

First steps in optimizing breast screening in Mongolia:

Understanding radiologists' performance in reading
mammograms and mammographic breast density

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Candidate's statement

I, Delgermaa Demchig, hereby certify that this thesis is the result of my full time study and my original work, which has not been published or accepted for an award of any other degree previously. 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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Dedication

This thesis is dedicated to the memory of my father Mr Demchig Duger (02.04.1946 – 18.06.1996). He was inspiration to pursue my doctoral degree and my life coach with his excellent knowledge and great attitude. His advice and comments would have added great source of perfections to my work.

He died due to delayed arrival of emergency service in Mongolia and this was the reason I choose medical profession. At present time, delay in diagnosis and health care service has still been occurred in Mongolia especially for cancer cases. I hope this thesis can help further in small ways to improve the diagnosis and better outcomes for all sufferers of breast cancer in Mongolia.

Publications and Presentations

Parts of the work presented in this thesis have been published and presented in the following forums:

Publications

[1] Demchig, D., C. Mello-Thoms, and P.C. Brennan, "Breast cancer in Mongolia: an increasingly important health policy issue." *Breast Cancer Targets and Therapy*, 2017. 9: p. 29-38.

[2] Demchig D, Mello-Thoms C, Khurelsukh Kh, Ramish A, and Brennan C "Mammographic Appearances in Mongolia: Casual Factors for Varying Densities." *Asian Pacific Journal of Cancer Prevention*, 2017 18(9): p. 2425-2430

[3] Demchig D, Mello-Thoms C, Lee W, Khurelsukh Kh, Ramish A, and P.C Brennan, "Observer Variability in Breast Cancer Diagnosis between Countries with and without Breast Screening." *Academic Radiology*, 2018, in press.

[4] Demchig D, Mello-Thoms C, Lee WB, Khurelsukh Kh, Ramish A, and Brennan P.C, "Mammographic detection of breast cancer in a non-screening country." *Br J Radiol* 2018; **91**: 20180071.

Conference presentations

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[2] Demchig D, Mello-Thoms C, Khurelsukh Kh, Ramish A, and Brennan C, "Mammographic density in Mongolia. 6th Asia Pacific Breast Cancer Summit," February 2017, Hong Kong.

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Preface

This thesis contains six chapters and each chapter was written to be read independently. The University of Sydney allows published papers that arose from the candidature to be included in the thesis.

- **Chapter one** is an introduction to the thesis and provides an overview of the aim and objectives addressed by this thesis.
- **Chapter two** is the literature review, which identified the key features of breast cancer in Mongolia. This paper is presented as published in the Breast Cancer Target and Therapy.
- **Chapter three** is the first study in observer performance, investigating the level of diagnostic accuracy of Mongolian radiologists, using difficult mammographic images. This chapter is presented as published in the British Journal of Radiology.
- **Chapter four** is the second study in observer performance exploring the mammographic performance of Mongolian radiologists using typical screening images. This chapter is presented as published in Academic Radiology.
- **Chapter five** investigated the distribution of mammographic breast density for women in Mongolia. This chapter is presented as published in Asian Pacific Journal of Cancer Prevention.

- **Chapter six** is the discussion, which describes the overview of the thesis, implications, limitations and future works and conclusions.

Each chapter includes its own reference list. Ethical and relevant institutional approvals were obtained for this work prior to the data collection from Mongolia. To ensure that the readers understand the thesis as a whole, a bridging section is inserted in the beginning of each chapter apart from chapter one. The appendices at the end of this thesis include the materials used in this study. For the observer studies, informed consent was obtained from each participating radiologist from Mongolia. The need for informed consent with respect to use of patient materials was waived. In Mongolia, patients do not fill consent form when they undergo medical procedures and it is understood that patient related information can be used for research purposes.

Abstract

Advanced diagnoses of breast cancer have become a serious public health issue in Mongolia. Whilst mammography has been proven to be an effective screening approach for breast cancer and well established amongst developed countries, such program has not been introduced in Mongolia. In addition in Mongolia, a lack of research around breast cancer continues to exist. The purpose of this thesis is to understand mammographic diagnostic accuracy and mammographic breast density (MD) in Mongolia, both of which are important considerations, which will inform a future national screening program. To address this aim, three studies were conducted; the first two were radiologists' performance studies in reading mammograms with different levels of difficulty. The mammographic detection of Mongolian radiologists (case sensitivity of 63% and lesion sensitivity of 34%) was substantially lower compared with that of Australian radiologists. The third study investigated the MD features of 1985 Mongolian women using the Breast Imaging Reporting and Data system (BI-RADS) density categories. The majority of women (58%) were found to have low-density categories (category A and B) and significant associations were observed between MD; age (OR = 6.8, 95% CI: 5.5, 8.0), weight (OR = 4.5, 95% CI: 3.4, 6.0) and BMI (OR=13.2, 95% CI: 8.6, 20.0). Findings from this research have demonstrated that mammographic diagnostic accuracy is sub-optimal in Mongolia. Moreover, images with different levels of difficulty did not alter the reading performance of Mongolian radiologists suggesting the need for improving breast cancer detection skills urgently. The output of this work also demonstrated that low density was predominant in Mongolia. The results will impact on health policy around screening in Mongolia. They will inform educational strategies that are

needed to transform diagnostic efficacy and will provide a good basis for decision making around screening modality choices.

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Chapter 1

Introduction

1.1 Background

1.1.1 Breast cancer in the world

Currently in the world, breast carcinoma is the most common cancer, constituting 25% of all female cancers with an estimated 1.7 million new cases in 2012 [1]. Based upon economic capacity, countries seem to have differences regarding the incidence and characteristics of the disease. Overall, higher incidence rates continue to exist among developed countries such as North America and Australia/New Zealand while low incidence is observed in most of developing countries such as most of Africa and Asia [1, 2]. Disparities can be illustrated with age and stage at onset and pathological subtypes of breast cancer. The median age of breast cancer diagnosis for Asian women is reported to be 10 years younger than their Western counterparts, with a high proportion of diagnosis occurring under the age of 40. [3-5]. Furthermore, variations exist on the stage of breast cancer diagnosis between countries. For example, more than 50% of breast cancers in developed countries are detected at stage I, whilst this figure is closer to 20% among developing nations [3]. These variations in breast cancer between countries are mostly attributed to variations in risk factors, availability of early detection programs and access to treatment options.

In addition, the disease appears to have favourable features among developed countries such as reduced mortality, stabilized incidence and high survival rates as a result of mammographic screening [6, 7] along with advancement in cancer treatment [8]. In contrast, the disease burden remains large among developing

countries due to high mortality, despite these nations having low incidence rates. It is well known that breast cancer is a disease of women in wealthy countries because a small occurrence of the disease has often been reported in developing countries due to the lack of screening. However, recent increases in incidence along with high mortality rates within a number of these developing nations require careful consideration from policy makers. Although the reasons are not fully understood, available explanations indicate that a transition to the westernised food, lifestyle and reproductive behaviour from a more traditional style plays an important role [1]. Understanding of these international variations is essential for cancer control strategies.

1.1.2 Breast cancer in Mongolia

Mongolia is a developing country in the north-central Asia with a population of just over three million people in 2017 [9]. In terms of ethnicity, the country has a quite homogenous population with about 90% and 10% of people belonging to Halh and non-Halh origins respectively [10]. Unlike most other countries, breast cancer is uncommon for women in Mongolia. In 2012, GLOBOCAN reported breast cancer to be the fifth most common cancer among Mongolian women with the age standardised rate (ASR) of 9.4/100,000 after liver, cervix uteri, stomach and oesophageal cancers [2]. However, similar to other Asian countries [3, 11] incidence rates are increasing on an annual basis. It also estimated breast cancer to be the sixth leading cause of cancer related death (3.7/100,000) for women in Mongolia. Within the country, geographical variations in incidence and mortality occur with the higher rates in urban areas where approximately 70% of population lives, [9] whilst

lower rates were recorded in rural areas with some regions having no data [12]. But, it should be acknowledged that quality of cancer registry in rural area remains unclear and therefore data quality is probably not high.

The characteristics of breast cancer among Mongolian women also appear to be distinct. Similar to other Asian women, [11, 13] the disease presents at a younger median age (45-55 years old) than westernised women [14]. The low incidence of breast cancer in Mongolia has been linked to a high consumption of meat and dairy products, high rates of breastfeeding, low consumption of alcohol and a few people using cigarettes [15, 16]. Traditionally, Mongolian women tend to have higher number of kids than women in elsewhere, which may also contribute to the low risk for breast cancer: fertility rates (births per women) were reported to be 7.0 in 1975, but since then this figure has gradually declined and reached the current rate of 2.9 in 2015 [17].

1.1.3 Breast cancer challenges in Mongolia

Mongolia has seen a consistent increase in breast cancer incidence particularly in the last decade. For example, the reported number of cases for breast cancer has increased from 84 in 2009 to 173 in 2013. In terms of age standardised incidence rate (ASR), this figure have accounted for 3.0/100,000 in 2009 however in 2013, it was reported 6.0/100,000 [18]. Delivering health service in a timely manner remains difficult in Mongolia due to the sparse distribution of the population with an average 1.9 people per square km [19]. This could be linked to the advanced presentation of breast cancer in the country. In Mongolia, delayed breast cancer diagnoses is

common with more than 90% of patients at an advanced stage [20, 21]. Although breast cancer incidence remains low, it has been increasing, highlighting the need to optimise diagnostic strategy. Whilst medical research is an essential part of any successful medical practice, in Mongolia there are very limited scientific publications around breast cancer. Although some data are available as described above, overall we are still unclear about type of women being affected, characteristics of breast cancer and underlying causes for advanced stage cancers in the country.

When compared with other conditions, little focus has been directed towards breast cancer in Mongolia due to its traditional low prevalence resulting in slow progress towards effective preventative management. For example, primary diagnosis for liver cancer is widely available at all types of hospitals nationwide due to good availability of ultrasound technology and trained staff. In contrast, breast cancer diagnosis is only available in the capital city, Ulaanbaatar, where mammography and breast ultrasound are available at three medical centres including the national cancer centre (NCC). Nonetheless, a gradual but consistent increase in incidence along with more frequent diagnoses of later stage cancers in Mongolia have encouraged a greater awareness of the need for improved diagnosis, and treatment for breast cancer. Since primary prevention for breast cancer is not possible, an effective breast screening strategy will be the optimum approach for breast cancer management in Mongolia.

1.2 Breast cancer diagnosis

Breast cancer is mostly detected with either *screening* or *diagnostic* examinations for women without and with symptoms. In both scenarios, mammography plays a key role in decision-making and is currently the front line tool for evaluating breast parenchyma. Whilst screening mammography ultimately aims to save lives throughout early detection of cancers, diagnostic mammography is designed to solve clinically presented findings, which are managed by radiologists. These two approaches also have very different characteristics and pathways such as cancer prevalence, later stage diagnoses are higher among diagnostic populations than the screening group, and therefore different procedures are required for interpretation. To date, strategies to diagnose breast cancer differs between countries, with developed countries relying heavily on screening program, whilst diagnostic examination remains dominant among developing nations. Perhaps this could be one of the main reasons why later stage cancers are not uncommon among developing countries; however, more scientific evidence is needed to understand potential causal factors of advanced disease presentation among developing countries.

1.2.1 Breast cancer screening in developed countries

Mammography is the frequently recommended screening approach worldwide and well established in developed countries. It is now strongly evident that mammographic screening (MS) has the advantage of an approximate 30% decrease in breast cancer death [6, 7, 22]. The supporting evidence of MS by a recent study revealed that the majority of breast cancer deaths (70%) occurred amongst unscreened women [23]. However, there has been much debate around the benefits

and risks of MS. For example, women with dense breasts have been central to the debate due to reported impact of density on sensitivity. Nonetheless, age to start screening varies between countries, being 50 years old in Australia [14] and Europe [24], whereas it ranges between 40 to 50 in the USA due to different recommendations by different institutions [24, 25]. With the debate around density, MS drawbacks further include overdiagnosis, false-positive (FP) results and variations in interpretation among radiologists. DCIS (ductal carcinoma in situ) diagnosed during screening round may be considered as an overdiagnosis, because of its probability of never becoming an invasive cancer [26] however differences between harmful and harmless DCISs remain unknown [27].

Mammography, whilst being the current front-line tool for breast cancer screening presents superimposed appearances of breast tissue, which limits diagnostic accuracy especially in dense background. To overcome overlying breast tissue, digital breast tomosynthesis (DBT) has recently been introduced in conjunction with conventional mammography. DBT provides more detailed structure of breast tissue especially better visualization of lesion margins and shapes than conventional mammography, which allows more confidence to reporting radiologists. When DBT is used for screening along with mammography, up to 50% increase and 15% decrease in cancer detection and recall rates (FPs) respectively were demonstrated [28-31]. Such promising results were reported for women regardless of their age and density status and therefore DBT may be the future of screening strategy. However, radiation dose is doubled when DBT is used along with mammography and therefore the reconstructed synthesised image (C-view) has gained approval in clinical use to replace conventional mammograms [32]. Preliminary work with C-views (with DBT)

show the same FPs and cancer detection as using DBT along with mammography and therefore it may be a possible alternative to mammography.

It is also important to note that unlike mammography, no alternative screening modality is proven to reduce mortality despite the fact that breast ultrasound (US) and magnetic resonance imaging (MRI) have greater sensitivity in detecting and characterising breast lesions especially for dense breasts [33-35]. Currently, these modalities are utilised as supplementary screening tools in addition to mammography for women with high breast density and elevated risk for breast cancer. Breast US and MRI result in increased cancer detection rates [34] but concomitant increases in FPs have been reported [35, 36]. In addition, inherent limitations of these modalities such as operator dependency and longer interpretation time for US and technical and cost issues for MRI restrict them for mass screening. Therefore, their screening usages remain debatable and they are used routinely in clinical practice for investigating extent of disease and additional evaluation of breast abnormalities [37, 38]. Several other emerging techniques have been developed, which includes contrast-enhanced mammography (CEM), positron emission mammography (PEM), CT dedicated for breast and CT laser mammography. For example, CEM and PEM are used to overcome some of the limitations of MRI techniques, however none of these approaches have gained widespread use in clinical practices and particularly in screening purposes. Currently, these techniques are under development with the hope of increasing cancer detection rates. Mammography is therefore more likely to remain the primary screening method in near future even though it is imperfect test [39].

1.2.2 Breast cancer screening in developing countries

While the introduction of MS has transformed breast cancer detection in developed countries, its introduction in developing countries continues to be delayed. As outlined by the World Health Organisation (WHO), [40] high cancer prevalence is the most important prerequisite for implementing an effective screening strategy, which guides low incidence countries to avoid adopting MS nationwide. MS is therefore not universally introduced and locally established programs for early detection remain in most of the developing countries. Clinical breast examination (CBE) is the first recommendation for breast screening however this approach is only useful when used along with mammography [41, 42]. In terms of cost effectiveness, CBE is also often considered where mammographic resources are limited [43]. In addition to CBE, breast self-exam (BSE) is another alternative for screening and continues to be used amongst low-income countries. However, to date, insufficient clinical benefit has been shown for BSE and CBE in screening settings following large randomised control trials conducted in China [44], Japan [45] and India [46]. Nonetheless, although no mortality benefits were reported to be associated with SBE and CBE, their positive impact on detecting early breast cancer should not be disregarded and therefore can be considered in resource-limited settings.

1.3 Difficulties in breast cancer detection

If breast cancer is detected in its early stage of development, survival is much better than when detected at later stages [47]. It is therefore important to detect preclinical breast cancer, however, it remains very difficult due to its complex and multifactorial

nature. Such challenges often appear to be associated with limitations of mammography since it is the main imaging modality. In fact, its sensitivity is linked to numerous factors such as the characteristics of patient and malignant lesion and as well as the ability of the interpreting radiologists. Any of these factors can be at least in part responsible for missed cancers and thereby it may not be surprising that up to 30% of cancers are reported to be missing during screening mammography [48, 49]. Among all contributing factors, radiologists' interpretive performance and mammographic breast composition arguably play the most critical roles in diagnostic accuracy and will be examined in the following two sub-sections. It should be noted that other factors including image quality regarding used techniques (positioning and exposure parameters) remain on important considerations when diagnostic accuracy discussed.

1.3.1 Interpretive performance of radiologists

Mammographic interpretation is not a straightforward task for radiologists. Therefore, diagnostic accuracy varies greatly between radiologists and substantially contributes to overall mammographic error. Malignant features can be missed due to ability of radiologists to properly interpret the image. Influential factors for such mistakes can be summarised into four main groupings. First, technical aspects including poor positioning, inadequate compression and exposure parameters can have the potential to alter reader performance [50-52]. If these are not optimised and, visualisation of all the relevant breast tissue may not be apparent, resulting in limited or no lesion visibility. Second, morphological features of the malignancy (lesion type and size) may reduce reader performance; particularly, it is well known that

architectural distortion and stellate lesions are amongst the most difficult lesion appearances for radiologists [53-55]. Third, reader performance may also be reduced with characteristics related to the reader itself: eye performance and its capability of detecting low contrast details, annual interpretive volume, experience in reading mammograms and training in breast imaging [56-58]. However, it should be noted that the literature has demonstrated inconsistent findings specifically for interpretive volume and number of mammograms read per year [59-61]. Finally, some part of variability can be explained with patient related factors such as body habitus and breast composition.

To reduce mammographic mistakes, understanding the nature and cause of the error should be important. In radiology, errors are classified into three types. First, when radiologist fails to continue to search for subsequent abnormalities (real lesions in question) after identifying an initial abnormality such as benign features. This type of error is called *satisfaction of search* (SOS) and it occurs frequently (42%) in mammography [62, 63]. In addition, according to visual search studies [64, 65], regardless of the cancerous nature of a lesion, initial detection of this abnormality may suppress the subsequent discovery of another abnormality thereby causing SOS effect. Second, *perceptual errors* account for approximately 32% of mistakes and occur when the abnormality is not seen in the initial interpretation but can be recognised retrospectively [66-68]. Several factors can cause such errors, including reader fatigue and inattention, distractors (cell phone, emails) and poor visibility of lesions [62, 69, 70]. Third, *cognitive errors* (decision-making) occur when radiologists detect the abnormality but do not understand its importance and thereby misdiagnose [69]. Factors associated with decision-making errors have been

reported: lack of knowledge of mammographic findings, misleading clinical information, absence of prior images and reading room environment [68, 71].

Varying strategies have been proposed to minimise mammographic errors. Despite being costly, some countries such as Australia, Singapore and European countries such as England and Denmark have implemented a double reading strategy, however its benefits are found to be contradictory. Considering possible variabilities in perceptual and cognitive abilities between interpreting radiologists, double reading initiatives aim to increase cancer detection however some authors have showed supporting findings [72, 73] whilst others did not [74, 75]. Computer aided systems (CAD) are another potential step to overcome reader limitations around detection and diagnostic tasks (that is differentiation between malignant or benign) for radiologists [76]. Nonetheless, findings from studies that looked at CAD systems are not always supportive of their usage in clinical practice due to their high FP rates [77-80]. In addition, to eliminate the potential impacts of external factors including technical quality, display tools and room environment on reader performance, it is important to optimise these parameters to assist radiologists' reporting [63].

Educational interventions are often found to be an effective strategy to improve reader performance [81-83]. The advantages of training were also confirmed by a recent randomised controlled trial, which demonstrated improved interpretive performances for radiologists who used DVD teaching cases [82]. Several training platforms have been implemented successfully, which provide self-auditing and subsequent feedback, such as: Breast Screen Reader Assessment Strategy (BREAST) in Australia and New-Zealand (NZ) and PERsonal perFORmance in

Mammographic Screening (PERFORMS) in the UK [82-84]. The importance of self-audit and subsequent feedback is to provide individual readers the opportunity to identify corrective needs in timely manner. For example, BREAST has involved 80% of breast screening radiologists in Australia and NZ since its introduction in 2011 and demonstrated that all accuracy measures have been improved such as lesion sensitivity by 28% between 2011 and 2013 [82]. BREAST is now accessible worldwide with radiologists already participating from countries such as Singapore, Vietnam, Italy, Jordan and Iran [85].

1.3.2 Mammographic breast density

Mammographic breast density (MD) is a very important feature that affects how easily cancers are detected. MD refers to the dominant appearance of glandular tissues (epithelial cells of ductal and lobular system) along with fibrous stromal particles (connective tissue, collagen and vessels) as opposed to the fatty component of breasts. It is well established that increased MD reduces the visibility of abnormal lesions and thereby reduces the sensitivity of mammography, known as the “masking effect” [86-88]. However, how much of dense tissue will obscure lesions is a matter of discussion and therefore accurate estimation of dense tissue is critical. On the other hand, high MD has been linked to an increased risk for development of breast cancer with odds ratio as high as 6.0 being reported [89-91]. It is also known that breast tissue is normally dense at younger ages and reduces as women ages. However, there is a possibility of older women being presented with high MD, as breast density relies greatly on genetics, hormone and parity status, lactation history and hormone replacement therapy [92, 93]. Considering the facts, it

may be argued that it is important to identify women who would not benefit from MS, so that alternative screening approaches can be recommended.

In the clinical practice, radiologists evaluate and describe breast density visually according to the Breast Imaging Reporting and Data System (BI-RADS, 5th edition), produced by American College of Radiology (ACR) and classify breasts into one of four categories: A- almost entirely fatty, B- scattered fibroglandular densities, C- heterogeneous density, which may obscure detection of small masses and D- extremely dense breast which lowers mammographic sensitivity. Among radiologists, BI-RADS is popular method of assessing breast density and it has been used for long period. In the latest edition (2013), emphasis is given to how likely abnormal features would be obscured by dense tissue based on the confidence of interpreting radiologists [94]. Despite being used widely among radiologists, BI-RADS assessment use remains controversial due to high variability between readers [95]. However, little is known about radiologists' behaviour when facing different parenchymal pattern [88]. The importance of understanding parenchymal patterns was first recognised by John Wolfe in 1976 [96] and later by Lazlo Tabar in 1997 [97]. However, density values failed to gain clinical significance due to the subjective nature of assessment. Consequently, quantitative and more sophisticated approaches have been proposed but their usage in clinical practice remains limited. Even though such quantifiable methods have potential to overcome reader limitations, its introduction to everyday clinical practice requires at least consistency across different vendors and feasibility to be integrated into clinical systems [98].

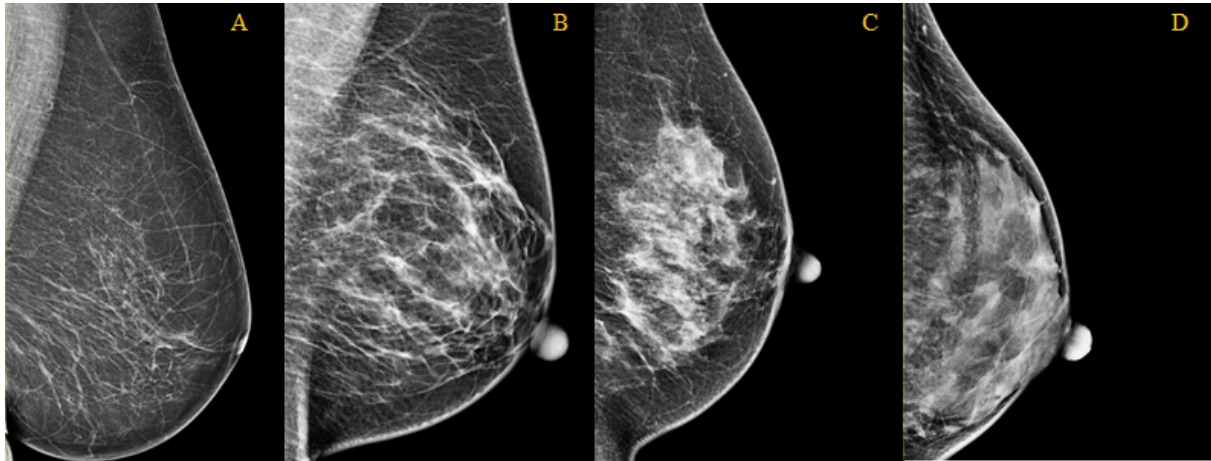


Figure 1. Mammograms of normal breast density, BI-RADS 2013 lexicon [95]. A-almost entirely fatty, B-scattered fibroglandular densities, C-heterogeneously dense, which may obscure detection of small masses, D-extremely dense which lowers mammographic sensitivity.

