



Rural dwellers are less likely to survive cancer – An international review and meta-analysis

Romi Carriere^a, Rosalind Adam^a, Shona Fielding^a, Raphae Barlas^a, Yuhan Ong^b, Peter Murchie^{a,*}

^a Institute of Applied Health Sciences, University of Aberdeen, Foresterhill, AB25 2ZD Aberdeen, Scotland, United Kingdom

^b Western General Hospital, EH42XU Edinburgh, Scotland, United Kingdom

ABSTRACT

Background: Existing research from several countries has suggested that rural-dwellers may have poorer cancer survival than urban-dwellers. However, to date, the global literature has not been systematically reviewed to determine whether a rural cancer survival disadvantage is a global phenomenon.

Methods: Medline, CINAHL, and EMBASE were searched for studies comparing rural and urban cancer survival. At least two authors independently screened and selected studies. We included epidemiological studies comparing cancer survival between urban and rural residents (however defined) that also took socioeconomic status into account. A meta-analysis was conducted using 11 studies with binary rural:urban classifications to determine the magnitude and direction of the association between rurality and differences in cancer survival. The mechanisms for urban-rural cancer survival differences reported were narratively synthesised in all 39 studies.

Findings: 39 studies were included in this review. All were retrospective observational studies conducted in developed countries. Rural-dwellers were significantly more likely to die when they developed cancer compared to urban-dwellers (HR 1.05 (95% CI 1.02 – 1.07)). Potential mechanisms were aggregated into an ecological model under the following themes: Patient Level Characteristics; Institutions; Community, Culture and Environment; Policy and Service Organization.

Interpretation: Rural residents were 5% less likely to survive cancer. This effect was consistently observed across studies conducted in various geographical regions and using multiple definitions of rurality. High quality mixed-methods research is required to comprehensively evaluate the underlying factors. We have proposed an ecological model to provide a coherent framework for future explanatory research.

Funding: None.

1. Introduction

There is growing evidence that rural dwellers might face a survival disadvantage after a cancer diagnosis. This association has been observed across multiple heterogeneous studies, conducted in numerous countries (Peng et al., 2016; Bonett et al., 1990; Campbell et al., 2000; Liff et al., 1991; Ngoma et al., 2016). However, the effects of rurality on cancer survival have not been systematically evaluated. This paper presents the first comprehensive systematic review of the global literature seeking to establish whether rural residence is associated with increased cancer-related mortality and the magnitude of any observed effect.

Differences in health outcomes between urban and rural populations have been described in a number of health conditions, and to date survival/health outcomes related to cancer have been the most extensively researched (Smith et al., 2008). Rurality has been associated with negative impacts on cancer outcomes in studies from the United Kingdom and elsewhere (Campbell et al., 2000; Coory et al., 2006;

Coughlin et al., 2008; Jones et al., 2008a; O'Brien et al., 2000; Pozet et al., 2008; Underhill et al., 2006; Westeel et al., 2007). However, as with rural health disadvantage overall, the underlying causes are uncertain (Turner et al., 2017). There is some evidence that rural populations are less likely to engage with screening services and receive lower rates of chemotherapy and surgery (Jones et al., 2008a; Campbell et al., 2002; Jones et al., 2008b; Lin et al., 2015; Murage et al., 2017). If restricted access to services was the major determinant of poorer cancer outcomes for rural populations, this should also be reflected in longer delays to diagnosis and treatment for cancer for those patients living more remotely. However, a recent study from the Northeast of Scotland contradicts this, finding that rural patients in Scotland were diagnosed and treated for their cancers quicker than their urban counterparts, but died earlier (Turner et al., 2017). Other studies have demonstrated equivalent outcomes between rural and urban-dwellers for certain cancers, and in some cases superior outcomes in rural areas (Bennett et al., 2007; Dasgupta et al., 2012). It is possible that these contradictory findings result from important differences between cancer sites,

* Corresponding author.

E-mail addresses: r01rac16@abdn.ac.uk (R. Carriere), rosalindadam@abdn.ac.uk (R. Adam), s.fielding@abdn.ac.uk (S. Fielding), raphae.barlas.13@aberdeen.ac.uk (R. Barlas), arielyhong@doctors.org.uk (Y. Ong), p.murchie@abdn.ac.uk (P. Murchie).

<https://doi.org/10.1016/j.healthplace.2018.08.010>

Received 29 May 2018; Received in revised form 15 August 2018; Accepted 22 August 2018

1353-8292/ © 2018 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

but equally, they may also have resulted from inadequately controlling for important socio-demographic factors in the analyses.

