RESEARCH ARTICLE

Risk Factors for Poorer Breast Cancer Outcomes in Residents of Remote Areas of Australia

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Abstract

To investigate patient, cancer and treatment characteristics in females with breast cancer from more remote areas of Australia, to better understand reasons for their poorer outcomes, bi-variable and multivariable analyses were undertaken using the National Breast Cancer Audit database of the Society of Breast Surgeons of Australia and New Zealand. Results indicated that patients from more remote areas were more likely to be of lower socio-economic status and be treated in earlier diagnostic epochs and at inner regional and remote rather than major city centres. They were also more likely to be treated by low case load surgeons, although this finding was only of marginal statistical significance in multivariable analysis (p=0.074). Patients from more remote areas were less likely than those from major cities to be treated by breast conserving surgery, as opposed to mastectomy, and less likely to have adjuvant radiotherapy when having breast conserving surgery. They had a higher rate of adjuvant chemotherapy. Further monitoring will be important to determine whether breast conserving surgery and adjuvant radiotherapy utilization increase in rural patients following the introduction of regional cancer centres recently funded to improve service access in these areas.

Keywords: Breast cancer - patient - provider and treatment characteristics - geographic remoteness - Australia

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Introduction

The need for an emphasis on health needs of rural and remote Australians has long been recognized by health authorities. This was indicated in the first National Rural Health Strategy endorsed by Australian Health Ministers in 1994 and the National Strategic Framework for Rural and Remote Health released in 2011 (National Rural Health Alliance, 1994; Australian Health Ministers' Conference, 2012).

Providing for specialized health service needs of rural and remote populations encounters difficulties relating both to geographic isolation and elevated health needs (Australian Health Ministers' Conference, 2012). These populations generally have poorer health status than city residents, reflected in higher mortality rates, lower life expectancies, and higher rates of road injures, diabetes, obesity, hypertension, mental health conditions, other chronic diseases, and more prevalent risk factors such as tobacco smoking and excess alcohol consumption (Australian Health Ministers' Conference, 2012). Use of telemedicine, other emerging technologies, and national funding of regional cancer centres and associated accommodation facilities are directed at improving service access for rural populations (Australian Government, 2012).

There are many challenges facing remote populations apart from geographic isolation, including lower levels of income, employment and education (Australian Health Ministers' Conference, 2012). In some rural areas, there are high numbers of Aboriginal and Torres Strait Islander residents with elevated mortality and morbidity rates (Australian Health Ministers' Conference, 2012). Although only 2% of Australians live in rural and remote areas, the figure is 24% for Aboriginal and Torres Strait Islander people. Food supplies can also be a challenge in remote areas, with poorer access to fresh fruit and vegetables (Australian Health Ministers' Conference, 2012).

Sixty nine per cent of Australians live in major cities with close access to specialized health services whereas another 20% live in inner regional areas and 11% in outer regional and more remote locations (Australian Health Ministers' Conference, 2012). In general it is those living in outer regional and more remote areas where access to specialized cancer services poses the greatest difficulties.

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Outcomes of cancer in more remote areas follow the general pattern of health disadvantage seen for other health conditions. Residents of these areas generally have lower cancer survivals. During 2006-2010, case fatality in the five years following diagnosis was higher among patients from remote and very remote areas than major cities for all cancers collectively (37% Vs 33%) and cancers of the colon/rectum (37% Vs 33%), cervix (42% Vs 26%) and tongue (78% Vs 71%) respectively (AIHW, 2012). Corresponding case fatalities for female breast cancer were 16% for remote and very remote areas and 10% for major cities (AIHW and CA, 2012). While these differences were not large, they were similar to those reported for earlier periods and appear to be real (AIHW and AACR, 2003; AIHW, 2008; AIHW and NBOCC, 2009).