1.4 Deficiencies in the literature

To date, the literature around breast cancer presentations is very limited in Mongolia. In total, there appears to be five works which have investigated some aspects of breast cancer in the country. Troisi et al published two studies focusing on the low incidence of breast cancer in Mongolia and its possible explanations. In 2012, Troisi et al first showed the relatively low incidence of breast cancer in Mongolia and hypothesised that this may be possibly linked to the unique diet (high consumption of meat and dairy products) [14], although it seems to be contrary to the existing evidence of possible association between high intake of animal fat and breast cancer risk [99, 100]. Therefore other dietary factors such as high consumption of tea, vitamin D and folate level along with the high consumption of fat may contribute to the low incidence of breast cancer for Mongolian women that need to be explored [14]. They also indicated that with only access to one mammographic unit at the

NCC, a large proportion of breast cancers may not be diagnosed and this may possibly contribute to the low incidence numbers in Mongolia. Also due to the origin of cancer site being difficult to identify when advanced stage cancers with multiple distant metastasis present, a significant number of such cancers may not have been recognised as being primary breast cancer. However, number of cancers with unknown origin was unclear in this study [14] and thus it is difficult to link low incidence of breast cancer to missed diagnoses. The last suggestion from this study was the possibility of unregistered cancer cases and this is especially true for rural areas where breast cancer may fail to be registered.

In 2014, Troisi et al further hypothesised that the hormonal status of Mongolian women may play a role in relatively low incidence and demonstrated that these women had substantially higher level of circulating oestradiol and progesterone and lower in testosterone than British women [15]. It is interesting to note that high oestradiol and progesterone levels are often linked to high risks of breast cancer among Western women [101], but not for Mongolian women and thereby, the authors suggested that unusual combination of lower level of testosterone along with high progesterone may provide protective effect women in low incidence settings [15].

The third study [20] was a national study investigating survival status of breast cancer in Mongolia involving more than 1000 breast carcinoma cases between 2003 and 2012. According to these findings, only 25% of patients in Mongolia were diagnosed during the early stages of breast cancer, which highlighted the urgent need for early detection programs in Mongolia. The last two studies were also

nationally-based and the unpublished outputs from PhD theses. The first by Dr Enkhtur (2009), focused on genetic and hormonal factors and demonstrated some interesting findings such as early menarche and nulliparity as possible risk factors for breast cancer. The second (2009) by Dr Ramish investigated mammographic features of breast cancer for Mongolian women. He looked at breast composition using Wolfe's grades of parenchymal pattern, involving 150 healthy women and concluded that majority of women had low (P1) and high (P2) density breast, which accounted for 40% and 27% of women retrospectively. Highest density (DY) pattern accounted for 12% and lowest density (N1) for 21%. However, this study has several limitations including a small sample size. More importantly, reliability of the density assessment seems questionable since number of readers and agreement between readers were unknown throughout the study.

Despite the above findings, the status of breast cancer continues to be less understood in Mongolia compared with many other countries. Nonetheless, all these studies demonstrated that incidence of breast cancer is on the rise. More importantly, it is now very clear that advanced breast cancers are not uncommon in the country. In Mongolia, lack of breast screening program plays a role in late diagnosis of breast carcinomas, however it is possible that other important causal factors such as breast cancer awareness and mammographic accuracy remain unknown. In particular, mammographic diagnostic accuracy has never been investigated and MD characteristics are less clear in the country, which are key determinants of mammographic sensitivity. Also there is lack of data on radiologists' level of diagnostic accuracy and without this information, it is unlikely that an effective screening approach will be introduced in the near future in Mongolia. In

view of these knowledge deficiencies, the current thesis was focused to specifically identify the radiologists' accuracy in reading mammograms and examine distribution of MD for women in Mongolia. By examining these issues, important data will be available to health care professionals, researchers and policy makers to initiate rapid discussion around implementation of the most effective Mongolian-relevant strategies to minimise the impact of the breast cancer.

1.5 Aims and objectives

The aim of this thesis is to provide information that would help in establishing a national screening program in Mongolia by exploring the interpretive accuracy of radiologists in reading mammograms and characterising MD in Mongolia. The objectives are:

- 1) To publish a literature review in an international peer-reviewed journal to identify the overall status of breast cancer in Mongolia in terms of incidence, mortality, survival features along with information of risk factors and breast cancer screening;
- 2) To investigate radiologists' accuracy in reading screening mammograms using two different test-sets with deliberately different levels of difficulty;
- 3) To examine the distribution of MD for Mongolian women and its relationship with age, body mass index and area of residency using the density categories of BI-RADS 5th edition.

1.6 Thesis structure

The thesis includes six chapters and each chapter was written to be read independently. Published papers of candidature are allowed to be included in the thesis by the University of Sydney. The work is arranged in the following manner:

Chapter 1 (the present chapter) provides an overview of the thesis framework and its purposes;

Chapter 2 demonstrates a detailed literature review on descriptive epidemiology of breast cancer for Mongolian women, which includes incidence, mortality and survival features along with information for risk factors and breast cancer screening. These data were presented in comparison with women in Asian and Western countries. This chapter was published in *Breast Cancer Target and Therapy* (a peer reviewed journal) as: Demchig, D., C. Mello-Thoms, and P.C. Brennan, "Breast cancer in Mongolia: an increasingly important health policy issue." *Breast Cancer : Targets and Therapy*, 2017. **9**: p. 29-38.

Chapter 3 examined the radiologists' performance using a *high difficulty* (HD) test-set with 60 mammograms. This chapter is provisionally accepted in the *British Journal of Radiology* (a peer-reviewed journal); Demchig D, Mello-Thoms C, Lee W, Khurelsukh Kh, Ramish A, and P.C Brennan, "Mammographic detection of breast cancer in a non-screening country."

Chapter 4 identified the radiologists' performance using a typical screening (TS) test-set with 60 mammograms and compared the findings with the previous results acquired from the HD test-set. This chapter was published in *Academic Radiology* (a peer-reviewed journal) as Demchig D, Mello-Thoms C, Lee W, Khurelsukh Kh, Ramish A, and P.C Brennan, "Observer Variability in Breast Cancer Diagnosis between Countries with and without Breast Screening." *Acad Radiol*, 2018.

Chapter 5 identified the distribution of MD for women in Mongolia. This chapter was published in the *Asia Pacific Journal of Cancer Prevention* (a peer-reviewed journal) as Demchig D, Mello-Thoms C, Khurelsukh Kh, Ramish A, and P.C Brennan, "Mammographic Appearances in Mongolia: Causal Factors for Varying Densities." *Asian Pacific Journal of Cancer Prevention*, 2017. 18(9): p. 2425-2430.

Chapter 6 provided a discussion on the significant findings, future directions of the research work and conclusion.

A bridging section is inserted at the beginning of each chapter.

Appendices attached in this thesis provide materials used in the studies.

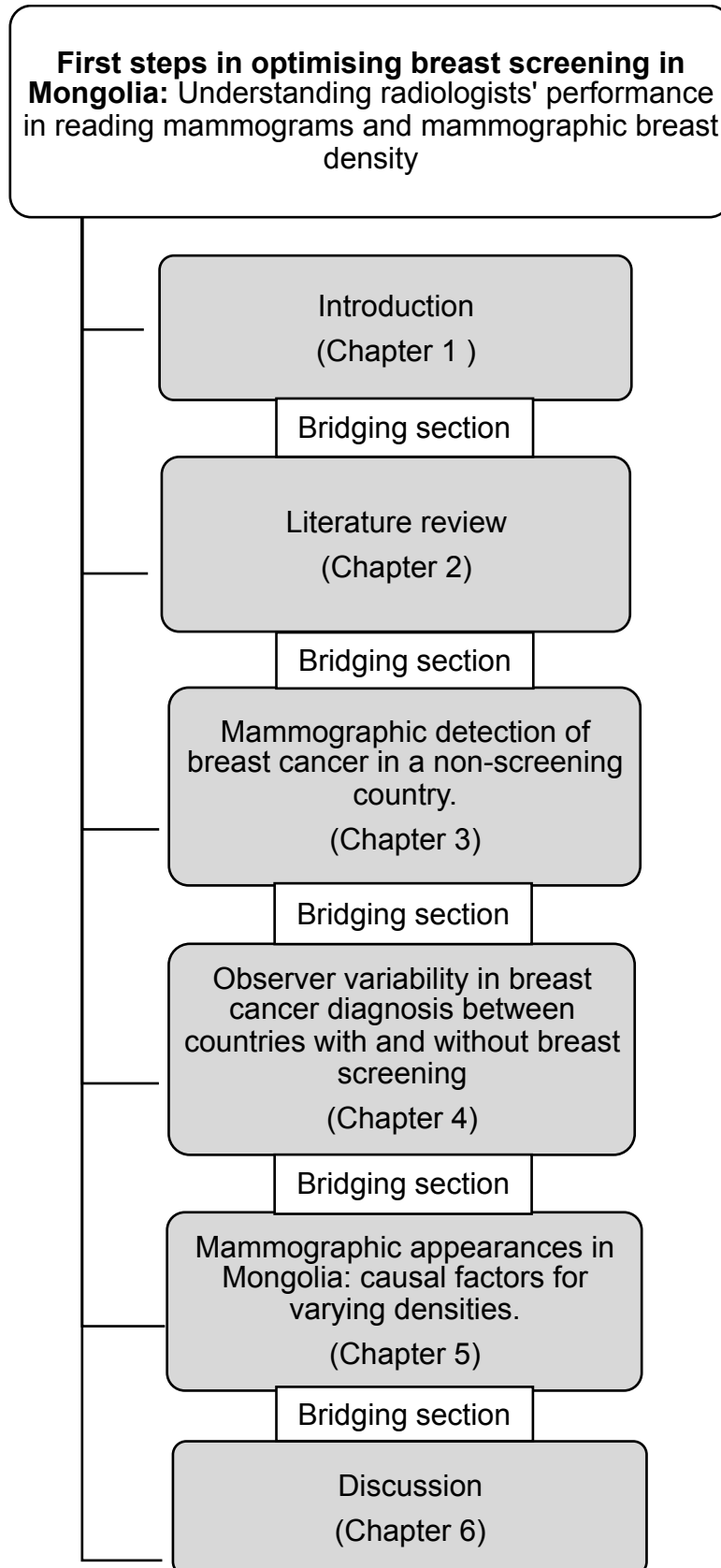


Figure 2: Thesis structure flowchart

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Chapter 2

“Breast cancer in Mongolia: an increasingly important health policy issue”

Literature review

Chapter 2 is published as:

Demchig, D., C. Mello-Thoms, and P.C. Brennan, “Breast cancer in Mongolia: an increasingly important health policy issue.” *Breast Cancer Targets and Therapy*, 2017. 9: p. 29-38

This paper is available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5268367/>.

2.1 Statement of Authorship

As Co-authors of the paper “Breast cancer in Mongolia: an increasingly important health policy issue”, we confirm that Delgermaa Demchig has made the following contributions:

- Conception and Design of work
- Literature search
- Writing the literature review
- Manuscript editing and critical appraisal of content

Professor Patrick C Brennan

Date: 14/06/2018

A/Professor Claudia Mello-Thoms

Date: 29/06/2018

2.2 Bridging section for chapter two

The statistics indicate that breast carcinoma is the highest occurring malignancy among women worldwide. However, depending on geographical location and economic resources of a country, patient outcomes vary between nations. To date, characterization of the disease is well recognized in developed countries supported by extensive research studies about: knowledge around risk factors, types of disease and women being affected, and treatment and diagnostic status. Based on this information, the management and control of breast cancer appear to be well maintained among Western countries, where effective breast screening programs exist and advanced treatment options are available. Unlike Western countries, available data on characteristics of breast cancer are difficult to find in Asia. However, we do know some basic features of the disease for women in this region, particularly around: epidemiological characteristics (low incidence and high mortality rates, younger age at onset), clinical features (high proportion of advanced stages), common risk factors such as MD (denser than those noted in the West) and molecular subtypes (high proportion of ER negative and HER2 positives) [1-3]

As previously discussed, breast cancer incidence in Mongolia is among the lowest in the world but advanced diagnoses are common and the disease may have specific features. It should be noted that the low rates of incidence and mortality of breast cancer in Mongolia could be due to the traditional lifestyle of Mongolian women such as longer duration of breastfeeding, high number of parity and low exposure to the consumption of smoking. Based on the available statistics between 2009 and 2013, incidence and mortality numbers appear to be increasing but it may not be

significant, as natural variations with such small data can exist. However in Mongolia, research data is rarely available when compared internationally and thereby the status of breast cancer remains less clear.

Located between two large countries, China and Russia, Mongolia has unique and diverse socio-cultural and lifestyle features. The country is mostly influenced by Russia, since the two countries had a long-lasting, strong relationship of more than 70 years until 1990, when democracy was introduced to Mongolia [4]. For example, until recently, Russian was the most popular language in the country and Soviet education was common among Mongolians. As of 1990, the country has opened up foreign relations with other countries such as the USA and UK and subsequently westernized culture and lifestyles have been introduced. In addition, the country has no access to the ocean with continental dominant climate (extremely cold and long winter, warm and dry summer) along with a high altitude location. Mongolia is therefore very distinct from the rest of Asian countries although geographically located in the same continent.

Indeed, Mongolia still relies on hospital care rather than preventative measures. It may be of no surprise that the current health system is designed based on the Soviet system (bed-based hospitals). To date, inpatient hospitals are still common practice, which requires a large healthcare budget [5] and this may contribute to lack of funds for other important strategies and policies such as the development of screening program when required. With the right policy direction, effective re-allocation of health funds is critically important to improve patient outcomes. For example, mammographic screening is well established and became a standard clinical

practice in Western countries, which subsequently contributed up to 30% of reduction in breast cancer mortality [6,7]. However, it should be acknowledged that the effectiveness of screening remains debatable due to its potential downwards and benefits. In particular, mammography is less sensitive for women with high-density breasts and therefore, alternative screening approaches such as clinical breast examination and breast ultrasound has been recommended. However, currently limited available data cannot support developing such strategies in Mongolia. But it is clear that a more functional approach is needed, since a high proportion of late stage diseases presents in the country. It is therefore very important to first determine the overall status of breast cancer in Mongolia, since without this information further progress is not achievable.

In view of the knowledge deficiencies, the focus of the current literature review is to provide an understanding of the overall characteristics of breast cancer in Mongolia in terms of incidence, mortality, survival, risk factors and breast screening activities. As benchmark, the Mongolian data were compared with Western and Asian countries and due to limited literature about breast cancer in Mongolia, sometimes-local unpublished studies are cited.

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Breast cancer in Mongolia: an increasingly important health policy issue

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Abstract: Breast cancer is a leading cause of cancer-related death for women in both developed and developing countries. The incidence and mortality of breast cancer in Mongolia, while low compared with other counties, has been increasing on an annual basis. In addition, in Mongolia, approximately 90% of the patients are diagnosed at a late stage, resulting in high mortality, with the majority of individuals diagnosed with breast cancer dying within 5 years of diagnosis. Breast cancer screening plays an important role in reducing mortality in Western countries and has been adopted by a number of Asian countries; however, no such approach exists in Mongolia. In a country of limited resources, implementation of expensive health strategies such as screening requires effective allocations of resources and the identification of the most effective imaging methods. This requirement relies on recent accurate data; however, at this time, there is a paucity of information around breast cancer in Mongolia. Until data around features of the disease are available, effective strategies to diagnose breast cancer that recognize the economic climate in Mongolia cannot be implemented and the impact of breast cancer is likely to increase.

Keywords: incidence, mortality, breast screening, Mongolia

Data source and material

The data used in this review mainly arose from 2 sources; the Cancer Registry, located in the National Cancer Center (NCC) in Mongolia,¹ and the International Association of Cancer Research (IACR).² The Cancer Registry in Mongolia was initiated as a hospital-based registry at the NCC in the early 1960s and has now developed as a population-based registry,³ where data on incidence and mortality of breast cancer between 2009 and 2013 are available. All newly diagnosed cancer and death cases along with the personal and clinical information are recorded at the primary- and secondary-level hospitals and submitted to the Cancer Registry via Health info-2 software.⁴

The quality of the data in Mongolia is not clear, as data collection relies on certain factors such as population coverage and collection method. For example, the limited availability of health facilities and trained health professionals in rural areas may result in a number of cancer cases not being diagnosed and many deaths not being recorded. Also, the comprehensiveness of the data is not well understood since histology and morphology records have only become available since 2012.⁴

Introduction

Breast cancer remains the major health concern since it is the most common cancer among women in the world.^{2,5} The rates in incidence and mortality, however, vary

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significantly by region. In general, developed nations demonstrate a greater incidence (greater than 80 per 100,000) compared with developing countries (less than 30 per 100,000), although the latter group is currently demonstrating more rapid increases in incidence.⁶ Women in low- and middle-income countries tend to be diagnosed at late stages largely due to lack of available routine mammographic screening and breast cancer awareness.^{7,8} In such low resource countries, research data are needed to understand the impact and tailoring of limited resources to maximize impacts on breast cancer.^{9–11}

Mongolia, with a population of 3 million, is one of the fastest developing countries in Asia, but encounters a substantial and unique cancer burden nationwide. While liver cancer is almost 4 times higher than the world average, being by far the most common cancer among both sexes,³ breast cancer is the 5th most common primary cancer among Mongolian women with a current rate of 6 per 100,000 women, accounting for 6% of all new cases of female cancer.¹ Despite these low figures, the incidence rate appears to be increasing on an annual basis.^{1,12} Also, since the majority of cancer patients are diagnosed at a relatively late stage, the disease has become a serious public health issue.^{13,14}

It should be acknowledged from the outset that in Mongolia, details on the incidence, nature and mortality around breast cancer, along with information on type of women affected are limited and without such data, future health policies or systems around this disease cannot be strategically planned or implemented. This review aims to bring together

the available data and provide an overview of the current status of breast cancer epidemiology in Mongolia. The data will be presented in the context of what is known about the disease in Asian countries and westernized populations.

Breast cancer incidence

While Mongolia has a relatively low breast cancer incidence rate, this value has been consistently increasing. An examination of the annual cancer registry in Mongolia between 2009 and 2013, which contains some of the most recent breast cancer data (Figure 1), demonstrated a substantial increase in the breast cancer incidence rate from 3.0 in 2009 to 6.0 in 2013.¹ However, the year on year increase was inconsistent, with the most rapid increase of 54% seen in the 2009–2010 period resulting in incidence rates of 3.0 and 4.6 per 100,000 in 2009 and 2010, respectively. An increasing trend in breast cancer has also been reported earlier by Troisi et al,¹² based on data between 1998 and 2005 from the IACR and the NCC in Mongolia.

As noted in other Asian countries, incidence rates within Mongolia vary by geographical regions (Figure 2). For example, some rural provinces of Khentii and Bayan-Ulgii have considerably higher rates of 10.1 and 11.0/100,000, respectively, compared with the national level at 6.0/100,000,¹ and it is interesting to note that these provinces are the home for most of the ethnic minorities of Mongolia. Such ethnic-dependent variation in incidence (and presentation) of breast cancer has been reported in the neighboring country of People's Republic of China.¹⁵ Although the cancer registry is

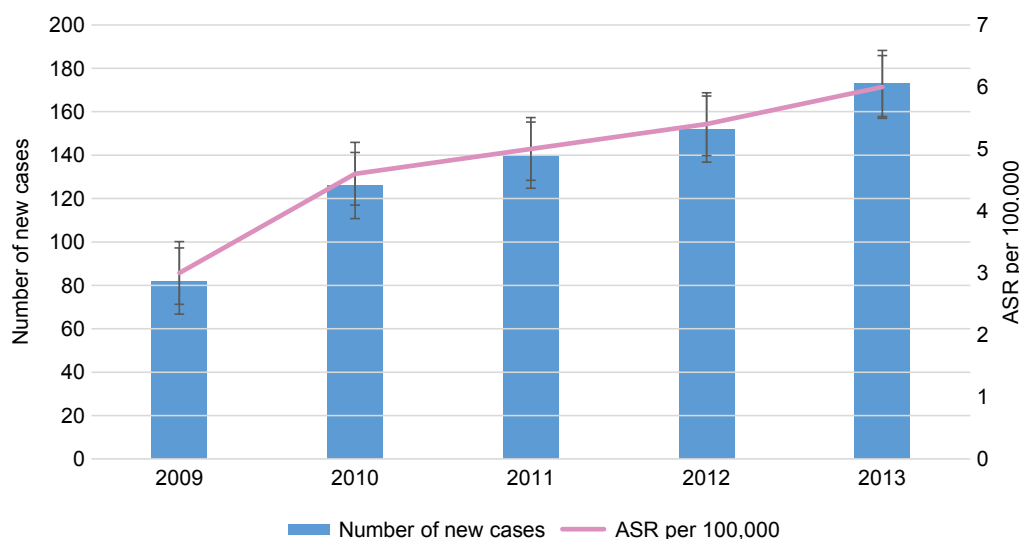


Figure 1 Incidence rate of female breast cancer, Mongolia, 2009–2013.

Note: Data from Cancer Registry Data, National Cancer Center, Mongolia, 2009–2013.¹

Abbreviation: ASR, age-standardized rate.

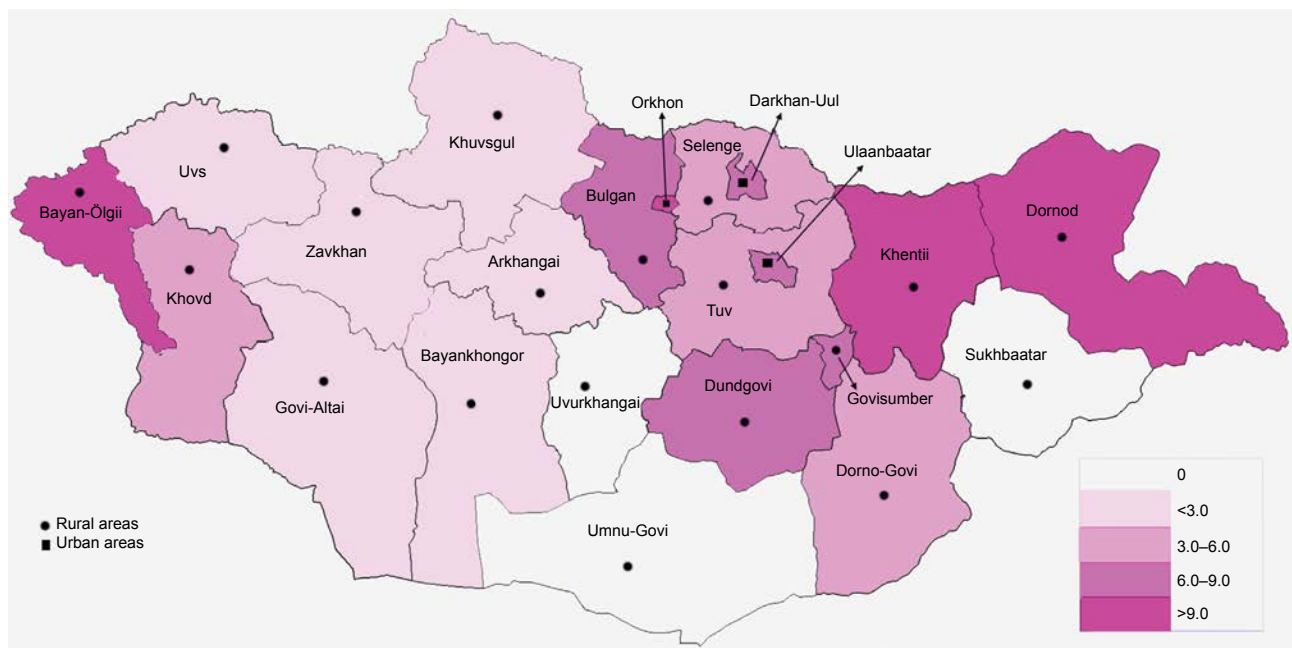


Figure 2 Age-standardized incidence rate by province, Mongolia, 2013.

Note: Data from Cancer Registry Data, National Cancer Center, Mongolia, 2009–2013.¹

available for collecting data across the whole of the country, data from rural areas may be impacted by limited health facilities, number of professionals and data distributions system compared with 3 urban locations in the country – the city of Ulaanbaatar (UB) and the larger provinces of Darkhan-Uul and Orkhon. A strong relationship between breast cancer and age has also been identified among Mongolian women with the highest incidence rate of 28.4/100,000 occurring among the 50–54 years old compared to 3.7 per 100,000 in the 15–39 age group.² Although the peak age appears to be closer to other Asian countries, at least a decade difference is noted when compared with westernized states (Figure 3).

