What is the appropriate role of bilateral breast ultrasound, as an adjunct to mammography, in the management of patients with positive findings?

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Abstract

Objective
The aim of the study is to assess the appropriate role of bilateral, whole-breast ultrasound as an adjunct to mammography, in the management of patients with positive imaging findings. Mammography has long been viewed as the gold standard for breast cancer detection, however there are well documented limitations in the effectiveness of mammography.

Materials and Methods
From January 1999 to December 2007 inclusive, 22,814 patients presented for breast imaging and of these, 1063 formed the study group as they required a breast tissue biopsies due to imaging results. The cancer detection rate was compared among those women with a baseline risk and those who had either an increased risk of breast cancer and / or had dense breast tissue,. All patients in the study group (1063) were imaged with mammography and bilateral whole breast ultrasound. The statistical measures of accuracy, sensitivity, specificity, positive predictive (PPV) and negative predictive values (NPV) were calculated using 2x2 contingency tables and the Fisher’s Exact test.

Results
55% of these patients had baseline risk factors while the remainder were documented as: BRCA1 or BRCA2 gene-positive (6), familial or personal risk factors (533), or dense breast tissue (307). Malignant lesions were detected in each patient group at the rate of 41.33%, 83.3%, 41.08% and 36.8% respectively. The percentage of high risk patients in this study (44.9%) was greater than similar research projects (Kolb, Lichy & Newhouse, (2002) 40.6%; Rosenberg et al. (2006) 21% & Berg et al. (2008) 21%) and this has contributed to the increased incidence of breast cancer.

The biopsy rate was 5.25% (1198/22,814) with 501 malignant and 697 benign lesions documented giving a detection rate of 2.19% for the screened population. Mammographically detected malignant lesions had a mean size of 19.11mm (SD 12.30) while ultrasound-only detected lesions had a mean size of 10.5mm (SD 8.12).
The prevalence of cancer in the screened population was 2.19% (501/ 22,814) or 22.05:1,000 patients. The prevalence of cancer in the high risk group was 410:1,000 patients and for women with dense breast tissue, the prevalence of breast cancer was 368:1,000 patients.

A 5.3% detection rate was ascribed to a cohort of ultrasound-only detected lesions giving an increase in the overall detection rate of 1.46:1,000 patients. 62.5% of these patients had significant risk factors.

The detection rate of cancers with mammography, mammography + ultrasound, and bilateral breast ultrasound were all proven to be statistically significant (\( p = <0.0001 \), Fisher’s exact test). For the cohort of lesions detected with ultrasound-only, \( p = 1.0000 \) (Fisher’s exact test), this result was not statistically significant due to the small cohort in this group, precluding a comparative assessment.

**Conclusion**

The cancer detection rate of 220:10,000 patients was greater than the stated minimum of 69:10,000 for initial examinations established by Breast Screen Aotearoa. The biopsy rate of 5.25% was raised compared with similar studies, a reflection of the increased percentage of at-risk patients (Crystal, Strano, Shcharynski & Koretz, (2004) 2.5% and Kolb et al. (2002) 3.2%).

Bilateral whole breast ultrasound detected an additional number of breast cancers (14), 2.78% of the total number detected and increased the detection rate by 1.46:1,000 patients. Moreover, the performance of bilateral whole breast ultrasound was further validated with the detection of 14 (2.78%) contralateral lesions that were detected after a negative mammographic examination.

Bilateral whole breast ultrasound achieved improved results when compared with combined imaging (mammography + ultrasound) or mammography alone. Accuracy percentages were (92.8%, 92.4% & 91.2%): sensitivity (96.8%, 94.4% & 91.9%); specificity (90%, 89.2% & 90%): PPV 87.4%, 86.6% & 86.3%); and NPV 97.5%, 97.5% & 95.4%). The percentage results for the high risk patients, those with dense breast tissue and those in both risk groupings were lower in all categories: accuracy (91%, 89%, 87%); sensitivity (95%, 93%, 92%); specificity (88%, 87%, 84%); PPV (85%, 81%, 79%); and NPV (96%, 96%, 94%) respectively.
In this study, bilateral whole-breast ultrasound significantly increased the cancer detection rate and should be considered as a normal part of the imaging process in the patient with positive imaging findings, and in the patient with high risk factors and/or dense breast tissue. Bilateral whole-breast ultrasound does have role as an adjunct to mammography in the management of these patients.
Acknowledgements

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<th>Description</th>
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<tbody>
<tr>
<td>ACRIN</td>
<td>American College of Radiology Imaging Network</td>
</tr>
<tr>
<td>ACR</td>
<td>American College of Radiology</td>
</tr>
<tr>
<td>ADH</td>
<td>Atypical ductal hyperplasia</td>
</tr>
<tr>
<td>ANDI</td>
<td>Aberrations of normal development and involution</td>
</tr>
<tr>
<td>BPBD</td>
<td>Benign proliferative breast disease</td>
</tr>
<tr>
<td>BSA</td>
<td>Breast Screen Aotearoa</td>
</tr>
<tr>
<td>CAPPS</td>
<td>Columnar cell alteration with prominent snouts and secretions</td>
</tr>
<tr>
<td>DCIS</td>
<td>Ductal carcinoma in situ</td>
</tr>
<tr>
<td>FCC</td>
<td>Fibrocystic change</td>
</tr>
<tr>
<td>FNA</td>
<td>Fine needle aspiration</td>
</tr>
<tr>
<td>FN</td>
<td>False negative</td>
</tr>
<tr>
<td>FP</td>
<td>False positive</td>
</tr>
<tr>
<td>HRT</td>
<td>Hormone replacement therapy</td>
</tr>
<tr>
<td>IDC</td>
<td>Invasive ductal carcinoma</td>
</tr>
<tr>
<td>NAD</td>
<td>No abnormality detected</td>
</tr>
<tr>
<td>NPV</td>
<td>Negative predictive value</td>
</tr>
<tr>
<td>PH</td>
<td>Public health funded patients</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive predictive value</td>
</tr>
<tr>
<td>TDLU</td>
<td>Terminal ductal lobular units</td>
</tr>
<tr>
<td>TP</td>
<td>True positive</td>
</tr>
<tr>
<td>TN</td>
<td>True negative</td>
</tr>
<tr>
<td>US</td>
<td>Ultrasound</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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1.0 Introduction

What is the appropriate role of bilateral breast ultrasound, as an adjunct to mammography, in the management of patients with positive findings?

The principal aim of this study was to:
- assess whether bilateral whole-breast ultrasound could have a role in the management of patients with positive findings

Additionally, sub-aims were related to:
- the role of bilateral whole-breast ultrasound in the management of the high risk patient
- the role of bilateral whole-breast ultrasound in the management of patients with dense breast tissue
- the role of bilateral whole-breast ultrasound in the management of patients with both high risk factors and dense breast tissue

Though breast imaging with ultrasound has been established as an adjunct to mammography in recent research, (Kolb et al. 1998; Berg, 2003B; Warner et al. 2004; & Berg, Blume, Cormack & Mendelson, 2006), its role has been primarily confined to the targeted confirmation of cystic lesions (Berg et al.). Its use in the patient with a positive imaging finding has not been as well established.

With the development of ultrasound technology, (Georgian-Smith et al. 2000; & Muradali, 2005), ultrasound is becoming accepted as a tool to differentiate benign from malignant breast lesions (Stavros et al. 1995). Since 2000, there is an emerging body of evidence that suggest the use of bilateral whole breast ultrasound is valid (Kaplan, (2001); Crystal et al. (2004); Wilkinson et al. (2005); & Berg, 2003A & 2008). It seems timely to investigate its role both in the management of patients with symptoms and/or positive findings from mammography and in patients with established risk factors.

For the purpose of this study, the risk factors for breast cancer were an individual’s prior history of breast cancer, an individual’s positive status for the BRCA1 or BRCA2 gene, a familial history of breast cancer, or the presence of dense breast tissue.
Women with these risk factors may be excluded from the national screening programme, Breast Screen Aotearoa (BSA). This program was established by the New Zealand government (Ministry of Health, 2007A) to screen women for the early detection of curable cancers. Appropriate imaging for these high risk women is of obvious importance and perhaps the addition of bilateral breast ultrasound could be used to achieve satisfactory breast screening.

1.1. The study population

A retrospective review of historical data was accessed from a private radiology practice in New Zealand for the period January 1999 to December 2007 inclusive. A database was compiled and documented relevant patient information, the type/s of imaging performed, along with interventional procedures and correlation of the tissue samples with the histology results.

A total of 22,814 consecutive patients presented for screening or diagnostic breast imaging during the study period and 1063 of these patients required 1198 breast tissue biopsies based on the imaging findings of mammography and/or ultrasound. The patient cohort was a mixture of those with a baseline and increased risk status for breast cancer. This research will investigate and evaluate the data from those 1063 patients assessing the benefit, if any, of bilateral whole breast ultrasound in the patient with positive imaging findings and increased risk factors. Correlation of the breast imaging findings from mammography, mammography + ultrasound, or ultrasound-only with the pathohistological result will be evaluated to determine if any true benefit to the patient has occurred.

1.2. Imaging of the breast tissue

The goal of breast imaging is to image the total mass of breast tissue, detecting lesions and areas of architectural distortion, while discerning whether the observed changes are a benign or malignant process. Imaging of the breast tissue with mammography and/or ultrasound was performed with the express intention of detecting these abnormalities.

Stavros et al. published a foundational study in 1995 describing the usual appearance of benign and malignant lesions, however not all lesions conform to the established criteria so tissue sampling becomes necessary to confirm the diagnosis.
The criteria for the tissue sampling in this study were based on the BSA programme and included:

- all new lesions > 10mm
- multiple lesions of similar appearance where one is sampled as a representative of the group (Ministry of Health, 2007A)
- an apparent change in a lesion since previous imaging
- an apparent change in a lesion previously biopsied
- evidence of or increased vascularity in a lesion
- development of micro-calcifications within a region of tissue change/s

Imaging of breast tissue in this study occurred with a combination of mammography and/or bilateral whole-breast ultrasound dependant upon the patient risk factors and clinical presentation. All patients in the study group (1063) had both mammographic and ultrasound examinations of breast tissue, with the point of difference being whether the mammographic examination came prior to or after the ultrasound examination; this was dependant on the patient’s age at presentation.

Whether imaging a targeted region or performing whole-breast imaging, the technique of scanning breast tissue and the associated reliance on the skill of the operator are well recognised variables and as such are important considerations if whole breast imaging is to be performed competently (Kolb et al. (1998); Baker & Soo, (2002); & Elmore, Armstrong, Lehman, & Fletcher (2005).

1.3. Patients with increased risk factors

Within the study group (1063) some patients were identified as being at an increased risk of breast cancer due to a previous history of breast cancer, a BRCA1 or BRCA2 gene-positive status, or a significant family history of breast cancer. Familial risk factors are known to be more acute if the age of the affected relative was < 50 years of age at the time of diagnosis and/or they were a first-degree relative (Claus, Petruzella, Matloff & Carter (2005). For patients with a previously diagnosed breast cancer, there is an established risk for the occurrence of ipsilateral or contralateral breast cancers (Hill-Kayser, Harris, Hwang & Solin (2006). For patients who are BRCA positive, Cortesi et al. (2006) and Robinson & Offit, (2007) estimate the risk of breast cancer by the age of 80 years as 90% for carriers of the BRCA1 mutation and 40% for the BRCA2 mutation, with a corresponding risk of ovarian cancer of 24% and
8% respectively. In comparison, the lifetime risk for New Zealand women is stated to be 11% (Ministry of Health, 2007A).

1.4. What of breast density?

Breast density can be described as adipose (fatty), average (moderate density) or dense. Increases in breast density can hamper the detection of malignant lesions in the mammographic image, as the denser tissue appears as nodular areas interspersed with linear densities. Increased breast density is known to cause a parallel decrease in mammographic sensitivity suggesting there is a need for additional imaging if adequate interrogation of breast tissue is to occur (Baker et al. 2005).

Recent research documents that increased breast density can be acknowledged as an independent risk factor for breast cancer, with imaging of both mammography and bilateral whole breast ultrasound now considered to be the best practice (Carney et al. 2003; Carter, H. 2006; & Tagliafico et al. 2009).

Patients with dense breast tissue may additionally have other risk factors (refer Section 1.3) and even though a mammographic examination may have a negative result, it is appropriate to provide additional imaging. In this study, bilateral whole-breast ultrasound was considered an integral part of the examination process for these patients.

It is appropriate to comment on hormone replacement therapy for this medication is known to be associated with an increase in breast density in some patients. For the duration hormone replacement therapy, these patients are considered “at risk” if there is evidence of a global or focal increase in breast density (Carney et al. 2003 & Chen et al. 2004).

1.5. Statistical assessment

The detection of breast cancers at the earliest stage is the primary aim of all breast imaging. Statistical analysis is necessary to determine the value of mammography, mammography + ultrasound, and ultrasound as imaging modalities. Analysis of these imaging modalities will be completed for the total study group of patients as well as the sub-groups as listed below:
- the total group of patients (22,814)
- patients who had a core biopsy of breast tissue (1063)
- patients with known high risk factors (533)
- patients with increased breast density (307)
- patients with high risk factors and increased breast density (159)

Statistical tests will be applied to the data obtained so assessment of accuracy, sensitivity, specificity, and positive (PPV) and negative predictive values (NPV) of each combination of imaging can be completed - mammography, mammography + ultrasound, and ultrasound.

These results will be compared to the standards established by Breast Screen Aotearoa (refer Section 2.2) and to current research projects that have investigated the use of bilateral whole breast ultrasound. It is hoped that this process will allow an evaluation as to the appropriate role for bilateral whole-breast ultrasound as an adjunct to mammography, in the management of patients with positive findings.

Figure 1 Study Flow chart

(following page)
30,756 breast examinations

1,063 patients require further evaluation

1,198 breast core tissue biopsies

139 patients had > one biopsy

697 with benign histology: no further evaluation, return to screening

236 patients with normal baseline risk

265 patients with risk factors *

22,065 mammographic exams

9,543 ultrasound examinations

21,747 patients need no further evaluation – return to screening

697 with benign histology: no further evaluation, return to screening

236 patients with normal baseline risk

533 patients with risk factors *

265 patients with risk factors *

22,814 patients

22,814 patients

22,065 mammographic exams

9,543 ultrasound examinations

21,747 patients need no further evaluation – return to screening

697 with benign histology: no further evaluation, return to screening

236 patients with normal baseline risk

533 patients with risk factors *

265 patients with risk factors *

66 with adipose density had a malignant finding

3 patients with malignant findings (adopted – no history known)

107 with dense tissue had a malignant finding

115 with average tissue had a malignant finding

43 with adipose tissue had a malignant finding

167 with average tissue had a malignant finding

769 patients with high risk factors*

107 with dense tissue had a malignant finding

115 with average tissue had a malignant finding

769 patients with high risk factors*

* refer Section 4.4 for definition
2.0 Background

2.1 Introduction

The purpose of imaging in the human body is to identify areas of disease, fracture, distortion or disruption to the normal architecture. The purpose of breast imaging is to detect areas of tissue distortion and breast cancers when they are small to improve patient mortality rates.

Regular, systematic imaging of breast tissue is fundamental to the detection of altered breast architecture, allowing for sampling, analysis and identification of benign or malignant potential. Imaging of breast tissue can be achieved with magnetic resonance imaging, mammography and ultrasound and it is mammography and ultrasound, alone and in combination, that will be evaluated in this research project. This background section will lay the foundation for this study by reviewing the following topics:
- the BSA mammographic screening programme
- variations in breast tissue
- abnormalities in breast tissue - benign, indeterminate and malignant
- ultrasound and vascularity characteristics of breast lesions
- micro-calcifications
- scan technique
- the sonographer – the limitations and variables

Many issues surround the topic of breast cancer, bearing in mind that all women and men have a lifetime risk of being diagnosed with breast cancer. Khatib & Modjtabai (2002) acknowledged that any decrease in mortality can only be achieved with regular mammographic screening.

Mammography is oft referred to as the gold standard of breast imaging (Benson et al. 2004), so achieving an understanding on the current use of and the place that Breast Screen Aotearoa (BSA) has for women in New Zealand is important. The BSA screening programme guidelines parallel those established internationally and enables women in New Zealand to have regular breast screening - the incidence rates of breast cancer in this country are among the highest percentages in the world.
Having an awareness and sound knowledge of the principal types of breast lesions (benign, indeterminate and malignant) and their appearance in mammographic and ultrasound images is important if the subtlety of presentation is to be appreciated. A seminal study by Stavros et al. (1995) will be discussed for it established the baseline appearances of benign, indeterminate and malignant breast lesions. The presence or absence of lesion vascularity, the use of power Doppler and the varying appearances of micro-calcifications in breast tissue will be discussed to clarify the myriad of possible imaging presentations that confront the ultrasonographer.

The skill involved in performing breast ultrasound and in manipulating the technical aspects should not be underestimated in the process of sighting and identifying change in breast tissue. A review of the pertinent issues that may affect the sonographer/radiologist when performing bilateral whole-breast ultrasound will be discussed.

To begin then, an explanation of the current status of mammographic breast screening in New Zealand.

2.2. Mammographic screening

Early detection of breast cancer facilitates the reduction in breast cancer mortality with mammography acknowledged as the “most established method for imaging the breast and the primary tool for breast disease evaluation” (Pruthi et al. 2007, p. 45). However there are acknowledged limitations, particularly when investigating dense breast tissue (Benson, Blue, Judd & Harman, 2004). The goal of imaging is to detect early tissue changes in the breast before the patient is aware of an abnormality (Elmore et al. 2005).

Breast screening programs aim to reduce breast cancer mortality by routinely screening an entire, well-defined population at regular intervals; improving the outcome for women through detection of breast cancer at the earliest stage possible (Dixon, 2006). It is acknowledged that patient survival times are inversely related to the staging of the cancers.

BreastScreen Aotearoa (BSA) was established in New Zealand in 1998 with “the aim of reducing the number of women who die from breast cancer, through the early
detection of curable cancers” (Ministry of Health, 2007A, para 3). This aim was to be achieved with the provision of free screening mammograms for women who are asymptomatic and free from breast cancer (or five years since previous diagnosis). Initially (1998-2000), breast screening was available for women aged 50-65 years of age with an age range revision in July 2000 that now included women aged 45-69 years. BSA set statistical targets for all those involved in mammographic screening aligning the national standard in concordance with international recommendations. These included:

- 95% confidence interval for rates of cancer detection
- positive predictive value of > 99%
- specificity is required to be > 93%
- false positive rate of <9% (minimum requirement), though the expectation was <6%
- cancer detection rates of 69:10,000 for initial screening examinations
- cancer detection rates for subsequent screening examinations of 34.5:10,000
- small invasive screen-detected cancers <10mm are to be detected at the rate of 17.3:10,000
- small invasive cancers <15mm are to be detected at the rate of 34.5:10,000
- > 70% of the screen-detected cancers should be node-negative - detection before lymph nodes are involved
- subsequent examinations should have a node-negative rate of > 75%
- interval cancers should be detected at a rate of <6.9:10,000 (cancers detected between regular screening examinations)

(National Screening Unit, 2004).

A similar breast cancer detection rate was the expectation of Berg (2003), who stated that the prevalence of cancer seen on an initial mammogram was to be 50-70 cancers per 10,000 populations, decreasing to 2-3 cancers per 10,000 in a regularly screened population.

Mammograms are stated to be “particularly effective in women over 50 years of age who have mammograms every two years, detecting 75% - 90% of all unsuspected cancers” (Ministry of Health, 2007A, p. 1). Inherent problems with mammography relate to radiation exposure for the patient and variability in image assessment and acquisition with these factors affecting the clinical outcome (Baker & Soo, 2002). Lesions located in areas that are difficult to image can be inherently challenging to
diagnose, specifically lesions located high in the chest wall, in the upper inner quadrant, near the sternum (medial), or in the posterior-inferior aspect of the breast (inframammary fold) (Majid, Shaw de Paredes, Doherty, Sharma, & Salvador, 2003: Youk, Kim, Kim, & Oh, 2008). Difficulties in positioning the breast and gaining adequate visualisation of these regions are well recognised.

The World Health Organisation (WHO) conducts and coordinates research on all forms of human cancer. The International Agency for Research on Cancer (IARC) is part of the WHO and states that breast screening “delivered through a properly organized programme is efficacious in reducing mortality from breast cancer for women aged 50-69 years by 30%” (International Agency for Research on Cancer, para 2). The IARC stated in 2002 that there was a 25% reduction in breast cancer mortality after reviewing mammographic screening programmes, with a further 10% reduction for women who were screened at regular intervals. Statistical evidence from an English study has also shown a reduction in mortality rates for women aged 50-70 years who undergo regular mammographic screening (Advisory Committee on Breast Cancer Screening, 2006).

Internationally, New Zealand’s annual breast cancer incidence is among the highest in the world (National Policy and Quality Standards for BreastScreen Aotearoa, 2004) with breast cancer the most common cause of cancer registration and cancer deaths among New Zealand women (Ministry of Health, 2007B). Table 1 shows the number of breast cancer deaths that have occurred in New Zealand since 1995.

The New Zealand Breast Cancer Foundation (National Screening Unit, 2004) state that approximately 2,400 women and 20 men are diagnosed with breast cancer every year, with more than 600 deaths statistically attributed to breast cancer. The number of people being diagnosed with breast cancer has increased (18% over the last decade) though the death rate has decreased by 27.8% from 1987 to 2002 (Ministry of Health, 2007B) Women in New Zealand, have an average life-time risk of 11% of being diagnosed with breast cancer, with this risk being lower when the woman is younger.
<table>
<thead>
<tr>
<th>Year</th>
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<th>Patient deaths</th>
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<tr>
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<td>1865</td>
<td>638</td>
</tr>
<tr>
<td>1996</td>
<td>1906</td>
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</tr>
<tr>
<td>2006</td>
<td>2339*</td>
<td></td>
</tr>
</tbody>
</table>

Table 1 Breast cancer deaths registered with the Department of Statistics, NZ

* Results are provisional pending clarification of clinical details (The New Zealand Breast Cancer Foundation, 2008)

<table>
<thead>
<tr>
<th>Age risk</th>
<th>Age risk</th>
<th>Risk %</th>
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<tr>
<td>40-50 yrs</td>
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<tr>
<td>50-60 yrs</td>
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<td>3.0%</td>
</tr>
<tr>
<td>70+ yrs</td>
<td>1:38</td>
<td>2.6%</td>
</tr>
</tbody>
</table>

Table 2 Guidelines adapted from the ACR* Standards for Breast US.

(Baker et al. 2002)

(The New Zealand Breast Cancer Foundation, 2008)

*ACR – American College of Radiologists
Table 2 shows the relative risk percentages for life (per age group) of being diagnosed with breast cancer; this risk peaking for women aged 60-70 years of age. The fact that eight out of nine women who develop breast cancer do not have an affected mother, sister or daughter was stated after a review of 52 epidemiological studies from 1983-1993 (Collaborative Group on Hormonal Factors in Breast Cancer, 2001). Women with a family history of breast cancer are known to be at an increased risk of the disease. For these women, there is a lifetime risk of breast cancer of 5.5% if a patient has one affected first-degree relative and 13.3% if there are two affected first-degree relatives. First-degree relatives are defined as a mother, father, sister or brother. The risk ratios for patients with a family history of breast cancer are increased; particularly when the affected risk-relatives were <50 years of age. Cortesi et al. (2006) stated that the risk ratio for breast cancer in relation to familial occurrence decreases with age, until the age of 60 years.

The New Zealand Breast Cancer Foundation comment that while 5-10% of breast cancers are attributed to family history, 90-95% of women who develop breast cancer do not have a family history of this disease. Berg (2003) states a similarly high percentage whereby 80% of women who develop breast cancer have no known risk factors. However, what constitutes a risk factor is variable depending upon the author or the research being reviewed. Risk factors suggested have included the patient’s age, the proportion of glandular breast tissue (breast density), an early age at onset of menarche, a late age at onset of menopause, a first full-term pregnancy after the age of 30 years, obesity, a history of premenopausal breast cancer for a mother or a sister, a personal history of breast cancer or the presence of benign proliferative breast disease.

The sensitivity of mammography in the diagnosis of breast cancer however, is “variable and influenced by age, breast density, family history or the use of hormone replacement therapy” (Crystal et al. 2004, p. 1). Elmore et al (2005) document sensitivity at 63% for women with dense tissue and up to 87% for women with adipose tissue, Baker et al. (2005) state 69% - 83% while Berg et al. (2004) extend the percentage range and state it to be 100% in adipose tissue and 30% - 48% in dense breast parenchyma. These authors suggest that one of the factors leading to false-negative findings and the failure to detect malignancies with mammography is the increased density of breast tissue.
Foxcroft, Evans, Joshua & Hirst (2000) comment that smaller tumours, and tumours found in dense breast tissue are less likely to be seen on mammography. In that 2000 study, the number of “mammographically occult cancers per 1,000 mammograms was almost twice as great in dense breast tissue” (Foxcroft et al. p. 1).

Mammographic sensitivity is commented on by several authors as being inversely related to breast density or the proportion of glandular tissue within the breast (Berg et al. 2004; Fasching et al. 2006; Osaka et al. 2007). The proportion of glandular tissue generally is expected to decrease with increasing age, with 62% of women <35 years having more than 50% glandular tissue. In comparison, for women >60 years, only 27% had more than 50% glandular tissue (Stomper, D'Souza, DiNitto & Arredondo, 1996; Elmore et al, 2005). Women aged 40 years or younger have a “lower incidence of breast disease, denser breast tissue and, on average, faster-growing cancers” (Elmore et al.). In a 2004 study involving 111 women, cancer was twice as prevalent in dense breasts as in fatty breasts, with percentages of 62.7% and 37.3% respectively (Berg, 2004).

Tot, Tabar & Dean (2000) comment that when mammographic screening occurs at regular intervals for a large numbers of women, there is an opportunity to “describe the dynamic changes of normal breast tissue as a function of aging”. Further, to observe “the transition between normal and aberrant development and involution” (p. 340) of breast tissue.

