The financial impact of a breast cancer detected within and outside of screening: lessons from the Australian Lifepool cohort

Karinna Saxby,[1] Carolyn Nickson,[2,5,7] G. Bruce Mann,[3,6] Louiza Velentzis,[2,5,7] Hannah L. Bromley,[4,5] Pietro Procopio,[2,5,7] Karen Canfell,[2,7] Dennis Petrie[1]

Abstract

Objective: To determine the government and out-of-pocket community costs (out-of-hospital medical services and prescription medicines) associated with screen-detected and community-detected cancers (i.e. cancers detected outside of Australia's organised screening program [BreastScreen]).

Methods: We analyse administrative data on government-subsidised medical services and prescription medicines for 568 Victorian women diagnosed with breast cancer or ductal carcinoma in situ (DCIS). Using multivariable regression analysis, we estimate the government and out-of-pocket community costs incurred in the three years after diagnosis for screen-detected cancers and community-detected cancers. Additionally, we estimate the government costs associated with diagnosis within and outside of BreastScreen.

Results: Average government costs for breast cancer diagnosis were similar within and outside of BreastScreen [$808 (lower limit 676; upper limit 940) vs $837 (95%CI 671; 1,003) respectively]; however, women with community-detected cancers incurred an additional $254 (95%CI 175; 332) out-of-pocket. Controlling for differences in known cancer characteristics, compared to screen-detected cancers, community-detected breast cancers were associated with an additional $2,622 (95%CI 644; 4,776) in government expenditure in the three years following diagnosis. Adverse cancer characteristics that were more prevalent in community-detected cancers (high grade, lymph node involvement, HER2 positive receptor status) were associated with increased government and out-of-pocket costs.

Conclusions: Community-detected breast cancers were associated with increased government and out-of-pocket costs.

Implications for public health: These costs should be considered when evaluating current and alternative breast cancer screening strategies.

Key words: breast cancer, screening, out-of-pocket, costs, healthcare use

Breast cancer is the most common cancer diagnosed and the second leading cause of cancer death in Australian women.[1] With the objective of reducing morbidity and mortality from breast cancer, in 1991, the Australian Government introduced biennial population-based mammography screening through BreastScreen Australia.[2] Given costs for treating advanced-stage breast cancer in Australia are greater than for early-stage disease,[3] earlier detection through screening may also reduce treatment costs.[4] Consistent with this hypothesis, several studies have found that screen-detected breast cancers cost less to treat than those detected outside of screening.[5,6] However, these economic gains are offset, to some degree, by the costs associated with the screening program and overdiagnosis (diagnosis and treatment of screen-detected breast cancers that would never become symptomatic in a women's lifetime).[4,5,7]

Although an understanding of the cost drivers is important when evaluating the costs and benefits of alternative screening strategies, there are limited Australian costing studies for primary breast cancer. Those available predominantly focus on hospital treatment costs, and, to date, there have been no studies exploring the association between cancer characteristics and costs for out-of-hospital medical services and prescription medicines ("community costs"). Additionally, no studies explore how these costs, and the costs of diagnosis, vary by the mode of breast cancer detection (i.e. screen-detected or detected outside of BreastScreen). Subsequently, recent evaluations of the BreastScreen program have relied on either overly simplified or assumed community costs.[8]

1. Centre for Health Economics, Monash Business School, Monash University, Victoria
2. Cancer Research Unit, Cancer Council NSW, New South Wales
3. The Breast Service, Royal Melbourne and Royal Women's Hospital, Victoria
4. Health Economics Unit, University of Birmingham, UK
5. Melbourne School of Population and Global Health, University of Melbourne, Victoria
6. Department of Surgery, The University of Melbourne, Victoria
7. School of Public Health, The University of Sydney, New South Wales
Correspondence to: Karinna Saxby, Centre for Health Economics, Monash University, Room 595, Building H Level 5, 900 Dandenong Road, Caulfield East, VIC 3145; e-mail: karinna.saxby@monash.edu
Submitted: July 2019; Revision requested: December 2019; Accepted: January 2020
The authors have stated the following conflict of interest: KS occasionally works on a contract basis for consulting companies that have clients in the pharmaceutical industry but does not directly receive funding from industry. KC has received equipment and a funding contribution for an unrelated trial from Roche Molecular Systems and Ventana Inc USA. However, neither KC or her institution (Cancer Council NSW) received direct funding from industry for this trial or any other project.

Aust NZ J Public Health. 2020; 44:219-26; doi: 10.1111/1753-6405.12976

The aims of this study were to compare the costs of breast cancer diagnosis within and outside of BreastScreen and to determine the extent to which community costs were associated with breast cancer characteristics at diagnosis and the mode of detection.

Methods

The study group used for this analysis comes from the Lifepool cohort, which comprises more than 50,000 Victorian women who were recruited predominantly through BreastScreen (more information available at www.lifepool.org). Lifepool includes sociodemographic and clinicopathological data for women diagnosed with breast cancer as well as administrative data on BreastScreen participation and, for women providing specific consent, Medicare claims (Australian Government-subsidised medical services and prescription medicines). Subsidies for out-of-hospital and private hospital medical services are provided under the Medicare Benefits Schedule (MBS) while subsidies for prescription medicines are provided under the Pharmaceutical Benefits Scheme (PBS).[9] Of women who had been diagnosed with breast cancer or ductal carcinoma *in situ* (DCIS) between 3 July 1991 and 8 February 2017 (based on Lifepool consent) and returned their Medicare consent form (n=568), 567 (99.8%) and 472 (83.1%) consented to sharing their MBS and PBS history, respectively. There were no significant differences in cancer characteristics for those consenting (Supplementary Material).

Medicare claims included provider charges and government benefits from 2012 through to 2017 for an average of four years of claims per woman (as per Medicare's data retention policy). As this analysis focused on community costs associated with a primary breast cancer, private hospital MBS items (n=993), as well as women with breast cancer recurrences (n=6) and deaths (n=5), were excluded. Additionally, women who were known to be treated for other cancers (based on chemotherapy PBS items, Supplementary Material) prior to their breast cancer diagnosis were excluded (n=3). MBS out-of-pocket costs were determined by subtracting the government benefit from the provider charge and PBS out-of-pocket costs were based on the stipulated PBS patient contributions.[10] All costs were inflated to 2018 prices (Supplementary Material).

