RESEARCH COMMUNICATION

Adherence to Recommended Treatments for Early Invasive Breast Cancer: Decisions of Women Attending Surgeons in the Breast Cancer Audit of Australia and New Zealand

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Abstract

Aim: The study aim was to determine the frequency with which women decline clinicians' treatment recommendations and variations in this frequency by age, cancer and service descriptors. Design: The study included 36,775 women diagnosed with early invasive breast cancer in 1998-2005 and attending Australian and New Zealand breast surgeons. Rate ratios for declining treatment were examined by descriptor, using bilateral and multiple logistic regression analyses. Proportional hazards regression was used in exploratory analyses of associations with breast cancer death. Results: 3.4% of women declined a recommended treatment of some type, ranging from 2.6% for women under 40 years to 5.8% for those aged 80 years or more, and with parallel increases by age presenting for declining radiotherapy ($p<0.001$) and axillary surgery ($p=0.006$). Multiple regression confirmed that common predictors of declining various treatments included low surgeon case load, treatment outside major city centres, and older age. Histological features suggesting a favourable prognosis were often predictive of declining various treatments, although reverse findings also applied with women with positive nodal status being more likely to decline a mastectomy and those with larger tumours more likely to decline chemotherapy. While survival analyses lacked statistical power due to small numbers, higher risks of breast cancer death were suggested, after adjusting for age and conventional clinical risk factors, (1) for women not receiving breast surgery for unstated reasons (RR=2.29; $p<0.001$); and (2) although not approaching statistical significance $p\geq 0.200$), for women declining radiotherapy (RR=1.22), a systemic therapy (RR1.11), and more specifically, chemotherapy (RR=1.41). Conclusions: Women have the right to choose their treatments but reasons for declining recommendations require further study to ensure that choices are well informed and clinical outcomes are optimized.

Keywords: Early breast cancer - declining treatment - survival

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Introduction

Adherence to recommended treatments has been linked to higher disease-free and overall survival for breast and other cancers (Li et al., 2000; Herbert-Croteau et al., 2004; McCowan et al., 2008; Wockel et al., 2010a,b; Hershman et al., 2011). Non-adherence can be a result of many clinical factors including treatment compromises to accommodate patient frailty or co-morbidity, clinician preference, poor service access or high user cost (Ruddy et al., 2009; Lebeau et al., 2011). Non-adherence has also been linked to sub-optimal coordination across multidisciplinary teams, inadequate organization and delivery of services, low clinician case load, and cancer features such as size of lesion and nodal status (Bloom et al., 2004; Gilligan et al., 2007; Lebeau et al., 2011).

Lack of adherence to recommended treatment can result from patient factors, including lack of knowledge, misunderstandings, forgetfulness, competing lifestyle pressures, attempts to avoid negative side effects, fear of cancer, cultural differences and personal beliefs (Bloom et al., 2004; Hoffman & Levin, 2005; Atkins & Fallowfield, 2006). In some settings, non-adherence has been associated with adverse health behaviours such as tobacco smoking and excess alcohol consumption (Land et al., 2011). Increased prescription of oral therapies has also led to lower adherence, raising concerns about potential for increased non-adherence as use of oral therapies increases (Partridge et al., 2002: 2003; Atkins et al., 2006; Chlebowski & Geller, 2006; Partridge et al., 2008; Ruddy

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& Partridge, 2009).

Patient adherence to recommended breast cancer treatments varies widely with treatment setting, but commonly poorer adherence has been associated with older age, low income status, some ethnic sub-groups, and lower educational status (Hebert-Croteau et al., 1999; Li et al., 2000; Truong et al., 2004; Schaapveld et al., 2005; Gilligan et al., 2007; Hershman et al., 2011; Lebeau et al., 2011; Weggelaar et al., 2011). Often adherence has been lower for adjuvant chemotherapies and radiotherapy than surgical interventions (Wockel et al., 2010a). As for other cancers, adherence issues have arisen with oral therapies (Partridge et al., 2003; Atkins et al., 2006).

The Breast Surgeons' Society of Australia and New Zealand (formerly the Breast Section of the Royal Australasian College of Surgeons) aims to maintain and enhance high quality care and optimal treatment outcomes by promulgation of evidence-based treatment guidelines, continued medical education, and monitoring of practice and identification of statistical outliers (Wang et al., 2008a; 2008b). There is concern that when women decline recommended therapies, technical quality may suffer and treatment outcomes may be jeopardized. Nonetheless it is recognized that the final choice of treatment is the patient's to make.

The aim of this study is to determine the extent to which patients decline recommended treatments, with a view to: (1) establishing benchmarks for future monitoring; and (2) considering policy and research implications. In this study, the frequency with which patients decline recommended treatments is investigated, overall and by treatment, age, cancer and health-system descriptor. Although reasons for declining recommendations are not recorded in the Audit, possible reasons and implications for policy development and research are discussed.

