year relative survival of 85 and 86 %, respectively, compared reasonably well with the Chinese cities but were well ahead of rural locations [99, 100].

Even though the survival rate from breast cancer varies across the country, it is clear from the data in Table 3 that the rate is generally increasing over time (with Qidong being the exception), highlighting improvements in prognosis in recent years [91, 92, 101]. This pattern has also been shown in other reports, with the 5-year relative survival in Beijing between 1982 and 1983 being 66.3 %, but increasing to 74.2 % for females diagnosed between 1987 and 1988 [102]. This continuing improvement is at least in part attributable to earlier diagnosis through screening, combined with more advanced treatments, such as adjuvant therapies [78, 103–109]. It is interesting that in another report, Qidong also demonstrated an increase from 1973–1977 (56.3 %) to 1998–2002 (63.1 %) [101], although this change not being noted by the International Agency for Research on Cancer (IARC) in Table 3.

One of the most important determinants of breast cancer survival is stage at diagnosis [110, 111]. Data on stage-specific 5-year relative survival from breast cancer amongst China, Australia and the U.S. are presented in Table 4 [13, 101, 112, 113]. However, direct international comparisons must be interpreted with caution because of the different time periods being considered and different levels of data availability. It is interesting to observe that similar to China, limited nationwide data are available in

Table 3 5-year relative survival from female breast cancer by time period, China, 1981–2000

Cancer registry	Period of diagnosis	5-year relative survival (%)	Period of diagnosis	5-year relative survival (%)
China–Qidong	1982–1991	59.50	1992–2000	59.40
China–Shanghai	1988–1991	72.00	1992–1995	78.70
China–Tianjing	1981–1990	80.10	1991–1999	84.80

Survival data in China was reported by cancer registries

Table 4 5-year relative survival from female breast cancer by stage at diagnosis, China, Australia and the United States

Country	Time period	Stage I (%)	Stage II	Stage III	Stage IV
Qidong, China	1972–2011	100	N/A	N/A	21 %
Shanghai, China	No date	94	84 %	65 %	N/A
Queensland, Australia	2001–2006	98	83 %[a]		
Unite States	1988–2001	100	86 %	57 %	20 %

N/A not available

[a] 5-year relative survival rate for combination of stage II, III and IV. Rates for specific stages other than Stage I are unavailable

Australia regarding survival by stage of breast cancer, although a report from Queensland indicated the 5-year relative survival at 98 % for stage I and 83 % for the combination of other three stages [112, 114, 115]. Conversely in the United States, stage-specific survival data are very comprehensive, and these demonstrate that 5-year relative survival of 100 % for stage I dropping to approximately 20 % for stage IV [99, 116].

Another prognostic factor associated with higher survival in China is age. Five-year relative survival is comparatively high for women aged 35–54 (in particular 35–44) years, compared to women of 65 and over [98, 101]. These data of China (1997–2011) are distinct from Australia (1997–2006) and the U.S. (1988–2001), where the 5-year relative survival is highest amongst women aged 50–69 and 65–84, respectively, although the time period over which the data were gathered was different [113, 117].

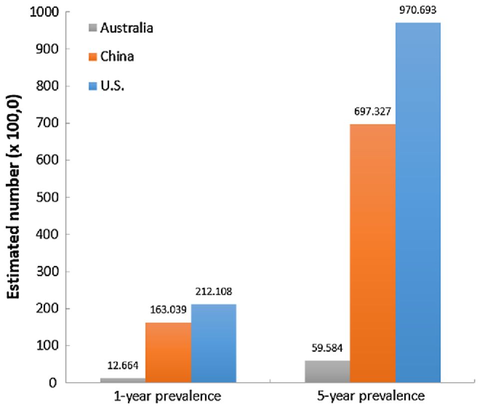

Fig. 4 Estimated number of prevalence of female breast cancer in China, Australia and the United States in 2012

Prevalence

The prevalence of breast cancer is rarely recorded or studied by researchers in China, resulting in extremely limited statistics. According to the International Agency for Research on Cancer, the 1- and 5-year prevalence for Chinese females (aged 15 years and older) were estimated to be 30 and 129 per 100,000 women, respectively, in 2012 [118]. These figures are around one-fifth of those in Australia (135 and 631 per 100,000) and the United States (165 and 754 per 100,000) [118]. In terms of the cancer cases, the estimated number for 1- and 5-year prevalence for female breast cancer in China are 77 % and 72 % of that in the U.S. although the overall Chinese population is larger by a factor of four than that in the U.S. (Fig. 4) [28]. Again it should be noted that like the other data discussed, these numbers are affected by the limited or incomplete data from cancer registries in China compared with the high-quality and comprehensive national information available elsewhere [28].

Due to the distinction of healthcare services across China, the prevalence of breast cancer varies geographically, with locations close to the more developed part (East coast) of China having a 1-year prevalence of close to 50 per 100,000 compared with the national average value of 30 per 100,000 females [28, 119]. The 10-year prevalence varies from 134 to 367 per 100,000 across different Chinese regions [119].

Conclusion

Breast cancer is a significant public health issue in China with incidence and mortality rates increasing rapidly since 1980s. This review has provided an overview of current patterns and long-term trends along with a discussion of regional variations, which should be of value to clinicians, researchers and policy makers. It is acknowledged there are some inconsistencies in the data reported, predominantly due to the variability and discrepancies in methods of data acquisition, analysis and presentation highlighting the requirement for standardisation within the country. In the current paper, some issues have not been fully addressed such as the existence and performance of screening programs and the importance of risk factors such as mammographic density; however, these contributors will be discussed further in the future.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

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TITLE: Descriptive epidemiology of breast cancer in China: incidence, mortality, survival and prevalence

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Supplementary material

Table A: Age-specific incidence rate of female breast cancer, China, 2004-2009

Age group	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**
0-4	0.40	0.99	1.53	0.13	0.00	0.00
5-9	0.00	0.00	0.00	0.17	0.16	0.00
10-14	0.17	0.06	0.00	0.12	0.00	0.05
15-19	0.09	0.05	0.19	0.09	0.19	0.15
20-24	0.60	0.75	0.66	0.60	1.10	1.21
25-29	4.87	3.75	4.15	4.53	4.92	4.45
30-34	13.80	12.78	13.43	12.45	14.53	13.60
35-39	26.18	25.11	27.70	31.11	33.24	29.97
40-44	54.74	60.05	60.29	61.67	61.25	52.87
45-49	88.83	88.40	88.80	86.20	92.12	83.91
50-54	87.81	92.21	97.51	104.37	108.27	100.78
55-59	85.93	88.97	92.28	98.34	103.38	96.75
60-64	77.87	75.22	80.91	82.08	89.00	88.65
65-69	80.29	85.08	80.04	79.79	89.23	77.77
70-74	84.08	79.65	85.60	85.30	90.19	80.02
75-79	67.31	72.69	71.05	81.32	81.35	74.31
80-84	65.34	68.43	66.95	65.93	59.07	63.32
85+	43.44	55.48	49.62	50.36	85.78	50.63

Table B: Age-specific incidence rate of female breast cancer, urban China, 2004-2009

Age group	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**
0-4	0.63	1.57	2.25	0.19	0.00	0.00
5-9	0.00	0.00	0.00	0.26	0.23	0.00
10-14	0.25	0.00	0.00	0.20	0.00	0.00
15-19	0.06	0.07	0.25	0.13	0.12	0.23
20-24	0.67	0.85	0.77	0.56	1.20	1.16
25-29	6.08	4.58	4.99	5.31	5.48	5.01
30-34	16.87	15.65	15.80	15.14	17.18	17.07
35-39	29.76	29.56	31.06	34.75	37.76	33.42
40-44	62.28	67.39	66.92	67.85	67.58	61.00
45-49	100.66	102.43	102.41	100.03	104.44	100.56
50-54	103.63	107.07	108.62	116.36	119.68	116.50
55-59	101.32	103.27	106.61	108.88	113.76	111.79
60-64	93.84	91.36	92.37	93.64	99.91	104.58
65-69	93.98	101.78	91.93	94.42	103.30	97.82
70-74	99.96	94.51	96.78	98.29	100.85	99.12
75-79	81.12	86.45	81.30	95.39	93.15	90.67
80-84	79.41	84.13	75.52	76.14	64.85	78.03
85+	51.91	67.77	55.84	59.44	101.66	64.30

Table C: Age-specific incidence rate of female breast cancer, rural China, 2004-2009

Age group	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**
0-4	0.00	0.00	0.00	0.00	0.00	0.00
5-9	0.00	0.00	0.00	0.00	0.00	0.00
10-14	0.00	0.18	0.00	0.00	0.00	0.11
15-19	0.18	0.00	0.00	0.00	0.41	0.00
20-24	0.39	0.39	0.22	0.72	0.63	1.32
25-29	1.74	1.70	1.32	2.39	2.63	3.19
30-34	5.85	5.86	6.25	6.15	6.26	7.28
35-39	16.13	13.37	15.97	20.18	17.49	23.06
40-44	27.25	34.67	32.70	40.53	37.57	36.45
45-49	43.61	38.48	32.17	38.85	40.96	46.59
50-54	37.86	41.07	48.91	57.54	55.16	60.39
55-59	40.58	42.51	51.78	59.81	55.72	59.69
60-64	27.76	24.90	33.18	42.86	44.37	52.92
65-69	28.16	27.68	28.45	29.52	33.49	36.08
70-74	26.32	24.42	32.76	32.51	41.05	32.77
75-79	22.75	25.89	26.21	28.38	25.28	32.48
80-84	27.63	18.41	30.95	29.53	33.05	27.48
85+	19.21	16.32	25.22	17.41	15.82	16.20

Table D: Age-specific mortality rate of female breast cancer, China, 2004-2009

Age group	2004	2005	2006	2007	2008	2009
0-4	0.00	0.00	0.00	0.00	0.00	0.08
5-9	0.00	0.00	0.00	0.00	0.00	0.00
10-14	0.00	0.00	0.00	0.00	0.00	0.00
15-19	0.00	0.00	0.00	0.05	0.00	0.00
20-24	0.14	0.18	0.04	0.00	0.00	0.11
25-29	0.52	0.54	0.56	0.13	0.63	0.39
30-34	1.71	1.72	1.39	1.45	1.16	1.34
35-39	3.69	4.43	3.94	3.68	3.55	3.29
40-44	6.78	6.95	7.45	7.68	8.03	7.24
45-49	14.56	14.36	14.46	12.09	12.35	11.39
50-54	19.12	18.65	18.24	19.54	19.59	21.29
55-59	20.28	24.19	20.97	19.45	22.65	22.64
60-64	19.43	19.81	20.02	18.96	21.22	23.17
65-69	21.77	24.39	23.27	21.05	23.41	22.44
70-74	28.29	25.01	24.88	29.47	29.2	29.55
75-79	31.86	32.26	28.42	31.08	36.22	35.3
80-84	51.53	51.39	39.67	46.51	41.83	47.49
85+	61.13	55.48	48.83	60.51	66.45	71.95

Table E: Age-specific mortality rate of female breast cancer by National Deaths Surveys and remoteness areas, China, 1973-2005

Age group	**1st (1973-1975)**			**2nd (1990-1992)**			**3rd (2004-2005)**		
	All	**Urban**	**Rural**	**All**	**Urban**	**Rural**	**All**	**Urban**	**Rural**
0-4	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5-9	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
10-14	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.00	0.02
15-19	0.02	0.02	0.03	0.04	0.03	0.04	0.02	0.00	0.03
20-24	0.12	0.11	0.13	0.13	0.14	0.12	0.17	0.00	0.25
25-29	0.36	0.35	0.36	0.64	0.67	0.63	0.60	0.62	0.58
30-34	1.15	1.47	1.06	1.80	2.20	1.62	1.49	1.62	1.43
35-39	2.80	3.20	2.65	3.72	4.65	3.33	4.59	4.76	4.49
40-44	4.91	5.32	4.77	5.53	6.67	5.08	7.67	9.46	6.57
45-49	7.49	8.43	7.16	8.23	9.58	7.67	10.42	12.32	9.26
50-54	9.80	11.39	9.20	9.94	12.95	8.54	17.66	21.05	15.58
55-59	11.69	14.17	10.86	11.77	16.33	9.76	17.89	22.51	15.15
60-64	13.32	15.84	12.38	13.10	18.94	10.75	14.77	19.46	12.01
65-69	15.13	18.52	14.10	12.24	16.32	10.72	18.52	23.06	15.81
70-74	17.76	22.46	15.96	16.83	24.37	14.14	16.88	24.07	12.69
75-79	18.95	24.45	17.13	17.70	27.57	14.12	22.12	30.47	17.36
80-84	22.79	29.63	20.20	22.81	38.04	17.47	25.37	37.49	18.82
85+	N/A	N/A	N/A	25.46	38.98	20.56	28.96	42.85	21.49
N/A: not applicable									

TITLE: Descriptive epidemiology of breast cancer in China: incidence, mortality, survival and prevalence

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GLOSSARY

Incidence rate: the number of new breast cancers cases diagnosed per 100,000 population during a specific time period, usually one year.

Mortality rate: the number of deaths per 100,000 population for which the underlying cause was breast cancer.

Age-specific incidence or mortality rates: the number of cases of (or deaths from) breast cancer for a given sex, age-group and year divided by the population for that same sex, age-group and year. These rates are often very small so are multiplied by 100,000 to present a more convenient magnitude. Consequently they are expressed as the number of cases (or deaths) per 100,000 population.

Age-standardised incidence or mortality rate: a weighted average of the corresponding age groups of a standard population. The potential confounding effect of age is reduced when comparing age-standardised rates based on the same standard population.

Standard population: A standard population for a geographic area, such as the Chinese Census or the world Segi, gives the proportions of the population falling into the age groups 0, 1-4, 5-9, ..., 80-84, and 85+.

Crude rate: The number of new cases of (or deaths from) breast cancer in a given period divided by the size of the population at risk in a specified time period.

Survival: a general term indicating the probability of being alive for a given amount of time after a diagnosis of cancer.

Observed survival: the proportion of breast cancer patients who remain alive for a given period of time following a diagnosis of cancer.

Expected survival: the proportion of people in the general population who remain alive for a given period of time. Expected survival estimates are crude estimates calculated from life tables (a table for a given population listing, for each sex and each age from 0 to 120, how many members die at that age and how many survive one more year) of the general population by age, sex and calendar year and, where applicable, remoteness and socioeconomic status.

Relative survival: the ratio of observed survival to expected survival. Relative survival describes the survival of individuals with breast cancer, adjusted for the underlying mortality in the general population.

Prevalence: the number of people alive who were diagnosed with breast cancer within a specified time period, such as the previous 1 or 5 years.

Chapter Three

Mammographic density and associated predictive factors for Chinese women: Using BI-RADS density classification

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The full original (non-contracted) manuscript is contained in Appendix 2.1.

Presentations on this paper was made at the following conferences:

- Sydney Cancer Conference, Sydney, Australia, September 2016 (Appendix 3.2)
- 4th International "Why Study Mammographic Density?" Meeting: The Measurement Challenge, Kingscliff, Australia, August 2016 (Appendix 3.3)
- 2016 Sydney Catalyst Postgraduate and Early Career Researcher Symposium, Sydney, Australia, April 2016 (Appendix 3.4)
- Asian Pacific Organisation for Cancer Prevention 8th General Assembly, Brisbane, Australia, April 2016 (Appendix 3.5)
- 2015 Postgraduate Cancer Research Symposium, Cancer Research Network, Sydney, Australia, December 2015 (Appendix 3.6)
- The 1st China-Australia Symposium on Breast Cancer Research, Guangzhou, China, November 2015 (Appendix 3.7)

3.1 Bridging section for chapter three

Based on the literature review, we found that the incidence of breast cancer in China has increased rapidly in the last decades and this disease has become a significant public health issue amongst Chinese women. The common risk factors include lifestyle and environmental factors and reproductive activities, but information regarding other significant risk factors is missing, for example, mammographic density. Mammographic density is well-documented to be an important risk factor of breast cancer for westernised women and knowledge around factors associated with density are well-studied. It is a major determinant of imaging modality selection for any screening program because the efficacy of these imaging solutions depends on the presentation of the breast. However features of mammographic density is very poorly understood in the Chinese context. Therefore, this chapter characterises the distribution of mammographic density and identified factors associated with density for Chinese women without breast cancer, based on data from a national screening program. The mammographic density in this chapter will be assessed using BI-RADS breast composition classification, the most commonly used method in density assessment in both screening and clinical settings in China.

The study "Mammographic density and associated predictive factors for Chinese women" was submitted to and accepted by *The Breast Journal*. This study examined the factors, including demographic, environmental, lifestyle, menstrual, reproductive and familial agents, associated with mammographic density for women in China. In this chapter, we include the paper accepted by *The Breast Journal* (in manuscript format), which is accompanied by nine supplementary tables (will be available online only in the journal website after being published). The full work which, due to word limits, could not be contained within the accepted article, but it is shown in Appendix 2.1.

3.2 Statement from author confirming authorship contribution of the PhD candidate

As a co-author of the paper "Mammographic density and associated predictive factors for Chinese women", we confirm that Tong Li has made the following contributions:

- Conception and design of the research
- Data collection
- Analysis and interpretation of the findings
- Manuscript preparation, editing and critical appraisal of content

Jing Li ......Jing Li...... Date ...28-5-2017...

Min Dai ......Min Dai...... Date ...28-5-2017...

Jiansong Ren ......Jiansong Ren...... Date ...31-5-2017...

Hongzhao Zhang ......Hongzhao Zhang...... Date: ...31-5-2017...

Zihan Mi ......Zihan Mi...... Date: ...31-5-2017...

Rob Heard ......Rob Heard...... Date: ...4-5-2017...

Claudia Mello-Thoms...... Date: ...8-5-2017...

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Mammographic density and associated predictive factors for Chinese women

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Key Words:	Mammographic density, Breast density, Chinese women, Predictive factors, Risk factor

Mammographic density and associated predictive factors for Chinese women

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Mammographic density (MD), representing the amount of fibrous and glandular tissues within the breasts, is consistently demonstrated to be an important risk factor of breast cancer with individuals experiencing the highest density having a 2-6 times risk of breast cancer compared to those with the lowest (1). However, characteristics of women's MD are poorly understood in China.

Data were collected from 4867 women from the National Cancer Screening Program in Urban Locations in China between 2013 and 2015. Eligible women were diagnosed as normal or having benign lesions by expert radiologists and MD values were acquired from the radiological report using the 4th edition of American College of Radiology BI-RADS density categories (See supplementary table S2). Spearman tests examined the relationship between BI-RADS values and continuous variables whilst Mann-Whitney or Kruskal-Wallis test assessed differences between median BI-RADS values of categorical variables. The BI-RADS MD was then recoded into a dichotomous variable: low density (BI-RADS 1&2) and high density (BI-RADS 3&4). For all variables that were statistically significant from Spearman, Mann-Whitney and Kruskal-Wallis tests, binary logistic regression was conducted to produce odds ratio (OR) and 95% confidence intervals (95% CI). Statistical model building was finally performed using multiple logistic regression adopting the significant variables.

Descriptive characteristics of participants and the distribution of MD are displayed in supplementary tables S1 and S2, respectively. The overall results from Spearman, Mann-Whitney and Kruskal-Wallis tests are shown in tables S3-S6. Table S7 shows the distribution of dichotomous MD and OR from binary logistic regression with 95% CI. The demographic, and menstrual and reproductive models from multiple logistic regression are presented in table S8 and these two models predicted 68.2% and 59.9% of the MD, respectively. Table 1 displays the final model of variables being statistically significant only and the overall percentage of prediction increased to 68.7%.

Women in this study predominately experienced scattered fibroglandular (37.64%) and heterogeneous MD (49.89%), however the density values were almost equally distributed between the lower (BI-RADS 1&2) (47.57%) and upper (BI-RADS 3&4) (52.43%) groupings. This density distribution was both consistent and inconsistent with previous China-based research: work covering four Chinese large cities demonstrated similar density distributions to the current work (2), however, a separate study based on another large Chinese city (Tianjin) reported that women had more dense breasts (BI-RADS 3&4) compared to fatty breasts (BI-RADS 1&2) (3), a finding consistent with studies involving Asian women living in western countries (4). Compared to international studies, MD here were higher than that of women from North America where a greater proportion of women have density of 50% or less (5, 6). This discrepancy once again highlights the variations in breast tissue composition according to geographical location and emphasises the need to explore the implications of these variations.

Thirty-one potential causal agents of MD were examined in this study. The negative associations of MD with increasing age and BMI has been known for several decades across many populations with our data agreeing with previous reports (1, 7). Education-dependent density differences have also been previously reported (7), with our data specifically suggesting that women in tertiary education experience densest breasts compared with those individuals experiencing either no or only primary education. The relationship between education and density will require future attention as people avail themselves of increasing education opportunities: the number of undergraduate and graduate students in China has approximately quadrupled in the last two decades (8). Density associations were also shown with geographic and occupational variations with women working as housewives and individuals from Gansu province having lowest density compared to other occupations and provinces, respectively. MD was higher in females with pre-menopausal status and nulliparity, which have been previously reported in North America and were linked to age and hormonal influences on the epithelial, stromal and adipose tissues in the breast (1, 7). Compared to women without personal history, approximately 1.3 times higher density was also found in women with personal history of benign breast disease, including hyperplasia, duct ectasia, fibroadenoma, mastitis and other benign lumps indicating that the density is associated with tissue proliferation and hyperplasia (9).

In conclusion, MD in women from urban locations in China distributed almost equally between high and low dense. The work has demonstrated important associations between MD and a variety of associated factors, and a statistical model was established to predict MD. The findings should be useful to policy makers responsible for breast cancer preventative strategies so that the impact of this increasingly important health policy issue is minimised.

Table 1 Final model

Factors	Adjusted OR	95% CI	P values
Age (years)	0.95	0.94-0.96	<0.001
BMI (kg/m^2)	0.91	0.87-0.96	<0.001
Province of residence			
Chongqing	1.00		
Gansu	0.11	0.08-0.15	<0.001
Guangxi	0.28	0.21-0.36	<0.001
Henan	2.98	2.08-4.27	<0.001
Shandong	0.18	0.14-0.24	<0.001
Xinjiang	0.33	0.26-0.43	<0.001
Yunnan	0.39	0.28-0.54	<0.001
Zhejiang	0.51	0.39-0.65	<0.001
Education			
Non-educated and primary	1.00		
Secondary	1.44	1.17-1.77	0.001
Tertiary	1.52	1.16-1.98	0.002
Occupation			
Professionals and technicians	1.00		
Managers and Administrators in public sectors	0.75	0.56-0.99	0.048
Clerical support and administrative related workers	0.83	0.64-1.07	0.148
Businesswomen	1.00	0.68-1.47	0.994
Agricultural workers	0.63	0.46-0.86	0.004
Plant and machine operators and assemblers	0.81	0.65-1.00	0.060
Service and sales workers	0.74	0.55-0.99	0.044
Housewives	0.60	0.46-0.77	<0.001
Others	0.61	0.43-0.87	0.007
Menopause			
Premenopausal	1.00		
Postmenopausal	0.48	0.42-0.56	<0.001
Parity			
Nulliparous	1.00		
Parous	0.64	0.48-085	0.002
Personal history of benign breast disease			
No	1.00		
Yes	1.39	1.15-1.68	0.001

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Supplementary tables

Table S1 Descriptive characteristics of participants			
Factors	**Number[a]**	**Percentage**	**Mean ± Standard deviation**
Demographic factors			
Age (years)	4867	100.00	53.96 ± 6.37
BMI (kg/m^2)[b]	4867	100.00	24.12 ± 3.60
Height (cm)	4867	100.00	159.40 ± 5.00
Weight	4867	100.00	61.34 ± 9.90
Province of residence	4867		
Chongqing	491	10.09	
Gansu	360	7.40	
Guangxi	720	14.79	
Henan	434	8.92	
Shandong	531	10.91	
Xinjiang	1259	25.87	
Yunnan	272	5.59	
Zhejiang	800	16.44	
Ethnicity	4867		
Han	4446	91.35	
Mongol	16	0.33	
Hui	108	2.22	
Manchu	14	0.29	
Zhuang	219	4.50	
Uyghur	40	0.82	
Kazakh	1	0.02	
Others	23	0.47	
Ethnic group	4867		
Non-Han	421	8.65	
Han	4446	91.35	
Education	4867		
None	127	2.61	
Primary school	547	11.24	
Junior secondary school	1394	28.64	
Senior secondary/vocational and technology school	1639	33.68	
Higher vocational and technical college	819	16.83	
University and above	341	7.01	
Education level	4867		
Non-educated and primary education	674	13.80	
Secondary education	3030	62.30	
Tertiary education	1160	23.80	
Occupation	4866		
Professionals and technicians	700	14.39	
Managers and administrators in public sectors	348	7.15	
Clerical support and administrative related workers	514	10.56	
Businesswomen	170	3.49	
Agricultural workers	381	7.83	
Plant and machine operators and assemblers	1497	30.76	
Service and sales workers	363	7.46	
Housewives	678	13.93	
Others	215	4.42	
Environmental and lifestyle factors			
Occupational radiation exposure	4867		

No	4682	96.20	
Yes	185	3.80	
Physical activity[c]	4867		
No	2988	61.39	
Yes	1879	38.61	
Smoker[d]	4867		
None	4575	94.00	
Former	55	1.13	
Current	237	4.87	
Lifetime smoking[d]	4867		
No	4575	94.00	
Yes	292	6.00	
Smoking intensity (cigarettes per day)[e]	284	100.00	17.82 ± 11.11
Cumulative duration of smoking (years)[e]	280	100.00	21.04 ± 10.76
Duration of smoking abstinence (years)[f]	31	100.00	7.06 ± 6.66
Passive smoking	4867		
No	1585	32.57	
Yes	3282	67.43	
Duration of passive smoking (years)[g]	3265	100.00	27.34 ± 10.93
Alcohol drinker[h]	4867		
None	3860	79.31	
Former	167	3.43	
Current	840	17.26	
Alcohol consumption[h]	4867	100.00	
Abstainer	3860	79.31	
Consumer	1007	20.69	
Duration of abstinence from alcohol (years)[i]	157	100.00	5.85 ± 6.18
Menstrual, reproductive and familial factors			
Age at menarche (years)	4852	100.00	14.13 ± 1.94
Menopause	4861		
Premenopausal	1887	38.82	
Postmenopausal	2974	61.18	
Age at menopause (years)[j]	2974	100.00	48.81 ± 4.25
Parity	4861		
Nulliparous	400	8.23	
Parious	4461	91.77	
Age at first delivery (years)[k]	4454	100.00	26.67 ± 4.04
Breastfeeding history	4461		
No	1206	24.80	
Yes	3655	75.20	
Cumulative duration of breastfeeding (months)[l]	3655	100.00	12.14 ± 9.63
Personal history of benign breast disease	4861		
No	790	16.25	
Yes	4071	83.75	
Family history of breast cancer	4850		
No	2711	55.90	
Yes	2139	44.10	
1st/2nd degree relatives diagnosed with breast cancer[m]	2135		
No	103	4.82	
Yes	2032	95.18	
Number of 1st and/or 2nd degree relatives diagnosed with breast cancer[n]	2032		
= 1	1140	56.10	
> 1	892	43.90	
1st degree relatives diagnosed with breast cancer before age of 50[o]	2036		
No	641	31.55	

Yes	1395	68.65

[a] Number of cases may vary due to missing and invalid data
[b] Calculated by Weight (kg)/[Height (m)]^2
[c] Defined as >30 minutes/time and >3 times/week
[d] Defined as smoking more than 1 cigarette per day and continuing or accumulating more than 6 months
[e] Restricted to current and former smokers
[f] Restricted to former smokers
[g] Restricted to passive smokers
[h] Defined as drinking more than once per week and continuing six months or above
[i] Restricted to former-alcohol drinker
[j] Restricted to postmenopausal women
[kj] Restricted to parous women
[l] Restricted to parous women who have breastfeeding history
[m] Restricted to women who have family history of breast cancer
[n] Restricted to women who have 1st and/or 2nd degree relatives diagnosed with breast cancer
[o] Restricted to women who have 1st degree relatives diagnosed with breast cancer