Breast cancer screening is designed to detect breast cancers earlier and improve patient mortality rates. The debate is whether this diagnosis would have been of significance to the patient in their lifetime or whether it would have not, had they not been screened. The real benefit of mammographic screening can be artificially inflated unless the length time and lead time biases are taken into consideration. The next section explains what these statistical terms mean, and the effect that they may have on mammographic screening programs.
2.3. Length-time and lead-time bias: relative to mammographic screening

Measuring the true benefit of screening mammography can be difficult due to length and lead time biases. The apparent benefit of an early diagnosis and intervention of a screen-detected breast lesion when compared with a lesion detected by the patient may appear to be of greater benefit.

Length time bias affects the data on screening tests as detection of the slower growing cancers occurs while the patient is asymptomatic. If these cancers were missed at screening, the opportunity for future detection still exists while the patient is asymptomatic. However, for cancers that are aggressive, detection is more likely to be from a clinical presentation than from a screening examination (Barratt, 2006). Slower-growing tumours may well be over-detected in a screening mammography examination and can erroneously indicate an improved survival time.

Lead-time bias is the length of time between the detection of a breast cancer and its clinical presentation and resultant diagnosis. Breast screening is intended to diagnose disease earlier than it would be detected without screening. This leads to the illusion that earlier detection may prolong the patient’s survival when really there was only an earlier diagnosis. Determining which breast cancers are of clinical significance and which are not may not be possible. Even if in both cases a person will die at the same time, because the disease was diagnosed early with screening, the survival time since diagnosis seems longer. No additional life has been gained though the patient has knowledge of the disease for longer. Statistically, it will appear that breast screening increases survival time or lead-time bias.

Breast tissue has many varied appearances and awareness of these different types and the effect on the mammographic image is important to appreciate the potential limitations of mammography. The next section describes these in detail, describing the inherent difficulties that can occur with detection of abnormalities in some types of breast tissue.
2.4. Variation in breast tissue: the effect on the mammographic image

The anatomic structure of the breast is described by Tot et al. (2000), as showing “great diversity with the relative proportion of the basic structural elements varying enormously in the different regions, over time and among different individuals” (p. 340). The functional tissue of the breast is called a terminal duct-lobular unit (TDLU) and is composed of milk glands held in place by fat and stroma (connective tissue framework containing blood vessels, nerves, and lymphatics). These units drain into a series of branching ducts, emptying into 12-15 major ducts converging behind the nipple in a radial arrangement (Tot et al.). In the mammographic image they can be seen as nodular densities when surrounded by adipose tissue. Mammographically, adipose or fatty tissue is radiolucent and fibrous tissue radiopaque, appearing as shades of white while the TDLU’s, ducts, vessels and fibrous strands appear as linear white structures of varying widths.

Five parenchymal patterns of breast tissue are described by Tabar, Gram & Funkhouser (1997) to classify how the different types of tissue appear in the mammographic image. Pattern One is described as adipose or fatty and is commonly associated with premenopausal women where the TDLU's are distributed throughout the whole breast. The scalloped anterior contours also seen are the Cooper’s ligaments. With involution, Pattern Two or Three is used to describe changes in breast tissue.

Pattern Two is characteristic of older women where the majority of the TDLU’s have become atrophic and been replaced by adipose tissue. Detection of small abnormalities in the breast becomes easier mammographically when they are observed surrounded in an adipose background.

Pattern Three is associated with older women, showing a difference in the “prominent retroareolar pattern due to dilated major ducts and/or periductal fibrosis” (p. 340). Pattern Two and Three were described in the mammographic reports of this study as being of average density. These two stages are the end-stage of involution with a predominance of adipose tissue and linear structures apparent.

Pattern Four is found in 10-12% of asymptomatic women aged 40 - 74 years where enlarged TDLU’s appear as 3-6mm nodular densities interspersed with linear
densities – these nodular densities make the detection of abnormalities in the breast tissue more problematic (Tabar et al. 1997).

*Pattern Five* occurs when the TDLU’s have been replaced by fibrous tissue rather than fat, limiting the effectiveness of mammography to adequately interrogate all tissue. Mammographically this is described as ‘ground glass’ (white) and obscures hyperplastic changes. Occurring in 5-6% of asymptomatic women, Pattern Five and Four appear to be resistant to the process of involution and often show no change with the patient’s increasing age. These patterns (Four and Five) were described as being dense tissue in the mammographic reports for this study.

Having gained an understanding of the different types of breast tissue, it is appropriate to discuss the types of breast lesions and the way these can appear mammographically. The next section examines the key types of benign, malignant and indeterminate lesions commonly seen in breast imaging. Of the large range of possible breast lesions, I have chosen to discuss only those lesions that commonly occurred in this study.

### 2.5. Abnormalities that occur in breast tissue: benign, indeterminate and malignant

Many breast lesions, both benign and malignant, have well-recognised characteristics in the ultrasound image. Benign breast lesions have a low probability of malignancy and exhibit stable, self-limiting growth patterns while remaining in the normal tissue planes and not invading the surrounding tissues. Common benign breast lesions to be reviewed include cysts, intramammary lymph nodes, fibroadenomas, focal fibrosis, fat necrosis, sclerosing adenosis and post-surgical scars.

#### 2.5.1. Benign breast lesions

Cysts are fluid-filled sacs (refer Figure 2) that develop in breast tissue, occurring naturally as the breast ages and changes. These cysts originate in the lobules and vary considerably in size and can develop anywhere in the breast, though more commonly in the upper half. Cysts may feel soft or hard depending on the degree of fluid distention – this is analogous to a partly blown up or a fully inflated balloon.
Cysts are most common in women aged 35 years old through to the onset of the menopause.

![Figure 2 Breast cyst](Image used with permission)

Fibroadenomas are the most common benign breast lesion in women under 25 years of age and the varied sonographic appearance of fibroadenomas was the topic of a study by Fornage, Lorigan & Andry (1999). While 92% of the lesions studied were “uniformly hypoechogenic and homogeneous in echotexture, 27% showed irregular margins and 10% were noted to have macro-calcifications” (p.673). The sonographic appearances of both benign and malignant lesions often overlap and may cause a confusion of differentiation – see Figure 3. Muradali (2005) described fibroadenomas as ellipsoid in shape, wider than tall, following the contour of the skin, with a sonographic negative predictive value of 99%. The growth of most fibroadenomas “remains within normal tissue planes” (Stavros et al. 1995, p.126) and this leads to

![Figure 3 Fibroadenomas - varied appearances](Images used with permission)
the ‘wider than tall’ appearance. Stavros et al. found that most fibroadenomas were isoechoic or mildly hypoechoic, relative to the surrounding fatty tissue. Weinstein et al. (2004) described fibroadenomas as a common mass appearing homogeneous or heterogenous in echotexture. However once a fibroadenoma “undergoes hyalinization, posterior acoustic shadowing may be seen” (p. 74), though this shadowing is not as dense as is seen when posterior to malignant lesions.

Focal fibrosis is described by Weinstein et al. (2004) as a common condition, accounting for at least 9% of the lesions diagnosed. Focal fibrosis has a variety of mammographic appearances, (as seen in Figure 4) and can appear as “well-circumscribed, asymmetric density, irregular masses with architectural distortion” (p. 80). With ultrasound, focal fibrosis may be hypoechoic, have posterior acoustic shadowing, be well defined or have indistinct boundaries.

![Figure 4 Focal fibrosis variation](Images used with permission)

Intramammary lymph nodes are a normal part of the breast structure and can often be mistaken as a breast lesion, appearing as an “ellipsoid or gently lobulated shape, showing a prominent fatty hilum and thin cortex” (Muradali, 2005, p. 276).
Fat necrosis is described as “a benign condition due to prior surgery or trauma” (Weinstein et al. 2004, p. 78). The appearance of fat necrosis in the breast is varied and it is the patient’s history that is a strong indicator as to the possible type of lesion for a history of trauma to breast tissue often results in an area of fat necrosis. Though the lesion may be very distinct in an ultrasound image and a palpable mass felt (refer Figure 5), the patient may be asymptomatic. Mammographic appearances of fat necrosis are diverse and include calcifications, irregular spiculation, and hypoechoic with posterior shadowing. In the latter stages of resolution, fat necrosis can appear as an oil cyst: a “circumscribed hypoechoic mass with or without posterior acoustic shadowing” (p. 78). Fat necrosis may also be seen as a complex mass of mixed echotexture or indeed show no apparent lesion.

![Figure 5 Fat necrosis](image_url)  
(Image used with permission)

Sclerosing adenosis occurs as part of aberrations of normal development and involution (ANDI) and is “a component of the proliferative fibrocystic change complex” (Weinstein et al. 2004, p. 82). Sclerosing adenosis may form a well-defined nodule or spiculated mass while in the mammographic image, there may be “a focal group of punctuate calcifications or a regional cluster of powdery calcifications” (p. 82). In the ultrasound image this will appear heterogenous with ill defined areas of altered echotexture.

Post-surgical scars can mimic a malignancy by showing an area of posterior acoustic shadowing, however the lack of a central mass is the identifying feature. Awareness of the individual patient’s medical history is important and all surgical scars should be assessed in several planes to correlate the shadowing in the image with the scar. In
addition, breast tissue within the region of the scar should be assessed for any recurrence of malignancy.

2.5.2. Indeterminate breast lesions

Indeterminate breast lesions show distinct localized alteration in the cellular structure and while benign in diagnosis, these changes are acknowledged as a precursor to breast cancer and herald the need for future surgical intervention. Atypical ductal hyperplasia and radial scars are the specific indeterminate lesions that will be discussed.

Atypical ductal hyperplasia (ADH) relates to a region of proliferative breast tissue identified by an increased growth of the cells lining the ducts as viewed in Figure 6. The presence of ADH increases a woman's risk of developing breast cancer by four or five times the normal risk (Cotran, Kumar & Robbins, 1994; Worsham et al. 2007). The risk is documented as being even higher in women who have additional familial risk factors.

![Figure 6 Atypical ductal hyperplasia (ADH)](Image used with permission)

Radial scars are viewed as a significant risk factor for breast cancer. Called a "complex sclerosing lesion of the breast" .... they “appear as spicules arising from a central nidus forming a stellate pattern” (Weinstein et al. 2004, p.75). In comparison with typical breast cancers, radial scars have a “dominant central mammographic density with shorter, broader based spiculations” (Cawson, 2005, p.356). This creates distortion of the parallel planes of normal tissue and mammographically, fat
can be trapped centrally and appear as a lucency. On ultrasound, they may seem as a hypoechoic mass with dense posterior shadowing, similar to the appearance of a malignant lesion (Figure 7). Tabar (2007) comments that 10-30% of radial scars commonly are associated with malignant potential lesions such as atypical lobular hyperplasia, low grade ductal carcinoma in situ (DCIS) and tubular carcinomas. Several researchers conclude that women with radial scars have a risk of breast cancer that is nearly twice the risk of the women without (Jacobs, Byrne, Colditz, Connolly & Schnitt, 1999) and surgical intervention is appropriate.

![Figure 7 Radial Scar](Images used with permission)

2.5.3. **Malignant breast lesions**

Breast cancers can start in any part of the breast tissue and while most originate in the TDLU’s or ducts, some do occur in the breast lobules. Malignant lesions are significantly different in appearance to benign lesions, and distort the normal tissue planes and invade surrounding tissue. A marked increased in vascularity is apparent with colour Doppler and these lesions have the potential to metastasize to distant tissues through lymphatic and vascular channels. Malignant lesions discussed in this
section include invasive ductal carcinoma (IDC), ductal carcinoma in situ (DCIS), invasive lobular and invasive tubular carcinomas.

2.5.3.1. Invasive ductal carcinoma
Invasive ductal cancers (IDC) were assessed in a study performed from 1993 - 2002 by Rotstein & Neerhut (2005) where the characteristics of Grade 3 IDC’s were evaluated - 87% of those tumours had “a margin with an echogenic rind, microlobulation or angular margins” (p.476). Posterior shadowing or enhancement and echogenicity were all assessed but it was the tumour margin that was most telling. Acoustic shadowing was absent in 70% of the cases. Rotstein & Neerhut comment that these lesions tend to be very cellular and show less distortion of the tissue planes in the breast. Assessment of the interface between the tumour and adjacent breast tissue is essential to determine the extent of the lesion.

IDC’s of the breast account for a high percentage of breast cancers (Perlmutter, 2008) where the cancer cells form in the lining of the ducts and may penetrate through the ductal wall and invade nearby healthy tissue. Younger women tend to have more aggressive forms of IDC and these appear on the ultrasound image as solid and circumscribed, with pushing margins. They infrequently appear as benign lesions due to their cellular nature and may even enhance, appearing brighter, due to their cellularity. The slower growing IDC’s often shadow in the ultrasound image as they are less cellular, appearing as a “poorly differentiated lesion surrounded by collagenous fibre”. Watermann, Tempfer, Hefler & Stickeler (2005) comment that the ultrasound appearance of these cancers vary significantly from an indistinct margin to posterior shadowing. Berg et al. (2004) documented that the sensitivity of a mammogram and an ultrasound examination varied for different types of cancer. IDC showed sensitivities of 81% and 94% respectively, while invasive lobular carcinoma had sensitivities of 34% and 86%. The accuracy of ultrasound diagnosis for invasive and intraductal cancers was described by Chen et al. (2003) as 92% and 84.8% respectively. Figure 8 illustrates the varying appearance of IDC.
2.5.3.2. Ductal carcinoma in situ

Ductal carcinoma in situ (DCIS) is described pathologically as a “malignant neoplasm of the breast that is confined to the ducts and lobules, without invasion into the surrounding breast stroma” by Boonjunwetwat, Chyutipraiwan, Sampatanukul & Chatamra (2007, p.539). Piccoli (2003, p. S83) describes ultrasound findings of DCIS as a “micro-lobulated, hypoechoic mass with calcifications and ductal extension”. The dilated ducts may appear as hypoechoic, well-defined, tubular structures, differing from the normal breast parenchyma (see Figure 9). DCIS was identified mammographically in 73-98% of cases by the presence of the micro-calcifications (Boonjunwetwat et al). Micro-calcifications may appear as hyperechoic foci that have reproducible positions, seen in both transverse and longitudinal images. The micro-calcifications associated with DCIS are always multifocal and have a variable appearance. Micro-calcifications are classified as being linear, granular and of a mixed form, with granular micro-calcifications most commonly associated with DCIS. Hashimoto, Kramer & Picozzi (2001), with a small cohort of patients (18), assessed the ultrasound characteristics of micro-calcifications in patients with biopsy-proven DCIS. These authors reported a 94% sonographic detection rate. Benson et al. (2004) comment that mammography was superior to ultrasound in the detection of DCIS due to the lack of soft tissue changes and the sensitivity for detection of micro-calcifications by mammography.
2.5.3.3. Invasive lobular carcinoma

Invasive lobular cancer was the focus of a study by Selinko, Middleton & Dempsey (2004). Evaluation of the comparative sensitivity of ultrasound and mammography in the detection of these lesions was undertaken with a cohort of 62 patients with pathologically proven invasive lobular cancer. Invasive lobular cancer infiltrates in a diffuse manner with no apparent architectural distortion to the breast tissue – a
histological analysis shows an ‘Indian file’ pattern of tumour cell arrangement (Tabar, 2007, p. D-34). Mammographically, invasive lobular cancer may be occult due to this permeative pattern of growth or appear as a typical malignant spiculated mass with associated architectural distortion. On ultrasound (Figure 10) lobular carcinomas can be seen as a hypoechoic mass without identifiable margins, with or without posterior shadowing. Sensitivity of mammography was 65% and 98% for ultrasound. Images of invasive lobular carcinomas can be seen in Figure 10.

Figure 10 Invasive lobular carcinoma – a varied appearance at presentation

(Images used with permission)

Malignant tumours other than invasive ductal or lobular were less common in this study. Infiltrating tubular carcinoma is slow-growing tumour that infrequently
metastasizes. It is defined as having “at least 75% of the tumour composed of tubular structures” (p. 159). Gunhan-Bilgen (2007) assessed tubular carcinomas in 2872 women, determining it to be seen on mammography as a small, spiculated mass, and then on ultrasound as an irregular mass with posterior acoustic shadowing. Tabar (2007) commented that 40% of patients with tubular carcinoma report a “positive family history among first degree relatives” (p.D-29). Examples of tubular carcinoma can be seen in Figure 11.

![Figure 11 Tubular carcinoma](Images used with permission)

Not all lesions fulfill the classic criteria of a given pathology. Ultrasonically the appearance of these lesions is quite different and while much research has been performed, the seminal study by Stavros et al. (1995) is still applicable in the practice of breast imaging today. Appreciating the ultrasonic features of benign, indeterminate and malignant breast lesions is vital if areas of altered echotexture are to be detected. The next section will describe the principal features of these lesions with the characteristics that may be present in the ultrasound image.
2.6. Ultrasound characteristics of lesions

Benign lesions are characterized by controlled cellular growth, with zero spread to adjacent tissue or distant tissues. Malignant lesions show uncontrolled cellular division, growth of abnormal cells, with the potential to infiltrate surrounding tissue and/or metastasize through the circulatory or lymphatic systems. Indeterminate lesions show neither definitive benign or malignant characteristics but rather have an altered cellular structure that requires further assessment either by a core tissue biopsy or through regular monitoring when imaging breast tissue.

The study by Stavros et al. (1995) set out to determine whether ultrasound could accurately define the different characteristics of breast lesions. 759 sonographically solid lesions were assessed, and in the process an initial system to describe the ultrasound appearance of breast lesions was developed. It is important to acknowledge that this study is still considered the landmark reference article from which future studies have been developed.

Malignant lesions were defined as:

- *taller than wide*: AP measurement is greater than the transverse measurement
- *microlobulations* are apparent on the surface of the lesion
- *angular margins* are seen at the interface between the iso- or hypoechoic central part of a lesion and the surrounding tissue
- *hypoechoogenicity* of the lesion in comparison with the adjacent breast tissue; such as fat or periductal tissue
- *posterior shadowing* is seen distal to the lesion
- *spiculation* appears as alternating layers of hypo- and hyperechoic straight lines radiating from the lesion surface
- *punctate calcifications* are visible within the lesion
- *duct extension* occurs radially around the lesion, or within a duct extending away from the lesion

In comparison, benign breast lesions can be defined as having these characteristics:

- *wider than tall*: transverse measurement is greater than the AP measurement
- **ellipsoid shape**: well-circumscribed lobulations with smooth margins are suggestive of a slow growing, non-infiltrating mass
- **well defined echogenic capsule**: clear demarcation of the lesion from the surrounding tissue
- **markedly hyperechoic**: uniform echotexture typical of fibrous tissue

Listed in the Table 3 is a summary of those ultrasound characteristics (Stavros et al. 1995).

<table>
<thead>
<tr>
<th>Ultrasound Characteristics of Lesions</th>
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<tr>
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<td>Duct extension</td>
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<td>Microlobulations</td>
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</table>

**Table 3 Ultrasound characteristics of lesions**

Stavros et al. (1995) stated that ultrasound was able to “accurately classify some lesions as benign, allowing imaging follow-up rather than biopsy” (p. 123), suggesting that ultrasound can improve the specificity of clinical and mammographic abnormalities. The current medico-legal environment “encourages an aggressive biopsy approach to breast problems” (Stavros et al. p. 133), indicating a medico-legal necessity for accurate imaging and diagnosis of all breast abnormalities. Based on the study by Stavros et al. (1995). The American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) developed the now internationally accepted system of lesion categorization.

Later studies in 2004 extended and confirmed the earlier work of Stavros et al. when 1203 Chinese females with palpable breast lesions were assessed ultrasonically by Chen et al. (2004). The patients involved had both an ultrasound examination and histological analysis of the excised tissue, with the results of the samples confirming
the suspected diagnosis as determined by the ultrasound appearance of the lesions. Chen et al. and Edeiken et al. (2003) suggest that “an irregular margin, irregular shape, posterior acoustic shadowing, non-uniform echotexture, skin involvement, hypoechogenicity and AP/width ratio” (p. 195) were the principal malignant markers. Normal breast tissue may demonstrate posterior acoustic shadowing due to the multiple tissue interfaces such as connective tissue or Cooper’s ligaments. This appearance can be easily resolved with dynamic imaging of the area in different planes, proving that the shadowing is due to tissue interfaces and not a discrete mass.

In assessing whether breast lesions should be core-biopsied, Muradali (2005) cite similar characteristics as the previous authors and comment that the ultrasonic characteristics help define the course of clinical action. Muradali identified a negative predictive value of 99% for the benign lesion if it was “ellipsoid in shape, wider than tall and following the contour of the skin” (p. 276). Buchberger, Niehoff, Obrist, De Koekkoek-Doll & Dunser (2000) state the sensitivity of ultrasound classification for malignancy was 100% and the specificity was 31%. Kaplan (2001) & Kolb et al. (1998) have also shown that sonography has the ability to detect malignancy in dense breast tissues.

One other distinguishing characteristic of malignant lesions that needs to be discussed is the presence and quantity of vascularity associated within and around a lesion. Power Doppler is most often used due to its sensitivity to the likely low-flow state of a malignant lesion and assesses “the amplitude of blood flow rather than direction or velocity” (Raza & Baum, 1997, p. 164).

2.7. Vascularity of lesions: what are the appearances

Increased vascularity is often seen when associated with rapid malignant tumour growth. Tumour angiogenesis or the development of new blood vessels facilitates tumour growth (Raza & Baum, 1997) and is critical for the growth and spread of cancers. These authors comment that blood vessels associated with malignant lesions often “penetrate the lesion from the periphery with an irregular branching pattern” (p. 167). Kook et al. (1999); Ozdemir et al. (2001) & Svensson (2002) all agree that power Doppler is more sensitive than colour Doppler and is a powerful indicator of malignancy.
Assessment of 86 solid lesions by Raza & Baum (1997) with power Doppler showed 29% of the lesions proven malignant. 84% of the malignant lesions showed penetrating or peripheral vessels while the remaining 16% showed no obvious blood flow on power Doppler yet were proven malignant histologically. Power Doppler demonstrated a diagnostic sensitivity of 68% and a specificity of 95%. A point worth of consideration is that 8% of the breast cancers in this study were detected with the use of power Doppler only, detecting an area of increased vascularity in the region of suspicion.

Duct extension or branching patterns in the ultrasound image are suggestive of a malignant process within breast tissue. Stavros et al. (1995) describe ductal extension as development towards the nipple, with branch patterns developing away from the nipple. Benign lesions often showed no detectable vessels or with a few exceptions, peripheral or small central vessels (Robinson and Offit, 2007).

Malignant breast lesions are often seen to have micro-calcifications or specks of calcium within the affected tissue. Part of the discussion on the varied appearances of malignancy must involve a review of the types of calcification that can be observed. The following section describes micro-calcifications and the lesions they are most likely associated with.

2.8. Micro-calcifications: how they present in breast tissue

Micro-calcifications present in breast tissue are an indicator of change at a cellular level, appearing as specks of calcium showing up in clusters or in patterns that may be visible on the mammographic image. Determining the presence of, the type and shape of micro-calcifications is important.

Determining whether these micro-calcifications are within the ducts, within the TDLU or outside the glandular tissue is important (Tabar, 2007) if the question of benign or malignant growth patterns are to be resolved. Within the ducts, micro-calcifications are described as a ‘casting type’ and may appear fragmented or dotted; Tabar et al. (1997) stated these micro-calcifications have a 96% probability of malignancy and may be associated with extensive DCIS. Fine linear or clustered calcifications have
a high association with malignancy (61%) though they are not often visible in ultrasound images unless they are within a mass. The remainder are known to be associated with fibrocystic change, fat necrosis, fibroadenomas or papillomas.

2.8.1. Mammographically visible calcifications

Many descriptions have been used to define the pattern, number and distribution of micro-calcifications and the following list details the principal descriptions commonly used in reporting:

- fine, linear, branching
- clustered
- skin or dermal calcifications
- egg-shell like calcifications
- radiolucent centre
- vascular calcifications
- teacup or rim calcifications
- pearl-like calcifications
- popcorn-like calcifications (coarse)
- large rod-like calcifications
- round and punctuate calcifications in a linear or segmental distribution
- suture calcifications
- dystrophic calcifications

(American College of Radiology, 2008)

Within the TDLU, the calcification may appear powdery, be hardly perceptible or seem like “crushed stone” on the mammographic image (Tabar, 2007). When micro-calcifications are seen in glandular tissue, the walls of blood vessels, in lymph nodes, post-surgical scars, oil cysts or in the skin, they are usually associated with benign conditions. Benign calcifications may often look like a “teacup” on a lateral mammographic view (horizontal ray), as the calcifications layer in the bottom of microcysts or cysts.

Micro-calcifications are often associated with invasive carcinomas and may be detectable on the ultrasound image within the hypoechogenic component of the tumour. The background of reduced brightness of the tumour can enhance the visibility of the echogenic punctate calcifications (Gugler et al. 2000). In normal breast parenchyma,
Micro-calcifications are more difficult to detect due to the reduced contrast relative to the micro-calcifications.

Mammography is sensitive to microcalcification detection with 17-56% of all excised clustered microcalcifications proven malignant on histology (Gufler et al. 2000). With ultrasound, the detection of micro-calcifications in breast cancers is possible with high-resolution transducers; particularly in lesions larger than 1cm according to Boonjunwetwat et al. (2007). However visualisation of micro-calcifications inside small masses or within thickened duct lesions may well be more problematic. A detection rate of 75% is stated by Gufler et al. when imaging clustered micro-calcifications whereas a 100% detection rate is documented when imaging invasive carcinoma associated with calcifications from carcinoma in situ. The area of the clustered micro-calcifications, the number per cm$^3$ and the total number of micro-calcifications are all part of the assessment.

Resolution in ultrasound is defined by the properties of the beam relative to the frequency of the transducer. For a 7.5MHz linear array transducer, the lateral resolution of is in the order of 1mm and yet most micro-calcifications are in the range of 0.1 – 1mm. Ultrasound detection of micro-calcifications is constrained by its own technical capabilities. As well as this technical constraint, detection of these micro-calcifications is dependent on the appropriate use of and attention to specific details to gain quality diagnostic images. The next section assesses the need for correct ultrasound scan techniques to be applied if consistent diagnostic images are to be obtained.