As there is an average of four years of Medicare claims per woman, we observed community costs at different times before, during and after their diagnosis (Supplementary Figure A.22). We therefore used linear regression analysis to estimate the change in community costs associated with diagnosis and treatment of DCIS/invasive breast cancer compared with their 'usual' historical costs (i.e. the reference period costs). Specifically, with reference to these historical costs, we estimated the extent to which cancer characteristics, mode of detection and patient characteristics were associated with additional government and out-of-pocket costs for MBS and PBS. Selection of covariates was informed by an expert panel comprising a breast cancer surgeon, epidemiologists and health economists. Model covariates included pathology (invasive or ductal carcinoma *in situ* [DCIS]) and, for invasive cancers, tumour grade and size (whether it was a large tumour [>20mm]) and the presence of lymph node metastasis. Tumour molecular subtypes were not available for all women; however, HER2 receptor information was available and further validated through PBS (only HER2 positive cancers should be given anti-HER2 therapy). In addition to observed cancer characteristics, the mode of detection was included to estimate the cost of diagnosis outside of BreastScreen and to further control for other unobserved pathology, such as symptomatic status.

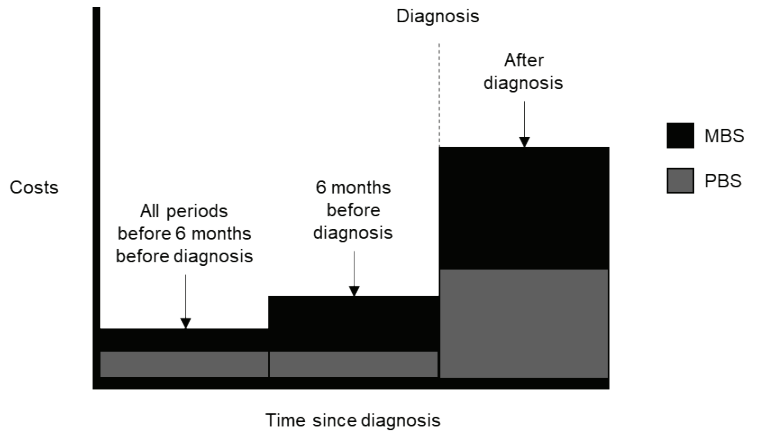
The mode of detection was categorised as either screen-detected or detected outside of BreastScreen (community detected). Community-detected breast cancers included diagnoses in women who: never participated in screening; last participated in screening more than two years ago; or were in-between screening rounds (interval-detected). To further explore possible differences in costs for community-detected cancers, we also estimated community costs separately for interval-detected breast cancers. However, we found that, when controlling for cancer characteristics, government and out-of-pocket costs for interval-detected cancers were similar to other community-detected cancers diagnosed in women who had never, or not recently, participated in screening (Supplementary Material).

In addition, private health insurance (PHI) and concession card status were included for MBS and PBS, respectively, and other patient characteristics associated with healthcare costs (age, body mass index [BMI] and smoking history) were included as covariates.

To minimise variability around cost estimates and account for censoring, MBS and PBS costs for each woman were calculated in six-month periods around their date of diagnosis (Supplementary Material). For PBS costs, as there were no prescription medicines associated with diagnosis, the historical reference period used was any period before diagnosis. However, for MBS costs, the reference period used was all periods more than six months preceding the diagnosis (Figure 1). The six months prior to a registered diagnosis captured non-BreastScreen out-of-hospital medical costs associated with the diagnosis. Changing the reference period for the PBS (to all periods more than six months preceding the diagnosis) did not significantly change our PBS cost estimates.

For the MBS and PBS analyses, the mode of detection and cancer characteristics at diagnosis were interacted across all included

Figure 1: Reference periods used for PBS and MBS costs. PBS costs after diagnosis were compared to all time periods before diagnosis while MBS costs were compared to time periods preceding the 6 months before diagnosis.



time periods. Additionally, PHI and concession status were interacted across all time periods for MBS and PBS, respectively.

To explore the types of additional services and medicines that were associated with breast cancer diagnosis and treatment, we estimated the association with different cost subgroups. MBS costs were split based on MBS categories;[11] namely attendances, pathology, therapeutic procedures and diagnostic procedures (diagnostic imaging services, procedures and investigations). Diagnostic MBS items were further categorised into breast cancer and heart monitoring-related items (Supplementary Material). PBS items were categorised based on items relating to chemotherapy, anti-HER2 therapy, endocrine therapy, depression/anxiety, pain/anti-inflammatory and colony-stimulating factor medications (for increasing white blood cells [WBCs]), see Supplementary Material.

The regression results were then used to estimate the total average costs for up to three years after diagnosis for DCIS cases and for base-case (grade 1 or 2, small tumour [≤20mm], no lymph node involvement and not HER2 positive) screen-detected and community-detected invasive cancers. Additional costs associated with invasive cancer characteristics (grade 3, large tumours, lymph node involvement and HER2 positive) were also estimated.

The cost of diagnosis within BreastScreen (which is government-funded outside Medicare), was estimated using publicly available annual and financial reports from AIHW and BreastScreen Victoria[12,13] and further refined through discussions with BreastScreen Victoria representatives. Costs included both variable costs and overheads associated with diagnosis through the program (see Supplementary Material). We assumed no out-of-pocket costs associated with a screen-detected diagnosis, as BreastScreen is free to participants.

Table 1: Summary statistics for the sample that consented to sharing their MBS information.