Asia in general has a low incidence of breast cancer compared with westernized countries. However, compared with Mongolia the disease is still common among Asian women^{6,16–20} and with a mean incidence of 29 per 100,000 in 2012, it is the most common cancer.² Also when compared with countries such as the US, UK and Australia, the younger median age at diagnosis (40–50 years as opposed to 50–60 years) and the more progressed stage of the disease when diagnosed in Asia are quite different.^{17–19} However, due to lifestyle and reproductive changes in Asia, differences from westernized states to some extent are diminishing; for example, the incidence rates are increasing rapidly in the former, even though in absolute terms the rates for the time being remain low.^{20–22}

In the westernized world, breast cancer is the most common cancer among women with a mean incidence of

90 per 100,000 in 2012.² It has been observed that while age-standardized rates (ASRs) for breast cancer are higher, the rates are beginning to stabilize within developed countries unlike developing countries where breast cancer is continuing to emerge as an increasingly important health issue.^{23,24}

Breast cancer survival

In Mongolia, data on survival of breast cancer are very limited. With the lack of an early detection program and limited diagnostic and therapeutic resources, breast cancer is diagnosed at late stages, leading to a 5-year survival rate of 57% that is considerably lower than that described in other countries as highlighted by the recent global study based on the data between 2005 and 2009.²⁵ Similar findings were shown in the report from the NCC for the period 2003–2013, which found that the average survival time for Mongolian patients with breast cancer was 3.2 years.¹⁴ Also in Mongolia, 88.7% of women diagnosed with breast cancer are reported to die from the disease within 5 years,¹⁴ which is significantly higher than westernized states where 5-year survival is closer to 90%. The limited access to health services in remote areas may play a role in delay of diagnosis resulting in poor survival outcome.

As a result of the advanced presentation of disease, the majority of breast cancer patients have radical mastectomy with axillary dissection combined with radiotherapy and chemotherapy, leading to a worse survival outcome compared

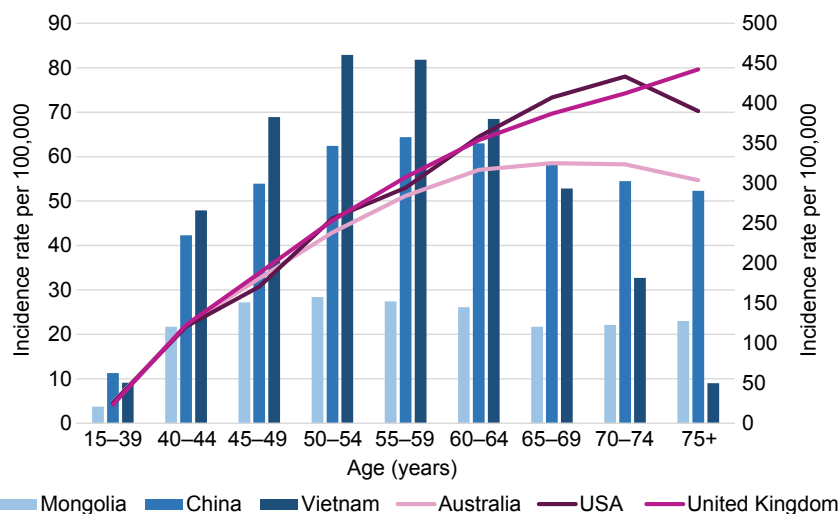


Figure 3 Age-specific incidence rate of female breast cancer, 2012.

Notes: The right axis indicates the incidence rates for Mongolia, China and Vietnam; the left axis indicates the incidence rates for Australia, USA and UK. Data from GLOBOCAN 2012.²

with the more developed treatments adopted elsewhere. Since early stage breast cancer is less frequent, the implementation of breast conserving surgery along with radiotherapy has only been conducted on a small proportion of patients. The use of radiation therapy remains low in Mongolia partially due to shortage of radiation oncologist and technologists. In addition, to treatment options, breast cancer survival can also be affected by other factors such as lifestyle, environmental, cultural and socioeconomic;²⁶ however, information on these factors and their association with survival is not well understood in Mongolia.

In Asia, inconsistency of early detection programs and the varying levels of access to appropriate treatment have led to the survival rates varying considerably across the region. In Japan, Republic of Korea and People's Republic of China, for example, 5-year survival rates of 85%, 83% and 82%, respectively, have been reported for invasive cancer cases during 2005–2009.²⁵ More similar to Mongolia, survival rate is reported to be lower in Malaysia and India, where the rate is closer to 68% and 60%, respectively.²⁵ In addition, the majority of breast cancer patients from developing countries in Asia continue to be diagnosed at a relatively late stage and over 50% of all managed patients present with locally advanced cancer at the time of diagnosis.^{21,27,28} It is important to note that even when detection and treatment opportunities exist, other factors, including estrogen receptor (ER) status, preexisting chronic disease and ethnicity impact upon variation in survival. For example, ER-negative cancers are more commonly reported among Asian women, which is associated with poor prognosis.¹⁹

The introduction of mammographic screening in westernized states highlights a potential way forward for Mongolia and other developing Asian states. Screening aimed at asymptomatic patients has led to marked improvements in overall survival. For example, In 1991, screening was introduced in Australia and 5-year survival rate was shown to increase from 72% to 89% between the periods 1982–1995 and 2006–2010.²⁹ However, the impact of changes in prevalence of risk factors and advances in diagnosis and treatment on favorable survival outcome cannot be ruled out. Such factors impact on stage of diagnosis and treatment. The former is a critically important determinant of survival, particularly regarding tumor size and the involvement of lymph nodes.^{30,31}

Breast cancer mortality

There is a paucity of quality data around mortality rates in Mongolia with some rural areas having no mortality data. A relatively recent national study¹³ demonstrated that 93.4% of the Mongolian women with breast cancer were diagnosed at advanced stages (Figure 4). The data that are available indicate that breast cancer is the 8th most common cause of cancer-related death in the country with age-standardized mortality rate of 2.7 per 100,000 in 2012.¹ Comparisons with Asian and Westernized countries are demonstrated in Table 1. Similar to other developing Asian countries, mortality rates (and incidence numbers) are predicted to increase due to adoption of westernized lifestyle and recent increased detection and treatment facilities in Mongolia.

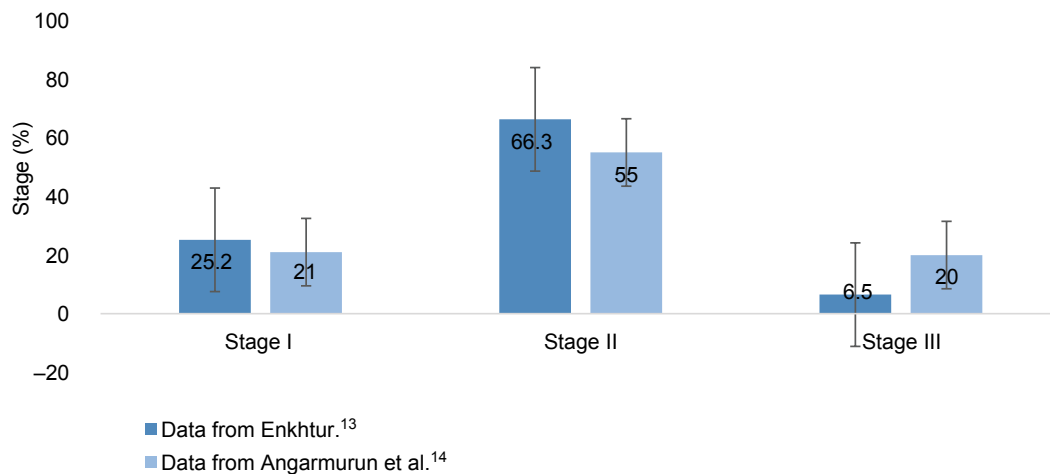


Figure 4 Breast cancer by stage, Mongolia.

Table 1 Estimated breast cancer incidence and mortality by country, 2012

Countries	Incidence		Mortality	
	Number	ASR (world)	Number	ASR (world)
Mongolia	125	9.4	50	1.6
Asia	650,983	29.1	231,013	6.4
Westernized countries*	127,016	89.5	26,906	7.3

Notes: The rates are age-standardized per 100,000 female population. *North America, Western and Northern Europe, Australia/New Zealand. Data from GLOBOCAN 2012.²

Abbreviation: ASR, age-standardized rate.

Although the ASRs for breast cancer in Mongolia historically have been consistent, a recent important increase has been described by recent national mortality data between 2009 and 2013 (Figure 5) where the rate was almost doubled from 1.4/100,000 in 2009 to 2.7/100,000 in 2012.¹ Interestingly, more than half of the deaths from breast cancer were registered in the capital city of UB in 2013. This figure is likely to be explained at least in part by population distributions since almost 50% of the Mongolian people live in UB³² and also by an urban lifestyle, which reflects westernized activities. Following the 2009–2012 increase, the mortality rate was declined to 1.6/100,000 in 2013. The explanation for this unusual change to the trend is unclear and may reflect incomplete data coverage.

Regional mortality variations in Mongolia, however, are not confined to the capital. Outside UB, variation in mortality rates is also evident with numbers being higher in rural provinces such as Bayan-Ölgii (4.4) and Dornod (4.0), while being lower in other regions such as Khuvsgul (0.8) (Figure 6).¹ While inconsistent registry data may have

contributed to these recorded variations, the stage of disease presentation is likely to be linked to these geographic variations.

While the rates are decreasing in many westernized nations,^{29,33,34} mortality rates continue to increase in Asian countries, aligning with rapid increases in incidence of breast cancer.^{19,22} In Asia, higher mortality rates are often observed in less developed countries despite these countries having low incidence rates.^{18,28,35} A variety of explanations have been proposed for these regional-dependent patterns around culture, socioeconomic factor, geographical isolation, inadequate diagnostic equipment and poor treatment facilities; however, a consistent casual parameter is delayed presentation of the disease.^{18,22,36}

In developed countries, breast cancer is the 2nd leading cause of cancer-related mortality after lung cancer, resulting in 198,000 deaths (15.4% of all cancer deaths) in 2012.² Mortality rates for breast cancer have steadily declined in most westernized countries,^{37–40} however, based on 2012 data, globally it is estimated that more than half million women will die from this disease annually, highlighting that breast cancer is not only the disease of developed countries.

Breast screening

Currently, in Mongolia, there is no population-based breast cancer screening; instead in 2010, guidelines were established for the prevention and management of the disease. As outlined in the guidelines, mammography is not recommended for early detection due to the relatively low incidence rates, limited resources for equipment and sparsely distributed populations in Mongolia.⁴¹ Therefore, clinical examination is the front line tool used for early

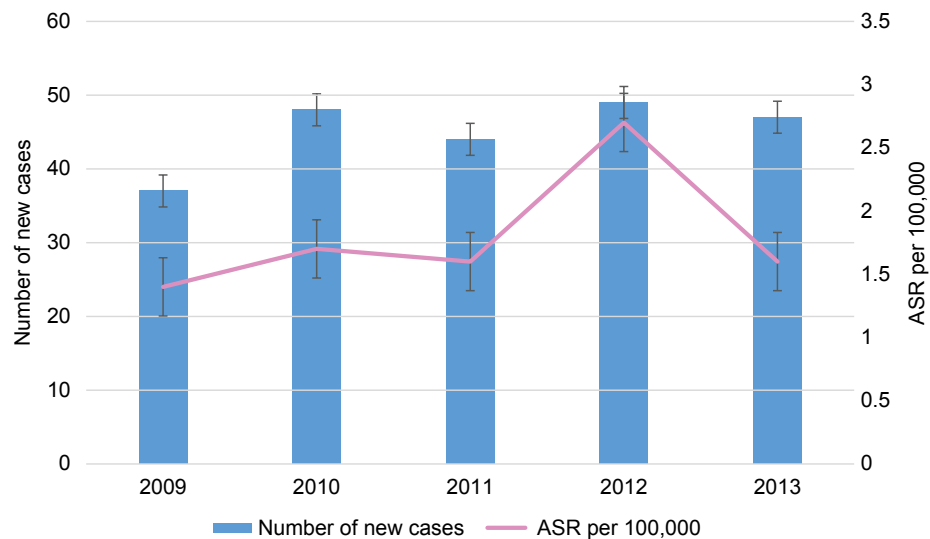


Figure 5 Mortality rate of female breast cancer, Mongolia, 2009–2013.

Note: Data from Cancer Registry Data, National Cancer Center, Mongolia, 2009–2013.¹

Abbreviation: ASR, age-standardized rate.

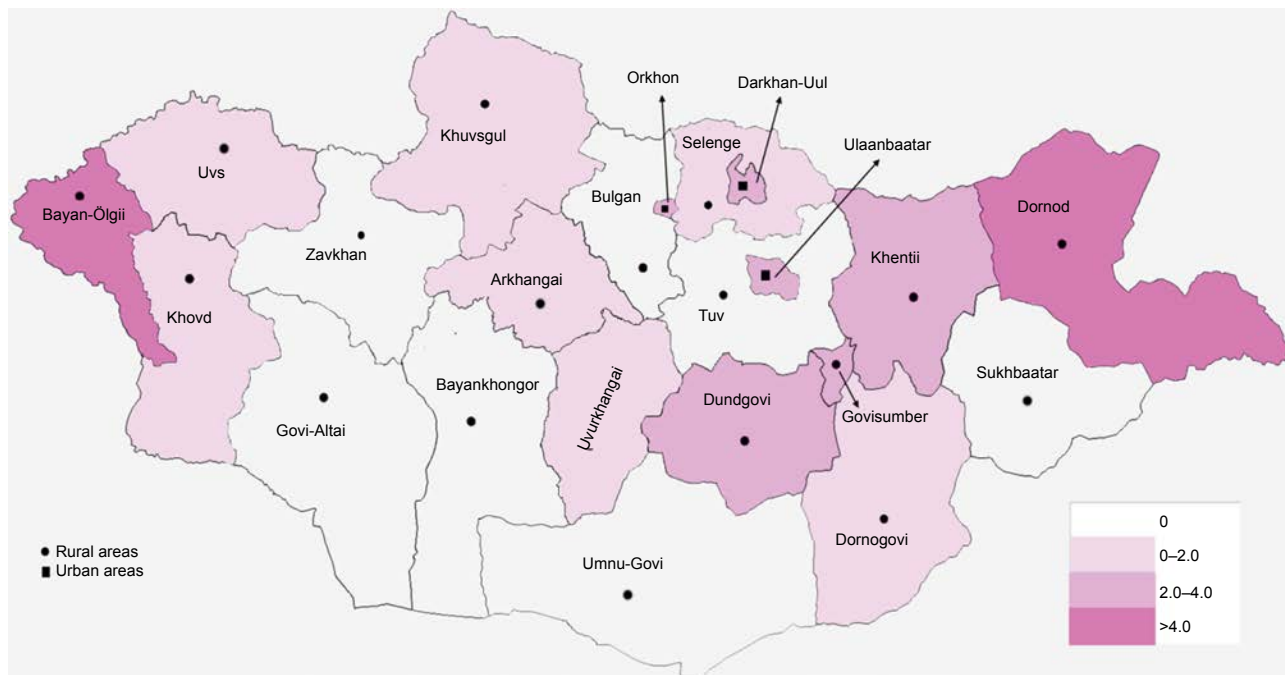


Figure 6 Age-standardized mortality rate by province, Mongolia, 2013.

Note: Data from Cancer Registry Data, National Cancer Center, Mongolia, 2009–2013.¹

detection of the disease, and all suspected cases in local hospitals refer to the NCC for further diagnostic evaluation. However, this screening approach is having a limited impact, with only 1 in 3 women reporting breast self-assessment and only 3.2% and 1.7% undergoing clinical breast examination and mammography, respectively, as reported in a recent WHO review.⁴²

In recent years, the importance of early detection for breast cancer has become a serious issue in Mongolia due to

increasing reports of late presentation and rapid increase in incidence of the disease.^{12–14} Since mammographic facilities have been established in both public and private hospitals in Mongolia, implementation of breast screening could be an effective approach to detect the disease at early stages. Although mammographic screening reduces mortality in westernized countries, there is no evidence that systems used elsewhere would be effective in Mongolia. Therefore, more investigations around breast types and breast cancer

presentations in Mongolia need to be carried out so that a country-specific solution can be found.

In Asia, compared with the Western nations, breast cancer screening is not so widespread. The effectiveness of mammographic screening in Asia is the subject of debate due to the low incidence of breast cancer across the region, the prevalence of smaller breasts and denser breast parenchyma among Asian women.^{43,44} Nonetheless, some Asian countries have adopted mammography for mass screening, such as Singapore, Japan and Taiwan, where some favorable outcomes have been reported.⁴⁵⁻⁴⁸ In Singapore for example (the first Asian country to introduce screening for 50–69 years old in 2002), the overall invasive cancer detection rate was reported to be 7.92 per 1000 women screened during 2002–2009 and a 12% increased rate of early stage cancers was recorded compared with prescreening period (before 2001).⁴⁸

In developed countries, breast screening with mammography is a well-established approach for the early detection of breast cancer and many experts agree that the benefit of mammography outweighs the harms. In particular, mammography is more accurate in older women than in young women.^{49,50} The overall impact of screening is debated with reported reductions in mortality from 15% to 58%.⁵⁰⁻⁵⁶

Risk factor

The causes for breast cancer are not fully understood but women with certain risk factors are more likely to develop the disease than others. In Mongolia, the risk factors associated with breast cancer are understudied. The only available case-control study¹³ involved 522 breast cancer patients and was locally published in 2009. Similar to other countries, this limited evidence proposes the following risk factors: reproductive factors including early menarche, irregular menstrual cycles, nulliparity and obesity; induced abortion, which was aligned with a recent Chinese meta-analysis;⁵⁷ and various disease states including ovarian chronic inflammation and cysts and uterine fibroids.¹³ It is also interesting to note that ethnic minority groups are expected to have low rates of incidence and mortality since these women generally adhere to more traditional lifestyles compared with their westernized counterparts; however, the opposite pattern was observed in Mongolia, which suggests a uniqueness around genetic and risk factors. While the aforementioned factors have been shown to be relevant to Mongolia, other important parameters reported for other countries such as family history, lifestyle factors and hormone replacement treatment (HRT) are currently poorly understood in Mongolia.

Current knowledge regarding breast presentation remains poor, which demands a better understanding of this disease among Mongolian women. For example, mammographic breast density has been shown to be one of the most important risk factors in westernized populations but nothing is known around this feature among Mongolian women. Westernized women with high density have been shown to have 4- to 6-fold increased lifetime risk of breast cancer.⁵⁸⁻⁶¹ This is a feature that can be assessed from mammographic examinations and while mammography occurs in Mongolia, little data are gathered on density distributions, particularly across ethnicity, age, body mass index and menopausal status. The absence of information is not the case across Asia; for example in China, breasts are known to be fatter than in American women in older age but denser in young age.⁶² The importance of understanding this feature for identifying risk and indeed for determining the optimal method of diagnostic imaging is emphasized so that prevention, early detection and intervention of the disease can be facilitated.

In Asia, while the prevalence and distribution of risk factors among Asian women vary between countries and studies, some common features have been noted in westernized studies.^{19,63-66} A recent Asian meta-analysis summarized that more than 3 abortions, family history, late age at first live birth (over 30 years old), smoking, no breastfeeding, alcohol consumption and longer usage of HRT are associated with breast cancer among Asian women.⁶⁷ Other risk factors reported among these women include body fat, which reduces and increases the risk of breast cancer in premenopausal and postmenopausal women, respectively.^{68,69} Uniquely to this region, however, a higher intake of soy food with their associated protective effect for breast cancer has been reported among Asian women,^{70,71} and in China, consumption of green tea was reported to be associated with risk of breast cancer,⁷² whereas this was not observed among Japanese women.⁷³

In developed countries, certain lifestyle activities, westernized diets, high socioeconomic status, physical inactivity and obesity are reported to be associated with breast cancer risk in these regions.⁷⁴⁻⁷⁶ For example, a European cohort study revealed that an increased risk of 31% for breast cancer is strongly associated with obesity among postmenopausal women.⁷⁶ Family history and gene mutations such as BRCA1 and BRCA2 are also well known, established risk factors.⁷⁷⁻⁸¹ In general, hormonal factors are different in prevalence between breast cancer subtypes; however,

hormone receptor-positive tumors were consistently being reported among Western women.^{82,83} Westernized women also tend to have shorter breastfeeding period and low parity compared with Asian women, resulting in high risk for developing breast cancer.^{84,85}

In summary, what is distinct about Mongolia?

With the limited available data, this review is the first attempt to describe the current situation of breast cancer in Mongolia while investigating different aspects of the disease. It is evident that breast cancer incidence rate in Mongolia is among the lowest in the world and there are several possible explanations that have been considered in the above sections and relate to lifestyle, health policy and quality of registry data. With regard to lifestyle, reproductive activities such as longer breast feeding⁸⁶ and higher number of full-term pregnancies probably play a significant role, and as described within the only peer-reviewed publication¹² on the topic, dietary habits around high-level consumption of tea, meat and dairy product may also be key. However, absence of a breast screening program must also be a contributory factor particularly since it is evident that rates of breast cancer have increased in those Asian countries that have recently introduced formal screening programs.^{48,87} Finally, reliability of cancer registry data cannot be excluded as incomplete data exist. Until screening procedures are formalized and accurate registry data become available, the importance of breast cancer to Mongolia cannot be fully appreciated. What is appreciated is that late disease presentation, poor survival and high mortality demand a coordinated effort between researchers, clinicians and health strategists to ensure that Mongolian women do not continue to suffer poorer health outcomes compared with their neighbors and westernized counterparts.

Conclusion

While breast cancer incidence is low in Mongolia compared with other Asian countries and westernized states, incidence rates are gradually increasing. Early detection with optimal imaging methods may be a key to minimizing the impact of this disease on Mongolian women; however, not enough is known about the type of cancer being presented, the regional distribution of the disease and the type of women most effected, which is needed to facilitate allocation of limited resources.

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Disclosure

The authors report no conflicts of interest in this work.

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Chapter 3

“Mammographic detection of breast cancer in a non-screening country”

Study

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3.1 Statement of Authorship

As Co-authors of the paper “Mammographic detection of breast cancer in a non-screening country”, we confirm that Delgermaa Demchig has made the following contributions:

- Conception and design of the research
- Data collection
- Analysis and Interpretation of the findings
- Writing the paper and critical appraisal of content

Professor Patrick C Brennan

Date: 14/06/2018

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Date: 21/05/2018

3.2 Bridging section for chapter three

Breast carcinomas have a fairly good prognosis if detected at their early phase of development [1]. Mammographic screening, amongst all approaches for early detection (breast self-exam and physical examinations) has proven to reduce death rates from the disease [2, 3]. Therefore, it is recommended frequently and well established in Western countries. But its introduction to Asian countries remains controversial due to its limited sensitivity for women in their 40s (peak ages for breast cancer in Asia) and as well as lack of data on cost effectiveness [4]. Nonetheless, in some wealthy Asian countries, where breast screening is available, the proportion of early stage diagnoses (Stage I and II) is reported to be closer to Western countries such as 60% in South Korea [5] and 70% in Singapore [6]. In contrast, advanced diagnoses are very common among less developed Asian countries such as India and Vietnam, where breast screening has not been introduced yet [7, 8]. Therefore, it can be understood that establishing screening approaches with mammography may have the potential to maximize patient benefits for developing countries including Mongolia. Although very affordable approaches for early detection of breast cancer are desirable in these nations, no such methods currently have been reported to be superior to mammography in terms of mass screening. Because of this fact, mammography will likely to remain the front-line tool for early detection.

As discussed in the literature review (Chapter 2), breast cancer in Mongolia is an important health issue. Its delayed diagnosis is common with more than 90% patients at an advanced stage [9] compared with 30% in Australia [10]. As noted with other nations in the same region, lack of diagnostic and treatment resources, lack of

awareness and limited access to the resources can contribute to these delayed diagnoses [11, 12]. Currently in Mongolia, nationwide screening has not been introduced and mammography is used in diagnostic settings. However, some of the private medical centers in Mongolia have recently initiated screening protocols for women who self-request to be screened. Whatever the reason for mammography, the challenge is that its performance depends on multiple factors such as patient age, image quality, breast density status and reporting ability of radiologists. In particular, early diagnosis and better patient outcome is heavily reliant on accurate radiologists' interpretation of breast images.

Although breast cancer incidence remains low in Mongolia, it has been consistently increasing [13], which highlights a need to focus attention and resources toward optimized diagnostic strategies. Additionally, reproductive and lifestyle behavior of Mongolian women have shifted to Westernized styles in recent years and thereby it can be predicted that increases in incidence are likely to continue. To initiate any early detection program, it is important to determine status of diagnostic accuracy. Since the introduction of the first mammographic unit at the National Cancer Center in 1996 (replaced with digital technology in 2013) [14], breast cancer diagnoses have improved in Mongolia however; the diagnostic efficacy of mammography is unknown. Identifying the level of diagnostic accuracy is therefore critical to improving the quality of breast cancer diagnoses. The current research was therefore conducted to establish radiologists' diagnostic accuracy when reading mammograms using high difficulty screening images collected from Australian women, for which we had benchmark performance measures from Australian and New Zealand radiologists. In this study, we used a research design and method validated by numerous previous studies focusing on observer performance in mammography [15-18].