It is plausible that patients from remote areas would have poorer cancer outcomes. Apart from less ready access to specialized cancer services, they are often socio-economically disadvantaged, which would predispose to poorer survivals (Australian Health Ministers' Conference, 2012). During 2006-2010, five-year case fatality was higher for the lowest than highest socio-economic quintile in Australia for all cancers collectively (37% Vs 29%) and female breast cancers specifically (12% Vs 9%) (AIHW, 2012). In addition, outcomes in remote areas would have been affected by proportionally more Aboriginal and Torres Strait Islander residents in those areas, for whom cancer outcomes generally are poor (e.g., five-year breast cancer case fatality (all causes of death) of 31% compared with 17% for other female breast cancers diagnosed in 2006-2010) (AIHW and CA, 2012). Previous data have shown a lower proportional participation in BreastScreen mammography screening of residents from very remote areas, which likely would also predispose to lower breast cancer survival (Taylor et al., 2004; Roder et al., 2008; Australian Government, 2009; Morrell et al., 2012a; Nickson et al., 2012; Australian Health Ministers' Conference, 2012).

In this study we investigate the comparative prevalence by place of residence of socio-demographic, cancer, treatment and service characteristics that have been shown in previous Australian studies to relate to poorer breast cancer outcomes (South Australian Cancer Registry, 2000; Roder et al, 2010; 2012a; 2012b). The purpose is to better understand factors that may be contributing to the poorer outcomes among patients from remote areas. The study includes Australian women with invasive breast cancers treated by breast surgeons participating in the Breast Cancer Audit conducted by the Breast Surgeons' Society of Australia and New Zealand (BreastSurgANZ). Opportunities for intervention suggested by the results are considered, together with research and health service implications.

Although breast cancers covered by the Audit were not selected to be representative of all early breast cancers in Australia, they comprise a majority and appear to be broadly representative in their survival outcomes (Roder et al., 2010). Also differences in survivals by conventional risk factors, such as tumour size, grade, nodal status and oestrogen receptor status, accord with differences seen in population-based studies indicating that Audit data may be a credible basis for population inference (South Australian Cancer Registry, 2000; Roder et al., 2010).

Ethics approval for this study was obtained from the research ethics committee of the Royal Australasian College of Surgeons.

Materials and Methods

Data for early invasive breast cancers treated by Australian breast surgeons participating in the BreastSurgANZ Breast Cancer Audit circa 1998-2010 were analysed. The number of patients covered by the Audit has increased progressively and now represents about 60% of women diagnosed with early breast cancer in Australia (Roder et al., 2010; 2012a). The Audit did not record residential postcode as part of its minimum data set throughout the study period. Data for 30,299 early invasive breast cancers diagnosed in Australian women for whom residential postcodes were recorded were analysed. This enabled analyses by remoteness of residential area, which was the principal item of interest.

Residential areas were classified as major city (the least remote), inner regional, outer regional and more remote (AIHW, 2012). Variables included as candidate predictors of residential remoteness were as follows: 1) Age at diagnosis (<30, 30-39, 40-49, 50-59, 60-69, 70-79, 80+ years). 2) Private health insurance status. 3) Socio-economic status (SEIFA Relative Index of Socioeconomic Disadvantage, inferred from residential postcodes), categorized into ordinal categories (Australian Bureau of Statistics, 1998). 4) Location of treatment centre (ordinal categories of remoteness from major city to inner regional, and outer regional and more remote areas) (AIHW, 2008; Roder et al., 2012b). 5) Surgeon mean annual case load (≤10, 11-30, 31-100, 101+). 6) Year of diagnosis. 7) Referral source (symptomatic, asymptomatic – BreastScreen, asymptomatic - other (e.g., "de facto" screening or medical surveillance). 8) Breast cancer size (<10, 10-14, 15-19, 20-29, 30-39, 40+ mm), histology type (ductal, lobular, other), grade (low, intermediate, high), lymphatic/vascular invasion (positive/negative), nodal involvement (positive/negative), oestrogen and progesterone receptor status (positive/negative respectively), HER-2 receptor status (positive/negative), breast cancer location (including whether multiple quadrants were affected), number of tumour foci (1, 2, 3+), and whether a unilateral or bilateral cancer. 9) Treatment by (1) neo-adjuvant radiotherapy, chemotherapy, hormone therapy, aromatase inhibitors, and "anti-HER-2" immunotherapy, (2) adjuvant radiotherapy, chemotherapy, hormone therapy, and aromatase inhibitors, and "anti-HER-2" immunotherapy; (3) ovarian ablation; and (4) history of prior ipsilateral or contralateral breast cancer treatment.