Table S2 Distribution of mammographic density (using BI-RADS classification)		
BI-RADS mammographic density	**Number**	**Percentage**
1. The breast is almost entirely fat (< 25% glandular)	483	9.92
2. There are scattered fibroglandular densities (approximately 25% - 50% glandular)	1832	37.64
3. The breast tissue is heterogeneously dense, which could obscure detection of small masses (approximately 51% - 75% glandular)	2428	49.89
4. The breast tissue is extremely dense. This may lower the sensitivity of mammography (> 75% glandular)	124	2.55
Total	4867	100

Table S3 Output from traditional tests: correlation coefficient (rho) for ratio and interval variables; mean and median of BI-RADS density values for ordinal and nominal variables				
Factors	**rho**[a]	**BI-RADS density**[b]		**p value**[c]
		Mean	**Median**	
Demographic factors				
Age (years)	-0.23			<0.001
BMI (kg/m²)[d]	-0.18			<0.001
Height (cm)	<0.01			0.870
Weight (kg)	-0.16			<0.001
Province of residence				
Chongqing		2.66	3.00	<0.05[e]
Gansu		2.10	2.00	
Guangxi		2.54	3.00	
Henan		2.91	3.00	
Shandong		2.06	2.00	
Xinjiang		2.41	2.00	
Yunnan		2.57	3.00	
Zhejiang		2.44	3.00	
Ethnic group				
Non-Han		2.41	2.00	0.152
Han		2.45	3.00	
Education				
None		2.18	2.00	<0.05[f]
Primary school		2.20	2.00	
Junior secondary school		2.41	3.00	
Senior secondary/vocational and technology school		2.49	3.00	
Higher vocational and technical college		2.57	3.00	
University and higher		2.65	3.00	
Education level				<0.05[f]
Non-educated and primary		2.20	2.00	
Secondary		2.45	3.00	
Tertiary		2.59	3.00	
Occupation				
Professionals and technicians		2.58	3.00	<0.05[g]
Managers and administrators in public sectors		2.49	3.00	
Clerical support and administrative related workers		2.53	3.00	
Businesswomen		2.57	3.00	
Agricultural workers		2.31	2.00	
Plant and machine operators and assemblers		2.42	3.00	
Service and sales workers		2.50	3.00	
Housewives		2.35	2.00	
Others		2.37	2.00	
Environmental and lifestyle factors				
Occupational radiation exposure				
No		2.45	3.00	0.650
Yes		2.46	3.00	
Physical activity[h]				
No		2.46	3.00	0.106
Yes		2.43	3.00	
Smoking[i]				
None		2.45	3.00	0.598
Former		2.35	3.00	
Current		2.43	3.00	

Lifetime smoking[i]				0.618
No		2.45	3.00	
Yes		2.41	3.00	
Smoking intensity (cigarettes/day)[j]	-0.04			0.496
Cumulative duration of smoking (years)[j]	-0.02			0.706
Duration of smoking abstinence (years)[k]	-0.15			0.429
Passive smoking				
Yes		2.44	3.00	0.054
No		2.48	3.00	
Duration of passive smoking (years)[l]	-0.10			<0.001
Alcohol drinker[m]				
None		2.44	3.00	0.193
Former		2.51	3.00	
Current		2.47	3.00	
Alcohol consumption[m]				0.096
Abstainer		2.44	3.00	
Consumer		2.48	3.00	
Duration of abstinence from alcohol (years)[n]	-0.01			0.905
Menstrual, reproductive and familiar factors				
Age at menarche (years)	-0.10			<0.001
Menopause				
Premenopausal		2.66	3.00	<0.001
Postmenopausal		2.32	2.00	
Age at menopause (years)[o]	-0.02			0.302
Parity				
Nulliparous		2.58	3.00	0.001
Parous		2.44	3.00	
Age at first delivery (years)[p]	0.11			<0.001
Breastfeeding history				
No		2.52	3.00	<0.001
Yes		2.43	3.00	
Cumulative duration of breastfeeding (months)[q]	-0.14			<0.001
Personal history of benign breast disease				
No		2.38	2.00	0.001
Yes		2.46	3.00	
Family history of breast cancer				
No		2.46	3.00	0.261
Yes		2.44	3.00	
1st/2nd degree relatives diagnosed with breast cancer[r]				
No		2.41	2.00	0.633
Yes		2.45	3.00	
Number of 1st and/or 2nd degree relatives diagnosed with breast cancer[s]				
= 1		2.38	2.00	<0.001
> 1		2.53	3.00	
1st degree relatives diagnosed with breast cancer before age of 50[t]				
No		2.43	3.00	0.534
Yes		2.45	3.00	

[a] Spearman's correlation coefficient for ratio and interval variables
[b] Mean and median values of BI-RADS mammographic density for ordinal and nominal variables Spearman's correlation coefficient for ratio and interval variables
[c] P values of Spearman's test for continuous variables, p value of Mann-Whitney test for ordinal and nominal variables with two independent groups; p values of main effect resulted from Kruskal-Wallis test for ordinal and nominal variables with more than two unmatched groups, and the post-doc tests adopting Bonferroni correction and corresponding p values for specific variables were shown in appendix only
[d] Calculated by Weight (kg)/[Height (m)]^2
[e] Refer to supplementary table S4 for results from post-hoc test.

[f] Refer to supplementary table S5-1 and S5-2 for results from post-hoc test.
[g] Refer to supplementary table S6 for results from post-hoc test.
[h] Defined as >30 minutes/time and >3 times/week
[I] Defined as smoking more than 1 cigarette per day and continuing or accumulating more than 6 months
[j] Restricted to current and former smokers
[k] Restricted to former smokers
[l] Restricted to passive smokers
[m] Defined as drinking more than once per week and continuing six months or above
[n] Restricted to former alcohol consumer
[o] Restricted to postmenopausal women
[p] Restricted to parous women
[q] Restricted to parous women who have breastfeeding history
[r] Restricted to women who have family history of breast cancer
[s] Restricted to women who have 1st and/or 2nd degree relatives diagnosed with breast cancer
[t] Restricted to women who have 1st degree relatives diagnosed with breast cancer

Table S4 P values of pairwise differences using the post-hoc test for province

Province	Chongqing	Gansu	Guangxi	Henan	Shandong	Xinjiang	Yunnan	Zhejiang
Chongqing	N/A*	<0.001	<0.001	<0.001	<0.001	<0.001	0.020	<0.001
Gansu	<0.001	N/A	<0.001	<0.001	0.324	<0.001	<0.001	<0.001
Guangxi	<0.001	<0.001	N/A	<0.001	<0.001	=0.001	0.413	0.083
Henan	<0.001	<0.001	<0.001	N/A	<0.001	<0.001	<0.001	<0.001
Shandong	<0.001	0.324	<0.001	<0.001	N/A	<0.001	<0.001	<0.001
Xinjiang	<0.001	<0.001	0.001	<0.001	<0.001	N/A	0.003	0.225
Yunnan	0.020	<0.001	0.413	<0.001	<0.001	0.003	N/A	0.045
Zhejiang	<0.001	<0.001	0.083	<0.001	<0.001	0.225	0.045	N/A

* N/A: not applicable

Note: the significant level was set at 0.05 for main effect from Kruskal-Wallis test and became 0.0017 after Bonferroni correction

Table S5-1 P values of pairwise differences using the post-hoc test for education (6 categories)

Education	None	Primary school	Junior secondary school	Senior secondary/vocational and technology school	Higher vocational and technical college	University and above
None	N/A*	0.950	=0.001	<0.001	<0.001	<0.001
Primary school	0.950	N/A	<0.001	<0.001	<0.001	<0.001
Junior secondary school	=0.001	<0.001	N/A	0.005	<0.001	<0.001
Senior secondary /vocational and technology school	<0.001	<0.001	0.005	N/A	0.003	<0.001
Higher vocational and technical college	<0.001	<0.001	<0.001	0.003	N/A	0.056
University and above	<0.001	<0.001	<0.001	<0.001	0.056	N/A

* N/A: not applicable

Note: the significant level was set at 0.05 for main effect from Kruskal-Wallis test and became 0.0033 after Bonferroni correction

Table S5-2 P values of pairwise differences using the post-hoc test for education (3 categories)

Education	Non-educated and primary education	Secondary education	Tertiary education
None-educated and primary education	N/A*	<0.001	<0.001
Secondary education	<0.001	N/A	<0.001
Tertiary education	<0.001	<0.001	N/A

* N/A: not applicable

Note: the significant level was set at 0.05 for main effect from Kruskal-Wallis test and became 0.0167 after Bonferroni correction

Table S6 P values of the pairwise differences using post-hoc test for occupation									
Occupation	**Professionals and technicians**	**Managers and Administrators in public sectors**	**Clerical support and administrative- related workers**	**Businesswomen**	**Agricultural workers**	**Plant and machine operators and assemblers**	**Service and sales workers**	**Housewives**	**Others**
Professionals and technicians	N/A*	0.025	0.231	0.866	<0.001	<0.001	0.041	<0.001	<0.001
Managers and Administrators in public sectors	0.025	N/A	0.259	0.154	0.003	0.170	0.816	0.010	0.060
Clerical support and administrative related workers	0.231	0.259	N/A	0.529	<0.001	0.002	0.362	<0.001	0.003
Businesswomen	0.866	0.154	0.529	N/A	<0.001	0.008	0.202	<0.001	0.004
Agricultural workers	<0.001	0.003	<0.001	<0.001	N/A	0.014	0.001	0.442	0.474
Plant and machine operators and assemblers	<0.001	0.170	0.002	0.008	0.014	N/A	0.088	0.053	0.264
Service and sales workers	0.041	0.816	0.362	0.202	0.001	0.088	N/A	0.004	0.033
Housewives	<0.001	0.010	<0.001	<0.001	0.442	0.053	0.004	N/A	0.891
Others	<0.001	0.060	0.003	0.004	0.474	0.264	0.033	0.891	N/A

* N/A: not applicable

Note: the significant level was set at 0.05 for main effect from Kruskal-Wallis test and became 0.0014 after Bonferroni correction

Table S7 Distribution of mammographic density by two categories and associated odds ratios with 95% confidence interval from binary logistic regression

Factors	Low density[a]		High density[a]		OR[d]	95% CI[e]	P
	N[b]	%[c]	N	%			value[f]
Age (years)	2315	N/A[g]	2552	N/A	0.93	0.93-0.94	<0.001
BMI (kg/m²)[h]	2315	N/A	2552	N/A	0.92	0.90-0.94	<0.001
Weight (kg)	2315	N/A	2552	N/A	0.97	0.97-0.98	<0.001
Province of residence	2315		2552				
Chongqing	164	7.08	327	12.81	1.00		
Gansu	265	11.45	95	3.72	0.18	0.13-2.43	<0.001
Guangxi	338	14.60	382	14.97	0.57	0.44-0.72	<0.001
Henan	55	2.38	379	14.85	3.45	2.46-4.85	<0.001
Shandong	371	16.03	160	6.27	0.22	0.17-0.28	<0.001
Xinjiang	634	27.39	625	24.49	0.49	0.40-0.62	<0.001
Yunnan	119	5.14	153	6.00	0.65	0.48-0.88	<0.001
Zhejiang	369	15.94	431	16.89	0.59	0.47-0.74	<0.001
Education	2315		2552				
None	78	3.37	49	1.92	1.00		
Primary school	347	14.99	200	7.84	0.92	0.62-1.37	0.671
Junior secondary school	695	30.02	699	27.39	1.60	1.10-2.32	0.013
Senior secondary/vocational and technical school	753	32.53	886	34.72	1.87	1.29-2.71	0.001
Higher vocational and technical college	324	14.00	495	19.40	2.43	1.66-3.57	<0.001
University and higher	118	5.10	223	8.74	3.01	1.97-4.58	<0.001
Education level	2315		2552				
Non-educated and primary	425	18.36	249	9.76	1.00		
Secondary	1448	62.55	1585	62.11	1.87	1.57-2.22	<0.001
Tertiary	442	19.09	718	28.13	2.77	2.28-3.37	<0.001
Occupation	2314		2552				
Professionals and technicians	271	11.71	429	16.81	1.00		
Managers and administrators in public sectors	164	7.09	184	7.21	0.71	0.55-0.92	0.009
Clerical support and administrative related workers	214	9.25	300	11.76	0.89	0.70-1.12	0.305
Businesswomen	67	2.90	103	4.04	0.97	0.69-1.37	0.867
Agricultural workers	211	9.12	170	6.66	0.51	0.40-0.66	<0.001
Plant and machine operators and assemblers	741	32.02	756	29.62	0.64	0.54-0.77	<0.001
Service and sales workers	168	7.26	195	7.64	0.73	0.57-0.95	0.180
Housewives	362	15.64	316	12.38	0.55	0.45-0.68	<0.001
Others	116	5.01	99	3.88	0.54	0.40-0.73	<0.001
Duration of passive smoking (years)[i]	1582	N/A	1683	N/A	0.98	0.98-0.99	<0.001
Age at menarche (years)	2309	N/A	1543	N/A	0.91	0.88-0.94	<0.001
Menopause	2312		2549				
Premenopausal	650	28.11	1237	48.53	1.00		
Postmenopausal	1662	71.89	1312	51.47	0.42	0.37-0.47	<0.001
Parity	2312		2549				
Nulliparous	2144	92.70	2317	90.90	1.00		
Parous	168	7.30	232	9.10	0.78	0.64-0.96	0.020
Age at first delivery (years)[j]	2143	N/A	2311	N/A	1.04	1.02-1.06	<0.001
Breastfeeding history	2312		2549				
No	1787	77.29	1868	73.28	1.00		

Yes	525	22.71	681	26.72	0.81	0.71-0.92	0.001
Cumulative duration of breastfeeding (months)[k]	1787	N/A	1868	N/A	0.97	0.96-0.98	<0.001
Personal history of benign breast disease	2312		2549				
No	1895	81.96	2176	85.37	1.00		
Yes	417	18.04	373	14.63	1.28	1.10-1.50	0.001
Number of 1st and/or 2nd degree relatives diagnosed with breast cancer[l]	992		1040				
= 1	590	59.48	550	52.88	1.00		
> 1	402	40.52	490	47.12	1.31	1.01-1.60	0.003

[a] Number of cases may vary due to missing data
[b] Number of cases
[c] Percentage of cases
[d] Adjusted odds ratio
[e] Confidence interval
[f] P values of binary logistic regression
[g] Not applicable
[h] Calculated by Weight (kg)/[Height (m)]^2
[i] Restricted to passive smokers
[j] Restricted to parous women
[k] Restricted to parous women who have breastfeeding history
[l] Restricted to women who have 1st and/or 2nd degree relatives diagnosed with breast cancer

Table S8 Distribution of mammographic density by two categories and associated odds ratios generated from multiple logistic regression with 95% confidence interval: 1. demographic model 2. menstrual and reproductive model

Factors	Low density (2308 cases)		High density (2543 cases)		AOR[c]	95% CI[d]	P value[e]
	N[a]	%[b]	N	%			
1. demographic model							
Age (years)	2308	N/A[f]	2543	N/A	0.93	0.92-0.94	<0.001
BMI (kg/m^2)[g]	2308	N/A	2543	N/A	0.92	0.87-0.96	<0.001
Province of residence							
Chongqing	164	7.10	326	12.80	1.00		
Gansu	265	11.50	95	3.70	0.12	0.09-1.17	<0.001
Guangxi	335	14.50	378	14.90	0.36	0.28-0.47	<0.001
Henan	54	2.30	379	14.90	3.37	2.36-4.83	<0.001
Shandong	371	16.10	159	6.30	0.21	0.15-2.27	<0.001
Xinjiang	631	27.30	622	24.50	0.36	0.28-0.46	<0.001
Yunnan	119	5.20	153	6.00	0.48	0.34-0.66	<0.001
Zhejiang	369	16.00	431	16.90	0.54	0.42-0.69	<0.001
Education level							
Non-educated and primary	424	18.40	248	9.80	1.00		
Secondary	1443	62.50	1578	62.10	1.47	1.20-1.80	<0.001
Tertiary	441	19.10	717	28.20	1.60	1.23-2.09	<0.001
Occupation							
Professionals and technicians	269	11.70	427	16.80	1.00		
Managers and administrators in public sectors	164	7.10	183	7.20	0.74	0.56-0.99	0.400
Clerical support and administrative related workers	214	9.30	299	11.80	0.83	0.65-1.07	0.155
Businesswomen	66	2.90	103	4.10	1.06	0.73-1.55	0.005
Agricultural workers	211	9.10	170	6.70	0.64	0.47-0.87	0.070
Plant and machine operators and assemblers	740	32.10	751	29.50	0.82	0.65-1.02	0.810
Service and sales workers	167	7.20	195	7.70	0.77	0.58-1.03	<0.001
Housewives	361	15.60	316	12.40	0.62	0.48-0.80	0.005
Others	116	5.00	99	3.90	0.60	0.43-0.86	<0.001
2. menstrual and reproductive model							
Age at menarche (years)	2308	N/A	2543	N/A	0.94	0.91-0.97	<0.001
Menopause							
Premenopausal	649	28.10	1234	48.50	1.00		
Postmenopausal	1659	71.90	1309	51.50	0.43	0.39-0.49	<0.001
Parity							
Nulliparous	2140	92.70	2312	90.90	1.00		
Parous	168	7.30	231	9.10	0.70	0.53-0.91	0.001
Personal history of benign breast disease							
No	1891	81.90	2170	85.30	1.00		
Yes	417	18.10	373	14.70	1.37	1.15-1.63	<0.001

[a] Number of cases
[b] Percentage of cases
[c] Adjusted odds ratio
[d] Confidence interval
[e] P values of binary logistic regression
[f] Not applicable
[g] Calculated by Weight (kg)/[Height (m)]^2

Chapter Four

Using AutoDensity percentage and area measures to characterise mammographic density and associated factors for women in China

Chapter four is submitted to The Oncologist as:

Li T, Tang L, Gandomkar Z, Heard R, Mello-Thoms C, Di G, Gu Y, Xiao Q, Shao Z, Nickson C, Brennan PC. *Using AutoDensity percentage and area measures to characterise mammographic density and associated factors for women in China.* The Oncologist. 2017.

Presentations on this paper was made at the following conferences:

- 5th World Congress on Breast Cancer, London, U.K., June 2017 (Appendix 3.8)
- 34th Annual Miami Breast Cancer Conference. Miami Beach, U.S. March 2017 (Appendix 3.9)

4.1 Bridging section for chapter four

BI-RADS classification is the most commonly used approach in mammographic density assessment across the world. It provides a description of possible implications of the assigned density categories on images of the likelihood that cancers will be obscured [1]. Similarly in China, BI-RADS approach is the standard assessment in both diagnosis and screening process with each case being read by at least two radiologists. However, the reproducibility of this classification is questionable because of the subjectivity of radiologists involved in the assessment process.

The accuracy and reliability of this visual approach is highly dependent on image quality (e.g. resolution and image contrast). In reality, there are many different manufacturers of mammographic equipment with various image acquisition parameters (e.g. Kilovolt Peak, Milliampere-second [mAs], anode/filter [targe/filter] combinations and calibration of Automatic Exposure Control [AEC] systems) which could result in variations in image appearance and perception of radiographic features [2]. Therefore it has been shown that the BI-RADS approach is likely to suffer reduced reproductively with wide inter-reader (kappa = 0.02-0.77) and intra-reader (kappa = 0.32-0.88) levels of agreement [3, 4]. This subjective variability has the potential to lead to inconsistency and excessive discrepancies in decision-making for mammographic density assessment and breast cancer risk prediction. Besides, visual approaches like BI-RADS is relatively time-consuming and labour-intensive compared to quantitative computer aided methods [5-7]. Therefore, quantitative approaches employing mathematical, statistical and physical principles are designed to offer more standardised assessment of mammographic density and they have the potential to be the future for density assessment.

The study “Using AutoDensity percentage and area measures to characterise mammographic density and associated factors for women in China” was submitted to *The Oncologist* and is under the process of peer-review. This study identified predictive factors of mammographic density for both Chinese women with and without breast cancer using a quantitative algorithm AutoDensity (BI-RADS was used to assess mammographic density in last chapter). AutoDensity is a fully automatic algorithm designed by the University of Melbourne in 2013 and verified with data collected from BreastScreen Victoria [8]. This algorithm uses interactive thresholding technique to segment and highlight the breast from the background within a mammogram, and then assesses the number of pixels over the intensity threshold providing a measure of breast area (Pixels of Breast Area). Simultaneously, an optimal threshold outlines and highlights the dense tissue within the breast and sums the pixels in this area (Pixels of Dense Area). The resultant percentage mammographic density is calculated by dividing Pixels of Dense Area by Pixels of Breast Area and multiplied by 100% (A detailed explanation of the algorithm is presented under Mammographic Density Measurement in the submitted paper).

In the previous chapter, we used the more traditional BI-RADS approach to assess mammographic density. In this section of the thesis, by using an automated algorithm to measure density, we can examine if these newer quantifiable measurements offer any additional or complimentary information.

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4.2 Submitted paper of 'Using AutoDensity percentage and area measures to characterise mammographic density and associated factors for women in China'

The Oncologist

Using AutoDensity percentage and area measures to characterise mammographic density and associated factors for women in China

--Manuscript Draft--

Manuscript Number:	
Full Title:	Using AutoDensity percentage and area measures to characterise mammographic density and associated factors for women in China
Short Title:	Predictors of breast density in Chinese women
Article Type:	Original Article
Section/Category:	Breast Cancer
Keywords:	Mammographic breast density, Predictive factors, Quantitative measurement, AutoDensity, Chinese women
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Manuscript Region of Origin:	AUSTRALIA
Abstract:	Background: Characteristics of mammographic density for Chinese women are under studied. This study aims to identify factors associated with mammographic density in China using a quantitative method. Materials and Methods: Mammographic density was measured for a total of 1071 (84 with and 987 without breast cancer) women using an automatic algorithm AutoDensity. Pearson tests examined relationships between density and continuous variables and t-tests compared differences of mean density values between groupings of categorical variables. Linear models were built using multiple regression. Results: Percentage density and dense area were positively associated with each other for cancer-free (r=0.487, p<0.001) and cancer groups (r=0.446, p<0.001), respectively. For women without breast cancer, weight and BMI (p<0.001) were found to be negatively associated (r=-0.237, r=-0.272) with percentage density whereas positively associated (r=0.110, r=0.099) with dense area; age at mammography was found to be associated with percentage density (r=-0.202, p<0.001) and dense area (r=-0.086, p<0.001) but did not add any prediction within multivariate models; lower percentage density was found within women with secondary education background or below compared to women with tertiary education. For women with breast cancer,

	percentage density demonstrated similar relationships with that of cancer-free women whilst breast area was the only factor associated with dense area (r=0.739, p<0.001). Conclusion: This is the first time that mammographic density was measured by a quantitative method for women in China and identified associations should be useful to health policy makers who are responsible for introducing effective models of breast cancer prevention and diagnosis.
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Title page

Title: Using AutoDensity percentage and area measures to characterise mammographic density and associated factors for women in China

Running title: Predictors of breast density in Chinese women

Authors:

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Key words: Mammographic breast density, Breast cancer, Predictive factors, AutoDensity, Chinese women

Funding: There is no funding source in this study

Abstract

Background: Characteristics of mammographic density for Chinese women are under studied. This study aims to identify factors associated with mammographic density in China using a quantitative method.

Materials and Methods: Mammographic density was measured for a total of 1071 (84 with and 987 without breast cancer) women using an automatic algorithm AutoDensity. Pearson tests examined relationships between density and continuous variables and t-tests compared differences of mean density values between groupings of categorical variables. Linear models were built using multiple regression.

Results: Percentage density and dense area were positively associated with each other for cancer-free (r=0.487, p<0.001) and cancer groups (r=0.446, p<0.001), respectively. For women without breast cancer, weight and BMI (p<0.001) were found to be negatively associated (r=-0.237, r=-0.272) with percentage density whereas positively associated (r=0.110, r=0.099) with dense area; age at mammography was found to be associated with percentage density (r=-0.202, p<0.001) and dense area (r=-0.086, p<0.001) but did not add any prediction within multivariate models; lower percentage density was found within women with secondary education background or below compared to women with tertiary education. For women with breast cancer, percentage density demonstrated similar relationships with that of cancer-free women whilst breast area was the only factor associated with dense area (r=0.739, p<0.001).

Conclusion: This is the first time that mammographic density was measured by a quantitative method for women in China and identified associations should be useful to health policy makers who are responsible for introducing effective models of breast cancer prevention and diagnosis.

Key words: Mammographic breast density, Predictive factors, Quantitative measurement, AutoDensity, Chinese women

Implication for Practice

It is the first study using a fully automatic algorithm to measure mammographic density for Chinese women. Two density metrics were considered - percentage density and dense area measures, and the impact of each metric on various associations were explored. Differences of predictors between the two density metrics emphasise the importance of understanding better what each metric represents for both women with and without breast cancer and ensuring that approaches are standardised, particularly for women with cancer. This information cancer be sued to help inform clinical decision making regarding the selection of appropriate density metrics in women with breast cancer at clinical environment in China.

Introduction

Breast cancer is the most commonly diagnosed neoplasm amongst women in China and it is one of the leading causes of cancer death in females [1]. Mammographic density, describing the amount of fibrous and glandular tissue within the breasts, is consistently demonstrated to be an important risk factor for breast cancer. Women with highest density were shown to have 2 to 6 times higher risk in developing breast cancer compared to those with the lowest [2]. Well-confirmed factors associated with higher density include younger age, lower body mass index (BMI), pre-menopausal status, nulliparity, late age at first delivery, a smaller number of live births and family history of breast cancer [3]. However, current knowledge around density data is largely based on women from westernised countries and the characteristics of mammographic density for women in China are under studied. From limited data that are available, Chinese mammographic density was shown to be positively associated with earlier age at menarche, pre-menopausal status, smaller number of children, later age at first delivery and personal history of benign breast disease [4, 5]. Also, larger breast size was found to be negatively associated with density amongst pre-menopausal women in China [6].

Even though the previously mentioned studies investigated Chinese mammographic density, the associations predominantly focused on reproductive agents. In addition, all previous studies used the qualitative method of Breast Imaging Reporting and Data System (BI-RADS) classifications. Despite being the most commonly used assessment approach of mammographic density in both clinical settings and screening programs in China and many other countries [7, 8], the BI-RADS classification has been shown to suffer limited reproducibility with wide inter- (kappa = 0.02-0.77) and intra-reader (kappa = 0.32-0.88) variations [9]. This subjectivity has the potential to result in inconsistent breast cancer risk prediction and unnecessary discrepancies in decision-making for density assessment [10]. As a consequence, quantitative methods using mathematical and physical principles have been designed to promote objective and consistent assessment of mammographic density.

The aim of the current work is to identify predictive factors of mammographic density for both Chinese women with and without breast cancer using a quantitative algorithm. Two density metrics will be considered - percentage density (PD) and dense area (DA) measures and the impact of each metric on various associations will be explored.

Material and Methods

Study design and population

This was a retrospective cross-sectional study. A total of 1000 women without breast cancer were recruited from the Breast Cancer Screening Program (BCSP) organised by Fudan University Shanghai Cancer Centre (FUSCC) from March 2015 to June 2016. Another 100 women who had a pathologically confirmed diagnosis of breast cancer (ductal carcinoma in situ included) were randomly selected by Excel RAND function from the clinical environment at FUSCC during the same time period.

Ethical approval was obtained from the Human Research Ethics Committee of the University of Sydney (Project number: 2014/768) and the Institutional Review Board of Fudan University Shanghai Cancer Centre (Project number 1503144-11). All data were collected anonymously at this retrospective study and informed consent were not applicable.