Considering the possible variations in breast morphology between ethnic groups, using mammograms of Australian women may raise a question on appropriateness of testing performance of Mongolian radiologists. However, radiologists are trained for interpreting variety of breast morphology (breast density) and therefore, image appearances could not have a big impact on reader accuracy. To appropriately test the diagnostic accuracy of the local readers, it is crucial to include Mongolian mammograms into the test-set, which would have potential to provide meaningful information regarding radiologists' accuracy. However, to meet the test-set criteria, breast cancer cases should be biopsy proven with early imaging findings, whilst normal images are required to be normal by radiologists, which should be confirmed with follow-up examinations. Compared with Australia, collecting such types of cancer images from Mongolia is extremely challenging and therefore we were unable to conduct this part. This is mostly due to lack of radiology and pathology reports, which are not recorded and stored at the hospital systems.

In addition, using the high-difficulty images for novice readers (Mongolian radiologists) may be questionable but breast radiologists should have the ability to report any types of mammograms regardless of its difficulty as long as they have high technically quality. The current test-set is also the standard images to test reader performance in Australia and New Zealand and therefore using these images in the present study should reasonably be valid. The radiologists in this study were the readers who involves in reporting breast images in Mongolia and Australia. Since the current work was the first study on radiologists' performance in reading mammograms in Mongolia, we did not have preliminary results to calculate the sample size and therefore power analysis was not feasible.

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FULL PAPER

Mammographic detection of breast cancer in a non-screening country

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E-mail: delgermaa.demchig@sydney.edu.au**Objective:** To compare the diagnostic accuracy between radiologists' from a country with and without breast cancer screening.**Methods:** All participating radiologists gave informed consent. A test-set involving 60 mammographic cases (20 cancer and 40 non-cancer) were read by 11 radiologists from a non-screening (NS) country during a workshop in July 2016. 52 radiologists from a screening country read the same test-set at the Royal Australian and New Zealand College of Radiologists' meetings in July 2015. The screening radiologists were classified into two groups: those with less than or equal to 5 years of experience; those with more than 5 years of experience, and each group was compared to the group of NS radiologists. A Kruskal-Wallis test followed by *post-hoc* multiple comparisons test were used to compare measures of diagnostic accuracy among the reader groups.**Results:** The diagnostic accuracy of the NS radiologists was significantly lower in terms of sensitivity

[mean = 54.0; 95% confidence interval (CI) (40.0–67.0)], location sensitivity [mean = 26.0; 95% CI (16.0–37.0)], receive operating characteristic area under curve [mean = 73.0; 95% CI (66.5–81.0)] and Jack-knifefree-response receiver operating characteristics figure-of-merit [mean = 45.0; 95% CI (40.0–50.0)] when compared with the less and more experienced screening radiologists, whilst no difference in specificity [mean = 75.0; 95% CI (70.0–81.0)] was found. No significant differences in all measured diagnostic accuracy were found between the two groups of screening radiologists.

Conclusion: The mammographic performance of a group of radiologists from a country without screening program was suboptimal compared with radiologists from Australia.**Advances in knowledge:** Identifying mammographic performance in developing countries is required to optimize breast cancer diagnosis.

INTRODUCTION

The burden of breast cancer remains high in low-income countries. For example, 5 year survival rate is approximately 90% in developed countries, but this figure is reported to be around 60% in less developed nations in the Asia Pacific region¹ and late stage at detection is a key contributory agent.^{2,3} Although multiple factors are linked to delayed diagnosis, advanced disease presentation suggests that diagnostic efficacy must be improved. Nonetheless, little attention or resources have been directed to this topic, and it is unclear whether it is patient knowledge, disease type, health policy or radiology efficacy that are responsible for disease diagnosis at such a late stage. Until more data around each of these potential causal factors are provided, effective allocation of funding and subsequent successful interventions cannot be initiated.

Currently, mammography is the only screening modality that is proven to reduce mortality from breast cancer, however, many countries still do not have a screening program, which is mostly due to lack of financial resources.^{4,5} Nonetheless, opportunistic screening approaches such as private or hospital-based screening have been implemented, yet their diagnostic efficacy is unclear. Interpreting mammograms, especially screening mammograms is a challenging task and prone to diagnostic error, where incorrect, missed or delayed diagnosis are not uncommon.^{6–9} Indeed among all imaging modalities, mammography is the most common focus for medical lawsuits against radiologists in the USA.^{6,10} Whilst the reasons for this are multifactorial,¹¹ perceptual and interpretive factors are critically important, and these largely depends on the radiologists' ability to interact effectively with the images being reported.¹² On

a positive note, perception and interpretation are modifiable and can be enhanced through appropriate education, training and experience. Nonetheless, diagnostic accuracy varies widely among radiologists,¹³⁻¹⁵ and in Australia, diagnostic accuracy varies from 85 to 95% for sensitivity and 80 to 83% for specificity.^{7,16} In the non-screening (NS) country where the NS radiologists recruited, these important measures of diagnostic accuracy have never been investigated, and until this first step happens, diagnostic accuracy cannot be optimized.

Australian breast radiologists have demonstrated better accuracy using various parameters when compared to readers from other countries having a screening program.^{15,16} This is often explained by differences in reader characteristics such as experience, practice and training. In the NS country, cancer diagnosis relies on diagnostic mammography, with imaging performed following a symptomatic concern. In diagnostic mammography, the expected prevalence of cancer is higher than in screening and presents a very different work process to reading screening mammography, where the expectation is that the very large majority of females will not have cancer.

In this study, we compared radiologists from a NS country to those from a screening country (Australia) using a single population test-set, with the aims of identifying possible differences in diagnostic accuracy and to determine causal factors linking observed measures of diagnostic accuracy with their level of expertise.

METHODS AND MATERIALS

Study participants

All radiologists gave informed consent. The study included a total of 63 breast radiologists. Details on demographic information (age and sex) and professional experience (number of years since qualification as a radiologist; number of cases and hours reading mammography; fellowship training in breast imaging) were self-reported by each reader.

Non-screening radiologists

11 NS radiologists were prospectively recruited and read the cases with no time limit during the BREAST (BreastScreen REader Assessment Strategy),¹⁷ a breast imaging workshop in July 2016 in Mongolia. These radiologists represented approximately 80% of the total number of radiologists involved in mammographic reading in the country, where no specific qualifications are required to report mammograms. The mean age for the NS was 32 years old [standard deviation (SD) = 3.7], the mean number of years reading mammograms was 1.6 years (SD = 1.9) and the mean number of years since being qualified as a radiologist was 4.0 years (SD = 3.6). Weekly reading volume was less than 4 h for all NS radiologists and none of them had completed fellowship training in breast imaging.

Screening radiologists

52 screening radiologists read the cases at the Royal Australian and New Zealand radiologist's meetings in September 2012 and July 2015. Since all our NS radiologists (see above) had less than 5 years' experience reading mammograms, the screen readers

were divided into two groups: up to 5 years of experience ($n = 27$), and more than 5 years of experience ($n = 25$).

For the less experienced screening radiologists, the mean age was 46 years old (SD = 10.6) and mean number of years since qualifying as a radiologist and working in a screening program were 6.0 years (SD = 7.0) and 2.2 years (SD = 2.0) respectively. 56% had completed fellowship training in breast imaging and 30% spent less than 4 h per week reading mammograms.

The mean age for the more experienced screening cohort was 56 years old (SD = 12) and mean number of years since qualifying as a radiologist and working in a screening program were 19 years (SD = 9.0) and 17 years (SD = 8.7) respectively. 16% had completed fellowship training, and 25% of them spent less than 4 h per week reading mammograms. The characteristics of all radiologists are shown in [Table 1](#).

Test-set

The Breast Screen Digital Imaging Library of New South Wales was the source of all images and all recorded data were deidentified. Each case comprised of craniocaudal and mediolateral views of the left and right breasts.

The test set included 60 digital mammograms with 20 cancer and 40 normal cases. The images were randomly ordered within the test-set and all participant were exposed with this same order. All 20 cancer cases were biopsy-proven, whilst the normal cases were interpreted as being cancer-free by two screen readers and then had a normal follow-up screening mammograms 2 years later with no interval cancer. Normal images were reported by these readers as being completely normal or containing benign appearances such as oil cysts, intramammary lymph nodes and calcified fibroadenomas. The cancer cases were consisted of four discrete masses, two calcifications, five non-specific densities, five stellate lesions and four spiculated masses. The types of cases selected were representative of those presenting in a breast screening environment.

Test-set reading

All images were read using a pair of five megapixel medical grade display monitors that were calibrated to the Digital Imaging and Communication in Medicine Gray Scale Display Function.

In line with routine radiology practice, each reader was asked to identify and locate lesions suspicious for malignancy or lesions that required further assessment, as well as to provide an interpretation scores in their decision. They were able to mark as many lesions as they could identify on each case using the following interpretation scale: 1, normal; 2, benign; 3, equivocal; 4, suspicious; 5, malignant. If no lesion was marked, the software automatically rated the case as being normal. Readers were not informed of the number of normal and abnormal cases.

Data analysis

Jackknife free-response receiver operating characteristics (JAFROC) figure-of-merit (FOM),¹⁸ receiver operating characteristic, area under curve (ROC AUC), case and location

Table 1. The characteristics of 63 radiologists included in the study

Reader characteristics	Categories	Non-screening radiologists (<i>n</i> = 11)	Screening radiologists with under 5 years' experience (<i>n</i> = 27)	Screening radiologists with over 5 years' experience (<i>n</i> = 25)
Readers' age	≤30	3 (27)	0	0
	31–39	8 (73)	11 (41)	1 (4)
	≥40	0	16 (59)	24 (96)
Number of years since qualification of radiologist	≤5	7 (64)	19 (70)	1 (4)
	6–10	4 (36)	2 (8)	3 (12)
	≥11	0	6 (22)	21 (84)
Number of years reading screening mammogram	0–5	11 (100)	27 (100)	0
	≥6	0	0	25 (100)
Number of cases reading mammograms per week	≤20	10 (91)	7 (26)	0
	21–50	1 (9)	6 (22)	3 (12)
	51–100	0	5 (18)	9 (36)
	101–150	0	4 (15)	3 (12)
	151–200	0	4 (15)	2 (8)
	≥200	0	1 (4)	8 (32)
No of hours reading mammograms per week	≤4	11 (100)	12 (45)	6 (24)
	5–10	0	6 (22)	13 (52)
	11–15	0	2 (7)	3 (12)
	16–20	0	4 (15)	1 (4)
	21–30	0	1 (4)	1 (4)
	≥30	0	2 (7)	1 (4)
Fellowship training in breast imaging	Yes	0	15 (56)	4 (14)
	No	11 (100)	12 (44)	21 (84)

Numbers in parenthesis for reader characteristics are the percentage values.

sensitivity and specificity were calculated for each individual participant. Case sensitivity was defined by the proportion of abnormal cases that were correctly identified as being abnormal. Location sensitivity was defined as the proportion of abnormal cases where the lesion was correctly marked (within 50 pixel of radius from the centre of lesion) and given a confidence score of 3 and above. Specificity was defined by the proportion of normal cases given a confidence score of 2 and below.

ROC is a case-based parameter and thus, when a reader did not locate the cancer correctly but correctly identified the case as abnormal, a correct score is given to that reader. To overcome this issue, a free-response receiver operating characteristics curve was also used.¹⁹ JAFROC is a lesion-based method for analysing free-response data (multiple reader and multiple case studies) and is calculated based on number of true lesion locations and number of normal cases rated by observers. For the observer studies, the JAFROC analysis is useful for assessing reader accuracy in locating cancerous lesions and has greater statistical power than conventional ROC analysis, which neglects location information.²⁰ JAFROC, therefore, takes into account when some readers correctly identify abnormal cases but incorrectly locate the lesion.

The three groups of radiologists were compared using Kruskal–Wallis test followed by the ranked-based version of Tukey's honest significant difference criterion. MATLAB software 2017 (Mathwork, Natick, MA, USA) was used to perform this statistical test. The individual comparisons were conducted between the following groups:

- NS vs screening readers with under 5 years' experience;
- NS vs screening readers with over 5 years' experience;
- Screening readers with under 5 years' experience vs screening readers with over 5 years' experience

Non-parametric analysis using Spearman's rank order correlation was used to explore the association between diagnostic accuracy and experience parameters of the readers. SPSS software (v. 22) was used for this statistical analysis. A difference with *p*-value of less than 0.05 was considered as significant.

RESULTS

With regards to reader characteristics, a number of statistical differences were found between the pairs of reader groups and these are shown in Table 2. The NS group was significantly younger than each group of the screen readers, whilst no differences in age were noted between the screening radiologists. The number of hours and number of mammogram

Table 2. Pairwise comparison of reader characteristics for the three groups

Reader characteristics	Non-screening radiologists	Screening radiologists (<5 years' experience)	Screening radiologists (>5 years' experience)	p-value
Reader's age	32.0 (29, 35)	43.0 (37, 55)	56.0 (43, 67)	^b <0.001 ^a ^c <0.001 ^a ^d 0.02 ^a
Number of years since qualification as a radiologist	4.0 (1.0, 8.0)	4.0 (1.0, 8.0)	20 (11.5, 22.5)	^b 0.66 ^c 0.001 ^a ^d 0.001 ^a
Number of years reading screening mammogram	0.0 (0, 3.0)	1.0 (0, 4.0)	16.0 (10, 22)	^b 0.23 ^c <0.001 ^a ^d 0.001 ^a
Number of cases read per week	1.0 ^a (1.0, 1.0)	3.0 ^b (1.0, 4.0)	2.0 ^c (2.0, 3.0)	^b <0.001 ^a ^c <0.001 ^a ^d 0.04 ^a
Number of hours reading per week	1.0 ^d (1.0,1.0)	2.0 ^e (1.0,4.0)	2.0 ^e (1.5,2.5)	^b 0.003 ^a ^c <0.001 ^a ^d 0.66

^aa statistically significant difference; (a), Indicates less than 20 cases; (b), Indicates 51–100 cases; (c), Indicates 21–50 cases; (d), Indicates less than 4 hrs; (e) Indicates 5–10 hrs.

^bDifference between non-screen and screen readers with under 5 years' experience.

^cDifference between non-screen and screen readers with over 5 years' experience.

^dDifference between screen readers with under and over 5 years' experience.

cases read per week was also significantly lower for the NS radiologists than it was for each of screening radiologists groups. Correlation analysis, which examined the relationship between the accuracy of all three groups of readers and their reader characteristics, demonstrated no statistically significant associations.

Case sensitivity, specificity, lesion sensitivity, ROC (AUC) and JAFROC (FOM) were calculated for all three groups and summarized in Table 3. For each of performance variables, Table 3 lists the observed means, the variable SDs and the lower and upper bounds for the calculated confidence intervals (CIs). The CIs were calculated using *t*-distribution, sample SD as an estimate for the population SD, σ and confidence level $c = 0.95$. The calculated mean scores for all performance metrics of the NS radiologists were lower than each of the screening groups of radiologists (Table 3). The lowest performance score for the NS radiologists were location sensitivity [$m = 0.26$; $SD = 0.16$; 95% CI (0.16–0.37)] whilst the

highest value was specificity [$m = 0.75$; $SD = 0.14$; 95% CI (0.7–0.81)].

Kruskal–Wallis test showed that there were significant differences in sensitivity ($p < 0.001$), location sensitivity ($p < 0.001$), ROC AUC ($p < 0.001$) and JAFROC FOM ($p < 0.001$) between the three groups of radiologists, whilst no significant difference was found in specificity ($p = 0.08$). When comparisons in accuracy were carried out between the NS radiologists and the less experienced screening radiologists, the scores for the NS radiologists were significantly lower in terms of case sensitivity ($p < 0.001$), location sensitivity ($p < 0.001$), ROC AUC ($p < 0.01$) and JAFROC FOM ($p < 0.001$), but not for specificity ($p = 0.84$). The NS group also demonstrated significantly lower accuracy in case sensitivity ($p < 0.001$), location sensitivity ($p < 0.001$), ROC AUC ($p < 0.001$) and JAFROC FOM ($p < 0.001$) compared with more experienced screening radiologists but no difference found in specificity ($p = 0.96$). When two groups of screening radiologists were compared there were no differences in any measured values.

Table 3. Mean performance metrics for the three groups of radiologists

Diagnostic accuracy	Non-screening radiologists		Screening radiologists (<5 years' experience)		Screening radiologists (>5 years' experience)	
	Mean (SD)	95% CI	Mean (SD)	95% CI	Mean (SD)	95% CI
Sensitivity	0.54 (0.2)	0.4–0.66	0.84 (0.1)	0.8–0.88	0.83 (0.15)	0.76–0.89
Specificity	0.75 (0.14)	0.7–0.81	0.76 (0.21)	0.68–0.84	0.81 (0.14)	0.75–0.87
Lesion sensitivity	0.26 (0.16)	0.16–0.37	0.76 (0.14)	0.7–0.81	0.75 (0.15)	0.68–0.81
ROC AUC	0.73 (0.1)	0.66–0.8	0.84 (0.97)	0.8–0.88	0.86 (0.73)	0.83–0.89
JAFROC FOM	0.44 (0.07)	0.4–0.49	0.78 (0.11)	0.73–0.82	0.79 (0.09)	0.75–0.83

CI, confidence interval; JAFROC (FOM), Jack-knife free-response receiver operating characteristics (figure-of-merit); ROC (AUC), receiver operating characteristics (area under curve); SD, standard deviation.

Numbers in parenthesis are the standard deviation (SD).

DISCUSSION

The process of image reporting is a vital component of patient management and it depends largely on individual radiologist's accuracy. The study has compared screening and NS radiologists in screening mammogram interpretation and indicates that radiologists from a NS country have lower sensitivity and accuracy than screening radiologists. It has not addressed the impact of training NS radiologists on performance. We found that the NS radiologists had lesion sensitivity and JAFROC FOM scores that were two and four times lower, respectively, than the less experienced group of screening radiologists. With a case sensitivity of 54% for the NS readers, it is not merely the localization of the abnormality that was a challenge, but also the ability to recognize an abnormal image.

JAFROC FOM presents the probability that a lesion will be given a higher rating score compared with a no-containing lesion location on a normal image. This requires a different understanding of the resultant AUC values as unlike a 0.5 value representing a random score for a normal ROC analysis, this is no longer the case with JAFROC. JAFROC does, however, take into account location information which is a powerful indicator of radiologists' accuracy and is, therefore, a valid and effective measure for assessing diagnostic accuracy of radiologists. In our cases, the JAFROC (0.44) scores for the NS radiologists is impacted by their number of normal images identified correctly, since the specificity was high (75%) whilst the lesion sensitivity was low (26%).

To understand this low performance better, it is worthwhile going back to the eye tracking studies,^{12,21} which explained how experts in radiology use an initial holistic review to identify areas of abnormality, followed by visual fixation on the abnormality in question. However, the fact that case sensitivity and lesion sensitivity for the NS radiologists was low may suggest that initial visual detection may be at least part of the reason why these readers missed so many cancers. Such detection relies on having a firm understanding of what constitutes a normal image, so that any abnormal features trigger a rapid response. This requires effective initial training coupled with substantial and ongoing experience. However, in Mongolia, it is difficult for radiologists to establish adequate practice and skills in mammographic interpretation under the current 2-year program in radiology residency, which does not include subspecialty training in breast imaging. In addition, workload in mammography units in Mongolia is relatively low because of the lack of a national screening program.

The ability to recognize normal images is also an important measure of accuracy and previous work⁹ has shown that when sensitivity is the same, specificity can be a powerful discriminator between expert and less-experienced observers. Interestingly, no significant differences were found for specificity between any of our groups of readers. Due to the low prevalence of breast cancer,²² the NS radiologists may have a higher decision threshold when declaring the presence of a cancer, thus potentially explaining both the specificity (the large majority of cases are not expected to have cancer) and sensitivity results

(abnormal cases have to be obvious to be declared as abnormal). This hypothesis is supported by number of studies,^{23–26} which suggest that *infrequent* targets are often missed, which may explain the overall accuracy of the NS radiologists. This prevalence effect may be ameliorated by exposure to an increasing number of abnormal images,²³ suggesting that tailored educational programs with a range of cancer types may be necessary, since clinical experience may not meet the demands for adequate practice in mammographic examination in Mongolia.

The underlying differences in reader characteristics may explain in part the observed findings on diagnostic accuracy. There was, e.g. no evidence of fellowship training amongst the NS radiologists, in contrast to the approximately 45 and 16% of less and more experienced screening radiologists, who had completed such a program. In addition, higher number of readings per year have been shown to be critically linked to better accuracy,^{9,15,27} but achieving such experience through clinical practice is unrealistic in Mongolia due to lack of a screening program. We did not find any significant relationships for any of the groups between the reader parameters and measures of diagnostic accuracy, although it has been showed in prior studies that radiologists' experience, practice volume^{9,15,28} and attendance of specialized training^{13,29} are associated with better accuracy. The absence of this finding may be the result of limited power³⁰ due to small number of individuals per category, as opposed to representing an acceptance of the null hypothesis.

It should be acknowledged that the test-set originated from Australian females undergoing screening mammography, and therefore, the diagnostic accuracy of the NS radiologists may in part result from the lack of experience dealing with images from such a cohort of females. Ethnically-dependent variations of breast morphology and density could have contributed to our findings. In addition, this study did not involve NS readers who have more than 5 years' experience in mammographic interpretation; however, this reflects the very limited number of experienced breast radiologists in the country. We should finally acknowledge possible screening group familiarity with BREAST test-sets which may have enhanced diagnostic accuracy.

In summary, mammographic performance of the radiologists in a country which does not employ screening is less good at detecting breast cancer in a test-set than radiologists from Australia. The absence of screening program and the associated educational and quality activities is most like a major contributing factor.

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Chapter 4

“Observer variability in breast cancer diagnosis between countries with and without breast screening”

Study

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4.1 Statement of Authorship

As Co-authors of the paper “Observer variability in Breast Cancer Diagnosis between Countries with and without Breast Screening”, we confirm that Delgermaa Demchig has made the following contributions:

- Conception and design of the research
- Data collection
- Analysis and Interpretation of the findings
- Writing the paper and critical appraisal of content

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Date: 14/06/2018

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4.2 Bridging section for chapter four

Diagnosing breast cancer at its early stage is critical, because effective treatment can be available to stop its progression. As one of the most important decision makers within multidisciplinary team, the radiologists' interpretation plays a vital role in diagnostic pathways. With mammographic screening programs (as well as advances in treatment), the numbers of deaths from breast cancer have been reported to be reduced by up to 40% [1, 2]. However, not all women benefit from mammography due to its reduced ability detecting abnormalities for young women with dense breasts. It is not surprising then a sizable proportion (30%) of breast malignancies are missed (false negatives) during screening examinations [3, 4]. Also, false positives occur commonly, causing unnecessary diagnostic workups, which are costly on several fronts. In consideration of their multifactorial nature, some errors are reviewed as inevitable [5]. However, understanding potential sources of error will enable the development of evidence-based solutions toward decreasing misdiagnoses, which further help to improve patient outcomes.

Although not well-understood, some of the reasons why radiologists fail to diagnose malignancies have been recognised such as characteristics related to the lesion (radiographically subtle – lesion that is difficult to be detected) [6, 7] and patient (high density – BI-RADS category C and D densities) [8, 9] as well as technical factors (positioning and compression) [10]. However, most of the missed cancers are visible when retrospectively reviewed and therefore must undetected or unrecognised, highlighting the importance of better understand reader performance [11, 12]. To date, the majority of current observer investigations have been conducted among

Western countries, where mammographic screening is well established and well maintained with rigorous quality assurance programs. In such countries, quality of radiology education appears to be favourable compared with less developed countries such as Mongolia. Even with such supportive settings, radiologists' miss rates in the West are still high. Unlike Western countries, such supportive system are less available in developing countries such as Mongolia, suggesting high rates of misdiagnoses among radiologists based in less developed nations, where advanced disease presentation occurs frequently and support structures are less available. Nonetheless, little is known about mammographic performance of radiologists among less developed countries including Mongolia.

In order to accurately measure the level of performance for Mongolian radiologists in reading mammograms, we first used a *high* difficulty (HD) image-set, because this was a standard test-set in Australia to measure and monitor mammographic performance of radiologists. However, since results of Mongolian radiologists were far lower than those observed among Australian radiologists and considering the lack of screening practice in Mongolia, image difficulty was then reduced in the second study. This was called the *typical* screening (TS) test-set, since it represented better typical mammographic screening case difficulty. It should be noted that inclusion of the local images could have potential to change the performance of Mongolian radiologists. However as mentioned in the previous chapter, collection of early cancer images from Mongolia remains very difficult.

