

RESEARCH ARTICLE

Geographic Disparities in Prostate Cancer Outcomes - Review of International Patterns

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Abstract

Background: This study reviewed the published evidence as to how prostate cancer outcomes vary across geographical remoteness and area level disadvantage. **Materials and Methods:** A review of the literature published from January 1998 to January 2014 was undertaken: Medline and CINAHL databases were searched in February to May 2014. The search terms included terms of 'Prostate cancer' and 'prostatic neoplasms' coupled with 'rural health', 'urban health', 'geographic inequalities', 'spatial', 'socioeconomic', 'disadvantage', 'health literacy' or 'health service accessibility'. Outcome specific terms were 'incidence', 'mortality', 'prevalence', 'survival', 'disease progression', 'PSA testing' or 'PSA screening', 'treatment', 'treatment complications' and 'recurrence'. A further search through internet search engines was conducted to identify any additional relevant published reports. **Results:** 91 papers were included in the review. While patterns were sometimes contrasting, the predominate patterns were for PSA testing to be more common in urban (5 studies out of 6) and affluent areas (2 of 2), higher prostate cancer incidence in urban (12 of 22) and affluent (18 of 20), greater risk of advanced stage prostate cancer in rural (7 of 11) and disadvantaged (8 of 9), higher survival in urban (8 of 13) and affluent (16 of 18), greater access or use of definitive treatment services in urban (6 of 9) and affluent (7 of 7), and higher prostate mortality in rural (10 of 20) and disadvantaged (8 of 16) areas. **Conclusions:** Future studies may need to utilise a mixed methods approach, in which the quantifiable attributes of the individuals living within areas are measured along with the characteristics of the areas themselves, but importantly include a qualitative examination of the lived experience of people within those areas. These studies should be conducted across a range of international countries using consistent measures and incorporate dialogue between clinicians, epidemiologists, policy advocates and disease control specialists.

Keywords: Prostate cancer - geography - inequalities - incidence - survival - mortality - PSA testing

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Introduction

Internationally, prostate cancer is the second most commonly diagnosed cancer and fifth most common cause of cancer death among men (Ferlay et al., 2013). Prostate cancer is particularly prevalent in developed countries such as Australia, United States and the Scandinavian countries, with about a 25-fold difference between high-incidence and low-incidence countries (Ferlay et al., 2013). In contrast to incidence, mortality rates are generally highest in the predominately black populations of the Caribbean and sub-Saharan Africa (Ferlay et al., 2013). This variation in the global distribution of prostate cancer demonstrates that the risk of being diagnosed and death from prostate cancer is strongly associated with where men live, and is particularly affected by Prostate Specific Antigen (PSA) testing practices, in addition to

health systems, life expectancy, and competing causes of mortality.

Problematically, how the risk of prostate cancer and its outcomes vary geographically within a country is currently not well described, hampering our understanding of where prostate cancer causes the greatest burden and what may underlie inequalities in outcomes. As a consequence there is also a knowledge gap about how geographically driven factors may relate to prostate cancer risk. Geographical location provides an indication of the population composition, physical and social environments, and the access of resources and services. A better understanding of geographical patterns in the burden of prostate cancer has the potential to lead to important hypotheses about risk factors, prevention and the access and delivery of clinical services (DeChello et al., 2006; Klassen and Platz, 2006), that can then be tested in intervention research.

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We recognise that the geographical differences in outcome measures are likely linked to a range of other factors relating to the composition of individuals within geographical areas. However, for the purposes of this review we have focused on describing the geographical disparities only, rather than any differences between the individuals living within those areas. This included geographical differences according to geographical remoteness and by area disadvantage, with the outcomes of PSA testing, prostate cancer incidence, access to and use of treatment, survival following a diagnosis of prostate cancer, and prostate cancer mortality. In doing so, this provides a greater scope than a recent and related literature review (Obertova et al., 2012).

When interpreting the results of this review, it is important to note the qualitative and conceptual differences between area-based socioeconomic measures and individual-level measures of socioeconomic status, the latter of which are beyond the scope of this review. Measures of area disadvantage reflect the possible influences of community, neighbourhood and/or social structures, that may in themselves contribute to the risk and burden of prostate cancer, independently of the individual level socioeconomic characteristics (Krieger et al., 1997; Adler and Ostrove, 1999).

Materials and Methods

A review of the literature published from 1 January 1998 to 31st January 2014 was undertaken: Medline and CINAHL databases were searched in February to May 2014. The search terms agreed on by the study investigators included keywords, subject heading and MeSH terms of ‘Prostate cancer’ and ‘prostatic neoplasms’ coupled with ‘rural health’, ‘urban health’, ‘geographic inequalities’, ‘spatial’, ‘socioeconomic’, ‘disadvantage’, ‘health literacy’ or ‘health service accessibility’. Outcome specific terms were ‘incidence’, ‘mortality’, ‘prevalence’, ‘survival’, ‘disease progression’, ‘PSA testing’ or ‘PSA screening’, ‘treatment’, ‘treatment complications’ and ‘recurrence’ (Figure 1). A further search was conducted through various internet search engines using the above search terms to identify any additional relevant publications such as government reports.

Potentially relevant articles were first identified by two reviewers examining the title and abstract. Those agreed upon as potentially meeting the selection criteria were retrieved for more detailed evaluation by one reviewer, in which an additional criterion was included to just consider those studies where geographical variation was described. In particular this excluded those studies that described the impact of individual-level socioeconomic variables (such as income) on prostate cancer outcomes. The references of selected articles were also reviewed for other potentially relevant articles. All study types addressing the criteria were included.

Each relevant article was summarised in table form by one reviewer identifying years studied, number of subjects/cases, outcome measures addressed, geographic unit of study, study type and main findings. This table was checked by a second reviewer with disagreements resolved

by discussion. No specific exclusions were made based on assessment of study quality.

Results

The process of identifying relevant articles for the review is outlined in Figure 1. The Medline search identified 881 articles. On examination of titles and abstracts, 664 were excluded, leaving 217 considered potentially relevant. The additional internet searches, investigator suggestions and reference search identified a further 51 relevant articles. In total, 268 potentially relevant articles were retrieved and summarised. Of these 91 were included in the review. Of the articles excluded, most did not specifically address geographic variations of the prostate cancer outcomes of interest, with many of the excluded papers relating to individual-level details of socioeconomic status or clinical variables, rather than area-level. In particular, while two studies (Gregorio et al., 2004; Johnson, 2004) described geographical variation in prostate cancer incidence, they did not provide sufficient information on rural or area disadvantage differentials to enable their inclusion.

PSA testing

Asymptomatic, as well as symptomatic, prostate cancer can be detected using PSA testing and Digital Rectal Examination (DRE). However there are very few country-specific estimates for the prevalence of PSA testing internationally and even fewer for DRE (Baade et al., 2009). What data is available suggests that PSA testing is most common in the United States, Australia and Canada, but becoming more common in several countries including Sweden and Japan (Baade et al., 2009). Consistent with the lack of country-specific data, there were only a relatively few studies reporting data on geographical differences in PSA testing. Of these, most reported that PSA testing was more common in urban areas or affluent areas (see Table 1).

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Query run on 22nd May, 2014 ("Prostate cancer"[All Fields]
OR "Prostatic neoplasms"[MeSH Terms]) AND ("Rural
health"[MeSH Terms] OR "urban health"[MeSH Terms]
OR "Geographic inequalities"[All Fields] OR Spatial[All
Fields] OR "Socioeconomic"[All Fields] OR ("vulnerable
populations"[MeSH Terms] OR ("vulnerable"[All
Fields] AND "populations"[All Fields]) OR "vulnerable
populations"[All Fields] OR "disadvantaged"[All Fields])
OR "health literacy"[MeSH Terms] OR "health services
accessibility"[MeSH Terms]) AND ("incidence"[MeSH
Terms] OR "mortality"[MeSH Terms] OR "prevalence"[MeSH
Terms] OR "survival"[MeSH Terms] OR "Disease
progression"[MeSH Terms] OR ("PSA testing"[All Fields]
OR "PSA screening"[All Fields]) OR ("therapy"[Subheading]
OR "therapy"[All Fields] OR "treatment"[All Fields]
OR "therapeutics"[MeSH Terms] OR "therapeutics"[All
Fields]) OR "treatment complications"[All Fields] OR
"prostatectomy"[All Fields] OR "brachytherapy"[All Fields]
OR "treatment"[All Fields] OR "recurrence"[MeSH Terms])
AND (("1998/01/01"[PDAT] : "2014/01/31"[PDAT]) AND
"humans"[MeSH Terms] AND English[lang])
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Figure 1. Electronic Search Strategy (www.pubmed.com)

United States: Based on the 2010 Behavioural Risk Factor Surveillance System (BRFSS) survey in the United States, and after adjusting for individual level variables, men living in urban areas had lower odds of screening for prostate cancer using either digital rectal exam or PSA tests, while men living in states with a lower prevalence of doctors had lower odds of having PSA tests (Garg et al., 2013). This is the reverse effect found in the 2001 version of the BRFSS, where men living in urban areas had higher prevalence of PSA testing (Jemal et al., 2005). In addition, based on a survey of men living in Maryland, USA, in 2006, Zhu and colleagues found that men living in urban areas were more likely to have repeated PSA tests (2 PSA tests in the preceding three years) than men in rural areas (Zhu et al., 2011).

