Section 1

Introduction and methods

Section 1 Introduction and methodology

The estimated incidence of breast cancer in Australia was over 19,000 cases, and it was the most diagnosed cancer in women, and the most diagnosed cancer overall [1]. There were over 3000 deaths from breast cancer in 2019, and this was the second most common cause of death from cancer for women, and the fourth most common overall. Over three quarters of breast cancers are diagnosed at stage I or stage II[1]. Approximately 55% of women aged 50 to 74 participated in breast cancer screening in the 2015 to 2016 period[1].

The five-year survival from breast cancer (2011 to 2015) was 90.8%, survival when diagnosed at stage I is almost 100%, however, when diagnosed at stage IV, the survival is 32%[1].

Hormone-receptor positive breast cancers are sensitive to oestrogen or progesterone, approximately 70% of breast cancers are hormone-receptor positive[2]. Adjuvant treatment with tamoxifen is recommended, followed by an addition five years for pre or peri-menopausal women, and an additional five years with tamoxifen or an aromatase inhibitor for post-menopausal women[2].

A PubMed search was conducted on 4 October 2021 to identify studies reporting patient experience, patient reported outcomes, and quality of life studies in the Australian hormone-receptor positive breast cancer community. Studies conducted more than five years ago were excluded, and studies that included multiple types of breast cancers that did not report hormone-receptor positive breast cancers separately (as a subgroup) were excluded. There were 12 studies identified of between 26 and 4891 participants. There was only one study identified that interviewed participants or used qualitative methods, this study was focused on endocrine therapy.

This PEEK study includes 52 people diagnosed with hormone-receptor positive breast cancer throughout Australia, including a qualitative structured interview and quantitative questionnaire. This study in hormone-receptor positive breast cancer is therefore the largest mixed method study reported in an Australian population. In addition, PEEK is a comprehensive study covering all aspects of disease experience from symptoms, diagnosis, treatment, healthcare communication, information provision, care and support, quality of life, and future treatment and care expectations.

Introduction

The estimated incidence of breast cancer in Australia was over 19,000 cases, and it was the most diagnosed cancer in women, and the most diagnosed cancer overall [1]. There were over 3000 deaths from breast cancer in 2019, and this was the second most common cause of death from cancer for women, and the fourth most common overall. Over three quarters of breast cancers are diagnosed at stage I or stage II[1]. Approximately 55% of women aged 50 to 74 participated in breast cancer screening in the 2015 to 2016 period[1].

The five-year survival from breast cancer (2011 to 2015) was 90.8%, survival when diagnosed at stage I is almost 100%, however, when diagnosed at stage IV, the survival is 32%[1].

Hormone-receptor positive breast cancers are sensitive to oestrogen or progesterone, approximately 70% of breast cancers are hormone-receptor positive[2]. Adjuvant treatment with tamoxifen is recommended, followed by an addition five years for pre or peri-menopausal women, and an additional five years with tamoxifen or an aromatase inhibitor for post-menopausal women[2].

Hormone therapy increases overall survival, decreases risk recurrence, and decreases risk of contralateral breast cancer[2,3]. However, risks from hormone treatment include menopausal symptoms, additional risks from tamoxifen included endometrial cancer, deep vein thrombosis or pulmonary embolism, and uterine cancer, additional risks from aromatase inhibitors include heart disease, and osteoporosis[2,4]

Personal Experience, Expectations and Knowledge (PEEK)

Patient Experience, Expectations and Knowledge (PEEK) is a research program developed by the Centre for Community-Driven Research (CCDR). The aim of PEEK is to conduct patient experience studies across several disease areas using a protocol that will allow for comparisons over time (both quantitative and qualitative components). PEEK studies give us a clear picture and historical record of what it is like to be a patient at a given point in time, and by asking patients about their expectations, PEEK studies give us a way forward to support patients and their families with treatments, information and care.

The research protocol used in PEEK studies is independently driven by CCDR. PEEK studies include a quantitative and qualitative component. The quantitative component is based on a series of validated tools. The qualitative component is the result of two years of protocol testing by CCDR to develop a structured interview that solicits patient experience data and provides patients with the opportunity to provide advice on what they would like to see in relation to future treatment, information and care. The structured interview has also been designed so that the outcomes of PEEK studies can inform policy, research, care, information, supportive care services and advocacy efforts.

Participants

To be eligible for the study, participants needed to have been diagnosed with hormone receptor-positive breast cancer, have experienced the healthcare system in Australia, be 18 years of age or older, be able to speak English, and be able to give consent to participate in the study. Recruitment commenced 1 April 2021 and was completed by 31 October 2021.

Ethics

Ethics approval for this study was granted (as a low or negligible risk research study) by the Centre for Community-Driven Research Ethics Committee (Reference CS_Q4_03).