	Screen-detected (n=396) No. (%)	Community-detected (n=157) No. (%)	Screen-detected vs. community-detected (χ^2 test)[b]	Total (n=553) No. (%)
Age at diagnosis (years)				
Under 50	7 (2)	13 (8)		20 (4)
50-59	124 (31)	57 (36)	*p*=0.01	181 (33)
60-69	200 (51)	66 (42)		266 (48)
More than 70	65 (16)	21 (13)		86 (16)
Pathology/behaviour at diagnosis[a]				
DCIS	76 (19)	19 (12)	*p*=0.05	95 (17)
Invasive	320 (81)	138 (88)		458 (83)
Invasive cancer grade				
Grade 1	81 (21)	14 (9)		95 (17)
Grade 2	146 (37)	53 (34)	*p*<0.001	199 (36)
Grade 3	79 (20)	58 (37)		137 (25)
Missing	14 (4)	13 (8)	-	27 (5)
Invasive tumour size				
20mm or less	240 (61)	72 (46)	*p*<0.001	312 (56)
Greater than 20mm	72 (18)	53 (34)		125 (23)
Missing	8 (2)	13 (8)	-	21 (4)
Lymph node involvement				
Node negative	315 (80)	81 (52)	*p*=0.01	396 (72)
Node positive	76 (19)	38 (24)		114 (21)
Missing	5 (1)	38 (24)	-	43 (8)
HER2 receptor status - invasive cancers				
HER2 negative	295 (75)	117 (75)	*p*=0.02	412 (75)
HER2 positive	25 (6)	21 (13)		46 (8)
Private health insurance status				
No private health insurance	82 (21)	38 (25)	*p*=0.25	120 (22)
Private health insurance	313 (79)	112 (75)		425 (78)
Concession card status				
No concession card	191 (48)	73 (47)	*p*=0.87	264 (48)
Concession card holder	141 (36)	52 (33)		193 (35)
Missing	64 (16)	32 (20)	-	96 (17)
Regular smoker status				
Never smoked regularly	239 (60)	81 (52)	*p*=0.08	320 (58)
Previous/current regular smoker	155 (39)	74 (47)		229 (41)
Missing	2 (1)	2 (1)	-	4 (1)
BMI status				
Quartile 1	114 (29)	70 (45)		184 (33)
Quartile 2	136 (34)	48 (31)		184 (33)
Quartile 3	118 (30)	25 (16)	*p*=0.001	143 (26)
Quartile 4	4 (1)	4 (3)		8 (1)
Missing	24 (6)	10 (6)	-	34 (6)

Notes:

a. Invasive cancers with DCIS present were classified as invasive cancers

b. All p values reported in text for mean values (age, BMI and smoking status) based on t-tests

Results

Descriptive statistics

The characteristics for those who consented to share their MBS information are shown in Table 1. 396 (72%) of cancers were screen-detected and 157 (28%) were community-detected. 94% of women with community-detected cancers had a screening history; with the interval-detected cancers and lapsed attenders averaging 1.3 years (95%CI 0.4; 1.9) and 2.2 years (95%CI 2.0; 2.8) between their last screen and diagnosis respectively. Compared to community-detected cancers, screen-detected cancers were more likely to be diagnosed in older women (mean age 63 vs 61 years, *p*<0.001) and less likely to be invasive (81 vs 88%, *p*=0.05). Additionally, screen-detected cancers were less likely to be grade 3 (20 vs 37%, *p*<0.001), have large tumours (size >20mm: 18 vs 34%, *p*<0.001), have positive lymph node involvement (19 vs 24%, *p*=0.01) or be HER2 positive (6 vs 13%, *p*=0.02). No significant differences were observed for PHI status (*p*=0.25) and concession card status (*p*=0.87), however, compared to community-detected cancers, screen-detected cancers had a slighter higher BMI (mean BMI 28 vs 26, *p*=0.001) and were less likely to be regular smokers (mean 39 vs 47%, *p*=0.08).

Costs preceding diagnosis

The estimated government cost for a BreastScreen diagnosis was $808 with an upper and lower bound of $940 and $676, respectively (Table 2). As expected, screen-detected cancers were not associated with increased out-of-hospital medical costs to the government in the six months before diagnosis (p=0.16), see Table 3. However, for community-detected cancers, out-of-hospital medical costs increased on average by $837 (95%CI 671; 1,003, p<0.001) to the government and $254 (95%CI 175; 332, p<0.001) to the individual. Government costs were largely attributable to breast cancer diagnostic, pathology and therapeutic-related medical services (Figure 2).

Costs following diagnosis

The costs incurred in six-month blocks following diagnosis for out-of-hospital medical services and prescription medicines are provided in Tables 3 and 4. For both the government and the individual, the majority of the additional costs were incurred in the first six months after diagnosis. The overall predicted additional treatment costs incurred over the full three years following diagnosis is provided in Table 5. We focus on interpreting these overall cost implications below.

For the government, the total average additional community costs incurred over the three years following diagnosis were $1,380 (95%CI -26; 3,059, p=0.06) for DCIS; $1,255 (95%CI 81; 2,327, p=0.03) for base-case (grade 1 or 2, no lymph node involvement, small tumour and HER2 negative) screen-detected invasive cancers; and $3,847 (95%CI 1,938; 5,953, p<0.001) for base-case community-detected invasive cancers (Table 5).

Compared to base-case diagnoses, invasive cancer characteristics (grade 3 tumours, large tumours, positive lymph node involvement and HER2 positive receptor status) were associated with additional government expenditure on out-of-hospital medical services and prescription medicines. In the three years following diagnosis, invasive cancers with grade 3 or large tumours were associated with an additional $3,963 (95%CI 2,286; 5,800, p<0.001) and $1,797 (95%CI $175; 3,439, p=0.03) in government expenditure, respectively. On average, invasive cancers with positive lymph node involvement were associated with an additional $3,202 (95%CI 1,573; 4,843, p<0.001) and HER2 positive cancers with an additional $19,111 (95%CI 16,759; 21,287, p<0.001). These additional government costs were predominantly associated with out-of-hospital diagnostic services, prescription medicines for increasing WBCs and, specifically for HER2 positive invasive cancers, anti-HER2 therapy (Figure 3, Figure 4). Approximately 46% of the additional HER2-related government costs for out-of-hospital medical services were attributed to diagnostic services relating to heart monitoring.

Controlling for invasive cancer characteristics, community-detected invasive cancers were associated with an additional $2,622 (95%CI 644; 4,776, p<0.01) in government costs compared to screen-detected invasive cancers. This additional government expenditure was largely attributable to out-of-hospital diagnostic medical services (Figure 3) and medication for increasing WBCs (Figure 4).

Out-of-pocket community costs over the three years following diagnosis were, on average, $419 (95%CI -59; 815, p=0.03) for DCIS; $621 (95%CI 306; 934, p<0.001) for a base-case, screen-detected invasive cancer; and $741 (95%CI 316; 1,180, p<0.001) for a base-case, community-detected invasive cancer. These out-of-pocket costs were mainly attributable to endocrine therapy medication (Figure 4). Invasive cancers with large tumours, positive lymph node involvement or positive HER2 receptor status were all associated with increased out-of-pocket costs for prescription medicines (Table 4). These additional costs were largely due to medications related to breast cancer treatment (such as chemotherapy, antiemetic medication and anti-HER2 therapy), see Figure 4.