Australia: Between 2001 and 2009, rates of PSA screening were higher among men living in capital cities of Australia versus the rest of the country, however even with this differential, more than 20% of the male population aged 50-79 living outside the capital cities had a PSA screening test (Baade et al., 2011). There were similar geographical differentials when considering both screening and monitoring PSA tests combined (Coory and Baade, 2005; Baade et al., 2011).

Canada: As part of the Canadian Community Health Survey in 2000/01, men aged 40 years and over living in the more rural areas of Canada were less likely to have had a PSA test in the last two years than men living in urban areas (Canadian Population Health Initiative, 2006).

United Kingdom: In a General Practitioner-based study in the United Kingdom, (Williams et al., 2011), of those men without a prior diagnosis of prostate cancer, men who lived in more deprived areas were less likely to have a PSA test in 2007 than men living in affluent areas.

Among an initially prostate cancer free cohort of nearly 100,000 men 40 years and over registered with a general practitioner in the Tayside region of Scotland, men living in affluent areas were more likely to have a PSA test between 2003 and 2008 than men living in disadvantaged areas (Morgan et al., 2013).

Incidence

At any given time, observed prostate cancer incidence reflects the combination of the underlying prevalence of undiagnosed disease, the inclination of men to be tested or screened for prostate cancer, and the capacity of the health care system to diagnose and report these

cases (Gregorio et al., 2004). In particular, geographical differences in the use of PSA testing has the potential to explain at least some of the geographical variation of prostate cancer incidence (Gregorio et al., 2004; Aarts et al., 2013; Gregorio and Samociuk, 2013). For example one study (Liu et al., 2001) reported no evidence of an area-based socioeconomic status incidence differential prior to 1987 (pre-PSA testing) however strong evidence of higher incidence in affluent areas after the introduction of PSA testing. However this effect has not been observed in all studies, with a UK study showing no apparent change in prostate cancer incidence between 1994 and 2003 despite an increase in the rate of PSA testing (Mokete et al., 2006). While the geographical pattern of prostate cancer incidence varied across countries and studies, the predominating pattern was for incidence to be higher among men in urban areas and more affluent areas (see Table 2), consistent with the PSA testing differential reported above.

United States: A study of localised stage prostate cancer incidence in the south-eastern United States found clusters with high relative risk of localised stage disease tended to occur in urban areas rather than rural areas, and this association remained after restricting the analyses to those areas with higher representation of either white or black men (Altekruse et al., 2010).

An analysis of the 1973-2001 Surveillance, Epidemiology, and End Results (SEER) data linked to the National Longitudinal Mortality Study, found that, after adjustment for a range of individual-level variables, there was no significantly increased risk of prostate cancer among residents of urban areas (Clegg et al., 2009). However, in a spatial analysis of prostate cancer risk in Louisiana, Mather and colleagues (Mather et al., 2006) reported that in their most recent time period (1997-1998), relatively low prostate cancer incidence rates persisted in central rural Louisiana for Caucasian males and central Louisiana and south coastal parishes for black males.

During the six year period of 1995-2000, there was an increase in prostate cancer incidence among men in USA corresponding to an increase in the degree of the counties' urbanisation (Jemal et al., 2005). There was no statistically significant urban:rural prostate cancer incidence differential for men living in the Mississippi in 1996 (Higginbotham et al., 2001).

Men living in the most affluent neighbourhoods (areas containing on average 1,500 residents) of California were

Table 1. Summary of Studies on Geographical Differentials in PSA Testing

Author, year	Location	Period	Cohort	Highest PSA testing
Urban : Rural differentials				
Baade et al., 2011	Australia	1982-2009	NS	Capital cities
Canadian Population Health Initiative, 2006	Canada	2000-2001	NS	Urban
Coory and Baade, 2005	Australia	1985-2003	NS	Capital cities
Garg et al., 2013	United States	2010	108,245	Rural
Jemal et al., 2005	United States	2001	NS	Metropolitan
Zhu et al., 2011	Maryland, United States	2006	1,721	Urban (repeated PSA tests)
Area disadvantage differentials				
Morgan et al., 2013	Scotland	2003-2008	96,484	Affluent areas
Williams et al., 2011	United Kingdom	2007	126,716	Affluent areas

*NS: Not stated

28% more likely to be diagnosed with prostate cancer between 1998 and 2002 than those living in the most disadvantaged neighbourhoods (Cheng et al., 2009). A similar finding for the same area and location was reported subsequently (Yin et al., 2010). Similarly, using the SEER data in the USA between 2000 and 2008, men living in affluent neighbourhoods were found to have a higher incidence of prostate cancer than those living in disadvantaged areas, (Yu et al., 2014a) while there was a consistent increasing gradient of annual prostate cancer incidence rates by increasing median household income for men living in Virginia between 1990 and 1999. (Oliver et al., 2006). A similar finding was reported for men in USA between 1988 and 1992, where men living in disadvantaged census tracts (higher poverty rate) had a lower prostate cancer incidence than those living in advantaged areas. (Singh et al., 2003) Finally, data from the large, prospective NIH-AARP Diet and Health study in the United States also showed that there was a significant decreasing gradient in prostate cancer incidence by area socioeconomic deprivation score among Caucasian males in America between 1995 and 2006, but not for African American men (Major et al., 2012). Within the

Los Angeles county of the United States, there was no association between area-level socioeconomic status and the incidence of prostate cancer prior to 1987, however once PSA testing became widely available after 1987 men living in affluent areas had higher incidence rates of prostate cancer (Liu et al., 2001).

In contrast to these other studies, a case control study in South Carolina (2000-2002) found that after adjustment for individual level variables, men living in the most affluent areas had a significantly lower risk of prostate cancer (Sanderson et al., 2006).

Australia: An analysis of prostate cancer incidence rates in Australia (Baade et al., 2011) found that the annual rural to urban incidence rate ratios fluctuated around or slightly below one between 1986 and 2005, suggesting similar incidence rates. An earlier report noted a significantly lower incidence in rural areas during the mid-late 1990s, however this differential subsequently decreased (Coory and Baade, 2005). However the authors suggested that the "rural" group (ie. those outside capital cities) contains a substantial proportion of men living on the outskirts of the capital city boundaries who experience similar access to diagnostic and treatment services as those

Table 2. Summary of Studies on Geographical Differentials in Prostate Cancer Incidence