Data collection

Data for the online questionnaire was collected using Zoho Survey (Zoho Corporation Pvt. Ltd. Pleasanton, California, USA, www.zoho.com/survey). Participants completed the survey from 1 April 2021 to 31 October 2021.

There were five researchers who conducted telephone interviews and used standardised prompts throughout the interview. The interviews were recorded and transcribed verbatim. Identifying names and locations were not included in the transcript. All transcripts were checked against the original recording for quality assurance.

Interview data was collected from 1 April 2021 to 31 October 2021.

Online questionnaire (quantitative)

The online questionnaire consisted of the 36-Item Short Form Health Survey (SF36) (RAND Health)[5], a modified Cancer Care Coordination Questionnaire for Patients (CCCQ)[6], the Short Fear of Progression Questionnaire (FOP12)[7], and the Partners in Health version 2 (PIH)[8]. In addition, investigator derived questions about demographics, diagnosis, treatment received and future treatment decisions making were included.

Structured Interview (qualitative)

Interviews were conducted via telephone by registered nurses who were trained in qualitative research. The first set of interview questions guided the patient through their whole experience from when symptoms were noticed up to the present day.

Questionnaire analysis

Statistical analysis was conducted using R included in the packages "car", "dplyr" and "ggplot2" (R 3.3.3 GUI 1.69 Mavericks build (7328). The aim of the statistical analysis of the SF36, CCCQ, FOP12, and PIH responses was to identify variations by disease stage, age, education, year of diagnosis, location of residence, and socio-economic status. Scales and subscales were calculated according to reported instructions[5-8].

The Location of participants was evaluated by postcode using the Australian Statistical Geography Maps (ASGS) Remoteness areas accessed from the Australian Bureau of Statistics[9].

The level of socio-economic status of participants was evaluated by postcode using the Socio-economic Indexes for Areas (SEIFA) accessed from the Australian Bureau of Statistics[10].

For comparisons by disease stage and year of diagnosis, a one-way analysis of variance (ANOVA) analysis was conducted. A Tukey HSD test was used post-hoc to identify the source of any differences identified in the one-way ANOVA test. Where the assumptions for the one-way ANOVA were not met, a Kruskal-Wallis rank sum test on care was conducted with post-hoc pairwise comparisons using Wilcoxon rank sum test. When the assumption of equal variances were not met, a Welch one-way test was used with post-hoc pairwise t-tests with no assumption of equal variances.

For all other comparisons between groups, a two-sample t-test was used when assumptions for normality and variance were met, or when assumptions were not met, a Wilcoxon rank sum test with continuity correction was used. Questions where participants were asked to rank preferences were analysed using weighted averages. Weights were applied in reverse, the most preferred option was given the largest weight equal to the number of options, the least preferred option was given the lowest weight of 1.

Structured interviews analysis

A content analysis was conducted using conventional analysis to identify major themes from structured interviews. Text from the interviews were read line-by-line by the lead researcher and then imported into NVivo 8 (QSR International)/MaxQDA. Each question within the interview was individually analysed. Initial categories and definitions were identified and registered in NVivo 8 (QSR International)/MaxQDA. The minimum coded unit was a sentence with paragraphs and phrases coded as a unit.

A second researcher verified the codes and definitions, and the text was coded until full agreement was reached using the process of consensual validation. Where a theme occurred less than 5 times it was not included in the study results, unless this result demonstrated a significant gap or unexpected result.

Data analysis and final reporting was completed in June 2021.

Position of this study

A PubMed search was conducted on 4 October 2021 to identify studies reporting patient experience, patient reported outcomes, and quality of life studies in the Australian hormone-receptor positive breast cancer community. Studies conducted more than five years ago were excluded, and studies that included multiple types of breast cancers that did not report hormone-receptor positive breast cancers separately (as a subgroup) were excluded.

There were 12 studies identified of between 26 and 4891 participants. There was only one study identified that interviewed participants or used qualitative methods, this study was focused on endocrine therapy[11].

There were 11 studies that collected patient experience/patient reported data by questionnaire. There were seven drug clinical trials of between 152 and 4891 participants[12-20], two studies of between 119 and 172 participants that was focused on endocrine therapy[21,22], and two studies of between 26 and 31 participants that was focused on symptoms and side effects[23,24].

This PEEK study includes 52 people diagnosed with hormone-receptor positive breast cancer throughout Australia, including a qualitative structured interview and quantitative questionnaire. This study in hormone-receptor positive breast cancer is therefore the largest mixed method study reported in an Australian population. In addition, PEEK is a comprehensive study covering all aspects of disease experience from symptoms, diagnosis, treatment, healthcare communication, information provision, care and support, quality of life, and future treatment and care expectations.