2.9. **Scan technique: imaging the breast with ultrasound**

The scan protocol for a bilateral whole-breast ultrasound examination appears standardised throughout the majority of studies that have been reviewed. Each breast is scanned individually, with the patient in a supine position and the ipsilateral arm extended over the head. If the breasts were large and pendulous, the patient would be rolled to a supine-oblique position, with a pillow supporting the patient while the outer breast was scanned.
The survey of each breast was performed “in both radial and anti-radial scanning planes with transverse and sagittal images” in overlapping linear strips (Berg et al. 2006; Crystal et al. (2004, p. 357). Breast tissue was scanned from the periphery to the nipple, with oblique views obtained in the retroareolar regions to ensure coverage of the entire breast. Stavros et al. (1995) likens scanning of the breast as to the spokes of a wheel with the nipple as the hub. The ductal system of the breast “courses in a radial direction toward the nipple” (p. 124) and ductal tumours are best visualized in this plane.

The entire mass of breast tissue was interrogated with a panoramic display in the lateral and superior portions of breast tissue. Scanning each axilla enables assessment of the adjacent lymph nodes, seeking out any thickening, lobulations, and eccentric lobulations of the cortex or disappearance of the hilum.

The scanning of breast tissue with ultrasound requires careful and considered use of technical parameters such as transducer frequency, field of view, focal zone/s and the frame rate. The transducer should be the highest frequency possible that can image the deepest breast tissue as this gives the best possible resolution and definition of tissue to enable detection of abnormalities.

The field of view in breast imaging must be adjusted for differing breast sizes with limited focal zones (usually one or two) used to ensure adequate screening of breast tissue. For areas of architectural change/ distortion, the field of view must include sufficient superficial tissue to assess the depth of the mass from the skin, and sufficient posterior tissue to evaluate the posterior transmission of the ultrasound beam. Focal zones are placed within 1cm from the anterior or posterior margins of the lesion under investigation.

Having briefly discussed the importance of correct scan techniques for breast imaging, the skill of the operator should be considered. Operator skill is remarked upon in many of the leading studies as is observer capability and reproducibility. These issues will be discussed in the following section, laying out the important issues if breast ultrasound is to be taken seriously in the future.
2.10. **The sonographer: dependence on the operator for a diagnostic image**

Ultrasound is acknowledged as a technically difficult modality, requiring high quality equipment, appropriate technical settings and a skilled operator to create the optimal image (Baker et al. 2000). Breast tissue can appear normal and yet be abnormal, or can simulate the impression of a breast lesion where there is not. With the development of improved ultrasound resolution, software and operator skills, ultrasound is becoming recognised as a viable imaging modality to discern benign from malignant breast lesions with increasing accuracy. Weinstein et al. (2004) stressed the importance of dynamic real-time scanning in the evaluation of subtle breast lesions rather than a reliance on the hard-copy images post examination.

Considerable observer variability may occur for diagnostic ultrasound is user-dependent (Cha et al. 2007). Chen et al. (2004) suggest that the subjective nature of assessing the ultrasound features in the image can lead to a misclassification of lesions. Elmore et al. (2005) comment that breast ultrasound will have limitations as a screening tool unless the operator involved is well-trained and skilled. Berg (2003) agrees with these authors and comments that “real-time adjustments of gain, focal zones, dynamic range, angle of insonation, pressure, patient positioning and recognition of abnormalities” (p. 361) is essential. Berg et al. (2006) in a later study stated that “success in lesion detection may be influenced by operator fatigue, large breast size, multiplicity of findings and lesion depth” (p. 364). In a later study, Berg et al. (2008) again remind the reader of the “dependence of free-hand screening breast ultrasound .... because an abnormality must be perceived while scanning” (p. 2152).

Evaluation of the hard-copy ultrasound image rather than the real-time assessment was the focus of a study by Rahbar et al. (1999). The hard copy image could potentially compromise and under- or over estimate the true accuracy of ultrasound for an abnormality may not be present in an image. It is suggested that any judgment on the accuracy of ultrasound should be based on its real-time or dynamic interpretation rather than on its hard-copy images (Houssami et al. 2003 & 2005).

The sonographer must have a combination of “extensive experience in breast ultrasound alongside a basic knowledge of mammography” (Kaplan, 2001, p. 648) if diagnostic results are to be consistently obtained. The frequent practice of breast ultrasound will then maintain those technical and observational skills.
The accuracy and reproducibility of ultrasound results is crucial to the reliability of this type of imaging if breast ultrasound is to be valued as an appropriate breast imaging tool (Kolb et al. 1998). Watermann et al. (2005) recognised that inconsistencies in the observation rates of ultrasound lesion criteria and variability in operator skill could lower the diagnostic value of breast ultrasound. Watermann et al. stated that the major disadvantage of ultrasound was its operator-dependence, with the associated variation of observation within the examination and between operators. In contrast with this was a statement by Berg et al. (2008) that said a “consistent breast ultrasound examination performance and interpretation is possible with minimal training” (p. 2152).

2.11. Conclusion

This background section has established the current status in mammographic screening, the BSA programme and the basis from which imaging is offered to patients involved in this study.

Descriptions of the different types of breast tissue, alongside an understanding of the types of breast lesions and their imaging characteristics, both mammographically and ultrasonically, assist the reader to realize the complexity involved in diagnosing areas of altered breast architecture while engaged in real-time or post imaging analysis.

The sensitivity of mammography to tissue alteration is most important when considering different types of breast tissue. Berg et al. (2004) described 100% sensitivity in fatty breast tissue, reducing to as little as 30-48% in dense breast tissue. The complex issues of risk status, mammographic sensitivity and breast density, risk factors, hormone replacement therapy, and breast density are well known concerns in the medical imaging community and a discussion these complex issues will be further researched in the light of current academic publications in the next section of this thesis.
3.0 Literature review

3.1. Introduction

This review will seek to establish the relevant key themes, gaining an understanding of the current status of research so to establish appropriate parameters for this study. Themes reviewed included:

- the current use of breast ultrasound
- the current use of bilateral whole-breast ultrasound
- the importance of breast density
- the use of hormone replacement therapy
- defining the high-risk breast cancer patient
- the risk of contralateral breast cancers
- the comparative sensitivity of ultrasound and mammography

Breast ultrasound has historically been used for targeted imaging, predominantly to clarify cystic from solid lesions within the breast. With significant technological advances over recent years, in parallel with the development of high frequency transducers, it is possible that ultrasound may have a role in breast imaging.

Additionally, bilateral breast ultrasound may have a role in:

- imaging breast tissue that is difficult to interrogate mammographically – inframammary fold (inferior breast tissue), axillae and medial breast tissue
- imaging breasts with increased density
- assessing the presence of multifocal or multi-centric lesions

There is an increasing body of reliable information concerning the high risk patient and key issues will be discussed as they relate to these patients. Increased breast density and hormone replacement therapy are recognised as independent risk factors for breast cancer and additional imaging of breast tissue needs to be considered if the exclusion of malignant lesions is to be achieved. One significant study is the ACRIN 666 trial in the United States of America (Berg et al. 2008) where the use of whole breast ultrasound for women at an elevated risk of breast cancer was under evaluation.
A unique genetic risk factor relative to three Maori tribes exists in the Bay of Plenty region in New Zealand (Richards et al. 1999). The presence of the E-cadherin gene confers higher than background risk of breast cancer, contributing to the risk factors that potentially exist for some women in this region of New Zealand.

Statistical analysis of the results is necessary if this study is to have any relevance in the breast imaging community or have a potential role in the changing face of breast imaging nationally. The principal statistical test to be applied is Fisher’s exact test, enabling a quantitative measure of the relationship between two variables, assessing whether an observed pattern is completely by chance. Discussion of this test will occur later in the literature review, establishing the necessary criteria for statistical robustness.

Before launching into a review of subjects as suggested by this introduction, it would be useful to determine the keywords employed in this process of researching databases, medical libraries and medical journals.

3.2. Keywords

The keywords used to research this topic included:

breast cancer; breast imaging, breast neoplasms; breast density; ultrasound; whole-breast ultrasound; mammography; diagnostic imaging; breast micro-calcifications; hormone replacement therapy; contralateral breast cancers; ipsilateral breast cancers; high risk breast cancer patients; BRCA1 and BRCA2 breast cancer genes; sensitivity; specificity; non-palpable breast lesions and Fischer’s exact test.

3.3. Literature search

Literature was researched from medical journals, the MEDLINE and Cochrane databases, and through the Philson Library (University of Auckland, New Zealand). The review of research papers was predominantly limited to articles published since the year 2000 due to the technological improvements that have occurred in medical imaging systems, particularly in relation to ultrasound.
While the majority of the publications reviewed were published later than 2000, two significant studies from 1995 (Stavros et al.) and 1998 (Kolb et al.) have been included. These two publications are considered landmark reference articles from which future studies have been based and even today, remain foundational in the understanding of the characteristic imaging appearances of breast lesions, and in the use of ultrasound for the imaging of dense breast tissue to detect lesions in mammographically negative breasts.

97 research based articles published between 2000 and 2008 were reviewed along with the two exceptions previously documented. Particular attention was paid to research with a focus on the diagnostic performance of ultrasound in the detection of breast cancer. The themes investigated were related particularly to the high risk breast cancer patient and the potential use of bilateral whole-breast ultrasound for these patients. Related issues meant the inclusion of the effect of breast density on imaging, the often commented on risk of increased false positive findings with ultrasound, along with a comparative assessment of imaging sensitivity.

It was appropriate to embark on this research process with a review and analysis of the current status of breast ultrasound, to establish what has been viewed as suitable imaging for women at increased risk of breast cancer and for women with positive imaging findings.

3.4. Breast ultrasound – as it has been

Breast ultrasound as is it known today, had its roots in military technology, with initial developments occurring more than 50 years ago. Warner et al. (2004) noted that ultrasound was “not seen as a breast screening tool … but (was) commonly used to evaluate breast abnormalities found at mammography” (p. 2). In the current clinical setting, breast ultrasound is often seen as an integral part of breast imaging programs. Dempsey (2004) comments that it “has revolutionized the evaluation of breast abnormalities …. providing a rapid, cost-effective, and accurate guidance method for a wide range of interventional techniques” (p. 1). Targeted breast ultrasound is used to interrogate a specific area of breast tissue, and is widely accepted as “a diagnostic tool for the evaluation of palpable and non-palpable breast abnormalities in conjunction with mammography” (Berg et al., 2006, p. 356).
Targeted scanning implies investigation only of the region of suspicion. Breast tissue that is predominantly adipose is the easiest to investigate and ultrasound provides a convenient form of imaging to confirm the presence of simple cysts.

Ultrasound has shown a steady increase in use during the 1990’s, “to identify and differentiate palpable lesions and to evaluate mammographic abnormalities” (Muradali, 2005, p. 1; Rahbar et al. 1999; Georgian-Smith et al. 2000). Ultrasound is of great value as a first line of imaging in the assessment of young or pregnant symptomatic women, followed by mammography if deemed necessary (Baker et al. 2002). Dummin, Cox & Planet (2007) comment that ultrasound has a “greater ability than mammography to demonstrate lesion characteristics ….. (as) the transducer can be maneuvered through multiple planes” (p. 44).

In a 2003 article, Stavros described the main goal of ultrasound as “preventing unnecessary biopsies of benign lesions and finding carcinomas that are missed by clinical and/or mammographic evaluation” (p. S83). Ultrasound is seen as “attractive for supplemental screening as it is widely available, well tolerated by patients, and relatively inexpensive, involving no radiation” (Berg, 2003A, p. 1226).

With the development of improved technology and higher-frequency transducers, ultrasound has been indicated as a tool to help differentiate benign from malignant solid breast masses (Stavros et al. 1995). “High resolution real-time ultrasound allows detailed visualisation of many abnormal breast masses” according to Svensson (2002, p. 99), with Baker et al. (2002) further stating in a 2002 study that ultrasound was vital in the diagnosis of breast cysts and has “shown promise in the differentiation of benign from malignant solid masses” (p. 1).

Concern for the use of ultrasound has been documented with issues raised by Baker et al. (2002) listed as:

“a lack of awareness of benign structures such as fat lobules, intramammary lymph nodes and extra-capsular silicone .... a lack of optimal scanning technique where dilated lactiferous ducts are considered to be a solid mass, where radial and anti-radial projections are not completed adequately” (p. 1).
Although no mandatory guidelines exist for the clinical use of ultrasound in targeted breast screening imaging, many practices choose to follow the standards set out by the American College of Radiology (ACR). These standards relate to the practical application of ultrasound, its technical requirements and technique needed to achieve optimal ultrasound images (Baker et al. 2002), as listed in Table 4.

**ACR Standards 2000-2001.**

- a linear-array transducer greater than 7-MHz should be used (at least 6-MHz centre frequency transducer for broadband systems)
- set the focal zone at the depth of the lesion
- gain settings should be adjusted to allow simple cysts to be distinguished from solid masses
- areas of interest or breast lesions should be viewed in two perpendicular projections
- the maximum dimensions of a mass should be included
- label images as to right or left breast, lesion location (specified by quadrant, clock position, distance from the nipple, or shown on a diagram of the breast), and orientation of the probe
- permanent identification label for each study should include patient’s first and last names, identification number and/or date of birth, facility name and location, examination date, and the sonographer’s identification

**Table 4 Guidelines adapted from the ACR Standards for Breast US, (Baker et al. 2002)**

It is well recognised that adequate visualisation of all breast tissue is inherently difficult with mammography alone. The inframammary fold (breast tissue adjacent to the chest wall inferiorly), the axillae and medial breast tissue (adjacent to the sternum) are the areas of concern. Women who have breast implants are another group of patients where mammography may not provide a complete examination due to the inherent difficulties that breast implants present. Bilateral whole-breast screening ultrasound is a topic that creates controversy, difficulty and hope all at the same time. The next section will review some of the literature that is currently available, seeking to establish a baseline from where this research may continue.
3.5. Bilateral whole breast ultrasound: present and future possibilities

The current issues surrounding bilateral whole-breast screening ultrasound are commented on by Berg (2004), Boonjunwetwat et al. (2007) & Kolb et al. (2002). “Screening bilateral whole-breast ultrasound significantly increases the detection of small breast cancers” (Kolb et al. p.166) and though many irregularities in the breast architecture may be noted, the problem of what to do with these findings is controversial. Boonjunwetwat et al. and Kolb et al. report that whole-breast ultrasound is a well-established practice in Thailand due to the majority of Thai women having increased breast tissue density; specifically 91% of women aged 35-44 years, 87% aged 45-54 years, 73% aged 55-64 years and 38% aged 65-74 years were identified with dense breast tissue.

In a study on whole-breast sonography by Kaplan (2001), 0.34% additional cancers were detected by ultrasound alone and of these cancers, 93% were detected in dense breast tissue. From those results it was determined that bilateral whole-breast ultrasound was “an effective adjunct imaging examination in the evaluation of women with dense breast tissue at mammography” (p. 647). Kaplan did comment that the number of additional breast cancers detected with bilateral whole-breast ultrasound in women with fat-replaced breasts would be markedly fewer than those with dense breast tissue.

Asymptomatic women (1517) were included in a study by Crystal et al. (2003) to evaluate the use of ultrasound as a screening tool in women with dense breasts. 94.1% of these women had no focal finding and the remaining 5.9% had complex cysts or solid lesions identified. A biopsy / FNA (fine needle aspiration) rate of 2.5% was recorded and the cancer detection rate was 0.46%. When this percentage was redefined into baseline risk and high risk patients, the cancer detection percentages were 0.25% and 1.3% respectively. A later study by Kaplan (2003) used ultrasound on 1862 asymptomatic women with dense breast tissue. 86.6% of these patients had no focal finding and 57 biopsies were performed for a biopsy rate of 3.06%. The cancer detection rate was 0.3% for this group of women (6/1862).

The contribution of bilateral whole-breast ultrasound in the diagnosis and management of women with newly diagnosed breast cancer was assessed by Wilkinson et al. (2005). Multi-focal or multi-centric disease was present in up to 40%
of women diagnosed with primary breast cancer. Bilateral whole-breast ultrasound “has a role not only in the diagnosis, but also in the staging of local and regional disease” (Wilkinson et al. p. 574).

One author warns that ultrasound should be considered only as a supplemental screening tool, not as a replacement for mammography for even when both mammography and ultrasound were performed; there was “at least a 2-4% risk that a cancer (would) remain undetected” (Berg, 2003A & Berg et al. 2004, p. 29).

**Screening breast ultrasound for high-risk women** (also known as ACRIN 666) was a study to “assess the value of integrated whole-breast screening ultrasound combined with mammography in the detection of breast cancer in high-risk women” (Berg, 2003B, p. 1225). ACRIN was a multi-centre clinical trial in 2004 involving institutions across North America with 2809 participants involved in both annual mammography and radiologist-performed screening ultrasound. The patients were assessed independently at entry point, and then at 12- and 24- month time lapses. The women involved were randomly assigned to initial mammography or ultrasound examinations, with the initial interpretation of results performed independently. A paper published in 2008 by Berg et al. discussed results from this trial and stated that “adding a single screening ultrasound to mammography yielded an additional 1.1 to 7.2 cancers per 1000 high-risk women” (p. 2151). Other issues discussed by these authors relate to the prevalence of heterogeneously and extremely dense breast tissue in > 50% of women less than 50 years and in a third of women > 50 years, effectively decreasing the sensitivity of mammography to as low as 30-48%. Associated with dense breast tissue was an increase in the rate of interval cancers and these are known to have a poor prognostic outlook.

When considering the potential of bilateral whole-breast ultrasound to detect “small, node-negative breast cancers not seen on mammography” (Berg et al. 2008, p. 2152), the author cautions an awareness of the associated high number of false positive findings is needed when assessing the overall appropriateness of whole-breast screening ultrasound. False positive results will be discussed in a later section.

What then is the value of a bilateral breast ultrasound examination when there has been a positive mammogram? What is the point of an additional procedure when a malignancy has already been detected? A personal communication with the
radiologists involved in this study highlighted several reasons why bilateral breast ultrasound should be considered:

- to assess if a lesion should be sampled with an ultrasound-guided biopsy, a surgical hook-wire excision biopsy or referred for a specialist stereotactic procedure
- to assist with lesion identification by provision of additional images with an alternate imaging modality
- to assess for contralateral or ipsilateral lesions known to occur (see Section 3.9)
- to assess areas of tissue difficult to image mammographically - the axillae and inframammary regions
- to assess the nodal status of the axillae, supra-clavicular and sternal nodes

Many researchers agree that for breast imaging to be optimal diagnostically, visualisation of all breast tissue is essential. Denser breast tissue may have a significant impact on the effectiveness of mammography and can markedly affect the clarity of the image. Breast density is known to vary considerably according to a woman’s culture, age and hormonal status and it is significant that there is an increasing body of information being published relative to this topic. Appreciation of dense breast tissue being seen as an independent risk factor is the subject of the next section.

3.6. Breast density: its relevance in imaging

Breast density is defined as a proportion of glandular to fatty breast tissue. It is well documented that mammographic sensitivity is inversely and directly related to breast density (Baker et al. 2005) so an awareness of the sensitivity of mammography is important if all breast tissue is to be interrogated.

Though there are proven benefits with mammography, the results are less convincing when breast tissue is dense according to Berg (2003). Berg stated that the younger age group was predictive of an increased prevalence of cancers seen only on ultrasound as “more than half of the women younger than 50 years have either heterogeneously dense or extremely dense breasts” (Berg et al. 2008, p. 2151) and that these women are susceptible to “much higher interval cancer rates, with a worse prognosis for clinically detected cancers” (p. 2152). In particular the “non-calcified
breast cancer is often obscured by surrounding and overlying dense parenchyma” (p. 2152) and is often not visible in the mammographic image.

Mammographically, dense breast tissue shows as hyperechoic nodular densities or patchy whitened areas with a ‘ground glass’ appearance, causing malignant lesions to ‘hide’ in the dense tissue. With ultrasound, cancers are frequently hypoechoic in dense tissue, enabling detection with ultrasound.

In women with dense breast tissue, Kolb et al. (2002) found that ultrasound was more sensitive than mammography with only 57% of cancers seen on mammogram and 70% of cancers seen on ultrasound. The combination of mammography and ultrasound detected 96% of the cancers in this group of patients. A documented rate of 0.48% cancers seen only sonographically and in dense breast tissue was stated by Kolb et al. with Buchberger et al. (2000) citing a similar rate of 0.39%.

Ultrasound was useful in screening for early breast cancers particularly in young women who are at risk of breast cancer (Huang et al. 1999; Foxcroft et al. 2000). The American College of Radiologists (ACR) recommends the use of ultrasound as the initial investigative tool for palpable masses in pregnant women and women < 30 years old due to the complete lack of radiation and the “maintenance of resolution even in dense breasts” (Benson et al. p. 382, 2004).

Dense breast tissue poses problems for optimal mammography as the longer radiation exposure times can lead to “motion un-sharpness, reduced image contrast, diminished spatial resolution and difficulty in optimally imaging the whole breast” (p. 198, Kolb et al. (1998). A later study by Kolb et al. (2002) showed that both the biopsy and cancer detection rates per 1,000 women screened were higher in women with dense breasts. Fasching et al. (2006) comment that ultrasound was “more accurate than mammography for assessing tumour size in breasts with a higher breast density” (p. 399).

Studies from 2006 (Carter, H.) suggested that “breast density was almost as important a risk factor as age and, after adjusting for age, the risk of cancer was three times greater for women with extremely dense breasts compared with women whose breasts were almost entirely fat” (p.1204). Carney et al. (2003) suggested that breast density may be “an undervalued and underused risk factor” (p. 168) in studies that investigate breast cancer occurrence, further, it is possible for dense
breast tissue “to mimic a cancer on mammography” (p.168). Tagliafico et al. (2009) comment that the risk of breast cancer is even higher than that suggested by Carter (2006) and state that the “risk of breast cancer is 4-6 times higher” (p.38) for women with dense breasts.

In an Italian multi-centre study (Podo et al. 2002), screening ultrasound more than “doubled the rate of breast cancer detection in women with dense breasts” (p. 115). A study of 1517 asymptomatic women with mammographically dense breasts was undertaken to evaluate the role of screening-ultrasound by Crystal et al. (2004). 318 women were deemed to be of high risk due to having a first degree relative with breast cancer or through a personal history of the disease. Seven breast cancers were diagnosed in that group – a 0.46% cancer detection rate. Kaplan (2001) cited a detection rate of 0.3%. Of further significance, the detection rate in the high risk group was 1.3% compared with the remainder. Among normal women with dense breasts, the detection rate was 0.23% with ultrasound alone, and for high-risk women the detection rate was 0.42% (Kolb et al. 2002); this result being a significant percentage increase for the high-risk woman. The addition of screening ultrasound in women with dense breasts increased the rate of negative biopsy findings to 74.6% from mammography alone, 65.9% (Kolb et al. 2002). These authors concluded that screening breast ultrasound in women with dense breast tissue was of benefit and a useful adjunct to screening mammography.

Whether ultrasound could detect non-palpable breast lesions, not visible on mammography in asymptomatic women with known dense breast tissue was the focus of a study by Buchberger, De Koekkoek-Doll, Springer, Obrist & Dünser (1999) when examining 6113 women. A detection rate of 0.31% was attained leading the authors to endorse the use of ultrasound as an adjunct to mammography in women with dense breasts. A further study by Buchberger et al. in 2000 reassessed the potential of ultrasound to detect the non-palpable breast cancer not visible with mammography. Involving a further 8,970 women, the overall prevalence of cancer was 0.41% and of this, ultrasound proportionally detected 22% of the malignant lesions.

Another imaging challenge relates to the patient with large breasts. Mammographically, the compression applied to attain the images is reduced due to the amount of breast tissue, causing a reduction in resolution and raising the possibility that lesions may be missed. Even scanning large breasts with ultrasound
poses a challenge as the tissue does not lie evenly on the chest wall. The significant increase in the depth of field and the sheer mass of breast tissue to be scanned can reduce the detection rate of lesions. When there was fibroadenosis, ANDI’S (aberrations of normal development and involution), breast implants or dense fibrotic tissue, imaging sensitivity was further decreased while the comparative risk for breast cancer increased.

Breast density can also be affected by the taking of hormone replacement therapy (HRT). This is known to have a significant impact on breast density for some women and it is appropriate to discuss issues relevant to this study. The next section will review the research on HRT, and on the effects that may be seen mammographically.

3.7. **Hormone replacement therapy (HRT)**

The relationship between hormone replacement therapy (HRT) and breast density has been the subject of much research in recent years. As stated previously, mammographic sensitivity is known to decline with increasing breast density and “breast density appears to be very responsive to HRT” (p. 35, Harvey, 2006) with the greatest change in density occurring during the first year of use. This change in breast density may be global, focal or multifocal and may not necessarily occur at all.

HRT is a prescription drug used to prevent or ease the discomfort caused by diminished circulating estrogen and progesterone hormones in the female body that occurs naturally around the time of menopause. The taking of this medication artificially elevates the woman’s hormone levels and relieves the related menopausal symptoms.

It is normal for a gradual decline in breast density to occur during the peri-menopausal period for non-users of this medication and HRT can slow that normal process of breast involution (Harvey, 2006). Carney et al. (2003) studied 329,495 women; comparing the breast density of women in all age groups for those who were, and were not taking HRT. For those who were taking HRT, there was a significant increase in breast density in many women, and in the number of breast cancers detected when compared with nonusers of HRT.
The effect of long term HRT use on breast density was studied by Chen et al. 2005) over an 8-year period. Results from the 1415 women involved showed that “a greater percentage of women developed more glandular tissue as seen on mammography” (p.1744). With the potential for an increase in breast density, the need for additional imaging is indicated in these women.

Potential risk factors for breast cancer are many, including the use of HRT. It is appropriate to review the other well recognised reasons that classify a patient as high risk for breast cancer. Genetic status, family history or a previous history of breast cancer are all considered significant grounds to increase an individual’s risk of breast cancer from the normal baseline risk. The next section will review those issues in depth, giving an understanding of why appropriate diagnostic imaging tools should be considered for these patients.

3.8. High-risk breast cancer patients

The consensus of authors on what constitutes a ‘high-risk’ patient includes genetic status (BRCA1 or BRCA2 positive), a previous history of breast cancer or familial risk factors (Berg, 2003B; Berg, 2004; Kuhl et al. 2005 & Mesurolle et al. 2007). Gail, Anderson, Garcia-Closas & Sherman (2007) and Claus, Risch & Thompson (1994) each developed risk estimates of breast cancer derived from statistical models with ‘high-risk’ status conferred with a lifetime risk of 20% or 25%.