Author, year	Location	Period	Cohort	Highest Incidence
Urban : Rural differentials				
AIHW, 2013b	Australia	2004-2008	NS	Inner Regional
Alam et al., 2009	NSW, Australia	2001-2005	24,333	Inner Regional
Altekruse et al., 2010	South East United States	1999-2011	66,468	Urban (localised disease only)
Baade et al., 2011	Australia	1982-2009	NS	No difference
Canadian Population Health Initiative, 2006	Canada	1986-1996	138,765	Urban
Clegg et al., 2009	United States	1973-2001	1,881	No difference
Coory and Baade, 2005	Australia	1985-2003	NS	Urban
Cramb et al., 2011a	QLD, Australia	1998-2007	2,522	Inner regional
Cramb et al., 2011b	QLD, Australia	1998-2007	NS	Regional
Higginbotham et al., 2001	Mississippi, United States	1996	1,501	No difference
Holowaty et al., 2010	Canada	1999-2003	NS	Little difference
Jarup et al., 2002	UK	1975-1991	24,457	No difference
Jemal et al., 2005	United States	1995-2000	NS	Urban
Marsa et al., 2008	Denmark	1994-2003	8,279	Urban
Mather et al., 2006	Louisiana, United States	1988-1999	31,159	Varies
Meijer et al., 2013	Denmark	2004-2008	14,612	No difference
NCIN, 2011	England	2004-2006	NS	Non-Urban
NCR and NICR, 2011	Ireland	1995-2007	NS	Least densely populated
Ocana-Riola et al., 2004	Granada, Spain	1985-1996	1,037	Urban
Oliver et al., 2006	Virginia, United States	1990-1999	37,373	Urban
Robson et al., 2010	New Zealand	2002-2006	13,139	Urban
Yu et al., 2014b	NSW, Australia	1982-2007	68,686	Inner regional and rural
Area disadvantage differentials				
Alam et al., 2009	NSW, Australia	2001-2005	24,333	Affluent
Aarts et al., 2013	Netherlands	1998-2008	12,706	Affluent
Cheng et al., 2009	California, United States	1998-2002	98,484	Affluent
Cramb et al., 2011a	QLD, Australia	1998-2007	2,522	Affluent
Cramb et al., 2011b	QLD, Australia	1998-2007	NS	Affluent
Liu et al., 2001	Los Angeles, United States	1972-1997	83,068	No difference (1972-1986) Affluent (1987-1997)
Major et al., 2012	United States	1995-2006	23,612	Affluent

*NS: Not stated; NY: New York State; SC: South Carolina

men living in capital cities (Baade et al., 2011). When considering the more detailed remoteness areas, a later publication demonstrated that, between 2004 and 2008, the highest prostate cancer incidence rate was experienced by men living in inner regional areas, with the lowest incidence rate being in remote and very remote areas (AIHW, 2013b). This latter result may reflect, at least in part, the lower prostate cancer incidence rates among all Australian Indigenous men, (Moore et al., 2010) who have greater representation in remote and very remote areas. This national result was also reflected in New South Wales studies, where the incidence of prostate cancer (adjusted for age) between 2001 and 2005 was significantly higher in Inner Regional areas compared with major cities, however there was no difference with the more remote areas (Alam et al., 2009). Between 1982 and 2007, the prostate cancer incidence rates were higher among men living in inner regional and rural areas compared with major cities (Yu et al., 2014b).

When considering socioeconomic area disadvantage, the age-standardised prostate cancer incidence rate was highest among Australian males living in the least disadvantaged areas and lowest among males living in the most disadvantaged areas (AIHW, 2013b). A similar pattern was also reported for New South Wales (Alam et al., 2009). There is also evidence of interaction between remoteness and area disadvantage, with Cramb and colleagues showing that prostate cancer incidence rates were highest among men living in Inner and outer regional areas, as well as affluent areas within major cities (Cramb et al., 2011b).

An analysis of prostate cancer incidence in Queensland, Australia between 1998 and 2007 (Cramb et al., 2011a) found strong evidence of geographical variation, with incidence being higher in most advantaged areas and lower in the most disadvantaged areas compared to the Queensland average. In addition, remote regions tended to have lower incidence rates compared to the Queensland average.

New Zealand: Between 2002 and 2006 in New Zealand, prostate cancer incidence was highest in urban areas compared to rural areas, particularly among non-Maori men. (Robson et al., 2010) While the authors reported no evidence of an association between incidence and area deprivation for non-Maori males, prostate cancer incidence was higher among Maori males living in deprived areas than those living in more affluent areas (Robson et al., 2010).

United Kingdom: In the United Kingdom, there was no evidence of marked geographical variation in prostate cancer incidence between 1975 and 1991, although there were some differences at a regional and small area level. (Jarup et al., 2002) Population density was not found to be a significant predictor of prostate cancer incidence (Jarup et al., 2002). Importantly, this was before the widespread introduction of PSA testing, and so provided evidence against a geographically varying environment factor for the development of prostate cancer (Jarup et al., 2002). A later study, looking at prostate cancer incidence rates in England between 2004 and 2006 found that men living outside urban areas had higher incidence rates than men

living in urban areas (NCIN, 2011). When comparing cancer incidence among South Asian migrants to England to the rest of the English population between 1986 and 2004, it was observed that among the combined cohort, prostate cancer incidence was higher among men living in affluent areas (Maringe et al., 2013).

A study in Scotland between 1991 and 2007 found that before 1998 there was little difference in prostate cancer incidence by area level socioeconomic status. However during the study period the rate of increase in prostate cancer incidence in affluent and intermediate areas was substantially higher than that for socioeconomically deprived areas, meaning that by 2003-2007 there was a significant gradient, with incidence rates higher among men living in affluent areas (Shafique et al., 2012). This latter finding was consistent with another study in the Tayside region of Scotland, where men living in affluent areas were more likely to be diagnosed with prostate cancer between 2003 and 2008 than men living in disadvantaged areas (Morgan et al., 2013).

In Ireland between 1995 and 2007 there was a weak relationship between prostate cancer incidence and population density, with men living in the least densely populated areas at greater risk. In addition, prostate cancer incidence among men living in areas with a smaller proportion of people with degree level qualifications was lower than in areas with higher proportions of people with degree level qualifications (NCR and NICR, 2011).

Canada: An analysis of prostate cancer incidence data from the Canadian Cancer Registry between 1986 and 1996 (Canadian Population Health Initiative, 2006) found higher rates among men living in urban areas compared with rural areas. A later study (1999-2003) conducted within the Ontario public health unit (Wellington-Dufferin-Guelph) found significantly higher prostate cancer incidence in the urban core of Guelph and the surrounding rural areas of Orangeville than the rest of the region, however the authors stated that there seemed to be little difference in risk depending on whether men lived in urban or rural areas (Holowaty et al., 2010).

Spain: Using cancer incidence data from Granada, Spain, the risk of being diagnosed with prostate cancer between 1985 and 1996 was higher in advantaged municipalities as defined by low illiteracy, and more urbanized areas (Ocana-Riola et al., 2004).

Netherlands: Using data from the South Netherlands Cancer Registry, Aarts and colleagues found that prostate cancer incidence between 1998 and 2008 was higher in those areas with higher socioeconomic status, and this disparity increased over time (Aarts et al., 2013).

Finland: Between 1971 and 1995 the incidence of prostate cancer in Finland was higher among men living in areas of higher social class than in areas defined as being of lower social class (Pukkala and Weiderpass, 2002).

Scandinavian countries: Men living in the Capital city areas of Denmark between 1994 and 2003 had a higher age-standardised prostate cancer incidence rate than men living in the provincial and rural areas of the country (Marsa et al., 2008). However, there was no association between the risk of Danish men aged 50-83 years being diagnosed with prostate cancer between 2004 and 2008

Table 3. Summary of Studies on Geographical Differentials in Advanced Stage Prostate Cancer

Author, year	Location	Period	Cohort	Highest advanced cancer
Urban : Rural differentials				
Clegg et al., 2009	SEER, USA	1973-2011	1,881	No difference
Haynes et al., 2008	New Zealand	1994-2004	25,078	Closest to cancer centres Closest to primary care
Holmes et al., 2012	NC, USA	2004-2005	2,251	Furthest from Urologists
Jemal et al., 2005	USA	1995-2000	NS	Rural
Jong et al., 2004	NSW, Australia	1992-1996	NS	Rural
Major et al., 2012	USA	1995-2006	22,523	Areas with fewer Urologists
McLafferty and Wang, 2009	Illinois, USA	1998-2002	42,291	Rural
Robson et al., 2010	New Zealand	1996-2006	29,185	No difference
Skolarus et al., 2013	USA	2008	11,368	No difference
Xiao et al., 2011	Florida, USA	1996-2002	60,289	Rural
Yu et al., 2014b	NSW, Australia	1982-2007	68,686	Rural
Area disadvantage differentials				
Byers et al., 2008	7 States, USA	1997	4,332	Disadvantaged
Chu et al., 2012	3 States, USA	1989-2010	2,502	Disadvantaged
Haynes et al., 2008	New Zealand	1994-2004	25,078	No difference
Liu et al., 2001	Los Angeles, USA	1972-1997	83,068	No difference (1972-1986) Disadvantaged (1987-1997)
Lyratzopoulos et al., 2010	UK	1998-2006	15,916	Disadvantaged
Niu et al., 2010	New Jersey, USA	1986-1999	69,417	Disadvantaged
Robson et al., 2010	New Zealand	1996-2006	29,185	Disadvantaged (non-Maori), equal (Maori)
Schwartz et al., 2003	Detroit, USA	1988-1992	11,896	Disadvantaged
Singh et al., 2003	USA	1975-1999	NS	Disadvantaged

*NS: Not stated; NC: North Carolina

and the population density of the neighbourhood in which they lived (Meijer et al., 2013).