Table 1.1: PEEK position

Author, Year	Location	Number of participants	Data collection	Focus	PEEK SECTION							
					2: Health status, co-morbidities	3: Diagnosis experience	4: Decision making	5: Treatment, healthcare system use	6: Information, communication and self-management	7: Care, support and navigating healthcare system	8: Quality of life, mental health, relationships	9 Expectations, preferences and messages
Sousa et al, 2018 [11]	Australia	32	Interviews	Endocrine therapy				x	x	x	x	
Pagani et al 2020[12], **Ribi et al 2020**[13], **Saha et al 2017**[14]**.**	International	4891	Questionnaire	Drug clinical trial	x							
Bines et al, 2021 [15]**.**	International	4808	Questionnaire	Drug clinical trial								
Tutt et al, 2021[16]	International	1836	Questionnaire	Drug clinical trial	x							
Ribi et al, 2019 [17]	International	956	Questionnaire	Drug clinical trial	x							
Fasching et al, 2020 [18]	International	726	Questionnaire	Drug clinical trial	x	x						
Timmins et al, 2021 [19]	Australia	159	Questionnaire	Drug clinical trial	x							

Author, Year	Location	Number of participants	Data collection	Focus	PEEK SECTION							
					2: Health status, co-morbidities	3: Diagnosis experience	4: Decision making	5: Treatment, healthcare system use	6: Information, communication and self-management	7: Care, support and navigating healthcare system	8: Quality of life, mental health, relationships	9 Expectations, preferences and messages
Cinieri et al, 2017 [20]	International	152	Questionnaire	Drug clinical trial	x							
Tucker et al, 2021 [21]	Australia	172	Questionnaire	Endocrine therapy	x	x						
Tucker et al, 2016 [22]	Australia	119	Questionnaire	Endocrine therapy	x	x					x	
Baker et al, 2018 [23]	Australia	31	Questionnaire	Symptoms and side effects	x	x						
Pearson et al, 2019 [24]	Australia	26	Questionnaire	Symptoms and side effects	x	x						

Abbreviations and terminology

ASGS	The Australian Statistical Geography Standard from the Australian Bureau of Statistics, defines remoteness and urban/rural definitions in Australia
CCDR	Centre for Community-Driven Research
dF	Degrees of Freedom. The number of values in the final calculation of a statistic that are free to vary.
f	The F ratio is the ratio of two mean square values, used in an ANOVA comparison. A large F ratio means that the variation among group means is more than you'd expect to see by chance.
ER	Estrogen-receptor
PR	Progesterone-receptor
FOP	Fear of Progression. Tool to measure anxiety related to progression
IQR	Interquartile range. A measure of statistical dispersion, being equal to the difference between 75th and 25th percentiles, or between upper and lower quartiles.
p	Probability value. A small *p*-value (typically ≤ 0.05) indicates strong. A large *p*-value (> 0.05) indicates weak evidence.
PEEK	Patient Experience, Expectations and Knowledge
PIH	Partners in Health
SD	Standard deviation. A quantity expressing by how much the members of a group digger from the mean value for the group/
SEIFA	Socio-Economic Indexes for Areas (SEIFA) ranks areas in Australia according to relative socio-economic advantage and disadvantage. This is developed by the Australian Bureau of Statistics.
SF36	Short Form Health Survey 36
t	t-Statistic. Size of the difference relative to the variation in your sample data.
Tukey HSD	Tukey's honestly significant difference test. It is used in this study to find 6significantly different means following an ANOVA test.
W	The W statistic is the test value from the Wilcoxon Rank sum test. The theoretical range of W is between 0 and (number in group one) x (number in group 2). When W=0, the two groups are exactly the same.
X^2	Chi-squared. Kruskal-Wallis test statistic approximates a chi-square distribution. The Chi-square test is intended to test how likely it is that an observed distribution is due to chance.