Initially bi-variable associations of these variables with residential remoteness were explored using the Pearson chi-square test, plus the Mann-Whitney U test for binary, Kruskal-Wallis ANOVA for multi-nominal, and Spearman rank correlation for ordinal variables (Armitage and Berry, 1987; StataCorp, 2011). Relative odds (i.e., odds ratios)

(95% confidence interval) of residence in inner regional, outer regional or more remote locations respectively were calculated (using major city as the reference category) (Armitage and Berry, 1987; StataCorp, 2011). In addition, multivariable ordinal logistic regression was used to determine key predictors of greater residential remoteness, assuming consistent differences across ordinal remoteness categories (StataCorp, 2011).

Results

Bi-variable analyses

Socio-economic status: Lower socio-economic status was associated with residence in regional and more remote treatment areas (p<0.001). Patients from low socio-economic areas had a 10 times higher odds than those from high socio-economic areas of residing in an inner regional compared with major city centre. The corresponding odds of lower socio-economic patients residing in outer regional or more remote areas were 33 and 17 times higher respectively (Table 1).

Diagnostic epoch

Residential location differed during the study (p<0.001 when analysed as a nominal and p=0.044 as an ordinal variable). In general the odds of residing outside a major city decreased over time, with this trend being more pronounced for patients from outer regional areas from 2003-2005 and more remote areas from 2000-2002 (Table 1). As a result, using major city as the reference category, patients diagnosed in 2009 or later had a 31% lower odds than those diagnosed in 1999 or earlier of being residents of outer regional areas and a 49% lower odds of being residents of more remote locations.

Referral source

Referral sources varied by area of residence (p=0.023 for location as a nominal and p=0.003 as an ordinal variable). Asymptomatic referrals (those from non-Breastscreen sources) were less likely for outer regional

Table 1. Relative odds (95% confidence limits) of Regional or More Remote Places of Residence, Compared with a Major City; Australia Breast Cancer Audit, Circa 1998-2010*

Characteristic	Numbers				Relative Odds			P values**
	Major City	Inner Region	Outer Region	More Remote	Inner Region	Outer Region	More Remote	
Socio-economic status:								
Low	5,708	3,668	2,005	337	1	1	1	X^2(LR) p<0.001
Mid	3,927	1,485	496	25	0.59 (0.55, 0.63)	0.36 (0.32, 0.40)	0.11 (0.07, 0.16)	Sp p<0.001
High	11,700	785	119	44	0.10 (0.10, 0.11)	0.03 (0.02, 0.04)	0.06 (0.05, 0.09)	
Diagnostic epoch:								
≤1999	692	215	124	26	1	1	1	X^2(12) p<0.001
2000-02	1,598	503	274	28	1.01 (0.84, 1.22)	0.96 (0.76, 1.21)	0.47 (0.26, 0.83)	Sp p=0.044
2003-05	3,530	925	425	71	0.84 (0.71, 1.00)	0.67 (0.54, 0.84)	0.54 (0.33, 0.87)	
2006-08	9,196	2,472	1,016	161	0.87 (0.74, 1.02)	0.62 (0.50, 0.76)	0.47(0.30, 0.73)	
2009+	6,319	1,823	781	120	0.93 (0.79, 1.10)	0.69 (0.56, 0.85)	0.51 (0.32, 0.80)	
Referral source:								
Symptomatic	11,617	3,247	1,480	232	1	1	1	X^2(6) p=0.002
BreastScreen	5,866	1,671	719	113	1.02 (0.95, 1.09)	0.96 (0.87, 1.06)	0.96 (0.76, 1.22)	KW p=0.003
Other	1,840	463	177	35	0.90 (0.81, 1.01)	0.76 (0.64, 0.89)	0.95 (0.65, 1.30)	
Treatment centre location:								
Major city	15,834	4,149	1,624	264	1	1	1	X^2(6) p=0.023
Inner regional	4,293	1,449	787	111	1.29 (1.20, 1.38)	1.79 (1.63, 1.96)	1.55 (1.23, 1.95)	Sp p<0.001
Other	1,208	340	209	31	1.07 (0.95, 1.22)	1.69 (1.44, 1.98)	1.54 (1.04, 2.27)	
Surgeon annual case load:								
≤10	1,647	532	285	37	1	1	1	X^2(9) p<0.001
11-30	4,671	1,352	555	98	0.90 (0.80, 1.01)	0.69 (0.59, 0.80)	0.93 (0.63, 1.39)	Sp p<0.001
31-100	11,712	3,186	1,385	211	0.84 (0.76, 0.94)	0.68 (0.59, 0.79)	0.80 (0.56, 1.16)	
101+	3,305	868	395	60	0.81 (0.72, 0.92)	0.69 (0.58, 0.82)	0.81 (0.52, 1.25)	
Number of cancer foci:								
1	12,544	3,693	1,673	260	1	1	1	X^2(6) p=0.295
2	1,336	351	168	20	0.89 (0.79, 1.01)	0.94 (0.79, 1.12)	0.72 (0.44, 1.16)	Sp p= 0.034
3+	1,516	428	179	32	0.96 (0.85, 1.08)	0.89 (0.75, 1.05)	1.02 (0.69, 1.50)	
Surgery type:								
Mastectomy	8,167	2,339	1,073	148	1	1	1	X^2(3) p=0.025
Breast Cons. Surg	13,165	3,598	1,546	258	0.95 (0.90, 1.01)	0.89 (0.82, 0.97)	1.08 (0.88, 1.33)	MW p=0.016
Adjuvant radiotherapy:								
No	4,964	1,481	665	93	1	1	1	X^2(3) p=0.11
Yes	13,825	3,869	1,693	259	0.94 (0.88, 1.00)	0.91 (0.83, 1.01)	1.00 (0.78, 1.28)	MW p=0.021
Adjuvant chemotherapy:								
No	7,842	2,209	924	135	1	1	1	X^2(3) p=0.036
Yes	9,412	2,719	1,254	187	1.03 (0.96, 1.09)	1.13 (1.03, 1.24)	1.15 (0.92, 1.45)	MW p=0.016