For women with a strong family history of breast cancer, there is a 20% chance of a genetic susceptibility and this is defined as:

- two first or second degree relatives diagnosed with breast cancer <50 years
- three first or second degree relatives diagnosed with breast cancer <60 years
- four relatives diagnosed with breast cancer at any age
- family history of ovarian and breast cancer or bilateral breast cancer diagnosed <50 years
- male breast cancer


The incidence of BRCA1 and BRCA2 mutations is commented on by Claus et al. (2005) as being “between 0.4% to 2.6% and 1.4% to 1.5% respectively across all
age groups” (p.1) in women diagnosed with invasive breast cancer. Kuhl et al. (2005) & Mesurolle et al. (2007) comment that BRCA gene-positive patients form 5-10% of all breast cancer cases. Women who are identified as gene-positive have a 50-85% lifetime risk of developing breast cancer (Cortesi, 2006; Kuhl, 2002; Department of Health, 2007). Warner et al. (2001) give similar comment stating “a lifetime risk of 80%, from the age of 25 years onward” (p.2). Cortesi et al. and Robinson & Offit (2007) estimate the percentage risk of breast cancer by the age of 80 years as 90% for carriers of the BRCA1 mutation and 40% for BRCA2 mutation, with corresponding risks of ovarian cancer of 24% and 8% respectively.

Women with familial breast cancer tend to develop the disease at a significantly younger age, often pre-menopausally, with 50% having breast cancer by the age of 50 years (Cortesi et al. 2006 & Kuhl et al. 2005). Schrag, Kuntz, Garber & Weeks (2000) describe BRCA1 and BRCA2 genes as “predisposing women to both breast and ovarian cancers, often at young ages” (p.1). Once cancer is diagnosed in one breast, there is a 30% risk of developing cancer in the contralateral breast within five years according to Warner et al. (2001). Schrag et al. state a higher recurrence percentage risk of up to 60% for BRCA-positive patients already diagnosed with the disease.

The risk profile of BRCA-positive patients is extended with the possibility of earlier development of breast cancers with features to suggest a “biologic aggressiveness, proving to be high grade and receptor-negative” (Kuhl et al. 2005, p. 1). Warner et al. (2004) stated that BRCA-related cancers were more “cellular with round pushing margins, rather than scirrhous with irregular infiltrating margins, resulting in a more benign mammographic appearance” (p.6). BRCA associated tumours are also less likely to be associated with micro-calcifications that lead to detection by mammography. The sensitivity of mammography in the high-risk population is affected by “rapid tumour growth patterns and extensive mammographic breast density” (Mesurolle et al. 2007, p.2).

In addition, for women with a strong family history of breast cancer the risk status was related not only to the presence of those family members but to the number of, the degree of and the age of those relatives when first diagnosed (Claus et al. 2005). The degree of relative is termed as first, second or third generational affectiveness with a mother, brother, father, sister, brother deemed first-degree relatives (Claus et al.).
The rate at which cancers are detected in women at high risk was “significantly higher than expected in an age-matched population” (Cortesi et al. 2006, p.2). Women who do not have these BRCA genetic mutations, have an “approximate lifetime risk of 10% of developing contralateral breast cancer and 2% lifetime risk for ovarian cancer” (Schrag et al. 2000, p.1). This is comparable to the 11% average life-time risk stated by the government department responsible for medical screening in New Zealand (National Screening Unit, 2004). Surveillance of women at high risk of breast cancer has the advantage of disease detection in the early stages.

The majority of hereditary breast cancers are diagnosed in premenopausal women in whom breast density is higher than average when compared with older women (Warner et al. 2001). In the 2004 study by Warner et al. the sensitivity and specificity of mammography, ultrasound and MRI were assessed in 196 women who were BRCA1 or BRCA2 gene-positive. The combined sensitivity of all three modalities was 95%, though this sensitivity decreased to 86% if the ultrasound imaging was not performed. Of the 236 women surveyed, ultrasound alone was responsible for detecting 9.5% of all the cancers in that study.

A risk factor unique to the Bay of Plenty region of New Zealand relates to the E-cadherin gene. This gene confers a higher than background risk of breast cancer (particularly invasive lobular carcinomas) as well as a predisposition to gastric cancer. Inherited germ-line mutations of the E-cadherin gene have been discovered in three Maori tribes with familial gastric cancer by Richards et al. (1999) and by Dr Parry Guilford, an Otago University Geneticist, who worked with an affected Maori iwi or tribe from the Bay of Plenty region. Richards et al describe the E-cadherin gene as a “homophilic cell adhesion molecule important for establishing cell polarity and maintaining normal tissue morphology and cellular differentiation” (p. 607). The loss of the E-cadherin gene has been linked to disease progression in invasive carcinomas of the breast (Kowalski, Rubin & Kleer, 2003) and the partial or complete loss of this gene has been found to correlate with a poor prognosis in breast cancer patients.

The need to improve the detection rate of breast cancers leads to the search and assessment of other screening methods, alongside improvements to mammography such as digital mammography and tomosynthesis. An additional risk for those who are diagnosed with a cancer is the possibility of contralateral or ipsilateral cancers
and multi-focal or multi-centric breast cancers. The following section will examine what these cancers are, what the likelihood ratio is and who are most likely to be diagnosed with such a cancer.

### 3.9. Contralateral, ipsilateral, multi-focal and multi-centric breast cancers

After diagnosis of a breast cancer, some women may subsequently develop a second cancer in the other breast - this is known as a contralateral cancer. The new lesion is a separate primary tumour and is not due to metastatic spread from the previous tumour (Vaittinen & Hemminki, 2000). These authors comment that contralateral breast cancers occur more frequently in young women, particularly those with a strong familial risk than would be apparent in the general population of breast cancer patients.

The Swedish Family-Cancer Database collates data for all Swedes from 1932 and Vaittinen & Hemminki (2000) reviewed 72,000 cases of breast cancer to assess the incidence of contralateral breast cancer finding that 3.5% of the women were affected. Of these women, 5.8% has a significant familial risk involving a first-degree relative. Vaittinen & Hemminki report that the risk of a contralateral breast cancer was 1.5 times higher for women with familial risk factors than for patients whose cancers were sporadic. And for women aged 30-49 years old with familial risk factors; the risk was 50 times those of similarly aged women in the general population.

An observation by Hill-Kayser et al. (2006) was that contralateral breast cancers are frequently invasive and that the risk of developing a contralateral cancer remains increased, relative to the normal population, for at least 20 years after the initial diagnosis.

A study in 1999 by Chen, Thompson, Semenciw & Mao showed that family history of breast cancer, an early age at initial diagnosis, and lobular histology of the cancer increased the risk of developing contralateral breast cancer. Chen et al. state that 2-11% of women diagnosed with breast cancer will develop a contralateral breast cancer with the effect of a family history was again noted particularly among women with an affected first-degree relative. Claus, Stowe, Carter & Halford (2003) cite a
similar increased risk estimate of 3.35 times greater for women with a history of breast cancer and agree that the risk is highest for women diagnosed with a lobular carcinoma.

Comment should also be made about an ipsilateral breast cancer. These are detected in the same breast as the original primary lesion, occurring either at the original time of diagnosis or at a later date and may present in the same quadrant as the original lesion. There is a greater incidence of ipsilateral breast cancers for those women with a family history of the disease, than there is for those without.

Multi-focal and multi-centric breast cancers are lesions all detected at the time of initial diagnosis. Multi-focal refers to the identification of more than one lesion in the same breast, arising from the original lesion and likely to be in the same quadrant. Multi-centric implies that there is more than one tumour in the same breast, all of which have formed separately from one another though the tumours are likely to be in different quadrants of the breast. Wilkinson et al. (2005) stated that multi-focal or multi-centric disease was present in up to 40% of women diagnosed with primary breast cancer and bilateral whole-breast ultrasound “has a role not only in the diagnosis, but also in the staging of local and regional disease” (p. 574).

The sensitivity of an imaging modality to detect lesions is of utmost importance if any confidence is to be assigned to breast screening. Sensitivity is a measure of the proportion of actual positive results that are correctly identified. Much has been documented as to the comparative sensitivity of ultrasound and mammography over recent years and the next section of the literature review will examine what current research has documented.

3.10. Comparative sensitivity of ultrasound and mammography in literature

Many authors comment on the comparative sensitivity of mammography and ultrasound and several studies have attempted to quantify the differences in sensitivity and detection rates relative to patient ages and breast density. There is an inconsistency between studies over whether the clinician was aware or not aware of the mammographic and/ or ultrasonic results prior to an examination; however this was not always stated and can leave the reviewer questioning the validity of the
results. Variation of results can also be related to whether the assessment was based on real-time imaging or the printed images post examination.

Several authors agree that the use of ultrasound and mammography may have a combined sensitivity as high as 96-100% (Berg, Blume, Cormack & Mendelson 2006; Georgian-Smith et al. 2000 & Houssami et al. 2003). When using mammography and ultrasound combined, Benson et al. (2004) stated that the sensitivity was higher, the tumour size smaller and the false-negative rate lower. Ultrasound was deemed superior to mammography for the “vast proportion of patients ... and worthy of consideration as a first-line diagnostic and screening tool, to stand alongside mammography in equal partnership” (p. 5). And further - “ultrasound was significantly better than mammography for the detection of invasive breast cancer in the symptomatic patient ... the combination of ultrasound and mammography together was an improvement on either modality used alone” (p. 1). Boonjunwetwat et al. (2007) agree with the previous authors stating that ultrasound had greater sensitivity than mammography in the detection of soft tissue abnormalities within the breast. Ultrasound was positive in 93% of cases and mammography 87%, whereas the combination of modalities proved positive in 96% of cases. Malur, Wurdinger, Moritz, Michels & Schneider (2001) document the sensitivity of mammography as 83.7% and ultrasound as 89.1%, with the combined sensitivity of mammography and ultrasound, 94.6%. Specificity was improved when mammography and ultrasound were combined (92%).

Improved sensitivity for symptomatic women less than 55 years with combined mammography + ultrasound examinations was a result from the study by Houssami, Irwig & Loy (2002). Included in this study were 240 women aged 25-55 years old with breast cancer, alongside a random sample of 240 age-matched women with no breast cancer. The increase in sensitivity ranged from 11% to 18% and was “clinically significant given the difficulty in diagnosing breast cancer in young women” (p. 39). Individual and combined tests had a high specificity of over 94%. Houssami et al. have shown that in this population with a breast cancer prevalence of 2%, combined imaging will detect one additional cancer.

In a later study, Houssami et al. (2003) assessed the appropriate age below which ultrasound would be the more accurate breast imaging test. The choice of imaging was based partly on age, though little evidence exists as to the appropriate age for specific imaging choices. “Experts suggest that women younger than 35 years be
examined with ultrasound .... and women older than this be examined with mammography as the primary modality” (p. 935). Results of this study showed that combining both mammography and ultrasound had a greater sensitivity (96%) than either sonography (81.7%) or mammography alone (75.8%).

A review of 22 studies (1990-2000) by Flobbe et al. (2002) assessed the role of ultrasound as an adjunct to mammography in the detection of breast cancer. Flobbe et al. suggested that breast ultrasound could “lower the number of indeterminate findings of mammography, by defining them as benign or malignant” (p. 148). In the Netherlands, “ultrasound is currently being used as a supplement to mammography in approximately 40% of patients who present for breast imaging” (p. 1045). A 6.3% prevalence of breast cancer was documented by mammography alone, with 8 additional malignancies detected only with breast ultrasound. The size of these lesions was not disclosed however, and three of the lesions were palpable.

A later study by this author (2003) stated that the “systematic application of breast ultrasound improved the overall diagnostic yield” (p. 1194). Although ultrasound may increase the sensitivity if used as an adjunct to mammography, Irwig, Houssami & van Vliet (2004) comment that it was “likely to increase substantially the number of women requiring biopsy for benign findings” (p. 2121). Kolb et al. (2002) assessed asymptomatic women, where screening breast ultrasound “significantly increased the number of women diagnosed with non-palpable invasive cancers by 42% and detected smaller cancers at an earlier staging” (p. 166). Robinson & Offit (2007) ascribe an additional 0.35% breast cancer detection rate when ultrasound was used in conjunction with mammography for screening asymptomatic women with non-fatty breasts.

Breast ultrasound has its own unique limitations and according to one author ultrasound has an “equivalent diagnostic ability to mammography for palpable lesions, but its sensitivity and accuracy are limited in small or non-palpable tumours and micro-calcifications” (Chen et al. 2004).

A prospective study on the “value of ultrasound as an adjunct to mammography” (p. 413) was undertaken by Zonderland, Coerkamp, Hermans, van de Vijver & van Voorthuisen et al. (1999). Classification of 4,811 mammograms according to a level of suspicion of malignancy was performed. Targeted ultrasound was used to further define specific areas. This included well-defined lesions or cysts, palpable lumps
that were either visible/ not visible on mammography and non-palpable lesions that were visible on mammography. Ultrasound was used in 23% of the cases. Adding ultrasound to mammography improved the sensitivity of screening for lesions from 78% to 97%. The major advantage of ultrasound was seen “in women less than 50 years where the sensitivity was up to 100%” (p. 6). This study confirmed the effect of age in the sensitivity of mammography: for women aged 30-39 and 40-49 years, the sensitivity was 68% and 78% respectively. Ultrasound provided more accurate identification and characterisation of lesions with the detection of an additional 25 cancers (7.4%). Zonderland et al. concluded that the “use of ultrasound as an adjunct to mammography resulted in a statistically significant improvement in breast cancer detection” (p. 422).

In an overview of breast cancer screening performed across seven randomised trials, Berg et al. (2003) showed that for women ≥ 50 years, a 22% reduction in breast cancer mortality occurred. A cancer detection rate of 0.27% to 0.9% was the result of imaging only with ultrasound. The false positive biopsy rate was 2-4% with 16% of the lesions detected proving malignant.

Supplemental screening ultrasound was studied by Berg in 2004, involving 42,838 examinations resulting in detection of 150 additional cancers (0.35%). Of the cancers detected, 90.5% of the patients had either “heterogeneously dense or extremely dense breast parenchyma” (p. 846). Berg states that for supplemental screening to be considered, the three measures of efficacy to be assessed are a high cancer detection rate (> 4 per 1,000 women screened), cancers that are small and node negative, and a low rate of interval cancers and false positives. Initial data seems compelling according to Berg, indicating that breast cancer detection will be improved, and that adding ultrasound to breast screening protocols for high-risk women could help detect 30% more cancers.

In 2004, Berg reported that the “cancer yield for ultrasound and mammography was 12.4 per 1,000 women screened with a diagnostic accuracy of 93% compared with mammography alone, 79%” (p. 845). In a later study, Berg (2007) commented that women at higher risk of breast cancer were two to three times more likely to have a cancer seen only with ultrasound.

The effect of knowledge of mammographic findings being available prior to an ultrasound examination was examined by Houssami et al. (2005). Improved
sensitivity percentages were shown when ultrasound was performed with the knowledge of mammographic findings (87.5%), than without this clinical knowledge (81.3%). Kopans (2004) comments that in previous studies (Kaplan, 2001; Kolb et al. 1998, 2002 & Leconte et al. 2003), ultrasound examinations were performed with the knowledge of the mammographic findings, and this could influence the examiner with respect to current ultrasound imaging findings.

It is important to consider that the benefits of ultrasound include its relative ease of use, a lack of radiation, comparative low cost with respect to other modalities, and patient accessibility and acceptability. Its use in tissue sampling for both screening and diagnostic purposes may make mammography and ultrasound the new gold standard in breast screening.

Several authors comment on the possibility of an increase in false positive biopsy results as more lesions are ‘seen’ on ultrasound, raising the potential for an increased number of biopsies to be performed. False positive results can be unsettling to the patient and the clinician – the following section will assess current thinking on effect of false positive results.

3.11. False positive results – what of them?

No screening program is perfect and there will always be false-positive and false negative results. These results occur when a discrepancy exists between imaging appearances in the breast and the histology result. A false positive indicates that imaging was positive for malignancy but the histology was negative and a false negative indicates that a ‘benign’ tissue sample was malignant or positive for cancer. The “psychological and physical harms” (p. 39) of false-positive and false-negative results are well recognized by Barratt (2006) as being of significance to the patient. Baker et al. (2005) suggest that “false-positive and false-negative tests may cause harm to people participating in screening programs” (p. 4), where people experience anxiety, unnecessary investigations, or feel falsely reassured that they do not have breast cancer.

Beyer (2003) comments that the majority of patients presenting for an examination due to a palpable lump or thickening of tissue, will most likely have a benign diagnosis or a true negative finding. Clinics that operate under the auspices of BSA
in New Zealand recall patients for further imaging and/or tissue biopsies if an abnormality is detected on reading of the mammographic images. This can stretch out the waiting time for patients in terms of gaining a definitive result and potentially elevate the levels of stress or anxiety.

A result revealed from a study of 1528 women by Ganott et al. (2006) showed that 97% of these participants decided, on review, that if an initial positive finding was followed by a true-negative result, the worry in the interim was worth it. Participants were aware that detecting cancer earlier increased their chance of survival.

Benson et al. (2004) comment that the majority of false-positive ultrasound results were related to indeterminate lesions and histological analysis was necessary for complete identification. If lesions were biopsied at the time initial consultation, and the patient then informed of the results within days, this avoided a patient recall and additional imaging, reducing the inconvenience and the stress associated with a mammographic false-positive. Benson et al. observed that the addition of bilateral whole-breast ultrasound increased diagnostic sensitivity without increasing unnecessary biopsies when performed in a specialty breast centre.

A higher rate of false-positive examinations was suggested by Kaplan (2001) and Kolb et al. (1998) as occurring with ultrasound rather than with mammography alone. Irwig et al. (2004) confirm this trend and document a false-positive rate ranging from 2.4% to 12.9% for ultrasound, in comparison with 0.7% to 6% for mammography. A review of a breast screening programme in New England (USA) demonstrated a false-positive rate was 7.8% for women aged 40-49 years, 7.4% for women 50-59 years and 5.3% for women aged 60-69 (Philpotts, 2003).

Berg et al. 2004) observed that the false positive rates associated with the ACRIN 666 trial occurred in 13% of the mammographic screening exams and in 28% of the ultrasound/mammography exams. In 2008 Berg et al. reported that “uncertainty for complicated cysts proved a major source of the false-positive results” (p. 2162). The hope was expressed that this false-positive rate would “diminish with subsequent ultrasound screening as has been seen with mammography” (p. 2162).

Establishing suitable methods for statistical analysis of the data obtained in this study is necessary to determine if there is value to these results. The most relevant, and often used statistical test in the literature reviewed was the Fisher’s exact Test. The
lead articles referenced for this study included Berg et al. (2004, 2008) and Kolb et al. (2002), and these authors focused primarily on bilateral whole breast imaging with reference to the high risk breast cancer patient. The following section will lay the foundation for the statistical analysis that will occur.

3.12. Statistical assessment

Statistical assessment implies a process of collection, collation, analysis and interpretation of data to explain a current situation, to review a current clinical practice or to highlight an inadequacy that exists. With reference to this study, the collation of data with analysis through the Fisher’s exact test will enable assessment of the current breast screening protocols as they relate to the groups of patients in this study.

3.12.1. Fisher’s exact test

Fisher’s exact test is sometimes known as the Fisher-Irwin test and was developed at by Fisher, Irwin, and Yates in the 1930's. This test looks at a contingency table which displays how different treatments have produced different outcomes. The null hypothesis could be that treatments do not affect outcomes, that the two are independent. In respect of this study, that the use of bilateral whole breast ultrasound detects all breast cancers (Weisstein, 2009).

This test is used to determine if there are non-random associations between two variables, calculating an exact probability value for the relationship between those two variables. This enables the researcher to calculate the difference between the data that has been observed and the data that was expected.

3.12.2. Statistical measures

Fisher’s exact test was used in conjunction with other statistical measures by these lead researchers to assess their collated data and these included the sensitivity, specificity, positive and negative predictive values of each grouping of patients with reference to a specific imaging modality (or combination). Section 4.6 discusses these statistical measures in greater depth.
3.13. Conclusion

Breast ultrasound has shown a marked improvement over recent years and is now a genuine contender for a significant role in imaging breast tissue. Practical uses well recognised now include the imaging of mammographically-difficult tissue, the imaging of women < 30 years of age and for the prevention of unnecessary biopsies (Stavros, 2003). While history has shown ultrasound to have a significant role when used in a targeted format, there is a growing body of evidence that suggests the role of breast ultrasound could be greatly expanded.

Bilateral whole breast ultrasound has been the focus of much recent and current research, in particular for its use on women who have dense breast tissue or are known to have significantly increased risk factors for breast cancer. Discussion has included topics such as the age of and number of relatives, the relationship of those relatives to the patient and women who are proven BRCA1 or BRCA2 gene-positive. This means that the 11% baseline lifetime risk for New Zealand women is exceeded, giving urgency to the search for appropriate breast imaging.

Dense breast tissue is recognised as an independent risk factor for cancer and this has been the motivation for several recent studies. Mammographic images of dense breast tissue lack diagnostic clarity, either globally or focally. Kolb et al. (2002) is one of the authors that state ultrasound has a greater sensitivity in the detection of breast cancers when compared to mammography in women with increased breast density. Mammography + ultrasound combined have a greater sensitivity than ultrasound alone and consideration can be given to the use of a combination of imaging modalities to form the baseline imaging criteria for these women.

The aim of this literature review was to establish the current status in breast cancer research, specifically with reference to bilateral whole breast imaging, the high risk breast cancer patient and the patient with positive findings. Finding agreement on which risk factors were deemed pertinent, what is currently accepted as the standard for breast imaging and to study what is the acknowledged role of ultrasound in breast imaging. So with this foundation laid, it is time to establish the specifics of this study, the parameters of the research undertaken, clarify the patient study group/s and perform statistical analysis of the imaging results.
4.0 Materials and Methods

4.1. The study aims

What is the appropriate role of bilateral breast ultrasound, as an adjunct to mammography, in the management of patients with positive results?

The principal aim of this study was to answer the above question, relating it primarily to the study group of patients who presented for breast imaging during the study period. Additionally, study of the sub-aims related to the appropriate role of bilateral breast ultrasound in the high risk patient and in the patient with risk factors that increase the baseline risk of breast cancer. The specific risk factors applied to the individual patient in this study related to a prior history of breast cancer, a known familial risk of breast cancer, a BRCA1 or BRCA2 gene-positive status, or increased breast density.

The majority of women in New Zealand aged 45-69 years of age attend a BreastScreen Aotearoa clinic for biennial breast imaging, however women deemed at high risk women or those with a personal history of breast cancer in the preceding five years are excluded. These women are funded to attend a private radiology practice by the local area health board where a greater range of breast imaging and surgical review is available. In this way high risk women are not disadvantaged due to their medical history.

Bilateral whole breast ultrasound examinations in conjunction with mammography were performed on all patients in this study population and statistical analysis will determine the sensitivity and specificity of mammography, mammography + ultrasound, and bilateral breast ultrasound for this group of patients. The breast cancer detection rate will be calculated for five groups of patients, with those results compared to the expected detection rate of women in New Zealand, and then compared to relative current research:

- the total screened population imaged (22,814)
- the study group who had a breast tissue biopsy (1063)
- the patients with high risk factors (533)
- the patients with dense breast tissue (307)
- the patients with dense breast tissue and high risk factors (159)
4.2. Ethics approval

The Research and Ethics committee of the Unitec Institute of Technology reviewed and approved this retrospective study. Verification of this approval is noted in Appendix 9.1.

Permission and approval for this study was obtained from the radiology practice involved and this is documented in Appendix 9.2.

4.3. The study design

The study was based on a retrospective review of historical data complied over a nine year period, to assess the potential of bilateral breast ultrasound as an adjunct to mammography in the detection of breast cancers in the high-risk breast cancer patient and in the patient with positive findings.

The study group (1063) was taken from a screened population (22,814) who presented consecutively for routine annual screening or diagnostic breast imaging at a private radiology practice in New Zealand. The study period was from January 1999 through to December 2007 inclusive. Patients were eligible for both mammography and ultrasound examinations with the patients’ age dictating which modality was used initially.

Individual patient consent was not required for this study and no exclusion criteria were applied to these patients. All relevant study data was accessed and retrieved from two sources: a medical database (COMRAD II) specific to this radiology practice and from a handwritten record of biopsy data. The handwritten record contained the patient’s name, the presumed pathology based on imaging results with the final pathology result following analysis by Pathlab. COMRAD II contained historical documentation of a patient’s personal information, a record of the referrer, all visits and procedures that had been completed, reports of previous examinations and any future booked appointments. This data was copied to a password-protected Microsoft Office Access 2003 database. Unique numerical identifiers were assigned to each participant to further protect patient confidentiality.
4.4. The patient population

The radiology practice involved in this study was not a dedicated breast imaging centre so all patients who presented for examination during the study period belonged to one of following three categories:

- private clients with known risk factor/s for breast cancer
- patients who were asymptomatic and between biennial breast screening years with BSA, choosing to have more regular imaging than that provided by the government (screening patients)
- patients who were symptomatic and between biennial breast screening years with BSA and were now aware of a new breast symptom (see Section 5.4) – (diagnostic patients)
- patients who were funded by the local area hospital board due to specific risk factors for breast cancer – high risk patients

Within the practice, there was an awareness that a greater percentage of cancers would be detected in those with risk factors or those who presented for a diagnostic examination.

The cost of all breast examinations was carried by the individual patient except for those patients who met criteria established by the New Zealand Government through its Health Department. The criteria for these patients included:

- those patients who had previously been diagnosed with a breast cancer
- those patients known to be positive for the BRCA1 or BRCA2 genes
- those patients known to have significant familial risk factors for breast cancer

Patients were required to have at least one, or a combination of these criteria to qualify for a Government-funded breast examination at the radiology practice. This funding was applied for by the patient’s general practitioner through a previously established referral process with the local area health board.

Of the 22,814 patients who attended for annual, biennial or diagnostic breast imaging, 1063 patients required 1198 breast tissue biopsies as an integral part of the
examination process and it was these patients that were deemed to be the study group.