Data collection

Women's characteristics were obtained from the registration form and the discharge summary contained within the health record for each woman with breast cancer and through a BCSP questionnaire for breast cancer-free women. All the information for women were de-identified, with dedicated study IDs used to link mammograms and other data.

Details on height, weight, age at menarche, age at menopause, age at first delivery and duration of breastfeeding were collected as continuous variables. Age at mammography was calculated by the assessment date and date of birth.

Ethnicities other than Han Chinese were classified into a single non-Han grouping and level of education was coded into a dichotomous variable in order to increase statistical power since these two variables with more than two groupings resulted in very uneven and low numbers in certain groups. Geographic location was also coded as a categorical variable with two groupings (Shanghai and other locations) since the program was conducted in Shanghai and consequently most of the participants came from Shanghai. Menopause status, parity history, number of children, breastfeeding history, personal history of breast cancer, family history of breast cancer, degree of consanguinity, smoking history and history of alcohol consumption were also classified into two groupings which were specific to each variable detailed in the results.

All of the factors of interest mentioned above were collected for women without breast cancer, however ethnicity, smoking, alcohol history, level of education and geographic location were unavailable for women with cancer since these details were not recorded on admission to FUSCC.

Image acquisition

Mammograms taken closest in time to the cancer diagnosis and to the questionnaire completion were obtained for women with and without breast cancer, respectively. For all women, cranio-caudal (CC) projection of both sides of breasts (where available) were accessed and these mammograms were acquired by Mammomat Inspiration (Siemens; Erlangen, Germany) or Selenia (Hologic, Inc., Bedford, MA, USA) units.

Mammographic density measurement

Mammographic density was measured by a fully automatic algorithm AutoDensity, which identifies both areas of dense tissue (dense area) and of breast tissue (breast area) in mammograms and then classifies percentage mammographic density. This algorithm, which has been validated elsewhere [11], automatically finds an optimal threshold for each mammogram independently from any other images in a data set, in order to segment the breast from the background within a mammogram and outline the dense tissue within the breast (Fig 1a). Both the dense area (Fig 1b) and breast area (Fig 1c) are highlighted and the resultant PD was produced by dividing the dense area (number of pixels) by the breast area (number of pixels) and expressing in a percentage.

Mammograms of both left and right breasts for each woman were assessed and the average value of both sides was used for all the statistical analyses.

Statistical analysis

The data derived from both the screening program (cancer-free women) and clinical settings (cancer-women) were subjected to two types of statistical analysis: univariable and multivariable analysis. Women with and without cancer were analysed as separate groups, because the variable sets available for each group differed slightly.

The relationship between PD and continuous variables was assessed using the Pearson correlation coefficient (r). Difference of mean values of PD was compared between the groupings of each dichotomous variable using t-tests.

To identify key factors associated with PD, linear model building was performed using stepwise multiple regression adopting the significant variables from Pearson tests and t-tests except those restricted to women with specific conditions[1]. Residuals of the PD were examined to check for assumptions of linear models by using regression scatterplots and histograms. R-squared statistics were used to assess the goodness of fit of the models.

All of the statistical tests performed for PD were repeated for DA.

SPSS (IBM SPSS statistics for windows, version 22.0) statistical package was used for all statistical analyses, and two-tailed tests of significance were employed using a significance level of 0.05.

Results

Characteristics of participants

After excluding cases with unilateral images, a total of 1071 (84 with and 987 without breast cancer) women were finally selected for statistical analysis. Table 1 shows the characteristics for both groups of women.

[1] For example, age at menopause was restricted to post-menopausal women only, so this variable was not used in the model building

Figure 2 depicts the distribution of PD, DA and breast area from AutoDensity algorithm for both cancer and cancer-free women.

Association between PD and DA

PD and DA were positively correlated for cancer-free women ($r = 0.487$, $p < 0.001$) and for women with cancer ($r = 0.446$, $p < 0.001$), respectively.

Determinants of mammographic density

The output from the Pearson and t-tests for both PD and DA are shown in table 2 for both cancer and cancer-free women.

Women without breast cancer

Age at mammography ($r = -0.202$), weight ($r = -0.237$), BMI ($r = -0.272$) and age at menarche ($r = -0.078$) were significantly and negatively associated ($p < 0.001$) with PD. Lower PD ($p < 0.001$) was found within post-menopausal women and women with secondary education background or below compared to pre-menopausal women and women with tertiary education.

DA was found to be positively associated with breast area ($r = 0.790$, $p < 0.001$), body weight ($r = 0.110$, $p < 0.001$) and BMI ($r = 0.099$, $p = 0.002$). Negative associations were shown between DA and age at mammography ($r = -0.086$, $p = 0.007$) and age at menarche ($r = -0.080$, $p = 0.012$). DA was also found to be lower in women with a history of nulliparity ($p = 0.014$) and lack of breastfeeding ($p= 0.002$) compared to women without such histories.

Women with breast cancer

Negative associations were found between PD and age at mammography ($r = -0.451$, $p < 0.001$), weight ($r = -0.495$, $p < 0.001$), BMI ($r = -0.520$, $p < 0.001$) and age at menopause ($r = -0.290$, $p = 0.046$). Reduced PD was also found in women with post- compared with pre-menopausal status ($p < 0.001$).

Within this group of women, breast area was positively associated with DA ($r = 0.739$, $p < 0.001$).

Linear models

Linear models were built for both PD and DA for each of the two groups of women (where for menopause status, 0 = Pre-menopausal and 1 = Post-menopausal, and for education level, 0 = Secondary and below and 1 = Tertiary). The equations of the 4 most-effective models (I-IV) are presented as follows and the residuals of these models were all normally distributed.

I: PD (cancer-free) = 57.91 - 1.00*BMI - 4.42*Menopause status + 2.19*Education level. This model predicted 12.13% of the variation in PD (F = 45.21, p < 0.001).

II: DA (cancer-free) = 49650.58 - 2251.99*BMI - 7921.84*Menopause status + 5582.45*Education level + 0.32*Breast area. This model successfully predicted 64.92% of DA variation for women without breast cancer (F = 606.26, p < 0.001).

III: PD (cancer) = 97.16 - 1.80*BMI - 0.43*Age. BMI and age can account for 38.82% of the variation in PD (F = 25.70, p < 0.001).

IV: DA (cancer) = 0.28*Breast area. This model with only one predictor predicted 54.56% of the variation in DA for cancer women (F = 98.48, p < 0.001).

Discussion

This study, for the very first time, identified a number of factors associated with mammographic density for women both with and without breast cancer in China by employing a fully automatic algorithm AutoDensity. Two measures provided by this algorithm were used to assess mammographic density in our study: PD and DA, which we found were moderately correlated with each other. Previous studies that compared the differences of prediction of breast cancer risk between these two measures suggested that the cancer risk associated with DA was stronger than or as strong as that with PD [12, 13]. By combining the effects of the constituting measures [14], PD delivers limited information regarding the absolute amount of dense tissues which are potentially at risk of undergoing a malignant transformation [15]. To illustrate, when a certain amount of dense tissue is measured within a small breast, a relatively higher percentage will be provided, compared to the identical amount of target tissue measured within a large breast. However, even though it may therefore be argued that PD is not an appropriate measure of choice in etiologic research, it is very commonly used to present mammographic density since it is an easily applicable and practicable prognostic factor of breast cancer risk [16]. This might partially result from the fact that percentage density appears to be less affected by technical issues such as the degree of breast compression [12].

Various determinants on both measures were demonstrated within our study, however predictors were not necessarily consistent for PD and DA. This effect is most clearly seen for breast area, which accounted for more than half of the DA variation for both cancer and cancer-free women, whereas it appeared to have no impact on PD. This discrepancy is most obvious in women diagnosed with cancer since breast area is the only factor arising from univariate analysis that was statistically significant.

Associations of body weight and BMI were dependent on which of the two measures were used. The negative associations of mammographic density with increasing BMI and increasing weight that have been shown for the percentage metric have been shown for several decades across many populations [17, 18]. In contrast, DA was found to be positively associated with weight and BMI, which is not aligned with most of the westernised-based literature [13, 16-18]. However a similar finding was shown in studies involving Chinese women living in westernised and developed countries [19, 20]. The alignment with our work suggests that the positive association (although not strong) between BMI/weight and DA might be unique to Chinese mammographic density. Nevertheless, this hypothesis will need further study to be proven or disproven. The question, however, remains of why would associations appear in opposite directions in our work focusing on Chinese women depending on whether PD or DA is used as the dependent variable.

Our work showed that the factors associated with PD of women with breast cancer were similar to those of women without cancer, but this again was not the case using DA. A possible explanation for the differences between the two metrics might be that cancer lesions contribute a greater or smaller amount (depending on tumour size) to the DA measurement than the percentage value. This is because once a space occupying lesion is evident, the size of the overall breast is likely to be increased to accommodate the cancer lesion [21, 22], or associated inflammation thereby contributing to both the numerator and denominator of the PD calculation (thus cancelling out or at least minimising any change in the measure due to the presence of cancer). The DA measurement on the other hand would include the cancer without any normal tissue compensation and because the cancer size will not be related to the independent variables, any possible associations are prone to be removed. This would support the use of PD as opposed to DA for at least breasts with cancer when true associations are being sought, despite the current popularity of area measures (see above).

Another important finding was that women in tertiary education appeared to have denser breasts compared to those women with lower level of education. This finding is consistent with previous studies from Europe and North American with a focus on Caucasian women [23, 24]. To our knowledge, this is the first time the relationship between mammographic density and education for women in China has been shown. This could have important future implications since Chinese people are increasingly keen to undergo tertiary education, for example, the graduation rate from tertiary education institutions increased by three times over the last two decades [25]. However, other socioeconomic factors, e.g. employment, household income, home ownership, urbanisation/ruralisation and social class, associated with higher education levels, may at least in part impact on this relationship [24].

Despite displaying a negative association with mammographic density within the univariate analysis, age at mammography did not add any prediction beyond other variables within the multivariate model for PD or DA in women without breast cancer. This is inconsistent with previous work based on either Chinese [6, 19] or other populations [13, 16, 26] and may suggest a characteristic only relevant to women in our study and not applicable to the general Chinese female population. Another explanation is that the contributions of other elements within the multivariate models had a much greater impact than that of age at mammography or that age has already been modelled by proxy through menopause, which is highly correlated to age in the optimal model ($r = 0.762$, $p < 0.001$).

The available data around associations between density and smoking history and alcohol consumption for populations other than Chinese are inconsistent. Some studies found a positive association with alcohol consumption [27, 28] and a negative association with smoking history [29, 30], whereas others showed no associations [26, 31]. We also failed to identify any association with these two lifestyle factors, which is consistent with two previous work focusing on Chinese women [4, 6], but may be partially explained by the low number of women in our study with a positive smoking or alcohol intake history (less than 15%), and information only being available for women without breast cancer. With regard to ethnic variations, this is the first time that density was studied between women of Han origin and non-Han origin in China and no associations were shown, which was different to that seen for ethnic variations in other populations [32, 33]. This finding however should be treated with some degree of caution since all the ethnic minority groups at data collection were recoded as Non-Han origin in order to increase statistical power, since the total number of women in this study belonging to specific ethnic minorities was very low (<2%). This aggregation could be obscuring minority-specific observations, an issue that needs to be addressed in further work.

This study used a fully automatic algorithm to measure mammographic density for women in China. Even though, in the clinical and screening settings in China, the BI-RADS scheme is the most commonly used classification to assess density, this visual approach is relatively time-consuming and requires more workload from radiologists compared to quantitative computer aided methods [34, 35]. Also, the reproducibility of BI-RADS classification is questionable due to the subjectivity of readers involved with density assessment [36]. Even though it is the first time that AutoDensity has been used for density assessment for Chinese women, it has been shown to be comparable to Cumulus, a globally employed semi-automatic algorithm, in terms of association with breast cancer risk and breast cancer screening outcomes in Australia [11]. This approach allowed important associations to be identified but also revealed that one must standardise and understand better the metric being used. In addition, AutoDensity is a breast area-based algorithm instead of a volume-based algorithm. AutoDensity is therefore based on the projected area, rather than the volume of breast tissues, and consequently finds a threshold between dense and non-dense areas. Therefore the thickness of the breast is not taken into account during the AutoDensity measurement. This potential source of error in measurement is likely to attenuate the observed association between percentage density/dense area and potential determinants and risk of breast cancer.

Nevertheless, this study has a few limitations. As menopause was shown to be an important and contributing factor for Chinese mammographic density, different menopausal status might have important influences on the density values. However, we did not separate pre-, peri- and post-menopausal women in our study, which will be the focus of further work. Also, the small sample size of women in the cancer group is noted. A larger sample of women with cancer may have revealed further relationships, and future studies seeking to recruit larger samples of women diagnosed with cancer are recommended.

In conclusion, this study for the first time in China demonstrated important determinants of mammographic density in AutoDensity-generated PD and DA values. Differences between the two density metrics emphasise the importance of understanding better what each metric represents for both women with and without breast cancer and ensuring that approaches are standardised. We believe our findings should be valuable to health policy makers who are responsible for introducing effective models of breast cancer prevention and diagnosis.

Conflict of interest

The authors declared no conflict of interest.

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Figure legends

Figure 1: Output from AutoDensity algorithm.

a: white line **delineates** the edge of the breast and the edge of dense tissue. b: mask of dense issue within the breast. c: mask of area of the breast

Figure 2: Distribution of mammographic features.

a: Percentage mammographic density (%) of women without breast cancer. b: Area of dense tissue (pixel) in mammograms of women without breast cancer. c: Area of breast tissue (pixel) in mammograms of women without breast cancer. d: Percentage mammographic density (%) of women with breast cancer. e: Area of dense tissue (pixel) in mammograms of women with breast cancer. f: Area of breast tissue (pixel) in mammograms of women with breast cancer.

Tables

Table 1 Characteristics of women with and without breast cancer

Variables	Women without breast cancer		Women with breast cancer	
Continuous	**N[a]**	**M±SD[b]**	**N**	**M±SD**
Percentage mammographic density (%)	987	32.69±11.66	84	30.84±13.64
Dense area (pixels)	987	67957.49±52047.44	84	73672.17±63341.33
Breast area (pixels)	987	210179.29±134555.93	84	248991.78±169934.14
Age at mammography (years)	987	48.94±9.49	84	52.99±11.19
Height (cm)[c]	987	160.63±4.74	84	159.73±3.80
Weight (kg)[d]	987	57.84±7.90	84	61.75±9.01
BMI (kg/m^2)[e]	987	22.40±2.81	84	24.19±3.34
Age at menarche (years)	987	14.22±1.88	84	15.20±1.62
Age at menopause (years)[f]	370	50.39±3.80	48	50.23±3.81
Age at first delivery[g]	926	27.84±3.48	84	25.54±3.46
Duration of breastfeeding[h]	762	7.21±4.14	77	15.92±14.03
Categorical	**N**	**%[i]**	**N**	**%**
Menopause status				
Pre-menopausal	617	62.50	36	42.86
Post-menopausal	370	37.50	48	57.14
Parity status				
Nulliparous	61	6.18	0	0.00
Parous	926	93.82	84	100.00
Number of children[g]				
=1	853	92.10	50	59.52
>1	73	7.90	34	40.48
Breastfeeding history				
No	225	22.80	7	8.33
Yes	762	77.20	77	91.67
Personal history of breast cancer				
No	977	98.99	83	98.81
Yes	10	1.01	1	1.19
Family history of breast cancer				
No	915	92.71	76	90.48

Yes	72	7.29	8	9.52
Degree of consanguinity[j]				
1st degree	47	65.28	7	87.50
2nd degree	25	34.72	1	12.50
Ethnicity				
Non-Han origin	11	1.11	N/A[k]	N/A
Han origin	976	98.89	N/A	N/A
Smoking history				
No	967	97.97	N/A	N/A
Yes	20	2.03	N/A	N/A
Alcohol consumption				
No	864	87.54	N/A	N/A
Yes	123	12.46	N/A	N/A
Level of education				
Secondary and below	176	17.83	N/A	N/A
Tertiary	811	82.17	N/A	N/A
Geographic location				
Shanghai	800	81.05	N/A	N/A
Others	187	18.95	N/A	N/A

[a] Number of cases

[b] Mean ± standard deviation for continuous variables

[c] Height range for women without breast cancer: 146.00-180.00, height range for women with cancer: 15.00-171.00

[e] Weight range for women without breast cancer: 38.00-90.00, weight range for women with cancer: 42.00-89.00

[e] Calculated by Weight (kg)/[Height (m)]^2, weight range (cancer-free):

[f] Restricted to post-menopausal women

[g] Restricted to parous women

[h] Restricted to women with breastfeeding history

[i] Percentage of cases for categorical variables

[j] Restricted to women with family history

[k] Not available

Table 2 Output from univariate analysis of percentage dense and dense area for women with and without breast cancer

Variables	Women without breast cancer				Women with breast cancer			
	Percentage density		Dense area		Percentage density		Dense area	
Continuous	**r[a]**	**P[b]**	**r**	**P**	**r**	**P**	**r**	**P**
Breast area (pixels)	-0.043	0.174	0.790	<0.001	-0.142	0.197	0.739	<0.001
Age at mammography (years)	-0.202	<0.001	-0.086	0.007	-0.451	<0.001	-0.011	0.920
Height (cm)	0.030	0.352	0.034	0.283	-0.028	0.803	0.041	0.708
Weight (kg)	-0.237	<0.001	0.110	<0.001	-0.495	<0.001	-0.075	0.498
BMI (kg/m^2)[c]	-0.272	<0.001	0.099	0.002	-0.520	<0.001	-0.088	0.425
Age at menarche (years)	-0.078	0.014	-0.080	0.012	-0.084	0.447	0.104	0.344
Age at menopause (years)[d]	0.007	0.887	-0.003	0.950	-0.290	0.046	-0.225	0.124
Age at first delivery[e]	-0.026	0.437	-0.014	0.678	0.157	0.155	-0.021	0.852
Duration of breastfeeding[f]	-0.068	0.059	0.058	0.110	-0.173	0.133	-0.081	0.486
Categorical	**M±SD[g]**	**P**	**M±SD**	**P**	**M±SD**	**P**	**M±SD**	**P**
Menopause status								
Pre-menopausal	34.85±10.89	<0.001	72178.87±53101.24	<0.001	37.06±11.36	<0.001	78641.39±60101.65	0.364
Post-menopausal	29.09±12.01		60918.05±49515.81		26.17±13.44		69945325±66046.94	
Parity status								
Nulliparous	34.00±9.96	0.367	53909.78±41139.40	0.014		N/A[h]		N/A
Parous	32.61±11.76		68882.88±52573.07					
Number of children[e]								
=1	32.74±11.58	0.250	69656.06±52925.99	0.101	33.02±13.06	0.075	72208.90±60232.08	0.954
>1	31.09±13.69		59848.41±47664.33		27.62±14.04		75824.03±68528.80	
Breastfeeding history								
No	31.76±11.15	0.173	58874.45±41826.50	0.002	39.18±14.20	0.091	95541.71±98622.02	0.380
Yes	32.97±11.80		70639.49±54436.41		30.08±13.43		71684.03±59713.81	
Personal history of breast cancer								
No	32.71±11.66	0.724	67935.83±52101.27	0.939	30.80±13.72	0.832	72544.88±62872.93	0.132
Yes	31.40±1.33		70073.65±48958.06					
Family history of breast cancer								
No	32.58±11.76	0.278	68018.35±52313.70	0.991	30.74±13.43	0.844	73065.19±63672.86	0.644
Yes	34.13±10.27		67184.01±48874.61		31.75±16.57		79438.44±63969.64	

Degree of consanguinity[i]								
1st degree	33.31±9.55	0.354	67363.28±46429.23	0.857	29.14±16.02	0.269	83744.14±67831.43	0.659
2nd degree	35.68±11.56		66846.98±54173.46		N/A		N/A	
Ethnicity								
Non-Han origin	37.25±3.81	0.192	98537.64±65684.04	0.255		N/A		N/A
Han origin	32.64±11.65		67612.84±51812.92					
Smoking history								
No	32.72±11.63	0.625	67877.39±51861.52	0.902		N/A		N/A
Yes	31.43±13.30		71830.55±61786.61					
Alcohol consumption								
No	32.84±11.61	0.291	68481.84±52155.77	0.365		N/A		N/A
Yes	31.65±11.99		64274.29±51338.71					
Level of education								
Secondary and below	28.67±12.19	<0.001	61590.39±47918.12	0.040		N/A		N/A
Tertiary	33.56±11.36		69339.25±52827.48					
Geographic location								
Shanghai	32.50±11.50	0.276	67946.45±51558.11	0.861		N/A		N/A
Others	33.53±12.30		68004.75±54233.54					

[a] Pearson's correlation coefficient for continuous variables

[b] P values from Pearson and t-tests for continuous and categorical variables, respectively

[c] Calculated by Weight (kg)/[Height (m)]^2

[d] Restricted to post-menopausal women

[e] Restricted to parous women

[f] Restricted to women with breastfeeding history

[g] Mean ± standard deviation

[h] Not applicable due to insufficient number/unavailable data

[i] Restricted to women with family history

Figures

Figure 1

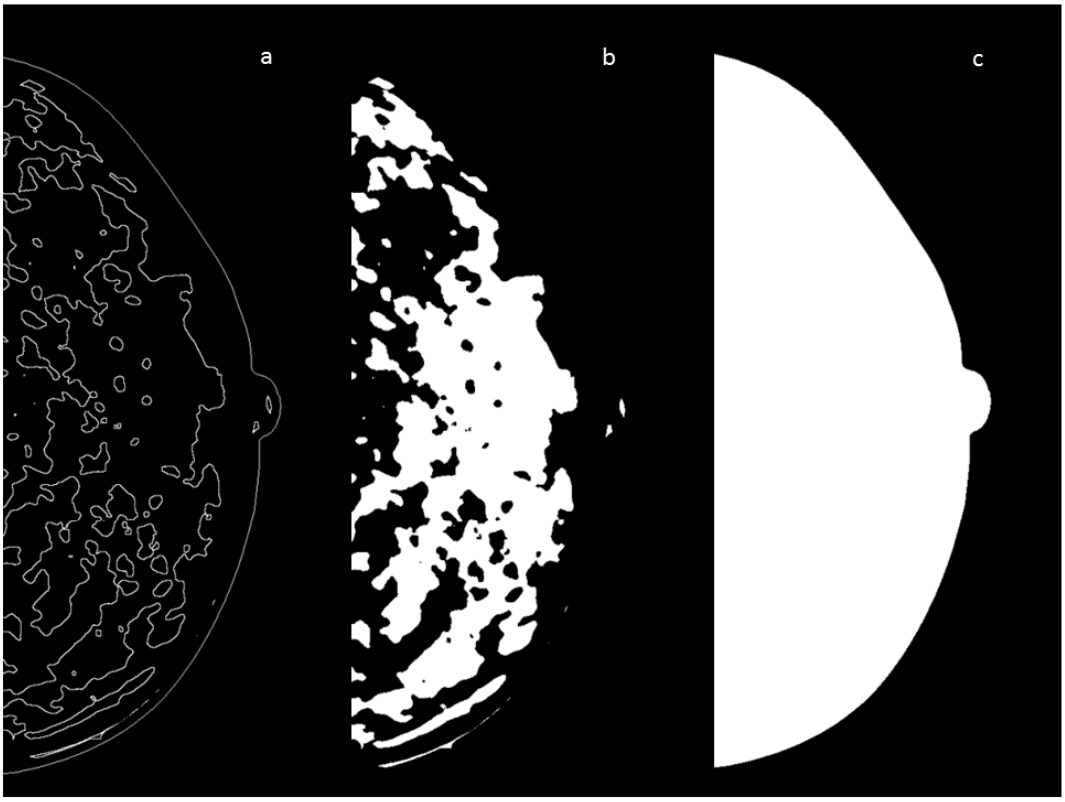
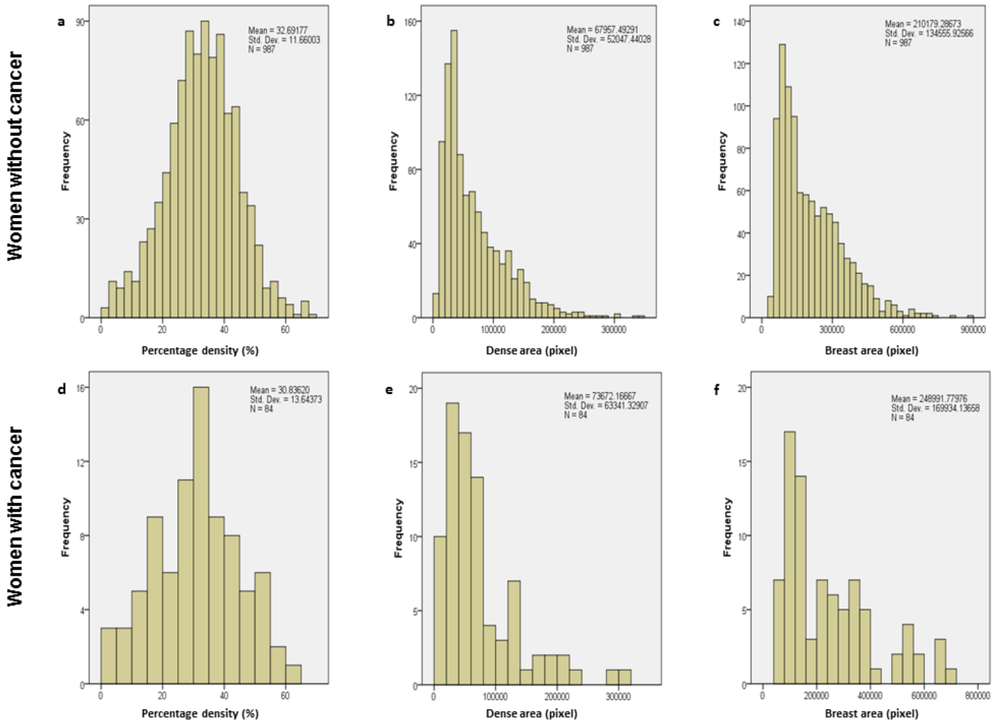


Figure 2



Women without cancer
Women with cancer
a
Mean = 32.69177
Std. Dev. = 11.66003
N = 987
Frequency
Percentage density (%)
b
Mean = 67957.49291
Std. Dev. = 52047.44028
N = 987
Frequency
Dense area (pixel)
c
Mean = 210179.28673
Std. Dev. = 134555.92566
N = 987
Frequency
Breast area (pixel)
d
Mean = 30.83620
Std. Dev. = 13.64373
N = 84
Frequency
Percentage density (%)
e
Mean = 73672.16667
Std. Dev. = 63341.32907
N = 84
Frequency
Dense area (pixel)
f
Mean = 248991.77976
Std. Dev. = 169934.13658
N = 84
Frequency
Breast area (pixel)

22

Chapter Five

Mammographic density and other risk factors for breast cancer amongst women in China

Chapter five is accepted for publication (In Press) as:

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The full original (non-contracted) manuscript is contained in Appendix 2.2.

Presentations on this paper was made at the following conference:

15th ST. Gallen International Breast Cancer Conference, Vienna, Austria, March 2017 (Appendix 3.10)

5.1 Bridging section for chapter five

The previous two chapters examined characteristics of mammographic density, including density distribution by BI-RADS classification, factors associated with BI-RADS density for women without breast cancer in national screening context, and predictive factors of percentage density and dense area for women with and without breast cancer. However the potential relationship between mammographic density and breast cancer was not covered in the previous two studies. Even though there are a large number of studies examined the relationship between density and cancer in westernised countries, limited studies are available on this topic for women in China (discussed in the deficiencies in Chapter one). Therefore we decided to further examine the potential risk factors of breast cancer to check whether this relationship in Chinese women is the same and as important as that in females from westernised countries.