After controlling for differences in observable cancer characteristics, community-detected invasive cancers incurred some additional chemotherapy-related out-of-pocket costs compared to screen-detected invasive cancers (particularly in the first six months after diagnosis, see Supplementary Material). However, after controlling for cancer characteristics, the total average out-of-pocket community costs for community-detected cancers over the three years after diagnosis were not significantly larger than screen-detected invasive cancers (p=0.61).

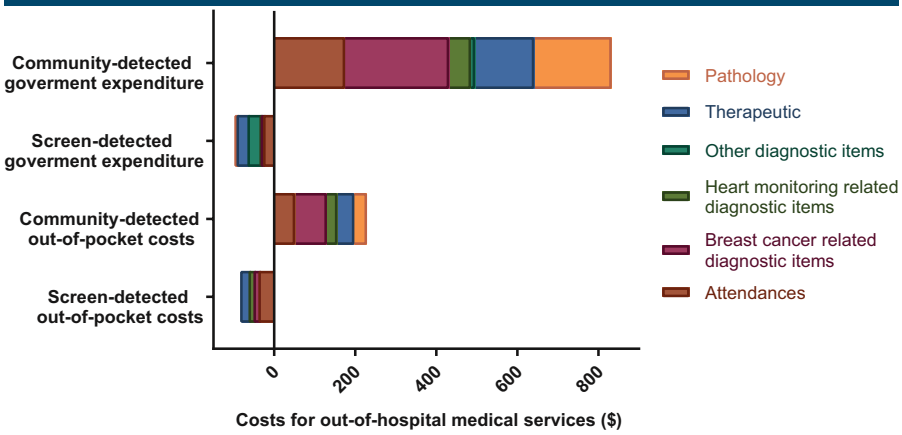
Across all time periods, women with PHI had increased out-of-pocket costs for out-of-hospital medical services (mean $592 [95%CI 353; 830, p<0.001] in the three years after diagnosis) and being a concession card

Table 2: Costs associated with a diagnosis within and outside of the BreastScreen program.

		Community-detected	
	Within BreastScreen government expenditure $ [lower bound; upper bound]	Government costs for out-of-hospital medical services $ [95%CI]	Out-of-pocket costs for out-of-hospital medical services $ [95%CI]
Cost of breast cancer diagnosis	808 [676; 940]	837 [671; 1,003]	254 [175; 332]

Note:
See Supplementary Material for full BreastScreen cost estimates.

Figure 2: Costs for out-of-hospital medical services incurred in the six months before diagnosis.



Notes:
Average costs shown for all diagnoses (DCIS and invasive cancers) within BreastScreen (screen-detected) and outside of BreastScreen (community-detected). All costs are shown with reference to historical out-of-hospital medical services for patients without private health insurance.

Table 3: Government expenditure and out-of-pocket costs for out-of-hospital medical services per six-month period.

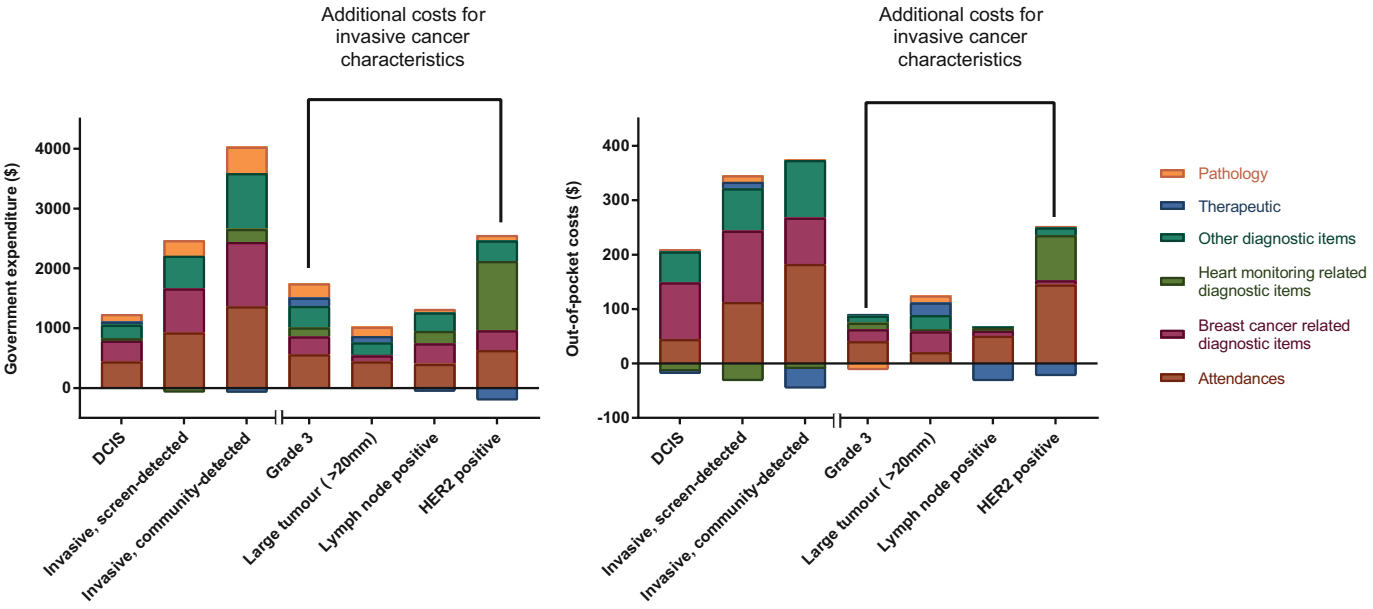
Time period relative to diagnosis	Interaction variable	Government expenditure ($ / 6 months) [95%CI]	*p* value	Out-of-pocket costs ($ / 6 months) [95%CI]	*p* value
6 months before diagnosis	Screen-detected DCIS / breast cancer (ref)	-96 [-228; 37]	0.160	-76** [-128; -24]	0.000
	Additional costs: Community-detected DCIS / breast cancer	837*** [671; 1,003]	0.000	254*** [175; 332]	0.000
	Additional costs: PHI	71 [-74; 217]	0.340	88** [27; 149]	0.000
0 – 6 months since diagnosis	DCIS (ref)	401** [135; 667]	0.000	-96** [-166; -26]	0.010
	Additional costs: Screen-detected invasive cancer (grade 1, grade 2)	813*** [584; 1,042]	0.000	34 [-21; 88]	0.230
	Additional costs: Community-detected invasive cancer (grade 1, grade 2)	1205*** [859; 1,550]	0.000	-25 [-113; 63]	0.580
	Additional costs: Grade 3 invasive cancer	470** [170; 770]	0.000	52 [-35; 140]	0.240
	Additional costs: Large invasive cancer (tumour size >20mm)	403** [137; 670]	0.000	62 [-27; 151]	0.170
	Additional costs: Lymph node positive invasive cancer	741*** [436; 1,045]	0.000	14 [-69; 97]	0.740
	Additional costs: HER2 positive invasive cancer	1,024*** [605; 1,443]	0.000	116 [-17; 249]	0.090
	Additional costs: PHI	208 [-32; 448]	0.090	303*** [248; 358]	0.000
6 – 12 months since diagnosis	DCIS (ref)	67 [-102; 236]	0.440	53* [0; 106]	0.050
	Additional costs: Screen-detected invasive cancer (grade 1, grade 2)	106 [-45; 257]	0.170	14 [-29; 57]	0.530
	Additional costs: Community-detected invasive cancer (grade 1, grade 2)	298** [76; 520]	0.010	53 [-16; 122]	0.130
	Additional costs: Grade 3 invasive cancer	255** [71; 438]	0.010	-6 [-57; 44]	0.810
	Additional costs: Large invasive cancer (tumour size >20mm)	212* [36; 387]	0.020	-6 [-62; 50]	0.840
	Additional costs: Lymph node positive invasive cancer	194* [15; 373]	0.030	16 [-41; 74]	0.580
	Additional costs: HER2 positive invasive cancer	717*** [395; 1,039]	0.000	-14 [-91; 63]	0.730
	Additional costs: PHI	150 [-5; 305]	0.060	77*** [35; 120]	0.000
1 – 3 years since diagnosis	DCIS (ref)	165 [-22; 353]	0.080	67* [14; 121]	0.010
	Additional costs: Screen-detected invasive cancer (grade 1, grade 2)	32 [-142; 206]	0.720	28 [-13; 69]	0.180
	Additional costs: Community-detected invasive cancer (grade 1, grade 2)	287* [36; 538]	0.030	45 [-15; 105]	0.140
	Additional costs: Grade 3 invasive cancer	238* [20; 456]	0.030	-13 [-63; 38]	0.620
	Additional costs: Large invasive cancer (tumour size >20mm)	111 [-80; 302]	0.250	25 [-24; 75]	0.320
	Additional costs: Lymph node positive invasive cancer	136 [-50; 322]	0.150	28 [-24; 79]	0.290
	Additional costs: HER2 positive invasive cancer	195 [-111; 501]	0.210	29 [-42; 101]	0.420
	Additional costs: PHI	124 [-57; 306]	0.180	53* [7; 99]	0.020
Observations		3,109		3,109	
R-squared		0.43		0.23	