Upon arrival all patients were given a questionnaire; a normal practice protocol to comment on changes that had occurred since the previous examination, to state any current concerns and to mention any familial risk factors that they were now aware of. This patient information was seen as an integral part of the examination process and attention was paid to the details it contained.

The range of personal patient information (unique identifier applied) stored in the database included all relevant examination, historical, genetic and pathological detail as listed below:

- date of birth
- date of examination
- relevant personal history
- age and number of the relatives when diagnosed
- age at time of breast tissue biopsy
- BRCA gene status
- screening or diagnostic examination
- palpability of the lesion/s
- mammographic breast density
- detection of lesion: whether by mammography or ultrasound
- measurement/s of the lesion/s
- scan range: targeted or whole breast imaging
- expected diagnosis based on imaging appearance
- histopathological analysis of breast tissue sample

This majority of this data was stored in the computer-generated patient database with specific biopsy data and analysis reported in both the database and the biopsy book. The biopsy book contained a handwritten record of all tissue biopsies performed during the nine year study period. The patient numbers for all breast mammographic and ultrasound examinations was taken from the COMRAD II records.

All patients presenting for breast imaging were labeled as screening or diagnostic based on whether the visit was motivated by a symptom/s or it was time for serial assessment. Screening patients were those who were asymptomatic and presented
for routine imaging with no known abnormalities. Diagnostic patients were those who were symptomatic and had their symptom/s documented: changes in the breast tissue, whether a lesion/s was palpable, the size of the lesion/s, the length of time the patient had been aware of the changes and whether there was any nipple discharge, skin puckering or discolouration.

For the majority of the patients, mammography was the first line of imaging and dependent upon the resultant images, the patient’s risk history and breast tissue density, further imaging of the breast with ultrasound would be offered and performed to enable adequate investigation of all tissue. Bilateral 4-view mammograms would be performed if it was > 6 months since a previous mammogram or a unilateral mammogram of the affected side if a recent mammogram (< 6 months) had occurred. For all those patients < 30 years of age, ultrasound was the initial imaging choice, followed by mammography if indicated by clinical or ultrasonic findings (refer to Table 5).

Table 5 Patient imaging process
Patients present for breast imaging

Women < 30 years of age

Ultrasound performed

- NAD** – no further action required

  Cystic structure confirmed

  Abnormality detected

    - No further action required

    - Proceed to mammography for completeness of imaging and correlation of findings

      - Biopsy performed for histology identification

Women > 31 years of age

Baseline risk

Mammography performed

- NAD** – return to screening

  Abnormality detected

    - Proceed to ultrasound for completeness of imaging & correlation of findings

    - Biopsy performed for histology identification

Increased baseline risk factors *

Mammography performed

- NAD** - ultrasound for completeness of imaging

  Abnormality detected

    - Proceed to ultrasound for completeness of imaging & correlation of findings

    - Biopsy performed for histology identification

* High risk patients - familial risk factors, previous history of breast cancer, BRCA1 or BRCA2 positive, dense breast tissue

** NAD – no abnormality detected
4.5. Imaging methods: mammography and ultrasound

The process of breast imaging was dictated by patient age and the level of clinical concern. The protocol for screening (asymptomatic) patients was a mammogram initially followed by an ultrasound scan if indicated. Indications for ultrasound comprised a mammographic region of suspicion or known increased risk factors as previously stated. Patients with global or focally dense breast tissue with no palpable lesions were part of the cohort offered routine breast ultrasound alongside mammography.

The protocol for diagnostic (symptomatic) breast patients was a mammogram first, with a lead marker over the area of clinical concern, followed by an ultrasound scan that was either targeted to the specific area or involved whole-breast imaging. Ultrasound was used for several reasons when an area of suspicion was identified mammographically:

- ultrasound enabled a more accurate assessment of the area of suspicion including the surrounding tissue for assessment for additional lesions
- ultrasound made the process of lesion localization and tissue sampling more efficient
- when it was not possible to biopsy the lesion mammographically
- to assess if a stereotactic biopsy was the best course of action

Patients who were < 30 years of age almost always presented with an area of clinical concern and were initially scanned with ultrasound. Dependent upon those images, mammography was used if the clinical or ultrasonic findings indicated further assessment was necessary. Mammography is still considered the best screening tool and it is important to check whether a lesion can be seen mammographically, enabling the follow-up process to be more robust.

All the patients within the study group (1063) had both mammography and ultrasound prior to the taking of a tissue sample for cellular clarification.

4.5.1. Mammography

Mammographic imaging was performed with a dedicated mammographic unit – the General Electric Senographe 800T. The mammography unit was under a national
quality control accreditation programme for the duration of this study. The standard cranio-caudal and medio-lateral-oblique views mammographic views were obtained. Extra views were performed as requested by the radiologist and these included a lateral view, spot compression or spot compression combined with a micro-focus magnification view to spread out the tissue planes, to assess for micro-calcifications and asymmetry (Dummin, Cox & Plant, 2007). A lead skin marker was used to indicate an area of clinical concern: indicated either by the patient or from the initial mammographic images.

Mammographic images were assessed for:

- the presence of mass/es
- asymmetric focal density
- architectural distortion
- the presence of micro-calcifications

The clinical findings of the mammographer were documented including comment on palpable lumps, tissue thickening, and skin puckering or nipple retractions. The size, shape, density and margins of all masses were noted. The distribution and morphology of micro-calcifications, multi-focal and multi-centric lesions, architectural distortion of the breast tissue and skin thickening were all reported.

Mammographic breast density was graded by the radiologist as low (adipose), average or dense: the density graded according to criteria established by Tabar et al. (1997) (refer Section 2.4). The grading of breast tissue, the presence of suspicious lesions, individual patient history and risk status influenced the course of imaging and breast tissue sampling.

Further examination of the patient with ultrasound was indicated and performed if:

- the mammographic findings were abnormal
- the mammogram was normal but the patient presented with a palpable abnormality
- the breast density was increased
- the risk status was increased: previous breast cancer, family history or positive with the BRCA1 or BRCA2 genes
4.5.2. Ultrasound

Breast ultrasound was performed after mammography for the majority of patients and was used to further define a tissue anomaly present in the mammographic images. The ultrasound examinations were performed either on the Toshiba Apio 80 or Toshiba Xario (Toshiba Corporation, Tokyo, Japan). High resolution 12-14MHz broadband linear array transducers were used to detect and evaluate solid masses and suspicious changes in breast architecture.

Ultrasound was performed by an accredited sonologist with extensive experience in breast imaging (> 19 years). Knowledge of the mammographic findings was available prior to ultrasound imaging, facilitating the detection of abnormalities seen on mammographic images.

The ultrasound scan was performed in a radial pattern, beginning at the periphery of the breast and moving inward. Each quadrant was scanned with overlap at the 12-, 3-, 6- and 9-o'clock positions followed by scanning in orthogonal planes to complete the assessment. Imaging of each axilla was deemed an essential part of the ultrasound examination. Images and measurements were obtained for all solid masses, complex cysts, areas of architectural distortion, acoustic shadowing and dominant simple cysts. For examinations with negative findings, representative images were obtained in each of the four quadrants bilaterally, including the axillae. Extended field of view or panoramic imaging was performed across the outer lateral and superior quadrants of each breast. Colour Doppler interrogation was performed on all lesions to assess the relative vascularity of a lesion.

Sonographic findings were classified as normal (no simple cysts, ductal ectasia or focal lesions), benign (simple cysts or sonographically benign solid lesions) or indeterminate / suspicious for malignancy. Lesion classification was based on criteria previously published by Stavros et al (1995) – see Section 2.5.

4.5.3. The post imaging process

Reading and double-reading of all the mammographic and ultrasound images was performed by two radiologists with >19 and 30+ years experience in diagnostic breast imaging; though it should be stated that double reading of the ultrasound images was limited only to the regions documented compared with the total breast images obtained with mammography (refer Section 6.3).
All mammographic and ultrasound images were reviewed by the radiologists with evaluations for mammography and ultrasound based on a collective established screening criteria including a multi-disciplinary review. When breast lesions were detected with ultrasound examination, a review of the patients’ mammographic images was then performed to identify the lesion. Breast density was graded according to the mammographic appearance and all lesions detected were assessed for shape, margin, orientation, echo, internal architecture, edge shadowing, presence of micro-calcifications, the degree of vascularity detected in colour Doppler, the antero-posterior diameter/width (AP/W) and presence of posterior acoustic transmission.

Ultrasound guided biopsy protocols of suspicious lesions and solid masses previously not sampled were performed using a disposable 14- or 16- gauge core-biopsy needle with a 15mm or 22mm throw depending on the lesion site. Between one and three samples were obtained from each lesion with the biopsy specimens processed according to standard Pathlab protocols: tumour grading was determined by the Elston and Ellis classification system. Biopsy of all of the benign appearing lesions was completed to prove the benign status.

Some axillary lymph nodes were sampled by FNA under ultrasound guidance - these cases were excluded from this study.

Mammographic stereotactic biopsy was an appropriate course of action for patients with micro-calcifications and no associated lesion, or lesions beyond the range of a core biopsy; these patients were excluded from this study as the procedure was performed at a different site.

The group of patients that had breast tissue sampling formed the basis for information gathered in the database. As the purpose of this research was to evaluate the usefulness of ultrasound as an adjunct to mammography, in patients with positive findings, those patients not requiring a tissue biopsy were excluded from the detailed analysis.
4.6. Statistical analysis: application in this study

The total number of breast biopsies performed and breast cancers detected were calculated for:

- the total screened population (22,814)
- the study group who had a breast tissue biopsy (1063)
- the high risk patients (refer Section 4.4) (533)
- the patients with dense breast tissue (307)
- the patients with dense breast tissue and high risk factors (159)

Performance characteristics were calculated with the use of GraphPad Software (2005) and Rosner’s 2x2 contingency table analysis (2009) for each grouping of patients in mammography, mammography + ultrasound and bilateral breast ultrasound. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy were calculated by using the true positive, true negative, false positive and false negative results.

True positive breast lesions (TP) were identified as malignancies with mammography or ultrasound imaging, and then proven malignant through the histological analysis of a tissue sample.

False positive results (FP) related to lesions that were suspicious for malignancy on imaging, however were proven benign in histology.

Traditionally, this type of statistical assessment would attribute a true negative (TN) or false negative (FN) result as meaning either an examination where no abnormality was detected on imaging and a biopsy was not performed (TN); or an examination where imaging suggested a benign lesion, though the tissue sample was proven malignant (FN). These standard definitions do not apply to this retrospective study, for there was no possibility for follow-up of the total screened population (22,814) who were imaged and declared to have no abnormality detected. Documentation of the total number of TN and FN cases has therefore been lost for the screened population (21,751); consequently the calculation of the specificity and sensitivity for the remaining patients was not performed in the usual manner. Only a portion of the ‘well’ patients (TN and FP) and the ‘sick’ patients (TP and FN) were able to be tracked consistently throughout the study.
So in this research, a TN result applied where there was detection of a benign-appearing lesion with a biopsy performed, as the lesion fulfilled the biopsy criteria that demanded tissue clarification. The result of the biopsy confirmed the benign status of the lesion (TN). Tissue sampling in this study was based on criteria from the BSA programme – refer Section 6.3.1. Likewise a FN result in this research applied where the imaging suggested a benign lesion that fulfilled the biopsy criteria (refer Section 6.3.1.), though the histology proved a malignant result.

The recognised calculations for accuracy, sensitivity, specificity, positive and negative predictive values are detailed in the coming paragraphs. Accuracy was defined as the percentage of lesions in which imaging correctly predicted the presence or absence of cancer (Kolb et al. 2002).

\[
\text{accuracy} = \frac{\text{true positive} + \text{true negative}}{\text{true positive} + \text{true negative} + \text{false positive} + \text{false negative}} = \frac{TP + TN}{TP + TN + FP + FN}
\]

Sensitivity measured the proportion of patients that were correctly diagnosed as having breast cancer; however in this retrospective study, sensitivity values applied only within the study foregoing comparison with other similar studies for reasons documented earlier in this section.

\[
\text{sensitivity} = \frac{\text{true positives}}{\text{total number with disease}} = \frac{TP}{TP + FN}
\]

Specificity measured the proportion of patients that were correctly identified as not having breast cancer though as stated earlier in this section, the specificity values applied only within the study, foregoing comparison with other similar studies.

\[
\text{specificity} = \frac{\text{true negatives}}{\text{total number without disease}} = \frac{TN}{TN + FP}
\]

The positive predictive value (PPV) was the proportion of patients with positive test results who were correctly diagnosed.

\[
\text{PPV} = \frac{\text{true positives}}{\text{true positives} + \text{false positives}}
\]
Negative predictive value (NPV) was the proportion of patients, reported as negative for breast cancer that were correctly diagnosed.

\[
NPV = \frac{\text{true negatives}}{\text{true negatives} + \text{false negatives}}
\]


The 2x2 contingency table (see Table 6) formed the basis for statistical analysis in this study enabling assessment of sensitivity, specificity, PPV and NPV, accuracy and a two-tailed \( p \) value by using Fisher’s exact test. All calculations were performed through the previously documented website calculators (see Section 4.6).

<table>
<thead>
<tr>
<th></th>
<th>Patients with disease</th>
<th>Patients without disease</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test positive</td>
<td>TP</td>
<td>FP</td>
<td>TP+FP</td>
</tr>
<tr>
<td>Test negative</td>
<td>FN</td>
<td>TN</td>
<td>FN+TN</td>
</tr>
<tr>
<td>Total</td>
<td>TP+FN</td>
<td>FP+TN</td>
<td></td>
</tr>
</tbody>
</table>

**Table 6 2x2 Contingency table**

Sensitivity and specificity, PPV and NPV were calculated for each imaging modality and for each sub-group of patients (refer Section 4.4). The mean age of patients, the sizes of breast lesions and the density of tissue were evaluated for each sub-group. A comparative assessment of the numbers of mammography and ultrasound examinations, the use of targeted and whole breast ultrasound and also the relationship of breast density to the presence of malignant breast lesions was completed. Statistical analysis of the results was performed using the Fisher exact test with statistical significance was assigned a \( p \) value of < 0.05. Refer to Section 5.16 and 6.7 for discussion and analysis of the results from this study.
5.0 Results

5.1. The study period
The study period was from January 1999 to December 2007 inclusive and consecutive patients who presented for breast imaging during this time were deemed part of this retrospective study. 1063 women required 1198 tissue biopsies due to suspicious mammographic or ultrasound findings and these were recruited to the study population.

5.2. Mammographic breast examinations
30,756 breast examinations were performed during the study period; including 22,065 (71.74%) mammographic investigations and 9,543 (31.02%) ultrasound investigations. The patients had a total of 1.34 procedures each with the usual course of imaging being a mammogram then bilateral breast ultrasound prior to tissue sampling.

The mammographic examinations performed had different codes dependent on the individual patient's requirements, the patient's prior breast history and changes that have occurred within the radiology practice due to relevant related research. Figure 2 shows the trend of mammographic examinations that occurred during the study period while Table 7 details the actual numbers of mammographic examinations that occurred.
Table 7 Mammographic examinations performed during the study period.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening mammogram</td>
<td>1394</td>
<td>1656</td>
<td>2114</td>
<td>2207</td>
<td>2569</td>
<td>2500</td>
<td>2373</td>
<td>2218</td>
<td>2021</td>
</tr>
<tr>
<td>Unilateral mammogram</td>
<td>28</td>
<td>5</td>
<td>14</td>
<td>64</td>
<td>77</td>
<td>8</td>
<td>82</td>
<td>70</td>
<td>84</td>
</tr>
<tr>
<td>Implants</td>
<td>3</td>
<td>6</td>
<td>10</td>
<td>19</td>
<td>14</td>
<td>16</td>
<td>26</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>* PH Diagnostic mammogram</td>
<td>0</td>
<td>0</td>
<td>47</td>
<td>148</td>
<td>180</td>
<td>188</td>
<td>224</td>
<td>256</td>
<td>346</td>
</tr>
<tr>
<td>* PH Screening mammogram</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>91</td>
<td>117</td>
<td>147</td>
<td>172</td>
<td>207</td>
<td>234</td>
</tr>
</tbody>
</table>

Screening: an annual breast exam.

* PH Diagnostic or PH Screening examinations were examinations of high-risk breast cancer patients funded by the NZ Health Department through the local Public Hospital.

Unilateral: single breast views due to a previous mastectomy, or recent bilateral mammogram so only unilateral performed.

Implants: for patients who have breast implants
Further examination of the mammographic statistics enabled each type of exam to be viewed as a percentage of the total number of patients and as a percentage of the study group (see Table 8).

<table>
<thead>
<tr>
<th>Exam Type</th>
<th>No. of Patients</th>
<th>% of Study</th>
<th>% of Mammograms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>17,145</td>
<td>54.92</td>
<td>77.69</td>
</tr>
<tr>
<td>PH* diagnostic</td>
<td>1389</td>
<td>4.51</td>
<td>6.29</td>
</tr>
<tr>
<td>PH* screening</td>
<td>973</td>
<td>3.16</td>
<td>4.40</td>
</tr>
<tr>
<td>Unilateral</td>
<td>508</td>
<td>1.65</td>
<td>2.30</td>
</tr>
<tr>
<td>Implants</td>
<td>136</td>
<td>0.04</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Table 8 Mammographic examinations during the study period

* PH – examinations of high-risk breast cancer patients funded by the NZ Health Department through the local Public Hospital.
5.3. Ultrasound breast examinations

Ultrasound imaging was coded dependent on the type of the examination performed, the patient’s history, their age, along with the changes that occurred in the practice of breast imaging during the study period. The types of ultrasound examinations performed have been detailed in Table 9 and Figure 13. As with the mammographic statistics, viewing of ultrasound examinations can be seen as a percentage of the total number of patients and as a percentage of the study group in Table 9.

<table>
<thead>
<tr>
<th>Exam Type</th>
<th>No. of Patients</th>
<th>% of Study</th>
<th>% of Ultrasound Exams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral whole-breast</td>
<td>6054</td>
<td>19.68</td>
<td>63.43</td>
</tr>
<tr>
<td>Targeted</td>
<td>2604</td>
<td>8.46</td>
<td>26.23</td>
</tr>
<tr>
<td>Ultrasound exam</td>
<td>749</td>
<td>2.43</td>
<td>7.84</td>
</tr>
<tr>
<td>Implants</td>
<td>136</td>
<td>1.27</td>
<td>1.42</td>
</tr>
</tbody>
</table>

Table 9 Ultrasound examinations during the study period.

Figure 13 Ultrasound examinations - trends during the study period.
Table 10 Ultrasound examinations performed during the study period.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Targeted ultrasound</td>
<td>47</td>
<td>38</td>
<td>143</td>
<td>542</td>
<td>546</td>
<td>518</td>
<td>333</td>
<td>283</td>
<td>154</td>
</tr>
<tr>
<td>Bilateral ultrasound</td>
<td>568</td>
<td>690</td>
<td>734</td>
<td>501</td>
<td>561</td>
<td>549</td>
<td>792</td>
<td>817</td>
<td>842</td>
</tr>
<tr>
<td>Ultrasound exam only</td>
<td>70</td>
<td>87</td>
<td>91</td>
<td>78</td>
<td>55</td>
<td>92</td>
<td>111</td>
<td>81</td>
<td>84</td>
</tr>
<tr>
<td>Implants</td>
<td>3</td>
<td>6</td>
<td>10</td>
<td>19</td>
<td>14</td>
<td>16</td>
<td>26</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>Breast biopsies</td>
<td>84</td>
<td>104</td>
<td>104</td>
<td>162</td>
<td>176</td>
<td>117</td>
<td>155</td>
<td>145</td>
<td>151</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>772</td>
<td>925</td>
<td>1082</td>
<td>1302</td>
<td>1352</td>
<td>1292</td>
<td>1417</td>
<td>1348</td>
<td>1251</td>
</tr>
</tbody>
</table>

Bilateral ultrasound was a whole-breast examination
Targeted: scanning confined to a particular region
Ultrasound exam only: used predominantly for women < 30 years.
Implants: all patients with implants had ultrasound and mammography
The comparative number of mammographic and ultrasound examinations can be seen in Figure 14, with an increasing proportion of ultrasound examinations evident each year. A large percentage of the study population required mammographic imaging only, for adequate breast assessment, with the radiologists satisfied there was no evidence of malignancy and any changes evident in the images could be classified benign. The majority of patients had a mammographic examination except for the 7.84% of patients who had an ultrasound-only examination. These patients were either <30 years of age, were pregnant at the time of the scan or refused to have imaging that involved radiation and opted for ultrasound imaging only. The exact percentage of patients having a mammographic examination only has not been calculated as these patients were not part of the study group in this research.

![Breast Examinations](image)

**Figure 14 Comparison of mammographic and ultrasound exam numbers per study year.**

21,747 or 95.32% of the screened population required no further assessment other than mammography. The remaining 4.68% of the patients became the study group. 1063 patients required further assessment resulting in 1198 breast ultrasound-guided tissue biopsies. The mean age of these patients was 53.5 years (SD 14.01) ranging from 15 to 92 years old inclusive, with a median age 46 years. Graphic representation of the patient’s age groupings at the time of breast tissue biopsy is shown in Figure 15.
While 904 patients had a single breast biopsy during the study period, 135 patients had two or more biopsies performed during the study period, either at different time periods or for more than one lesion contemporaneously. Of these 1063 patients, 14 (2.78%) had a new breast lesion diagnosed in the other breast: a contralateral cancer (refer Section 3.9). Table 11 documents the number of biopsies performed on patients.

<table>
<thead>
<tr>
<th>Patients</th>
<th>No. of Biopsies</th>
</tr>
</thead>
<tbody>
<tr>
<td>904</td>
<td>1</td>
</tr>
<tr>
<td>115</td>
<td>2</td>
</tr>
<tr>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 11 Number of biopsies performed for patients.

As previously stated, all patients were classified as diagnostic (symptomatic) or screening (asymptomatic) and the next section assesses the balance between these groups of patients and the types of lesions that were detected.
5.4. Diagnostic or screening examination: how did the patients present

Diagnostic implies that the patient or their referrer was concerned about specific breast symptoms including nipple discharge, generalised or localised soreness / tenderness, unexplained redness, lumpy area/s, lump/s, increasing tenderness, pain, intermittent pain, a change in the size of a lump, change / roughness in the skin surface, dimpling or puckering of the skin or nipple.

Screening implies that the patient was asymptomatic, having no specific concerns and was presenting for annual or biennial breast imaging.

732 (61.10%) of the examinations in the study group were for diagnostic reasons and in 346 (47.26%) cases, a malignant lesion was detected (see Figure 16).

Figure 16 Malignant lesions in the diagnostic patients

466 (38.89%) of the examinations in the study group were for asymptomatic reasons (screening) and in 157 (33.69%) cases; a malignancy was detected (see Figure 17).
An important issue to be considered when assessing breast tissue for the presence of lesions was the density of that tissue. Over recent years, breast density has been recognised as an independent risk factor for breast cancer (refer Section 3.6) and the following section will assess the relative breast density of the patients in the study group.

## 5.5. Breast density of the study patients

Mammographic breast density was classified as adipose, average or dense according to the classification of Tabar et al. (1997) (refer Section 2.4). Within the study group of patients, 173 (14.44%) had adipose, 718 (59.93%) had average and 307 (25.62%) had dense tissue. The relevance of age on the differentiation of breast density for those in the study group is seen in Figure 18.
Figure 18 Breast density in age groups

Of the 307 patients with dense tissue, 113 (36.8\%) had new malignant lesions detected. The ratio of malignant to benign lesions in dense tissue was 1:1.93 and in adipose breast tissue was 1:1.66. A graphic representation of the types of breast tissue for those with malignant lesions is shown in Figure 19. It was notable that in the group with dense breast tissue, 159/307 (51.79\%) had significant risk factors, and they accounted for 113 (22.46\%) of the malignant breast lesions diagnosed in the whole study. Further discussion on these patients will occur in Section 5.13.

Figure 19 Breast density - comparison of benign and malignant lesions

While patients with dense breast tissue are known to have an increased risk of breast cancer, there was a cohort of patients whose breast density was affected by the ingestion of hormone replacement therapy (HRT). The following section will
review the numbers of patients concerned, offering a comparison by age and of the number of malignant proved lesions.

5.6. HRT: the patients and their results

HRT can cause an increase in breast density that appears as a global, focal or multifocal pattern. The information on patients taking HRT was derived from medical records and / or the individual patient questionnaires. 85 (7.09%) patients were on HRT during the course of this study, ranging from one to 30 years – giving an average of 15.93 years. The patient ages ranged from 39-79 years old with a median age of 58.09 years (SD 10.00).

Breast density was documented for these patients: 10 patients had adipose tissue, 56 average, and 19 with dense breast tissue. 39 (7.78%) malignant or indeterminate (ADH or radial scars) breast lesions were detected in the group of patients taking HRT. 8 lesions were in dense breast tissue, 27 in average and the remaining 4 lesions were in adipose breast tissue. It was notable that this group of 8 women with dense tissue, 7 of them had significant familial risk factors. These malignant lesions ranged in size from 3-50mm, with a median size of 14.8mm (SD 10.00). Table 12 documents these statistics.

Some of these patients had been taking HRT for years before the study period and there was no satisfactory way to prove that the breast density was related to this medication.
### Table 12: Breast imaging in women with dense breasts, by age and hormone replacement therapy (HRT)

<table>
<thead>
<tr>
<th>AGE GROUP</th>
<th>No HRT</th>
<th>HRT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (n)</td>
<td>Dense (n)</td>
</tr>
<tr>
<td>35-39</td>
<td>95</td>
<td>24</td>
</tr>
<tr>
<td>40-44</td>
<td>233</td>
<td>59</td>
</tr>
<tr>
<td>45-49</td>
<td>247</td>
<td>72</td>
</tr>
<tr>
<td>50-54</td>
<td>133</td>
<td>33</td>
</tr>
<tr>
<td>55-59</td>
<td>99</td>
<td>26</td>
</tr>
<tr>
<td>60-64</td>
<td>64</td>
<td>12</td>
</tr>
<tr>
<td>65-69</td>
<td>63</td>
<td>9</td>
</tr>
<tr>
<td>70-74</td>
<td>70</td>
<td>18</td>
</tr>
<tr>
<td>75-79</td>
<td>42</td>
<td>7</td>
</tr>
<tr>
<td>80-84</td>
<td>41</td>
<td>4</td>
</tr>
<tr>
<td>85-89</td>
<td>9</td>
<td>2</td>
</tr>
</tbody>
</table>

### 5.7. Targeted or whole-breast imaging: the scan range

Ultrasound scanning, targeted or whole-breast imaging, was used for 30.58% of the patient population during the study period. The scan range or percentage of breast tissue imaged was defined as either targeted or whole-breast where all breast tissue was interrogated including both axillae. In the study period, targeted ultrasound was used for 2604 (27.28%) of the patients and whole-breast ultrasound for 6939 (72.71%); this included patients with breast implants and those who only had an ultrasound examination. Graphic representation of the examinations performed on a year by year basis is apparent in Figure 20, with the use of targeted ultrasound decreasing during the study period and the use of whole-breast scanning increasing as this became the more normal method of ultrasound imaging.
Figure 20 Comparative scan range of the ultrasound examination

The ultrasound scan range applied in breast imaging often had a direct correlation with areas of breast tissue that were palpable to the patient, assessing the area of concern only unless there was specific risk factors. Many patients presented for imaging, aware of such an area and the following section will establish what the patients in this study reported.