*Invasive breast cancers treated by Australian breast surgeons (see text). ** X^2 (LR) = Likelihood ratio chi-square; X^2(df) = Pearson chi-square (degrees of freedom); Sp= Spearman correlation; KW=Kruskal-Wallis; MW=Mann-Whitney residents, the relative odds being 24% lower for outer regional residents than metropolitan residents) (Table 1). Differences in referral source were not observed between patients from inner regional or more remote areas and metropolitan residents (p>0.100).

Treatment centre location

Treatment centre location was strongly related to place of residence (p<0.001). Compared with major city residents, those from inner regional areas had higher odds of treatment at an inner regional than major city centre (relative odds=1.29) whereas residents of outer regional and more remote areas had higher odds of being treated at outer regional or more remote treatment locations than in a major city (relative odds ≥1.54) (Table 1).

Surgeon case load

Surgeon case load varied by patients' place of residence (p<0.001), with higher odds of low case load surgeons (i.e., ≤10 cases per annum) applying to patients from outer regional areas and with an elevation also applying for patients from inner regional areas (Table 1). While a similar difference applied to patients from more remote areas, the relative odds had wide confidence intervals and results were not statistically significant (p=0.446 for location as a nominal and p=0.157 as an ordinal variable).

Surgery type

Surgery type varied by place of residence (p=0.025 for location as a nominal and p=0.016 as an ordinal variable), with lower odds of breast conserving surgery for residents of outer regional areas (relative odds=0.89) but with similar odds for more remote and inner regional compared with major city areas (Table 1).

Adjuvant radiotherapy

Adjuvant radiotherapy varied by place of residence as an ordinal variable (p=0.021) but not as a nominal variable (p=0.118). Lower odds of this treatment tended to apply to patients from outer regional areas than a major city, although this did not achieve statistical significance (p=0.065). No variation was evident in adjuvant radiotherapy exposure by region for mastectomy cases (p=0.469 and p=0.478 for location as a nominal and ordinal variable respectively). However, a variation was indicated by place of residence for cases treated by breast conserving surgery (p=0.083 and p=0.012 for location as a nominal and ordinal variable respectively). The proportion of breast conserving surgery not accompanied by adjuvant radiotherapy increased from 26.9% for residents of major cities and 27.9% for inner and outer regional areas to 30.0% for more remote areas.