Notes:

95%CI in brackets, robust standard errors clustered at individual level. All costs are referenced to historical out-of-hospital MBS costs. Model controls for individual patient characteristics observed across all time periods (age, BMI, smoking status, PHI). Full cost estimates and the number of women included in each 6-month time period are provided in the Supplementary Material.

****p<0.01, **p<0.05, *p<0.10*

Figure 3: Government costs (left) and out-of-pocket costs (right) for out-of-hospital medical services by MBS item category in the three years following DCIS or breast cancer diagnosis.



Notes:

Additional costs associated with specific invasive cancer characteristics are referenced to a base-case invasive cancer (i.e. grade 1 or 2, small tumour, lymph node negative and HER2 negative receptor status). All costs are shown with reference to historical costs for out-of-hospital medical services and are shown for patients without private health insurance.

Table 4: Government expenditure and out-of-pocket costs for prescription medicines per six-month period.

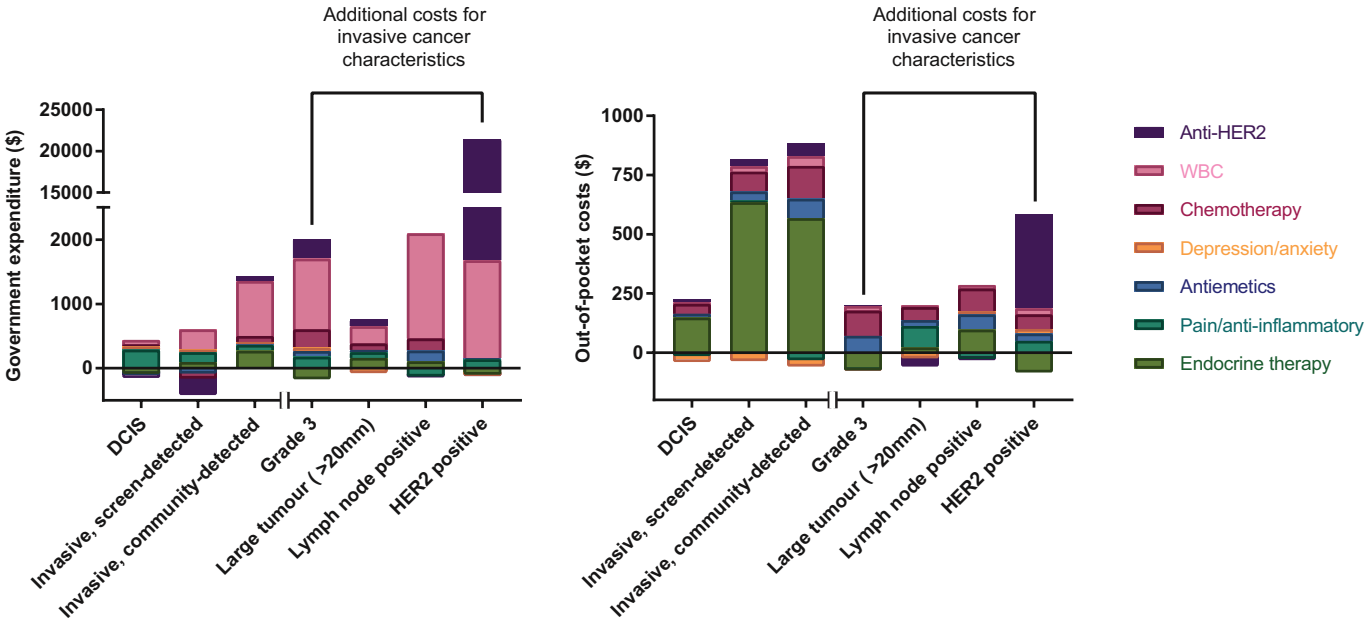
Time period relative to diagnosis	Interaction variable	Government expenditure ($ / 6 months) [95%CI]	*p* value	Out-of-pocket costs ($ / 6 months) [95%CI]	*p* value
0 – 6 months since diagnosis	DCIS (ref)	110 [-65; 285]	0.220	83*** [42; 123]	0.000
	Additional costs: Screen-detected invasive cancer (grade 1, grade 2)	299 [-84; 683]	0.130	154*** [95; 213]	0.000
	Additional costs: Community-detected invasive cancer (grade 1, grade 2)	963* [214; 1713]	0.010	280*** [185; 375]	0.000
	Additional costs: Grade 3 invasive cancer	1,307** [478; 2136]	0.000	187*** [98; 276]	0.000
	Additional costs: Large invasive cancer (tumour size >20mm)	148 [-608; 903]	0.700	90* [6; 174]	0.040
	Additional costs: Lymph node positive invasive cancer	1,707*** [871; 2544]	0.000	148*** [60; 236]	0.000
	Additional costs: HER2 positive invasive cancer	7,261*** [5,864; 8,659]	0.000	295*** [133; 458]	0.000
	Additional costs: Concession card holder	-186 [-673; 301]	0.450	-236*** [-296; -177]	0.000
6 – 12 months since diagnosis	DCIS (ref)	29 [-77; 136]	0.590	33 [-8; 73]	0.120
	Additional costs: Screen-detected invasive cancer (grade 1, grade 2)	-81 [-288; 126]	0.440	84*** [51; 117]	0.000
	Additional costs: Community-detected invasive cancer (grade 1, grade 2)	-115 [-368; 138]	0.370	91*** [50; 132]	0.000
	Additional costs: Grade 3 invasive cancer	372* [88; 655]	0.010	-6 [-41; 29]	0.730
	Additional costs: Large invasive cancer (tumour size >20mm)	168 [-197; 534]	0.370	28 [-12; 67]	0.170
	Additional costs: Lymph node positive invasive cancer	192 [-115; 499]	0.220	7 [-33; 47]	0.720
	Additional costs: HER2 positive invasive cancer	8,851*** [7,738; 9,964]	0.000	197*** [113; 281]	0.000
	Additional costs: Concession card holder	-3 [-269; 263]	0.980	-71*** [-102; -41]	0.000
1 – 3 years since diagnosis	DCIS (ref)	81 [-139; 300]	0.470	19 [-29; 68]	0.430
	Additional costs: Screen-detected invasive cancer (grade 1, grade 2)	-108* [-205; -11]	0.030	58** [19; 97]	0.000
	Additional costs: Community-detected invasive cancer (grade 1, grade 2)	88 [-107; 283]	0.380	43 [-1; 87]	0.050
	Additional costs: Grade 3 invasive cancer	146 [-62; 355]	0.170	-1 [-40; 38]	0.970
	Additional costs: Large invasive cancer (tumour size >20mm)	117 [-45; 279]	0.160	15 [-46; 76]	0.620
	Additional costs: Lymph node positive invasive cancer	-47 [-194; 99]	0.530	29 [-23; 81]	0.270
	Additional costs: HER2 positive invasive cancer	1,285*** [843; 1,727]	0.000	57 [-28; 142]	0.190
	Additional costs: Concession card holder	220 [-10; 450]	0.060	-34 [-72; 5]	0.090
Observations		2,539		2,539	
R-squared		0.67		0.37	