5.8. Lesions: palpable or non-palpable

The patients had documented any changes they had become aware of in their breasts prior to imaging and these observations were correlated with the number of lesions, benign and malignant, that were detected in the mammographic or ultrasound images. 681 (56.84%) of the lesions documented as palpable by the patient were visible on imaging. 296 (43.46%) of these lesions were proven malignant giving a ratio of 1:2.3 (malignant to benign palpable lesions). 517 (43.15%) of the lesions detected were non-palpable to the patient and yet were visible in mammographic or ultrasound images. 202 (39.07%) of these lesions were proven malignant giving a ratio of 1:1.55 (malignant to benign non-palpable lesions).

Figure 21 separates the palpable from the non-palpable lesions, differentiating the benign from the malignant tumours. It was reasonable to assume that non-palpable lesions would be smaller than palpable ones and the results of this study attest to that. Non-palpable malignant lesions were significantly smaller in size (mean size
14.37 mm, SD 10.13) than those that were palpable lesions (mean size 19.16 mm, SD 11.13).

![Figure 21 Palpability of benign and malignant lesions](image)

And so to a review of the types and number of breast lesions detected in this study. Benign lesions in this study accounted for 58.01% of all lesions biopsied. The following section will review the types and quantities of benign lesions detected.

5.9. Lesions: benign

Benign lesions were histologically proven in 697 (58.18%) of the tissue biopsies with the median age of these patients was 45 years (SD 11.48), ranging from 15 to 92 years. Table 13 and Figure 22 list the type and number of benign lesions that were sampled.

The remaining 41.81% of lesions biopsied were proven malignant and these will be discussed in the next section.
<table>
<thead>
<tr>
<th>Benign Lesions</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibroadenoma</td>
<td>274</td>
</tr>
<tr>
<td>Fibrosis or fibrocystic change</td>
<td>208</td>
</tr>
<tr>
<td>Benign tissue</td>
<td>62</td>
</tr>
<tr>
<td>Hyperplasia (no atypia) *</td>
<td>22</td>
</tr>
<tr>
<td>Fat necrosis</td>
<td>18</td>
</tr>
<tr>
<td>Benign proliferative breast disease</td>
<td>16</td>
</tr>
<tr>
<td>Fatty tissue</td>
<td>15</td>
</tr>
<tr>
<td>CAPPS **</td>
<td>12</td>
</tr>
<tr>
<td>Sclerosing adenosis</td>
<td>13</td>
</tr>
<tr>
<td>Tissue inflammation</td>
<td>10</td>
</tr>
<tr>
<td>Lipoma</td>
<td>10</td>
</tr>
<tr>
<td>Papilloma (final histology)</td>
<td>7</td>
</tr>
<tr>
<td>Lactating adenoma</td>
<td>6</td>
</tr>
<tr>
<td>Mammary duct ectasia</td>
<td>5</td>
</tr>
<tr>
<td>Scar tissue</td>
<td>3</td>
</tr>
<tr>
<td>Tubular adenoma</td>
<td>3</td>
</tr>
<tr>
<td>Connective tissue</td>
<td>3</td>
</tr>
<tr>
<td>Mastitis</td>
<td>2</td>
</tr>
<tr>
<td>Tissue necrosis</td>
<td>2</td>
</tr>
<tr>
<td>Intramammary lymph node</td>
<td>2</td>
</tr>
<tr>
<td>Inclusion cyst</td>
<td>1</td>
</tr>
<tr>
<td>Granulomatous change</td>
<td>2</td>
</tr>
<tr>
<td>Phylloides tumour (benign)</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 13 Benign lesions

* no atypia – no atypical cells were present in the tissue sample

** CAPPS = columnar cell alteration with prominent snouts and secretions
5.10. Lesions: malignant

Malignant lesions were histologically proven in 501 (41.81%) of the breast tissue biopsies taken in this study; this included all cases of ADH and radial scars (indeterminate lesions). The median age of these patients was 56 years (SD 14.01), ranging from 30 to 92 years. Table 14 and Figure 23 document the types and numbers of malignant lesions sampled.
## Malignant Lesions

<table>
<thead>
<tr>
<th>Malignant Lesions</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade One invasive ductal carcinoma</td>
<td>116</td>
</tr>
<tr>
<td>Grade Two invasive ductal carcinoma</td>
<td>111</td>
</tr>
<tr>
<td>Grade Three invasive ductal carcinoma</td>
<td>79</td>
</tr>
<tr>
<td>Infiltrating lobular carcinoma</td>
<td>45</td>
</tr>
<tr>
<td>Ductal carcinoma in situ (DCIS) *</td>
<td>79</td>
</tr>
<tr>
<td>Atypical ductal hyperplasia (ADH) **</td>
<td>22</td>
</tr>
<tr>
<td>Papillary carcinoma ***</td>
<td>17</td>
</tr>
<tr>
<td>Radial scar ***</td>
<td>11</td>
</tr>
<tr>
<td>Invasive tubular carcinoma</td>
<td>9</td>
</tr>
<tr>
<td>Mucinous carcinoma</td>
<td>5</td>
</tr>
<tr>
<td>Reoccurrence of high grade cancer</td>
<td>4</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>2</td>
</tr>
<tr>
<td>Spindle cell neoplasm</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 14 Malignant lesions.

* DCIS was graded as a low, intermediate or high grade lesion
** Atypical ductal hyperplasia: a lesion with malignant potential that requires excision, classed as an indeterminate lesion
*** Papillary carcinoma: papillary lesion on core biopsy, papillary on surgical excision
**** Radial scar: a lesion with malignant potential that requires excision, classed as an indeterminate lesion

Having established the number of and types of breast lesions detected, it was appropriate to assess the patient’s age at the time of biopsy as well as investigate the biopsy rates on an annual basis during the course of this study. The next section will determine these numbers.
5.11. Patient age: at time of diagnosis

The patient's age at the time of biopsy for both benign and malignant lesions (refer Section 5.9 and 5.10) is shown graphically in Figure 24 with the weighting of benign and malignant biopsy results apparent. Benign lesions occurred predominantly in women < 50 years and malignant lesions occur predominantly for women > 50 years.

**Figure 24 Patient age at diagnosis**

Proportionally, the number of breast tissue biopsies has risen over the study period (refer Figure 25) with the dip in 2004 due principally to changes in the BSA age range allowable for breast screening.

**Figure 25 Number of breast biopsies performed**
5.12. Lesion sizes: benign and malignant

Lesion sizes were measured during the ultrasound scan and were recorded in the hard copy image. The measurements were tabled in 93.07% of the cases. 83 (6.93%) of the lesions sizes were not documented and accordingly these were not included in the statistical assessment. Measurements for the lesions biopsied ranged from 3 - 90mm with a mean of 18.16mm (SD 10.41), and a median of 21mm. Benign lesions had a mean of 15.31mm (SD 8.36), with a median of 13mm. Malignant lesions had a mean of 19.11mm (SD 12.30), with a median of 16mm.

Among the histologically confirmed breast cancers, 189 were <10mm, 136 were 1.1-20mm and 158 were > 20mm (measurement of these was a subjective assessment). Figures 26 & 27 show the size and number of the benign and malignant lesions.

![Benign Lesions (n)](image)

Figure 26 Benign lesions
Figure 27 Malignant lesions

For the 84 lesions with no documented measurement, information was recorded relative to their appearance in the breast tissue as seen in the ultrasound image. These observations were due to recognition of change that had occurred in the breast tissue relative to prior imaging. The reasons were varied but broadly fit into the following categories:

- architectural distortion of breast tissue 7
- ill-defined/indeterminate cluster of micro-calcifications 32
- diffuse increase in density 5
- asymmetrical nodularity 7
- asymmetry of breast tissue 7
- palpable/ridge-like lumpiness 19
- complex stellate-appearing lesion 5
- skin thickening 2

All these lesions were biopsied under ultrasound guidance and 20 were proven malignant lesions: ADH (9), DCIS (6), radial scar (1), infiltrating lobular carcinoma (1) and Grade II IDC (3).

With the groundwork now laid, it is time to address the issue of the high risk breast cancer patient in this study, establishing the number of these, highlighting the relevant risk factors, and detailing the comparative numbers of malignant breast lesions detected.
5.13. The high risk patient: reasons and results

Patients were deemed high-risk when the normal baseline risk was elevated due to a BRCA1 or BRCA2 positive status (refer Section 3.8), a personal history of or a relevant family history of this disease. Women without any of these risk factors were considered to be at the normal or baseline risk.

In the study group, 0.55% of the women were BRCA1 gene-positive, 6% had a personal history of previous breast cancer, 35.72% had a family history of breast cancer and 28.11% of these had a primary family member (father, brother, mother, sister or daughter) with a history of breast cancer. Only a small percentage of the patients in this study were tested for the BRCA gene and they met the specific criteria laid down by the relevant genetic testing facility. Table 15 documents the risk factors for the patients involved in the study.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>No. of Patients</th>
<th>%</th>
<th>Malignant Lesions</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA gene-positive</td>
<td>6</td>
<td>0.56</td>
<td>5</td>
<td>0.99</td>
</tr>
<tr>
<td>Previous breast or ovarian cancer</td>
<td>72</td>
<td>6</td>
<td>36</td>
<td>7.18</td>
</tr>
<tr>
<td>Family history</td>
<td>428</td>
<td>35.72</td>
<td>180</td>
<td>35.92</td>
</tr>
<tr>
<td>Multiple risks *</td>
<td>33</td>
<td>2.54</td>
<td>10</td>
<td>1.99</td>
</tr>
<tr>
<td>No risk factors</td>
<td>659</td>
<td>55</td>
<td>272</td>
<td>54.29</td>
</tr>
<tr>
<td>Adopted (risk unknown)</td>
<td>6</td>
<td>0.05</td>
<td>4</td>
<td>0.79</td>
</tr>
<tr>
<td>Dense breast tissue</td>
<td>307</td>
<td>25.62</td>
<td>112</td>
<td>22.23</td>
</tr>
<tr>
<td>Dense breast tissue + high risk factors</td>
<td>159</td>
<td>13.27</td>
<td>63</td>
<td>12.57</td>
</tr>
</tbody>
</table>

* Multiple risks meant a combination of any of the stated risk factors

The study group of patients can be divided simply into those with a normal baseline risk and those with increased risk factors. The baseline risk group numbered 659 women (55%) and of these, 285 (41.24%) were diagnosed with a malignant lesion.
Patients at increased risk numbered 539 patients (44.99%) and 219 of these patients (41.08%) had a malignant breast lesion diagnosed.

Family history risk assessment relates to the incidence of breast and/or ovarian cancer among relatives, the number of relatives who have been affected, the age of those relatives when the cancer was diagnosed, and the type of relationship that person had to the patient. Relationship to one’s relatives was defined as first degree (mother, father, sister or brother); second-degree (grandparents, aunt, cousin and niece); or third-degree relatives (great aunt or great grandmother). The patient questionnaire completed prior to imaging sought to establish any known links. Table 16 defines these familial risk factors relative to the individual patient.

<table>
<thead>
<tr>
<th>Familial Risk Factors</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one first degree relative</td>
<td>300</td>
</tr>
<tr>
<td>First degree relative &lt; 50 yrs</td>
<td>136</td>
</tr>
<tr>
<td>Two first degree relatives</td>
<td>37</td>
</tr>
<tr>
<td>Three first degree relatives</td>
<td>1</td>
</tr>
<tr>
<td>Two first or second degree relatives &lt;50 yrs</td>
<td>83</td>
</tr>
<tr>
<td>Three first or second degree relatives &lt;60 yrs</td>
<td>73</td>
</tr>
<tr>
<td>Four relatives at any age</td>
<td>23</td>
</tr>
<tr>
<td>Family history of ovarian/breast cancer &lt;50 years</td>
<td>42</td>
</tr>
<tr>
<td>Male breast cancer (father, brother)</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 16 Family history risk factors.

Of further consideration was the group of patients who have dense breast tissue. Of the 307 patients with mammographically dense breast tissue, 159 had known increased risk factors. Within this group of 159, 39.62% (63) had malignant lesions detected during this study accounting for 12.57% of all malignant lesions detected.

From an initial cohort of 533 patients who were known to have a high risk status, 236 were added to this initial number by the conclusion of this study, due to detection of a malignant lesion. When undergoing future breast imaging, these women would all be classified as being at an increased risk.
The next section relates to those patients whose malignancy was detected purely by ultrasound. Though small in number, the results were significant for the patients concerned.

**5.14. Ultrasound-only detected lesions**

The malignant lesions discussed so far have been mammographically detected, followed by ultrasound correlation prior to a core-biopsy sampling of the tissue.

During the course of this study, 16 additional lesions were identified with ultrasound and of these, 14 were proven malignant, even though the mammogram was initially negative. A subsequent review of the mammographic images revealed no abnormality. Detection of the suspect lesions occurred while a whole-breast ultrasound examination was performed; a normal imaging process in this radiology practice for women with increased risk factors, dense breast tissue or a positive mammography finding.

The patients with an ultrasound detected lesion were aged 30 – 60 of years, with a median of 49 years (SD 7.42). The lesions measured 5 - 35mm in diameter with a median size of 10.5mm (SD 8.12). The breast density in these patients was classified as being adipose (8%), average (59%) and dense (33%) – refer Figure 28. The patients’ breast cancer risk status was documented and it was notable that 10 of these women (62.5%) had significant risk factors while 4 (25%) of the women with risk factors also had dense breast tissue

![Breast Density in Ultrasound Detected Lesions](image)

**Figure 28** Breast density in the ultrasound-detected lesions.
These patients can be further defined by their presentation status – whether their presentation for imaging was based on diagnostic or screening reasons. 7 of these 16 women presented for diagnostic reasons and all of these women had a malignant lesion proven with tissue analysis. The remaining 9 women presented for a screening examination and 7 of this group had a malignant lesion proven with tissue analysis.

These lesions were considered suspicious for malignancy based on the ultrasound appearance and verification with core biopsy was deemed appropriate. Three (3) lesions considered most likely benign in appearance and thought to be fibroadenomas or fibrocystic change but were proven Grade I (1) and II (2) invasive ductal carcinomas, giving a false negative result. Two lesions were false positives; malignancy was suspected and the histology proved the lesions were a lipoma and fibroadenoma. The remaining eleven lesions were proven malignant, giving a true positive result for Grade I invasive ductal carcinomas (3) and Grade II invasive ductal carcinomas (4), invasive tubular carcinoma (1) and invasive lobular carcinomas (3).

<table>
<thead>
<tr>
<th>Age</th>
<th>Risk Factor</th>
<th>Diagnosis</th>
<th>Lesion Size (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>Baseline</td>
<td>Grade 1 IDC *</td>
<td>10</td>
</tr>
<tr>
<td>41</td>
<td>Baseline</td>
<td>Infiltrating lobular</td>
<td>11</td>
</tr>
<tr>
<td>45</td>
<td>Family history</td>
<td>Grade 1 IDC</td>
<td>12</td>
</tr>
<tr>
<td>45</td>
<td>Family history</td>
<td>Grade 1 IDC</td>
<td>14</td>
</tr>
<tr>
<td>47</td>
<td>Baseline</td>
<td>Grade 2 IDC</td>
<td>12</td>
</tr>
<tr>
<td>48</td>
<td>Family history</td>
<td>Lipoma</td>
<td>15</td>
</tr>
<tr>
<td>48</td>
<td>Multiple risk</td>
<td>Grade 1 IDC</td>
<td>35</td>
</tr>
<tr>
<td>49</td>
<td>Family history</td>
<td>Grade 1 IDC</td>
<td>11</td>
</tr>
<tr>
<td>50</td>
<td>Multiple risk</td>
<td>Invasive tubular</td>
<td>10</td>
</tr>
<tr>
<td>52</td>
<td>Family history</td>
<td>Grade 2 IDC</td>
<td>7</td>
</tr>
<tr>
<td>53</td>
<td>Baseline</td>
<td>Grade 1 IDC</td>
<td>11</td>
</tr>
<tr>
<td>53</td>
<td>Family history</td>
<td>Grade 1 IDC</td>
<td>7</td>
</tr>
<tr>
<td>55</td>
<td>Baseline</td>
<td>Grade 1 IDC</td>
<td>5</td>
</tr>
<tr>
<td>57</td>
<td>Family history</td>
<td>Grade 2 IDC</td>
<td>8</td>
</tr>
<tr>
<td>57</td>
<td>Family history</td>
<td>Fibroadenoma</td>
<td>9</td>
</tr>
<tr>
<td>60</td>
<td>Baseline</td>
<td>Infiltrating lobular</td>
<td>10</td>
</tr>
</tbody>
</table>

* IDC = invasive ductal carcinoma

Table 17 Ultrasound detected breast lesions
Table 17 documents the patients’ risk status, lesion size and the final diagnosis. Imaging concordance with the pathology results for these lesions gave a true positive rate of 75%, false negative rate of 18.75% and false positive rate of 6.25%.

The ultrasound-only detection rate of cancers was 5.3% (501 cancers / 9543 ultrasound examinations) giving an increase in the overall detection rate of 1.46 cancers per 1000 ultrasound patients. While this 2.79% detection rate of cancers (14/501) cancers with ultrasound was small, it was of obvious significance to the patients concerned. The overall rate of ultrasound-only detected breast cancers showed an increasing trend in numbers over the years of the study. Figure 29 shows that ultrasound detection rate on a year by year basis during the study. It is important to state that all the mammographically identified cancers were additionally imaged with ultrasound.

![Ultrasound Detected Cancers (n)](image)

*Figure 29 Lesions detected by ultrasound*

Concordance of imaging findings is the subject of the next section and will document the statistical results for this study prior to the analysis and discussion (refer Section 6).

### 5.15. Concordance of imaging findings with histopathological analysis

An interim lesion diagnosis, based on imaging appearances prior to histology confirmation, was included in the patient database along with the pathology results to
enable an assessment of breast imaging. Concordance of these results would show the TP, TN, FP and FN numbers for the study group (see Table 18). The definition for TN and FN results in this study have been previously discussed (refer Section 4.6), for these differ from conventional understanding of these terms due to the retrospective nature of this research.

Though atypical ductal hyperplasia (ADH) and radial scars were classified as indeterminate lesions by the radiologist (as previously discussed in Section 2.5.2); these lesions were statistically counted as TP findings because of their known malignant potential, indicating a necessity for further management even if that management was not required immediately.

<table>
<thead>
<tr>
<th>Mammography (No.)</th>
<th>Ultrasound (No.)</th>
<th>Mammography + ultrasound (No.)</th>
<th>Ultrasound (detected lesions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positive</td>
<td>470</td>
<td>484</td>
<td>485</td>
</tr>
<tr>
<td>True negative</td>
<td>622</td>
<td>625</td>
<td>622</td>
</tr>
<tr>
<td>False positive</td>
<td>75</td>
<td>72</td>
<td>75</td>
</tr>
<tr>
<td>False negative</td>
<td>31</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>1198</td>
<td>1198</td>
<td>1198</td>
</tr>
</tbody>
</table>

**Table 18 Imaging results**

With combined imaging (mammography + ultrasound), 485 (96.42%) of the malignant lesions were TP results while 622 (97.49%) of the benign lesions were TN results. Table 19 and 20 detail the FN and FP pathologies (from mammography + ultrasound combined imaging) that precluded an accurate diagnosis. For discussion of the FN and FP results refer to Section 6.6.
### Table 19 False negative pathologies

<table>
<thead>
<tr>
<th>Pathology</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCIS</td>
<td>8</td>
</tr>
<tr>
<td>Grade I IDC</td>
<td>2</td>
</tr>
<tr>
<td>Grade II IDC</td>
<td>3</td>
</tr>
<tr>
<td>Infiltrating lobular carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Invasive tubular carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Papillary carcinoma</td>
<td>1</td>
</tr>
</tbody>
</table>

16

### Table 20 False positive pathologies.

<table>
<thead>
<tr>
<th>Pathology</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibroadenoma</td>
<td>15</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>19</td>
</tr>
<tr>
<td>Fibrocystic change</td>
<td>9</td>
</tr>
<tr>
<td>Ductal ectasia</td>
<td>5</td>
</tr>
<tr>
<td>CAPPS</td>
<td>4</td>
</tr>
<tr>
<td>Micro-calcifications</td>
<td>2</td>
</tr>
<tr>
<td>Inflammatory changes</td>
<td>6</td>
</tr>
<tr>
<td>Hyperplastic changes</td>
<td>6</td>
</tr>
<tr>
<td>Fat necrosis</td>
<td>3</td>
</tr>
<tr>
<td>Sclerosing adenosis</td>
<td>3</td>
</tr>
<tr>
<td>Adenoma</td>
<td>2</td>
</tr>
<tr>
<td>Lipoma</td>
<td>1</td>
</tr>
</tbody>
</table>

75

The biopsy rate in this study was 5.25% (1198/22,814) with 501 malignant and 697 benign lesions documented. Malignant lesions accounted for 41.81% of all the breast lesions biopsied with the ratio of malignant to benign lesions 1:1.39 (mammography + ultrasound).

Ultrasound-only examinations detected 2.79% (14/501) of the total number of malignant lesions and increased the detection rate of malignant lesions by 0.146% (1.46:1,000 patients).
The prevalence of breast cancer in the screened population was 2.19% (501 cancers from 22,814 women), or 22.05:1,000 patients. The prevalence of cancer in the high risk patients was 41.08% (219 cancers from 533 high risk women), or 410:1,000 patients.

For women with dense breast tissue, the prevalence of breast cancer was 36.8% (113 cancers from 307 women), or 368:1,000 patients. And lastly, for the women with high risk factors and dense breast tissue the prevalence was 39.62% (63 cancers from 159 women), or 396:1,000 patients.

Having assessed the imaging concordance of findings, it was appropriate to determine if these results held any statistical significance. The next section will review the statistics in the light of mammography, ultrasound, mammography + ultrasound and ultrasound detected lesions; with regard to the screened population, and specific sub-groups of patients: the high risk patient, the patient with dense breast tissue and the patient with both these risk factors.

5.16. **Statistical results from imaging: mammography, ultrasound, and mammography + ultrasound combined**

This section will document the results for cancer detection by mammography, ultrasound, and mammography + ultrasound for the screened population and for the sub-groups of patients: the patient at high risk, with dense breast tissue and with both the risk factors.

This 2x2 contingency table (Table 21) relates to the study group of patients (1063) whose lesions were detected with mammography. As all patients in the study group, regardless of age, had mammographic and ultrasound imaging, it is possible to assess the value of these modalities, separately and in combination.
### Table 21 Mammographic detection of cancers

GraphPad Software, 2005

The Fisher’s exact test two-tailed *P* value was <0.0001 and this was deemed a statistically significant result. TP and TN results were breast lesions that had a concordance of both imaging and histology for malignant or benign status. FP means a positive for malignancy on imaging but a negative on histology. A FN result, within the terms of this research, applied to benign-appearing lesion on imaging that was sampled and proven malignant on histology.

All patients in the study group (1063) had an ultrasound examination during their examination process and Table 22 documents this. The Fisher’s exact test two-tailed *P* value was deemed an extremely statistically significant result (<0.0001) for this form of malignant lesion detection.

### Table 22 Ultrasound detection of cancers

GraphPad Software, 2005

Table 23 relates to the study group of patients (1063) who had 501 malignant lesions detected by mammography + ultrasound combined.
<table>
<thead>
<tr>
<th>Patients + disease</th>
<th>Patients - disease</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test positive</td>
<td>485</td>
<td>75</td>
</tr>
<tr>
<td>Test negative</td>
<td>16</td>
<td>622</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>501</strong></td>
<td><strong>697</strong></td>
</tr>
</tbody>
</table>

**Table 23 Combined imaging (mammography + ultrasound) detection of cancers**

GraphPad Software, 2005

The Fisher’s exact test two-tailed $p$ value was <0.0001 and this was deemed a statistically significant result. The sensitivity, specificity, PPV and NPV percentages for this and the following tables (22-27) are documented in Table 28.

A small number of malignant breast lesions (14) were detected only with bilateral whole breast ultrasound imaging; these results are documented in following Table (24). These patients had undergone both mammographic and ultrasound breast imaging prior to a tissue biopsy, however these malignant lesions were not detected mammographically.

<table>
<thead>
<tr>
<th>Patients + disease</th>
<th>Patients - disease</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test +</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Test -</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>14</strong></td>
<td><strong>2</strong></td>
</tr>
</tbody>
</table>

**Table 24 Ultrasound-only detection of cancers**

GraphPad Software, 2005

The Fisher’s exact test two-tailed $p$ value equals 1.0000 - this was not a statistically significant result and therefore could have arisen by chance. The numbers of patients in this category were too low to form a hypothesis however, for the patients concerned, detection of these malignant lesions was important. For discussion on this and the other results refer to Section 6.6.
Patients who are considered to be at an elevated risk for breast cancer relative to the baseline risk (Table 25) were assessed as a sub-group of patients, the criteria for these patients was documented in Section 4.4.