Materials and Methods

Audit data were collected by participating surgeons for an estimated 60% of early breast cancers diagnosed in Australia and New Zealand during the study period (Wang et al., 2008[a, b]; Roder et al., 2011). Although breast cancers included in the Audit are not selected to be representative of all early breast cancers, their characteristics appear similar. The Audit database has shown, for example, similar survivals to those for early breast cancers recorded at a population level in New South Wales and the USA [Surveillance Epidemiology and End Results (SEER) data] (Roder et al., 2010: 2011). In addition, differences in survival by conventional risk factors, such as tumour size, grade, nodal status and oestrogen receptor status, have accorded with differences expected from population-based data, which has added credibility to the Audit database (Roder et al., 2010).

Breast Cancer Audit data have been collected by members of the Breast Surgeons' Society of Australia and New Zealand since 1998 (Wang et al., 2008[a, b]). Data items include patient age, breast surgery type (i.e., mastectomy or complete local excision), axillary lymph node surgery, and referral for radiotherapy, chemotherapy, hormone therapy, and other systemic therapies. Patients' decisions to accept or decline treatments have been recorded. Data are collected on tumour histology, size, grade, lymphatic/vascular invasion, hormone receptor status, and axillary nodal status, using a minimum data set with clear data dictionary definitions. Names of treatment centres have been collected plus women's private health insurance status.

Survival data are not collected from surgeons but are derived for Australian women through linkage with the National Death Index at the Australian Institute of Health and Welfare, using the first three digits of the surname, dates of birth and jurisdiction of residence for probabilistic matching (Roder et al., 2010). Linkage accuracy was investigated in a pilot investigation of data for 1,179 women treated by South Australian surgeons. Accuracy of linked death data was compared with death information recorded on the South Australian Cancer Registry for the same women where full names were available for linkage and resolution of doubtful links had been undertaken by Registry staff through active follow-up. The results showed a high accuracy, with a linkage sensitivity of breast-cancer death detection of 93.1%, a specificity of 99.9%, a predictive value positive of 96.4%, and a predictive value negative of 99.8% (Roder et al., 2010).

Following the pilot, death data were obtained from the National Death Index for all Australian women recorded on the Audit database. The date of censoring of live cases in the survival follow-up was December 31st, 2007. In New Zealand, a similar follow-up of deaths was undertaken through the National Mortality Collection by deterministic matching using the National Health Index. This Index comprises a unique alphanumeric identifying number for each New Zealander.

Data for patients diagnosed in 1998-2005 were used in this study to allow enough follow-up time for survival assessment. A total of 36,755 cases and 2,410 breast cancer deaths were included. They excluded a small number for whom data were unavailable on whether treatment had been declined. The mean follow-up period from diagnosis was 58 months, with a range from less than one to 119 months.

Cross-tabulations were first undertaken to produce rate ratios (95% confidence limits) for declining a treatment (Garlinger & Abramson, 1995), both for treatment of any type collectively, and for individual treatment types, and by age, tumour characteristic, patient insurance status, annual case load of surgeon (i.e., ≤20, 21-100, >100), and location of treatment centre (major city, inner regional and more remote, using the Australian Standard Geographic Classification (AIHW et al., 2008) and equivalent geographic groupings for New Zealand). Statistical testing of associations with treatment adherence was undertaken using the Pearson chi-square test for binary and nominal variables and the Mann-Whitney U test for ordinal variables (Armitage & Berry, 1987; StataCorp, 2005).

Multiple logistic regression was used to confirm findings from these cross-tabulations, with a separate analysis undertaken for each treatment type. Declining treatment (yes/no) was the dependent variable in these analyses and explanatory variables were those which achieved statistical significance (p<0.05) in backwards elimination. Underlying assumptions such as lack of co-linearity were tested and found to be met (Armitage & Berry, 1987; StataCorp, 2005).

Although only 81 breast cancer deaths were available for analysis among women declining treatment, which substantially reduced statistical power. Relative risks of case fatality (i.e., hazards ratios) and 95% confidence intervals were calculated using Cox proportional hazards regression (Armitage & Berry, 1987; StataCorp, 2005). Survival times were calculated from diagnosis to December 31st, 2007 or date of death, whichever occurred first. Variables entered as predictors included declining treatment (yes/no), and as co-variables, age at diagnosis and clinical risk factors (i.e., histology type, tumour size, grade, nodal status, lymphatic/vascular invasion and oestrogen receptor status) categorized as shown in Tables 1 and 2. Proportionality and lack of co-linearity assumptions were checked and found to be satisfied.