Notes:

95%CI in brackets, robust standard errors clustered at individual level. All costs are referenced to historical PBS costs. Model controls for individual patient characteristics observed across all time periods (age, BMI, smoking status, concession card holder). Full cost estimates and the number of women included in each 6-month time period are provided in the Supplementary Material.

****p<0.01, **p<0.05, *p<0.10*

Figure 4: Government costs (left) and out-of-pocket costs (right) for prescription medicines by PBS item category in the three years following DCIS or breast cancer diagnosis.



Notes:

Additional costs associated with specific invasive cancer characteristics are referenced to a base-case invasive cancer (i.e. grade 1 or 2, small tumour, lymph node negative and HER2 negative receptor status). All costs are shown with reference to historical costs for prescription medicines and are shown for patients without a concession card.

holder was associated with reduced out-of-pocket costs for prescription medicines (mean -$443 [95%CI -645; -241, $p<0.001$] in the 3 years after diagnosis). Increased PHI out-of-pocket costs were largely due to attendances, while concession card holders incurred less out-of-pocket costs for endocrine therapy, chemotherapy and antiemetic medication (Supplementary Material).

Discussion

This paper considered the community costs associated with breast cancer diagnosis and treatment in Australia. Although government expenditure for a diagnosis was similar inside and outside of BreastScreen ($777 vs $837), women diagnosed outside of screening incurred an additional $254 (95%CI 175; 332, $p<0.001$) in out-of-pocket costs. These out-of-pocket costs were mainly attributable to co-payments required for diagnostic services that are accessible free-of-charge through BreastScreen, such as mammographies and biopsies.

Invasive cancer prognostic factors (large tumours, grade 3 tumours, HER2 positive tumours and positive lymph node involvement) were associated with significantly higher expenditure. This is consistent with these characteristics being associated with more intense treatment, such as chemotherapy.[14,15] With the exception of HER2 positive invasive cancers, a large proportion of these additional costs were largely due to out-of-hospital diagnostic services and prescription medicines for increasing WBCs. The additional diagnostic costs are consistent with guidelines that recommend staging investigations for those with more advanced prognosis factors.[16] Moreover, the extra diagnostic services related to heart monitoring and medication for increasing WBCs accords with treatment recommendations for those undergoing chemotherapy and anti-HER2 therapy.[15-17]

The substantial government PBS costs associated with a HER2 positive invasive cancer were sustained even up to three years after diagnosis (mean $5,140 [95%CI 3,372; 6,907, $p<0.001$] per person between the end of year one until three years following diagnosis) and were largely attributable to the anti-HER2 therapy trastuzumab. While some of these costs might be attributable to a small proportion of our sample having HER2 positive metastatic breast cancer[18] (and thereby potentially requiring longer trastuzumab therapy), there is likely some sustained use in non-metastatic cases. This is particularly relevant as a recent study by Earl et al. (2018) found that six months of trastuzumab treatment may be sufficient for treatment of early-stage HER2 positive invasive breast cancer.[19] Therefore, our prescription medicine cost estimates imply that substantial cost savings may be possible if this study were to be practice-changing.