Puerto Rico: Between 1992 and 2004, the incidence of prostate cancer was generally higher among men living in areas of higher socioeconomic status (Soto-Salgado et al., 2012).

Advanced stage cancer

The risk of mortality from prostate cancer is strongly influenced by the stage of the cancer at diagnosis, with survival outcomes being lowest when the cancer is diagnosed at an advanced stage (Yu et al., 2012; Howlader et al., 2013). Most of the published studies on geographical disparities in stage at diagnosis reported the risk of advanced prostate cancer was highest in rural areas or in areas furthest from or with fewer urologists, and in disadvantaged areas compared to affluent areas (see Table 3).

United States: Between 1988 and 1999, men living in the lowest poverty areas (affluent areas) of the United States had the highest percentage of local/regional staged cancers, while men living in high poverty areas (disadvantaged areas) had higher percentages of advanced cancers (Singh et al., 2003). In the Los Angeles county of the United States, there was no association observed between area-level socioeconomic status and the stage of prostate cancer for those diagnosed prior to 1987, however once PSA testing became widely available after 1987 men living in affluent areas were more likely to be diagnosed with localised and regional prostate cancers, but less likely to be diagnosed with distant disease (Liu et al., 2001).

Based on data from the North Carolina Physician Workforce study (men diagnosed in 2004-2005), men who lived further from a urologist were more likely to be

diagnosed with advanced prostate cancer (Holmes et al., 2012). There was no independent effect of urban:rural location on top of this distance effect (Holmes et al., 2012). A similar finding among African American men was reported from the prospective NIH-AARP Diet and Health study in the United States, where the risk of being diagnosed with advanced prostate cancer was higher in areas with fewer urologists; however no association was found for Caucasian American men (Major et al., 2012).

In an analysis of 1973-2001 SEER data linked to the National Longitudinal Mortality Study, Clegg and colleagues found that, after adjustment for a range of individual-level variables, there was no significantly increased risk of advanced prostate cancer among residents of urban areas compared to rural areas (Clegg et al., 2009).

In Illinois between 1998 and 2002, the risk of prostate cancer patients being diagnosed with advanced prostate cancer was lower among those living outside Chicago than those living in the city, although there was a slight increase in risk among the most isolated rural areas (McLafferty and Wang, 2009). The authors also found that the observed geographical differences resulted mainly from differences in the patients' age and racial composition, and the social and spatial characteristics of where they lived (McLafferty and Wang, 2009). This finding was consistent with a study of prostate cancer incidence across 30 cancer registries in the United States between 1995 and 2000, in which the incidence of late-stage disease was lower in non-metro areas than metro areas (Jemal et al., 2005), while in Florida between 1996 and 2002, men were more likely to be diagnosed with advanced stage disease when living in the 'Big Bend' region (one of the most rural regions) (Xiao et al., 2011).

In contrast, a study of US veterans diagnosed with prostate cancer in 2008 found no difference between urban or rural patients in relation to tumour grade or stage (Skolarus et al., 2013).

When considering area disadvantage, an analysis of men undergoing radical prostatectomy between 1989 and 2010 at several equal-access Veteran Affairs Medical Centres in California, Georgia and North Carolina found that men living in areas with lower socioeconomic status were more likely to have high grade disease than those men living in more affluent areas (Chu et al., 2012). An earlier study using data from the National Program of Cancer Registries Patterns of Care study in the United States found that of men diagnosed with prostate cancer in 1997, those living in disadvantaged areas were more likely to have more advanced stage cancer than those in affluent areas (Byers et al., 2008). The greater risk of men living in high poverty areas being diagnosed with advanced prostate cancers compared with men living in more affluent areas was also observed in New Jersey between 1986 and 1999, (Niu et al., 2010) and for men living in the Detroit area between 1988 and 1992 (Schwartz et al., 2003).

Australia: Between 1992 and 1996, incidence rates of advanced prostate cancer were higher in rural areas of New South Wales than urban areas. (Jong et al., 2004) Among prevalent cases between 1982 and 2007 in New South Wales, those living in inner regional or rural areas were less likely to have localised disease and more likely to be diagnosed with cancer of an unknown stage than cases in major cities (Yu et al., 2014b).

New Zealand: Although one study found that there was no significant evidence that men living in more socioeconomically deprived areas of New Zealand between 1994 and 2004 had greater risks of being diagnosed with advanced prostate cancer, (Haynes et al., 2008) another study, when splitting the results by Maori and non-Maori (Robson et al., 2010) reported that the chance of non-Maoris being diagnosed with distant staged prostate cancer between 2002 and 2006 increased with increasing deprivation. No such differential was observed for Maori men.

There was no evidence of an urban:rural differential in stage at diagnosis for prostate cancers diagnosed in New Zealand between 2002 and 2006 (Robson et al., 2010), nor was there any evidence that area socioeconomic disadvantage was associated with stage at diagnosis in New Zealand between 1994 and 2004 (Haynes et al., 2008). Surprisingly, men who lived the furthest distances from cancer centres in New Zealand tended to present with less advanced prostate cancer and those remote from primary care also tended to be diagnosed at an earlier stage than average (Haynes et al., 2008).

United Kingdom: In a study of men diagnosed with prostate cancer in UK, stage information was collected for those diagnosed between 1998 and 2006. (Lyratzopoulos et al., 2010) There was no difference in the ascertainment of stage by deprivation postcode. However, among those men with stage information collected, men living in more socioeconomically deprived postcodes were significantly more likely to have been diagnosed with advanced disease.

Survival

Any interpretation of geographical differences in prostate cancer survival needs to be considered in light of the impact of PSA testing. Typically, PSA testing increases the likelihood that many latent prostate cancers are included in the clinical population of prostate cancer patients, leading to observed disparities in survival when in reality they are an artefact of the less-aggressive cancers being detected (Hall et al., 2005). Of the studies included in this review, survival was typically higher among men living in urban centres or closest to cancer centres, and higher in affluent areas (see Table 4).

United States: Based on data from the SEER-11 cancer registries, men diagnosed with prostate cancer between 1988 and 1994 while living in high poverty census tracts had lower survival than men living in more affluent census tracts (Singh et al., 2003). This pattern held for older men diagnosed with prostate cancer, with men aged 65 years and over diagnosed with local or regional stage prostate cancer between 1992 and 1999 while living in disadvantaged areas being more likely to die from prostate cancer before the end of 2002 than those living in affluent areas, after adjustment for grade (Du et al., 2006). Men living in affluent areas of the United States when diagnosed with prostate cancer between 1973 and 1995 were shown to have better survival than those men in more disadvantaged areas (Mariotto et al., 2002).

Similarly, for men diagnosed with localised or regional prostate cancer in Detroit, USA between 1988 and 1992, those living in disadvantaged localities (more than 20% of households below poverty level) had poorer survival than those localities where more than a third of the employed persons were in supervisory or executive positions (Schwartz et al., 2009). This pattern by area disadvantage was also reported for men diagnosed with prostate cancer in Texas between 1995 and 2002, with higher survival in more affluent areas, however there was no significant difference by rural residence (White et al., 2011).

In contrast, a study considering men diagnosed with prostate cancer from seven states of USA in 1997 found no significant evidence of a Census-based poverty differential in survival, nor an urban:rural differential (Schymura et al., 2010).

Men diagnosed with prostate cancer while living in high poverty areas of New Jersey between 1986 and 1999 had poorer survival than men living in more affluent areas of the State, after adjustment for stage at diagnosis (Niu et al., 2010).