The Cox models can be regarded as multivariate equivalents of disease-specific survival analyses. Disease-specific survivals have been shown in population-based studies in Australia to correspond closely with relative survival (Armitage & Berry, 1987; SACR 2000, 2007). Disease-specific survivals are often preferred in clinical studies where, due to referral practices, patients may not have risks of competing causes of death equivalent to population norms (a required assumption for relative survival).

Results

Percentage declining a treatment

Overall, 1,246 (3.4%) women declined some form of treatment (33.9 per 1,000). Data on the treatments declined were available for 873 (70.1%), indicating that the most common treatment declined was chemotherapy (23.6%), followed by hormone therapy (19.8%), radiotherapy (17.0%), breast conserving surgery (14.0%), mastectomy (8.5%), axillary surgery (7.0%), and multiple non-specified treatment types (10.2%).

Characteristics associated with declining treatment

Bivariate analyses: associations of person and health system descriptors with declining treatment are shown in Table 1. Univariate predictors of declining a treatment included:

- Age at diagnosis (p<0.001): The percentage declining a treatment increased from 2.6% in women under 40 years to 5.8% in those aged 80 years or more. Declining a treatment increased with age for axillary surgery (p=0.006), radiotherapy (p<0.001), and mastectomy (for women aged 80 years or more) (p<0.001). By comparison, age was not associated with declining breast conserving surgery (p=0.131), chemotherapy (p=0.809), hormone therapy (p=0.107) or multiple therapies (p=0.168).
- Annual surgeon case load (p<0.001): The percentage declining a treatment was higher for lower case loads, ranging from 2.6% where the case load exceeded 100 cases per year to 6.3% where the case load was ≤ 20 cases per year. Declining treatment was higher for lower case load for breast conserving surgery (p<0.001), mastectomy (p<0.001), axillary surgery (p<0.001), radiotherapy (p<0.001), chemotherapy (p=0.015), and multiple treatments (p=0.008). No association was evident for hormone therapy (p=0.648).
- Treatment location (p<0.001): The percentage declining a treatment increased with remoteness of treatment centre from 2.9% for major cities to 4.9% for inner regional and 8.9% for more remote areas. This trend applied for breast conserving surgery (p<0.001), mastectomy (p<0.001), radiotherapy (p<0.001), chemotherapy (p=0.005) and hormone therapy (p<0.001), but not for axillary surgery (p=0.518) or multiple treatments (p=0.537).
- Private health insurance: Although not statistically significant (p=0.070), declining a treatment tended to be more common among women without private health insurance, due to differences for declining mastectomy (p=0.014) and multiple treatments (p<0.001).

The only tumour descriptor associated with declining a treatment as a univariate predictor was low or intermediate as opposed to high grade (p=0.011) (Table 2). The percentage declining a treatment was 3.6% for low, 3.4% for intermediate and 3.0% for high grade, due to differences for declining axillary surgery (p=0.024), hormone therapy (p<0.001), and possibly radiotherapy (p=0.053). By comparison a reverse trend was indicated for declining chemotherapy (p<0.001).

Multiple logistic regression: the key predictors of declining a treatment were older age (p<0.001), lower case load (p<0.001), treatment at a greater distance from a major city (p<0.001) and low grade (p=0.030). The odds ratios (95% confidence limits) were:

- For age - compared with under 40 years, 1.15 (0.86,

Table 1. Rate Ratios (95% Confidence Limits) of Women Declining Clinician Recommendations for Breast Cancer Treatment by Age and Health-System Characteristics; BreastSurgANZ National Breast Cancer Audit, 1998–2005

Characteristic	No. of women: Not declining	No. of women: Declining	Rate ratio	P value*
Age at diag. (yrs):				
< 40	2,267	61	1.00 (ref)	
40–49	7,087	226	1.18 [0.89, 1.56]	
50–69	18,469	587	1.18 [0.91, 1.52]	MW p < 0.001
70–79	5,287	223	1.54 [1.17, 2.04]	
80+	2,419	149	2.21 [1.65, 2.96]	
Annual surgeon case load:				
≤ 20	3,751	253	1.00 (ref)	
21–100	20,870	707	0.52 [0.45, 0.60]	MW p < 0.001
> 100	10,953	289	0.41 [0.35, 0.48]	
Treatment location:				
Major city	26,781	810	1.00 (ref)	
Inner#	5,919	291	1.60 [1.40, 1.82]	MW p < 0.001
More remote	902	80	2.78 [2.23, 3.45]	
Private health insurance:				
No	6,957	423	1.00 (ref)	$X^2_{(1)}$ p = 0.070
Yes	7,780	416	0.89 [0.78, 1.01]	

*MW = Mann-Whitney U test; $X^2_{(1)}$ = Pearson chi-square test (1 degree of freedom); #regional

Table 2. Rate Ratios (95% Confidence Limits) of Women Declining Clinician Recommendations for Breast Cancer Treatment by Cancer Characteristic; BreastSurgANZ National Breast Cancer Audit, 1998–2005