Adjuvant chemotherapy

Adjuvant chemotherapy also varied (p=0.036 for location of residence as a nominal and p=0.016 as an ordinal variable). The relative odds of adjuvant chemotherapy were elevated for patients from outer regional as opposed to major city areas (relative odds 1.13) (Table 1). An elevated relative odds was also suggested for more remote areas (relative odds=1.15) but confidence intervals were broad and the difference not statistically significant (p= 0.208).

Table 2. Relative Odds (95% confidence limits) of Increasingly Remote Place of Residence from a Major City, Australian Breast Cancer Audit, Circa 1998-2010 {Multivariable ordinal logistic regression}*

Characteristic	Relative odds
Socio-economic category:	
Cat 1 (lowest) (ref.) [n=5,881]	1
Cat 2 [n=5,837]	0.55 [0.51, 0.59]
Cat 3 [n=5,933]	0.34 [0.32, 0.37]
Cat 4/5 [n=12,648]	0.06 [0.05, 0.06]
Diagnostic epoch:	
≤1999 (ref.) [n=1,057]	1
2000-2002 [n=2,403]	0.98 [0.83, 1.16]
2003-2005 [n=4,951]	0.82 [0.70, 0.95]
2006-2008 [n=12,845]	0.75 [0.65, 0.87]
2009-2010 [n=9,043]	0.84 [0.72, 0.97]
Treatment centre location:	
Major city (ref.) [n=21,871]	1
Inner regional [n=6,640]	1.31 [1.23, 1.40]
Outer regional [n=1,759]	1.04 [0.93, 1.17]
More remote [n=29]	6.55 [3.26, 13.13]
Surgeon annual case load:	
11+ (ref.) [n=27,798]	1
≤10 [n=2,501]	1.09 [0.99, 1.20]
Surgery type:	
Mastectomy (ref.) [n=11,727]	1
Breast cons. Surg. [n=18, 567]	0.94 [0.89, 0.99]
Adjuvant radiotherapy:	
No (ref.) [n=7,203]	1
Yes [n=19, 646]	0.93 [0.87. 0.99]
(Unknown [n=3,450])	(0.84 [0.75, 0.93])
Adjuvant chemotherapy:	
No (ref.) [n=11,110]	1
Yes [n=13,572]	1.10 [1.04, 1.17]
(Unknown [n=5,617])	(1.02 [0.94, 1.11])

*Ordinal logistic regression (see Methods); Unknown surgery type (n=5) (relative odds not stated due to small "n")

Other analyses were suggestive of a difference in prevalence of multifocal cancers, with these cancers being more common in women from a major city than inner or outer regional area (p=0.034 for location as an ordinal variable) but the relative odds for specific residential categories had wide confidence intervals and none achieved statistical significance (p>0.050). Similarly, statistically significant differences were not found between place of residence and other patient, provider, cancer and treatment variables.

Multivariable analysis

Table 2 include results of multivariable ordinal logistic regression, indicating that key predictors of increasing remoteness of residence included: (1) lower socio-economic status; (2) earlier diagnostic periods; (3) inner regional or more remote treatment centre locations; (4) not receiving breast conserving surgery; (5) not receiving adjuvant radiotherapy; and (6) receiving adjuvant chemotherapy.

There was also the indication that attending low case load surgeons was more common for more remote places of residence, although this was of marginal statistical significance only (p=0.074).

Discussion

Most Australian women with early invasive breast cancer treated by surgeons in the BreastSurgANZ Breast Cancer Audit resided in major cities (70%), whereas 20% were from inner regional and 11% from outer regional and more remote areas. Factors associated with increasing remoteness included lower socio-economic status, diagnosis in an earlier diagnostic epoch, treatment in an inner regional or more remote centre rather than in a major city centre, and potentially treatment by a low case-load surgeon, although the latter result was only of marginal statistical significance in the multivariable analysis (p=0.074). Although tumour characteristics such as size, grade, nodal involvement and hormone receptor status were not found to vary by remoteness of residence, there were treatment differences, with increasing remoteness being associated with lower odds of breast conserving surgery, adjuvant radiotherapy overall and adjunctive radiotherapy in association with breast conserving surgery, and higher odds of chemotherapy.