In Connecticut between 1984 and 1998, Gregorio and colleagues identified only one broad geographical cluster for which male residents diagnosed with prostate cancer had lower survival times (Gregorio et al., 2007). While the authors did not specifically mention the characteristics of the geographical cluster, comparisons with population density maps suggested it was a predominately high density area (Gregorio et al., 2007).

Australia: A comparison of prostate cancer survival for men living in capital cities of Australia and those living in the rest of Australia, (Baade et al., 2011) found that the survival differential increased over time, to the extent that

Table 4. Summary of Studies on Geographical Differentials in Prostate Cancer Survival

Author, year	Location	Period	Cohort	Highest Survival
Urban : Rural differentials				
AIHW, 2013a	Australia	2006-2010	NS	No difference
Baade et al., 2011	Australia	1982-2009	NS	Capital cities
Campbell et al., 2000	Scotland	1991-1995	6,833	Closest to cancer centres
Cramb et al., 2011a	QLD, Australia	1998-2007	2,522	Urban
Gregorio et al., 2007	Connecticut, USA	1984-1998	27,189	Lower density
Hall et al., 2005	WA, Australia	1982-2001	14,123	Urban
Jones et al., 2008b	Nth England	1994-2002	20,688	Closest to GP
Jong et al., 2004	NSW, Australia	1992-1996	NS	Urban
Robson et al., 2010	New Zealand	1996-2006	29,185	Urban
Schymura et al., 2010	7 States, USA	1997	3,297	No difference
Thursfield et al., 2010	Victoria, Australia	2006-2010	4,438	Capital city
White et al., 2011	Texas, USA	1995-2002	87,449	No difference
Yu et al., 2014b	NSW, Australia	1982-2007	68,686	Urban
Area disadvantage differentials				
Aarts et al., 2013	Eindhoven, Netherlands	1998-2008	11,086	Affluent
AIHW, 2013a	Australia	2006-2010	NS	Affluent
Coleman et al., 2004	England and Wales	1996-1999	73,921	Affluent
Cramb et al., 2011a	QLD, Australia	1998-2007	2,522	Affluent
Du et al., 2006	United States	1992-1999	61,228	Affluent
Hall et al., 2005	WA, Australia	1982-2001	14,123	Affluent
Haynes et al., 2008	New Zealand	1994-2004	25,078	No difference
Jones et al., 2008b	Nth England	1994-2002	20,688	Affluent
Mariotto et al., 2002	United States (SEER-9)	1973-1995	NS	Affluent
Niu et al., 2010	New Jersey, USA	1986-1999	69,417	Affluent
Robson et al., 2010	New Zealand	1996-2006	29,185	Affluent (non-Maori)
Rowan et al., 2008	England and Wales	1996-1999	201,000+	Affluent
Schwartz et al., 2009	Detroit, USA	1988-1992	8,679	Affluent
Schymura et al., 2010	7 States, USA	1997	3,297	No difference
Shafique et al., 2013	Scotland	1991-2007	15,292	Affluent
Singh et al., 2003	USA	1988-1994	NS	Affluent
White et al., 2011	Texas, USA	1995-2002	87,449	Affluent
Yu et al., 2014b	NSW, Australia	1982-2007	68,686	Affluent

*NS: Not stated; (s): Adjusted for some measure of spread of disease, including stage or Gleason score

men diagnosed with prostate cancer while living outside the capital cities were 24% more likely to die within 5 years of diagnosis. While these results were not adjusted for stage at diagnosis, two studies in New South Wales showed that the poorer survival for men living in rural and remote areas remained after adjustment for stage at diagnosis, for men diagnosed in 1992-1996 (Jong et al., 2004) and between 1982 and 2007 (Yu et al., 2014b). An analysis of Australian survival estimates between 2006 and 2010 reported no differential by remoteness for prostate cancer survival (AIHW, 2013a). In the same analysis, prostate cancer survival was shown to be lower among men living in socioeconomically disadvantaged areas of Australia than those cases in least disadvantaged areas, (AIHW, 2013a) a result that held in New South Wales even after adjustment for stage (Yu et al., 2014b). These were consistent with a study of 3-year all cause survival for men diagnosed with prostate cancer in Western Australia between 1982 and 2001, where men from socioeconomically disadvantaged groups or living in rural areas were also more likely to die; however, men in remote areas did not fare worse (Hall et al., 2005).

An analysis of prostate cancer survival in Queensland, Australia between 1998 and 2007 (Cramb et al., 2011a) found strong evidence of geographical variation, with survival being lower in the remote and outer regional

areas of the state compared to the Queensland average, and lower in areas of socioeconomic disadvantage.

In Victoria, Australia, residents of Melbourne, its capital city, diagnosed with prostate cancer between 2006 and 2010 had better survival than those living in the rest of the State (Thursfield et al., 2010).

New Zealand: Men diagnosed with prostate cancer in New Zealand between 1996 and 2006 while living in rural areas had worse survival than men living in urban areas of the country, after adjusting for stage. (Robson et al., 2010). In addition, men living in affluent areas had better survival than men living in disadvantaged areas, although the disparity was limited in non-Maori men (Robson et al., 2010). In contrast, another study found no significant evidence that living in more socioeconomically deprived areas of New Zealand between 1994 and 2004 had any association with prostate cancer survival (Haynes et al., 2008).

United Kingdom: Increasing distance from a cancer centre was associated with poorer survival for prostate cancer diagnosed in Scotland between 1991 and 1995. (Campbell et al., 2000). In addition, there was a persistent and increasing socioeconomic deprivation gap in Scotland between 1991 and 2007, with poorer survival among men living in areas of higher socioeconomic deprivation, after adjustment for age and Gleason grade (Shafique

and Morrison, 2013). This pattern, and increase in the differential, was also observed in England and Wales, with the result that prostate cancer survival was lower for those living in the most socioeconomically deprived areas than those living in more affluent areas between 1996 and 1999 (Coleman et al., 2004; Rowan et al., 2008) reflecting an increase in the differential since the late 1980s. Lower survival was also observed among men diagnosed with prostate cancer in Northern England between 1994 and 2002 while living in more deprived areas (Jones et al., 2008b). The same study found that men living further (by road) from their GP had poorer survival from prostate cancer than those living closer (Jones et al., 2008b).

Netherlands: Men diagnosed with prostate cancer in Eindhoven, Netherlands, between 1998 and 2008 while living in postcodes classed as affluent had better 10-year survival than those men living in more disadvantaged areas, even after stratifying by stage at diagnosis (Aarts et al., 2013).

Access and use of services

In addition to being important outcomes in their own right, having a better understanding of how men access prostate cancer related health services, or have the potential to access those services, can help guide our understanding of why disparities in the other outcomes exist. Most studies included in this review reported greater access or use of health services by men living in urban areas, while all studies reported greater access or use of services in affluent areas (see Table 5).

United States: While there has been a strong increase in the number of primary health providers and urologists per 1,000 habitants in Florida between 1981 and 2007, the increase was substantially greater among metropolitan counties compared to non-metropolitan counties (Goovaerts and Xiao, 2011).

Among men diagnosed with prostate cancer in seven states of the USA in 1997 (Schymura et al., 2010), there was no significant evidence that urban-rural residence was associated with the mode of initial treatment for prostate cancer, nor was there any urban:rural differential in prostate cancer survival. However, men living in census tracts that had higher education, or were classed as non-working class or non-poverty were more likely to be surgically treated (Schymura et al., 2010). A similar geographical disparity was reported by Singh and colleagues, who, when analysing data from the SEER-11 registries from 1995 to 1999, found that men residing in higher poverty areas when diagnosed with prostate cancer were less likely to undergo radical prostatectomy (Singh et al., 2003).

Of the US veterans diagnosed with prostate cancer in 2008, rural men were less likely to be treated at facilities with comprehensive cancer resources than urban men, although they received equivalent or better quality of care for most of the quality measures employed in the study (Skolarus et al., 2013). There was no urban-rural differential in the time to prostate cancer treatment, despite rural patients needing to travel further to access treatment (Skolarus et al., 2013).

An analysis of data from the National Program of

Cancer Registries Patterns of Care study in the United States found that of men diagnosed with prostate cancer in 1997, those living in low socioeconomic status areas were less likely to have been treated by either radical prostatectomy or radiation therapy than men in high socioeconomic status areas (Byers et al., 2008).