In the previous study (Chapter 3), mammographic performance for Mongolian radiologists was examined using HD mammograms and was demonstrated to be

relatively lower than that noted for Australian readers. In particular, case and location sensitivities at 54% and 26% respectively were lower than that of not only Australians but also readers from other countries [13, 14]. With limited experience in screening practice, Mongolian readers may have faced challenges in reading high *difficulty* mammograms (since images from BREAST program were used in the previous study), since the country does not have a formal screening program. By acknowledging the absence of a screening program in Mongolia, the next piece of the work was conducted with TS images, which can be less difficult than the previously reported images. The reading scores were then compared between these difficult and typical image-sets to better understand the actual level of performance existing in Mongolia. As used in the previous study, validated design and methods of assessing reader performance were used [15].

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Observer Variability in Breast Cancer Diagnosis between Countries with and without Breast Screening

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Rational and Objectives: Image reporting is a vital component of patient management depending on individual radiologists' performance. Our objective was to explore mammographic diagnostic efficacy in a country where breast cancer screening does not exist.

Materials and Methods: Two mammographic test sets were used: a typical screening (TS) and high-difficulty (HD) test set. Nonscreening (NS) radiologists ($n = 11$) read both test sets, while 52 and 49 screening radiologists read the TS and HD test sets, respectively. The screening radiologists were classified into two groups: a less experienced (LE) group with ≤ 5 years' experience and a more experienced (ME) group with ≥ 5 years' experience.

A Kruskal–Wallis and Tukey–Kramer post hoc test were used to compare reading performance among reader groups, and the Wilcoxon matched pairs tests was used to compare TS and ND test sets for the NS radiologists.

Results: Across the three reader groups, there were significant differences in case sensitivity ($\chi^2 [2] = 9.4, P = .008$), specificity ($\chi^2 [2] = 10.3, P = .006$), location sensitivity ($\chi^2 [2] = 19.8, P < .001$), receiver operating characteristics, area under the curve ($\chi^2 [2] = 19.7, P < .001$) and jack-knife free-response receiver operating characteristics (JAFROCs) ($\chi^2 [2] = 18.1, P < .001$).

NS performance for all measured scores was significantly lower than those for the ME readers ($P < .006$), while only location sensitivity was lower ($\chi^2 [2] = 17.5, P = .026$) for the NS compared to the LE group. No other significant differences were observed.

Conclusion: Large variations in mammographic performance exist between radiologists from screening and nonscreening countries.

Key Words: Breast cancer; mammographic screening; reader performance; observer variability; developing country.

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INTRODUCTION

The incidence of early diagnoses of breast cancer remains low in developing countries (1) due to differences in disease profile, health-care systems, and socioeconomic conditions compared to wealthier countries. For example, more than half of breast cancers in developed countries are detected at stage I, while this figure appears to be approximately 20% among developing nations, where population screening is often not available (2,3). It is well reported that more advanced breast cancers lead to worse outcomes (4); however, this unfavorable prognosis can be effectively mitigated through early detection. It is therefore important for nonscreening (NS) countries (countries with no official breast

cancer screening program) to establish functional and effective strategies to increase early diagnosis of breast cancer.

Mammographic screening (MS) has been confirmed as an effective approach to detecting most breast cancers at a pre-clinical stage and therefore results in mortality reduction (5–7). However, the level of MS implementation among NS countries varies largely (8,9), resulting from limited economic resources, inadequate health infrastructure, and low incidence settings. While an alternative screening method such as clinical breast examination (CBE) has thus been proposed (10), there is insufficient evidence to support CBE as a screening tool (11,12). Indeed, CBE detects cancers when they become palpable, and therefore, treatment and survival outcome is less likely to be favorable than those captured by MS (13). Undoubtedly, MS will be the future of breast cancer prevention among NS countries.

Diagnostic accuracy is critically important in enabling the early detection of breast cancer; however, the level of accuracy remains unknown among NS countries. Interpreting radiologists play an important role in early diagnoses, but unfortunately, errors that have the potential to impact upon subsequent patient management can occur. For example, in developed countries, 30% of all types of radiological examinations and 3%–30% of screening mammograms have not been reported accurately (14,15) due to system and technical factors

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but also reader-based errors (16,17). In developing countries, we have little idea of the extent of radiological error in mammography.

In a previous study by our group (18) focusing on high-difficulty (HD) mammograms, where cancers were missed by at least one of the two radiologists in Australia (in Australia there is a dual-reader strategy for screening), we found that the performance of NS radiologists was substantially lower than both high- and low-experience radiologists based in a country with MS. This is not surprising because there are large differences in health systems, radiology practices, and training between the two countries. Nonetheless, differences seen between the NS and screening populations cannot be generalized to routine mammographic readings because difficult mammograms were employed in the previous study (18). To better understand the actual differences between the two reader populations, it is necessary to use mammograms that represent routine radiological reporting. Once a more realistic appraisal of differences between the two groups of radiologists is available, the type and extent of solutions required to standardize diagnostic efficacy can be explored.

This study therefore aims to explore the level of mammographic diagnostic efficacy in an NS country where breast cancer screening does not exist. As a baseline comparison, the performance of radiologists from a screening country, Australia, where screening exists, will also be recorded.

MATERIALS AND METHODS

The institutional review board approved this study (2016/406). All 112 participating radiologists gave informed consent.

Test Sets

All screening-based mammograms were sourced from the Breast Screen Imaging Library of New South Wales (NSW), and all recorded data were de-identified. The cases were selected by a senior radiologist who works for BreastScreen NSW and has more than 20 years' breast screen reading experience. No diagnostic cases were included in the test sets, and each case comprised craniocaudal and mediolateral projections of both breasts.

During the study period, two reading sessions were conducted, each separated by a 1-year interval, with each reading session using a unique mammographic test set. In total, each test set had 60 mammographic cases including 20 abnormal and 40 normal images. All images containing cancer were biopsy proven, while normal cases were verified by two radiologists who reported independently that these were normal, or they were confirmed to be normal after further diagnostic tests. Normal images were reported by these readers as being completely normal or containing benign appearances such as oil cysts, intramammary lymph nodes, and calcified fibroadenoma.

The two test sets had different levels of difficulty. The first was called the typical screening (TS) test set, and the second was called the HD test set. The TS test set, which was the

main focus of this work, was created with the aim of representing images that would present within a TS environment in Australia. The HD test set is typically used in test-set reader assessment strategies such as BreastScreen Reader Assessment Strategy (BREAST) (19) and was used in our previous study (18).

TS Test Set

The aim of this test set was to create an image grouping that would be typical of a screening environment, where at least 80% of sensitivity was achieved (19). We initially used 180 mammographic cases including 60 cancers from the Breast Screen Imaging Library of NSW that had been used by the BREAST platform and read by 311 radiologists. First, the total number of readers who correctly identified each cancer case was calculated, and those cases correctly identified by more than 80% of the readers were selected, which resulted in 24 cases. These 24 cases were then examined by three breast radiologists, two with more than 20 years and one with 3 years of screen reading experience. Of these cancer cases, 20 were chosen to represent a typical level of difficulty within a screening environment. The cancer lesions were five stellate lesions, three architectural distortions, three stellate/architectural distortions, two nonspecific densities, two discrete masses/calcifications, three speculated masses, and two calcifications. Normal cases ($n = 40$) in this test set were randomly selected and validated as described above.

HD Test Set

This set of images was one of the standard test sets that were designed for assessing and monitoring BreastScreen readers in Australia using the BREAST platform (19). *Difficult* refers to the fact that all cases containing cancers were missed by at least one radiologist at the time of screening (in Australia, two independent radiologists read all screening images) (20). Normal images in this test set were selected randomly from the NSW screening database.

Study Participants

Two observer groups were involved in this work, one from a developing country (the NS country) where mammographic breast screening does not occur and the other from a developed country (Australia) where biennial MS occurs.

It should be acknowledged that medical training for these two countries differ greatly. For example, in the NS country, radiologists have to be a graduate of a 6-year medical university with a subsequent 2-year radiology residency training. This is in contrast to Australia, where, to become a radiologist, one must complete 4–60 years of medical school with a subsequent 5-year postgraduate radiology education. In addition, in Australia, radiology graduates need to have completed an additional subspecialty training in breast imaging to become a breast radiologist, whereas this is not required in the NS.

Details on demographic (age and gender), experience (number of years since radiology qualification; number of years interpreting mammography), and practice (number of hours

TABLE 1. Characteristics of All Radiologists Included in the Study

Reader Parameters	NS Group (n = 11)	LE Screening Group (n = 46)	ME Screening Group (n = 55)
Age	32 (6)	41 (9)	51 (17)
Number of years reading mammograms	0 (3)	2 (5)	15 (10)
Number of hours reading mammograms per week			
≤4	10 [91]	23 [50]	17 [31]
5–15	1 [9]	12 [26]	32 [58]
≥16	0	11 [24]	6 [11]
Number of cases reading mammograms per week			
≤20	9 [82]	21 [46]	13 [24]
21–100	2 [18]	14 [30]	23 [42]
≥101	0	11 [24]	19 [34]
Fellowship training of more than 3 months			
Yes	0	22 [48]	39 [71]
No	11 [100]	24 [52]	16 [29]

Note: Numbers in rounded parentheses represent interquartile range, while those in square parentheses indicate percentage values. LE, less experienced screening radiologists; ME, more experienced screening radiologists.

and number of cases read per week) were obtained using a questionnaire. The participating readers were also asked whether they had been involved in fellowship training in breast imaging consisting of more than 3 months. The characteristics of participating radiologists are shown in Table 1.

THE NS GROUP

A total of 11 radiologists from an NS country were recruited and read both test sets independently during BREAST (19) workshops at the first internationally accredited hospital in the country located in the capital city. These readers were collectively called the NS group because they did not interpret screening mammograms (breast screening does not exist currently in the country). They were affiliated to three medical centers and represented approximately 80% of the total number of breast readers involved in mammographic interpretation nationwide. They had a range of 1–5 years of experience in a diagnostic setting.

THE SCREENING GROUP

In total, 101 readers were involved in the study from a developed country where breast screening was performed, and 52 and 49 radiologists read the TS and HD test sets, respectively. These reading sessions were conducted at BREAST (19) workshops held during the Royal Australian New Zealand

College of Radiologists' scientific meetings between 2013 and 2017. With a frequent interpretation of screening mammograms as part of clinical practices, these readers were denoted as the *screening* group. To match the duration of mammographic interpretation experience with the NS group, screening readers were further subdivided into a less experienced (LE) group with up to 5 years of experience and a more experienced (ME) group with more than 5 years of experience (Table 1).

Test Set Reading

All readings were performed on a pair of five-megapixel medical-grade display monitors that were calibrated using the Digital Imaging and Communication in Medicine Gray Scale Display Function. Of 11 readers, 3 radiologists mostly interpret mammograms using film technology while the rest regularly read full field digital images. The 60 cases were displayed in the same randomized order, and cancer prevalence was unknown for each radiologist, but participants were told that test sets were cancer enriched. A detailed instruction was displayed on the screen at the start of each reading and explained verbally before the experiment began. Postprocessing tools such as zooming and panning were available to each observer, and a time limit was not imposed while reading the test sets. The observers were unable to access prior images.

The observers were able to access the online BREAST platform (19) to record their decisions. They were asked to mark the location of as many lesions as they could identify on each projection and score each location using the following confidence scale: 2 = benign, 3 = equivocal, 4 = suspicious, 5 = malignant. If no lesion was marked, the software automatically rated the case as being normal and gave a score of 1. In radiology, while the Breast Imaging Reporting and Data System is used in the United States, this system is not applicable in the Australian setting, where a different standardized reporting system is being used. Therefore, because the baseline group were Australians, the current study follows the Australian standard in reporting mammograms.

The Performance Metrics

Performance was assessed using the following metrics: case sensitivity, specificity, location sensitivity, receiver operating characteristics (ROCs), area under the curve (AUC), and jack-knife free-response receiver operating characteristics (JAFROCs), figure of merit (FOM). Case sensitivity was defined by the proportion of correctly identified abnormal cases given a confidence score of 3 and more, while specificity was defined by the fraction of correctly identified normal cases given a score of 2 and below. Location sensitivity was defined by the proportion of abnormal cases where location was correctly marked within a 50-pixel radius from the center of the lesion and given a score of 3 and higher.

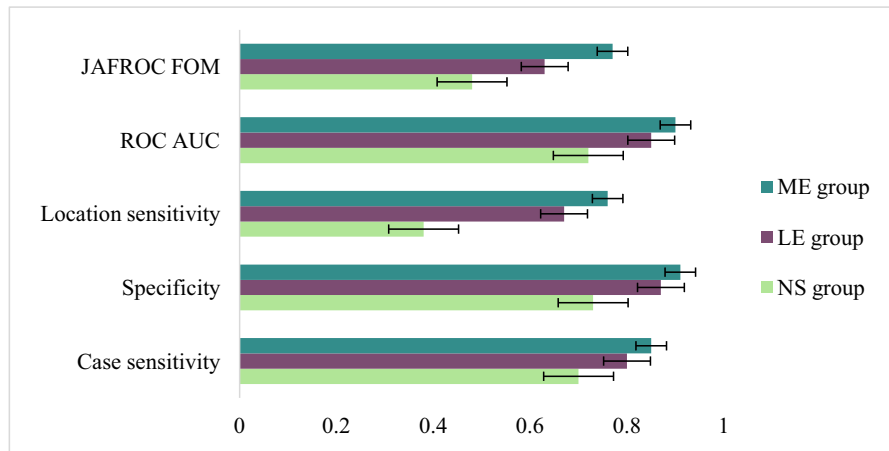


Figure 1. The median performances for each of the three groups of radiologists when reading a typical screening test set.

Data Analyses

Three groups of radiologists were compared using the Kruskal–Wallis test followed by multiple comparisons using the Tukey–Kramer post hoc test. The individual comparisons are shown below:

- NS group vs LE screening group
- NS group vs ME screening group
- LE screening group vs ME screening group.

In addition, because the same NS radiologists read both test sets, the performance of the NS readers were compared between TS and HD test sets using the Wilcoxon matched pairs test to specifically examine if reading a TS test set improved performance levels compared to the previously reported performance values for the HD test set.

In order to explore any association between performance scores and the experiences of each of the three radiologist groups, a nonparametric Spearman test was conducted. The SPSS software (version 22) (IBM, Armonk, NY) was used for all statistical analyses. A difference with a *P* value of equal to or less than .05 was considered a significant finding.

RESULTS

Case sensitivity, specificity, location sensitivity, ROC AUC, and JAFROC FOM were calculated for all three groups of radiologists and are summarized in Figure 1. Across the three groups, there were significant differences in case sensitivity ($\chi^2 [2] = 9.4, P = .008$), specificity ($\chi^2 [2] = 10.3, P = .006$), location sensitivity ($\chi^2 [2] = 19.8, P < .001$), ROC AUC ($\chi^2 [2] = 19.7, P < .001$), and JAFROC ($\chi^2 [2] = 18.1, P < .001$).

The comparison between the NS and LE groups demonstrated that only location sensitivity ($\chi^2 [2] = 17.5, P = .026$) was significantly different while the NS performance in all measured values were significantly lower than those for the ME readers (*P* values are summarized in Table 2). When the two groups of screening readers were compared, only the ROC (AUC) score for the LE group was significantly lower than that for the ME group (Table 2).

TABLE 2. Pairwise Differences between Reader Cohorts across the Three Groups; the Numbers Represent *P* Values

Performance Metrics	NS vs LE Screening Readers	NS vs ME Screening Readers	LE vs ME Screening Readers
Case sensitivity	.153	.006*	.646
Specificity	.429	.006*	.185
Location sensitivity	.026*	<.001*	.14
ROC (AUC)	.132	<.001*	.029*
JAFROC (FOM)	.077	<.001*	.088

* Statistically significant *P* value.

The false-positive (FP) rates were also significantly different ($\chi^2 [2] = 9.6, P = .008$) across the three groups with the highest rate for the NS readers (27.0 ± 13.2), followed by the LE (25.5 ± 27.8) and ME groups (13.2 ± 20.9). When the pairwise comparison was carried out, the FP rate for NS readers were significantly higher ($\chi^2 [2] = 2.9, P = .009$) than that for the ME group but nonsignificant with the rate for the LE group.

In addition, the case sensitivity by the lesion types was also calculated for all three groups and demonstrated in Table 3. Significant differences in speculated mass ($\chi^2 [2] = 8.6, P = .01$) and stellate lesions ($\chi^2 [2] = 12.0, P = .002$) were noted across the three groups. The NS performances in speculated mass ($39.3 \pm 29.0, P = .01$) and stellate lesion ($61.0 \pm 20.3, P = .002$) were significantly lower than that for the ME group but nonsignificant when compared with the LE performance (Table 3).

When the performance of the NS group was compared between the HD and TS test sets, no significant changes were observed in any of the measured scores (Table 4).

No associations were found between reader characteristics and performance metrics in any of the three groups of radiologists.

DISCUSSION

Reduced diagnostic accuracy can result in delayed diagnoses. This study aimed to identify possible differences in screening

TABLE 3. Case Sensitivity by Lesion Type in the TS Test Set among Three Groups

Lesion Types	NS Group (n = 11)	LE Screening Group (n = 19)	ME Screening Group (n = 30)	P value
Architectural distortion/stellate	84.8 (17.4)	84.2 (23.2)	90.0 (17.4)	.372
Nonspecific density	72.7 (41.0)	81.5 (29.8)	86.6 (22.5)	.661
Architectural distortion	66.6 (29.8)	77.1 (29.5)	83.3 (22.7)	.201
Stellate lesion	61.0 (20.3)	74.4 (26.0)	88.0 (12.5)	.002*
Discrete mass/calcifications	59.0 (43.7)	68.4 (41.5)	73.3 (28.4)	.687
Calcifications	59.0 (37.5)	73.8 (33.9)	71.6 (34.0)	.491
Speculated mass	39.3 (29.0)	64.8 (36.0)	73.3 (28.2)	.013*

Numbers in parenthesis are standard deviations.

* Statistically significant P values (NS vs ME groups).

LE, less experienced; ME, more experienced; NS, nonscreening.

TABLE 4. The Performance Metrics of the NS Group in TS and HD Test Sets

Performance Metrics	TS Median (IQR)	HD Median (IQR)
Case sensitivity	0.7 (0.12)	0.57 (0.07)
Specificity	0.73 (0.14)	0.83 (0.1)
Location sensitivity	0.38 (0.21)	0.31 (0.3)
ROC (AUC)	0.72 (0.13)	0.77 (0.06)
JAFROC (FOM)	0.48 (0.14)	0.46 (0.07)

Note: None of the comparisons were statistically significant.

IQR, interquartile range; JAFROC (FOM), Jack-knife Free-response receiver operating characteristics, figure of merit; ROC (AUC), receiver operating characteristics, area under the curve.

performance between the NS readers from a developing country and the screening readers from a developed country using a TS test set. The previous study with an HD test set had indicated that the performance of the NS readers was relatively lower than both expert and nonexpert groups of readers, and therefore, this study aimed to identify possible changes in the performance of the NS radiologists between the HD and TS image sets. The data demonstrated that even with a more typical test set, performance measures arising from the NS group were significantly lower than those for the ME screening group, while location sensitivity was lower than that of the LE screening group. Importantly, NS performance was not shown to be improved with the TS test set compared with the HD test set, reinforcing the conclusion of the previous study that a low level of performance exists for these NS radiologists.

The persistently low level of performance of the NS radiologists with those that screen read regularly can be explained to some extent by expertise level. When expert readers interpret an image, a holistic response initiates and directs an ensuing visual fixation of potential abnormalities (21). However, with the NS radiologists, 63% and 34% in case and location sensitivities, respectively, averaged across both test sets would suggest that this expert sequence of events is not occurring. Specifically, the ability to extract sufficient information from an initial global impression requires having a firm understanding of normal imaging finding so that abnormal features

trigger a useful response. This type of expertise requires substantial experience that can only be established through minimum annual readings facilitated by an active screening program (22,23). While effective training and ongoing clinical practice can develop these skills, in the country where the NS radiologists were recruited, it is difficult to achieve proper knowledge and skills under the current 2-year radiology residency program, which does not include a subspecialty training in breast imaging. This is in contrast to the 5 years of training program in many other countries (24,25), where better performance of readers has been reported (26).

Another important finding of our study was the FP rates for NS readers, which were significantly higher (27%) than that for the ME screening group (13%), when reading the TS test set. This finding is not surprising because Australia employs a well-established screening protocol with double reading, which can potentially influence the numbers of FPs, whereas this does not happen in the NS country. It should also be acknowledged that there are no practice guidelines on recall rates in the NS country, and therefore, the NS reader may feel less restricted about recalling patients unnecessarily compared to elsewhere.

In terms of lesion types that were missed, the NS readers also demonstrated lower sensitivity in detecting all types of lesions in the TS test set than the two groups of screening readers. Specifically, their performance in detecting speculated mass (39%) and stellate lesions (61%) were significantly lower than that for the ME group. It is important to note that the lesions included in the test set were selected from small and subtle findings, and in the NS country, the expectations in reporting mammograms are different from those in Australia. For example, in the NS country, a small number of patients is expected to have cancer, and therefore, radiologists have a tendency not to recall women with a small lesion but rather to put them on the list of regular monitoring. Therefore, early cancer findings such as stellate and small speculated mass lesions may not be familiar and interpretable among radiologists from the NS country, highlighting the need for dedicated training to encourage best practice.

The underperformance of the NS radiologists may also be linked to other factors. These individuals may have a high

decision threshold when declaring the presence of abnormality due to the very low prevalence of breast cancer in the country (27); therefore, cancer cases may have to be quite obvious to be declared as abnormalities. This would explain both (low) sensitivity and (high) specificity results, a hypothesis supported by a number of cognitive physiology studies (28,29) showing the association between a high miss rate and a low probability of a target being present. However, it is important to note that this hypothesis may not be supported by recent radiologist-based studies, including those by our own group (30,31).

Based on the potential reasons for error, educational initiatives may be the best solution for improving individual performance because the low prevalence setting does not encourage such skills. For example, a dedicated training program that includes a high number of abnormal images may ameliorate the prevalence impact (32). Even within a relatively high prevalence setting, it can be difficult to develop reading skills in screening due to the low absolute number of cancers that present among the screening population. Therefore, Australia and UK have provided successful and effective educational platforms known as the BREAST and PERsonal perFORmance in mammographic screening to assess and improve individual performance (32,33). For example, radiologists who regularly read BREAST image sets have demonstrated improved performance in cancer detection (32), suggesting that the adoption of this type of activity in NS locations may help to improve the NS radiologists' performance.

This study has several limitations. As the focus was on comparing the performance of NS radiologists between two test sets, the study was not designed to enable an understanding of the possible effect of different image sets or different reader groups on performance. Also it is possible that due to insufficient power with our arguably small sample sizes (34), we were not able to observe any relationship between reader parameters and performance metrics, although previous workers (26,35) did demonstrate links between factors such as reader volume and diagnostic efficacy. Nevertheless, our NS readers represent 80% of the breast readers nationwide. We should finally acknowledge that our images were sourced from Australia, and therefore, the NS radiologists may lack experience in dealing with such a specific cohort of women.

In conclusion, these data provide more evidence that there is a substantial variation in diagnostic performance between readers from NS and screening countries. This suggests the need for initiating a strategic solution in these countries in order to maximize the detection of early breast cancers.

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Chapter 5

“Mammographic appearances in Mongolia: causal factors for varying densities”

Study

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5.1 Statement of Authorship

As Co-authors of the paper “Mammographic appearances in Mongolia: Causal Factors for Varying Densities”, we confirm that Delgermaa Demchig has made the following contributions:

- Conception and design of the research
- Data collection
- Analysis and Interpretation of the findings
- Writing the paper and critical appraisal of content

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Date: 14/06/2018

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5.2 Bridging section for chapter five

Mammographic breast density (MD) is a major risk factor for breast cancer. This term refers to the appearance in combination of epithelial, stromal and collagen components of breast on mammograms. Since its first recognition as a risk factor in 1976, MD has been extensively investigated and its causative link to breast cancer has been reported with varying level up to 6.0 times, when women with highest and lowest MD were compared [1-3]. In addition, mammographic sensitivity varies between 80-93% for women with low MD and 30-70% for those with high MD [4-6]. The importance of MD is twofold. Firstly, as high MD means greater amounts of epithelial and stromal tissue elements, where most breast cancers develop, the chances of having the disease is greater for women with high MD than low MD women [7]. Secondly, it is difficult to examine breast tissue details for women with high MD due to lack of contrast between dense and malignant area on mammograms. This is called the “masking effect” which contributes to delayed diagnoses of breast cancer [8, 9]. Since high MD obscures appearance of cancerous tissues on mammograms, incidence of interval cancers (cancers detected following a negative screening mammography) is higher among high MD population compared with low MD women [10-12]. This effect can also be illustrated with a recent fact that 81% of ultrasound detected cancers were not seen on mammograms [13].