Characteristic	No. of women: Not declining	No. of women: De-clining	Rate ratio	P value*
Histology type:				
Ductal	26,208	945	1.00 (ref)	
Lobular	3,943	122	0.86 [0.72, 1.04]	MW p=0.090
Other	3,751	114	0.85 [0.70, 1.03]	
Diameter (mm):				
<10	7,706	278	1.00	
10-14	5,236	183	0.97 [0.81, 1.17]	
15-19	6,391	210	0.91 [0.77, 1.09]	MW p=0.747
20-29	7,707	271	0.98 [0.83, 1.15]	
30-39	3,191	121	1.05 [0.85, 1.29]	
40+	3,874	127	0.91 [0.74, 1.12]	
Grade:				
Low	8,327	314	1.00 (ref)	
Intermediate	14,530	520	0.95 [0.83, 1.09]	MW p=0.011
High	10,246	316	0.82 [0.71, 0.96]	
Nodal status:				
Ve-	19,294	587	1.00 (ref)	$X^2_{(1)}$ p=0.903
Ve+	11,964	361	0.99 [0.87, 1.13]	
Oestrogen receptor:				
Ve-	7,188	230	1.00 (ref)	$X^2_{(1)}$ p=0.094
Ve+	25,698	932	1.13 [0.98, 1.30]	
Vascular invasion:				
Ve-	21,415	788	1.00 (ref)	$X^2_{(1)}$ p=0.093
Ve+	8,101	264	0.89 [0.78, 1.02]	
No. cancer foci:				
1	26,374	947	1.00 (ref)	
2	2,472	87	0.98 [0.79, 1.22]	MW p=0.633
3+	3,305	113	0.95 [0.79, 1.16]	

*MW = Mann-Whitney U test; $X^2_{(1)}$ = Pearson chi-square test (1 degree of freedom)

1.53) for 40-49 years, 1.12 (0.85, 1.47) for 50-69 years, 1.44 (1.08, 1.92) for 70-79 years, and 2.06 (1.52, 2.80) for 80+ years.

• For case load – compared with up to 20 cases, 0.57 (0.49, 0.67) for 21-100 cases and 0.51 (0.42, 0.61) for over 100 cases.

• For treatment location – compared with major city, 1.35 (1.16, 1.56) for inner regional and 2.33 (1.80, 3.01) for more remote area.

• Grade – compared with low grade, 0.96 (0.83, 1.10) for intermediate grade and 0.84 (0.71, 0.98) for high grade. Private health insurance status was not associated with declining a treatment (p>0.200).

Characteristics associated with declining specific treatment types

• Breast conserving treatment: Descriptors associated with declining breast conserving treatment in bivariate analyses included: low case load (p<0.001); inner regional treatment location (p<0.001); and fewer cancer foci (p=0.010). Multiple regression analysis confirmed that declining this treatment was related to case load (p<0.001), inner regional treatment location (p<0.001) and fewer breast cancer foci (p=0.042). Odds ratios were: for annual case load – compared with up to 20 cases, 0.19 (0.13, 0.27) for 21-100 cases and 0.06 (0.03, 0.14) for over 100 cases; for treatment location – compared with major city, 2.03 (1.38, 2.99) for inner regional and 0.45 (0.11, 1.86) for more remote areas; and for number of cancer foci – compared with one focus, 0.62 (0.27, 1.43) for two foci and 0.35 (0.13, 0.97) for three or more foci.

• Mastectomy: Bivariate analyses showed associations of declining mastectomy with low case load (p<0.001), inner regional treatment location (p<0.001), lack of private health insurance (p=0.014), larger tumour diameter (p=0.013), and positive nodal status (p=0.008). Multiple regression analysis confirmed that declining mastectomy

Table 3. Rate Ratios (95% Confidence Limits) of Women Declining Clinician Recommendations for Breast Cancer Treatment by the treatment Type and Case Characteristic; BreastSurgANZ National Breast Cancer Audit, 1998–2005

Characteristic	Treatment type*: Any	BCS	Mast	Axill	Radiotherapy	Chemotherapy	Horm ther
Older age at diagnosis	+ve (p<0.001)	-	-	+ve (p=0.003)	+ve (p<0.001)	-	-
Higher case load	-ve (p<0.001)	-ve (p<0.001)	-ve (p<0.001)	-ve (p=0.003)	-ve (p<0.001)	-ve (p=0.004)	-
Treatment outside major city	+ve (p<0.001)	+ve (p<0.001)[a]	-	-	+ve (p<0.001)	-	+ve (p<0.001)
Having private health insurance	-	-	-ve (p<0.001)	-	-	-	-
Ductal histology	-	-	-	-	-	-	+ve (p=0.036)
Large diameter	-	-	-	-	-	+ve (p=0.030)	-ve (p=0.001)
Higher grade	-ve (p=0.030)	-	-	-ve (p=0.049)	-	-	-ve (p=0.050)
Positive nodal status	-	-	+ve (p<0.001)	-	-	-	-ve (p<0.001)
Increasing number of cancer foci	-	-ve (p=0.042)	-	-	-	-	-