For older men (65 years and over) diagnosed with prostate cancer in the United States between 1991 and 2005, men living in areas with lower education and income were more likely to be treated with androgen deprivation therapy (Gilbert et al., 2011).

An adjusted analysis of SEER data in the United States found that men diagnosed with prostate cancer between 2004 and 2006 and living in rural areas were less likely to receive definitive treatment for their early-stage prostate cancer than those living in urban areas (Baldwin et al., 2013).

United Kingdom: Several studies have used a measure of cancer diagnosis at death as an indication of access to services. (Campbell et al., 2000; Jones et al., 2010) Jones and colleagues found that in northern England, the odds of a post-mortem diagnosis of prostate cancer increased with distance to the nearest cancer centre, and also for men living in rural areas, while men living closest to a frequent bus service were less likely to be diagnosed at death (Jones et al., 2010). No similar difference for prostate cancer was found in Scotland between 1991 and 1995 (Campbell et al., 2000).

An analysis of men diagnosed in the north of England between 1994 and 2002 found that men living in areas of least deprivation were more likely to have any kind of treatment, and specifically more likely to have radiation treatment than men living in areas of deprivation (Jones et al., 2008a).

Among men aged over 50 and diagnosed with prostate cancer between 1995 and 2006 in the United Kingdom, those from more socioeconomically disadvantaged postcodes were substantially less likely to be treated with radical surgery or radiotherapy than men living in more affluent areas (Lyratzopoulos et al., 2010).

Australia: While the rates of radical prostatectomy have increased sharply in Australia between 1995 and 2010, men living in regional and rural areas of the country continued to be significantly less likely to have a radical prostatectomy than their capital city counterparts (Baade et al., 2011). A study in Western Australia found a lower rate of radical prostatectomy surgery for men diagnosed with prostate cancer (1982-2001) who lived in more socioeconomically disadvantaged areas, whereas the lower rate among rural residents was not statistically significant (Hall et al., 2005).

A study of nearly 40,000 men diagnosed with prostate cancer in New South Wales, Australia, between 1993 and 2002 found that those residents of rural areas at diagnosis or in more socio-economically disadvantaged areas were significantly less likely to undergo a radical prostatectomy after adjusting for age and disease stage (Hayen et al., 2008). Contrasting geographical patterns held for the use of orchiectomy, with rates higher in rural areas and socioeconomically disadvantaged areas.

Netherlands: When examining the treatment patterns

Table 5. Summary of Studies on Geographical Differentials in Access and Use of Services

Author, year	Location	Period	Cohort size	
Urban : Rural differentials				
Baade et al., 2011	Australia	1995-2010	NS	Capital city more likely to have surgical treatment
Baldwin et al., 2013	SEER, United States	2004-2006	51,982	Rural areas less likely to receive definitive treatment for early stage prostate cancer
Campbell et al., 2000	Scotland	1991-1995	6,833	No difference in likelihood of diagnosis at death
Goovaerts and Xiao, 2011	Florida, United States	1981-2007	226,435	Greater incidence of clinicians in metro areas
Hall et al., 2005	WA, Australia	1982-2001	14,123	No difference in surgical treatment
Hayen et al., 2008	NSW, Australia	1993-2002	33,200	Rural areas less likely to undergo radical prostatectomy, and more likely to have orchiectomy.
Jones et al., 2010	United Kingdom		20,997	Rural areas more likely to be diagnosed at death
Schymura et al., 2010	United States	1997	3,328	No difference in initial treatment
Skolarus et al., 2013	United States	2008	11,368	Rural less likely to be treated at comprehensive facilities. No difference in quality of care or time to treatment
Area disadvantage differentials				
Aarts et al., 2013	Netherlands	1998-2008	11,086	Affluent areas more likely to have prostatectomy and brachytherapy Affluent areas less like to have external beam radiotherapy, hormonal therapy and watchful waiting.
Byers et al., 2008	USA	1997	4,332	Affluent areas more likely to have surgical or radiation therapy
Gilbert et al., 2011	United States	1991-2005	28,053	Androgen deprivation therapy greater in areas with lower income and education.
Hall et al., 2005	WA, Australia	1982-2001	14,123	Affluent areas more likely to have surgical treatment
Hayen et al., 2008	NSW, Australia	1993-2002	33,200	Affluent areas more likely to undergo radical prostatectomy, and less likely to have orchiectomy.
Jones et al., 2008a	Northern England	1994-2002	20,688	Affluent areas more likely to have any treatment Affluent areas more likely to have radiation treatment
Lyratzopoulos et al., 2010	UK	1995-2006	35,171	Affluent areas more likely to have surgical or radiation treatment
Schymura et al., 2010	United States	1997	3,328	Affluent areas more likely to be surgically treated
Singh et al., 2003	SEER, United States	1995-1999	NS	Highest frequency of radical prostatectomy being in the most affluent areas

*NS: Not stated

of over 11,000 men newly diagnosed with prostate cancer in Eindhoven, Netherlands, between 1998 and 2008, Aarts and colleagues found that men living in affluent areas were more likely to have prostatectomy and brachytherapy, but less likely to have external beam radiotherapy, hormonal therapy and watchful waiting (Aarts et al., 2013).

Mortality

While survival can be influenced by lead time bias, particularly as an artefact of PSA testing or screening, mortality is considered a more valid end point. Differences in prostate cancer mortality rates, which take changes in population into effect, either over time or geographically, can be influenced by the severity of the cancer, the diagnosis, management and treatment of the cancer, and individual characteristics of the cancer (AIHW, 2013b). Of the studies considered in this review, mortality due to prostate cancer was typically higher in rural/regional/farming areas and in socioeconomically disadvantaged areas (see Table 6).

United States: While there was little if any area deprivation variation in prostate cancer mortality rates in the United States between 1975 to 1989, from 1990 to 1999 there was a widening of the area socioeconomic gradient, meaning that men living in areas with highest deprivation experienced higher prostate cancer mortality rates than men living in more affluent areas (Singh et

al., 2003). This pattern has continued. Across America between 2003 and 2007, men in more deprived groups and in rural areas had significantly higher prostate cancer mortality rates than their more affluent and urbanized counterparts, respectively, with area deprivation showing a four-fold greater impact on prostate cancer mortality than urbanisation, and more pronounced in urban areas. (Singh et al., 2011). However, even after adjusting for deprivation, there was still a significantly higher prostate cancer mortality rate in rural areas (Singh et al., 2011). Between 2001 and 2005, prostate cancer mortality rates in the United States were highest in counties classified as non-metropolitan, those with lower median per capita income, along with those with no urologist practicing in their county (Odisho et al., 2010). A similar rural differential in prostate cancer mortality was observed across states in United States between 2000 and 2003, with higher prostate cancer mortality rates observed among areas with lower urologist population density and urbanisation, (Colli and Amling, 2008) while there was also support for a reverse rural-urban gradient (i.e. high mortality in rural areas) in prostate cancer mortality across the United States between 1968 and 1998 (Rogerson et al., 2006). Higher prostate cancer mortality rates were also reported for rural areas in Mississippi in 1996 compared to urban areas (Higginbotham et al., 2001).