References

1. Ribi K, Luo W, Bernhard J, et al. Adjuvant Tamoxifen Plus Ovarian Function Suppression Versus Tamoxifen Alone in Premenopausal Women With Early Breast Cancer: Patient-Reported Outcomes in the Suppression of Ovarian Function Trial. *J Clin Oncol* 2016; **34**(14): 1601-10.
2. Burstein HJ, Temin S, Anderson H, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: american society of clinical oncology clinical practice guideline focused update. *J Clin Oncol* 2014; **32**(21): 2255-69.
3. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2013; **381**(9869): 805-16.
4. Pagani O, Regan MM, Walley BA, et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *N Engl J Med* 2014; **371**(2): 107-18.
5. Ussher JM, Perz J, Gilbert E. Information needs associated with changes to sexual well-being after breast cancer. *J Adv Nurs* 2013; **69**(2): 327-37.
6. Young JM, Walsh J, Butow PN, Solomon MJ, Shaw J. Measuring cancer care coordination: development and validation of a questionnaire for patients. *BMC Cancer* 2011; **11**: 298.
7. Hinz A, Mehnert A, Ernst J, Herschbach P, Schulte T. Fear of progression in patients 6 months after cancer rehabilitation-a- validation study of the fear of progression questionnaire FoP-Q-12. *Support Care Cancer* 2015; **23**(6): 1579-87.
8. Petkov J, Harvey P, Battersby M. The internal consistency and construct validity of the partners in health scale: validation of a patient rated chronic condition self-management measure. *Qual Life Res* 2010; **19**(7): 1079-85.
9. Centre" NBaOC. Breast cancer risk factors: a review of the evidence [Internet]. Surry Hills: National Breast and Ovarian Cancer Centre. 2009. p. viii-x.
10. Anothaisintawee T, Wiratkapun C, Lerdsitthichai P, et al. Risk factors of breast cancer: a systematic review and meta-analysis. *Asia Pac J Public Health* 2013; **25**(5): 368-87.
11. Sousa M, Peate M, Lewis C, et al. Exploring knowledge, attitudes and experience of genitourinary symptoms in women with early breast cancer on adjuvant endocrine therapy. *Eur J Cancer Care (Engl)* 2018; **27**(2): e12820.
12. Pagani O, Francis PA, Fleming GF, et al. Absolute Improvements in Freedom From Distant Recurrence to Tailor Adjuvant Endocrine Therapies for Premenopausal Women: Results From TEXT and SOFT. *J Clin Oncol* 2020; **38**(12): 1293-303.
13. Ribi K, Luo W, Walley BA, et al. Treatment-induced symptoms, depression and age as predictors of sexual problems in premenopausal women with early breast cancer receiving adjuvant endocrine therapy. *Breast Cancer Res Treat* 2020; **181**(2): 347-59.
14. Saha P, Regan MM, Pagani O, et al. Treatment Efficacy, Adherence, and Quality of Life Among Women Younger Than 35 Years in the International Breast Cancer Study Group TEXT and SOFT Adjuvant Endocrine Therapy Trials. *J Clin Oncol* 2017; **35**(27): 3113-22.
15. Bines J, Clark E, Barton C, et al. Patient-reported function, health-related quality of life, and symptoms in APHINITY: pertuzumab plus trastuzumab and chemotherapy in HER2-positive early breast cancer. *Br J Cancer* 2021; **125**(1): 38-47.
16. Tutt ANJ, Garber JE, Kaufman B, et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. *N Engl J Med* 2021; **384**(25): 2394-405.
17. Ribi K, Luo W, Colleoni M, et al. Quality of life under extended continuous versus intermittent adjuvant letrozole in lymph node-positive, early breast cancer patients: the SOLE randomised phase 3 trial. *Br J Cancer* 2019; **120**(10): 959-67.
18. Fasching PA, Beck JT, Chan A, et al. Ribociclib plus fulvestrant for advanced breast cancer: Health-related quality-of-life analyses from the MONALEESA-3 study. *Breast* 2020; **54**: 148-54.
19. Timmins HC, Li T, Trinh T, et al. Weekly Paclitaxel-Induced Neurotoxicity in Breast Cancer: Outcomes and Dose Response. *Oncologist* 2021; **26**(5): 366-74.
20. Cinieri S, Chan A, Altundag K, et al. Final Results of the Randomized Phase II NorCap-CA223 Trial Comparing First-Line All-Oral Versus Taxane-Based Chemotherapy for HER2-Negative Metastatic Breast Cancer. *Clin Breast Cancer* 2017; **17**(2): 91-9 e1.
21. Tucker PE, Cohen PA, Bulsara MK, Jeffares S, Saunders C. The impact of bilateral salpingo-oophorectomy on sexuality and quality of life in women with breast cancer. *Support Care Cancer* 2021; **29**(1): 369-75.
22. Tucker PE, Saunders C, Bulsara MK, et al. Sexuality and quality of life in women with a prior diagnosis of breast cancer after risk-reducing salpingo-oophorectomy. *Breast* 2016; **30**: 26-31.
23. Baker MK, Peddle-McIntyre CJ, Galvao DA, Hunt C, Spry N, Newton RU. Whole Body Vibration Exposure on Markers of Bone Turnover, Body

Composition, and Physical Functioning in Breast Cancer Patients Receiving Aromatase Inhibitor Therapy: A Randomized Controlled Trial. *Integr Cancer Ther* 2018; **17**(3): 968-78.
24. Pearson A, Booker A, Tio M, Marx G. Vaginal CO2 laser for the treatment of vulvovaginal atrophy in women with breast cancer: LAAVA pilot study. *Breast Cancer Res Treat* 2019; **178**(1): 135-40.