As MD is an important feature in clinical practice, assessment methods should be robust and accurate. To date, varying methods have been used in clinical and research settings including qualitative (radiologists’ visual estimation) and quantitative (computer software) approaches [14]. However, no such methods are

credited as a standard tool for measuring MD, since limitations have been consistently reported. For example, a number of computer software have been proposed to objectively measure MD based on volume of breast tissue such as Quantra™ and Volpara™, however, their clinical use has not yet been proved and therefore, although subjective, breast imaging reporting and data system (BI-RADS) remains the most clinically used tool. BI-RADS has 4 grades: A-almost entirely fatty and B-scattered fibroglandular densities are combined for low MD, C-heterogeneously dense, which may obscure detection of small masses and D-extremely dense which lowers mammographic sensitivity, which together represent high MD.

The impact of high MD on radiologists' performance has been investigated with inconsistent results. Whilst most (film-based) literature has shown that high MD contributes to reduced accuracy of radiologists [6, 15], some recent studies demonstrated alternative findings [16, 17]. For example, Al Mousa et al., demonstrated the positive association between high MD and increased cancer detection of experienced radiologists [18]. With the increased awareness of the association between MD and risk for breast cancer, radiologists demonstrated increased attention and scrutiny of high density breasts and therefore cancers were located more effectively with the assistance of windowing, levelling and zooming functions available with digital technology but not with film-screen based technologies [18]. It is generally believed that the sensitivity of mammography decreases with increased breast density, high density being not uncommon (approximately 50%) among general population, raising the concern of MS implementation [19]. Some authors [20] suggest that the first round of screening

mammography should allow an evaluation of density status and then those women recognised as having high MD (high risk) maybe recommended for alternative screening pathways since mammography may have reduced benefit.

In this thesis's previous two studies, the low performance of Mongolian radiologists was documented. Since high MD is a key determinant for mammographic sensitivity, it is very important to understand better the distribution of MD amongst Mongolian women thus ensuring we provide the best pathways for early detection. Nonetheless, information about density remains less clear for women in Mongolia. Therefore in this chapter, the distribution of MD was examined in relation to age, body mass index and area of residency amongst a reasonably large number of women (n=1985) from the National Cancer Centre of Mongolia (NCC).

The first effort to identify MD in Mongolia was conducted by Dr Ramish A., (2009) involving 150 health women using Wolfe categories of density. In this unpublished study, number of readers, validation of breast density scores and reader experience were unclear. More importantly, determinant factors for MD variations including body size and socioeconomic status were not considered, which is significant factors when investigating MD. To better understand MD among Mongolian women, it is therefore essential to characterize MD along with its influential factors, which will further help to understand optimum imaging method for breast cancer screening.

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RESEARCH ARTICLE

Mammographic Appearances in Mongolia: Causal Factors for Varying Densities

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Abstract

Objective: Mammographic density (MD) is a significant risk factor for breast cancer and an important determinant for establishing efficiency of any screening program. Currently, the distribution and influential factors of MD is unknown among Mongolian women. This work aims to characterize MD of Mongolian women. **Methods:** The ethical approval was obtained from Research Ethics Board of the University of Sydney (2014/973) and National Ethic Committee from Ministry of Mongolia (2015/04). We recruited 1985 women aged 16-83 from the National Cancer Center in Mongolia for whom MD and age of each woman was known. From this total group, 983 women also had additional available details on height, weight, body mass index (BMI) and area of residency. We investigated the association of each of these variables with breast density, which was assessed by using the Breast Imaging Reporting and Data System (BIRADS) lexicon. Univariate and multivariate regression analyses were conducted to explore the importance of these variables as predictors of MD. **Results:** Category B (33%) was the most common type of MD, whereas 25%, 18% and 24% of women belonged to the category A, C and D respectively. The univariate analysis demonstrated that, younger women had more dense breasts than their older counterparts (OR=6.8). Also, increased MD was significantly ($p<0.05$) associated with decreased weight (OR=4.5), increased height (OR=0.4) and lower BMI (OR=13.2). Urban women had significantly higher MD compared with rural counterparts (OR=2.2). In the multivariate analysis, 75% of variation in MD was explained by age (OR=4.5) and BMI (OR=7.3). **Conclusion:** A high proportion of Mongolian women have very high density breasts and age and body size are key factors determining MD among these women.

Keywords: Breast cancer- mammographic density- Mongolia

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Introduction

Among women in the world, breast cancer remains the most commonly diagnosed cancer. The breast cancer incidence (age standardized rate, ASR) was reported in Mongolia as 6.0 per 100,000 women in 2013 (Breast cancer statistics 2009-2013, NCC, Mongolia). This measure, whilst relatively low compared with other countries, has been rapidly increasing on an annual basis (Troisi et al., 2012) and between 2009 and 2013, the number of new cases of breast cancer more than doubled. In addition, approximately 90% of breast cancer patients in Mongolia are diagnosed at a relatively late stage, resulting in a high mortality rate.

Many risk factors have been reported to be associated with breast cancer in the westernized world and these include family history, lifestyle activity and hormonal factors. However, in recent years, it is increasingly recognized that mammographic density (MD) is a critically important determinant. Previous authors have linked high density with up to 6 times higher risk of

breast cancer resulting in a plethora of research around causal factors of, or associations with MD (McCormack and Silva, 2006; Boyd et al., 2007). Researchers have also linked increased breast density to the aggressiveness of tumors particularly for younger women (Bertrand et al., 2013). Despite all this increasing evidence around density, in Mongolia we know little about MD. It is not known for example what is the distribution of density within Mongolian women, we have no data associated to risk factors and we do not understand the influence of age and body size measures. Without this information, it is difficult to optimize preventative strategies for breast cancer in Mongolia.

It has also been argued that increased MD can hinder the visualization of breast cancer by obscuring underlying abnormalities, which contributes to reduction in the sensitivity of screening mammography and therefore affect optimum imaging protocols (Freer, 2015). Currently, routine screening mammography is not established in Mongolia. The breast screening guidelines in Mongolia have to date not included details on modality

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choice, instead focusing on breast self-assessment and clinical breast examination. These guidelines however are of limited value since only one in three women undergo breast self-assessment and only 3.2% have experienced clinical breast examination as reported in a recent WHO review (WHO, 2013). Whilst mammographic screening reduces mortality by 15% to 32 % in western countries (AIHW, 2014; Pace and Keating, 2014) there is no evidence that systems used elsewhere would be effective in Mongolia. There is urgency therefore, to identify density distributions among Mongolian women so that more sophisticated and relevant screening approach are employed, facilitating early detection and intervention in the disease.

Breast density can be assessed by various qualitative and quantitative methods, involving mostly mammography. To date, there is no standard for density assessment however, the Breast Imaging-Reporting and Data System (BIRADS) is the most common method in clinical practice (Sickles et al., 2013), and the only method in Mongolia used to report breast density. The objectives of the current study are therefore to identify the density distribution among Mongolian women using BIRADS density categories to establish the relationship between density and women's age and body size and to explore differences in MD between urban and rural areas of Mongolia.

Materials and Methods

The ethical approval was obtained from Research Ethics Board of the University of Sydney (2014/973) and National Ethic Committee from Ministry of Mongolia (2015/04).

Sample size

This cross-sectional study was based on digital mammograms from 1985 women aged 16-83, who underwent mostly diagnostic mammography at the National Cancer Center (NCC) in Mongolia between September 2014 and September 2015. We randomly collected all available images for which two standard views were accessible. Otherwise, no selection criteria were applied for data collection.

From the total group, 983 women also had available details on height, weight and body mass index (BMI)

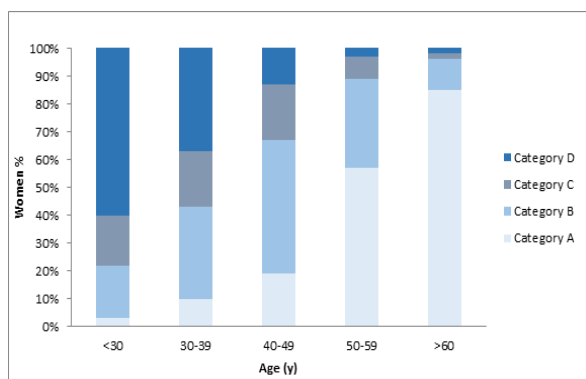


Figure 1. Frequency of Women Allocated to One of the Four Breast Density Grouping According to Age Group (n=1985).

which were obtained from the hospital registry. The area of residency was also recorded for these women and women are allocated to the following grouping: Ulaanbaatar-UB (urban, capital city) and non-UB (rural) groupings.

Breast density by Radiologists

The evaluation of breast density was determined by an experienced breast radiologist and validated with density reading from three breast radiologists who independently examined a random sample of 400 of the total number of cases. Absolute agreement was used as a measure of overall agreement between radiologists and a high inter rater reliability was found between the three radiologists.

Each mammogram was evaluated according to BIRADS density categories A-D (Sickles EA et al., 2013): Category a – almost entirely fatty; Category b- scattered areas of fibroglanduar density; Category c- heterogeneously density; Category d- extremely dense.

Statistical analysis

Logistic regression analysis was used to explore univariate and multivariate associations between dichotomized MD (categories a and b as low vs c and d as high densities) and independent variables age, weight, height, BMI and geographical location. Odds ratio (ORs) and confidence intervals (95% CIs) were estimated. All analyses were performed using SPSS software (version 22.0). A p value of less that 0.05 was considered as significant.

Results

The mean age of the 1985 Mongolian women examined was 40.55 (±11.8) years with a range of 16-83 years. Whilst category B (33% of women) was the most common type of MD, 25%, 18% and 24% of women belonged to the category A, C and D respectively.

The investigated variables were available for 983 women and table 1 demonstrates the summary characteristics of the study sample on all parameters

Table 1. The Baseline Characteristics of the Study Population (n=983)

Variables	BIRADS ^a density			
	Category A	Category B	Category C	Category D
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Age (years)				
Mean ± SD	52±10.5	41.6±9.0	37.4±8.8	32±7.5
Weight (kg)				
Mean ± SD	71.8±14.2	66.0±10.7	62.3±9.2	56.8±8.4
Height (m)				
Mean ± SD	1.57±0.06	1.59±0.06	1.61±0.07	1.6±0.05
BMI ^b (kg/m ²)				
Mean ± SD	35.9±6.4	31.3±4.9	28.9±4.4	26.3±3.9
Area of residency (N%)				
Urban	197 (82)	289 (90)	146 (92)	250 (94)
Rural	44 (18)	30 (10)	12 (8)	15 (6)

^a, BIRADS: Breast Imaging and reporting system, 2013; ^b, BMI: Body mass index

Table 2. The Association between MD and the Factors

Variables	Univariate OR 95%CI	Multivariate OR 95%CI
Age (n=1985)		
<40	6.8 (5.5-8.3)*	
>40	1	
Age (n=983)		
<40	7.3 (5.4-9.8)*	4.5 (3.4-6.2)*
>40	1	1
Weight (kg)		
<64	4.5 (3.4-6.0)*	
>64	1	
Height (m)		
<1.6	0.43 (0.3-0.6)*	
>1.6	1	
BMI ^a (kg/m ²)		
Normal	13.2 (8.6-20.0)*	7.3 (4.6-11.5)*
Overweight	5.1 (3.8-7.0)*	3.6 (2.6-5.0)*
Obese	1	1
Area of residency		
Urban (UB)	2.2 (1.4-3.5)*	1.5 (0.9-2.5) ^a
Rural (non-UB)	1	

^a, Body mass index; *p<0.05; ^ap, 0.12

examined.

Univariate analysis

Age

The overall age distribution of MD was examined for 1985 women. Figure 1 demonstrates the age distribution of four categories of BIRADS according to five age

Table 3. Age and BMI Distribution by Area of Residency

Variables	Area of residency	
	Urban N (%)	Rural N (%)
Age (years)	<40	484 (55)
	>40	37 (37)
Mean ± SD	398 (45)	64 (63)
BMI ^a (kg/m ²)	Normal	40.0 (11.4)
	Overweight	45.0 (12.5)
	Obese	156 (18)
Mean ± SD	327 (37)	23 (23)
	399 (45)	65 (64)
	30.3 (6.0)	32.3 (6.0)

^a, Body mass index

groups. The frequency of extremely dense breast (category D) was the largest (60%) among the youngest age group, consistently declining as age increases and reaching its lowest point (2%) among women in the oldest age groups. The two oldest age groups contained the highest number of women with fatty breasts (Figure 1).

The association between MD and age was explored for all 1985 women along with a separate estimation for 983 women. Since only a small number of women belonged to the high density categories among older ages, women were then grouped into two groups (below and above 40 years old) to identify the relationship between age and dichotomized MD. Table 2 shows the univariate and multivariate associations between MD and all the factors examined. Age was shown to be an important predictor for MD; a significantly increased risk of having higher dense breasts noted for women aged below 40 years old, compared with women aged above 40 years old.

Table 4. Distribution and Association of MD and Investigated Factors

Variables	Age < 40 (N%)			Age > 40 (N%)		
	Low density	High density	OR (95% CI)	Low density	High density	OR (95% CI)
Weight (kg)						
>64	95 (60)	63 (40)	1	234 (86)	39 (14)	1
<64	93 (26)	270 (74)	4.3	137 (73)	51 (27)	2.2
Height (m)						
>1.6	92 (33)	185 (97)	1	127 (75)	43 (25)	1
<1.6	96 (40)	148 (60)	0.7	245 (84)	47 (16)	0.5
			(0.5, 1.0)			(0.3, 0.9)*
BMI ^a (kg/m ²)						
Obese	88 (65)	48 (35)	1	265 (88)	35 (12)	1
Overweight	64 (30)	147 (70)	4.2	88 (72)	35 (28)	3
			(2.6, 6.6)*			(1.7, 5.1)*
Normal	36 (21)	138 (79)	7	16 (47)	18 (53)	8.5
			(4.2, 11.6)*			(3.9, 18.2)*
Area of residency						
Rural (non-UB)	18 (47)	20 (53)	1	57 (88)	8 (12)	1
Urban (UB)	170 (35)	313 (65)	0.6	315 (79)	82 (21)	0.5
			(0.3, 1.2) ¹			(0.2, 1.1) ²

^a Body mass index; *p<0.05; ¹ p, 0.14; ² p, 0.12

Weight, height and BMI

Body size data were available for 983 women. The mean weight was 57.0 kg (± 8.4) and 72.0 kg (± 14.2) for extremely dense and almost fatty categories respectively (Table 1). The mean height was 1.59 m (± 0.06) and was similar across four density groupings. Majority of women (83%) were classified in the overweight and obese groupings whereas 17% of women grouped in normal BMI category.

Associations were found between MD and body size measurements (Table 2). Increased risk of having high MD was significantly ($p < 0.05$) associated with decreased weight (OR=4.5, 95% CI: 3.4, 6.0), increased height (OR=0.43, 95% CI: 0.3, 0.6) and decreased BMI (OR=13.2, 95% CI: 8.6, 20.0).

Area of residency

Table 3 demonstrates the age and BMI distribution by area of residency. In total 882 and 101 women were allocated to UB and non-UB groupings respectively with UB residents having significantly (OR=2.2, 95% CI: 1.4, 3.5 $p < 0.05$) higher density breasts than non-UB residents, however, the association was not significant after controlling for age and BMI (Table 2). Since the Non-UB women came from across the country, these were then further classified by geographical locations, but no statistical differences were noted between north vs south ($p = 0.56$) nor east vs west ($p = 0.92$) regions of Mongolia.

Distribution and determinant of MD within women of different age categories

To identify the differences in determinant factors of MD, women over ($n = 462$) and under 40 ($n = 522$) years old were compared (Table 4). For the young women, the magnitude of odd ratios for some factors were different for the two groups of women. This is summarized in table 4.

Multivariate analysis

Multivariate logistic regression model was built to explore the relative importance of the dichotomous variables of age, area of residency and BMI as predictors of MD, dichotomized into high and low density.

In the full model, 76% of variation in MD was explained by the measured risk factors. After entering age, BMI and area of residency into a regression model, age (OR=4.5, 95% CI: 3.4-6.2), BMI (OR=7.3, 95% CI: 4.6-11.5) were the significant predictors for MD whilst area of residency did not contribute to the model (Table 2).

Discussion

The current study was carried out to explore variations of mammographic density (MD) among Mongolian women using the fifth edition of BI-RADS lexicon. The results demonstrated interesting patterns of MD and statistically significant relationships between MD and age, body size and area of residency.

Although density values were almost equally distributed between low and high density groupings, we expected to observe predominantly low density mammographic appearance since the majority of women

in our study have much greater BMI compared with those described by the previous studies (Dai et al., 2014). However, a large proportion (24%) of women in our study was classified as having an extremely dense pattern (BI-RADS category D) compared with 7.4% and 8.6% in USA and China respectively (Dai et al., 2014; Sprague et al., 2014) which could be linked to our age profile (see below). In general, Asian women have consistently been reported to have higher density than other ethnic populations (del Carmen et al., 2007; Mariapun et al., 2015) yet, the amount of women within the highest density category was unusually higher than that described for these other countries. Conversely, the overall proportion of high density (BI-RADS categories C and D) within the age groups was lower than those reported in other ethnic populations (Kim et al., 2000; Sprague et al., 2014), suggesting a paucity of category C women. In particular, high density (C and D) was described for 31% of women in our study between the ages of 40 to 49 years old whilst this value was approximately 74% in USA and 80% in Korea for the same age category (Checka et al., 2012; Youn et al., 2016). The variation may be due to differences in the studies samples however the influence of geographical location cannot be ruled out.

We examined age and body size, as two main determinants of MD. In agreement with other studies (McCormack and Silva, 2006; Checka et al., 2012), an overall inverse association between age and MD was identified, however age-density relationship was very clear in our study with under 40 year olds having 6 times higher density than over 40 year olds. It should be acknowledged that the mean age for women in our study is younger than that generally examined elsewhere in previous Western and Asian studies (Ellison-Loschmann et al., 2013; Youn et al., 2016). For example, the magnitude of our finding was greater than the odds ratio of 2 described in a recent Japanese study (Kawahara et al., 2013), however this latter comparison was for women under compared with over 45 year olds. Nonetheless, other causal factors for this large age-dependent change need to be considered. Firstly, the statistical method we employed could be a factor: unlike some of the previous work in our study, age was treated as a categorical variable which tends to provide systematically higher odds ratio (Lovasi et al., 2012) and although, odd ratios do not accurately characterize individuals' risk (Pepe et al., 2004), as a method to identify the population risks, our approach is valid and has been used in numerous studies elsewhere. Secondly, this finding may actually be unique for Mongolian women. To our knowledge, this preliminary work is the first study regarding breast density in a large sample of Mongolian women, however, important factors of breast density peculiar to Mongolia such as lifestyle and reproductive factors (which were not available to us) need to be explored if we are to better understand causal agents for specific temporal and spatial density patterns and distributions.

A greater weight and BMI were associated with lower MDs in our study which aligns well with the existing evidence across many populations (Boyd et al., 2006; Sung et al., 2010). However, consistent with some but

not all previous studies (Sellers et al., 2007; Boyd et al., 2009; Dorgan et al., 2012), height showed a weak but significant association with MD. Whilst less is known regarding the relationship between this latter measure and breast density, some authors have investigated possible associations and a direct relationship between the height in childhood and young adulthood and density has been previously shown (Dorgan et al., 2012; Andersen et al., 2014). Specifically, two studies (Boyd et al., 2009; Dorgan et al., 2012) focusing on young women (15 to 30 years old), demonstrated a significant height density association which aligns reasonably well to the current paper particularly since the majority of women in our study were below 40 years old. The physiological mechanism underlying this association is unclear, however factors associated with breast development in early life such as increased growth hormone may mediate this association (Dorgan et al., 2012). The interaction between height of older adults and MD has not been previously investigated. We also compared women over and below 40 years old to identify any differences in determinant factors of MD and some subtle differences were noted, particularly related to patient weight.

Geographical location appears to be an important indicator of variation in breast density. The present study provides evidence that women living in urban areas (Ulaanbaatar-UB) have higher MD than rural (non UB) women, although no differences was found within rural parts of Mongolia. This aligns with several studies which found positive associations between urbanization and breast density (Viel and Rymzhanova, 2012; Emaus et al., 2014; van der Waal et al., 2015), the authors of which suggested that exposure to increased socio-economic status (SES) was at least in part responsible. Similarly, our data suggest that SES is an important causal agent since UB women tend to be more educated and more willing to adopt westernized culture than their rural counterparts (Dickson, 2012). In addition, as shown elsewhere, reproductive factors are probably contributing to this location discrepancy, since urban mothers are two times less likely to breastfeed for longer than 6 months compared to rural mothers in Mongolia (Dickson, 2012). However, the location density association shown in the univariate analysis was not significant after controlling for age and body size. We should acknowledge that our study participants consisted mainly of urban women (90%) which may have impacted on the results.

The main limitation of this study was the unavailability of information on important determinants of MD. For example, we were unable to collect comprehensive data on reproductive and lifestyle factors, all of which would have provided more thorough understanding of breast density risk factors. It could also be argued that BIRADS density assessment is an imperfect method since high rates of inter radiologist variability have been previously reported, however, this measure is the most widely used and accepted method in clinical practices and the only method to assess density used in Mongolia. Furthermore, we successfully validated our BIRADS scores in a subset of 400 women with three breast radiologists demonstrating high inter-rater reliability. On a positive note, this study has

for the first time systematically examined mammographic density patterns among Mongolian women and since our study population was gathered from the National Cancer Center, the only cancer center in Mongolia, we can be fairly sure that most types of Mongolian women have been reasonably represented.

In conclusion, this work has shown that age, body size and geographical location are key determinants of breast density among Mongolian women. The data from the work should be valuable to those health strategists exploring effective screening programs, however the link between breast density and breast cancer risk amongst this population of women needs first to be established and quantified.

Conflict of interest

The authors declare no potential conflicts of interest.

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Chapter 6

Discussion

6.1 An overview of the thesis

Breast cancer is the most prevalent cancer for females globally. Early-detected breast cancer enables effective treatment and therefore better patient outcomes are achievable. Amongst our early detection tools, mammographic screening (MS) is proven to be the most effective, reducing breast cancer mortality by up to 40% [1-3]. In developed nations, with the implementation of organised MS programs, breast cancer diagnoses have been transformed from a high proportion of advanced cancers to large numbers of early cancers such as DCIS [4, 5]. The reduction in the incidence of late stage diagnoses (T2 to T4) in Italy, for example, was shown from the 3rd year of implementation of MS program and to be as high as 20-30% by the eighth year [6]. Unfortunately, the majority of breast cancer patients in developing countries such as Mongolia where MS is currently unavailable are being diagnosed at late stages of the disease [7]. Also, incidence rates among developing countries are on the rise, whilst this figure remains stable in developed countries. It is therefore important for developing countries to identify an effective but affordable strategy for early detection of breast cancer particularly when self and clinical examinations have not been proven to reduce mortality and are considered inadequate as a screening tool [1].

Although, the incidence rate for breast cancer in Mongolia appears to be low when compared globally, the large proportion (90%) of advanced diagnoses along with a consistent increase of incidence highlight the need to initiate early detection strategies [8, 9]. The increase in incidence rate of breast cancer in Mongolia has also been previously noticed between 1998 and 2005 [8]. However, consistent increase in

incidence rate of breast cancer in Mongolia may not be significant, since we observed the data covering short period of time between 2009 and 2013. This may be caused by the natural fluctuation of the short-term data and therefore long period of observation is necessary. As a country with limited economic and health care resources, starting an organised MS program is currently unrealistic in Mongolia but tailored MS, targeting high risk women may help to decrease delayed diagnoses, particularly since mammographic facilities operate in the country. However the effectiveness of mammography is unknown in Mongolia, particularly since the density characteristics of Mongolian women are poorly understood. As mammography is the front-line tool for breast cancer diagnoses, its accuracy is critically important. However, detecting breast lesions on a mammogram is a challenging task for radiologists and therefore approximately 30% of cancers are not reported during screening examinations [10]. On the other hand, mammographic breast density (MD) is a strong and independent risk factor for breast cancer and a key determinant for mammographic efficacy. Unfortunately, information around radiologist efficacy or mammographic density is unavailable in Mongolia. Without this information, mammographic efficacy will remain unclear, which will likely to contribute to poor patient outcomes in Mongolia.

This PhD thesis, to our knowledge, is the first study that was specifically designed to provide specific information that would help in establishing a screening program in Mongolia, particularly by investigating interpretive accuracy of radiologists in reading mammograms and characteristics of MD. With this information, we will be able to understand the effectiveness of mammography in Mongolia which will further help to optimize screening approaches specific to these women.

The objectives of this study are:

- 1) To publish a literature review in an international peer-reviewed journal to identify the overall status of breast cancer in Mongolia in terms of incidence, mortality, survival features along with information of risk factors and breast cancer screening;
- 2) To investigate radiologists' accuracy in reading screening mammograms using two different test-sets with deliberately different levels of difficulty;
- 3) To examine the distribution of MD for Mongolian women and its relationship with age, body mass index and area of residency using the density categories of BI-RADS 5th edition.