*BCS=breast conserving surgery; Mast=mastectomy; Axill=axillary surgery; Horm ther=hormone therapy; [a]Inner regional was related to case load (p<0.001), private health insurance status (p<0.001), and nodal status (p<0.001), but not treatment location or tumour diameter (p>0.077). Odds ratios were: for annual case load – compared with up to 20 cases, 0.45 (0.26, 0.78) for 21-100 cases and 0.17 (0.07, 0.41) for over 100 cases; for private health insurance - compared with having private insurance, 1.88 (1.11, 3.18) for not having this insurance; and for nodal status – compared with negative, 2.10 (1.11, 4.00) for positive nodal status.

• Axillary surgery: Declining axillary surgery was found in bivariate analyses to be associated with low case load (p<0.001), older age (p=0.006), smaller tumour diameter (p=0.009), and low grade (p=0.024). Multiple regression analysis confirmed the association of declining treatment with case load (p=0.003), age (p=0.003), and grade (p=0.049). Odds ratios were: for annual case load – compared with up to 20 cases, 0.56 (0.30, 1.05) for 21-100 cases and 0.20 (0.08, 0.50) for over 100 cases; for age – compared with under 40 years, 2.09 (0.26, 16.95) for 40-49, 2.72 (0.37, 20.41) for 50-69, 6.45 (0.85, 47.62) for 70-79, and 7.41 (0.93, 58.82) for 80 years and over; and for grade – compared with low, 0.50 (0.28, 0.90) for intermediate and 0.56 (0.30, 1.08) for high grade.

• Radiotherapy: Bivariate analyses indicated an association between declining radiotherapy and low case load (p<0.001), older age (p<0.001), treatment location (p<0.001), and potentially a low grade of tumour (p=0.053). Multiple regression analysis confirmed that declining treatment related to case load (p<0.001), age (p<0.001), and treatment location (p<0.001). Odds ratios from the model were: for annual case load – compared with up to 20 cases, 0.44 (0.30,64) for 21-100 cases, and 0.21 (0.12, 0.38 (1.30, 4.78) for over 100 cases; for age – compared with under 40 years, 1.33 (0.45, 3.95) for 40-49, 1.49 (0.54, 4.15) for 50-69, 3.82 (1.36, 10.75) for 70-79, and 7.75 (2.75, 21.74) for 80 years and over; and for treatment location – compared with major city, 1.38 (0.94, 2.03) for inner regional and 2.49 (1.30, 4.78) for more remote areas.

• Chemotherapy: Declining chemotherapy was found in the bivariate analyses to relate to case load (p=0.015), treatment location (p=0.005), larger tumour diameter (p<0.001), higher grade (p<0.001), node positive status (p=0.008) and presence of lymphatic/vascular invasion (p=0.022). Multiple logistic regression confirmed the association with case load (p=0.004) and tumour diameter (p=0.030), but not with treatment location (p=0.207), grade (p=0.161), nodal status p=0.371) or lymphatic/vascular invasion (p=0.537). Odds ratios were: for annual case load – compared with up to 20 cases, 0.54 (0.37, 0.80) for 21-100 cases and 0.49 (0.31, 0.77) for over 100 cases; and for tumour diameter– compared with under 10 mm, 1.86 (1.04, 3.32) for 10-14 mm, 2.09 (1.89, 3.30) for 15-19 mm, 1.90 (1.09, 3.25) for 20-29 mm, 1.88 (1.36, 4.59) for 30-39 mm and 2.50 (1.14, 3.88) for 40 mm or more.

• Hormone therapy: Declining hormone therapy was associated in the univariate analyses with more remote treatment location (p<0.001), smaller tumour diameter (p<0.001), lower grade (p<0.001), negative nodal status (p<0.001), absence of lymphatic/vascular invasion (p<0.001), fewer cancer foci (p=0.006), and ductal histology type (p=0.036), Multiple logistic regression confirmed that declining hormone therapy was related to treatment location (p<0.001), tumour diameter (p<0.001), nodal status (p<0.001), grade (p=0.050); and histology type (p=0.036). Odds ratios were: for treatment location – compared with major city, 1.37 (0.94, 2.00) for inner regional and 2.91 (1.59, 5.33) for more remote areas; for tumour diameter – compared with under 10 mm, 0.74 (0.48, 1.12) for 10-14 mm, 0.44 (0.26, 0.73) for 15-19 mm, 0.66 (0.42, 1.04) for 20-29 mm, 0.39 (0.16, 0.92) for 30-39 mm, and 0.44 (0.19, 1.01) for 40 mm or more; for nodal status – compared with node negative status, 0.37 (0.22, 0.61) for node positive status; for grade – compared with low grade, 0.71 (0.50, 1.00) for intermediate and 0.58 (0.34, 1.00) for high grade; and for histology type – compared with ductal, 0.52 (0.28, 0.99) for lobular and 0.54 (0.30, 0.96) for other histology types.