Several studies have consistently found that prostate

Table 6. Summary of Studies on Geographical Differentials in Prostate Cancer Mortality

Author, year	Location	Period	No. deaths	Highest Mortality
Urban : Rural differentials				
AIHW, 2013b	Australia	2006-2010	NS	Inner and Outer regional areas
Alam et al., 2009	NSW, Australia	2001-2005	4,776	Outer regional areas
Baade et al., 2011	Australia	1985-2007	NS	Non-capital cities
Colli et al., 2008	United States	2000-2003	NS	Rural
Canadian Population Health Initiative, 2006	Canada	1986-1996	NS	Rural
Coory and Baade, 2005	Australia	1985-2002	NS	Non-capital cities
Devesa et al., 1999	United States	1970-1994	NS	Less populated areas
Higginbotham et al., 2001	MS, USA	1996	430	Rural
Jemal et al., 2002	USA	1970-1989	453,896	Rural
Lagace et al., 2007	Canada	1986-1996	NS	Rural
Lagace et al., 2007	Australia	1997-1999	NS	Regional
NCIN, 2011	England	2004-2006	NS	Non-Urban
Odisho et al., 2010	USA	2001-2005	NS	Non-metropolitan
Pampalon et al., 2006	Quebec, Canada	1998-2000	NS	No difference
Robson et al., 2010	New Zealand	2002-2006	2,850	No difference (non-Maori) Small towns (Maori)
Rogerson et al., 2006	United States	1968-1998	NS	Rural
Rusiecki et al., 2006	USA	1975-2000	NS	Rural
Singh et al., 2011	USA	2003-2007	NS	Rural
Smailyte and Kurtinaitis, 2008	Lithuania	1993-2004	NS	No difference
Yang and Hsieh, 1998	Taiwan	1982-1991	NS	Urban
Area disadvantage differentials				
AIHW, 2013b	Australia	2006-2010	NS	Disadvantaged
Alam et al., 2009	NSW, Australia	2001-2005	4,776	No difference
Cheng et al., 2009	California, USA	1999-2001	8,997	Disadvantaged
Dupont et al., 2004	Quebec, Canada	1994-1998	1,396	No difference
Jemal et al., 2002	USA	1970-1989	453,896	No difference
Martinez-Beneito et al., 2013	Spain	1996-2003	NS	No difference
Morgan et al., 2013	Scotland	2003-2008	822	No difference
Odisho et al., 2010	USA	2001-2005	NS	Areas with lower per capital income
Pukkala and Weiderpass, 2002	Finland	1971-1995	3,020	Higher social class areas
Robson et al., 2010	New Zealand	2002-2006	2,851	Disadvantaged areas (non-Maori), no difference (Maori).
Romeri et al., 2007	England and Wales	1999-2003	NS	Affluent
Singh et al., 2003	USA	1995-1999	165,417	Disadvantaged
Singh et al., 2011	USA	2003-2007	NS	Disadvantaged
Soto-Salgado et al., 2012	Puerto Rico	1992-2004	NS	Disadvantaged
Tovar-Guzman et al., 1999	Mexico	1980-1995	32,349	Areas with greater industrial and socioeconomic development
Wan et al., 2011	Texas, USA	1996-2004	14,036	Disadvantaged (Small areas) Affluent (Counties)

*NS: Not stated; MS: Mississippi

cancer mortality rates in the United States were highest in the lower population-density US Northern Plains states (Devesa et al., 1999; Jemal et al., 2002; Rusiecki et al., 2006).

The geographical variation observed in prostate cancer mortality rates between 1970 and 1989 in the United States could not be explained by the selected area-based demographic and socioeconomic factors (Jemal et al., 2002). There were, however, significant area-level socioeconomic disparities in prostate cancer mortality in Texas between 1996 and 2004, with higher prostate cancer mortality observed in least advantaged groups (Wan et al., 2011). Importantly though, this effect only held for the small block groups and tract level indicators, and when using the broader county level information the association reversed, with white men living in the least advantaged counties being less likely to die from prostate cancer (Wan et al., 2011).

Australia: The prostate cancer mortality rates in areas outside the capital city areas of Australia have been shown to be higher than for the rest of Australia (Coory and Baade, 2005; Baade et al., 2011). In addition, mortality disparity has increased gradually over that period (Baade et al., 2011). When separating these broad geographical categories further, a later analysis of prostate cancer mortality between 2006 and 2010 in Australia found that the higher mortality rates was primarily among males living in Inner regional and Outer regional areas, while there was little difference with the mortality rate in remote and very remote areas (AIHW, 2013b). This pattern was also observed in Australia during 1997-1999. (Lagace et al., 2007). A national study of prostate cancer mortality (AIHW, 2013b) reported that prostate cancer mortality was highest in the most disadvantaged areas of the county between 2006 and 2010. In contrast, an earlier study in New South Wales looking at prostate cancer mortality

between 2001 and 2005 found no significant variation in mortality by area socioeconomic disadvantage, while significant variation in remoteness by mortality was limited to higher mortality in outer regional areas compared to major cities (Alam et al., 2009).

Canada: Compared to metropolitan areas, prostate cancer mortality in Canada between 1986 and 1996 was elevated in all rural areas except those closest to the metropolitan areas (Lagace et al., 2007). A similar result based on access to metropolitan areas for the same period was reported elsewhere (Canadian Population Health Initiative, 2006). An earlier study in Quebec, Canada, reported no significant difference in prostate cancer mortality by area-based deprivation levels during 1994 and 1998. (Dupont et al., 2004), nor was there any evidence of an urban:rural differential in prostate cancer mortality in Quebec between 1998 and 2000 (Pampalon et al., 2006).

New Zealand: Between 2002 and 2006, the mortality rate due to prostate cancer was highest in the more disadvantaged areas, primarily among non-Maori men, and lowest in the most affluent areas (Robson et al., 2010). The same study reported no difference in prostate cancer mortality by urbanisation for non-Maori men, however there was increased mortality due to prostate cancer among men living in independent urban areas (i.e. small towns) than in main urban areas (Robson et al., 2010).

Mexico: The increasing prostate cancer mortality trends in Mexico between 1980 and 1995 were characterised by higher mortality rates in areas with greater industrial and socioeconomic development (Tovar-Guzman et al., 1999).

Puerto Rico: Between 1992 and 2004, the mortality due to prostate cancer was higher among men aged 55-64 years living in more disadvantaged areas than similarly aged men living in affluent areas, although the disparity for all ages combined did not reach statistical significance (Soto-Salgado et al., 2012).

United Kingdom: The mortality rates from prostate cancer in England and Wales between 1999 and 2003 showed only a slight inverse relationship between area deprivation, with mortality rates in the most deprived areas being significantly lower than in the most affluent areas (Romeri et al., 2007). A later study, looking at prostate cancer mortality rates in England between 2004 and 2006, found that men living outside urban areas had higher mortality rates than men living in urban areas (NCIN, 2011).

Among cohort of nearly 100,000 men 40 years and over who were originally prostate cancer free while registered with a general practitioner in the Tayside region of Scotland, there was no difference in the mortality rate due to prostate cancer between 2003 and 2008 between deprivation groups (Morgan et al., 2013).

Spain: Within the MEDEA (Socioeconomic and environmental inequalities in mortality in small areas in Spanish cities) project, investigations of the geographical distribution of mortality due to prostate cancer (among other causes of death) in eleven of the largest cities in Spain between 1996 and 2003 found no evidence of an association between area deprivation and prostate cancer mortality (Martinez-Beneito et al., 2013).

Finland: Between 1971 and 1995 the mortality due to

prostate cancer in Finland was higher among men living in areas of higher social class than in areas defined as being of lower social class (Pukkala and Weiderpass, 2002).

Taiwan: In Taiwan between 1982 and 1991, the mortality caused by prostate cancer in urban areas was higher than that among men in rural areas (Yang and Hsieh, 1998).

Lithuania: Between 1993 and 2004, there was no difference in prostate cancer mortality rates between men living in urban and rural areas (Smailyte and Kurtinaitis, 2008).

Discussion

This review found very strong evidence that prostate cancer outcomes are associated with where men live. This finding is of key importance for prostate cancer researchers and health care providers, government and the broader community. Specifically, while there was some discordance between the studies, the general patterns were that men living in urban or affluent areas had higher rates of PSA testing, higher prostate cancer incidence, lower risk of advanced prostate cancer, better survival, greater access or use of medical services and lower mortality than men living in rural or disadvantaged areas respectively. With increasing stakeholder and media attention, and the implementation of health policies and programs designed to reduce the urban-rural inequality, (Newman et al., 2006) it could be anticipated that the magnitude of the differential in prostate cancer outcomes would reduce over time. However there are several studies suggesting that, if anything, the opposite has been occurring (Singh et al., 2003; Coleman et al., 2004; Rowan et al., 2008; Baade et al., 2011; Yu et al., 2014b). Given the high prevalence of prostate cancer in the developed world and increasing incidence in Asia, these substantial and increasing disparities are a cause for local, national and global action, and highlight the importance of designing and assessing targeted interventions to reduce the disparities.