It is plausible that lower socio-economic status would contribute to poorer survival outcomes in more remote areas through higher levels of co-morbidity and less complete treatment, as observed for example in Aboriginal and Torres Strait Islander patients who are disproportionately represented in lower socio-economic areas (Chong and Roder, 2010; Australian Health Ministers' Conference, 2012). Australian data for 2006-2010 indicated higher five-year case fatalities for the lowest than highest socio-economic quintile for all cancer types combined (37% Vs 33%) and for individual cancer types including cancers of the colon/rectum (35% Vs 31%), lung (86% Vs 84%), prostate (9% Vs 6%), cervix (34% Vs 23%) and non-Hodgkin lymphoma (32% Vs 26%) (AIHW, 2012). For female breast cancers, five-year case fatality was 12% for the lowest and 9% for the highest socio-economic quintile (AIHW, 2012).

Aboriginal and Torres Strait Islander residents concentrate disproportionately in more remote areas (Australian Health Ministers' Conference, 2012), and their five-year case fatality rates are substantially higher for all cancers combined, as indicated by population-based data for 1977-2007 (60% Vs 43%) and 1999-2007 (47% Vs 35%) (Chong and Roder, 2010; Morrell et al., 2012b). This also applied for female breast cancer (39% Vs 20% for South Australia and 21% Vs 12% for New South Wales) (Chong and Roder, 2010; Morrell et al., 2012b). Meanwhile Australian data for 2006-2010 indicate case fatalities for breast cancer cases from all causes of death of 31% for Aboriginal and Torres Strait Islander women compared with 17% for other women (AIHW and CA, 2012). These differences are attributed to more advanced stages at diagnosis, higher levels of co-morbidity, including diabetes, cardiovascular, respiratory, kidney disease and various chronic infections, and less complete treatment (Chong and Roder, 2010; Morrell et al., 2012b).

There has been a steady secular increase in case survivals from female breast cancer in Australia which is attributed to real gains from screening and treatment, together with artificial effects of screening through changes in lead time and related effects (AIHW and CA, 2012; Morrell et al., 2012a). It is likely therefore that the stronger representation of patients from more remote areas in the earlier diagnostic periods (i.e., periods when survivals were lower) would have contributed to the higher case fatality for these areas. Also these patients tended more than those from major cities to be treated in inner regional treatment centres and potentially by low case-load surgeons, where lower survival outcomes have been suggested (Roder et al., 2012b).

Another possible influence on outcomes would be sub-optimal exposure to adjuvant radiotherapy of patients receiving breast conserving surgery, which was more likely in more remote areas (note: the percentage of patients not receiving adjuvant radiotherapy increased from 27% for residents of major cities to 30% of those from remote areas). This correlates with higher mastectomy rates in more remote areas (Roder et al., 2013), attributed in part to avoiding radiotherapy (note: this group of patients, if treated by breast conserving surgery, may need to travel to, and gain accommodation in city locations for around 5-6 weeks for adjuvant radiotherapy). Differences in treatment modalities for women in remote areas may also reflect a lack of access to multi disciplinary care which has previously been shown to be more available to women living in metropolitan regions. (Marsh et al., 2008).

Steps have been taken to increase access of rural patents to specialized services through the use of telemedicine and emerging technologies, and the funding of regional cancer centres (Australian Government, 2012). These and related initiatives are likely have beneficial effects, which should be investigated in ongoing monitoring.

More recent data indicate lower immediate breast reconstruction rates following mastectomy for residents of remote than major city locations, which may reflect their more limited access to specialized treatment centres (Roder et al., 2012c). The extent of satisfaction with cosmetic outcomes of patients from remote areas, given their higher rates of mastectomy and lower rates of immediate breast reconstruction, is unknown and warrants investigation.

In conclusions, these data indicate that in addition to geographic isolation, patients from more remote areas are more often of lower socio-economic status, less likely to be treated in major city than inner regional or more remote centres, and potentially more likely to be treated by surgeons with low case loads, although this latter finding did not achieve statistical significance. In addition they have a lower rate of breast conserving surgery as opposed to mastectomy, a lower rate of radiotherapy as an adjuvant to breast conserving surgery, and a higher probability of having adjuvant chemotherapy. The comparative satisfaction of more remote compared with city breast cancer patients with cosmetic outcomes of breast cancer care is not known and warrants investigation.

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