Survival

The number of breast cancer deaths available for analysis was small among women declining treatment (n=81) and smaller again by sub-category of treatment type declined. As a consequence, statistical power for detecting survival differences was very low. Nonetheless, after adjusting for age and conventional clinical risk factors, the relative risk (hazards ratio) was: for breast

Table 4. Relative Risks (95% Confidence Limits) of Breast Cancer Death According to Whether Recommended Treatments were Declined, by Treatment Type; BreastSurgANZ National Breast Cancer Audit, 1998–2005*

Treatment type	Whether declining	No. of women	Relative risk	
			Unadjusted	Adjusted**
Breast surgery:	Treatment received (ref)	35,564	1.00	1.00
	Treatment declined	47	3.95 [2.12, 7.36]	1.25 [0.67, 2.36]
	Treatment not offered	507	5.44 [4.60, 6.45]	2.29 [1.86, 2.82]
Radiotherapy:	Treatment received (ref)	22,731	1.00	1.00
	Treatment declined	103	1.79 [0.93, 3.45]	1.22 [0.63, 2.35]
	Treatment not offered	11,105	1.10 [1.01, 1.20]	0.99 [0.90, 1.09]
Systemic therapy:	Treatment received (ref)	29,679	1.00	1.00
	Treatment declined	166	1.01 [0.53, 1.95]	1.11 [0.57, 2.13]
	Treatment not offered	4,521	0.89 [0.79, 1.01]	1.00 [0.87, 1.15]

*Cox proportional hazards regression; date of censoring of live cases = Dec 31st, 2007, **Adjusted for age and diameter, grade, nodal status, oestrogen receptor status, vascular invasion, and number of cancer foci (see Tables 1 & 2), categories included for unknown values.

surgery (mastectomy and breast conserving surgery) – compared with surgery received, 2.29 (1.86, 2.82) when it was not recorded to have been offered, and 1.25 (0.67, 2.36) when it was declined; for radiotherapy - compared with radiotherapy received, 1.22 (0.63, 2.35) when it was declined; and for systemic therapy, compared with systemic therapy received, 1.11 (0.57, 2.13) when it was declined (note: the corresponding relative risk for declining chemotherapy was 1.41 (0.83, 2.40)). An analysis stratified by treatment type gave an unadjusted relative risk of 2.40 (1.27, 3.53) for declining treatment and a corresponding adjusted figure of 1.19 (0.71, 1.67).

Discussion

Only 3.4% of women were reported to have declined a recommended treatment, indicating that clinician recommendations were largely followed. While reasons for declining treatments were not recorded, differences in declining treatments were investigated by age, treatment location and other health-system descriptors, which generally accorded with results of other studies (Bloom et al., 2004; Truong et al., 2004; Gilligan et al., 2007; Wockel et al., 2010a ; Hershman et al., 2011; Lebeau et al., 2011; Weggelaar et al., 2011).

These results provide a basis for hypothesis generation, particular when supported by other study results. For example, consistent with results of prior studies of non-adherence, the percentage of women declining different treatments was higher for chemotherapy than surgery (Wockel et al., 2010[a]). This may reflect the lesser importance attributed by women to adjuvant therapy and a desire to avoid side effects.

Low surgeon case load has also been found previously to relate to non-adherence to recommended clinical guidelines (Gilligan et al., 2007). In the present study, the percentages of women declining breast conserving surgery, mastectomy, axillary surgery, radiotherapy and chemotherapy, respectively, were higher where the surgeon case load was lower. This applied in multivariable analysis after adjusting for age, cancer and health-system descriptors. The reasons are unknown but may relate to multidisciplinary care. A report from the National Breast and Ovarian Cancer Centre found a negative association of low case load with provision of multidisciplinary care (NBOCC, 2008). Qualitative research should be directed at low case-load settings to explore reasons and promotional strategies.

In general, older women were more likely to decline a treatment recommendation, which is consistent with non-adherence results from other studies (Truong et al., 2004; Schaapveld et al., 2005; Wockel et al., 2010[a]; Lebau et al., 2011; Weggelaar et al., 2011). Declining treatment recommendations was most apparent for radiotherapy. This may reflect the duration of this care (often about six weeks) and access issues due to the more limited numbers of treatment outlets available. Older women may be deterred from seeking treatments under these circumstances, due to effects of increasing age-related frailty and co-morbidity on physical capacity and self-confidence. Given their stage of life, these women may be more inclined to forego treatment, particularly radiotherapy and other treatments seen as having an adjuvant role.