The study "Mammographic density and other risk factors for breast cancer amongst women in China" was submitted and accepted as a paper in *The Breast Journal*. The study examined the relationships between potential risk factors and breast cancer, with a particular focus on mammographic density. The sample in this study included women in China only and came from a localised (on city level) screening program in Shanghai, China. The work was shortened to accommodate the Journal's requirements and therefore in this chapter we include the publication (in accepted manuscript format) accompanied by two supplementary tables (will only be available online in the journal website after being published). The full work which, due to word limits, could not be contained within the accepted article, but it is shown in Appendix 2.2.

5.2 Statement from author confirming authorship contribution of the PhD candidate

As a co-author of the accepted paper "Mammographic density and other risk factors for breast cancer amongst women in China", we confirm that Tong Li has made the following contributions:

- Conception and design of the research
- Data collection
- Analysis and interpretation of the findings
- Manuscript preparation, editing and critical appraisal of content

Lichen Tang .... Date 10-5-2017

Ziba Grandomkar .... Date 4-5-2017

Rob Heard .... Date 4-5-2017

Claudia Mello-Thoms .... Date: 8/5/2017

Zhimin Shao .... Date: 10/5/2017

Patrick Brennan .... Date 8/5/17

The Breast Journal

Mammographic density and other risk factors for breast cancer amongst women in China

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Key Words:	Mammographic density, Breast density, Risk factor, Breast cancer, Chinese women

TITLE: Mammographic density and other risk factors for breast cancer amongst women in China

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KEY WORDS: Mammographic breast density, Risk factor, Breast cancer, China, Chinese women.

Breast cancer is the most common neoplasm diagnosed amongst females in China and it is one of the leading causes of female cancer death, however the risk factors for breast cancer are not fully understood for Chinese women (1). One of the key risk factors shown to be relevant for westernised women is mammographic density but previously used observer Breast Imaging Reporting and Data System (BI-RADS) technique to assess density is shown to have wide inter- and intra-observer variations (2). Therefore quantitative techniques are increasingly recommended to assess this important parameter (3). The aim of the current study is to identify risk factors of breast cancer for Chinese women, with attention paid to mammographic density using quantitative measurements.

This study was approved by the Human Research Ethics Committee of the University of Sydney (Project number: 2014/768). Women of 84 with and 987 without breast cancer were randomly selected from FUSCC from March 2015 to June 2016.The women with breast cancer were diagnosed within the hospital environment at FUSCC, whilst the other women were recruited from the Breast Cancer Screening Trail (BCST) organised by FUSCC. Demographic, lifestyle and reproductive characteristics were obtained from the registration form and the discharge summary in health record for each woman with breast cancer and through a BCST questionnaire for breast cancer-free women. For all of the women, mammograms were acquired for cranio-caudal projection of both breasts. Mammographic density was measured by a fully automatic algorithm AutoDensity (4), which identifies both dense and breast areas in mammograms and then classifies mammographic density. Differences in characteristics between cancer and cancer-free women were assessed using t tests and chi-square tests. Binary logistic regression was then conducted for variables that were statistically significant from either the t test or the chi-square test to produce odds ratios and 95% confidence intervals. Categorical variables with 0 frequency in any one of the categories were excluded from this test. The whole data set was then divided into two subsets based on menopause status, one for pre-menopausal and another for post-menopausal women. The statistical tests mentioned above were repeated for each subset.

Table 1 shows the baseline differences of characteristics for two groups of women, and the outputs from binary logistic regression. Overall it appears that large breast area, increasing age, increasing BMI, later age at menarche, earlier age at first delivery, longer duration of breastfeeding, post-menopause status, greater number of children and a breastfeeding history are important agents. The results for pre- and post-menopausal women are shown in supplementary tables S1 and S2, respectively. The rest of this commentary however will focus on the implications around our findings on mammographic density.

We failed to identify any association for mammographic density with breast cancer using percentage or dense area parameters, a finding which is consistent and inconsistent with previous work: one previous study which recruited 86 and 28,302 women with and without breast cancer, respectively, from a screening trial across 4 Chinese cities of similar size to our study also showed no association between density and cancer (5); in contrast another large cross-sectional study, involving 2,527 cancer and 3,394 cancer-free women, reported that, compared to women without breast cancer, mammographic density was lower and higher for cancer women within the 40-49 and 55-71 age groups, respectively, however there was no association for women aged 50-54 (6). This difference between our work and the latter study might be explained by the fact that age-dependent variations were not assessed in our work, thereby obscuring specific observations. Instead we focused on categorising our women based on menopausal status. Another possible explanation is that, unlike other studies that used qualitative (i.e. BI-RADS classification) assessment, we used quantitative approach to assess mammographic density, thus potentially impacting on the results, but the possibility of this impact requires further study. Nonetheless from our findings and that of previous studies, the possibility remains that the relationship between mammographic density and breast cancer for women in China may not be as strong as or at least could be different from that demonstrated in other populations, particularly those involving western women. This hypothesis will need further work to be proven or disproven.

In summary, this study demonstrated risk factors of breast cancer for Chinese women with a particular focus on quantitative methods of mammographic density. The lack of association between breast cancer and mammographic density could have significant implications for breast cancer screening strategies.

Table 1 Baseline difference and output from binary logistic regression

Variables	Cancer-free		Cancer		P[a]	OR (95% CI)[b]	P[c]
	N	%	N	%			
Percentage mammographic density (%)	987.00	100.00	84.00	100.00	0.230		

M±SD	32.69±11.66		30.84±13.64				
Dense area (10,000 pixels)	987.00	100.00	84.00	100.00	0.343		
M±SD	6.80±5.20		7.37±6.33				
Breast area (10,000 pixels)	987.00	100.00	84.00	100.00	0.044	1.018 (1.004, 1.033)	0.014
M±SD	21.02±13.46		24.90±16.99				
Age (years)	987.00	100.00	84.00	100.00	0.002	1.040 (1.018, 1.062)	<0.001
M±SD	48.94±9.49		52.99±11.19				
BMI (kg/m^2)	987.00	100.00	84.00	100.00	<0.001	1.204 (1.123, 1.290)	<0.001
M±SD	22.40±2.81		24.19±3.34				
Age at menarche (years)	987.00	100.00	84.00	100.00	<0.001	1.264 (1.139, 1.403)	<0.001
M±SD	14.22±1.88		15.20±1.62				
Age at first delivery[d]	926.00	100.00	84.00	100.00	<0.001	0.777 (0.715, 0.845)	<0.001
M±SD	27.84±3.48		25.54±3.46				
Duration of breastfeeding[e]	762.00	100.00	77.00	100.00	<0.001	1.223 (1.164, 1.286)	<0.001
M±SD	7.21±4.14		15.92±03				
Ethnicity							
Non-Han origin	11.00	1.11	0.00	0.00	1.000[f]		
Han origin	976.00	98.89	84.00	100.00			
Menopause status							
Pre-menopausal	617.00	62.50	36.00	42.86	<0.001	1.000	
Post-menopausal	370.00	37.50	48.00	57.14		2.223 (1.416, 3.490)	<0.001
Parity status							
Nulliparous	61.00	6.18	0.00	0.00	0.012[f]		
Parous	926.00	93.82	84.00	100.00			
Number of children[g]							
=1	853.00	92.10	50.00	59.52	<0.001	1.000	
>1	73.00	7.90	34.00	40.48		7.946 (4.834, 73.060)	<0.001
Breastfeeding history							
No	225.00	22.80	7.00	8.33	0.003	1.000	
Yes	762.00	77.20	77.00	91.67		3.248 (1.447, 7.142)	0.003
Family history							
No	915.00	92.71	76.00	90.48	0.596		
Yes	72.00	7.29	8.00	9.52			
Degree of consanguinity							
1st degree	47.00	65.28	7.00	87.50	0.264[f]		
2nd degree	25.00	35.72	1.00	12.50			
Smoking history							
No	967.00	97.97	84.00	100.00	0.395[f]		
Yes	20.00	2.03	0.00	0.00			
Alcohol consumption							
No	864.00	87.54	84.00	100.00	0.001		
Yes	123.00	12.46	0.00	0.00			

[a] P values from t test for continuous variables; P values from Chi-square for categorical variables
[b] Odds ratio and 95% Confidence Interval of being cancer cases from binary logistic regression for factors that were statistically significant ($p<0.05$) from t tests or chi-square tests
[c] P values from binary logistic regression
[d] Restricted to post-menopausal women
[e] Restricted to parous women
[f] P values from Fisher's exact test
[g] Restricted to women with breastfeeding history

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Table S1 Baseline difference and output from univariate analysis of pre-menopausal women with and without breast cancer

Variables	Cancer-free		Cancer		P[a]	OR (95% CI)[b]	P[c]
	N	%	N	%			
Percentage mammographic density (%)	617.00	100.00	36.00	100.00	0.238		
M±SD	34.85±10.89		37.06±11.36				
Dense area (10,000 pixels)	617.00	100.00	36.00	100.00	0.481		
M±SD	7.22±5.31		7.86±6.01				
Breast area (10,000 pixels)	617.00	100.00	36.00	100.00	0.679		
M±SD	21.03±13.72		22.02±16.80				
Age (years)	617.00	100.00	36.00	100.00	0.784		
M±SD	43.34±4.94		43.67±6.93				
BMI (kg/m^2)	617.00	100.00	36.00	100.00	0.024	1.181 (1.065, 1.310)	0.002
M±SD	22.13±2.71		23.68±3.87				
Age at menarche (years)	617.00	100.00	36.00	100.00	<0.001	1.502 (1.233, 1.830)	<0.001
M±SD	13.88±1.56		15.00±1.67				
Age at first delivery[d]	572.00	100.00	36.00	100.00	<0.001	0.720 (0.620, 0.836)	<0.001
M±SD	27.96±3.59		25.44±2.48				
Duration of breastfeeding[e]	490.00	100.00	33.00	100.00	<0.001	1.260 (1.166, 1.363)	<0.001
M±SD	6.61±3.77		12.15±6.47				
Ethnicity							
Non-Han origin	7.00	1.13	0.00	0.00	1.000[f]		
Han origin	610.00	98.87	36.00	100.00			
Parity status							
Nulliparous	45.00	7.29	0.00	0.00	0.164[f]		
Parous	572.00	92.71	36.00	100.00			
Number of children[g]							
=1	553.00	96.68	26.00	72.22	<0.001	1.000	
>1	19.00	3.32	10.00	27.78		11.194 (4.733, 26.476)	<0.001
Breastfeeding history							
No	127.00	20.58	3.00	8.33	0.115		
Yes	490.00	79.42	33.00	91.67			
Family history							
No	573.00	92.87	33.00	91.67	0.738[f]		
Yes	44.00	7.13	3.00	8.33			
Degree of consanguinity							
1st degree	26.00	59.09	2.00	66.67	1.000[f]		
2nd degree	18.00	40.91	1.00	33.33			
Smoking history							
No	602.00	97.57	36.00	100.00	1.000[f]		
Yes	15.00	2.43	0.00	0.00			
Alcohol consumption							
No	531.00	86.06	36.00	100.00	0.009[f]		
Yes	86.00	13.94	0.00	0.00			

[a] P values from t test for continuous variables; P values from Chi-square for categorical variables
[b] Odds ratio and 95% Confidence Interval of being cancer cases from binary logistic regression for factors that were statistically significant (p<0.05) from t tests or chi-square tests
[c] P values from binary logistic regression
[d] Restricted to post-menopausal women
[e] Restricted to parous women
[f] P values from Fisher's exact test
[g] Restricted to women with breastfeeding history

Table S2 Baseline difference and output from univariate analysis of post-menopausal women with and without breast cancer

Variables	Cancer-free		Cancer		P[a]	OR (95% CI)[b]	P[c]
	N	%	N	%			
Percentage mammographic density (%)	370.00	100.00	48.00	100.00	0.119		
M±SD	29.09±12.01		26.17±13.44				
Dense area (10,000 pixels)	370.00	100.00	48.00	100.00	0.255		
M±SD	6.09±4.95		6.99±6.60				
Breast area (10,000 pixels)	370.00	100.00	48.00	100.00	0.021	1.029 (1.009, 1.049)	0.005
M±SD	20.99±13.01		27.06±16.99				
Age (years)	370.00	100.00	48.00	100.00	0.156		
M±SD	58.27±7.77		59.98±8.31				
BMI (kg/m^2)	370.00	100.00	48.00	100.00	<0.001	1.198 (1.087, 1.320)	<0.001
M±SD	22.86±2.93		24.57±2.86				
Age at menarche (years)	370.00	100.00	48.00	100.00	0.086		
M±SD	14.79±2.20		15.35±1.58				
Age at menopause (years)	370.00	100.00	48.00	100.00	0.784		
M±SD	50.39±3.80		50.23±3.81				
Age at first delivery[d]	354.00	100.00	48.00	100.00	<0.001	0.822 (0.743, 0.909)	<0.001
M±SD	27.65±3.30		25.60±4.07				
Duration of breastfeeding[e]	272.00	100.00	44.00	100.00	<0.001	1.182 (1.110, 1.260)	<0.001
M±SD	8.29±4.54		18.75±17.25				
Ethnicity							
Non-Han origin	4.00	1.08	0.00	0.00	1.000[f]		
Han origin	366.00	98.92	48.00	100.00			
Parity status							
Nulliparous	16.00	4.32	0.00	0.00	0.235[f]		
Parous	354.00	95.68	48.00	100.00			
Number of children[g]							
=1	300.00	84.75	24.00	50.00	<0.001	1.000	
>1	54.00	15.25	24.00	50.00		5.556 (2.942, 10.490)	<0.001
Breastfeeding history							
No	98.00	26.49	4.00	8.33	0.01	1.000	
Yes	272.00	73.51	44.00	91.67		3.963 (1.388, 11.317)	0.01
Family history							
No	342.00	92.43	43.00	89.58	0.566[f]		
Yes	28.00	7.57	5.00	10.42			
Degree of consanguinity							
1st degree	21.00	75.00	5.00	100.00	0.559[f]		
2nd degree	7.00	25.00	0.00	0.00			
Smoking history							
No	365.00	98.65	48.00	100.00	1.000[f]		
Yes	5.00	1.35	0.00	0.00			
Alcohol consumption							
No	333.00	90.00	48.00	100.00	0.014[f]		
Yes	37.00	10.00	0.00	0.00			

[a] P values from t test for continuous variables; P values from Chi-square for categorical variables
[b] Odds ratio and 95% Confidence Interval of being cancer cases from binary logistic regression for factors that were statistically significant (p<0.05) from t tests or chi-square tests
[c] P values from binary logistic regression
[d] Restricted to post-menopausal women
[e] Restricted to parous women
[f] P values from Fisher's exact test
[g] Restricted to women with breastfeeding history

Chapter Six

Discussion

6.1 An overview of the thesis

Within the breast, fibroglandular tissue attenuates more of the X-ray beam (shows as radio-opaque on an X-ray image) than fatty tissue and mammographic density describes the extent of radio-opaque tissue (dense area) [1]. Increased mammographic density has been shown to be associated with increased (2-6 times) risk of breast cancer [2]. Also, the two dimensional images produced by mammography are characterised by breast tissue overlap, particularly when dense tissue is involved, thereby leading to concealment or a masking effect which may obscure breast cancer [3, 4]. Many factors have been shown to be associated with lower density including aging, increased BMI, early age at menarche, post-menopause, parity, early age at first delivery, a large number of children, no family history of breast cancer, no history of hormone replace therapy, physical activity, no smoking history, lack of alcohol consumption and intake of calcium and vitamin D as well as high intake of vegetables [5-9]. However these associations are largely based on studies relevant to women from westernised countries and cannot be applied directly to Chinese women since the characteristics of mammographic density for this oriental population is under-studied.

This PhD thesis, to our knowledge, is the first study that was specifically designed to investigate the features of mammographic density for women in China and the objectives are:

- To identify demographic, lifestyle, reproductive and familial factors associated with mammographic density for Chinese women without breast cancer, based on data from a national screening program, using the BI-RADS breast composition classification.
- To identify factors associated with mammographic density using a recently developed algorithm, and based on the data to establish statistical models of mammographic density prediction for Chinese females both with and without breast cancer.

- To initially examine the possibility of mammographic density being a potential risk factor for breast cancer for Chinese females.

This thesis provides new knowledge around the distribution of mammographic density in Chinese women and the factors associated with density for women in China. Mammographic density was assessed by a qualitative (i.e. BI-RADS classification) method (Chapter three). Some previous studies showed that Chinese women living in western countries had more dense breasts (BI-RADS 3&4) compared to fatty breasts (BI-RADS 1&2) [10, 11]. However our study found that density values were almost equally distributed between the lower (BI-RADS 1&2) and upper (BI-RADS 3&4) groupings. An array of demographic, environmental and lifestyle, and menstrual, reproductive and familial factors were explored and assessed to identify possible associations with mammographic density. This examination provided a comprehensive understanding of characteristics of mammographic density amongst women in China.

This thesis also provides insights on the predictors of density on Chinese women by designing a study involving women with and without breast cancer using a quantitative and fully-automatic (i.e. AutoDensity algorithm) assessment approach (Chapter four). We explored the predictors of density using both percentage and dense area measures to establish the level of agreement between these two commonly used measures and establish recommendations for future studies.

6.2 Significant findings

The objectives were achieved through three studies. The first study recruited a large number of women (4,867 women without breast cancer) from the National Cancer Screening Program in China, and mammographic density was assessed using the BI-RADS density classification (4th edition). This part of the work determined density distribution amongst Chinese women and identified factors associated with density. The second study was a cross-sectional study employing a total of 1071 (84 with and 987 without breast cancer) women. This study's purpose was to identify associated factors with mammographic density using a fully automatic algorithm. In addition, it sought to establish statistical models of mammographic density prediction for Chinese females both with and without breast cancer. Finally, the impact on density associations arising from two different but commonly used metrics from quantitative approaches was explored. The third study examined the relationship between breast cancer and quantitative measured mammographic density, based on screening data from China. The three complementary studies provide a better understanding of the characteristics of mammographic density within the Chinese female population in the screening context.

The work showed that most women in China had scattered fibroglandular and heterogeneous mammographic density compared to a minority of women who had almost extremely fatty or extremely dense breasts, however the density values were almost equally distributed between the lower (BI-RADS 1&2) and upper (BI-RADS 3&4) groupings. This finding is consistent with one previous China-based study [12], however, another study reported that women had more dense breasts (BI-RADS 3&4) compared to fatty breasts (BI-RADS 1&2) [13]. Nonetheless it is important to point out that these previous studies were based on a local screening program, which covered limited areas in China. Also, the BI-RADS density values in our work appeared to be higher than that of western women [14, 15]. This difference suggested that breast tissue composition may vary according to geographic location or ethnicity.

Based on our BI-RADS (Chapter three) and AutoDensity (Chapter four) studies, we presented results that sometimes agreed and sometimes did not agreed with previous studies. Those that agreed include: younger age, earlier age at menarche and pre-menopausal status were associated with higher mammographic density, which agree with what is known about density for several decades across many non-Chinese populations [8, 16-21]; education-dependent density differences have also been previously reported in Europe and America [9, 22, 23], with our work specifically showing that women with a background of tertiary education having densest breasts compared with those having none or only primary education. Whilst this association, does not specifically identify causal agents, this finding is important to China, particularly since the number of undergraduate and graduate students has risen by more than three times (8 million in 1998 and 26 million in 2017) over last 20 years [24]. Conversely, less agreement was shown between ours and previous work in the following factors; age at menopause, smoking history and alcohol consumption which were not related to density in either of the approaches we used (particularly the positive association with alcohol intake [25-30] and negative association with smoking [31-33] that were found in other populations do not appear to be pertinent in our studies); positive association between density and family history of breast cancer, which was demonstrated for western women [34], was not found in Chinese women in either of our methods; ethnic variation in Chinese mammographic density was also not found between women of Han origin and non-Han origin in both of our studies, which was different from what was seen for ethnic variations in other populations [35, 36].

One important finding from this work was related to the dependency of findings based on the method used to assess breast density. Whilst body weight and BMI were shown to be important associated factors for density with both the BI-RADS and AutoDensity approaches, the relationship was in opposite directions for the two quantitative metrics (percentage and dense area) provided by AutoDensity. This latter finding suggests that predictive factors of mammographic density are highly reliant on the different metrics used to describe density. Likewise, nulliparity and lack of breastfeeding history were found to be associated with BI-RADS density and dense area but not percentage density; geography-dependent differences and association with age at first delivery were only reported for BI-RADS density but not for either metric from AutoDensity. These inconsistent findings might highlight the requirement for a standardised, reproducible and predictive unit of density, otherwise it is very difficult to paint a true picture of the causal associations and the predictive factors of mammographic density. In addition, there were also some associations shown within our BI-RADS but not our AutoDensity chapter since these factors were unavailable in the latter study, for example, occupation and personal history of benign breast disease.

Both the BI-RADS and quantitative approaches provided statistical models for mammographic density prediction for women in China based on factors mentioned in the last two paragraphs. Even though the elements of the models were not completely consistent across the two methods, the results provide preliminary and effective models for mammographic density assessment to inform breast cancer prevention and diagnostic strategies.

The AutoDensity study also provided extra information on mammographic density in Chinese females with breast cancer, in that higher percentage density was associated with younger age, lower BMI and body weight, pre-menopausal status and earlier age at menopause, whilst higher dense area was associated with larger breast area. These results suggested that factors associated with percentage density of women with breast cancer were similar to those of women without cancer, but this was not the case using dense area. This discrepancy was explained in the AutoDensity study as being possibly linked to the fact that cancer lesions depending on tumour size, have a greater impact on the measurement of dense area (even though the dense area strictly should not be influenced by the presence of a cancer) than the percentage value. This presents a unique understanding of the impact of different matrices on Chinese mammographic density and might encourage the practice of percentage density as opposed to dense area for at least breasts with cancer, when true associations are being sought. This is discussed more in the Implications section below.

Additionally, even though we did not find any statistically significant association between mammographic density and breast cancer for women in Shanghai, China (Chapter five), we cannot rule out the potential relationship between these two factors due to limitations in our study:

- Unmatched group size for women with and without cancer (at a ratio of 1:10) resulting in decreased statistical power;
- Different sources of selection for the two groups of women might have resulted in selection bias (due to limited accessibility of FUSCC data for international collaborators), which possibly could limit the internal validity of the study.

However, since our finding that mammographic density was not associated with breast cancer was consistent with one previous study and inconsistent with another [12, 13], we suggested that the relationship between mammographic density and breast cancer for women in China may not be as strong as, or at least could be different from that demonstrated in other populations, particularly those involving westernised women. This is however a very important assumption with major implications, and therefore further testing of this hypothesis is required. Therefore, it would be very unwise to eliminate a link between mammographic density and breast cancer for now.

6.3 Implications

Mammographic density is a significant risk factor of breast cancer and it is also a major determinant of the type of imaging modality we should use on a screening program. The recent wholescale migration towards digital screening environments offers the potential to optimise cancer detection using novel and established algorithms, however the assumption that breast compositions are consistent between global regions underestimates the complexity of the subject. Until the differences are evaluated comprehensively, methods of enhancing image details and improving cancer detection cannot be optimised since current algorithms are based on what we understand regarding the breast cancer profile in westernised countries.

Our new findings coupled with the previous evidence suggest that the mammographic density amongst Chinese women is distributed almost evenly between low and high dense breasts and overall density appears to be higher than that of westernised women. This finding should provide insights on the recommendation of the type of imaging modality that should be used for breast cancer screening in China. For example, should mammography be used as the main technique and ultrasonography be a supplementary procedure, particularly since it appears in China currently that the latter technique is often the first line modality in the early detection of cancer and our current findings would suggest that we could re-consider the current paradigm. Mammography followed by supplementary ultrasound approach may offer a potential solution to the fact that density is possibly higher in China than in westernised countries, yet still a large proportion of women have low dense breasts. Ultrasonography has been shown to improve cancer detection in women with medium to high dense breasts compared with mammography alone and some studies based on Asian women suggested that the addition of ultrasonography to mammography increases screening sensitivity and detection rates [37-40]. This could have an important impact on the output of screening programs, but requires further investigation.

The examination of factors associated with mammographic density provide statistical models with density predictors of age, BMI, education, menopausal status being the key predictive agents. However it is important to note that not all the important predictors were included in our models, for example, breastfeeding. This might be because the contributions of other elements within the models had a much greater impact than that of breastfeeding and therefore any weak relationships were eliminated from the model. The relationship (even though it may be weak) between breastfeeding and mammographic density is interesting since breastfeeding is a potentially modifiable behaviour and accurate knowledge about potential protective effects could be of practical importance to Chinese women aiming to reduce breast cancer risks and of value to policy makers focusing on breast cancer preventative strategies. A clearer picture in the relationship between breastfeeding and density is therefore required.

These models provide preliminary and effective modelling strategy for mammographic density assessment in breast cancer prevention and early detection, which may be applied in initial risk assessment in both the screening environment and clinical settings. For example, the National Cancer Screening Program in Urban China (see BI-RADS chapter) employed an initial assessment through a questionnaire prior to the mammography examination. However, mammographic density, as an important risk factor, was not considered during the initial assessment phase, partially due to the lack of a predictive model that included density, but also due to the lack of information available on women's mammographic density from typical radiological readings. However, it should be acknowledged that for density to be included in a risk prediction strategy, a solid and well-confirmed link between density and cancer should be demonstrated. Our study failed to identify such an association for mammographic density, which as previously discussed may be linked to the methodological approach used or may be possibly due to unique ethnic dependencies. In order to establish the definite relationship between density and cancer, we must further explore this part of this research program so that we have larger sample sizes for both cancer and cancer-free women, use a case-control approach and have more representative populations from urban and rural areas as well as across ethnic minority populations. This density cancer relationship is extremely important to breast cancer screening programs and will be the focus of further investigations.

The difference in conclusions that can be derived from the two commonly used metrics (percentage density and dense area) provided by the fully automatic and quantitative algorithm is highlighted in our study (Chapter four). This has major implications for future work when trying to understand the implications of varying densities, as shown in this work. For example, the density predictors were similar for cancer and cancer-free women when percentage density was used but this was not the case when using dense area. This discrepancy might result from the fact that cancer lesions actually contribute to the dense area measurement but not to the percentage value. To illustrate, the overall breast size may increase to accommodate the cancer lesion when the lesion or associated inflammation is evident [41-43] and this therefore will contribute to both the numerator (dense area) and denominator (overall breast area) of the calculation of percentage. Therefore any change in the measurement because of the existence of cancer will be eliminated or at least minimised. However, the metric using the area of dense tissue will include the cancer without any normal tissue compensation. Also, as the size of cancer will not be related to the preventative factors, any possible association is expected to be irrelevant and therefore this finding to some extent supports the use of percentage density in the screening context.

Finally, the current work has raised a number of issues around mammographic density for Chinese women which are different from that for women in western countries. These issues should now be addressed so that the level of data available to Chinese policy makers and government, who are responsible for breast cancer prevention and screening strategies, is increased, potentially impacting on screening policies and practise. Such strategies should benefit from the new knowledge provided here on a number of factors associated with Chinese mammographic density and thus should impact favourably the health of women in China.

6.4 Limitations and future directions

This research had several limitations. Due to the data that was available from our Chinese collaborators, women in our studies were mainly from urban locations and rural women were generally not included. Given the substantial disparities in breast cancer incidence between these two regions, the mammographic density profile of Chinese women may differ significantly in urban and rural areas. This subject will be addressed in further research which will allow for a much more expansive investigation involving a more generalised Chinese population.

The candidate also acknowledges the number of women with breast cancer was relatively lower than that of females without cancer, a ratio of 1:10, respectively. These numbers could have resulted in a failure to demonstrate important associations of potential predictive factors of mammographic density and may have been responsible for the absence of a significant relationship between mammographic density and breast cancer. Due to data unavailability from our international collaborators, this limitation could not be addressed in the current work.