<table>
<thead>
<tr>
<th>Patients + disease</th>
<th>Patients - disease</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test +</td>
<td>218</td>
<td>36</td>
</tr>
<tr>
<td>Test -</td>
<td>9</td>
<td>280</td>
</tr>
<tr>
<td>Total</td>
<td>217</td>
<td>316</td>
</tr>
</tbody>
</table>

Table 25 Detection of cancers in the high risk patient (mammography + ultrasound)

533 high risk patients were identified with 217 new malignancies through imaging with mammography and/or ultrasound. The Fisher’s exact test two-tailed \( P \) value was <0.001, this was considered a statistically significant result.

Dense breast tissue has been acknowledged through research as an independent risk factor for breast cancer (refer Section 3.6). Table 26 documents the results for patients with mammographically dense breast tissue. From a total of 307 patients, 113 new breast malignancies were detected. The Fisher’s exact test two-tailed \( P \) value was <0.001, again a statistically significant result.

<table>
<thead>
<tr>
<th>Patients + disease</th>
<th>Patients - disease</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test +</td>
<td>106</td>
<td>24</td>
</tr>
<tr>
<td>Test -</td>
<td>7</td>
<td>170</td>
</tr>
<tr>
<td>Total</td>
<td>113</td>
<td>193</td>
</tr>
</tbody>
</table>

Table 26 Detection of cancers in patients with dense breast tissue (mammography + ultrasound)

GraphPad Software, 2005
Patients with a combination of these risks (high risk factors and dense breast tissue) are shown in Table 27. 63 new malignancies were detected from a total cohort of 159 patients, with the Fisher’s exact test two-tailed \( P \) value being <0.001, a statistically significant result.

<table>
<thead>
<tr>
<th></th>
<th>Patients + disease</th>
<th>Patients - disease</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test +</td>
<td>59</td>
<td>14</td>
<td>73</td>
</tr>
<tr>
<td>Test -</td>
<td>4</td>
<td>82</td>
<td>86</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>63</strong></td>
<td><strong>96</strong></td>
<td><strong>159</strong></td>
</tr>
</tbody>
</table>

**Table 27 Mammography + US for the high risk patient with dense breast tissue**

A summary of the accuracy, sensitivity, specificity and predictive values for each of the imaging modalities used in this study is documented in Table 28. A discussion of all these statistical results can be found in Section 6.6.
### Table 28 Analysis of the results for mammography and ultrasound in the detection of breast cancers

<table>
<thead>
<tr>
<th></th>
<th>Mammography exam only</th>
<th>Ultrasound exam only</th>
<th>Mammography + US* #</th>
<th>Ultrasound-detected lesions</th>
<th>Mammography + US* in HR** patients</th>
<th>Mammography + US* - dense breast tissue</th>
<th>Mammography + US* in HR** patients + dense breast tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancers detected</td>
<td>471/22,065</td>
<td>485/9,543</td>
<td>485/22,814</td>
<td>14/1198</td>
<td>219/533</td>
<td>113/307</td>
<td>64/159</td>
</tr>
<tr>
<td>Accuracy</td>
<td>91.2%</td>
<td>92.8%</td>
<td>92.4%</td>
<td>99.83%</td>
<td>91.66%**</td>
<td>89.86%</td>
<td>87.42%</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>94%</td>
<td>96.8%</td>
<td>96.8%</td>
<td>95.9%</td>
<td>93.8%</td>
<td>92.1%</td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>89.2%</td>
<td>90%</td>
<td>89.2%</td>
<td>99.8%</td>
<td>88.7%</td>
<td>87.6%</td>
<td>84.4%</td>
</tr>
<tr>
<td>Positive Predictive value</td>
<td>86.3%</td>
<td>87.4%</td>
<td>86.6%</td>
<td>87.5%</td>
<td>85.4%</td>
<td>81.5%</td>
<td>79.5%</td>
</tr>
<tr>
<td>Negative Predictive value</td>
<td>95.4%</td>
<td>97.5%</td>
<td>97.5%</td>
<td>96.9%</td>
<td>96.0%</td>
<td>94.2%</td>
<td></td>
</tr>
</tbody>
</table>

*US – ultrasound
** HR – high risk patients, refer Section 4.4
# for discussion of these results refer to Section 6.4.1
6.0 Analysis and Discussion

6.1. Introduction

Breast cancer is a common malignancy among women and early detection of malignant lesions is significant in reducing the mortality rate. Robust assessment of bilateral whole-breast screening ultrasound is essential to determine if this modality can add to the mammographic diagnosis for women with positive mammographic findings or are known to be at an increased risk for breast cancer. High risk patients have been identified through criteria previously discussed (refer Section 4.1); however appropriate diagnostic imaging does not appear to be so easily accomplished.

Mammographic sensitivity is proven to be significantly compromised when imaging dense breast tissue and research now documents dense tissue as an independent risk factor (refer Section 3.6). Imaging with both mammography and bilateral whole breast ultrasound is now suggested by several authors (Baker et al. 2005; Carter, 2006; Fasching et al. 2006; Carney, 2006 & Berg et al. 2008) as best practice for these patients, with mammography no longer viewed as the gold standard of imaging.

This chapter will discuss the results of bilateral whole breast ultrasound from this study and assess those results with reference to current literature. Consideration as to the types of breast lesions detected with whole breast ultrasound is important as these lesions may be more difficult to perceive with mammography. Diffuse, rapid spreading malignancies are often known to be subtle in presentation and a skilled eye is necessary to perceive the often subtle changes in breast tissue.

This patient cohort differs markedly from those who attend BSA as an increased proportion of patients have raised risk factors. Detection of breast lesions in this high risk population has an increased urgency as their relative risk is significantly raised relative to the 11% baseline risk status attributed to New Zealand women. These issues, along with the relevant limitations and variables applicable to this study will be addressed in the following pages.
6.2. Limitations and variables for this retrospective study

In any study the inherent limitations and variables imposed by the nature of the study can have an effect on the outcome and conclusions. Unique variables and limitations apply to a retrospective study and having an awareness of these is important if valid conclusions are to be drawn.

The data for this study was obtained from two sources; a patient database (COMRAD II) and a handwritten record of biopsy information documented during the nine year study period. The accuracy of the COMRAD II database information was dependent on those who input the data and contained principal data of the patient and their breast imaging history. All cases in this study had a complete dataset and no patients were excluded due to incomplete information.

The handwritten record of biopsy data added further information, specific to the tissue sampling procedure and I note that there was no discrepancy of biopsy numbers between these two records, leading to a statistical stability during the study period, enabling the results to be viewed robustly. The nine year study period provided a large patient population of 22,814 who underwent 30,756 examinations including 1198 core tissue biopsies.

The body of data does exist; the practice of radiology and breast imaging has occurred and this offers a genuine, unbiased opportunity to review those practices and the trends that developed during the study period. The data used in this study was initially recorded as a means of documenting the day to day practice of breast imaging; not with the express intention to be used for research, reducing the possibility of manipulation or bias by the record keepers.

6.2.1. Limitations

The data and the patient population had long been defined as were changes that occurred in practice, thus limiting the options for additional information to be acquired. This could be viewed as a limitation of research however retrospective reviews may also be viewed as being enhanced by pure data, for the data has not been tampered with or directed by the thrust of ongoing research.
As previously discussed in Section 4.6, definition of the TN and FN results vary from the conventional statistical meanings due to the availability of data in this retrospective study. This could be considered a limitation when evaluating this study in the light of similar research; however the body of data available can not be changed and needs to be seen in its own right, with a small study group of 1063.

Berg et al. (2004) comment that a prior knowledge of an abnormality can “artificially inflate the performance of (any) supplemental imaging, since findings that might be otherwise be dismissed will be targeted specifically” (p.28). There is a truth in this statement if one considers scanning breasts that are predominantly of adipose or average density. This statement is less likely to be valid when imaging breasts of increased density. Where breast tissue is dense, mammography is limited in detecting abnormalities and ultrasound could be considered necessary to interrogate all tissue adequately. Knowledge of mammographically apparent cysts or solids, or clinical awareness of a palpable area may initially direct the ultrasound scan to a targeted area though this would have little bearing on the remainder of the ultrasound scan as all breast tissue was imaged for completeness of assessment.

Sonographer skill can be seen as both a limitation and a variable as an inexperienced sonographer may inadequately visualize all breast tissue raising the probability of missed breast abnormalities, even when directed by the clinical or mammographic result. Berg et al. (2008) reflected on the “dependence of freehand screening breast ultrasound because an abnormality must be perceived while scanning” (p. 2152).

The importance of accurately recording pertinent data on the ultrasound image may be a limiting factor and should not be underestimated, for the radiologist who would double-read the images relies on those who have been at work before her / him. Documenting which breast was imaged; the region of the breast, the relative measurement of a lesion, or where an area of altered echotexture or increased vascularity was located can only assist with accurate reporting. The ultrasound images were viewed in tandem with the mammographic films - a correlation of imaging is essential if a concordant result was to be reached. As the hard-copy images were reviewed retrospectively, the concordance of imaging results could be limited if any of these issues were not adequately dealt with.
The technical requirements necessary to gain optimal images of breast tissue have been discussed in Section 2.10 and can be viewed as a limitation if inappropriate or wrong settings were used and this can preclude visualisation of any architectural change in the tissue. Sonographer skill can be a limitation and a variable when there is inattention to the image or failure to completely interrogate all breast tissue.

6.2.2. Variables

Although some research projects have reported reasonable results from breast ultrasound screening, inter-observer variability and intra-observer variability top the list of concerns in research published to date. There seems to be an awareness of a lack of consistency and reliability of those who image breast tissue, and this needs to be addressed before ultrasound can be seen as a reliable and effective tool in the detection of breast cancers, particularly in those with dense tissue.

The knowledge of the current and past mammographic and clinical findings was available and used in all cases prior to an ultrasound scan in this radiological practice. If the patient was <30 years at presentation, the ultrasound findings were be viewed in the light of a subsequent mammographic image (refer Section 4.5).

This knowledge could be considered to be a variable as the ultrasound imaging would be guided by prior results. However whole-breast ultrasound imaging was and is a complete examination in its own right, complimentary to and separate to mammography, examining breast tissue through a different lens.

A variable relating to the improvement in ultrasound technology was evident even during the course of this research. For example, recently acquired new ultrasound machines gave a noticeable improvement in resolution; due to a combination of advances in transducer design and application of the latest technology. It would be difficult to quantify whether an actual improvement in the detection rate occurred with this new technology; perhaps a greater appreciation of the subtle ultrasound appearance of lesions would be more likely.

An important variable relates to an individual patient’s risk status, in particular the familial risk factors. Familial risk information was provided anecdotally and the true value for an individual patient could vary from that which was recorded. This was evidenced when patients “remember” more information on subsequent visits and a
researcher could question where the absolute truth was. Patients were often aware that their relatives died of “cancer of something” but were not always able to be specific about the “where” it was. It has been well documented that for a relative to be < 50 years of age at the time of diagnosis increases the relative risk for the patient, particularly if this was a first-degree relative (Collaborative Group on Hormonal Factors in Breast Cancer, 2001). It was more difficult in this study to determine the age of affected relatives rather than define than the relationship of the relative to the patient.

In the recording and reporting of pertinent patient data in COMRAD II there was always the potential for inaccuracy to occur. The human factor did exist though it was hoped that this was limited.

A further variable relates to the reduced threshold for breast ultrasound, particularly bilateral whole-breast ultrasound that has occurred within the practice over the course of the study period. These changes have occurred due to relevant clinical research and with improvements in the practice of ultrasound. As the number of ultrasound scans has increased, there has been a parallel increase in the number of biopsies performed and in the number of malignant lesions detected. It is reasonable to assume that these lesions would have been detected in future imaging when the lesion size was increased and potentially palpable or visible on imaging. The percentage of node-negative patients in this study was not assessed, however it would be expected that with the detection of the smaller lesions with ultrasound that a greater percentage of the patients would have a node-negative status.

### 6.3. Imaging with ultrasound: scan protocol

As previously discussed, mammography was the initial form of imaging for the majority of women though 4.25% (51) of the participants had ultrasound imaging initially due to their age at presentation.

The scan protocol for bilateral breast ultrasound was discussed in Section 4.5.2 though it should be stated that individual imaging decisions were based on the mammographic and ultrasonic findings at the time of presentation, in conjunction with any clinical concerns. Bilateral breast ultrasound was offered and performed on 9,543 patients if:
- an abnormality was present in the mammographic image
- a change in breast tissue had occurred since previous imaging
- microcalcifications were detected
- a palpable area of suspicion was documented by the patient or mammographer
- the breasts were mammographically dense
- the patient had a known high-risk factor/s

All ultrasound scans in this study were undertaken with a full knowledge of the current and/or previous mammographic and clinical findings. As a real-time imaging modality, it was Baker (p.35, 2002) who questioned “what if the cancer is not in the images?” It is important to note that a large proportion of current research based their findings on the hard-copy image only (post examination); this could be to the detriment of ultrasound when assessing it as an imaging modality. The issue of operator dependence is relevant (previously discussed in Section 2.10) for lesions need to be identified in real-time scanning and then documented in the hard-copy image.

Targeted breast ultrasound had a limited use in this study, predominantly for the non-high risk patient with mostly adipose breast tissue to clarify cystic lesions, intramammary lymph nodes and to review previously biopsied benign lesions, ensuring no interval change had occurred. 27.28% of the patients were documented as having a targeted breast ultrasound in this study, though its use declined markedly during the study period as whole breast ultrasound became incorporated as part of best practice (refer Figure 13).

It should be documented that the actual number of targeted ultrasound exams performed was lower than it statistically appears. At the discretion of the radiologists, some patients were charged for a targeted ultrasound exam when a full bilateral examination had occurred, falsely elevating those examination numbers. The policy of the practice was, and is currently, to give women a complete imaging examination without making the cost prohibitive. The decrease in number of targeted ultrasound examinations was predominantly related to advances in medical research and the associated improvement evidenced in the increased detection of breast cancers with improved technology. These changes were reflected also in research studies by authors such as Kaplan et al. (2001), Kolb et al. (2002) and Boonjunwetwat et al. (2007) – refer Section 3.4.
The number of bilateral breast ultrasound examinations performed showed a steady increase during the study period, matching both the increase in patient numbers and the decreasing number of targeted examinations performed (see Figure 13). All 9,543 breast ultrasound scans performed for this study were performed and reviewed by a sonologist with > 19 years of experience and a radiologist with > 30 years experience, each assessing > 1,000 breast examinations per year. Evaluation of bilateral breast ultrasound and the detection rate achieved will determine if there has been value in imaging breast tissue this way, as an adjunct to mammography. The next section will seek to address this issue.

6.4. Bilateral whole-breast ultrasound: the current perspective

Prior to 2000, ultrasound was predominantly used in a targeted scan, for resolution of cystic from solid masses. Whole-breast ultrasound was rarely commented on and its value was questioned; seen either a waste of time or a nuisance due to the detection of additional breast lesions with low specificity.

Research relative to whole-breast imaging has principally occurred since 2001 with the majority of authors stating that the mammographic results were not available prior to the ultrasound scan - an important consideration when evaluating research and the results of this study. Knowledge of the mammographic findings in this study was available to the sonologist prior to whole breast imaging.

During this study period, whole breast ultrasound was used for all 1063 women and though relatively small in number, the size of this study population was comparable with similar published research projects. The study populations for those relevant studies were listed as:

- Kaplan et al. (2001) 1862 subjects
- Kolb et al. (2002) 1862 subjects
- Crystal et al. (2003) 1517 subjects
- Flobbe et al. (2003) 3835 subjects
- Benson et al. (2004) 796 subjects
- Osako et al. (2007) 165 subjects
The ACRIN 666 trial that ran concurrently in several centres in United States of America assessed the use of bilateral whole breast ultrasound in high risk women (refer Section 3.5), reporting that an additional 1.1-7.2 cancers per 1,000 high-risk women were detected (Berg et al. 2008). Similar studies by Kolb et al. (2002) documented 2.3:1,000 cancers for patients at a baseline risk and 4.2:1,000 for high risk patients. Earlier studies by Berg (2003) stated a detection rate of 2.7-9:1,000 while in 2004, Berg et al. reported a rate of 3.5:1,000 patients. In this study, the total ultrasound detection rate was 5.24% (501/9543) or 52.7:1,000 patients; the result a direct reflection of the high proportion of at-risk patients.

However, some may still question the value of a bilateral breast ultrasound examination when there has been a positive mammogram (refer Section 3.5). Apart from the obvious application of assessing an appropriate method for biopsy, providing additional views, completing a diagnostic evaluation of all breast tissue including the associated nodes, consideration must be given to the established possibility of contralateral or ipsilateral lesions. 14 patients (2.78%) in this study were proven to have at least one contralateral malignant lesion (refer Section 3.9).

The hope is that this method of imaging will detect malignant lesions previously not seen mammographically in tissue that is of increased density and be used also for the patient who presents with significant risk factors. A group of patients in this study had their malignant breast lesions detected only with bilateral whole breast ultrasound imaging and these will be discussed in the next section.

6.4.1. Additional lesions detected with ultrasound in this study

The use of bilateral breast ultrasound in this study yielded a number of ultrasound-detected lesions. 14 additional lesions were detected giving a percentage rate of 0.15% (14/9543). Though this represents only a small percentage of the total breast cancers detected, it is important to state that these 14 lesions may well have gone undetected for at least another year. A potential delay in the diagnosis could have a marked effect on a patient’s treatment and possibly their long-term survival.

11 of these lesions were a TP result, 3 were FN and 2 were FP. The FN lesions were proven Grade I IDC while the FP’s were a fibroadenoma and lipoma. The
varied appearances of lesions and the often diffuse presentation account for these results (refer Section 2.6). Though the number of malignant ultrasound-detected lesions was not statistically large, it was nonetheless significant for the 14 patients whose lesions were malignant ($P = 1.000$, Fisher exact test).

The accuracy of lesion detection with ultrasound-only was 99.83% and this compares favorably with mammography (90.23%) and mammography + ultrasound (91.4%). It is reasonable to suggest that the percentage for ultrasound alone was elevated due to the small number in that sample size in that group. Kolb et al. (2002) posted percentages of 98.6% for mammography and 96.6% for ultrasound-only – there was no result for mammography + ultrasound. Other results affected by the sample size were the specificity (99.8%) and PPV (87.5%). Calculation of the sensitivity and NPV were not possible due to the small sample size.

The ultrasound-only detection rate was 0.15% (14 cancers from 9543 ultrasound examinations) and this gave an increase in the overall detection rate of 1.46 cancers per 1000 ultrasound patients - this percentage detection rate compares favourably with similar studies listed below:

- Kaplan (2001) 0.3%
- Kolb et al. (2002) 0.23%
- Flobbe et al. (2003) 0.20%
- Crystal et al. (2003) 0.46%
- Cortesi et al. (2006) 0.45%
- Berg et al. (2008) 0.29%

The positive biopsy rate (concordance of imaging and histology) was discussed in several studies with a percentage of 25.3% quoted by Kolb et al. (2002) for mammography + ultrasound, and 10.3% for the ultrasound-only detected lesions. In this study the overall positive biopsy rate for mammography + ultrasound was 41.98% and for ultrasound alone, the percentage was 87.5%. Consideration must be given to the increased proportion of high risk patients in this study relative to similar research (refer discussion in Section 6.6.1) and also to the depth of skill and experience by the specialists involved.
The criteria for tissue sampling were based on the BSA programme where all new lesions > 10mm were sampled and multiple lesions of a similar appearance had at least one lesion sampled as a representative of the group. 5/14 of these lesions were <10mm (5-9mm) at the time of biopsy, nevertheless, a biopsy was indicated based on the imaging appearance – Grade I IDC (3), invasive tubular carcinoma (1) and a fibroadenoma (1).

Mammographically, the median size for malignant lesions in this study was 18.9mm (SD 10.41) while ultrasonically; the median size of lesions detected was 10.5mm (SD 8.12). The two-tailed $p$ value was 0.0029, with this difference considered to be very statistically significant. The t-test gave a result of $t = 2.9921$.

The ultrasound detected lesions ranged in size from 5-35mm with 50% of these lesions measuring <1cm, compared with Kolb et al. (2002) where 70% were <1cm. It should be documented that the largest lesion detected with ultrasound (35mm) was an invasive lobular carcinoma; while 10/16 were invasive ductal carcinomas of varying grades of severity. These lesions are not so easily appreciated in a mammographic image when compared with ultrasound. A study by Berg et al. (2004) documented sensitivity of 94% for IDC with ultrasound (81% with mammography) and 86% for lobular carcinomas (34% with mammography).

Defining the precise area of change can be difficult when assessing invasive lesions and measurement becomes a subjective process. A diffuse infiltrative pattern and ill-defined borders are well recognised characteristics of invasive lobular and ductal carcinomas and only attention to detail would detect the subtle changes apparent in the image. As there was no obvious pattern of tissue change to these lesions; the measurement of them becomes a subjective process rather than a precise art.

While the majority of breast lesions can be characterized by their ultrasound appearance, there was an inherent difficulty in determining the status of some lesions. It has been widely acknowledged that some benign lesions may appear sonographically malignant and vice versa. The ultrasound appearance of fibrocystic change, fibroadenomas and lipomas may mimic malignancy when there is posterior acoustic shadowing; irregular borders and altered echogenicity that disrupts the architectural planes of the breast (refer to Section 2.5). Definitive proof as to the status of a lesion can only be through tissue sampling, and this was the process for the ultrasound detected lesions.
Additional criteria for tissue biopsy applied within the practice related to the detection of change within a lesion, evident or increased vascularity or development of microcalcifications. Ideally, lesions were detected early in their development (<1cm) and with a node negative status. The nodal status of patients post surgery was not available for assessment.

Ultrasound can have an important role in defining breast abnormalities and assist in the simplest form of obtaining a tissue sample. Mammographic imaging is accepted as the gold standard of breast imaging and still remains an essential part of all women’s imaging in this practice. The next section will assess the current practice of mammography and the changes that have occurred during the study years.

6.5. Mammographic imaging in this study

As an initially new and developing radiology practice, the number of imaging procedures performed in the early years of this study was less compared with the later years. The increase in numbers during the study period reflected the development process of a new business, in conjunction with publicity and community education. Development in the practice of radiology and the evolving trends in breast cancer research have also dictated some of the changes for what is considered to be best practice in breast imaging, and in breast health for women. The education of women in the community with regard to breast health was an important consideration and still is, with that education continuing on a daily basis as the staff interacts with the women attending.

The number of mammographic examinations performed showed a steady increase through to 2004 when a slight reduction in numbers occurred principally due to changes in age eligibility for the BSA screening programme (refer Figure 12) (refer Section 2.2) with more patients choosing to accept a free breast screening examination than pay to attend a private radiology practice. Since 2005 the number of mammographic examinations has stabilized.

The overall cancer detection rate (mammography + ultrasound combined) in this study was 220:10,000 patients ($P = <0.0001$, Fisher exact test) – significantly higher than the BSA stated rate (refer Section 2.2) and considered to be a direct reflection
of the increased percentage of high risk patients that presented for imaging (refer Section 6.6.1). 45% of the patients were deemed high risk with > 25% documented as having dense breast tissue.

In addition, the hospital funded-referral process that allowed women who were ineligible for BSA imaging to attend must be considered a contributing factor (refer Section 2.2). The number of PH (public health) breast examinations performed was 2362 (10.69%) and as shown in Figure 30, the number of these patients has shown a steady increase during the study period as women have become educated as to the benefits of regular mammograms and their referrers now utilize the Government sponsored scheme, enabling breast imaging through a private radiology practice. The greater percentage of these patients presented for diagnostic reasons (58.8%) while the remainder were asymptomatic (41.49%).

![Public Hospital Patients (n)](image)

**Figure 30 Number of PH patients presenting for breast examination**

The different types of mammographic examinations performed were related to the needs of the individual patient - screening, unilateral, implant, PH diagnostic and PH screening examinations (refer Table 7 and Figure 12). The majority of patients presented for screening mammography (77.69%): routine annual or biennial breast imaging while the remainder were assigned to other categories. The implant code (0.61%) was primarily a pricing decision for a longer period of time was necessary to complete a diagnostic mammographic examination for these women. A unilateral
mammographic code was used either for patients with a prior mastectomy or for patients who recently had bilateral mammography and needed assessment for a new change that had developed.

Mammography detected 94% of all malignant lesions in this study \( (P = <0.0001, \text{ Fisher exact test}) \). The accuracy of mammography was 91.2%, sensitivity 94%, specificity 89.2%, PPV 86.3% and NPV 95.4%.

It is important to comment that most of the soft tissue densities seen on the initial mammographic films were additionally imaged with spot compression to resolve or highlight the nature of the density. Those extra views were performed at the request of the radiologist viewing the films. Double reading of all mammographic images occurred, with at least two radiologists viewing and interpreting all images recorded. Previous studies have found that double reading increased the cancer detection rate by 3 to 11 per 10,000 women screened (Dinnes, Moss, Melia, Blanks, & Kleijnen, 2001) and in this practice there were a number of cases where a patient was recalled for further imaging due to the double reading process. Though the number of these cases has not been statistically recorded, it is important to document that this occurred.

So while mammography has been the gold standard of breast imaging for the majority of patients, there are now well documented limitations relating to resolution in dense breasts, imaging of abnormalities in patients with large pendulous breasts, detection of lobular carcinomas and detection of small node-negative lesions. The need for an improved detection rate motivates the search for better imaging solutions and the use of whole breast ultrasound may be one of the answers. Though the patient cohort in this study was not large, the increased percentage of high risk patients when compared with other studies is significant. The following section will look at some of relevant issues as they relate to this patient population.

6.6. **The study group of patients**

Statistically there is an 11% lifetime risk of being diagnosed with breast cancer in New Zealand (National Screening Unit, 2004) regardless of risk factors and as has previously been discussed, the percentage of ‘at risk’ patients was great. This led to a greater number of biopsies per patient population and an increased number of...
malignant lesions detected. Of the 22,814 patients, 1063 required 1198 breast tissue biopsies giving a 5.25% biopsy rate which was higher but nevertheless comparable with other significant studies:

- Kolb et al. (2002) 3.2%
- Crystal et al. (2003) 2.5%
- Flobbe et al. (2003) 2.2%
- Benson et al. (2004) 3.42%

The biopsy age groupings (Figure 15) showed that the greatest percentage of patients was aged 40-50 years of age. A wide variety of benign lesions were detected with the largest number of these proven as benign fibroadenomas. Even though the majority of these lesions fulfilled the accepted benign criteria for lesion differentiation (Stavros et al. 1995), the malignant potential existed until proven with a tissue biopsy. Fibrocystic change, areas of fibrosis and surgical scars are known to have malignant-appearing characteristics and amidst a background of dense breast tissue, accurate differentiation of lesions is difficult. Ductal ectasia, inflammation and fat necrosis are all benign conditions and these too can present as malignant change in breast tissue.