By involving over 80% of national breast readers and a large number of mammograms (n=1985) for MD evaluation, the current thesis provides new knowledge around mammographic diagnostic accuracy and MD features in Mongolia. In chapter 3 and 4, the performance of the Mongolian radiologists in reading mammograms was assessed using a standard mammographic test-set (BREAST [11]). The Australia based initiative, BREAST [11] is a well-known platform for testing radiologists' performance not only in Australia but also internationally such as Vietnam, Singapore, Iran, Italy and Jordan. These two studies provided a detailed understanding of radiologists' diagnostic accuracy in reading mammograms in Mongolia.

In other to accurately measure the level of performance, we first used the *difficult* image-set (chapter 3), because this was a standard test-set in Australia and New-Zealand to measure and monitor mammographic performance of radiologists and this was called the *high difficulty* (HD) test-set. These images were sourced from the Australian screening images by specifically including mammograms with early cancer findings such as stellates and architectural distortions that were missed by one radiologist. In Australia, double reading strategy applies for breast screening programs and a third reader is involved when two readers disagree in their decision.

However, since results of Mongolian radiologists were far lower than those observed among Australian radiologists and considering the lack of screening practice in Mongolia and difficulty of the images used in the previous study, we then decided to reduce image difficulty in the second study. This was called the *typical screening* (TS) test-set (chapter 4), since we feel it represented better typical mammographic screening case difficulty. Unlike the HD test-set, cancer image difficulty was reduced in the TS test-set by only including the images with more than 80% sensitivity scores which was based on the performance data of 311 Australian readers. Normal images in this test-set were randomly selected from the normal image bank which was previously proven to be cancer free and re-validated by three radiologists to be represent as typical normal images within the screening environment.

In chapter 5, MD was explored for Mongolian women and mammograms were collected from the National Cancer Centre of Mongolia (NCC). For the MD assessment, the 5th edition of breast imaging reporting and data system (BI-RADS)

categories were used [12]. This study was performed in a geographically diverse population within the country, since the NCC is the only cancer institution nationwide and generalizability of the study is therefore fairly reasonable. Although the BI-RADS density assessment is a subjective method, it is currently the most commonly used approach amongst radiologists. In the present study, breast density was assessed by the experienced radiologist with more than three years of screen reading experience in Australia. To validate density assessment of the radiologist, the three breast radiologists from both Mongolia and Australia read a sub-set of 400 mammograms and a high inter-rater reliability (ICC=0.91, 95% CI: 0.90-0.93) was found between these readers. In addition, age; BMI and area of residency, which are the important predictors for MD, were examined along with MD.

6.2 Significant findings

The thesis set out to explore mammographic diagnostic accuracy and characteristics of MD that would help in establishing of a breast-screening program in Mongolia. The objectives listed earlier were achieved. First, the literature review was published in *Breast Cancer: Targets and Therapy* (a peer-reviewed journal) which identified the epidemiological characteristics of breast cancer in Mongolia and the differences between the Asian and Westernised world [13]. It became evident from the literature review that advanced disease presentation played an essential role in reducing good patient outcomes whilst the incidence of breast cancer is consistently increasing in Mongolia.

Second, radiologists' accuracy in reading mammograms was explored with two studies. The first was conducted with the high *difficulty* test-set, which included 60 mammographic cases. This work involved 11 and 52 breast radiologists from Mongolia and Australia respectively. The aim of this work was to identify the level of diagnostic accuracy of Mongolian radiologists and it was found to be low for all measured metrics. Particularly, it was shown that, with only 26% lesion sensitivity, locating the lesion was the most difficult task for the Mongolian radiologists. With the *typical* (less difficult) test-set, again including 60 mammographic cases, the second study re-tested the performance of these readers. Whilst the same participants from Mongolia (n=11) read the cases, performance data of different 101 Australian readers were used to compare the accuracy metrics in the second study. This work confirmed the existence of low interpretive accuracy of radiologists in reading mammograms in Mongolia. Again the location sensitivity (38%) was the worst accuracy metric for the Mongolian radiologists.

It is interesting to note that average specificity (77%) for both test-sets was the parameter in which the Mongolian radiologists scored highest. However, specificity can only be valuable when sensitivity is also high [14], since high specificity with low sensitivity implies a low operating point on the ROC curve and therefore, despite this relatively high recognition of normal images, overall the metrics for Mongolian radiologists suggest poor performance. Whilst little is known about the mammographic performance of radiologists from developing countries like Mongolia, our findings were consistent with some studies which demonstrated better performances amongst Australian breast radiologists compared with those in Singapore and Vietnam [15, 16]. Nonetheless, it should be noted that the vast

majority of the existing literature on radiologists' performance was conducted in developed countries, where breast screening is well established.

The third study investigated MD features for women in Mongolia. When two categories of MD classification were considered, the proportion of low MD was more prominent (58%) than high MD (42%) for women in Mongolia. However, when taking the 4-grades of MD classification into account, the proportion of category 4 (extremely dense) was noticeably high (24%), whilst the majority of women (33%) were allocated to the category 2 (scattered areas of fibroglandular density). These results are closer to the previous findings for both Western and Asian studies, which showed an overall equal distribution of MD between low and high-density categories [17, 18]. However, less agreement in age-specific density distribution between our study and the previous Asian studies were noted; the proportion of high density for women aged over 40 years old was much higher among Korean [19] and Chinese women [20] than ours and while the later demonstrated the discriminatory age between high and low density as 55 years old whilst this figure found to be 40 in our study. Our finding of the high proportion of low-density breasts among women above 40 years old (85%) as opposed to high density may be an indicative of the potential for using mammography for population screening in Mongolia. In addition, the purpose of this study was to identify the factors associated with breast density. Whilst the positive association was found between age and BMI and MD, relationship between area of residency and MD was not strong for women in Mongolia. Due to the lack of MD studies arising from Mongolia, we were unable to compare our result within Mongolian setting however, these findings were aligned with the existing literature elsewhere [21, 22].

6.3 Implications

The thesis provides useful information required for optimizing a national program for early detection of breast cancer in Mongolia and has two major implications. The *first* implication is that for the first time, we demonstrated the need for improving early detection of breast cancer in Mongolia. Breast cancer diagnosis in Mongolia has been shown to be less than optimal with radiology performance measures being substantially lower than those in countries such as Australia, Singapore and Vietnam [15]. Although there are several causal factors, lack of training in breast imaging plays a key role. Effective training and ongoing clinical practice can develop these skills, however in Mongolia, it is difficult to achieve proper knowledge and skills under the current 2-years radiology residency program which does not include a subspecialty training in breast imaging. This is in contrast to the 5-years training program in many countries [23, 24] where better performance of readers is reported [25]. Since early diagnosis and better patient outcome are heavily reliant on accurate radiologists' interpretation of breast images, a radiology educational program such as BREAST [11] should be implemented in Mongolia. This may assist improving the health outcomes for Mongolian women with breast cancer through more accurate and earlier diagnosis. In particular, BREAST has been shown to be effective strategy for enhancing reader accuracy in mammography and up to 34% of improvement was found for radiologists who regularly participated in BREAST workshops [26]. Therefore, we strongly recommend such types of learning activity in Mongolia so that optimal performance can be achievable. Meanwhile however, teleradiology may have potential to facilitate the reading of mammograms during transition period of local radiologists are being up skilled.

The *second* implication is that by providing a comprehensive understanding of MD amongst Mongolian women, we can start optimising screening methods. In particular, our findings coupled with previous evidence suggest that MS may have potential in Mongolia for early detection since majority of screening age women (>40 years old) were found to have low density breasts. In particular in our study, the percentage of high density across the age groups were found to be low when compared with other Asian nations [17, 27]; for example with only 13% high density, women aged 40-49 may be good candidates for MS in Mongolia, whilst this age group in other countries has usually been found to have a large number of dense breasts, which limits mammography screening implementation [28]. However, prior to establishing a screening program, it would be important to explore the association between MD and breast cancer risk amongst Mongolian women so that an appropriate screening method can be chosen. It is also necessary to verify MD distribution amongst Mongolian women along with causal factors such as hormonal and lifestyle status (which were not available to us).

In this discussion it is worth acknowledging the high proportion of women with extremely dense breasts that was reported in our study. For these specific women, it may be necessary to consider supplementary ultrasound examination; however, 85% of women in this category were aged below 40 years old and therefore, specific screening approaches may not be necessary, since this age group is currently not recommended for breast cancer screening. Overall however, it should be noted that almost 80% of women in our study were aged below 50 years old and the mean age (40 years old) was younger than that usually investigated elsewhere and of note is

that the majority of women in their 40s in our study was found to have low density breasts. This is in contrast to the data arising from other Asian studies, where a much higher prevalence of high density for this age group was noted, which has added to the debate around the optimum imaging modality in Asia [29, 30].

The images was obtained from the National Cancer Centre of Mongolia, which is the only cancer centre in the country where breast cancer patients are provided by diagnostic and treatment services. Therefore, the data should reasonably cover all types of women including screening population. Although other screening method such as self and clinical breast examinations are recommended in Mongolia, these methods are having limited impact on detection of early breast cancers and therefore mammography will likely to remain on front line tool for breast cancer diagnosis. Based on our findings therefore, mammography appears to be the effective screening approach in Mongolia especially considering the peak age of breast cancer incidence for Mongolian women (45-49 years old), although advantage of using mammography for screening purposes requires further studies.

Mongolia remains to have low incidence rate of breast cancer, which limits the implementation of screening program since low incidence disease does not qualify to require early detection program. However, with consistent increase in incidence and advanced disease presentation, it is necessary to discuss early detection approach for breast cancer in Mongolia. When the national guideline was proposed in 2012, Mongolia had limited mammographic facilities but nowadays, this technique has become more common in practice and hence mammography could be considered for screening purposes. However, running a screening approach involving all women

routinely is expensive and not recommended for low resource countries like Mongolia.

In consideration of the current low rate of incidence, tailored screening approach, targeting high-risk women may have potential to reduce breast cancer mortality in the country. Indeed, risk factors for breast cancer vary by multiple factors including ethnicity, cancer biology and environmental factors. It is therefore extremely important to identify risk factors specific to Mongolian population in order to correctly classify women into high-risk group. According to the national study [9], early menarche, nulliparity and obesity were the risk factor for developing breast cancer for Mongolian women however; the level of association was unclear. Given with the limited information on risk factors in Mongolia, risk assessment could be based on the well-established risk factors including family and high breast density. Nonetheless, risk factors, contributing to develop invasive breast cancer among Mongolian women remain unclear, which suggest that implementation of screening program could be misleading and unnecessary at the present time.

6.4 Limitations

The three studies outlined here have provided new knowledge of radiologists' diagnostic accuracy in mammography and characteristics of MD in Mongolia. However, we cannot rule out some of possible limitations that have impacted upon our findings.

In the first two studies (chapter 3 and 4), the small number of radiologists in each group resulted in limited statistical power. Therefore for example, due to there only being 11 radiologists within our Mongolian readers, we were not able to observe relationships between reader characteristics such as number of mammograms read per year and number of years since the qualification of radiologist and accuracy metrics, in contrast to the findings from other studies [14, 25]. However, recruiting radiologists into the experimental study was very difficult and after much effort we can confidently say that we involved 80% of national breast readers, indicating that our findings must at least reasonably demonstrate the actual level of mammographic performance existing in Mongolia. Moreover, it may seem to be unrealistic to compare the screening performance of Mongolian radiologists with Australian readers due to the wide variations in cancer (high and low prevalence settings in Australia and Mongolia) and reader (radiology training, clinical experience and practice volume) associated factors, which all can have impact on reader performance. It can also be argued that the well-established screening practice in Australia since 1991 [31] allowed Australian radiologists to develop skills required in image interpretation, whilst this opportunity does not exist in Mongolia. However, quality diagnostic imaging service should be available for cancer patients regardless of their geographical locations.

Another limitation is around the fact that mammograms used were sourced from Australia and may have resulted in a higher number of false negatives amongst the Mongolian radiologists due to their lack of experience in dealing with such a cohort of women. Specifically, breast morphology (breast density) differs by ethnicity and therefore Australian mammograms can be different from Mongolian mammograms,

but demonstrated variations of breast density in literature between different populations appear to be fairly small and therefore less likely to affect in a massive way reader performance [27, 32]. In addition, type of breast lesions presenting in Australia vary greatly than those occur in Mongolia, which could be understood rare features for Mongolian radiologists and therefore may impact on decision making of Mongolian radiologists (prevalence effect) [33]. However, the standard test-sets used for testing and monitoring reader performance in Australia and New Zealand and the validated research method used in the current study minimised the impact of image bias. Also, comparisons have shown that actual clinical performance can reasonably be predicted with test-set images (used in our study), suggesting the validity of our results [34].

In the third study (chapter 5), information around important determinants of MD such as reproductive (menopausal and parity status), and lifestyle factors (smoking and alcohol consumption) were noticeably absent. These factors could have helped our understanding of causal agents responsible for MD variations for women in Mongolia. However in Mongolia, patient and clinical information are recorded in an individual-based medical file, which is kept with patients, causing a challenge in collecting research data. Nonetheless, this information can be obtained with a dedicated survey questionnaire when the patient undergoes mammographic examination. In addition, it may be argued that breast density assessment (BI-RADS) is as an imperfect method for assessing breast density since it has wide inter- and intra- reader variability [35]. But, the BI-RADS is the most widely used and accepted method among radiologists in clinical practice and the only available

method to assess the breast density in Mongolia. Also, in our study, three radiologists validated density scores from the BI-RADS method.

6.5 Future directions

From the limitations mentioned above, it is clear that future work should be designed to address those deficiencies. First, testing reader performance with Mongolian data (mammograms) would have helped to better understand the interpretive accuracy of radiologists in reading mammograms. This is particularly important since we used Australian screening images, which is uncommon practice for Mongolian radiologists [36]. Therefore, our findings have raised a question whether the readings of familiar images (Mongolian mammograms) by Mongolian radiologists would be different from their readings of Australian images. It would be interesting to know such differences, which would further provide information to establish sophisticated strategic solutions such as educational intervention, clinical auditing and administrative regulations.

Second, whilst our MD study demonstrated interesting and valid information, this should now be confirmed using objective methods such as area based approaches (Cumulus and Auto Density) and volumetric software tools (VolparaTM and QuantraTM). It will be helpful to know the prediction of density status in Mongolia with these methods since the evidence from Westernised populations, using automated methods showed that the estimation of breast density can be more robust and precise than assessed subsequently by radiologists (BI-RADS) [37]. It is also important to investigate factors (as mentioned in the previous paragraph) influencing MD, because these are not only determinants for MD but also contribute to breast

cancer risk [38]. Thus, we would have a better understanding of aetiology of the disease specifically for Mongolian women. This could be achieved by a well-designed research method with survey questionnaires involving women who undergo mammography either for screening or diagnostic purposes.

Finally, in the current work, the link between breast cancer and high MD was not explored due to the lack of cancer images from Mongolia. As high MD is not only a risk for developing breast cancer but also determinant of mammographic sensitivity, the identification of MD risk for Mongolian women would have two important outcomes: first, it would help to improve our understanding of breast cancer aetiology; second, prevention strategies of the disease can be facilitated with individual-based screening recommendation. At the present time, cancer image collection from Mongolia is challenging because of the lack of electronic hospital systems at the NCC. Although, biopsy proven cancer cases can be obtained retrospectively from the paper-based archive, it is unlikely that the associated images will be readily available and therefore patients need to be recalled bringing their mammograms with them. Despite this complicated process for retrieving cancer images, it can be achievable prospectively with a cleverly designed method involving pathology and radiology departments as well as consumer representatives.

6.6 The way forward in Mongolia

Although mammography appears to be a suitable modality for breast screening in Mongolia, we found that mammographic diagnostic accuracy was sub-optimal with a cancer sensitivity of 54% that needs to be addressed urgently. What is more

worrying is that lesion sensitivity ranges from 26-38% which may contribute to continued poor patient outcomes if immediate strategy to improve reader accuracy in mammography is not initiated.

Having seen how quality mammographic services play essential roles in breast cancer diagnosis in Australia and how challenging the diagnostic service is in my home country, Mongolia, it is clear that continuing medical education is critically important for professional development. However, this type of training specific to mammography is not often available in Mongolia, therefore I believe it is necessary to set up a non-governmental organisation (NGO) that will enable me to lead the educational needs required for early cancer diagnoses.

We have successfully registered the NGO, radiology education centre (RE: centre) in April 2018 in Mongolia. The main function of the RE: centre will be working on devising postgraduate educational programs including online and local teaching courses, to enhance radiologists' ability to diagnose early cancers. We have proposed the first project, BREAST Mongolia: Transforming breast cancer detection in Mongolia and to support this activity we have applied for two grants funded by the Australian and Canadian governments.

BREAST Mongolia will be a robust educational program including a teaching course and interactive online assessment platform to enhance the quality of breast cancer diagnosis in the country. The project will be based on BREAST [11] currently employed in Australia which demonstrated to contribute to improved diagnostic performance of radiologists [26]. We have a world-class collaboration in place to

deliver this project: Professor Patrick C Brennan, a world expert on testing radiologist performance; Professor Mary Rickard, a global leader in breast imaging education and Professor Asai Ramish, Chief Radiologist at the National Cancer Centre of Mongolia, who will ensure maximum Mongolian radiologist engagement.

We hope BREAST is specifically important in Mongolia because mammographic training does not exist in the country and without such training it is unlikely that radiologists develop necessary skills required in mammographic interpretation, in particularly with a low incidence setting. In addition, the NGO will not only work for breast specific projects, we will be focusing on other areas of radiology such as chest and abdominal imaging, since currently specialist professional training in radiology is not available in Mongolia. To ensure maximum engagement of radiologists, we will closely collaborate with the public hospitals along with the private clinics. However the main collaborator of the NGO will be the National Cancer of Mongolia since this the only cancer specialised hospital nationwide, where cancer diagnoses and treatments are available.

6.7 Conclusion

This work has explored mammographic diagnostic performance of radiologists and MD features in Mongolia, which are important factors for establishing strategies for early detection of breast cancer. First, the study found the existence of sub-optimal mammographic diagnostic accuracy, suggesting an urgent need to initiate a strategic solution to maximise early cancer diagnosis. At the present time, this is a very important issue since breast cancer has subjected Mongolia to a heavy health

service burden due to the high proportion of advanced cancer diagnoses. Second, distribution of low-density breasts has found to be predominant in Mongolia, which is a good indicator for mammographic screening efficacy. This study also showed that age and body mass index were the main determinants for varying level of MD in Mongolia.

Whilst our findings are in line with what has been previously known about the mammographic diagnostic accuracy and MD characteristics in other countries, a number of findings were unique to Mongolia. The data provided in the thesis should be useful in optimising national screening program and cancer prevention policy and presents important information for clinicians, researchers and policy makers in Mongolia. However, future work is necessary to develop the current evidence of mammographic performance and MD features for Mongolian women.

6.8 References

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Appendix 1

Materials used in the studies

These include:

- Appendix 1.1 Ethical approval – The University of Sydney
- Appendix 1.2 Ethical approval – The Ministry of Health, Mongolia
- Appendix 1.3 Data collection approval – National Cancer Centre of Mongolia
- Appendix 1.4 Data collection approval – BREAST
- Appendix 1.5 Participant information sheet
- Appendix 1.6 Participant consent form
- Appendix 1.7 Safety protocol

Appendix 1.1

Ethical approval – The University of Sydney

Research Integrity

Human Research Ethics Committee

Wednesday, 17 December 2014

Assoc Prof Claudia Mello-Thoms
Medical Imaging and Radiation Sciences; Faculty of Health Sciences
Email: claudia.mello-thoms@sydney.edu.au

Dear Claudia

I am pleased to inform you that the University of Sydney Human Research Ethics Committee (HREC) has approved your project entitled "**Characterizing breast density and breast cancer amongst Mongolian women**".

Details of the approval are as follows:

Project No.: 2014/973
Approval Date: 16 December 2014
First Annual Report Due: 16 December 2015
Authorised Personnel: Mello-Thoms Claudia; Brennan Patrick; Demchig Delgermaa;

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:

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.



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

Professor Glen Davis
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

Thursday, 2 June 2016

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 "**Radiologist performance on ethically different databases.**".

Details of the approval are as follows:

Project No.: 2016/406

Approval Date: 1 June 2016

First Annual Report Due: 1 June 2017

Authorised Personnel: Brennan Patrick; Mello-Thoms Claudia; Demchig Delgermaa

Documents Approved:

<u>Date</u>	<u>Type</u>	<u>Document</u>
27/05/2016	Participant Info Statement	Participant information statement
23/05/2016	Participant Consent Form	Amended PCF

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:

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.

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

Associate Professor Rita Shackel
Chair
Human Research Ethics Committee (HREC 3)

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 & Ethics Administration
Human Research Ethics Committee

Friday, 21 July 2017

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

Dear Patrick,

Your request to modify this project, which was submitted on 26th April 2017, has been considered.

After consideration of your response to the comments raised the project has been approved to proceed with the proposed amendments.

Details of the approval are as follows:

Project Title: Radiologist performance on ethically different databases.

Project No.: 2016/406

Next Annual Report due: 1st June 2018

New Approved Documents:

Date Uploaded	Type	Document Name
19/06/2017	Participant Info Statement	PIS
19/06/2017	Participant Info Statement	PIS

Special Condition/s of Approval

- There are a couple of minor formatting issues in both of the PIS documents provided (e.g. section title and content on separate pages, missing line breaks between bullet point list and next paragraph). If the CI decides to address these, he is requested to provide a final copy of the amended documents to the Ethics Office.

Please contact the Ethics Office should you require further information or clarification.

Sincerely,

Dr Jim Rooney
Chair
Modification Review Committee

The University of Sydney HRECs are constituted and operate in accordance with the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Human Research (2007) and the NHMRC's Australian Code for the Responsible Conduct of Research (2007).

Appendix 1.2

Ethical approval – The Ministry of Health, Mongolia

ЭРҮҮЛ МЭНД, СПОРТЫН ЯАМ

АНАГААХ УХААНЫ ЁС ЗҮЙН ХЯНАЛТЫН ХОРООНЫ
ТОГТООЛ

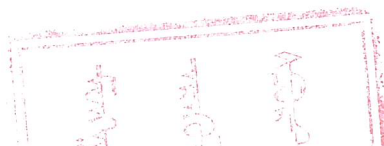
2015 оны 03 дугаар сарын 23 -ний өдөр

№ 04

210648 Улаанбаатар хот
Сүхбаатар дүүрэг,
Олимпийн гудамж-2
Засгийн газрын VIII байр,
Эрүүл мэнд, спортын яам
Утас: 263734, Факс: 323541
Цахим хаяг:
oyunbileg@mohs.gov.mn

Анагаах ухааны ёс зүйн хяналтын хорооны 2015 оны 03 дугаар сарын 23-ний өдрийн 1 дүгээр хурлын протоколыг үндэслэн ТОГТООХ нь:

1. “Монгол эмэгтэйчүүдийн хөхний нягт бүтэц ба хөхний өмөнгийн эрсдлийг судлах нь” (Д.Дэлгэрмаа / Австрали Сидней Их сургууль) судалгааг 2015-2017 онд багтаан хэрэгжүүлэхийг зөвшөөрсүгэй.
2. Төгсгөлийн тайланг судалгаа дууссан хугацаанаас хойш 2 сарын дотор багтаан анагаах ухааны ёс зүйн хяналтын хороонд ирүүлэхийг төслийн удирдагчид үүрэг болгосугай.



MINISTRY OF HEALTH AND SPORT

DECISION OF MEDICAL ETHICS MONITORING COMMITTEE

March 23, 2015

№ 04

Ministry of Health and Sport

Government building VIII,

Olympic street-2

Sukhbaatar district,

Ulaanbaatar city 210648

Tel: 263734, Fax: 323541

E-mail: oyunbileg@mohs.gov.mn

It is declared under the decision of protocol of 1st meeting, Medical Ethics Monitoring Committee, dated to March 23, 2015.

1. Authorizing to implement research “Study breast thick structure and cancer of Mongolian women” (Delgermaa. D, University of Sydney, Australia) within 2015 and 2017.
2. Obligate to project leader to deliver a report of research to Medical Ethics Monitoring Committee within 2 months after research had been done.