6.5 Conclusions

This work has provided important and new knowledge on the distribution and characteristics of mammographic density for women in China and has shown that there is an approximately even distribution of mammographic density between high and low dense breasts. Key factors associated with high mammographic density include increasing age, increasing BMI/body weight, level of education, earlier age at menarche, pre-menopausal status, nulliparity, later age at first delivery, lack of breastfeeding, shorter duration of lactation and personal history of benign breast disease. The data provided should improve our understanding on the usage of mammographic density in the Chinese screening context.

Our work failed to show a substantive link between breast cancer and mammographic density. The candidate acknowledges that this failure may be due to methodological limitations however until further work is conducted, we cannot rule out the possibility that the well-established relationship between density and cancer amongst western women, may be less relevant in China.

In addition to the most commonly used assessment method BI-RADS, Chinese mammographic density was measured for the first time by a fully automatic and quantitative method using two metrics (percentage density and dense area). Predictive factors of density using each metric were shown which should help optimise the assessment methods in both screening and clinical environments.

This thesis and its associated outputs should question the assumption that breast compositions are consistent between global regions and should recommend to researchers, clinicians and policy makers in China that western paradigms may not be entirely relevant to other populations and should be adjusted to suit the specific circumstances in China.

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Appendix 1

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Pat Lynch

==========
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On Apr 24, 2017, at 9:13 AM, Tong Li <donotreply@wordpress.com> wrote:

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Email: toli7326@uni.sydney.edu.au

Comment or question: Dear Patrick Lynch,

This is Tong Li, a PhD Candidate form Faculty of Health Sciences, The University of Sydney, Australia. I am currently working on my PhD thesis, Characteristics of breast density in Chinese women, which requires a figure of breast anatomy. I found out a great image on the following website (https://commons.wikimedia.org/wiki/File:Breast_anatomy_normal_scheme.png#filelinks) that

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Kind regards,
Tong Li

Tong Li
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Appendix 2

The full original (non-contracted) manuscripts

Appendix 2.1 The full original (non-contracted) manuscript for the accepted paper contained in Chapter Three

Variation in mammographic density and associated predictive factors for Chinese women: Results from the National Cancer Screening Program in Urban China

Journal:	*The Breast Journal*
Manuscript ID	TBJ-00096-2017
Manuscript Type:	Manuscripts
Date Submitted by the Author:	19-Feb-2017
Complete List of Authors:	Li, Tong; University of Sydney Faculty of Health Sciences, Li, Jing Dai, Min Ren, Jiansong Zhang, Hongzhao Mi, Zihan Heard, Rob; Behaviour and Social Sciences, Faculty of Health Sciences, The University of Sydney Mello-Thoms, Claudia; Department of Medical Imaging & Radiation Sciences, Faculty of Health Sciences, The University of Sydney He, Jie Brennan, Patrick; University of Sydney Faculty of Health Sciences
Key Words:	Mammographic density, Breast density, Chinese women, Predictive factors, Risk factor

53Title page

TITLE: Variation in mammographic density and associated predictive factors for Chinese women: Results from the National Cancer Screening Program in Urban China

RUNNING TITLE: Predictive factors of mammographic density

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Abstract

Background: Mammographic density is considered an independent risk factor for breast cancer; however, characteristics of women's mammographic density are poorly understood in China. This study aims to determine density distribution amongst Chinese women and to identify factors associated with density.

Methods: Mammographic cases for 4867 women were collected from the National Cancer Screening Program in in China. Mammographic density was assessed using the Breast Imaging Reporting and Data System density classification (4^{th} edition). Spearman correlations examined the relationship between density values and ratio and interval variables, whilst Mann-Whitney Tests and Kruskal-Wallis Tests were conducted to assess ordinal and nominal variables. Variables that were statistically significant from the above tests were entered into binary logistic regression Statistical model building was finally conducted by multiple logistic regression.

Results: Significant associations ($P<0.001$) were shown between mammographic density and age (rho=-0.23), BMI (rho=-0.18) and weight (rho=-0.16). Density was statistically significantly different ($P<0.05$) across educational, province of residence and occupation groups. Women with a history of early age of menarche, pre-menopausal status, nulliparity, no breastfeeding and benign breast disease demonstrated increased mammographic density compared with women without such histories ($P<0.05$). The final model consisting of age, BMI, province of residence, education, occupation, menopausal status, parity history and personal history of benign breast disease predicted 68.7% of mammographic density variation.

Conclusions: Our work has demonstrated mammographic density variations for women from urban regions in China, and important associations between density and a variety of predictive factors, with a statistical model being established to predict mammographic density.

KEY WORDS

Mammographic density, Breast density, Chinese women, Predictive factors, Risk factor

Introduction

Breast cancer is the most common neoplasm diagnosed among women in China and it is one of the leading causes of female cancer deaths (1). Mammographic density, representing the amount of fibrous and glandular tissues within the breasts, is consistently demonstrated to be an independent and important risk factor of breast cancer with individuals experiencing the highest density having a 2-6 times risk of breast cancer compared to those with the lowest (2, 3). Well confirmed and probable factors associated with higher density include lower body weight or body mass index (BMI), smoking and alcohol consumptions, lack of physical activity, high level of education, intake of saturated fat and low-carbohydrate diet, pre-menopausal status, nulliparity, late age at first delivery and family history of breast cancer (4-6).

Current knowledge around density data however are largely based on women from western countries, and little attention has been paid to the relationship between mammographic density and demographic, lifestyle and reproductive factors in China, even though a study has showed that density was a strong risk factor for breast cancer for Chinese women living in the United States (7). From the paucity of data that are available it appears that density is almost equally distributed between the higher and lower categories of Breast Imaging Reporting and Data System (BI-RADS) density classification, negatively associated with late age at menarche, postmenopausal status and increased number of children, and positively associated with benign breast disease and late age at first delivery (8, 9).

Even though some associations between reproductive factors and mammographic density have been shown, a comprehensive assessment of potential associations with density amongst women in China has not been previously undertaken. The current study therefore explores the relevance of a large number of demographic, environmental, lifestyle, menstrual, reproductive and familial factors, some of which are known to be important for westernised women, whilst others are not. The focus here in the first instance will be on women at risk. The ultimate aim of the work is to provide data that will improve our understanding of breast cancer risk for an understudied population where breast cancer is becoming one of the most important health policy issues.

Methods

Data source:

Participants were recruited from the National Cancer Screening Program in Urban Locations (defined as cities with a population of more than 1 000 000) in China. This program targets people who are 40-69 years old and live in residential communities for more than 3 years. The program is based on two stages:

1. A free cancer risk assessment where personal risk for specific cancer is calculated by applying a locally modified version of the Harvard Cancer Risk Index (HCRI) (10). This risk assessment tool is overseen by the Multidisciplinary Steering Committee of the screening program.
2. Inviting individuals, identified as high risk in Stage 1, for further screening. For breast cancer, women aged 45-69 years old undergo mammography and ultrasound whilst younger women have an ultrasound examination followed by mammography only when suspicious lesions present.

Each program participant gave informed consent for the utilisation of data in this work. This study was approved by the Human Research Ethics Committee of the University of Sydney (Project number: 2014/768) and the Ethics Committee of Cancer Institute and Hospital, Chinese Academy of Medical Sciences (Project number 15-062/989).

Study design and population

This was a cross-sectional multicentre study. Data were collected from a total of 4867 women aged 45-69 attending 12 centres between December 2013 and September 2015. All eligible women were diagnosed as normal or having benign lesions by expert radiologists using the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) assessment classification (11). Women's demographic, environmental, lifestyle, menstrual, reproductive and familial details were obtained from the Risk Assessment Questionnaire completed by all women involved in stage 1 of the screening procedure. All data gathered were considered below. The number of cases in individual analyses may vary due to missing and invalid data for specific variables of interest.

Quality control

All 12 centres are accredited as 3A (highest accreditation) institutions according to the Hospital Stratified Management System (12). Quality assurance procedures ensure that all data were double-entered into the database by one investigator and reviewed independently by another.

Mammographic density assessment

Mammographic density values were acquired for both cranio-caudal and mediolateral-oblique mammograms of both breasts from the radiological report provided by two expert radiologists with more than 5 years' reading experience. Mammographic density was coded by using the 4th edition of ACR BI-RADS density categories (11);

1. The breast is almost entirely fat (< 25% glandular)
2. There are scattered fibroglandular densities (approximately 25% - 50% glandular)
3. The breast tissue is heterogeneously dense, which could obscure detection of small masses (approximately 51% - 75% glandular)
4. The breast tissue is extremely dense. This may lower the sensitivity of mammography (> 75% glandular)

Categorisation of mammographic density for each woman was determined by the two radiologists.

Statistical analysis

The data derived from the screening program were subjected to two types of statistical analysis: univariate and multivariate analysis.

Correlation analysis using Spearman rank-order correlation examined the relationship between BI-RADS mammographic density values and ratio or interval independent variables with the strength of association determined by Spearman's correlation coefficient (rho). Difference of median values of BI-RADS density was compared across categories for each ordinal or nominal variable, and mean values were used for descriptive purpose. The non-normal distribution of the data resulted in the employment of the following non-parametric statistical tests: Mann-Whitney U test for two independent groups; and Kruskal-Wallis H test for more than two unmatched groups, followed by Mann-Whitney U test as the post-hoc test (13). Bonferroni corrections were applied to adjust the significant level for all post-hoc tests.

The BI-RADS mammographic density was then recoded into a dichotomous variable: low density (BI-RADS 1&2) and high density (BI-RADS 3&4). For all variables that were statistically significant from the above traditional tests (Spearman, Mann-Whitney and Kruskal-Wallis tests), binary logistic regression was conducted to produce odds ratio (OR) and 95% confidence intervals (95% CI).

Statistical model building was finally performed by using multiple logistic regression adopting the significant variables except those restricted to women with specific conditions (e.g. duration of passive smoking was restricted to women who had history of passive smoking only, so this variable was not used in the model building). A total of 4851 cases were included in the multiple logistic regression after excluding missing and invalid data. Models were initially built for demographic, and menstrual and reproductive factors, respectively, prior to the construction of final model with all of the significant variables.

For all statistical analyses, SPSS (version 22.0) statistical package for windows was used and two-tailed tests of significance were employed using a significance level of 0.05, for Bonferroni corrections. When Bonferroni corrections were applied, 0.05 was the target significant level over the entire set of comparisons and stricter significance levels were used for individual comparisons.

Results

Descriptive characteristics of participants and density distribution

Participants' numbers and percentages of cases, mean values and standard deviation (SD) for the three sections of demographic, environmental and lifestyle, menstrual, reproductive and familial characteristics are shown in table 1. The distribution of mammographic density is displayed in table 2.

Determinants of BI-RADS mammographic density

The overall results from traditional tests (see statistical analysis) were shown in table 3 with a range of significant findings being established for density values. A power analysis showed that with the sample size used in this study, the power was above 81% for variables that were statistically significant at the traditional tests. The statistics from post-hoc tests are not included in the table and these are described as follows: each category of education was found statistically significant from each other one (P<0.003), except for: no education vs primary school (P=0.95); junior secondary vs senior secondary/vocational and technical school (P=0.005); higher vocational and technical college vs university and higher (P=0.06). As the post-hoc tests of 8 provinces of residence and 9 occupations did not show a clear hierarchical pattern, pairwise differences were shown in supplementary tables S1 and S2.

Distribution of dichotomous mammographic density and associations with determinants

Table 4 shows the distribution of dichotomous mammographic density for each significant variable from traditional tests (see statistical analysis), and odds ratios from binary logistic regression with 95% confidence intervals. The demographic, and menstrual and reproductive models from multiple logistic regression are presented in table 5. Weight (P=0.764) and breastfeeding history (P=0.609) were not shown to be statistically significant in these models.

Table 6 displays the final model with adjusted odds ratio and 95% confidence interval of variables being statistically significant only. Weight (P=0.750), breastfeeding history (P=0.198) and age at menarche (P=0.215) were excluded as non-statistically significant contributors.

Discussion

This study investigated variations of mammographic density of Chinese women from urban regions and associated risk factors. Women in this study predominately experienced scattered fibroglandular and heterogeneous mammographic density compared to a minority of women having almost extremely fatty or extremely dense breasts, however the density values were almost equally distributed between the lower (BI-RADS 1&2) and upper (BI-RADS 3&4) groupings. This density distribution was both consistent and inconsistent with previous China-based research: work covering four Chinese large cities of comparable size to those in this study demonstrated similar density distributions to the current work (8), however, a separate study based on another large Chinese city (Tianjin) reported that women had more dense breasts (BI-RADS 3&4) compared to fatty breasts (BI-RADS 1&2) (9), a finding consistent with studies involving Asian women living in western countries (14, 15). Compared to international studies, density values here appear to be higher than that of women from North America. In North America, as shown with BI-RADS (16, 17), and more quantitative measures a greater proportion of women have density of 50% or less compared with the rest of the subjects (3, 18, 19). This discrepancy once again highlights the variations in breast tissue composition according to geographical location and emphasises the need to explore the implications of these variations.

Thirty-one potential causal agents of mammographic density were examined in this study and these were divided into demographic, environmental and lifestyle, and menstrual, reproductive and familial categories. Demographic factors were shown to be important with associations being demonstrated with age, body weight and BMI, education, geographical location and occupation. The negative associations of breast density with increasing age, BMI and weight has been known for several decades across many populations with our data agreeing with previous reports (4, 20-25) even though body weight did not add any prediction beyond other variables in our final model. Education-dependent density differences have also been previously reported with our data specifically suggesting that women in tertiary education experience densest breasts compared with those individuals experiencing either no or only primary education. This finding is consistent with previous reports from Italy (26), U.K. (27) and the U.S. (5). Even though the development level of living area might impact on this relationship (26), it was not shown in our study. The relationship between education and density therefore will require tracking as people avail themselves of increasing education opportunities: the number of undergraduate and graduate students in China has approximately quadrupled in the last two decades (28). It was interesting to note that we failed to detect any disparity in density between women of Han origin and ethnic minorities. This latter finding however should be treated with some degree of caution since the seven ethnic minority groups examined here were recorded as non-Han population for the purpose of increasing statistical power. Nevertheless, this aggregation could be obscuring minority-specific observations, an issue that needs to be addressed in further work. Finally with regard to demography, density associations were also shown with geographic and occupational variations with women working as housewives and individuals from Gansu providence having lowest density compared to other occupations and provinces, respectively. The differences of mammographic density across provinces, except Henan province, were mainly consistent with the local economic power that provinces with higher breast density were more likely to have higher level of economic development (29). Women in Henan province had the highest risk having high mammographic density (at least 3.5 times) compared with other provinces. Even though the incidence of breast cancer is continuously and rapidly increasing in this region, the difference (over 6 fold) in low vs high density group size may be overestimated by the odds ratio.

Menstrual and reproductive factors are also important agents associated with varying mammographic density in Chinese women. Mammographic density was higher in females with earlier age of menarche, pre-menopausal individuals, nulliparity, and later age of first delivery even though age at menarche was excluded from the multivariate analyses. These density-related factors have been previously reported in North America (4, 5, 20, 30), and were linked to age and hormonal influences on the epithelial, stromal and adipose tissues in the breast (30, 31). Lower dense breasts were evident in females who ever breastfed, being consistent with a study involving Chinese women in Singapore (32), with density values being lower with longer lactation duration. Again, breastfeeding was excluded after model building but it was still a significant predictor in the bivariate analysis. Despite the weak association shown (the weakness possibly resulting from our approach of combining pre- and post-menopausal women in the analysis), breastfeeding is a potentially modifiable behaviour, which may be of intermediate and practical importance to Chinese women aiming to reduce breast cancer risks. Compared to women without personal history, approximately 1.3 times higher density was also found in women with personal history of benign breast disease, including hyperplasia, duct ectasia, fibroadenoma, mastitis and other benign lumps indicating that the density is associated with tissue proliferation (33, 34) and hyperplasia (35).

Most of the factors discussed above were entered into the multiple logistic regression. For further screening programs and clinical practice, two models were built separately for demographic, and menstrual and reproductive factors. These two models predicted 68.2% and 59.9% of the mammographic density, respectively. The overall percentage of prediction increased to 68.7% with our final model with predictors of age, BMI, providence, education and occupation, menopausal status, parity history and personal history of benign breast disease being key agents.

It is interesting that this study highlighted features that did not necessarily agree with what is known about breast density in other populations. For example, a relationship was not found between density and family history of breast cancer whilst, for the subset of women who had a family history, density was only very weakly associated with the number of 1^{st} and 2^{nd} degree relatives with the cancer. Besides, previously reported associations based on other populations around alcohol consumption (36, 37) and smoking history (5, 38) did not appear to be relevant here. However with regard to the latter, it was paradoxical that whilst there was no difference between smokers and non-smokers we did show that the longer one was exposed in passive smoking environment, the lower the density was. Again, caution is necessary here since self-reporting of passive smoking is imprecise.

The authors stress discrepancies between our work and that reported elsewhere, particularly around the absence of statistical findings which may be explained at least in part by the sample size of our study and potentially impaired statistical power. This possibility could have resulted in a failure to demonstrate a significant discrepancy rather than the absence of an actual difference. However the sizeable sample of approximately 5000 women (with standard error of 0.72 at 95% CI of 0.49-0.51) used here highlights the need to look at possible other explanations for the discrepancies: population-dependent variations might be a factor, particularly since a study based on Singaporean Chinese women also reported no association between density and family history of breast cancer, although the authors did acknowledge that few sample of cases with family history may have given rise to falsely null findings (39). Another possibility is that the BI-RADS classification used here, which is typical of Chinese clinical practice, might be an insufficiently sensitive metric, therefore more quantitative methods to assess density will be the focus of further work.

Finally and importantly, one cannot rule out the fact that the link between mammographic density and breast cancer may not be as strong in all populations as it is within westernised groups of women.

This study has many strengths. Our study population came from a national cancer screening program, individuals from which completed a comprehensive questionnaire covering a large range of potential agents of mammographic density. To our knowledge, this is the first study focussing on China that has studied an array of demographic, environmental and lifestyle, and menstrual, reproductive and familial factors, and also provided some preliminary data on mammographic density differences between ethnic groups in China although no differences were seen. We do acknowledge however that the women involved in the work mainly came from urban areas of China, and given the substantial breast cancer incidence differences between urban and rural locations (40), the mammographic density may vary considerably in these two regions. This will be addressed in further work which will also allow for a much more expansive treatment of ethnic-dependent variations. Furthermore, women employed in this study were individuals identified as high risk of developing breast cancer by the Harvard Cancer Risk Index, which might underestimate the variation of women from a more generalised population. In addition, the measurement of mammographic density in our work was based on the 4th edition of BI-RADS classification (the standard assessment in China) and did not refer to the BI-RADS 5th edition which could modify the current density distribution and determinants if the standard was updated. Therefore, more reproducible and automated methods will be the focus of further work.

In conclusion, women from urban locations in China experience scattered fibroglandular and heterogeneous mammographic density, which is distributed almost equally between high and low dense breasts. The work has demonstrated important associations between mammographic density and demographic, environmental, lifestyle, menstrual, reproductive and familial factors, and a statistical model was established to predict mammographic density. The findings should be useful to policy makers responsible for breast cancer preventative strategies so that the impact of this increasingly important health policy issue is minimised.

Conflict of interest

The authors declare that they have no conflict of interest.

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Tables

Table 1 Descriptive characteristics of participants			
Factors	**Number[a]**	**Percentage**	**Mean ± Standard deviation**
Demographic factors			
Age (years)	4867	100.00	53.96 ± 6.37
BMI (kg/m^2)[b]	4867	100.00	24.12 ± 3.60
Height (cm)	4867	100.00	159.40 ± 5.00
Weight	4867	100.00	61.34 ± 9.90
Province of residence	4867		
Chongqing	491	10.09	
Gansu	360	7.40	
Guangxi	720	14.79	
Henan	434	8.92	
Shandong	531	10.91	
Xinjiang	1259	25.87	
Yunnan	272	5.59	
Zhejiang	800	16.44	
Ethnicity	4867		
Han	4446	91.35	
Mongol	16	0.33	
Hui	108	2.22	
Manchu	14	0.29	
Zhuang	219	4.50	
Uyghur	40	0.82	
Kazakh	1	0.02	
Others	23	0.47	
Ethnic group	4867		
Non-Han	421	8.65	
Han	4446	91.35	
Education	4867		
None	127	2.61	
Primary school	547	11.24	
Junior secondary school	1394	28.64	
Senior secondary/vocational and technology school	1639	33.68	
Higher vocational and technical college	819	16.83	
University and above	341	7.01	
Education level	4867		
Non-educated and primary education	674	13.80	
Secondary education	3030	62.30	
Tertiary education	1160	23.80	
Occupation	4866		
Professionals and technicians	700	14.39	
Managers and administrators in public sectors	348	7.15	
Clerical support and administrative related workers	514	10.56	
Businesswomen	170	3.49	
Agricultural workers	381	7.83	
Plant and machine operators and assemblers	1497	30.76	

Service and sales workers	363	7.46	
Housewives	678	13.93	
Others	215	4.42	
Environmental and lifestyle factors			
Occupational radiation exposure	4867		
No	4682	96.20	
Yes	185	3.80	
Physical activity[c]	4867		
No	2988	61.39	
Yes	1879	38.61	
Smoker[d]	4867		
None	4575	94.00	
Former	55	1.13	
Current	237	4.87	
Lifetime smoking[d]	4867		
No	4575	94.00	
Yes	292	6.00	
Smoking intensity (cigarettes per day)[e]	284	100.00	17.82 ± 11.11
Cumulative duration of smoking (years)[e]	280	100.00	21.04 ± 10.76
Duration of smoking abstinence (years)[f]	31	100.00	7.06 ± 6.66
Passive smoking	4867		
No	1585	32.57	
Yes	3282	67.43	
Duration of passive smoking (years)[g]	3265	100.00	27.34 ± 10.93
Alcohol drinker[h]	4867		
None	3860	79.31	
Former	167	3.43	
Current	840	17.26	
Alcohol consumption[h]	4867	100.00	
Abstainer	3860	79.31	
Consumer	1007	20.69	
Duration of abstinence from alcohol (years)[i]	157	100.00	5.85 ± 6.18
Menstrual, reproductive and familial factors			
Age at menarche (years)	4852	100.00	14.13 ± 1.94
Menopause	4861		
Premenopausal	1887	38.82	
Postmenopausal	2974	61.18	
Age at menopause (years)[j]	2974	100.00	48.81 ± 4.25
Parity	4861		
Nulliparous	400	8.23	
Parious	4461	91.77	
Age at first delivery (years)[k]	4454	100.00	26.67 ± 4.04
Breastfeeding history	4461		
No	1206	24.80	
Yes	3655	75.20	
Cumulative duration of breastfeeding (months)[l]	3655	100.00	12.14 ± 9.63
Personal history of benign breast disease	4861		
No	790	16.25	

Yes	4071	83.75
Family history of breast cancer	4850	
No	2711	55.90
Yes	2139	44.10
1st/2nd degree relatives diagnosed with breast cancer[m]	2135	
No	103	4.82
Yes	2032	95.18
Number of 1st and/or 2nd degree relatives diagnosed with breast cancer[n]	2032	
= 1	1140	56.10
> 1	892	43.90
1st degree relatives diagnosed with breast cancer before age of 50[o]	2036	
No	641	31.55
Yes	1395	68.65

[a] Number of cases may vary due to missing and invalid data
[b] Calculated by Weight (kg)/[Height (m)]^2
[c] Defined as >30 minutes/time and >3 times/week
[d] Defined as smoking more than 1 cigarette per day and continuing or accumulating more than 6 months
[e] Restricted to current and former smokers
[f] Restricted to former smokers
[g] Restricted to passive smokers
[h] Defined as drink more than one time per week and continuing six months or above
[i] Restricted to former-alcohol drinker
[j] Restricted to postmenopausal women
[k] Restricted to parous women
[l] Restricted to parous women who have breastfeeding history
[m] Restricted to women who have family history of breast cancer
[n] Restricted to women who have 1st and/or 2nd degree relatives diagnosed with breast cancer
[o] Restricted to women who have 1st degree relatives diagnosed with breast cancer

Table 2 Distribution of mammographic density (using BI-RADS classification)		
BI-RADS mammographic density	**Number**	**Percentage**
1. The breast is almost entirely fat (< 25% glandular)	483	9.92
2. There are scattered fibroglandular densities (approximately 25% - 50% glandular)	1832	37.64
3. The breast tissue is heterogeneously dense, which could obscure detection of small masses (approximately 51% - 75% glandular)	2428	49.89
4. The breast tissue is extremely dense. This may lower the sensitivity of mammography (> 75% glandular)	124	2.55
Total	4867	100

Table 3 Output from traditional tests: correlation coefficient (rho) for ratio and interval variables; mean and median of BI-RADS density values for ordinal and nominal variables

Factors	rho[a]	BI-RADS density[b] Mean	BI-RADS density[b] Median	p value[c]
Demographic factors				
Age (years)	-0.23			<0.001
BMI (kg/m2)[d]	-0.18			<0.001
Height (cm)	<0.01			0.870
Weight (kg)	-0.16			<0.001
Province of residence				<0.05
Chongqing		2.66	3.00	
Gansu		2.10	2.00	
Guangxi		2.54	3.00	
Henan		2.91	3.00	
Shandong		2.06	2.00	
Xinjiang		2.41	2.00	
Yunnan		2.57	3.00	
Zhejiang		2.44	3.00	
Ethnic group				0.152
Non-Han		2.41	2.00	
Han		2.45	3.00	
Education				<0.05
None		2.18	2.00	
Primary school		2.20	2.00	
Junior secondary school		2.41	3.00	
Senior secondary/vocational and technology school		2.49	3.00	
Higher vocational and technical college		2.57	3.00	
University and higher		2.65	3.00	
Non-educated and primary		2.20	2.00	<0.05
Secondary		2.45	3.00	
Tertiary		2.59	3.00	
Occupation				<0.05
Professionals and technicians		2.58	3.00	
Managers and administrators in public sectors		2.49	3.00	
Clerical support and administrative related workers		2.53	3.00	
Businesswomen		2.57	3.00	
Agricultural workers		2.31	2.00	
Plant and machine operators and assemblers		2.42	3.00	
Service and sales workers		2.50	3.00	
Housewives		2.35	2.00	
Others		2.37	2.00	
Environmental and lifestyle factors				
Occupational radiation exposure				0.650
No		2.45	3.00	
Yes		2.46	3.00	
Physical activity[e]				0.106
No		2.46	3.00	
Yes		2.43	3.00	

Smoking history[f]				
None		2.45	3.00	
Former		2.35	3.00	0.598
Current		2.43	3.00	
No		2.45	3.00	0.618
Yes		2.41	3.00	
Smoking intensity (cigarettes/day)[g]	-0.04			0.496
Cumulative duration of smoking (years)[g]	-0.02			0.706
Duration of smoking abstinence (years)[h]	-0.15			0.429
Passive smoking				
Yes		2.44	3.00	0.054
No		2.48	3.00	
Duration of passive smoking (years)[i]	-0.10			<0.001
Alcohol consumption[j]				
None		2.44	3.00	
Former		2.51	3.00	0.193
Current		2.47	3.00	
Abstainer		2.44	3.00	0.096
Consumer		2.48	3.00	
Duration of abstinence from alcohol (years)[k]	-0.01			0.905
Menstrual, reproductive and familiar factors				
Age at menarche (years)	-0.10			<0.001
Menopause				
Premenopausal		2.66	3.00	<0.001
Postmenopausal		2.32	2.00	
Age at menopause (years)[l]	-0.02			0.302
Parity				
Nulliparous		2.58	3.00	0.001
Parous		2.44	3.00	
Age at first delivery (years)[m]	0.11			<0.001
Breastfeeding history				
No		2.52	3.00	<0.001
Yes		2.43	3.00	
Cumulative duration of breastfeeding (months)[n]	-0.14			<0.001
Personal history of benign breast disease				
No		2.38	2.00	0.001
Yes		2.46	3.00	
Family history of breast cancer				
No		2.46	3.00	0.261
Yes		2.44	3.00	
1st/2nd degree relatives diagnosed with breast cancer[o]				
No		2.41	2.00	0.633
Yes		2.45	3.00	
Number of 1st and/or 2nd degree relatives diagnosed with breast cancer[p]				
= 1		2.38	2.00	<0.001
> 1		2.53	3.00	
1st degree relatives diagnosed with breast cancer before age of 50[q]				
No		2.43	3.00	0.534