It has been demonstrated that the ability to detect geographical variation in outcomes, including prostate cancer incidence and mortality, can depend on the geographical level being used, such as States, counties or Census tracts (Krieger et al., 2002; Gregorio et al., 2006; Meliker et al., 2009; Wan et al., 2011). Studies based on area-level socioeconomic indicators may lead to an underestimate of the true disparity in prostate cancer mortality, principally because of the increased heterogeneity of socioeconomic conditions as the size of the geographical area increases (Wan et al., 2011). Not only can the magnitude of the observed socioeconomic disparity depend on the choice of geographical area, but also the direction of the effect (Wan et al., 2011). While investigations into geographic health disparities need to look beyond just the urban/rural split (McLafferty and Wang, 2009), because the greatest differences can be areas that straddle the typical urban/rural divide, this can be difficult to achieve in practice. This is particularly so when using administrative or registry data, where temporal changes in geographical classifications (Baade et al., 2011) or privacy concerns mean that broader rather than

precise geographical areas need to be analysed. However there remains a need to focus geographical investigations on the smallest available geographical classification, and importantly to recognise the potential for misclassification of geographical patterns the larger the geographical areas are.

The lack of consistency across studies extends to how area disadvantage is measured. The assessment of area-disadvantage is based on different measures between studies, including the Socio-economic Index For Areas (SEIFA) in Australia (ABS, 2008), the Carstairs deprivation scores in the UK (Romero et al., 2007) and the US deprivation index, (Singh et al., 2011) each of which are developed using different methods and variable sets. We are not aware of any study that has systematically compared the impact of using the different measures within the one geographical jurisdiction. Efforts to either quantify this impact, or standardise the measures across countries should be a priority if we are to better understand the impact of area disadvantage on health outcomes from an international perspective.

There is little doubt that differential access to screening or early diagnosis probably contributes to the geographical variation in survival for prostate cancer, (Coleman et al., 2004; Gregorio et al., 2004; Jong et al., 2004; Rowan et al., 2008; Cheng et al., 2009; Yu et al., 2014b) and the results of this review are consistent with areas having increased rates of PSA testing also having better survival. This is likely due to the combination of lead time bias through the detection of incident cases earlier, the detection of prostate cancers that have low potential to progress to cause symptoms, and the ability to treat localised cancers curatively through surgery. However, the persistence in the survival differential after adjustment for stage in several studies, (Jong et al., 2004; Schwartz et al., 2009; White et al., 2011; Shafique and Morrison, 2013; Yu et al., 2014b) along with treatment differentials by geographical location (Lyratzopoulos et al., 2010; Baade et al., 2011) suggest that treatment variation may also be important in explaining at least some of the survival disparities (Jong et al., 2004; Chu and Freedland, 2010). It has been identified that further research is needed to understand whether differences in comorbidities or treatment explain the observed inequalities in prostate cancer outcomes (Shafique et al., 2012).

The inconsistent geographical definitions used across studies, even those within the same country, pose a limitation in any summary of the geographical differentials and make a specific meta-analysis impossible to conduct (Obertova et al., 2012). There were also various statistical methods used, making comparisons across studies difficult. We have deliberately not reported risk estimates in this review for specific studies due to the inherent difficulty and questionable validity of comparing risk estimates across study types.

The majority of studies included in this review were from developed countries. Even though there is socioeconomic variation within these countries, from a global perspective these included studies represent the more affluent areas of the world, rather than a fully global perspective of the burden of prostate cancer. The lack of

published information for more disadvantaged cancers is due in part to the higher importance of other diseases in these countries, in addition to the lack of systematic population-based data collection processes.

While our intent was to conduct a comprehensive literature review, we acknowledge that we may have missed published studies that have reported on geographical differences in prostate cancer outcomes. There are many published reports and peer-reviewed manuscripts that are intended to describe the epidemiology of all cancer types, but only include incidental comments in the text or tables specifically relating to geographical variation in prostate cancer, rather than in the titles, abstracts or summaries. As such these may not have all been identified through our search strategy, however by also searching through reference lists of included publications we have endeavoured to minimise the impact of this gap.

As well, we have not included studies dealing specifically with quality of life in our analysis. Typically these studies involve the completion of questionnaires to assess quality of life among patients, and so the outcomes are reported more based on individual-level measures of socioeconomic status rather than ecological measures. In addition we felt that the breadth of measures relating to quality of life issues were different in scope and context to those of standard population-based measures of disease burden such as incidence, treatment, survival and mortality. This is an area for future research.

Importantly, the studies included in this review only provide evidence about the observed associations between remoteness, area-level socioeconomic status and prostate cancer outcomes. They do not establish causality or provide significant insight into why these associations exist (Wan et al., 2011). For this reason, more complex and comprehensive research studies are required if we are going to better understand these reasons and hence guide future interventions designed to reduce these disparities.

The example from the US Veterans database has the potential to provide optimism that the differences can be reduced, in that while rural US Veterans who have poorer access to comprehensive oncology resources than their urban counterparts still receive a similar quality of care to urban patients (Skolarus et al., 2013). However this needs to be balanced by the implications of the specific characteristics unique to US veterans, in which they are generally more educated and financially better off than the general US population (Morgan et al., 2005). In addition, the substantial variation in geographical and health system environments between countries limits the ability to directly extrapolate the findings to other jurisdictions.

In a context of increasing demand on already stretched health budgets, combined with generally better outcomes for hospitals having high caseload, the ability to provide patients living in more remote and less populated areas will remain difficult. One innovation that has intuitive appeal is the use of telemedicine, in which specialist medical oncologists and other clinicians can provide consultations to patients through videoconferencing, removing the barrier of travelling for both the clinicians and their patients (Sabesan and Piliouras, 2009; Saliba et al., 2012). However it is important not to view increasing

available technology as the only solution without recognising the complexity of the issues involved. A recent Australian study of rural men treated with radical prostatectomy that found the influence of stoic attitudes and normative expectations provided greater challenges to seeking support than simply increasing service provision (Corboy et al., 2014).

There has been increasing interest in the context in which individuals live, work and play, and its impact on the health of those individuals (Dixon and Welch, 2000). This is covered within a framework called the *Social Determinants of Health*, which refers to the economic, social and cultural factors that influence individual and population health directly and indirectly, through their impact on psychosocial and biophysiological responses (Dixon and Welch, 2000). These factors are by definition complex and multifaceted, and it has been recognised that previous approaches to reduce inequalities in cancer outcomes have not adequately addressed the interplay between community- and individual-level factors that can influence our health and health behaviours, and so have failed to have an impact on reducing these inequalities (King et al., 2010).

In a review of the role of group or macro level variables in the determination of disease in a population, Frohlich and colleagues (Frohlich et al., 2001) identified two key constructs: *space* and *place*. The study of *space* identifies quantifiable attributes of a particular area, such as the number of full time equivalent general practitioners who work in the area, or the average income of resident individuals. The study of *place* however is primarily concerned with processes, including the social and economic relations that join together within areas, such as community norms and attitudes that may influence why people access general practitioners or the barriers to finding employment. Studies of *place* provide unique insights into what it is like to live in a specific community. For men living in rural communities, this may need to include the implications of having lower utilisation of general practitioners (Turrell et al., 2004), the differing views of health generally compared to men living in urban areas, (Smith, 2012) and the implications that a lack of anonymity in smaller towns may have on discussing sensitive health topics.

Typically, epidemiological studies such as those included in this review tend to focus on the role of space, but are unable to examine the equally important role of *place* in identifying potential reasons for geographical inequalities. Therefore future studies that aim to understand why these inequalities exist may need to utilise a mixed methods approach, in which the quantifiable attributes of the individuals living within areas are measured along with the characteristics of the areas themselves, but importantly include a qualitative examination of the lived experience of people within those areas, or *place*.

It is crucial that these studies be conducted across contexts. While examining the differentials in rural and remote areas of large countries such as Australia and the USA may provide more informative scales of difference than for small countries such as the UK, restricting future studies to these countries would limit our potential to

appropriately understand the complex reasons for these differentials. Depending on the specific barriers to appropriate prostate cancer diagnosis and management, accessing appropriate services may be just as difficult for a man living within fifty kilometres of a medical centre in the UK as one living within 500 kilometres in Australia.

Finally, dialogue between clinicians, epidemiologists, policy advocates and disease control specialists is essential when discussing data requirements and methods of disease surveillance if we are to better understand the important factors that influence the differing burden of prostate cancer according to where men live (Gregorio and Samociuk, 2013). The extent to which this focussed multidisciplinary approach is facilitated will likely influence the amount by which these disparities can be reduced.

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