Compared to screen-detected invasive cancers, community-detected invasive cancers were more likely to have prognosis factors associated with greater costs (large tumours, grade 3 tumours, HER2 positive tumours and positive lymph node involvement). However, after controlling for these prognostic factors, community-detected invasive cancers were associated with an additional $2,407 (95%CI 246; 4,568) in government expenditure over the three years following diagnosis. This difference was largely attributed to additional diagnostic procedures and medicines for increasing WBCs in the community-detected cancers. The increased WBC costs is consistent with our finding that community-detected cancers had more chemotherapy-related costs than screen-detected cancers; however, the additional diagnostic procedure costs may be driven by unobservable differences in pathology at diagnosis, such as symptomatic status, the presence of multiple tumours, tumour molecular subtypes and the extent of lymph node invasion.[20]

Following diagnosis, the observed increase in out-of-pocket costs was largely attributed to prescription medicines, particularly for

Table 5: Total change in community costs associated with a DCIS or breast cancer diagnosis and additional costs associated with invasive cancer characteristics (from the day after diagnosis and up to 3 years after diagnosis). Figures are based on regression analyses estimates.

Mode of detection, pathology, patient characteristics and invasive cancer characteristics	Total additional community costs[a] (up to 3 years after diagnosis)		Total additional costs for out-of-hospital medical services (up to 3 years after diagnosis)		Total additional costs for prescription medicines (up to 3 years after diagnosis)	
	Government expenditure $ [95%CI]	Out-of-pocket costs $ [95%CI]	Government expenditure $ [95%CI]	Out-of-pocket costs $ [95%CI]	Government expenditure $ [95%CI]	Out-of-pocket costs $ [95%CI]
DCIS (no concession card, no *P*HI)	1,380 [-26; 3,059] p=0.062	419 [59; 815] p=0.028	1,129 [168; 2,090] p=0.021	227[-39; 493] p=0.095	462 [-563; 1,486] p=0.376	193 [-44; 430] p=0.111
Screen-detected invasive cancer (grade 1, grade 2, lym*p*h node negative, tumour size ≤20mm, HER2 negative, no concession card, no *P*HI)	1,225 [81; 2,327] p=0.034	621 [306; 934] p<0.001	1,047 [145; 1,949] p=0.023	160 [-56; 376] p=0.146	-214 [-859; 430] p=0.513	471 [262; 680] p<0.001
Community-detected invasive cancer (grade 1, grade 2, lym*p*h node negative, tumour size ≤20mm, HER2 negative, no concession card, no *P*HI)	3,847 [1,938; 5,953] p<0.001	741 [316; 1,180] p<0.001	2,650 [1,313; 3,988] p<0.001	208 [-105; 521] p=0.193	1,200 [69; 2,331] p=0.038	543 [314; 772] p<0.001
Difference: Community-detected invasive cancer – screen-detected invasive cancer (grade 1 or grade 2)	2,622 [644; 4,776] p=0.004	120 [-283; 565] p=0.610	1,603 [380; 2,827] p=0.010	48 [-245; 341] p=0.747	1,415 [199; 2,631] p=0.023	72 [-129; 273] p=0.481
Additional costs: invasive cancer grade 3	3,963 [2,286; 5,800] p<0.001	175 [-248; 564] p=0.386	1,677 [540; 2,814] p=0.004	-4 [-278; 269] p=0.975	2,264 [1,085; 3,444] p=<0.001	177 [-22; 376] p=0.081
Additional costs: large invasive cancer (>20 mm)	1,797 [175; 3,439] p=0.032	344 [-100; 810] p=0.126	1,059 [67; 2,050] p=0.036	157 [-111; 426] p=0.249	785 [-317; 1,887] p=0.162	179 [-107; 465] p=0.219
Additional costs: invasive cancer node *p*ositive	3,202 [1,573; 4,843] p<0.001	413 [-23; 863] p=0.06	1,479 [485; 2,472] p=0.004	141[-134; 416] p=0.315	1,710 [649; 2,770] p=0.002	272 [18; 526] p=0.036
Additional costs: invasive cancer HER2 *p*ositive	19,111 [16,759; 21,287] p<0.001	686 [314; 1,113] p<0.001	2,522 [945; 4,099] p=0.002	221[-149; 590] p=0.241	21,252 [18,641; 23,863] p=<0.001	720 [272; 1,168] p=0.002

Notes:

a: Total community costs (out-of-hospital MBS and PBS) calculated using bootstrap method and significance testing performed using percentile method.

endocrine therapy. Several studies have reported substantially higher out-of-pocket costs associated with breast cancer treatment[21,22]; however, these higher out-of-pocket costs are mostly associated with in-hospital treatment as a private patient or through other costs also not included in this study, such as loss of income due to time away from work.

There are several limitations to this study. Firstly, given this cohort was largely recruited through BreastScreen, we have a high proportion of lapsed attenders and interval-detected cancers in our community-detected group. Subsequently, our sample of community-detected cancers may not be wholly representative; particularly for women who have never participated in screening. In particular, as women who never participate in screening generally have a poorer prognosis at diagnosis, they thus undergo more intensive and likely costly treatment.[14,15] Therefore, the average costs for community-detected cancers from our sample may under-estimate the costs for women detected in the community due to an underrepresentation of women who have never been screened.

Additionally, as this study only investigated costs associated with a primary breast cancer, longer-term follow-up for women with breast cancer is required to estimate the additional costs associated with recurrence or palliative care. Ongoing data compilation from Lifepool and other sources will be essential in achieving sample representability and further enhancing our understanding around the cost drivers for breast cancer diagnosis, treatment and recovery.