Yes	2.45	3.00

[a] Spearman's correlation coefficient for ratio and interval variables
[b] Mean and median values of BI-RADS mammographic density for ordinal and nominal variables Spearman's correlation coefficient for ratio and interval variables
[c] P values of Spearman's test for continuous variables, p value of Mann-Whitney test for ordinal and nominal variables with two independent groups; p values of main effect resulted from Kruskal-Wallis test for ordinal and nominal variables with more than two unmatched groups, and the post-doc tests adopting Bonferroni correction and corresponding p values for specific variables were shown in appendix only
[d] Calculated by Weight (kg)/[Height (m)]^2
[e] Defined as >30 minutes/time and >3 times/week
[f] Defined as smoking more than 1 cigarette per day and continuing or accumulating more than 6 months
[g] Restricted to current and former smokers
[h] Restricted to former smokers
[i] Restricted to passive smokers
[j] Defined as drive more than one time per week and continuing six months or above
[k] Restricted to former-alcohol drinker
[l] Restricted to postmenopausal women
[m] Restricted to parous women
[n] Restricted to parous women who have breastfeeding history
[o] Restricted to women who have family history of breast cancer
[p] Restricted to women who have 1st/2nd degree relatives diagnosed with breast cancer
[q] Restricted to women who have 1st degree relatives diagnosed with breast cancer

Table 4 Distribution of mammographic density by two categories and associated odds ratios with 95% confidence interval from binary logistic regression

Factors	Low density[a]		High density[a]		OR[d]	95% CI[e]	P value[f]
	N[b]	%[c]	N	%			
Age (years)	2315	N/A[g]	2552	N/A	0.93	0.93-0.94	<0.001
BMI (kg/m^2)[h]	2315	N/A	2552	N/A	0.92	0.90-0.94	<0.001
Weight (kg)	2315	N/A	2552	N/A	0.97	0.97-0.98	<0.001
Province of residence	2315		2552				
Chongqing	164	7.08	327	12.81	1.00		
Gansu	265	11.45	95	3.72	0.18	0.13-2.43	<0.001
Guangxi	338	14.60	382	14.97	0.57	0.44-0.72	<0.001
Henan	55	2.38	379	14.85	3.45	2.46-4.85	<0.001
Shandong	371	16.03	160	6.27	0.22	0.17-0.28	<0.001
Xinjiang	634	27.39	625	24.49	0.49	0.40-0.62	<0.001
Yunnan	119	5.14	153	6.00	0.65	0.48-0.88	<0.001
Zhejiang	369	15.94	431	16.89	0.59	0.47-0.74	<0.001
Education	2315		2552				
None	78	3.37	49	1.92	1.00		
Primary school	347	14.99	200	7.84	0.92	0.62-1.37	0.671
Junior secondary school	695	30.02	699	27.39	1.60	1.10-2.32	0.013
Senior secondary/vocational and technical school	753	32.53	886	34.72	1.87	1.29-2.71	0.001
Higher vocational and technical college	324	14.00	495	19.40	2.43	1.66-3.57	<0.001
University and higher	118	5.10	223	8.74	3.01	1.97-4.58	<0.001
Non-educated and primary	425	18.36	249	9.76	1.00		
Secondary	1448	62.55	1585	62.11	1.87	1.57-2.22	<0.001
Tertiary	442	19.09	718	28.13	2.77	2.28-3.37	<0.001
Occupation	2314		2552				
Professionals and technicians	271	11.71	429	16.81	1.00		
Managers and administrators in public sectors	164	7.09	184	7.21	0.71	0.55-0.92	0.009
Clerical support and administrative related workers	214	9.25	300	11.76	0.89	0.70-1.12	0.305
Businesswomen	67	2.90	103	4.04	0.97	0.69-1.37	0.867
Agricultural workers	211	9.12	170	6.66	0.51	0.40-0.66	<0.001
Plant and machine operators and assemblers	741	32.02	756	29.62	0.64	0.54-0.77	<0.001
Service and sales workers	168	7.26	195	7.64	0.73	0.57-0.95	0.180
Housewives	362	15.64	316	12.38	0.55	0.45-0.68	<0.001
Others	116	5.01	99	3.88	0.54	0.40-0.73	<0.001
Duration of passive smoking (years)[i]	1582	N/A	1683	N/A	0.98	0.98-0.99	<0.001
Age at menarche (years)	2309	N/A	1543	N/A	0.91	0.88-0.94	<0.001
Menopause	2312		2549				
Premenopausal	650	28.11	1237	48.53	1.00		
Postmenopausal	1662	71.89	1312	51.47	0.42	0.37-0.47	<0.001
Parity	2312		2549				
Nulliparous	2144	92.70	2317	90.90	1.00		
Parous	168	7.30	232	9.10	0.78	0.64-0.96	0.020
Age at first delivery (years)[j]	2143	N/A	2311	N/A	1.04	1.02-1.06	<0.001
Breastfeeding history	2312		2549				
No	1787	77.29	1868	73.28	1.00		
Yes	525	22.71	681	26.72	0.81	0.71-0.92	0.001
Cumulative duration of breastfeeding (months)[k]	1787	N/A	1868	N/A	0.97	0.96-0.98	<0.001
Personal history of benign breast disease	2312		2549				

No	1895	81.96	2176	85.37	1.00		
Yes	417	18.04	373	14.63	1.28	1.10-1.50	0.001
Number of 1st and/or 2nd degree relatives diagnosed with breast cancer[l]	992		1040				
= 1	590	59.48	550	52.88	1.00		
> 1	402	40.52	490	47.12	1.31	1.01-1.60	0.003

[a] Number of cases may vary due to missing data
[b] Number of cases
[c] Percentage of cases
[d] Adjusted odds ratio
[e] Confidence interval
[f] P values of binary logistic regression
[g] Not applicable
[h] Calculated by Weight (kg)/[Height (m)]^2
[i] Restricted to passive smokers
[j] Restricted to parous women
[k] Restricted to parous women who have breastfeeding history
[l] Restricted to women who have 1st/2nd degree relatives diagnosed with breast cancer

Table 5 Distribution of mammographic density by two categories and associated odds ratios generated from multiple logistic regression with 95% confidence interval: 1. demographic model 2. menstrual and reproductive model

Factors	Low density (2308 cases)		High density (2543 cases)		AOR[c]	95% CI[d]	P value[e]
	N[a]	%[b]	N	%			
1. demographic model							
Age (years)	2308	N/A[f]	2543	N/A	0.93	0.92-0.94	<0.001
BMI (kg/m^2)[g]	2308	N/A	2543	N/A	0.92	0.87-0.96	<0.001
Province of residence							
Chongqing	164	7.10	326	12.80	1.00		
Gansu	265	11.50	95	3.70	0.12	0.09-1.17	<0.001
Guangxi	335	14.50	378	14.90	0.36	0.28-0.47	<0.001
Henan	54	2.30	379	14.90	3.37	2.36-4.83	<0.001
Shandong	371	16.10	159	6.30	0.21	0.15-2.27	<0.001
Xinjiang	631	27.30	622	24.50	0.36	0.28-0.46	<0.001
Yunnan	119	5.20	153	6.00	0.48	0.34-0.66	<0.001
Zhejiang	369	16.00	431	16.90	0.54	0.42-0.69	<0.001
Education							
Non-educated and primary	424	18.40	248	9.80	1.00		
Secondary	1443	62.50	1578	62.10	1.47	1.20-1.80	<0.001
Tertiary	441	19.10	717	28.20	1.60	1.23-2.09	<0.001
Occupation							
Professionals and technicians	269	11.70	427	16.80	1.00		
Managers and administrators in public sectors	164	7.10	183	7.20	0.74	0.56-0.99	0.400
Clerical support and administrative related workers	214	9.30	299	11.80	0.83	0.65-1.07	0.155
Businesswomen	66	2.90	103	4.10	1.06	0.73-1.55	0.005
Agricultural workers	211	9.10	170	6.70	0.64	0.47-0.87	0.070
Plant and machine operators and assemblers	740	32.10	751	29.50	0.82	0.65-1.02	0.810
Service and sales workers	167	7.20	195	7.70	0.77	0.58-1.03	<0.001
Housewives	361	15.60	316	12.40	0.62	0.48-0.80	0.005
Others	116	5.00	99	3.90	0.60	0.43-0.86	<0.001
2. menstrual and reproductive model							
Age at menarche (years)	2308	N/A	2543	N/A	0.94	0.91-0.97	<0.001
Menopause							
Premenopausal	649	28.10	1234	48.50	1.00		
Postmenopausal	1659	71.90	1309	51.50	0.43	0.39-0.49	<0.001
Parity							
Nulliparous	2140	92.70	2312	90.90	1.00		
Parous	168	7.30	231	9.10	0.70	0.53-0.91	0.001
Personal history of benign breast disease							
No	1891	81.90	2170	85.30	1.00		
Yes	417	18.10	373	14.70	1.37	1.15-1.63	<0.001

[a] Number of cases
[b] Percentage of cases
[c] Adjusted odds ratio
[d] Confidence interval
[e] P values of binary logistic regression
[f] Not applicable
[g] Calculated by Weight (kg)/[Height (m)]^2

Table 6 Adjusted odds ratio and 95% confidential interval generated from multiple logistic regression for the full model

Factors	Adjusted OR[a]	95% CI[b]	P values[c]
Age (years)	0.95	0.94-0.96	<0.001
BMI (kg/m^2)[d]	0.91	0.87-0.96	<0.001
Province of residence			
Chongqing	1.00		
Gansu	0.11	0.08-0.15	<0.001
Guangxi	0.28	0.21-0.36	<0.001
Henan	2.98	2.08-4.27	<0.001
Shandong	0.18	0.14-0.24	<0.001
Xinjiang	0.33	0.26-0.43	<0.001
Yunnan	0.39	0.28-0.54	<0.001
Zhejiang	0.51	0.39-0.65	<0.001
Education			
Non-educated and primary	1.00		
Secondary	1.44	1.17-1.77	0.001
Tertiary	1.52	1.16-1.98	0.002
Occupation			
Professionals and technicians	1.00		
Managers and Administrators in public sectors	0.75	0.56-0.99	0.048
Clerical support and administrative related workers	0.83	0.64-1.07	0.148
Businesswomen	1.00	0.68-1.47	0.994
Agricultural workers	0.63	0.46-0.86	0.004
Plant and machine operators and assemblers	0.81	0.65-1.00	0.060
Service and sales workers	0.74	0.55-0.99	0.044
Housewives	0.60	0.46-0.77	<0.001
Others	0.61	0.43-0.87	0.007
Menopause			
Premenopausal	1.00		
Postmenopausal	0.48	0.42-0.56	<0.001
Parity			
Nulliparous	1.00		
Parous	0.64	0.48-085	0.002
Personal history of benign breast disease			
No	1.00		
Yes	1.39	1.15-1.68	0.001

[a] Adjusted odds ratio
[b] Confidence interval
[c] P values of binary logistic regression
[d] Calculated by Weight (kg)/[Height (m)]^2

Supplementary table S1: p values of pairwise differences using the post-hoc test for province

Province	Chongqing	Gansu	Guangxi	Henan	Shandong	Xinjiang	Yunnan	Zhejiang
Chongqing	N/A	<0.001	<0.001	<0.001	<0.001	<0.001	=0.02	<0.001
Gansu	<0.001	N/A	<0.001	<0.001	=0.324	<0.001	<0.001	<0.001
Guangxi	<0.001	<0.001	N/A	<0.001	<0.001	0.001	0.413	=0.083
Henan	<0.001	<0.001	<0.001	N/A	<0.001	<0.001	<0.001	<0.001
Shandong	<0.001	=0.324	<0.001	<0.001	N/A	<0.001	<0.001	<0.001
Xinjiang	<0.001	<0.001	0.001	<0.001	<0.001	N/A	=0.003	=0.225
Yunnan	=0.02	<0.001	0.413	<0.001	<0.001	=0.003	N/A	=0.045
Zhejiang	<0.001	<0.001	0.083	<0.001	<0.001	=0.225	=0.045	N/A
N/A: not applicable								
Note: the significant level was set at 0.05 for main effect from Kruskal-Wallis test and became 0.0017 after Bonferroni correction								

Supplementary table S2: p values of the pairwise differences using post-hoc test for occupation

Occupation	Professionals and technicians	Managers and Administrators in public sectors	Clerical support and administrative related workers	Businesswomen	Agricultural workers	Plant and machine operators and assemblers	Service and sales workers	Housewives	Others
Professionals and technicians	N/A	=0.025	=0.231	=0.866	<0.001	<0.001	=0.041	<0.001	<0.001
Managers and Administrators in public sectors	=0.025	N/A	=0.259	=0.154	=0.003	=0.170	=0.816	=0.010	=0.060
Clerical support and administrative related workers	=0.231	=0.259	N/A	=0.529	<0.001	=0.002	=0.362	<0.001	=0.003
Businesswomen	=0.866	=0.154	=0.529	N/A	<0.001	=0.008	=0.202	<0.001	=0.004
Agricultural workers	<0.001	=0.003	<0.001	<0.001	N/A	=0.014	=0.001	=0.442	=0.474
Plant and machine operators and assemblers	<0.001	=0.170	=0.002	=0.008	=0.014	N/A	=0.088	=0.053	=0.264
Service and sales workers	=0.041	=0.816	=0.362	=0.202	=0.001	=0.088	N/A	=0.004	=0.033
Housewives	<0.001	=0.010	<0.001	<0.001	=0.442	=0.053	=0.004	N/A	=0.891
Others	<0.001	=0.060	=0.003	=0.004	=0.474	=0.264	=0.033	=0.891	N/A
N/A: not applicable									
Note: the significant level was set at 0.05 for main effect from Kruskal-Wallis test and became 0.0014 after Bonferroni correction									

Appendix 2.2 The full original (non-contracted) manuscript for the accepted paper contained in Chapter Five

The Breast Journal

Mammographic density and other risk factors for breast cancer amongst women in China

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Key Words:	Mammographic density, Breast density, Risk factor, Breast cancer, Chinese women

Title Page

TITLE: Mammographic density and other risk factors for breast cancer amongst women in China

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RUNNING TITLE: Breast density and breast cancer in Chinese women

KEY WORDS: Mammographic density, Breast density, Risk factor, Breast cancer, China, Chinese women.

Abstract

Background: The risk factors of breast cancer are not fully understood for Chinese women and, particularly, the association between mammographic density and cancer risk remains under-studied. This study aims to examine risk factors for breast cancer for women in China, with a particular focus on the relationship between mammographic density and cancer by using a quantitative measurement of density.

Methods: Eight-four cancer and 987 cancer-free women were selected from the Fudan University Shanghai Cancer Centre. Mammographic density was assessed by an automatic algorithm AutoDensity. Baseline differences in the characteristics of the two groups of women were examined using t tests and chi-square tests, and odds ratios (OR) were produced by binary logistic regression. A statistical model was built by multiple logistic regression.

Results: Statistically significant associations were found between breast cancer and large breast area (OR: 1.02, 95% CI: 1.00-1.03), increasing age (OR: 1.04, 95% CI: 1.02-1.06), increasing BMI (OR: 1.20, 95% CI: 1.12-1.29), later age at menarche (OR: 1.26, 95% CI: 1.14-1.40), earlier age at first delivery (OR: 0.78, 95% CI: 0.72-0.85), longer duration of breastfeeding OR: (1.22, 95% CI: 1.16-1.29), post-menopause status (OR: 2.22, 95% CI: 1.42-3.49), greater number of children (OR: 7.95, 95% CI: 4.83-73.06) and a breastfeeding history (OR: 3.25, 95% CI: 1.45-7.14) for all women. No significant associations were found between breast cancer and mammographic density amongst all (p=0.230), pre-menopausal (p=0.238) and post-menopausal women (p=0.119). Statistical models were built with success rates around 90% for each of the total, pre-menopausal and post-menopausal women.

Conclusion: This study demonstrated risk factors of breast cancer for Chinese women, with mammographic density for the first time being assessed by the quantitative method. The lack of association between breast cancer and mammographic density should have significant implications for breast cancer screening strategies and one that requires further investigations.

Introduction

Breast cancer is the most common neoplasm diagnosed amongst females in China and it is one of the leading causes of cancer death in Chinese women (1, 2). The incidence of breast cancer has increased by nearly 30% over the past three decades and the age-standardised rate reached 29 per 100,000 in 2011 (3, 4). According to previous epidemiological studies conducted for women in China and elsewhere, established and emerging risk factors of breast cancer include increasing age, early age of menarche, late age of menopause, nulliparity, late age at first pregnancy, lack of lactation and family history of breast cancer (5-14). However these studies focused on women from clinical settings, who are more likely to be symptomatic at admissions. Our work will be one of the first studies that uses screening data to examine relevant risk factors of breast cancer, extending the relevance of suggested risk factors to a more general population.

One of the key risk factors shown to be relevant for westernised women is mammographic density which is described as the amount of fibroglandular tissue in the breasts (15, 16). However, this potential association remains under-studied and has not been consistently shown in Chinese females (17, 18). Besides, the assessment approach used in these studies relied on the qualitative method of Breast Imaging Reporting and Data System (BI-RADS) breast composition classifications. Even though BI-RADS classification is the most commonly used assessment in both clinical and screening settings in China and many other countries (19, 20), it was shown to demonstrate wide inter- (kappa=0.02-0.77) and intra-observer (kappa=0.32-0.88) agreement ranges (21, 22). Therefore quantitative techniques using mathematical, statistical and physical principles are increasingly recommended to assess mammographic density objectively and consistently (23), in order to prevent unnecessary differences in decision-making from the subjectivity and variability of BI-RADS classification (24).

The aim of the current study is to provide data that will improve our understanding of risk factors of breast cancer for Chinese women based on screening data, with a particular attention paid to mammographic density by using quantitative measurement.

Material and Methods

Study design

This was a retrospective cross-sectional study. Ethical approval was obtained from the Human Research Ethics Committee of the University of Sydney (Project number: 2014/768) and the Institutional Review Board of Fudan University Shanghai Cancer Centre (FUSCC) (Project number 1503144-11).

Data collection

An initial set of 1100 cases, of which 100 had breast cancer and 1000 did not, were randomly collected from FUSCC form March 2015 to June 2016.

The 100 women were diagnosed with biopsy-proven breast cancer (ductal carcinoma in situ included) within the hospital environment at FUSCC, whilst the other 1000 women who were not diagnosed with cancer were recruited from the Breast Cancer Screening Program (BCSP) organised by FUSCC. Demographic, lifestyle and reproductive characteristics were obtained from the registration form and the discharge summary in health record for each woman with breast cancer and through a BCSP questionnaire for breast cancer-free women.

Image acquisition

For all of the women, mammograms were acquired for cranio-caudal (CC) projection of both breasts (where available). Two full field digital mammography units were used in this study: Mammomat Inspiration (Siemens; Erlangen, Germany) and Selenia (Hologic, Inc., Bedford, MA, USA). Images were displayed on two 5-megapixel (MP) monitors during the reading process. The quality assurance was performed by well-trained radiographers.

Measurement of variables

Mammographic density was measured by a fully automatic algorithm AutoDensity (25), which identifies both dense and breast areas in mammograms and then classifies mammographic density. This algorithm automatically finds an optimal threshold for each mammogram independently from any other images in a data set, in order to segment the breast from the background within a mammogram and outline the dense tissue within the breast. The resultant percentage mammographic density was produced by dividing the breast area (number of pixels) by the dense area (number of pixels) and expressing in a percentage. The values obtained from the left and right CC images for each woman were averaged.

Age, height, weight, age at menarche, age at menopause, age at first delivery and duration of breastfeeding were self-reported at admission (cancer patients) or self-filled in the BCSP questionnaire (cancer-free women) and measured as continuous variables. BMI was calculated from height and weight.

Ethnicities other than Han Chinese were classified into a single non-Han grouping in order to increase statistical power. Menopause status, parity history, number of children, breastfeeding history, personal history of breast cancer, family history of breast cancer, degree of relationship by consanguinity, smoking history and alcohol consumption were classified into two groupings based on the status of each woman.

Statistical analysis

Differences in characteristics between women with and without breast cancer were assessed by using independent samples t tests for continuous variables and chi-square tests for categorical variables. Mean and standard deviation (SD) were used for continuous variables for descriptive purposes.

Binary logistic regression was then conducted for variables that were statically significant from either the t test or the chi-square test in order to produce odds ratios (OR) and 95% confidence intervals (95% CI). Categorical variables with 0 frequency in any one of the categories were excluded from this test.

Statistical model building was finally performed by using multiple logistic regression adopting the significant variables except those restricted to women with specific conditions (e.g. duration of breastfeeding was restricted to women who had history of breastfeeding only, so this variable was not used in the model building).

The whole data set consisting of all women was then divided into two subsets based on menopause status, one for pre-menopausal and another for post-menopausal women. The statistical tests mentioned above were repeated for each subset.

For all statistical analyses, SPSS (IBM SPSS statistics for windows, version 22.0) statistical package was used and two-tailed tests of significance were employed using a significance level of 0.05.

Results

987 women without and 84 women with breast cancer were finally selected for statistical analysis after excluding cases with unilateral images. Figure 1 depicts the descriptive statistics of percentage density, dense areas and breast areas for all, pre-menopausal and post-menopausal women based on the status of cancer.

Table 1 shows the baseline differences of characteristics for cancer and cancer-free groups of all participants, and the outputs from binary logistic regression. The power analysis showed a statistical power of at least 87% at significant level of 0.002 for all variables that were significant. Results specific to the 653 pre-menopausal women (617 without and 36 with cancer) and 418 post-menopausal females (370 cancer-free and 48 cancer women) are shown in tables 2 and 3, respectively. Table 4 represents the odds ratio and 95% confidence interval from multiple logistic regression. The statistical models predicted 91.88%, 94.49% and 88.28% of variation of percentage mammographic density in all, pre-menopausal and post-menopausal women, respectively.

Discussion

This work has examined the association between mammographic density and breast cancer, using for the first time a quantitative method to measure mammographic density for women in China. We failed to identify any association for mammographic density with breast cancer using percentage or dense area parameters, a finding which is consistent and inconsistent with previous work: one previous study which recruited 86 and 28,302 women with and without breast cancer, respectively, from a screening trial across 4 Chinese cities of similar size to our study also showed no association between density and cancer (17); in contrast another large cross-sectional study, involving 2,527 cancer and 3,394 cancer-free women, reported that, compared to women without breast cancer, mammographic density was lower and higher for cancer women within the 40-49 and 55-71 age groups, respectively, however there was no association for women aged 50-54 (18). This difference between our work and the latter study might be explained by the fact that age-dependent variations were not assessed in our work, thereby obscuring specific observations. Instead we focused on categorising our women based on menopausal status. Another possible explanation is that, unlike other studies that used qualitative (i.e. BI-RADS classification) assessment, we used quantitative approach to assess mammographic density, thus potentially impacting on the results, but the possibility of this impact requires further study. Nonetheless from our findings and that of previous studies, the possibility remains that the relationship between mammographic density and breast cancer for women in China may not be as strong as or at least could be different from that demonstrated in other populations, particularly those involving western women. This hypothesis will need further work to be proven or disproven.

The current work found that larger breast area increased the risk of developing breast cancer. Similar findings were reported in previous studies (26-28), however after separating the women in our study based on menopausal status, this breast size association was only identified for post-menopausal women, which is consistent with an investigation involving Caucasian and Asian women (29). This relationship between breast size and cancer may be explained by the fact that adipose tissue is a dominant component of the breast among post-menopausal women and functions as a slow-release depot for lipid-soluble carcinogens (30) as well as providing mature adipocytes that promote the growth of several breast cancer cells (31). However, it should be noted that our method of measuring breast area from mammograms assesses breast size as a two-dimensional structure and eliminates the three-dimensional features of the breast. Also, the results need to be interpreted with caution since the 95% CIs spans the null value, which may overestimate the association of breast area. Therefore, further research is needed by using volumetric techniques in order to confirm this potential positive relationship between breast size and cancer risk.

It is important to note that a number of findings in our study are clearly at odds with what is reported in the literature: later age at menarche appears to be a risk factor of breast cancer rather than a protective one; women with breastfeeding history and women with longer duration of lactation seem to have a greater chance of developing breast cancer compared to women without such a history; and women with more than one child are more likely to have breast cancer compared with women with only one. These unexpected results might be unique to Chinese women but this is unlikely since our results are inconsistent with previous studies conducted in same or similar locations as the one used in our work (5-9, 13, 14, 32). Another more acceptable explanation is that, unlike other studies, we involved cancer-free women from a screening program rather than those came from clinical environment who are more likely to be symptomatic women. Therefore these unusual findings may be specifically relevant to the women attending a screening program, but emphasises the need for clear declaration of methodological approaches. Again further work is needed. In addition, compared with our cancer-free group of women, a larger group of women without breast cancer was used. The few women with cancer may not have been the representative of cancer features in the general population, and hence lead to skewed results.

In the current work, a fully automatic algorithm was applied to measure mammographic density. It has been suggested that the application of fully automated methods eliminates inter- and intra-reader variability associated with BI-RADS classifications (21, 22). Nonetheless it is reassuring that quantitative methods do correlate well with BI-RADS categories (22, 24). We do acknowledge however that the relationship between BI-RADS and AutoDensity scores has not yet been examined, but AutoDensity has been shown to be comparable to Cumulus, a globally employed semi-automatic algorithm, in terms of cancer risk assessment (24, 25).

It is acknowledged that our study has limitations. The small sample size within the cancer group is noted and the subsequent unbalanced number of cases between cancer and cancer-free women potentially decreases statistical power. This may have been responsible for the absence of certain associations such as the lack of findings around breast cancer and personal and family histories (statistical power of 5% and 11%, respectively). Besides, unlike the data from women with breast cancer, which were collected from a well-structured screening program questionnaire, the details gathered for women with cancer were gathered from health records based on self-reported information, potentially impacting upon the values of odds ratios. Furthermore, our study did not detail the stage of the menstrual cycle at the time of examination. It is suggested that estrogen and progesterone will encourage the proliferation of breast epithelial cells (33) and positively associate with mammographic density (34, 35). From a recent study using 3-dimensional magnetic resonance imaging, fibroglandular tissue volume and percent mammographic density measured at weeks 1 and 4 of the menstrual cycle were shown to be higher than those measured at weeks 2 and 3 (36). However the impact of menstrual stages on mammographic density is unknown.

In summary, this study demonstrated risk factors of breast cancer for Chinese women with a particular focus on quantitative methods of mammographic density. The lack of association between breast cancer and mammographic density could have significant implications for breast cancer screening strategies, but this finding requires further investigation and refinement. Whilst some alignment with previous knowledge around breast cancer risk and westernised women was noted, some findings unique to the population studied here have been presented.