More recently, the National Breast and Ovarian Cancer Centre developed guidelines for hypofractionation radiotherapy techniques in breast cancer that older women may find more convenient and may lead to stronger adherence to radiotherapy recommendations (CA, 2011). Furthermore, abbreviated partial breast radiotherapy may be a suitable option for some older women with breast cancer undergoing breast conserving surgery. The availability of this treatment may also lead to stronger adherence to radiotherapy recommendations.

Remoteness is well-known to reduce opportunities to gain recommended treatments (Li et al., 2000; BCNA, 2011). This was also demonstrated in the present study where women treated in more remote areas were more likely to decline a treatment recommendation. This applied in particular for radiotherapy, where travel and accommodation requirements would have been greatest. The use of hypofractionation and abbreviated partial breast irradiation may also assist in increasing adherence to radiotherapy recommendations by this sub-group of women. Remoteness of location was also demonstrated to reduce adherence for hormone therapy recommendations. The reason for this is not clear.

Tumour grade has been linked to non-adherence in a number of studies, although results have been inconsistent (Lebau et al., 2011). In the present study, women with low-grade tumours were more likely to decline recommended axillary surgery and hormone therapy. Again, the reasons are unclear, although it may be that low grade tumours would appear less life-threatening and women may feel that they have more latitude to decline recommended treatments.

Other more specific findings included a greater tendency to decline a recommended mastectomy in the absence of private health insurance and when axillary nodal status was positive. This may reflect variations in access to treatment through the public and private hospital system and potentially, a perspective that mastectomies are less likely to clear cancers that have already spread beyond the breast. Meanwhile the greater likelihood of refusing chemotherapy when tumour sizes were larger, and hormone therapy when diameters were smaller, nodal status was negative, and the histology type was ductal, is unexplained.

Priority ideally is given to randomized trial evidence in the development of clinical guidelines. However evidence from observational research can also be of value. Cohorts of women who have declined treatments provide an opportunity to investigate effects of treatment shortfalls on multiple outcomes, including daily function and quality of life, and broader effects on families, in addition to recurrence-free and overall survival. These and other research opportunities should be pursued.

Non-adherence to treatment recommendations have been shown to correlate with lower cancer survivals in previous studies cancers (Li et al., 2000; Herbert-Croteau et al., 2004; McCowan et al., 2008; Wockel et al., 2010[a, b]; Hershman et al., 2011). While the statistical power available to demonstrate similar associations in the present study was very low due to small numbers, point estimates were suggestive of higher case fatalities when treatments were declined.

It is important that further research be undertaken to determine reasons for declining treatments. These should include qualitative studies that have greater flexibility to explore differences in knowledge, attitudes, perceived risks, barriers to care, and perhaps other patient factors such as ethnicity and educational status.

In conclusions, women justifiably have the right to choose their treatment and can elect to decline clinician recommendations. Reasons for declining recommendations require further investigation however, to ensure that choices are well informed and clinical outcomes are optimized.

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References

Armitage P, Berry G (1987). Statistical methods in medical research. Second edition. Blackwell Scientific Publications, Oxford.

Atkins L, Fallowfield L (2006). Intentional and non-intentional non-adherence to medication amongst breast cancer patients. *Eur J Cancer*, **42**, 2271-6.

Australian Institute of Health and Welfare, Cancer Australia & Australasian Association of Cancer Registries (2008). Cancer survival and prevalence in Australia: cancers diagnosed from 1982 to 2004. Cancer series no. 42. Cat. No. CAN 38. AIHW, Canberra.

Breast Cancer Network Australia (2011). Women living in rural and remote regions. BCNA, Melbourne.

Bloom BS, De Pouvourville N, Chhatre S, Jayadevappa R, Weinberg D (2004). Breast cancer treatment in clinical practice compared to best evidence and practice guidelines. *Br J Cancer*, **90**, 26-30.

Cancer Australia (2011). Recommendations for use of hypofractionated radiotherapy for early (operable) breast cancer. CA, Sydney.

Chlebowski RT, Geller ML (2006). Adherence to endocrine therapy for breast cancer. *Oncology*, **71**, 1-9.

Garlinger PM, Abramson JH (1995). Computer programs for epidemiologic analysis. Unicorn Software Development, Inc., Stone Mountain.

Gilligan MA, Neuner J, Sparapani R, Laud PW, Nattinger AB (2007). Surgeon characteristics and variations in treatment for early-stage breast cancer. *Arch Surg*, **142**, 17-22.

Hebért-Croteau N, Brisson J, Latreille J, Blanchette C, Deschénes L (1999). Compliance with consensus recommendations for the treatment of early stage breast carcinoma in elderly women. *Cancer*, **85**, 1104-13.