Despite these limitations, to our knowledge, this study represents the first analysis exploring the association between specific cancer characteristics and the mode of detection on out-of-hospital medical services and prescription medicine costs in Australian women with breast cancer. Accounting for these community costs is essential for performing robust evaluations of current and future breast cancer screening and treatment scenarios. In particular, understanding how these costs vary by mode of detection and cancer characteristics at diagnosis will be essential for estimating the costs associated with overdiagnosis as well as alternative screening scenarios that are expected to affect cancer characteristics at diagnosis, such as risk-based screening.[15]

Conclusion

Government expenditure for breast cancer diagnosis was similar within and outside of BreastScreen; however, women diagnosed in the community incurred additional out-of-pocket costs. Following diagnosis, we found that costs for out-of-hospital medical services and prescription medicines were significantly associated with the mode of detection and cancer characteristics at diagnosis. Compared to screen-detected cancers, community-detected cancers were more likely to incur additional costs relating to extra diagnostic procedures, professional attendances and medicines for breast cancer treatment. This was in part due to community-detected cancers having more advanced cancer characteristics at diagnosis; however, unobservable characteristics and pathological differences may also be driving treatment decisions and, in turn, community costs. These costs should be included in future evaluations of the BreastScreen program, in particular when considering screening strategies that might affect cancer characteristics at diagnosis.

Acknowledgements

Resources provided by the Lifepool cohort contributed to this published research. The authors wish to thank Lifepool participants, investigators and the cohort funding body, National Breast Cancer Foundation. We would like to thank Peter Ghijben from the Monash University Centre for Health Economics for his assistance with PBS pricing; Lisa Devereux for assistance with accessing the Lifepool data; and BreastScreen Victoria representatives Luke Neill, Doris Whitmore and Genevieve Web for their assistance with estimating BreastScreen costs.

Funding

This work was funded by the Cancer Australia National Priority Grant 1066771.

References

1. Ghoncheh M, Pournamdar Z, Salehiniya H. Incidence and mortality and epidemiology of breast cancer in the world. *Asian Pac J Cancer Prev*. 2016;17(S3):43-6.
2. Department of Health and Ageing. *Evaluation of the BreastScreen Australia Program—Evaluation Final Report*. Canberra (AUST): AGPS; 2009.
3. Butler JR, Furnival CM, Hart RF. The costs of treating breast cancer in Australia and the implications for breast cancer screening. *Aust N Z J Surg*. 1995;65(7):485-91.
4. Salkeld G, Gerard K. Will early detection of breast cancer reduce the costs of treatment? *Aust J Public Health*. 1994;18(4):388-93.
5. Kauhava L, Immonen-Raiha P, Parvinen I, Helenius H, Kaljonen A, Rasanen O, et al. Lower costs of hospital treatment of breast cancer through a population-based mammography screening programme. *Eur J Public Health*. 2004;14(2):128-33.
6. Legorreta AP, Brooks RJ, Leibowitz AN, Solin LJ. Cost of breast cancer treatment: A 4-year longitudinal study. *Arch Intern Med*. 1996;156(19):2197-201.
7. Carter SM, Rogers W, Heath I, Degeling C, Doust J, Barratt A. The challenge of overdiagnosis begins with its definition. *BMJ*. 2015;350:h869.
8. BreastScreen Australia Evaluation Advisory Committee. *BreastScreen Australia Evaluation: Evaluation Final Report. Screening Monograph*. Melbourne (AUST): Breast Cancer Network Australia; 2009.
9. Harris A, Bulfone L. Getting value for money: The Australian experience. Health care Coverage Determinations: An International Comparative Study. 2 In: Jost TS, editor. *Health Care Coverage Determinations: An International Comparative Study*. Maidenhead (UK): Open University Press; 2004. p. 25-56.
10. Australian Pharmaceutical Benefits Scheme. *Fees, Patient Contributions and Safety Net Thresholds*. Canberra (AUST): Australian Department of Health; 2018.
11. Department of Health. *The July 2018 Medicare Benefits Schedule*. Canberra (AUST): Government of Australia; 2018.
12. BreastScreen Victoria. *Reports and Statistics*. Melbourne (AUST): Breast Screen; 2017.
13. Australian Intstitute of Health and Welfare. *BreastScreen Australia Monitoring Report*. Canberra (AUST): AIHW; 2018.
14. Elder K, Nickson C, Pattanasri M, Cooke S, Machalek D, Rose A, et al. Treatment Intensity Differences After Early-Stage Breast Cancer (ESBC) Diagnosis Depending on Participation in a Screening Program. *Ann Surg Oncol*. 2018;25(9):2563-72..
15. Saxby K, Nickson C, Mann B, Elder K, Bromley H, Velentzis L, et al. *Treatment patterns and treatment-related morbidity in women with early stage invasive breast cancers detected within and outside of screening*. Unpublished Observations.
16. Senkus E, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rutgers E, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2013;24 Suppl 6:vi7-23
17. Henry ML, Niu J, Zhang N, Giordano SH, Chavez-MacGregor M. Cardiotoxicity and cardiac monitoring among chemotherapy-treated breast cancer patients. *JACC Cardiovasc Imaging*. 2018;11(8):1084-93.
18. Lord SJ, Marinovich ML, Patterson JA, Wilcken N, Kiely BE, Gebski V, et al. Incidence of metastatic breast cancer in an Australian population-based cohort of women with non-metastatic breast cancer at diagnosis. *Med J Aust*. 2012;196(11):688-92.
19. Earl HM, Hiller L, Vallier A-L, Loi S, Howe D, Higgins HB, et al. PERSEPHONE: 6 versus 12 months (m) of adjuvant trastuzumab in patients (pts) with HER2 positive (+) early breast cancer (EBC): Randomised phase 3 non-inferiority trial with definitive 4-year (yr) disease-free survival (DFS) results. *J Clin Oncol*. 2018;36(15 suppl):506.
20. Viale G, Maiorano E, Pruneri G, Mastropasqua MG, Valentini S, Galimberti V, et al. Predicting the risk for additional axillary metastases in patients with breast carcinoma and positive sentinel lymph node biopsy. *Ann Surg*. 2005;241(2):319-25.
21. Gordon LG, Elliott TM, Olsen CM, Pandeya N, Whiteman DC. Out-of-pocket medical expenses for Queenslanders with a major cancer. *Med J Aust*. 2018;208(11):1.
22. Gordon L, Scuffham P, Hayes S, Newman B. Exploring the economic impact of breast cancers during the 18 months following diagnosis. *Psychooncology*. 2007;16(12):1130-9.

Supporting Information

Additional supporting information may be found in the online version of this article.