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Tables

Table 1 Baseline difference and output from univariate analysis of all women with and without breast cancer

Variables	Women without cancer		Women with cancer		P value[c]	OR (95% CI)[d]	P value[e]
	N[a]	%[b]	N	%			
Percentage mammographic density (%)	987.00	100.00	84.00	100.00	0.230		
Mean ± standard deviation	32.69±11.66		30.84±13.64				
Dense area (10,000 pixels)	987.00	100.00	84.00	100.00	0.343		
Mean ± standard deviation	6.80±5.20		7.37±6.33				
Breast area (10,000 pixels)	987.00	100.00	84.00	100.00	0.044	1.018 (1.004, 1.033)	0.014
Mean ± standard deviation	21.02±13.46		24.90±16.99				
Age at mammography (years)	987.00	100.00	84.00	100.00	0.002	1.040 (1.018, 1.062)	<0.001
Mean ± standard deviation	48.94±9.49		52.99±11.19				
Height (cm)	987.00	100.00	84.00	100.00	0.088		
Mean ± standard deviation	160.63±4.74		159.73±3.80				
Weight (kg)	987.00	100.00	84.00	100.00	<0.001	1.056 (1.029, 1.083)	<0.001
Mean ± standard deviation	57.84±7.90		61.75±9.01				
BMI (kg/m^2)[f]	987.00	100.00	84.00	100.00	<0.001	1.204 (1.123, 1.290)	<0.001
Mean ± standard deviation	22.40±2.81		24.19±3.34				
Age at menarche (years)	987.00	100.00	84.00	100.00	<0.001	1.264 (1.139, 1.403)	<0.001
Mean ± standard deviation	14.22±1.88		15.20±1.62				
Age at menopause (years)[g]	370.00	100.00	48.00	100.00	0.754		
Mean ± standard deviation	50.39±3.80		50.23±3.81				
Age at first delivery[h]	926.00	100.00	84.00	100.00	<0.001	0.777 (0.715, 0.845)	<0.001
Mean ± standard deviation	27.84±3.48		25.54±3.46				
Duration of breastfeeding[i]	762.00	100.00	77.00	100.00	<0.001	1.223 (1.164, 1.286)	<0.001
Mean ± standard deviation	7.21±4.14		15.92±03				
Ethnicity							
Non-Han origin	11.00	1.11	0.00	0.00	1.000[j]		
Han origin	976.00	98.89	84.00	100.00			
Menopause status							
Pre-menopausal	617.00	62.50	36.00	42.86	<0.001	1.000	
Post-menopausal	370.00	37.50	48.00	57.14		2.223 (1.416, 3.490)	<0.001
Parity status							
Nulliparous	61.00	6.18	0.00	0.00	0.012[j]		
Parous	926.00	93.82	84.00	100.00			
Number of children[k]							
=1	853.00	92.10	50.00	59.52	<0.001	1.000	
>1	73.00	7.90	34.00	40.48		7.946 (4.834, 73.060)	<0.001
Breastfeeding history							
No	225.00	22.80	7.00	8.33	0.003	1.000	
Yes	762.00	77.20	77.00	91.67		3.248 (1.447, 7.142)	0.003
Personal history of breast cancer							
No	977.00	98.99	83.00	98.81	0.595[j]		
Yes	10.00	1.01	1.00	1.19			
Family history of breast cancer							
No	915.00	92.71	76.00	90.48	0.596		
Yes	72.00	7.29	8.00	9.52			
Degree of consanguinity							
1st degree	47.00	65.28	7.00	87.50	0.264[j]		
2nd degree	25.00	35.72	1.00	12.50			
Smoking history							
No	967.00	97.97	84.00	100.00	0.395[j]		
Yes	20.00	2.03	0.00	0.00			
Alcohol consumption							
No	864.00	87.54	84.00	100.00	0.001		
Yes	123.00	12.46	0.00	0.00			

[a] Number of cases
[b] Percentage of cases

[c] P values from t test for continuous variables; P values from Chi-square for categorical variables
[d] Odds ratio and 95% Confidence Interval of being cancer cases from binary logistic regression for factors that were statistically significant ($p<0.05$) from t tests or chi-square tests
[e] P values from binary logistic regression
[f] Calculated by Weight (kg)/[Height (m)]^2
[g] Restricted to post-menopausal women
[h] Restricted to parous women
[i] Restricted to women with breastfeeding history
[j] P values from Fisher's exact test

Table 2 Baseline difference and output from univariate analysis of pre-menopausal women with and without breast cancer

Variables	Women without cancer		Women with cancer		P value[c]	OR (95% CI)[d]	P value[e]
	N[a]	%[b]	N	%			
Percentage mammographic density (%)	617.00	100.00	36.00	100.00	0.238		
Mean ± standard deviation	34.85±10.89		37.06±11.36				
Dense area (10,000 pixels)	617.00	100.00	36.00	100.00	0.481		
Mean ± standard deviation	7.22±5.31		7.86±6.01				
Breast area (10,000 pixels)	617.00	100.00	36.00	100.00	0.679		
Mean ± standard deviation	21.03±13.72		22.02±16.80				
Age at mammography (years)	617.00	100.00	36.00	100.00	0.784		
Mean ± standard deviation	43.34±4.94		43.67±6.93				
Height (cm)	617.00	100.00	36.00	100.00	0.586		
Mean ± standard deviation	160.96±4.67		160.64±3.34				
Weight (kg)	617.00	100.00	36.00	100.00	0.033	1.055 (1.015, 1.096)	0.006
Mean ± standard deviation	57.37±7.66		61.11±10.00				
BMI (kg/m^2)[f]	617.00	100.00	36.00	100.00	0.024	1.181 (1.065, 1.310)	0.002
Mean ± standard deviation	22.13±2.71		23.68±3.87				
Age at menarche (years)	617.00	100.00	36.00	100.00	<0.001	1.502 (1.233, 1.830)	<0.001
Mean ± standard deviation	13.88±1.56		15.00±1.67				
Age at first delivery[g]	572.00	100.00	36.00	100.00	<0.001	0.720 (0.620, 0.836)	<0.001
Mean ± standard deviation	27.96±3.59		25.44±2.48				
Duration of breastfeeding[h]	490.00	100.00	33.00	100.00	<0.001	1.260 (1.166, 1.363)	<0.001
Mean ± standard deviation	6.61±3.77		12.15±6.47				
Ethnicity							
Non-Han origin	7.00	1.13	0.00	0.00	1.000[i]		
Han origin	610.00	98.87	36.00	100.00			
Parity status							
Nulliparous	45.00	7.29	0.00	0.00	0.164[i]		
Parous	572.00	92.71	36.00	100.00			
Number of children[g]							
=1	553.00	96.68	26.00	72.22	<0.001	1.000	
>1	19.00	3.32	10.00	27.78		11.194 (4.733, 26.476)	<0.001
Breastfeeding history							
No	127.00	20.58	3.00	8.33	0.115		
Yes	490.00	79.42	33.00	91.67			
Personal history of breast cancer							
No	611.00	99.03	35.00	97.22	0.329[i]		
Yes	6.00	0.97	1.00	2.78			
Family history of breast cancer							
No	573.00	92.87	33.00	91.67	0.738[i]		
Yes	44.00	7.13	3.00	8.33			
Degree of consanguinity							
1st degree	26.00	59.09	2.00	66.67	1.000[i]		
2nd degree	18.00	40.91	1.00	33.33			
Smoking history							
No	602.00	97.57	36.00	100.00	1.000[i]		
Yes	15.00	2.43	0.00	0.00			
Alcohol consumption							
No	531.00	86.06	36.00	100.00	0.009[i]		
Yes	86.00	13.94	0.00	0.00			

[a] Number of cases
[b] Percentage of cases
[c] P values from t test for continuous variables; P values from Chi-square for categorical variables
[d] Odds ratio and 95% Confidence Interval of being cancer cases from binary logistic regression for factors that were statistically significant ($p<0.05$) from t tests or chi-square tests
[e] P values from binary logistic regression
[f] Calculated by Weight (kg)/[Height (m)]^2
[g] Restricted to parous women
[h] Restricted to women with breastfeeding history
[i] P values from Fisher's exact test

Table 3 Baseline difference and output from univariate analysis of post-menopausal women with and without breast cancer

Variables		Women without cancer		Women with cancer		P value[c]	OR (95% CI)[d]	P value[e]
		N[a]	%[b]	N	%			
Percentage mammographic density (%)		370.00	100.00[b]	48.00	100.00	0.119		
	Mean ± standard deviation	29.09±12.01		26.17±13.44				
Dense area (10,000 pixels)		370.00	100.00	48.00	100.00	0.255		
	Mean ± standard deviation	6.09±4.95		6.99±6.60				
Breast area (10,000 pixels)		370.00	100.00	48.00	100.00	0.021	1.029 (1.009, 1.049)	0.005
	Mean ± standard deviation	20.99±13.01		27.06±16.99				
Age at mammography (years)		370.00	100.00	48.00	100.00	0.156		
	Mean ± standard deviation	58.27±7.77		59.98±8.31				
Height (cm)		370.00	100.00	48.00	100.00	0.150		
	Mean ± standard deviation	160.09±4.82		159.04±4.01				
Weight (kg)		370.00	100.00	48.00	100.00	0.005	1.051 (1.015, 1.088)	0.005
	Mean ± standard deviation	58.62±8.24		62.23±8.27				
BMI (kg/m^2)[f]		370.00	100.00	48.00	100.00	<0.001	1.198 (1.087, 1.320)	<0.001
	Mean ± standard deviation	22.86±2.93		24.57±2.86				
Age at menarche (years)		370.00	100.00	48.00	100.00	0.086		
	Mean ± standard deviation	14.79±2.20		15.35±1.58				
Age at menopause (years)		370.00	100.00	48.00	100.00	0.784		
	Mean ± standard deviation	50.39±3.80		50.23±3.81				
Age at first delivery[g]		354.00	100.00	48.00	100.00	<0.001	0.822 (0.743, 0.909)	<0.001
	Mean ± standard deviation	27.65±3.30		25.60±4.07				
Duration of breastfeeding[h]		272.00	100.00	44.00	100.00	<0.001	1.182 (1.110, 1.260)	<0.001
	Mean ± standard deviation	8.29±4.54		18.75±17.25				
Ethnicity								
	Non-Han origin	4.00	1.08	0.00	0.00	1.000[i]		
	Han origin	366.00	98.92	48.00	100.00			
Parity status								
	Nulliparous	16.00	4.32	0.00	0.00	0.235[i]		
	Parous	354.00	95.68	48.00	100.00			
Number of children[g]								
	=1	300.00	84.75	24.00	50.00	<0.001	1.000	
	>1	54.00	15.25	24.00	50.00		5.556 (2.942, 10.490)	<0.001
Breastfeeding history								
	No	98.00	26.49	4.00	8.33	0.01	1.000	
	Yes	272.00	73.51	44.00	91.67		3.963 (1.388, 11.317)	0.01
Personal history of breast cancer								
	No	366.00	98.92	48.00	100.00	1.000[i]		
	Yes	4.00	1.08	0.00	0.00			
Family history of breast cancer								
	No	342.00	92.43	43.00	89.58	0.566[i]		
	Yes	28.00	7.57	5.00	10.42			
Degree of consanguinity								
	1st degree	21.00	75.00	5.00	100.00	0.559[i]		
	2nd degree	7.00	25.00	0.00	0.00			
Smoking history								
	No	365.00	98.65	48.00	100.00	1.000[i]		
	Yes	5.00	1.35	0.00	0.00			
Alcohol consumption								
	No	333.00	90.00	48.00	100.00	0.014[i]		
	Yes	37.00	10.00	0.00	0.00			

[a] Number of cases
[b] Percentage of cases
[c] P values from t test for continuous variables; P values from Chi-square for categorical variables
[d] Odds ratio and 95% Confidence Interval of being cancer cases from binary logistic regression for factors that were statistically significant (p<0.05) from t tests or chi-square tests

[e] P values from binary logistic regression
[f] Calculated by Weight (kg)/[Height (m)]^2
[g] Restricted to parous women
[h] Restricted to women with breastfeeding history
[i] P values from Fisher's exact test

Table 4 Output from multivariate analysis of all, pre- and post-menopausal women

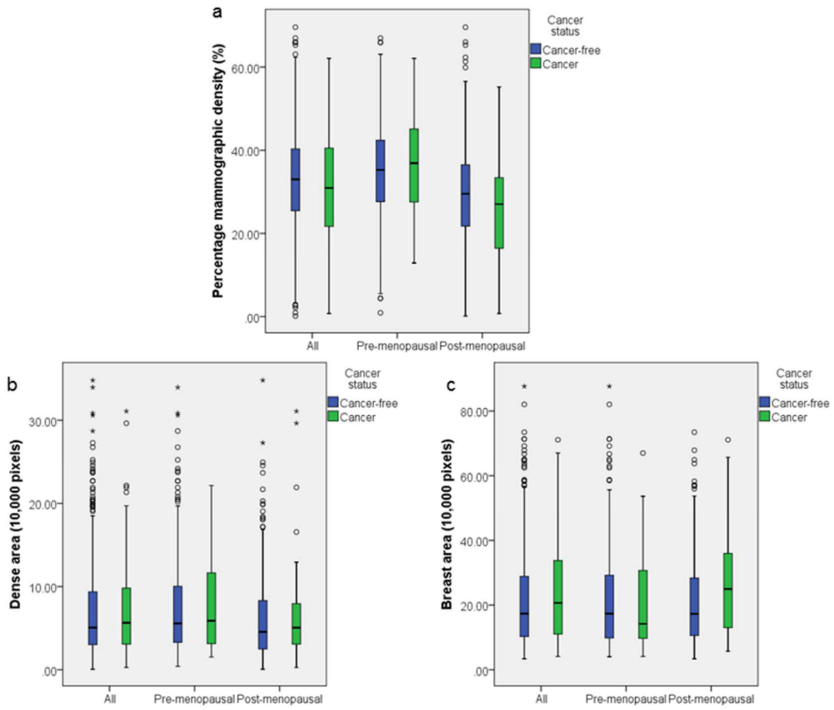
Variables	All		Pre-menopausal		Post-menopausal	
	OR (95% CI)[a]	P value[b]	OR (95% CI)	P value	OR (95% CI)	P value
Breast area (10,000 pixels)	1.008 (0.992, 1.023)	0.344	N/A[c]	N/A	1.019 (0.998, 1.041)	0.076
Age at mammography (years)	0.966 (0.960, 1.033)	0.829	N/A	N/A	N/A	N/A
Weight (kg)	0.970 (0.909, 1.036)	0.368	0.970 (0.880, 1.070)	0.970	0.951 (0.874, 1.033)	0.235
BMI (kg/m^2)[d]	1.274 (1.061, 1.529)	0.009	1.179 (1.058, 1.314)	0.003	1.330 (1.056, 1.674)	0.015
Age at menarche (years)	1.201 (1.071, 1.347)	0.002	1.464 (1.207, 1.775)	<0.001	N/A	N/A
Menopause status						
Pre-menopausal	1.00		N/A		N/A	
Post-menopausal	1.789 (0.868, 3.684)	0.115	N/A	N/A	N/A	N/A
Breastfeeding history						
No	1.00		N/A		1.00	
Yes	3.043 (1.363, 6.794)	0.007	N/A	N/A	3.722 (1.285, 10.782)	0.015

[a] Odds ratio and 95% Confidence Interval of being cancer cases from multiple regression
[b] P values from multiple logistic regression
[c] Not applicable
[d] Calculated by Weight (kg)/[Height (m)]^2

Figure legend

Fig. 1 a: Box plots of percentage mammographic density by status of cancer for all, pre-menopausal and post-menopausal women. b: Box plots of dense areas by status of cancer for all, pre-menopausal and post-menopausal women. c: Box plots of breast areas by status of cancer for all, pre-menopausal and post-menopausal women.

Figure



Appendix 3

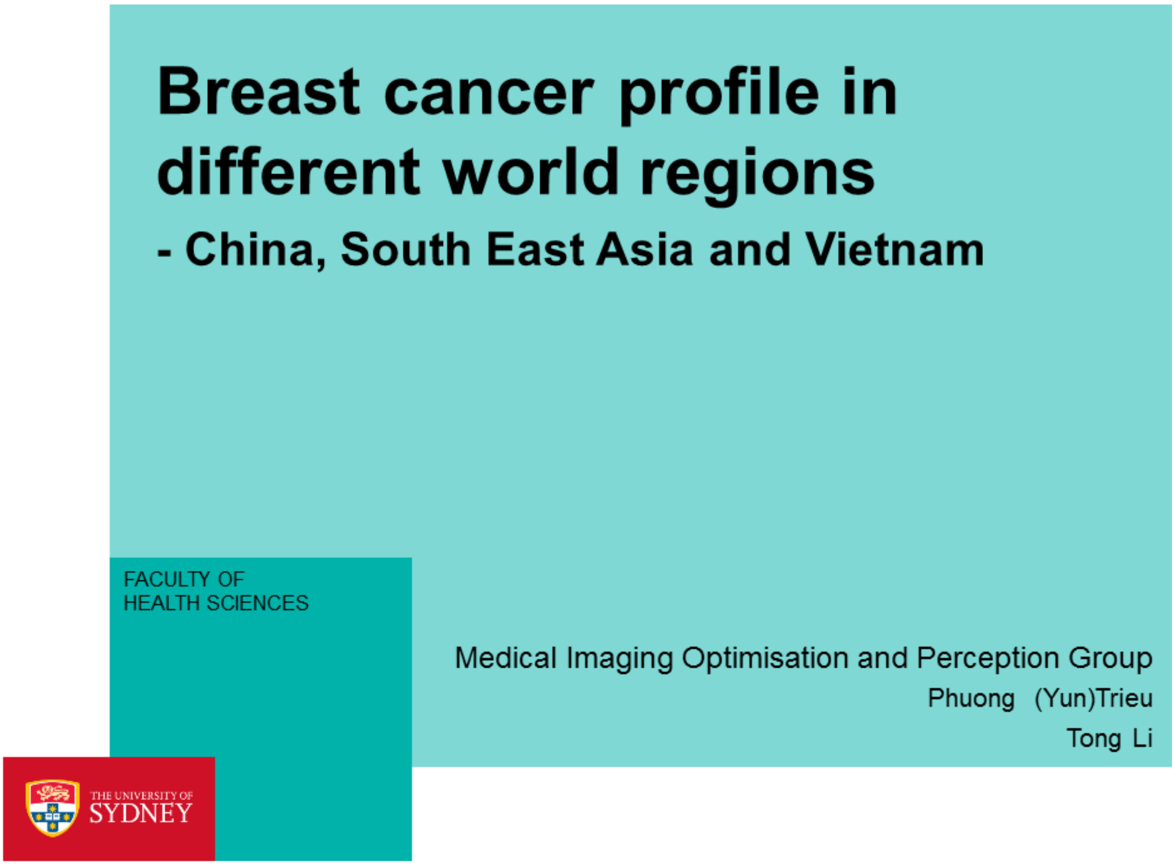
Presentations

Appendix 3.1 Lab Meeting at Brain and Mind Centre

Sydney, Australia

17th April 2015

This oral presentation was given in association with the paper described in Chapter Two.

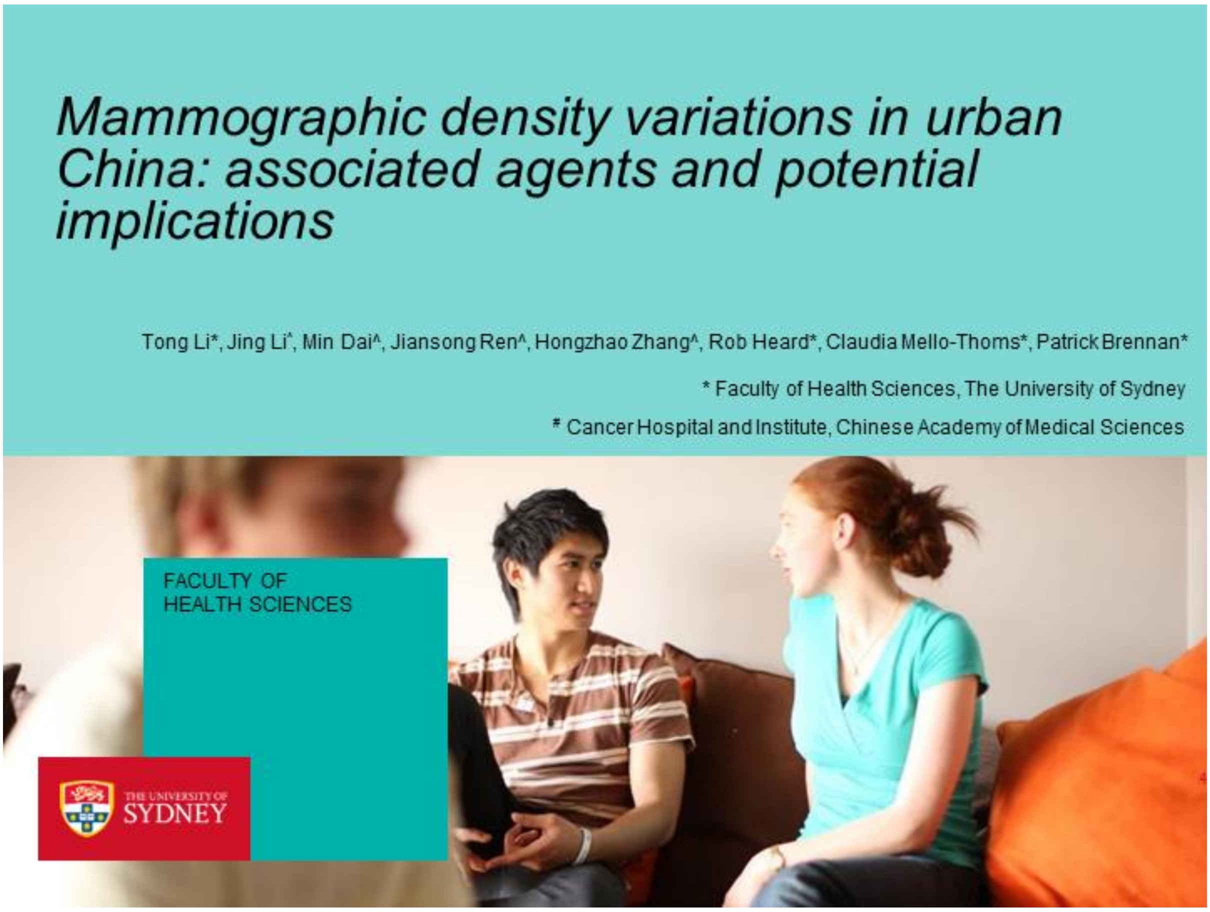


Appendix 3.2 Sydney Cancer Conference 2016

Sydney, Australia

22nd – 23rd September 2016

This oral presentation was given in association with the paper described in Chapter Four.

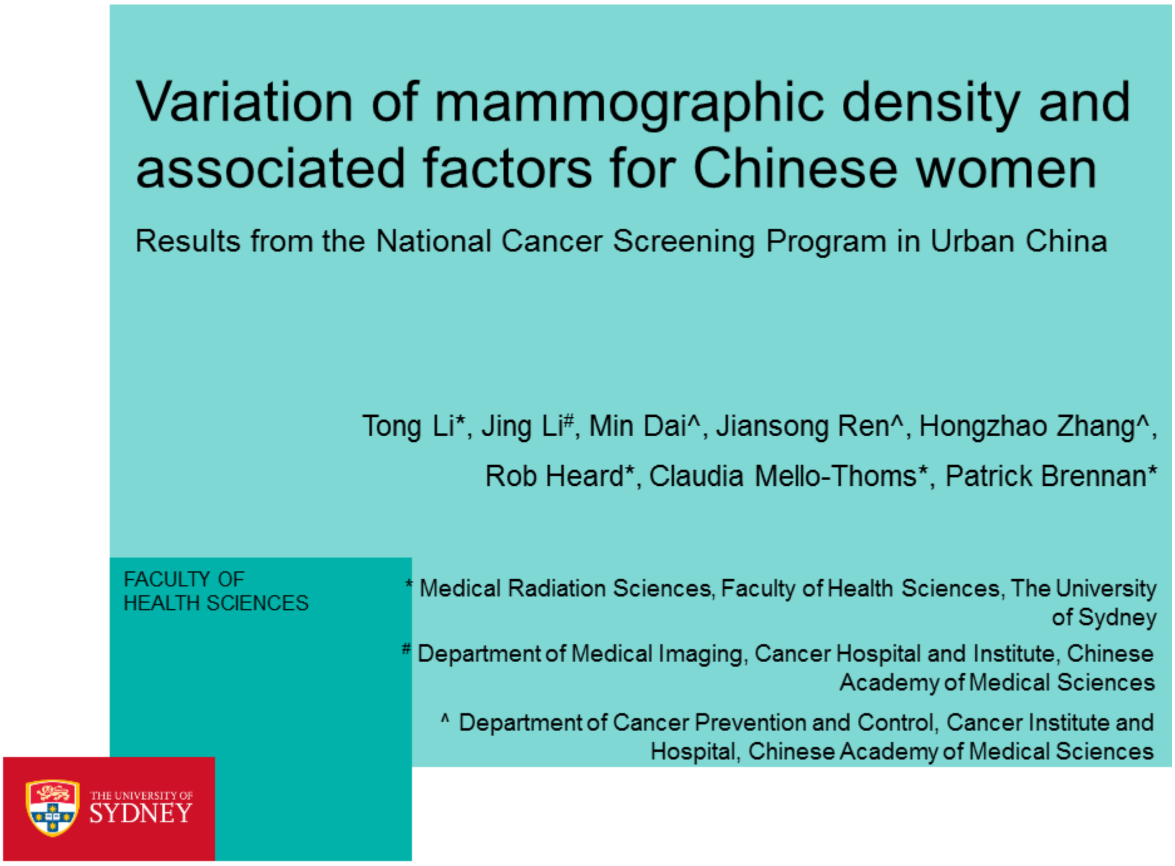


Appendix 3.3 4th International "Why Study Mammographic Density?" Meeting: The Measurement Challenge

Kingscliff, Australia

15th – 16th August 2016

This oral presentation was given in association with the paper described in Chapter Four.

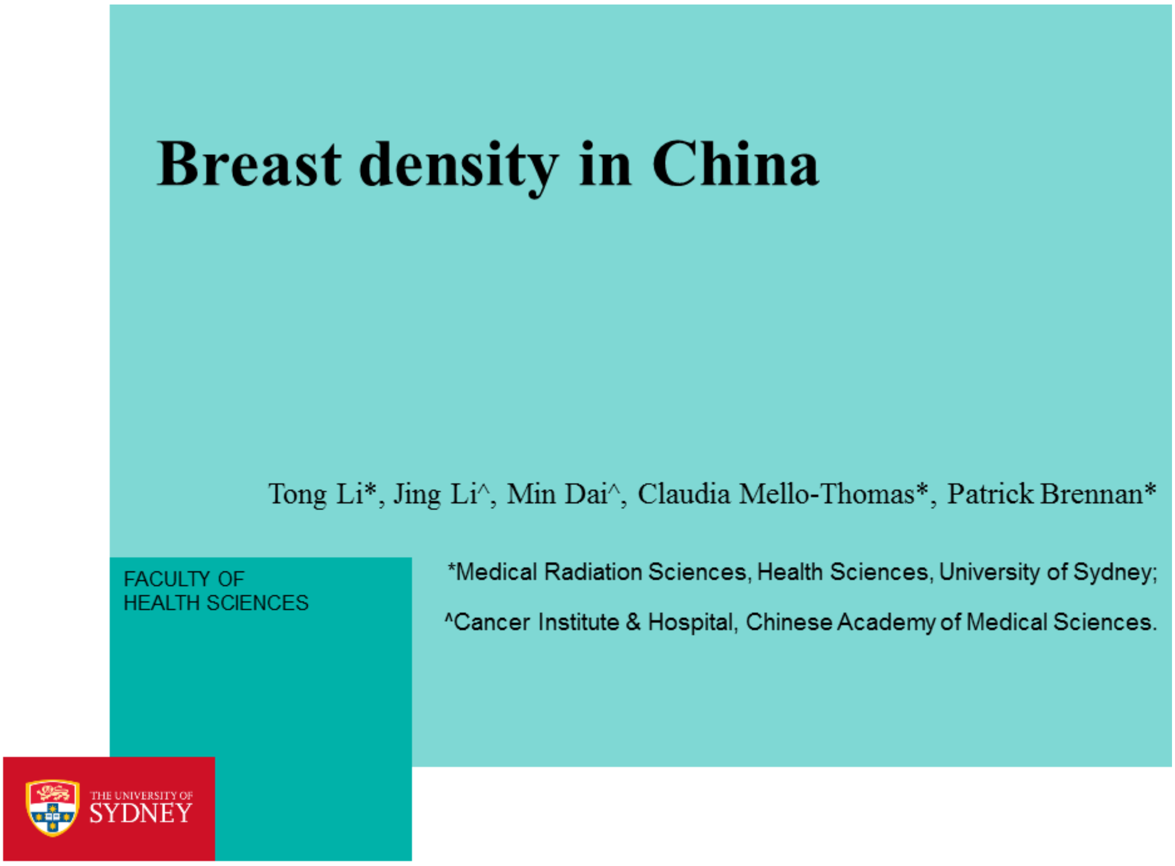


Appendix 3.4 2016 Sydney Catalyst Postgraduate and Early Career Researcher Symposium

Sydney, Australia

22nd April 2016

This 3-minute oral presentation was given in association with the paper described in Chapter Four.