Hébert-Croteau N, Brisson J, Latreille J, et al (2004). Compliance with consensus recommendations for systemic therapy is associated with improved survival of women with node-negative breast cancer. *J Clin Oncol*, **22**, 3685-93.

Hershman DL, Shao T, Kushi LH, et al (2011). Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. *Breast Cancer Res Treat*, **126**, 529-37.

Hoffman M, Levin TT (2005). Doctor, I don't want chemotherapy! *J Support Oncol*, **3**, 97-8.

Land SR, Cronin WM, Wickerham DL, et al (2011). Cigarette smoking, obesity, physical activity, and alcohol use as predictors of chemoprevention adherence in the national surgical adjuvant breast and bowel project P-1 breast cancer prevention trial. *Cancer Prev Res*, **4**, 1393-400.

Lebeau M, Mathoulin-Pélissier S, Bellera C, et al (2011). Breast cancer care compared with clinical Guidelines: an observational study in France. *BMC Public Health*, **11**, 45.

Li BD, Brown WA, Ampil FL, et al (2000). Patient compliance is critical for equivalent clinical outcomes for breast cancer treated by breast-conservation therapy. *Ann Surg*, **231**, 883-9.

McCowan C, Shearer J, Donnan PT, et al (2008). Cohort study examining tamoxifen adherence and its relationship to mortality in women with breast cancer. *Br J Cancer*, **99**, 1763-8.

(NBOCC) National Breast and Ovarian Cancer Centre (2008). MDIA-A national audit investigating the implementation of multidisciplinary cancer care in Australia. NBOCC publications, Sydney

Partridge AH, LaFountain A, Mayer E (2008). Adherence to initial adjuvant anastrozole therapy among women with early-stage breast cancer. *J Clin Oncol*, **26**, 556-62.

Partridge AH, Avorn J, Wang PS, Winer EP (2002). Adherence to therapy with oral antineoplastic agents. *J Natl Cancer Inst*, **94**, 652-61.

Partridge AH, Wang PS, Winer EP, Avorn J (2003). Non-adherence to adjuvant tamoxifen therapy in women with primary breast cancer. *J Clin Oncol*, **21**, 602-6.

Roder D, Wang JX, Zorbas H, Kollias J, Maddern G (2010). Survival from breast cancers managed by surgeons participating in the National Breast Cancer Audit of the Royal Australasian College of Surgeons. *ANZ J Surg*, **11**, 776-80.

Roder DM, De Siva P, Zorbas HN, et al (2011). Age effects on survival from early breast cancer in clinical settings in Australia. *ANZ J Surg*, **11**, 776-80.

Ruddy K, Mayer E, Partridge A (2009). Patient adherence and persistence with anticancer treatment. *CA Cancer J Clin*, **59**, 56-66.

Ruddy KJ, Partridge AH (2009). Adherence with adjuvant hormonal therapy for breast cancer. *Ann Oncol*, **20**, 401-2.

SACR (South Australian Cancer Registry) (2000). Epidemiology of cancer in South Australia. Incidence, mortality and survival 1977 to 1999. Incidence and mortality 1999. Openbook Publ., Adelaide

SACR (South Australian Cancer Registry) (2007). Cancer in South Australia 2004 with incidence projections to 2007. Government of South Australia, Adelaide.

Schaapveld M, De Vries EG, Otter R, et al (2005). Guideline adherence for early breast cancer before and after introduction of sentinel node biopsy. *Br J Cancer*, **93**, 520-8.

StataCorp (2005). Stata Statistical Software. Release 9.2. StataCorp LP, College Station, Texas.

Truong PT, Wong E, Bernstein V, Berthelet E, Kader HA (2004). Adjuvant radiation therapy after breast-conserving surgery in elderly women with early-stage breast cancer: controversy or consensus? *Clin Breast Cancer*, **4**, 407-14.

Wang J, Boult M, Tyson S, et al (2008a). Trends in surgical treatment of younger patients with breast cancer in Australia and New Zealand. *ANZ J Surg*, **78**, 665-9.

Wang J, Boult M, Roder D, Kollias J, Maddern G (2008b). Commentary: how surgical audits can be used to promote the update of surgical evidence. *ANZ J Surg*, **78**, 437-8.

Weggelaar I, Aben KK, Warlé MC, Strobbe LJ, Van Spronsen DJ (2011). Declined guideline adherence in older breast cancer patients: a population-based study in the Netherlands. *Breast J*, **17**, 239-45.

Wöckel A, Kurzeder C, Geyer V, et al (2010b). Effects of guideline adherence in primary breast cancer – a 5-year multi-center cohort study of 3976 patients. *Breast*, **19**, 120-7.

Wöckel A, Varga D, Atassi Z, et al (2010b). Impact of guideline conformity on breast cancer therapy: results of a 13-year retrospective cohort study. *Onkologie*, **33**, 21-8.