HEAD /signed and sealed/ Chojjamts.G



Translated and verified by “NOMT-AJIN” Translation bureau
Juilchin street -10,1st khoroo, Chingeltei district, Ulaanbaatar, Mongolia,
Tel: 95737177, E-mail: nomt.orchuulga@yahoo.com

Appendix 1.3

Data collection approval – National Cancer Centre of Mongolia



**Н.НЯМДАВААГИЙН НЭРЭМЖИТ
ХАВДАР СУДЛАЛЫН ҮНДЭСНИЙ ТӨВИЙН ЭРДМИЙН ЗӨВЛӨЛ**

2014 оны 10-р сарын 30-ны өдөр

№ 03

Улаанбаатар хот

ЭРДМИЙН ЗӨВЛӨЛИЙН ТОГТООЛ

ХСҮТ-ийн эрдмийн зөвлөлийн 2014 оны 10-р сарын 30-ны өдрийн хурлын үеэр эрдмийн зөвлөлийн гишүүдээс гарсан саналыг үндэслэн тогтоох нь:

1. “Монгол эмэгтэйчүүдийн хөхний нягт бүтэц ба хөхний өмөнгийн эрсдэлийг судлах нь” сэдэвт судалгааны арга, аргачлалд гишүүдийн саналыг тусгаад АШУУИС-н ёс зүйн хороогоор хэлэлцүүлсүгэй.
2. “Монгол эмэгтэйчүүдийн хөхний нягт бүтэц ба хөхний өмөнгийн эрсдэлийг судлах нь” сэдэвт судалгааны ажлыг ХСҮТ-ийг клиник баазыг түшиглэн хийхийг зөвшөөрсүгэй.

ЭРДМИЙН ЗӨВЛӨЛИЙН ДАРГА

ЭРДМИЙН ЗӨВЛӨЛИЙН ЭРДЭМТЭ
НАРИЙН БИЧГИЙН ДАРГА



Г. ПҮРЭВСҮРЭН,
АУ-НЫ ДОКТОР

Ц. БАДАМСҮРЭН,
АУ-НЫ ДОКТОР

COMMITTEE ON EDUCATION AND SCIENCE,
NATIONAL CANCER CENTER OF MONGOLIA

October 30, 2014

#03

Ulaanbaatar city

On the day of 30th of October, 2014, the Meeting of the Committee on Education and Science decides to:

1. Submit the study titled "Mammographic appearance of Mongolian women and its risk for breast cancer" to the Ethic Committee at Mongolian National University of Medical Science for getting approval;
2. Conduct the study titled "Mammographic appearance of Mongolian women and its risk for breast cancer" on the clinic database of the National Cancer Center of Mongolia.

G. Purevsuren Ph.D., Head of the Committee
/signed and sealed/


Ts. Badamsuren Ph.D., Secretary
/signed and sealed/

Officially translated and verified by "Kherlen's" Translation Bureau, "Mongolian Professional English Language Translation Association NGO"
The present translation was registered at the translation service registration book
Add: Room #6, Choijin Temple Building, Juvshin Street-5, Sukhbaatar district, Ulaanbaatar city, Mongolia
Mobile: 976-99138517; email: dkherlengol@gmail.com



Appendix 1.4

Data collection approval - BREAST

Resource APPLICATION FOR ACCESS Submit completed forms to breastaustralia@sydney.edu.au					
1. PROJECT TITLE					
Radiologist performance using ethically different mammograms					
2. CHIEF INVESTIGATOR'S DETAILS (SENIOR RESEARCHER)					
Name (full name and title)		Professor Patrick Brennan			
Department		Medical Radiation Science, Faculty of Health Science			
Institution		The University of Sydney			
Postal Address		PO box 170			
City/Suburb		Lidcombe	State	NSW	Postcode 2141
Phone	2 90367402	Fax		Mobile	
Email	patrick.brennan@sydney.edu.au				
3. RESEARCH PROJECT INFORMATION					
3.1 Summary of research project in lay language (maximum 200 words)					
<p><i>Please note this information may be used to inform stakeholders about your research project. It must be written clearly in lay language.</i></p>					
3.2 Please provide a detailed research plan, (maximum length 3 pages)					
Overview:					
<p>Despite having low rates of incidence and mortality, breast cancer has become a serious health issue in Mongolia in terms of advanced disease presentation. To date, age standardized incidence rate is 6.0 per 100,000 Mongolian women and approximately 90% of the patient dying within 5 years due to mostly late presentation of the disease. A relatively recent national study demonstrated that 93.4% of the Mongolian women with breast cancer were diagnosed at advanced stages. Many possible explanations existed such as limited diagnostic facilities, lack of breast screening and breast cancer awareness however, nothing is known regarding the breast density which is not only significant risk factor for breast cancer but may have an impact on diagnostic performance. This study will be identifying the variability of radiologist to address what factors influence their performance.</p>					
3.2.1 Aim(s)					
<p>The aim of this study is to evaluate variability and accuracy of individual reader performance by comparing two ethnically different data sets. Developing easy, accessible and quality training model for breast radiologist in Mongolia will be our further aim of this study.</p>					

3.2.2 Project methodology

Ethical approval will be obtained from the University of Sydney. Five Radiologist who works as a breast radiologist in three different hospitals in Mongolia will be involved in this study. At least one year of experience in digital mammography will be the selection criteria for the radiologists. This study will apply two ethnically different data sets with standard two views each breast corresponding to Australian and Mongolian women. Each dataset will be consisted of total 60 images including 20 cases of breast cancer and 40 cases of non-cancer images.

In first part, radiologist will review Australian test-set. These dataset are obtained and created from the database of NSW breast cancer screening. The readers will describe each mammography using overall and density BIRADS categories. Australian dataset consisted of both medio-lateral oblique (MLO) and craniocaudal (CC) projections including early stage cancers, benign masses, microcalcifications and normal cases along with radiologist reports. Inter radiologist agreement will be assessed using concordance and kappa statistic.

In second part of this study, readers will evaluate Mongolian data set in terms of same diagnostic tasks performed in former part. Whilst Australian test-set has previously been created and it is ready to use, Mongolian data set, involving breast cancer and non-cancer cases will be created randomly by collecting mammographic (MLO and CC) images using previously collected images from National Cancer Center (public) and Inter-med Hospital (private). All mammographic images selected will be de-identified and coded. The performance of each reader on this data set and on both data sets will be compared and analyzed using statistical tests.

3.2.3 Number of readers from whom data are requested and/or number and type of cases requested and/or equipment for which access is requested. Please include statistical justification where relevant.

The breast radiologists in National Cancer Centre and Intermed Hospital will be attended in this project. However, at the moment the name lists are not available as the invitation letter have not been submitted.

We need a data set which includes both cases of early stage breast cancer and non cancer images along with the results.

3.2.4 Significance and output:

Training module that we develop can improve not only knowledge of the individuals also contribute to increase the quality of breast cancer diagnosis in Mongolia. This would furthermore help to improve detection rate of early stage cancers. We also believe that this training module can be added to radiology residency program with the aim of contributing to prepare breast specialist.

3.2.5 Proposed time period

1. Ethical approval: Jan-Feb 2016
2. Data collection : Feb-April 2016
3. Data analysis: April –May 2016
4. Preparing for manuscript: May-Jun 2016
5. Submission for publication: June 2016

3.3 Planned start and end date of the project	Start date:	15 January 2016	End date:	30 June 2016
3.4 Please list all other researchers collaborating on this project, including their name, title,	Name (full name and title)	Department	Institution	
	1. Delgermaa Demchig, HDR Student	Medical Radiation Science, Faculty of Health Science	The University of Sydney	


appointment and institution	2. Associate prof Claudia Mello-Thoms	Medical Radiation Science, Faculty of Health Science	The University of Sydney
	3.		
	4.		
	5.		
	6.		
	7.		
	8.		
	4. FUNDING		
4.1 Have you secured funding for the research project?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>	Pending <input type="checkbox"/>
4.2 If 'yes' or 'pending', please detail the funders who have approved/are considering your project	Funding body	Length of approved funding period in years	Funding amount in Australian dollars. (place a 'P' next to the \$ amount for pending funding applications eg \$565,000 P)
Funder 1			
Funder 2			
Funder 3			
Funder 4			
4.3 If you haven't secured funding, what is the status of your research project?	Please provide details below (maximum 200 words):		
5. ETHICS			
5.1 Do you have Human Research Ethics Committee (HREC) approval to conduct this research project?	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Pending <input checked="" type="checkbox"/>
	If No, we advise you to seek ethical approval. Access to any resource will not be facilitated until proof of ethical approval is submitted to us.		
6. RESOURCES REQUIRED			
	Please tick all that apply: IMAGES		

<p>6.1 What BREAST resources do you require for your project? [Specific details should be discussed with BREAST project staff at the EOI stage]</p>	<p>EXISTING TEST SET(S) <input checked="" type="checkbox"/> <i>Name(s) of test set(s):</i> <i>File type (DICOM, jpeg):</i></p> <p>IMAGES NOT IN AN EXISTING TEST SET <input type="checkbox"/> <i>Number of images:</i> <i>Case details:</i> <i>File type (DICOM, jpeg):</i></p> <p>READER DATA READER TYPE <i>General radiologist</i> <input checked="" type="checkbox"/> <i>BreastScreen radiologist</i> <input checked="" type="checkbox"/> <i>Registrar / Fellow</i> <input type="checkbox"/> <i>Other reader</i> <input type="checkbox"/> <i>Please specify:</i></p> <p>NUMBER OF PARTICIPANTS: <u>50</u></p> <p>QUESTIONNAIRE DATA <input checked="" type="checkbox"/></p> <p>SCORES FROM TEST SET <input checked="" type="checkbox"/></p> <p>RAW DATA FROM TEST SET <input checked="" type="checkbox"/></p> <p>ADDITIONAL INFORMATION FROM PARTICIPANTS <input type="checkbox"/> * <u>No.</u> *[E.g. If you need to contact participants to complete an additional survey or for clarification. If Yes to 'additional information' required, please provide details at 6.2.]</p> <p>ACCESS TO THE MOBILE IMAGING LAB PATHOLOGY SLIDE SCANNER <input type="checkbox"/> <u>No.</u> <i>Dates and times required:</i></p> <p>MAMMOGRPAHY PACS WORKSTATIONS <input checked="" type="checkbox"/> <i>Number of workstations:</i> = <u>1</u> <i>Dates and times required:</i> = <u>June (1 month)</u></p> <p>OTHER EQUIPMENT <input type="checkbox"/> <i>Type of equipment:</i> <i>Dates and times required:</i></p>
<p>6.2 Any additional questionnaires or surveys intended for distribution to participants by BREAST MUST be supplied for review by the Management team</p>	<p>Please list the documents and provide a brief description here. [Documents should be attached to this application].</p>

--	--

7. CERTIFICATION BY APPLICANT**Certification by applicant**

In signing this page, you certify that all details given in this application are correct and you agree to carry out the project according to the terms and conditions as described by the BREAST Access Policy


Applicant Name: PATRICK BRENNAN (Please print in block letters)	Signature: 	Date: 13/3/16
--	---	-------------------------

8. APPLICANT CHECKLIST

This sheet must be completed – please mark the check boxes to confirm you have attached / included all of the required documentation and information.

Documents to be attached to application :	Yes	Pending	N/A
CV of Chief Investigator (Senior Researcher)	<input type="checkbox"/>	-	-
Proof of funding	<input type="checkbox"/>	-	-
Copies of any questionnaires or surveys you wish to have BREAST distribute to a participant group	<input type="checkbox"/>	-	<input type="checkbox"/>
Ethics			
For projects with pending ethical approval :			
(a) <u>If an ethics submission is already in deliberation</u> , please attach:	<input type="checkbox"/>	<input type="checkbox"/>	
- a copy of all relevant Ethics Applications you have made for the research project, and	<input type="checkbox"/>	<input type="checkbox"/>	
- any reviewer comments you may have received.			
For projects with ethical approval :			
(b) <u>If Ethics Approval has already been granted</u> by any HREC/IRB for this project, please attach:			
- a copy of the approved Ethics Application	<input type="checkbox"/>	<input type="checkbox"/>	
- letter(s) of Ethics approval, and	<input type="checkbox"/>	<input type="checkbox"/>	
- all approved documents for the research project.	<input type="checkbox"/>	<input type="checkbox"/>	

Thank you. Please submit completed form to breastaustralia@sydney.edu.au

<p>Low Risk Category Resource APPLICATION FOR ACCESS Submit completed forms to breastaustralia@sydney.edu.au</p>					
1. PROJECT TITLE					
The performance comparison: Do the challenging and typical mammographic images have similar effect on reader performance.					
2. CHIEF INVESTIGATOR'S DETAILS (SENIOR RESEARCHER)					
Name (full name and title)	Professor. Patrick C Brennan				
Department	Medical Radiation Science				
Institution	Faculty of Health Science, University of Sydney				
Postal Address	75 East st, Cumberland Campus				
City/Suburb	Lidcombe	State	NSW	Postcode	2141
Phone	Fax	Mobile			
Email	patrick.brennan@sydney.edu.au				
3. RESEARCH PROJECT INFORMATION					
3.1 Summary of research project in lay language (maximum 200 words)					
<p><i>Please note this information may be used to inform stakeholders about your research project. It must be written clearly in lay language.</i></p> <p>This work will be the 2nd part of our previous study that has conducted in Mongolia using Sydney test-set in 2016. We found that the performance for Mongolian readers were lower than Australian fellows. Sydney test-set is considered as a challenging since the images were selected from difficult findings of early breast cancers. In addition, clinical practice in Mongolia does not support to practise these type of “difficult” images and it is therefore logical to conclude that their low performance can be acceptable at some point. Nonetheless, whatever the reason, it is not unreasonable to expect a similar level of interpretive skill regardless of where a woman is radiologically examined.</p> <p>In this work, we will replace the images as the “typical” images which the reader may encounter at everyday clinical practices. We would like to investigate whether there is any difference in performance of readers exist or not when they interpret typical images.</p>					
3.2 Please provide a brief research plan, (maximum length 3 pages)					
<ul style="list-style-type: none"> • 20 Mar – 15 May 2017: The modelling of “typical” test-set based on the current BREAST data. • May-June 2017: The experiment in Mongolia. • June – Sep 2017: Data analysis and drafting the manuscript for the publication • Oct 2017: Final submission of the result 					
3.2.1 Aim(s)					
To identify the possible effect of typical images on the level of performance of breast readers. To propose the educational program will be our second aim.					
3.2.2 Proposed project methodology					
This work will include two parts.					
<ol style="list-style-type: none"> 1. The preparation of mammographic images for “typical” test-set. 					

This consists of the selection and validation of images and technical work for the designing of test-set. The test-set will then be validated by the senior radiologists. The email communication with the participants will be done to set up the appropriate dates for each of these readers. Also experiment room will be arranged.

2. The experiment

The same eleven participants will be attending in this experiment and read 60 images consisting of 20 abnormal and 40 normal cases. This work will be done in radiology department of the Intermed Hospital in Mongolia.

3.2.3 Number of readers from whom data are requested and/or number and type of cases requested and/or equipment for which access is requested.

In other to select the typical images, we may need three test-set with the raw data of 300 reader's information. The equipment is not required.

3.3 Planned start and end date of the project	Start date: 20 Mar 2017		End date: 30 Sep 2017	
3.4 Please list all other researchers collaborating on this project, including their name, title, appointment and institution	Name (full name and title)	Department	Institution	
	1. Delgermaa Demchig.MD (HDR student)	MRS, Faculty of health science	The University of Sydney	
	2. Khulan Khurelsukh.MD	Radiology department	The Intermed Hospital	

1. ETHICS

4.1 Do you have Human Research Ethics Committee (HREC) approval to conduct this research project?

Yes

No

Pending

If No, we advise you to seek ethical approval. Access to any resource **will not** be facilitated until proof of ethical approval is submitted to us.

2. RESOURCES REQUIRED

5.1 What BREAST resources do you require for your project? [Specific details should be discussed with BREAST project staff at the EOI stage]

120 Mammographic images
Reader data (approximately 300)

5.2 Any additional questionnaires or surveys intended for distribution to participants by BREAST MUST be supplied for review by the Management team

Please list the documents and provide a brief description here. [Documents should be attached to this application].

No additional questionnaire is required.

3. CERTIFICATION BY APPLICANT (STUDENT / RESEARCHER)**Certification by applicant**

In signing this page, you certify that all details given in this application are correct and you agree to carry out the project according to the terms and conditions as described by the BREAST Access Policy

Applicant Name: Delgermaa Demchig (please print in block letters)	Signature: 	Date: 17 March 2017
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Thank you. Please submit completed form to breastaustralia@sydney.edu.au

Appendix 1.5

Participant information sheet

ABN 15 211 513 464

Professor. Patrick Brennan
Professor of Diagnostic Radiography

Room 221
M Building C42
Cumberland Campus
The University of Sydney
PO box 170 Lidcombe
NSW 2006 AUSTRALIA
Telephone: +61 2 90367402
Facsimile: +61 2 90367402
Email: Patrick.brennan@sydney.edu.au
Web: <http://www.sydney.edu.au/>

Radiologist performance on ethically different populations

PARTICIPANT INFORMATION STATEMENT

(1) What is this study about?

You are invited to take part in a research study about the radiologist performance when interpreting ethnically different data sets. The study compares readers' performance using two data sets, which involving 60 mammograms respectively. This proposed research is expected to provide knowledge around the diagnostic accuracy and variability among radiologists. Based on our results, we will develop training modules which will contribute to improving the quality of breast cancer diagnosis and help to improve detection rate of early cancer in Mongolia.

You have been invited to participate in this study because *you are a radiologist*. This Participant Information Statement tells you about the research study. Knowing what is involved will help you decide if you want to take part in the research. Please read this sheet carefully and ask questions about anything that you don't understand or want to know more about.

Participation in this research study is voluntary. So it's up to you whether you wish to take part or not. By giving your consent to take part in this study you are telling us that you:

- ✓ Understand what you have read.
- ✓ Agree to take part in the research study as outlined below.
- ✓ Agree to the use of your personal information as described.

You will be given a copy of this Participant Information Statement to keep.

(2) Who is running the study?

The study is being carried out by the following researchers:

- Prof Patrick C Brennan (Professor of Diagnostic Radiography)
- Prof Claudia Mello-Thoms (Associate Professor of Diagnostic Radiography)

- Dr Delgermaa Demchig (HDR Student, The University of Sydney)

Dr Delgermaa Demchig is conducting this research for the Degree of Doctor of Philosophy at the University of Sydney. This will take place under the supervision of Professors Patrick Brennan and Mello-Thoms.

(3) What will the study involve for me?

In this study, you will be asked to interpret two data sets; each consists of 60 mammograms. The reading section will be divided into two parts and you will be expected to evaluate each mammogram using the Breast Imaging Reporting and Data System (BI-RADS) categories. Each mammographic case contains medio-lateral oblique (MLO) and craniocaudal (CC) views as a standard. During each reading section, you will identify and localize every abnormality within the digital mammograms.

(4) How much of my time will the study take?

Each reading section will take approximately 1.5-2 hours to complete. Altogether, 3-4 hours will be required to complete the work.

(5) Who can take part in the study?

This study is open to all breast readers (radiologists) in Mongolia who are involved in interpreting mammography.

(6) Do I have to be in the study? Can I withdraw from the study once I've started?

Being in this study is completely voluntary and you do not have to take part. Your decision whether to participate will not affect your current or future relationship with the researchers or anyone else at the University of Sydney and Hospitals in Mongolia.

If you decide to take part in the study and then change your mind later, you are free to withdraw at any time. You can do this by sending an email to ddem2574@uni.sydney.edu.au. Any collected data will be also deleted, should you choose to withdraw from the study at any later stage.

(7) Are there any risks or costs associated with being in the study?

Aside from giving up your time, we do not expect that there will be any risks or costs associated with taking part in this study.

(8) Are there any benefits associated with being in the study?

You will not receive any direct benefits from being in the study.

(9) What will happen to information about me that is collected during the study

Your information will be stored securely and your identity/information will be kept strictly confidential. Study findings may be published, but you will not be individually identifiable in any publication.

We will keep the information we collect for this study. We will only use the data for our current study. If we do need to use the data for a future study, we will seek appropriate ethical approval before using the information.

By providing your consent, you are agreeing to us collecting personal information about you for the purposes of this research study. Your information will only be used for the purposes outlined in this Participant Information Statement, unless you consent otherwise.

(10) Can I tell other people about the study?

Yes, you are welcome to tell other people about the study.

(11) What if I would like further information about the study?

When you have read this information, [Dr Delgermaa Demchig](#) or [Prof Patrick Brennan](#) will be available to discuss it with you further and answer any questions you may have. If you would like to know more at any stage during the study, please feel free to contact Dr Delgermaa Demchig (HDR Student in Medical Radiation Science) at ddem2574@uni.sydney.edu.au or Prof Patrick Brennan (Professor of Diagnostic Radiography) at Patrick.brennan@sydney.edu.au or +61 2 90367402.

(12) Will I be told the results of the study?

You have a right to receive feedback about the overall results of this study. You can tell us that you wish to receive feedback by emailing us at Patrick.brennan@sydney.edu.au. This feedback will be in the form of word document summary. You will receive this feedback after the study is finished.

(13) What if I have a complaint or any concerns about the study?

Research involving humans in Australia is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this study have been approved by the HREC of the University of Sydney [*INSERT protocol number once approval is obtained*]. As part of this process, we have agreed to carry out the study according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect people who agree to take part in research studies.

If you are concerned about the way this study is being conducted or you wish to make a complaint to someone independent from the study, please contact the university using the details outlined below. Please quote the study title and protocol number.

The Manager, Ethics Administration, University of Sydney:

- **Telephone:** +61 2 8627 8176
- **Email:** ro.humanethics@sydney.edu.au
- **Fax:** +61 2 8627 8177 (Facsimile)
-

Local contact: Professor Asai Ramish, the chief radiologist Radiology department of National Cancer

- Mobile: 99085881
- Email: asai.ramish@yahoo.com

This information sheet is for you to keep

Appendix 1.6

Participant consent form

ABN 15 211 513 464

Professor. Patrick Brennan
Professor of Diagnostic Radiography

Room 221
M Building C42
Cumberland Campus
The University of Sydney
PO box 170 Lidcombe
NSW 2006 AUSTRALIA
Telephone: +61 2 90367402
Facsimile: +61 2 90367402
Email: Patrick.brennan@sydney.edu.au
Web: <http://www.sydney.edu.au/>

Radiologist performance on ethically different data sets

PARTICIPANT CONSENT FORM

I, [PRINT NAME], agree to take part in this research study.

In giving my consent I state that:

- ✓ I understand the purpose of the study, what I will be asked to do, and any risks/benefits involved.
- ✓ I have read the Participant Information Statement and have been able to discuss my involvement in the study with the researchers if I wished to do so.
- ✓ The researchers have answered any questions that I had about the study and I am happy with the answers.
- ✓ I understand that being in this study is completely voluntary and I do not have to take part. My decision whether to be in the study will not affect my relationship with the researchers or anyone else at the University of Sydney and hospitals in Mongolia now or in the future.
- ✓ I understand that I can withdraw from the study at any time.
- ✓ I understand that personal information about me that is collected over the course of this project will be stored securely and will only be used for purposes that I have agreed to. I understand that information about me will only be told to others with my permission, except as required by law.
- ✓ I understand that the information about me will only be used for this study.

- ✓ I understand that the results of this study may be published, and that publications will not contain my name or any identifiable information about me.

I consent to:

- **Being contacted about future studies** YES NO
- **Receiving feedback about my personal results** YES NO

Would you like to receive feedback about the overall results of this study?

YES NO

If you answered **YES**, please indicate your preferred form of feedback and address:

Postal: _____

Email: _____

.....
Signature

.....
PRINT name

.....
Date

Appendix 1.7

Safety protocol



Professor Patrick Brennan
Professor Diagnostic Imaging, Medical Radiation Sciences
Associate Dean, International

17 May 2016

RE: SAFETY PROTOCOL

TO WHOM IT MAY CONCERN

The researcher (Delgermaa Demchig) will be conducting the study "Evaluating radiologist performance using ethically different data sets". She will organize a workshop and experiment for radiologists in Mongolia. There is no need for a local interpreter as the researcher is from Mongolia. No safeguard is required either.

The safety and performance of the experiment will be discussed with the supervisor before travelling to Mongolia. A schedule including date, time and place of experiment will also be provided to the supervisor. During the field work, local and supervisor contacts will be made via mobile or email at least on a weekly basis.

The researcher will take advice from the following local institutions regarding the safety of the planned research process: National Cancer Center in Mongolia. The researcher's local contact person is: Prof. Asai Ramish. He can be contacted by mobile: 99085881 and email asai.ramish@yahoo.com

The researcher has confirmed there is mobile phone coverage in Mongolia that has access to global roaming and will have her mobile phone during her field work. There is currently no travel warning from the Department of Foreign Affairs and Trade for Mongolia. The researcher has subscribed to the travel advice to receive email updates each time the travel warning is reissued. No visa is required as the researcher is from Mongolia.

The researcher undertakes to follow the University of Sydney guidelines on Fieldwork Safety Standards.

This safety protocol has been agreed and accepted by the researcher and the supervisor.

Professor Patrick Brennan (Supervisor)

Delgermaa Demchig (Researcher)