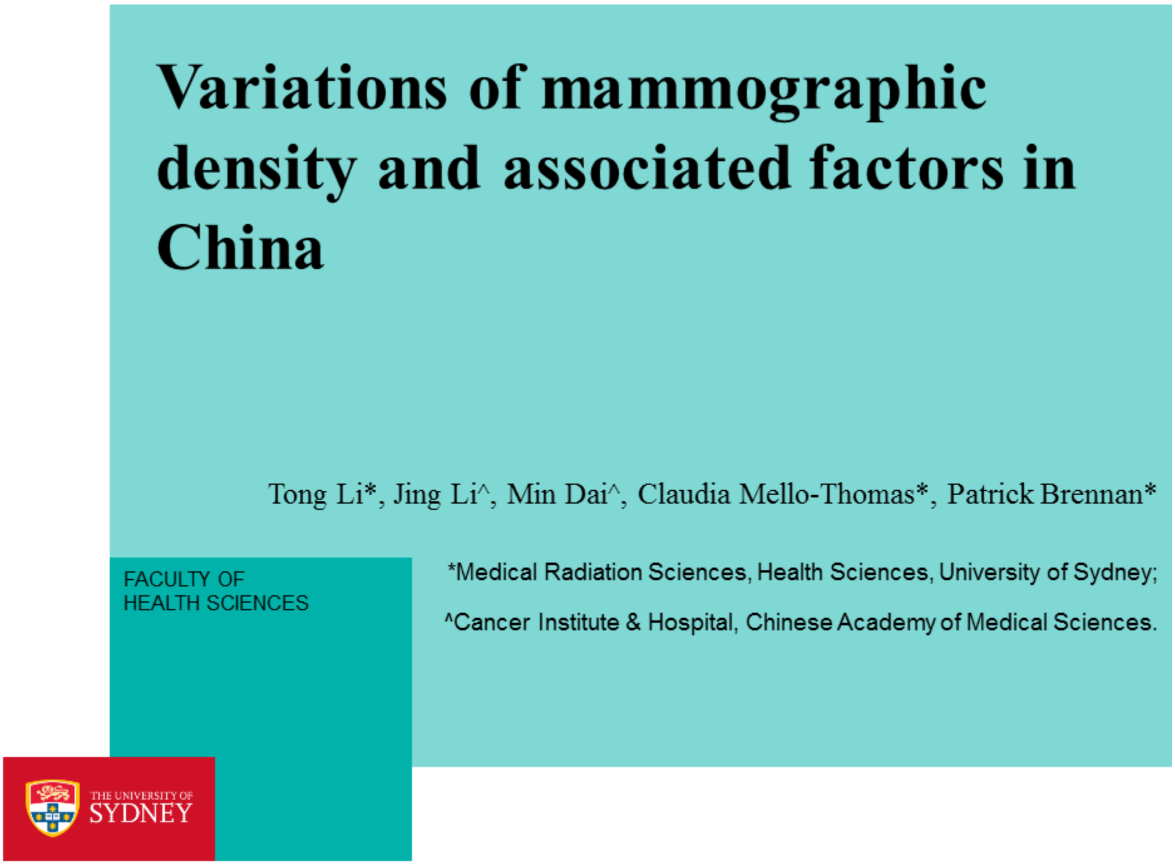


Appendix 3.5 Asian Pacific Organisation for Cancer Prevention 8th General Assembly

Brisbane, Australia

13th – 14th April 2016

This oral presentation was given in association with the paper described in Chapter Four.

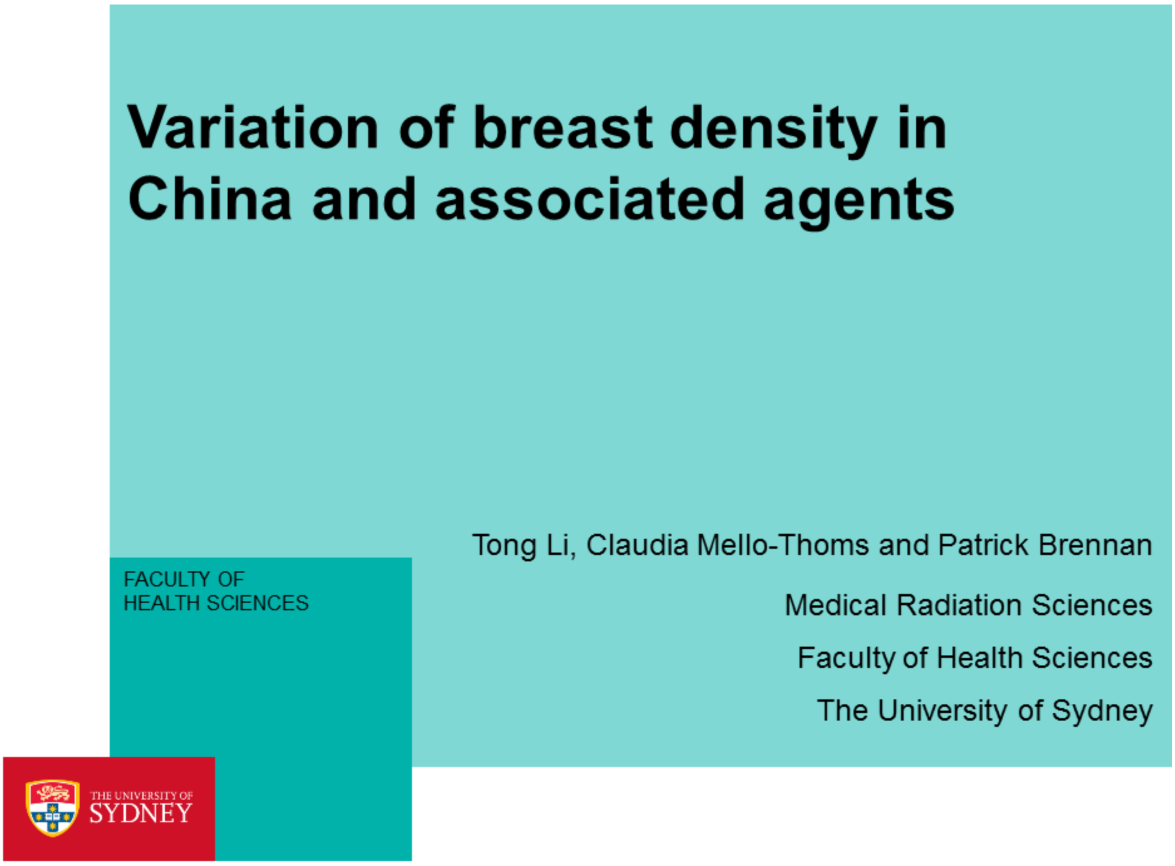


Appendix 3.6 2015 Postgraduate Cancer Research Symposium

Cancer Research Network, Sydney, Australia

4th December 2015

This oral was given in association with the paper described in Chapter Four.

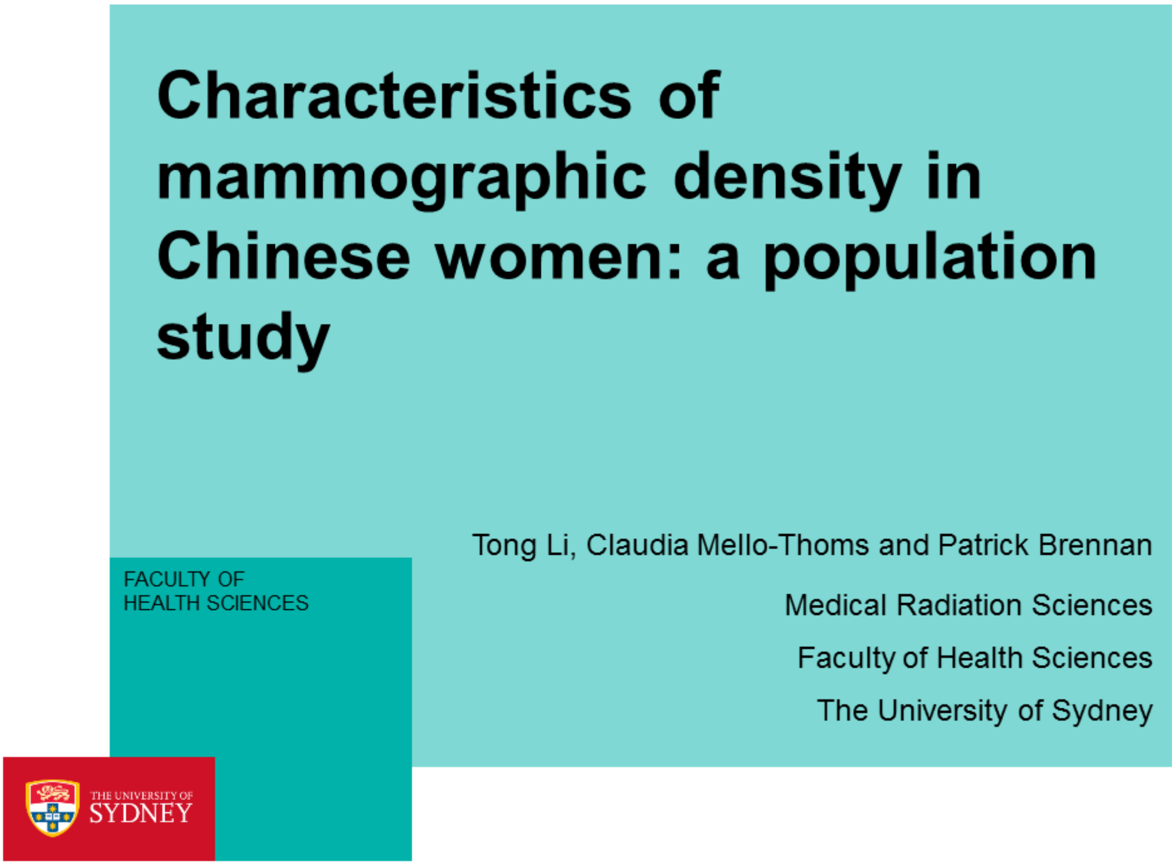


Appendix 3.7 The 1st China-Australia Symposium on Breast Cancer Research

Guangzhou, China

28th November 2015

This oral presentation was given in association with the paper described in Chapter Four.



Appendix 3.8 5th World Congress on Breast Cancer

London, U.K.

15th -17th June 2017

This oral presentation was given in association with the paper described in Chapter Five.

Appendix 3.9 34th Annual Miami Breast Cancer Conference

Miami Beach, U.S.

9th -12th March 2017

This poster presentation was given in association with the paper described in Chapter Five.

Determinants of mammographic density in Chinese women: using percentage and area measures from AutoDensity algorithm

THE UNIVERSITY OF SYDNEY

Li T[a], Tang L[b], Gandomkar Z[a], Heard R[a], Mello-Thoms C[a], Di G[b], Gu Y[b], Xiao Q[a], Shao Z[b], Nickson C[c], Brennan PC[a]
[a] Faculty of Health Sciences, The University of Sydney, Australia.
[b] Fudan University Shanghai Cancer Center, China.
[c] Melbourne School of Population and Global Health, University of Melbourne, Australia.

Introduction

Breast cancer is the most commonly diagnosed neoplasm amongst women in China and it is one of the leading causes of cancer death in females. Mammographic density (MD), describing the amount of fibrous and glandular tissue within the breasts, is consistently demonstrated to be an independent and important risk factor for breast cancer. Women with highest density were shown to have a 2-6 times higher risk of developing breast cancer compared to those with the lowest [1]. However, current knowledge around density data is largely based on women from westernised countries and the characteristics of MD for women in China are poorly understood. This study **aims to** identify factors associated with MD in Chinese women using a quantitative method.

Methods

❖ **Data collection**

A total of 1071 (987 without and 84 with breast cancer) women were recruited from Shanghai Cancer Centre, China. MD was measured by an automatic algorithm AutoDensity [2], which outlines the dense tissue within the breast (Fig. 1a). Both dense area (Fig. 1b) and breast area (Fig. 1c) are highlighted and the resultant MD was produced by dividing the dense area (number of pixels) by the breast area (number of pixels) and expressing this value as a percentage (%).

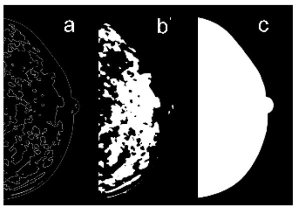


Fig. 1. AutoDensity algorithm Output **a:** the edge of the breast and edge of the dense tissue. **b:** mask of dense tissue within the breast. **c:** mask of area of the breast

❖ **Statistical analysis**

Pearson tests were performed to exam relationships between density and continuous variables and t-tests were conducted to compare differences of mean density values between groupings of categorical variables.

Multivariate models were built by using stepwise multiple regression adopting variables that were statistically significant from the Pearson and t-tests.

Results

❖ **Characteristics of participants**

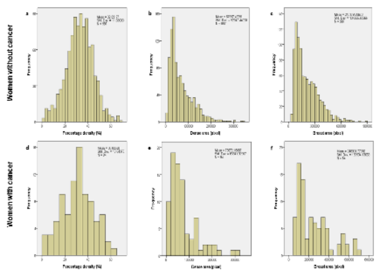


Fig. 2: Distribution of mammographic features. **a:** Percentage MD (%) of cancer-free women. **b:** Area of dense tissue (pixel) in mammograms of cancer-free women. **c:** Area of breast tissue (pixel) in mammograms of cancer-free women. **d:** Percentage MD (%) of cancer women. **e:** Area of dense tissue (pixel) in mammograms of cancer women. **f:** Area of breast tissue (pixel) in mammograms of cancer women.

❖ **Association between percentage density and dense area**

Percentage density (PD) and dense area (DA) were positively correlated for cancer-free women (r=0.487, p<0.001) and for women with cancer (r=0.446, p<0.001), respectively.

❖ **Determinants of mammographic density**

- For **cancer-free** women, weight and BMI were found to be negatively associated (r=-0.24, r=-0.27) with PD whereas positively associated (r=-0.50, r=-0.52) with DA; age at mammography was found to be associated with PD (r=-0.20) and DA (r=-0.09) but did not add any prediction within multivariate models; lower PD was found within women with secondary education background or below compared to women with tertiary education.
- For women with **cancer**, PD demonstrated similar relationships with that of cancer-free women whilst breast area was the only factor that was associated with DA (r=0.74).

❖ **Linear models**

The 4 most-effective models (I-IV) were built and the residuals of these models were all normally distributed;

- I: PD (cancer-free)=57.91-1.00*BMI-4.42*Menopause +2.19*Education. (R^2=12.13, F=45.21, p<0.001).
- II: DA (cancer-free)=49650.58-2251.99*BMI-7921.84*Menopause+5582.45*Education+0.32*Breast area. (R^2 = 64.92, F = 606.26, p < 0.001).
- III: PD (cancer)=97.16-1.80*BMI-0.43*Age. (R^2=38.82, F=25.70, p<0.001).
- IV: DA (cancer)=0.28*Breast area. (R^2=54.56, F=98.48, p<0.001).

The coding methods:
- Menopause: 0=Pre-menopausal, 1=Post-menopausal;
- Education: 0=Secondary and below, 1=Tertiary.

Conclusions

This is the first time that MD was measured by a quantitative method for Chinese women and important associations were identified for both percentage and area measures. The findings should be useful to health policy makers who are responsible for introducing effective models of breast cancer prevention and diagnosis.

[1] McCormack VA, Silva IDS. Breast density and parenchymal patterns as markers of breast cancer risk: A meta-analysis. Cancer Epidemiol Biomarkers Prev. 2006; 15(6):1159-1169.
[2] Nickson C, Arzhaeva Y, Aitken Z, et al. AutoDensity: An automated method to measure mammographic breast density that predicts breast cancer risk and screening outcomes. Breast Cancer Res. 2013; 15(5):R80-R80.

Appendix 3.10 15th St. Gallen International Breast Cancer Conference

Vienna, Austria

15th – 18th March 2017

This poster was presented in association with the paper described in Chapter Three.

Breast density and other factors for breast cancer risk for Chinese women

Tong Li[*], Lichen Tang[#], Ziba Gandomkar[*], Rob Heard[^], Claudia Mello-Thoms[*], Genhong Di[#], Yajia Gu[$], Qin Xiao[$], Zhimin Shao[#], Patrick Brennan[*]

[*] Department of Medical Radiation Sciences, Faculty of Health Sciences, The University of Sydney

[#] Department of Breast Surgery, Fudan University Shanghai Cancer Center

[^] Behaviour and Social Sciences, Faculty of Health Sciences, The University of Sydney

[$] Department of Radiation, Fudan University Shanghai Cancer Center

Aims: The risk factors of breast cancer are not fully understood for Chinese women and, particularly, the association between breast density and cancer risk remains under-studied. This study aims to examine risk factors for breast cancer for women in China, with a particular focus on the relationship between breast density and cancer by using a quantitative measurement of density.

Methods: 84 breast cancer and 987 cancer-free women were selected from the Fudan University Shanghai Cancer Centre (FUSCC). Mammograms were acquired with the cranio-caudal projection of both breasts and breast density was measured by an automatic algorithm AutoDensity.

Results: Statistically significant associations were found between breast cancer and large breast area (OR: 1.02, 95% CI: 1.00-1.03), increasing age (OR: 1.04, 95% CI: 1.02-1.06), increasing weight (OR: 1.06, 95% CI: 1.03-1.08), increasing BMI (OR: 1.20, 95% CI: 1.12-1.29), later age at menarche (OR: 1.26, 95% CI: 1.14-1.40), earlier age at first delivery (OR: 0.78, 95% CI: 0.72-0.85), longer duration of breastfeeding OR: (1.22, 95% CI: 1.16-1.29), post-menopause status (OR: 2.22, 95% CI: 1.42-3.49), greater number of children (OR: 7.95, 95% CI: 4.83-73.06) and a breastfeeding history (OR: 3.25, 95% CI: 1.45-7.14) for all women. No significant associations were found between breast cancer and mammographic density amongst all (p = 0.230), pre-menopausal (p = 0.238) and post-menopausal women (p = 0.119). Statistical models were built with success rates around 90% for each of the total, pre-menopausal and post-menopausal women.

Conclusion: This study identified risk factors of breast cancer for Chinese women, with breast density for the first time being measured by the quantitative method. The lack of association between breast cancer and density should have significant implications for both breast cancer screening strategies and clinical diagnostic processes in China.

Appendix 4

Ethical approval

Appendix 4.1 Ethical Approval from the Human Research Ethics Committee of the University of Sydney

Research Integrity
Human Research Ethics Committee

Tuesday, 4 November 2014

Prof Patrick Brennan
Medical Imaging and Radiation Sciences; Faculty of Health Sciences
Email: patrick.brennan@sydney.edu.au

Dear Patrick

I am pleased to inform you that the University of Sydney Human Research Ethics Committee (HREC) has approved your project entitled "**Comparison of breast density and cancer presentation between women in Australia and China.**".

Details of the approval are as follows:

Project No.: **2014/768**

Approval Date: **21 October 2014**

First Annual Report Due: **21 October 2015**

Authorised Personnel: **Brennan Patrick; Brennan Patrick; Li Tong; Mello-Thoms Claudia;**

HREC approval is valid for four (4) years from the approval date stated in this letter and is granted pending the following conditions being met:

Special Condition/s of Approval

- It is a condition of approval that correspondence confirming the waiving of consent by the local Ethics Committee is obtained and kept on file as part of your records prior to this research commencing.

Condition/s of Approval

- Continuing compliance with the National Statement on Ethical Conduct in Research Involving Humans.
- Provision of an annual report on this research to the Human Research Ethics Committee from the approval date and at the completion of the study. Failure to submit reports will result in withdrawal of ethics approval for the project.
- All serious and unexpected adverse events should be reported to the HREC within 72 hours.
- All unforeseen events that might affect continued ethical acceptability of the project should be reported to the HREC as soon as possible.
- Any changes to the project including changes to research personnel must be approved by the HREC before the research project can proceed.
- Note that for student research projects, a copy of this letter must be included in the candidate's thesis.

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Research Portfolio
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ABN 15 211 513 464
CRICOS 00026A

THE UNIVERSITY OF SYDNEY

Chief Investigator / Supervisor's responsibilities:

1. You must retain copies of all signed Consent Forms (if applicable) and provide these to the HREC on request.

2. It is your responsibility to provide a copy of this letter to any internal/external granting agencies if requested.

Please do not hesitate to contact Research Integrity (Human Ethics) should you require further information or clarification.

Yours sincerely

Dr Stephen Assinder
Chair
Human Research Ethics Committee

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Human Research (2007), NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007) and the CPMP/ICH Note for Guidance on Good Clinical Practice.

Research Integrity
Human Research Ethics Committee

Friday, 17 April 2015

Prof Patrick Brennan
Medical Imaging and Radiation Sciences; Faculty of Health Sciences
Email: patrick.brennan@sydney.edu.au

Dear Patrick

Your request to modify the above project submitted on 23rd March 2015 was considered by the Executive of the Human Research Ethics Committee at its meeting on **14th April 2015**

The Committee had no ethical objections to the modification/s and has approved the project to proceed.

Details of the approval are as follows:

Project No.: **2014/768**

Project Title: **Comparison of breast density and cancer presentation between women in Australia and China.**

Approved Documents:

Date Uploaded	**Type**	**Document Name**
23/03/2015	External Ethics Approval	Letter of Ethic Approval from FUSCC

Please do not hesitate to contact Research Integrity (Human Ethics) should you require further information or clarification.

Yours sincerely

Professor Simon Willcock
Chair
Human Research Executive Committee

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Human Research (2007), NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007) and the CPMP/ICH Note for Guidance on Good Clinical Practice.

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CRICOS 00026A

Appendix 4.2 Ethical Approval from the Ethics Committee of Cancer Institute and Hospital, Chinese Academy of Medical Sciences

中国医学科学院肿瘤医院伦理委员会**审批报告**

Approval Letter of Ethics Committee of Cancer Institute and Hospital, Chinese Academy of Medical Sciences

审批号 **15-062/989**　　　　审批日期 2015 年 05 月 21 日
Approval No.　　　　Issued Date

研究题目及编号：　中西方女性乳腺腺体密度和乳腺癌 X 线影像特征的对比研究
Study title：　（方案编号：CH-BC-037）
试验方案版本号及日期：　版本号：1.0，版本日期：2015 年 03 月 16 日
Protocol No.& version date
知情同意书版本号及日期：　知情同意书豁免申请
Informed Consent Form version and date：
研究药物名称(中/英文)：　非药物研究/不适用（NA）
临床试验批文单位及批文号：　研究者发起/不适用（NA）
Clinical trial approval No. and issued by
临床研究类别和期别：　研究者发起/非分期
Trial class & phase
研究单位及主要负责人：　中国医学科学院肿瘤医院影像诊断科：李静
Study site and principal investigator　Cancer Hospital, CAMS
申办单位名称 Sponsor name:　中国医学科学院肿瘤医院

审批意见 Evaluation comments:

伦理委员会于 2015 年 05 月 21 日对上述试验方案、知情同意书豁免申请及有关内容（详见附件）进行了认真的讨论并进行了投票表决，投票人数 7 人，同意：6 票，修改后同意：1 票，修改后重审：0 票，反对：0 票。伦理委员会认为上述资料基本符合 GCP 原则，可以开始临床研究。

此批文有效期自签字之日起 1 年，到期后请按规定年审

伦理委员会副主任委员签名 徐震纲　　日期 2015. 6. 10
Signature of Vice Chairman of the Ethics Committee　　Date

抄送： 1.临床研究人员签收 李静　　日期 2015. 6. 19
Signature of investigator　　Date

会议地址：北京朝阳区潘家园南里 17 号，医科院肿瘤医院内科会议室， 邮编：100021　　电话：8610－87788495

第 1 页 共 2 页

附件：伦理委员会审批的文件目录

1. 中国医学科学院肿瘤医院临床研究申请表(01 号表)
2. 中国医学科学院肿瘤医院临床研究伦理审批申请表（02 号表）
3. 中国医学科学院肿瘤医院临床研究小组成员名单（03 号表）
4. 医科院肿瘤医院 GCP 中心临床研究人员简历（04 号表）
5. 试验方案（版本号：1.0，版本日期：2015 年 03 月 16 日）

以下无正文

Appendix 4.3 Ethical Approval from the Institutional Review Board of Fudan University Shanghai Cancer Centre

Fudan University Shanghai Cancer Center Institutional Review Board

Approval Letter

Project No.: 1503144-11

Assessment Date	2015.3.2
Assessment Venue	Seminar Room 5, Level 5, Building 2
Project	Comparison of breast density and cancer presentation between women in Australia and China
Supplementary Documents	**Please tick the box/es for selecting submitted documents with √ or the unsubmitted documents with ×. The unavailable reference is labelled with _** ☒The approval letter from The China Food and Drug Administration, certificate No.: _ ☑Proposal, version No.: 1.0 (2015.1.1) ☒Project, reference No:. _ ☒ Pharmaceutical product license and assessment report /Registration certificate for medical device ☑Consent form, reference No.: application of waivier of consent ☑The CV of authorised personnel ☑Others: version 1.0 of Health Report (2014.12.1)
Department of Investigation	Department of Breast Cancer/Radiology
Chef investigator	Prof. Zhimin Shao
Applicant/s	Prof. Zhimin Shao
Assessment mode/s	☑Board □ Expedited
Attendance	Total: 17 Attendance: 15 Abstention: None
Outcome	Fudan University Shanghai Cancer Center Institutional Review Board (SCCIRB) has assessed the project entitled "Comparison of breast density and cancer presentation between women in Australia and China" and supplementary documents applied by Prof. Zhimin Shao, on 2/3/2015. This committed is attended by 15 members with 2 apologies. Outcome: Fudan University Shanghai Cancer Center Institutional Review Board (SCCIRB) approved the project entitled "Comparison of breast density and cancer presentation between women in Australia and China" and approved the application of wavier of consent for this project. This approval is valid since the date of being signed. Signature (EC Chair): Stamper: Fudan University Shanghai Cancer Center Institutional Review Board (SCCIRB) Approval date: 2nd March 2015

Condition/s of Approval:

1. This project will be reviewed in 12 mouths from the approval date for the annual review conducted by express mode. First annual review due is by 2nd March 2016.
2. This letter of approval will be kept on file in either local or candidate's Ethics Committees.
3. The approved project must follow the approved proposal and continue compliance with all the principles of SFDA/GCP and Declaration of Helsinki.
4. Any changes or suspension to the project must be reported to the HREC as soon as possible.
5. All serious and unexpected adverse event against to the project must be reported to the HREC immediately
6. Any changes to the project including changes to consent form and research personnel must be approved by the HREC before the research project can proceed.
7. Any incidence against the approved project must be reported to the HREC immediately.
8. The annual report must be submitted one month before the due day of annual review regardless of the actual commencement date.
9. The final report must be submitted to the HREC at the completion of the study.
10. All the supplementary documents approved by HREC are included in this Letter.

Appendix 5

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