6.6.1. The ‘at risk’ patients in the study group

In this study 45.14% of the patients were deemed to be high risk due to reasons previously discussed (refer Section 3.8) and a contributing factor was the referral system for patients exempt from BSA screening. 7.15% of the patients had a prior breast cancer, 35.78% had significant familial risk factors and 0.56% (6) of the patients were BRCA1 or BRCA2 gene positive and it is important to document that 5/6 of these BRCA patients were diagnosed with a malignant lesion. This number of high risk patients was significantly elevated when compared with studies by Berg et al. (2008). In that study, 6% had a previous breast cancer and 15% had familial risk factors; Rosenberg et al. (2006) had 6% and 15% respectively while Kolb et al. (2002) stated 16.7% and 23.9% respectively. Berg’s study used a group of women with known breast lesions while Rosenberg et al. and Kolb et al. used an asymptomatic patient cohort.

It has been interesting to compare the breast cancer detection rates from this study with similar research. Patients with a baseline risk in this study had a cancer
detection rate of 1.01% while those patients deemed high risk had a detection rate of 1.19%. Patients with mammographically dense breast tissue had a detection rate of 1.73% and for those who were both dense breast tissue and high risk factors; the detection rate was 2.36%. Crystal et al. (2004) ascribe a 0.25% for those with a baseline risk and 1.3% for the high risk patient.

It is notable that 41.08% (219/533) of the patients with risk factors had a new malignancy diagnosed and 36.80% (113/307) of those with dense breast tissue had a new malignancy detected.

The accuracy of imaging with mammography + ultrasound for the high risk patients was 91%, the sensitivity 95%, specificity 88%, PPV 85% and NPV was 96.9%. Statistical results for those with dense tissue were 89.86%, 93.8%, 87.6%, 81.5% and 96% respectively. Similar statistics were documented for those with high risk factors and dense breast tissue – 87.42%, 92.1%, 84.4%, 79.5% and 94.2%. For discussion on these and other statistics refer to Section 6.6.

It is important to state that by the end of the study, the number of ‘at risk’ patients had increased from an initial group of 533 patients to 769 (see Figure 1), representing an increase of 19.03% in the number of patients deemed to be at-risk for breast cancer.

It was of interest though expected, that the group of patients with risk factors and dense breast tissue had a disproportionate number of affected first degree relatives compared with other groups of patients (refer Section 3.8). 31.92% of these patients had affected first degree relatives, while those with no risk factors and adipose tissue had 22.54%. Research by Kolb et al. (2002) documented a 16% incidence of affected first-degree relatives, the percentage differences indicative of the high risk population group in this study. Though the relationship of affected relatives to the subjects in this study was not a focus of this research, it is nevertheless interesting to document that there was a significant correlation of familial risk factors to patient outcome.

6.6.2. Breast density of patients in the study group

It is known that the density of breast tissue evolves and involutes over time (Tot et al. 2000) and documentation of a patient’s breast density was considered a standard part of the examination process. Breast tissue was documented based on
mammographic appearance with the relative breast tissue density for the patients shown in Figure 7. The breast density documentation for the 21,751 patients who did not require a tissue biopsy was not recorded and no comment can be offered.

It was noted that there was not an expected increase in the proportion of patients with truly adipose breast tissue when at an advanced age. In a personal communication with the radiologists involved in this study, there was a level of surprise that the changes and decrease in density expected around the time of menopause did not occur until the patients were > 80 years old, well past the completion of menopause.

The ratio of benign to malignant lesions in adipose breast tissue was 1:1.66 and in dense breast tissue, the ratio was 1:1.93. It was expected and proven that a higher rate of cancers was detected in dense breast tissue (28.8% of all malignant lesions detected in this study - \( P = <0.001 \), Fisher exact test). Berg (2004) stated that breast cancers were twice as prevalent in patients with dense tissue when compared with those who had adipose tissue (62.6% and 37.3% respectively).

This radiology practice has always considered increased mammographic density as an independent risk factor and routine bilateral ultrasound breast screening was considered an integral part of breast imaging and was offered to all patients with increased density even if there were no other risk factors (refer Section 3.6). Berg et al. (2008) commented that such patients were susceptible to “much higher interval cancer rates, with a worse prognosis for clinically detected cancers” (p. 2152).

In dense breasts, small cancers statistically have a mammographically decreased detection rate, as the lesion is unlikely to obviously distort the tissue planes while in adipose tissue; malignant lesions are invariably detected when they are smaller due to their ease of visibility. The number of additional cancers detected with bilateral whole-breast ultrasound in women with fat-replaced breasts would likely be markedly fewer than in those with dense breast tissue.

Ultrasound has been documented as more effective in dense tissue by authors such as Kolb et al. (2002); Flobbe et al. (2003); Benson et al. (2004); Cortesi et al. (2006); and Berg et al. (2008). In women with dense breasts, the combination of mammography and ultrasound is stated to have greater sensitivity than mammography alone. There is a need for effective diagnostic imaging to be
available for patients with dense tissue so they can benefit from a level of imaging sensitivity comparable to those with adipose tissue.

6.6.3. Patient’s awareness of change in breast tissue

There are inherent difficulties for patients in self-detecting breast lesions due to the variability of breast tissue as not all breast tissue is homogeneous. Awareness of change/s in breast tissue was a precipitating factor for many patients to present for imaging.

61.10% of the patients presented for diagnostic reasons due to a detected change in the breast tissue and 68.78% of all malignancies detected were in these patients. The reasons for diagnostic presentation were discussed in Section 6.5.4.

The remaining 38.89% of patients who attended were asymptomatic and a significant number of these had a malignant lesion detected (33.69%). The percentage of diagnostic and screening patients was similar to a study by Benson et al. (2004) where the figures were 67% and 33% respectively. That study was performed at a different women's health centre in New Zealand, so it was not unexpected that the study population would be alike given the demographics and type of patient population presenting.

6.6.4. Lesions: benign and malignant

BSA states the goal for detecting small invasive cancers and lesions <10mm are to be detected at the rate of 17.3:10,000 and those < 15mm at the rate of 34.5:10,000. This study returned figures of 391:1,000 and 623:1,000 respectively enabling a comparison of the results even though the patient populations differ markedly; namely the proportion of high risk patients.

Measurement of lesions occurred where there was a clear margin and this occurred in 92.99% of cases. For the remainder of cases, descriptive terms were used to describe appearances of tissue changes. Measurement was dependent on the pattern of growth, either across the hypoechoic nucleus or from the breaks in the tissue planes where the natural architecture of the breast was disrupted. Lesions
previously biopsied were reassessed when subsequent imaging occurred, determining if an interval change would raise a level of suspicion.

The median size of palpable malignant lesions was 16mm – identical to that documented by Benson et al. (2004). Non-palpable malignant lesions had a median size of 14.37mm. Many of the larger malignant lesions detected were widespread DCIS, Grade II and Grade III IDC; a result not unexpected as these lesions can spread over a large area and be difficult to detect. The ratio of benign to malignant lesions for palpable and non-palpable lesions was 1: 2.3 (malignant: benign) and 1: 1.55 for non-palpable lesions.

The predominance of malignant lesions were seen in women aged 50-55 years old while the majority of benign lesions were detected in those aged 40-50 years old. The number of malignancies on a yearly basis (see Figure 31) showed a linear trend in detection, due in part to an increased number of patient presentations and a greater number of ultrasound examinations. Subjectively, though hard to quantify, the improvement in ultrasound technology and operator skill could be also considered.

The slight slowing of the increase in numbers from 2004 was related to a parallel slowing of numbers in mammography examinations due to changes in age eligibility by BSA (refer Section 2.2).

![Figure 31 Prevalence of malignant lesions detected](image)
Comment is necessary on the indeterminate lesions = 34 lesions (23 ADH and 11 radial scars) were proven with tissue sampling and though these were not deemed frankly malignant; there is well-documented evidence of malignant association. Radial scars are known to have a 10-30% risk association with malignancy (refer Section 2.5.3) and are often detected in conjunction with ADH, atypical lobular hyperplasia, low grade DCIS and tubular carcinomas (Tabar, 2007).

Management of indeterminate lesions in this study was with a tissue biopsy following detection of posterior shadowing, altered echotexture, or the diffuse hypoechoic tissue changes associated with these lesions. With a positive histology result for an indeterminate lesion, a surgical referral for a hook-wire excision biopsy was put in place so that complete removal of the lesion could occur. Post surgery, serial scanning of the affected region/s would occur as and when the patient presented for imaging, assessing for recurrence. This process of patient management has been confirmed as the appropriate course of action and is in concordance with similar studies (Worsham et al. 2007; & Tabar, 2007).

The ratio of benign: malignant: lesions were 1:1.38 in this study. The biopsy rate for the screened population was 5.25% compared with the 2.5% of Crystal et al. 2003 and the 3.2% for Kolb et al. 2002. Reasons for the elevated biopsy rate include the percentage of high risk patients, the number of patients with dense breast tissue and the number of whole breast ultrasound examinations performed.

The low threshold for performing a breast tissue biopsy in this practice can be seen as a contributing factor to the cancer detection rate of 220:10,000 patients. Other studies researching the value of bilateral whole-breast ultrasound had cancer detection rates of 45:10,000 (Crystal et al.), 35:10,000 (Ganott et al. 2006), 79.4:10,000 (Kolb et al.) and 118:10,000 (Berg et al. 2008).

So what was the value of performing a biopsy in this study where 40.48% of the lesions were a TP result and 52.17% of lesions were a TN result? Is there potential for a change/s in biopsy protocols based on the ultrasound findings of this study?

Stavros et al. (1995) stated that ultrasound could “accurately classify some lesions as benign, allowing imaging follow-up rather than biopsy” (p. 123). This is likely true in the case of patients with baseline risk status, nevertheless the false negative results in this study are clearly an indicator that not all lesions could be accurately identified
with imaging. Mammography had a false negative rate of 5.98%, and with the addition of bilateral whole breast ultrasound, this rate decreased to 3.19%. However, a rate of 6.34% for the high risk patient with dense tissue clearly establishes the difficulty of ‘accurately classifying’ lesions in some patients. The potential for change in biopsy protocols therefore becomes greatest in the patient with adipose tissue and no risk factors; where a lesser degree of suspicion could be leveled at lesions that appear frankly benign on ultrasound. This state of affairs can not be permitted in patients in any other category for the increased risk and occurrence of malignancy has been clearly established and the ease of imaging with ultrasound may well be compromised.

Concordance of the clinical and imaging findings is imperative if this study is to have validity in the imaging community. The next section will assess the imaging in light of the statistical results, enabling a comparison of these results with relevant published research.

### 6.7. Concordance of imaging findings with histopathological analysis

Concordance of the clinical and imaging findings simply means an agreement between the imaging appearance of a breast lesion and its histological analysis. A high concordance of findings in clinical practice establishes a level of professional confidence between the patient and the clinician, and with regards to this study, seeks to establish the validity of bilateral breast ultrasound in conjunction with mammography for the high risk patient and for the patient with dense breast tissue.

In this study, bilateral whole-breast ultrasound was routinely offered and / or performed for all high risk patients and for those with dense breast tissue, even when no obvious mammographic abnormality was detected, as an additional form of imaging to improve assessment of the tissue. The use of bilateral breast ultrasound was considered a normal part of imaging for these patients due to their risk status, and not seen as an optional extra.

There was an expectation of accuracy of diagnosis in breast imaging, both from the patient and the clinician. The accuracy rate of an imaging modality reflects the percentage of lesions that were correctly diagnosed, taking into consideration the
skill of the person performing the ultrasound scan (refer Section 2.10). Accuracy of diagnosis is however, affected by factors that are variable such as the operator, whether the mammographic findings were available prior to the ultrasound scan, the patient’s breast tissue density, and whether the lesion conformed to benign or malignant criteria.

The accuracy rates in this study for mammography; bilateral breast ultrasound and mammography + ultrasound combined were 91.2%, 92.8% and 92.4% respectively (see Table 23). It was expected that the accuracy rate for combined imaging would be greater than for mammography alone as mammography and ultrasound assess tissues and the tissue interfaces differently. The increase in accuracy was 1.2% for combined imaging and though small, this result is tempered by the areas of tissue alteration that do not conform to the typical appearance of benign or malignant lesions making accurate identification problematic.

For those patients with an elevated risk status, the accuracy rates were assessed for each subgroup: the high patient, those with mammographically dense tissue and those with risk factors and dense tissue. The percentages were 91%, 89% and 87% respectively. Dense tissue has a noticeable effect on diagnostic accuracy with the lower percentages an obvious result. It is important to state that 22.55% of all malignant lesions detected in this study were in the patients with dense breast tissue.

The accuracy percentage for the cohort of lesions detected only with ultrasound was 99%, a result tempered by the small number of patients in this category.

Sensitivity percentages relate to those patients who were correctly diagnosed with breast cancer: the results were 94%, 96.8% and 96.8% for mammography, bilateral breast ultrasound and mammography + ultrasound combined (see Table 23). The increase in sensitivity (2.8%) was modest when ultrasound was used in conjunction with mammography though consideration should be given to those lesions that contest the normal appearance of malignant or benign status.

The sensitivity assessment for the patients with the 14 ultrasound detected lesions was not possible due the lack of a TN factor. However it was detection of these lesions that gave the improved result for the ultrasound and the combined imaging percentages.
Sensitivity percentages of 95%, 93% and 92% respectively were for patients deemed high risk, had dense tissue or both these risk factors furnished. The ability to accurately diagnose lesions in these patients is constrained by the effect of breast tissue in the mammography and ultrasound images. The number of FP results (refer Tables 25-27) in each of these categories had an effect the sensitivity percentages that could be achieved. As previously discussed, lesions that do not confirm to an expected appearance are problematic.

Several authors comment that the sensitivity of using both ultrasound and mammography is higher, the tumour size is smaller, the false-negative rate is lower, and the false-positive rate is likely to be decreased when compared with mammography alone (Kolb et al.; Flobbe et al. 2003; Crystal et al. 2003; Benson et al. 2004; and Berg et al. 2008).

Specificity is related to the number of patients who were correctly diagnosed as not having a breast cancer. For mammography, bilateral breast ultrasound and mammography + ultrasound combined the results were 89.2%, 90% and 89.2% respectively. The lesions deemed a FN result had a noticeable impact on these specificity percentages as areas of FCC and fibrosis were proven to be invasive ductal carcinomas, DCIS, tubular and lobular carcinomas. These malignant lesions express themselves in breast tissue as indistinct areas of architectural alteration or distortion with shadowing, similar to the effect that FCC and fibrosis create.

A specificity of 99% was calculated for the small cohort of patients (14) who had ultrasound detected lesions. This percentage may be considered falsely elevated when related to the small sample size in this grouping of patients and the 90% specificity for the study group of patients (1063).

For the patients with risk factors, dense tissue or known to have both these risk factors, the specificity percentages were 88%, 81% and 79% respectively. The effect that dense breast tissue has on an accurate imaging diagnosis is obvious by the lower percentage results, and this coupled with the indistinct spreading margins of fibrotic or malignant tissue, within the background of denser tissue, makes it difficult to appreciate what is actually being seen.

Positive predictive values concern the number of patients with breast cancer who were correctly diagnosed in the study and the percentages were 86.3%, 87.4% and
86.6% respectively for mammography, bilateral breast ultrasound and mammography + ultrasound. The results for those who were deemed to be at high risk, had dense tissue or had both these risk factors were 85%, 81% and 79%. Kolb et al. (2002) cited a PPV of 98.6% for mammography and 96.6% for ultrasound imaging. In that study, 16.7% of the patients were high risk whereas the percentage for this study was 45.14%.

The PPV values for the at-risk patients, those with dense tissue and those with both risk factors were lower than for those at a baseline risk; 88%, 87% and 84% respectively for mammography, bilateral breast ultrasound and mammography + ultrasound.

The negative predictive value assesses the percentage of patients who were correctly diagnosed as not having cancer. The values of 95.4%, 97.5% and 97.5% were attributed to mammography, ultrasound and mammography + ultrasound respectively with additional results for those at high risk, with dense breast tissue and with both risk factors tabled as 96%, 96% and 94%. These percentages are all affected by the number of FP lesions which appeared as areas of inflammatory change, ductal ectasia, necrotic tissue, fibrosis or fibrocystic change and ultimately proven malignant.

Due to the small sample size of ultrasound-only detected lesions the NPV could not be calculated.

In assessing the benefit of any imaging protocol, the negative aspects must be evaluated as well to test if there is any overall validity. The use of bilateral whole-breast ultrasound has been questioned by many listing the cost of a core biopsy, the cost of subsequent diagnostic procedures and the increased stress to the patient as valid reasons. All patients in this study were given the opportunity to decline an interventional process through consultation and consent was achieved prior to tissue sampling.

Further, many authors have commented on the ‘high false positive rate’ of breast ultrasound imaging and it is important to state that in those studies, ultrasound was used in a targeted format only and not as a whole breast screening tool. Those authors provided little comment on the false positive rate of mammography, making mammography appear superior as an imaging modality.
BSA state a mandatory FP rate of <9% with an expected rate of <6% for asymptomatic patients. The false positive rate for mammography + ultrasound was 6.25%, with 6.17% for mammography and 6.25% for ultrasound – results all affected the patient population in this study.

The majority of FP results in this study were due to areas of tissue that were proven to be necrotic or fibrotic, appearing as areas of altered echotexture and displaying an increase in regional vascularity suggestive of malignancy (refer Section 2.7).

Comparable FP rates from similar studies have been documented as: Kolb et al. (2002) 2.4%, Irwig et al. (2004) 2.4-12.9% while Philpotts et al. (2003) grouped the FP by age groups, 7.8% (40-49 years), 7.4% (50-59 years), and 5.3% (60-69 years). In this study the FP rates were similar for the age groups: 8.19% (40-49 years), 6.11% (50-59 years) and 6.29% (60-69 years).

Many topics have been raised and discussed in this chapter, assessing what has been achieved in other research projects and enabling a comparison where applicable, to the specific results of this study determining if there is any true clinical value. The following section will seek to draw conclusions from the numerous threads that have been woven throughout this research.

6.8. Conclusion

What is the appropriate role for bilateral breast ultrasound, as an adjunct to mammography, in the management of patients with positive findings?

Evaluation of bilateral whole breast ultrasound imaging in the patient with positive findings was the principal aim of this study; to determine if this was an appropriate role for this form of imaging. Supplementary aims involved the use of bilateral whole breast ultrasound in the high risk patient and / or in the patient with dense breast tissue.

Imaging of breast tissue primarily occurred with a mammographic examination though there is an awareness and acceptance that mammography does have limitations (refer Section 2.2). Mammographic sensitivity is known to be inversely
proportional to mammographic density (Baker et al. 2002) and questions can be raised as to the appropriate course of imaging for patients with whom that sensitivity is reduced. Several authors have reported that a combined imaging approach of mammography and bilateral whole breast ultrasound provide the best diagnostic course of action (Baker et al., Carter, 2006; Carney et al. 2003; & Berg et al. 2006).

An unforeseen result in this study was related to the expected involution of, and decrease in breast tissue density that occurs with age (see Figure 18). Expected to occur around menopause, these results show that decrease did not occur until patients were truly at an advanced age (> 80 years of age); leaving a greater number of patients than expected many at an increased risk for a longer period of time than.

Bilateral whole-breast ultrasound imaging has been a significant part of this radiology’s practice policy and is been validated by the number of contraleral and ipsilateral lesions along with the ultrasound detected lesions. But what of the clinician who performs the scan?

Sonographer skill is pivotal to the detection of breast tissue changes and the 30+ year’s experience of the lead sonologist in detecting these change/s enhances the results of this study. The skill required to discern and appreciate the subtleties of tissue presentation is significant and Berg et al. (2008) described this as “the dependence of free-hand screening breast ultrasound …. because an abnormality must be perceived while scanning” (p. 2152).

The patient population (1063) involved in this study was comparable with similar studies completed since 2001 (refer Section 6.2) though a major difference was the greater number of at-risk patients in this study. 44.99% of the patients had significant risk factors with an additional 12.35% having dense breast tissue. Kolb et al. (2002) reported a high risk cohort of 40.6%, Rosenberg et al. (2006) 21% and Berg et al. (2008) 21%, so it is reasonable to propose that a greater number of cancers would be detected with this patient population.

The results bear out this fact whereby malignant lesions were detected in 42.85% of those at increased risk, in 36.8% of those with dense breast tissue and in 39.62% of these with both risk factors. The detection rate in the patients who were BRCA1 or BRCA2 gene-positive was 83.3%. The hospital referral system (refer Section 6.5)
contributed also to this high detection rate with 46.87% of those patients diagnosed with a malignant lesion.

The cancer detection rate of 220:10,000 patients far surpassed the BSA stated minimum of 69:10,000 (initial) and 34.5:10,000 (subsequent imaging) though it should be remembered that the risk status of the patient populations differed widely. This result was highly probable – this study did not take place in a BSA centre, and a great proportion of the participants were excluded from BSA (refer 2.2). The biopsy rate of 5.25% in this study was raised compared with similar studies and again was a reflection of the increased percentage of at-risk patients (Crystal et al. (2004) 2.5% and Kolb et al. (2002) 3.2%).

The performance of bilateral whole breast ultrasound scans was further validated with the detection of 14 (2.78%) contralateral lesions in patients for whom a malignant lesion was diagnosed. Other studies quote detection rates of 3.5% (Vaittinen & Hemminki, 2000) and 2-11% (Chen et al. 1999). Hill-Kayser et al. (2006) comment that this risk for contralateral cancer/s remains increased for at least 20 years after the initial diagnosis indicating a need for careful surveillance during subsequent breast screening examinations (refer Section 3.5 & 4.5).

Bilateral whole-breast ultrasound has been well documented in research for detecting an additional number of breast cancers compared with mammography alone or targeted breast ultrasound (Kolb et al. 2002; Boonjunwetwat et al. 2007; & Berg, 2004). In this study, bilateral breast ultrasound increased the detection rate by 1.46:1,000 patients; this result comparing favourably with the ACRIN 666 trial (Berg et al. 2008) and other similar studies (refer Section 6.4.1). These lesions (invasive ductal and lobular carcinomas) create subtle tissue changes, often in a diffuse and infiltrative pattern (refer Section 2.6) that can be difficult to detect mammographically. The median size of the ultrasound detected lesions was smaller those detected mammographically (Kolb et al. 2002; Flobbe et al. 2003; Crystal et al. 2003; and Berg et al. 2008) and this finding was in line with similar research.

Raised false positive results are a source of discussion in the research community and often posed as a reason for not performing bilateral whole breast ultrasound imaging (Kolb et al. 1998; Kaplan, 2001; Philpotts, 2003; Irwig et al. 2004; and Berg et al. 2004). The proven increased cancer detection rate with bilateral whole breast ultrasound in this study may well be considered an acceptable trade-off against the
additional number of false positives that may occur. I suggest a statement by Kolb et al. (2002) to summarise this debate:

“since the cost of (an) ultrasound guided core tissue biopsy is more cost effective and less invasive than surgical biopsy, the benefit of a large increase in early stage cancer detection with screening ultrasound may outweigh the risk of an increase in false positives” (p. 169).

Concordance of results or agreement between imaging and histological analysis was best displayed with bilateral whole breast imaging (refer Table 28). Ultrasound imaging achieved higher percentages, principally because additional lesions were detected with this modality (accuracy 92.8%, sensitivity 96.8%, specificity 90%, PPV 87.4% and NPV 97.5%). Further, combined imaging (mammography and whole-breast breast ultrasound) gave better results than mammography alone. Combined imaging and mammography gave the following results respectively: accuracy (92.4%, 91.2%), sensitivity (94.4%, 91.9%) specificity (89.2%, 90%), PPV (86.6%, 86.3%) and NPV (97.5%, 95.4%).

The percentage results for patients with risk factors and / or dense breast tissue were lower in all cases (see Table 28). This was as expected due to the acknowledged inherent difficulties in examining denser tissue. Other studies identified in the literature review (Kolb et al. 2002; Flobbe et al. 2003; Crystal et al. 2003; Benson et al. 2004 and Berg et al. 2008) reported similar findings, however a direct comparison was not possible (as previously discussed Section 4.6) due to the nature of this study.

This study has shown that bilateral whole-breast ultrasound does have role as an adjunct to mammography, in the management of patients with positive findings. This was evident in the detection of an increased number of malignant breast lesions in the patient with risk factors, dense breast tissue, contralateral cancers and in the detection of malignant lesions where the mammographic examination was negative. It seems appropriate to conclude this discussion with a statement from Berg et al. (p.2162, 2008) that describe the merits of bilateral whole breast ultrasound as evidenced in this study:
“the addition of …. a screening ultrasound examination to mammography for women at elevated risk of breast cancer results in increased detection of breast cancers that are predominantly small and node-negative.”
7.0 Recommendations

- recognising the need for competence of the operator in bilateral whole breast ultrasound, an assessment of current sonographer training in New Zealand could be undertaken with a view to incorporating the necessary skills as a regular part of sonographer training.

- recognising there is a need for regular scan experience to establish and maintain competence in performing bilateral whole breast ultrasound, the establishment of minimum yearly examination numbers is necessary so that diagnostic competence is maintained.

- establishment of a national protocol whereby the patient with risk factors and/or dense breast tissue could be clearly identified – for patients attending BSA this could mean additional imaging be performed at specialist imaging centre.

- enabling the use of bilateral whole breast ultrasound in all radiology or breast imaging practices through the teaching and mentoring of sonographers and sonologists.

- follow-up research could be performed on the full cohort of 22,814 patients in this study; gaining additional information on patient risk factors, breast density and whether the given true negative and false negative results for these patients was accurate by reviewing patient data from subsequent imaging.
8.0 References


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http://www.ajronline.org/cgi/content/abstract/180/6/1675


9.0 Appendix

9.1. Ethics approval from Unitec Institute of Technology

9.2 Approval for research from the radiology practice