Any assessment of the impact of rurality on disease outcomes is incomplete without also considering and adjusting for socioeconomic status (SES) or area deprivation. Areas of deprivation are known to cluster geographically. SES is an important determinant of poorer health outcomes in its own right and it is likely that rurality and deprivation could interact to lead to greater disadvantage through lack of access to appropriate healthcare (Reijneveld et al., 2000). While investigating the effect or rurality, the SES must be considered.

In this complex milieu, it is not yet possible to determine how health services can be best configured to ensure equality in urban-rural cancer outcomes. It has been argued that systematically reviewing existing research to map the extant knowledge base is the essential first step to providing policy-relevant evidence (Smith et al., 2008). The current study aimed to systematically review the literature in order to evaluate and quantify the association between place of residence (urban or rural) and overall cancer survival. The secondary aim was to narratively synthesise potential explanatory mechanisms.

2. Methods

2.1. Search strategy and selection criteria

A systematic review conducted to identify epidemiological studies which reported on the differential impact of place of residence (urban vs rural) on cancer survival. The review was conducted in line with the Cochrane Handbook and according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidance [PRISMA GUIDANCE]. A review protocol was registered and is available at: https://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42016051949.

There were three groups of search terms relating to cancer, survival, and geography or place of residence. Keywords and Boolean operators were explored and combined on the advice of a senior medical librarian. Keywords and Boolean operators were explored and combined on the advice of a senior medical librarian. MEDLINE, CINAHL and EMBASE (1946 to August 2016) were searched in September 2016 and an updated search was conducted in December 2017 to cover the period September 2016 to June 2017. Detailed search strategies and dates are shown in Appendix 1. Reference lists of included papers were also screened, and key journals were manually screened over the last year to ensure that no other papers were missed.

2.2. Inclusion and exclusion criteria

Included studies were quantitative observational studies, which compared survival from any cancer between rural areas and other geographical settings, and which made adjustments in the full survival analysis for socioeconomic status. Excluded studies were other systematic reviews, qualitative studies, letters, or editorials, not published in English, focused on non-melanoma skin cancer, did not include comparative data from urban and rural populations and/or did not include socio-economic status as a confounder (Table 1).

Socioeconomic status (SES) was defined as any measure that included an economic and social position in relation to others, based on area deprivation, income, education, and/or occupation. Insurance status, unique to the United States and Australia, were considered a proxy to the measure of socioeconomic status because it has been found to be vital in determining survival in relation to health care access (Singer and Ryff, 2001).

We anticipated substantial heterogeneity in the definitions of rurality used by the included studies. We were interested in these context dependent definitions of rurality and adopted an inclusive approach. Studies considering urban and rural differences in cancer survival, however measured or defined, were included and summarised.

Table 1
Inclusion-exclusion criteria.

Inclusion	Exclusion
Quantitative observational studies	Other systematic reviews, letters, qualitative or editorials
Definitive measurements of SES (income, education, and occupation)	
Definitive measurements of rurality or distance (Distance, Postcode, Environment, etc.)	
All cancers apart from non-melanoma skin cancer	
English language	
Comparative data of urban and rural data	
Survival analysis	
Cancer-specific survival or all-cause mortality	

Included studies were to assess cancer-related mortality or all-cause mortality within a study. Those studies which fit into which type of survival, whether all-cause or cancer-specific are stated within Table 1.

2.3. Study selection

Study titles and abstracts were screened independently by two authors (RA and RB). Full texts were retrieved for all relevant abstracts and independently reviewed by at least two authors (RA, RB, RC, PM, SF, and YO). Disagreements regarding study eligibility were resolved by discussion with a third reviewer.

2.4. Data extraction

A data extraction form was created in Microsoft Word and an Excel file for data management. Data extracted included primary and secondary outcomes, eligibility criteria, study details and administrative details. Of the reviewers, two of the six conducted extraction of a portion of the studies. RC had read all the studies, compiling and reviewing all extraction forms for consistency. Disagreements were discussed with a second reviewer or a third if there was a large discrepancy between the initial reviewers.

2.5. Risk of bias assessment

Risk of bias for each study was determined independently by two authors (combinations of RA, RB, RC, PM, SF, and YO). Risk of bias was considered as part of an overall assessment of the quality of each study which was guided by the National Institute of Health *Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies* (Shuang et al., 2014). This quality assessment tool is widely used to critically appraise observational studies. It assesses 14 different aspects of study quality including study design, bias, confounding and quality of reporting. The checklist is designed to enable a focus on key concepts for evaluating the quality of an observational study and covering 14 aspects of study quality including bias, confounding and quality of reporting. It is not intended to create a list that is simply tallied-up to arrive at a summary judgement. In our consideration of overall study quality each reviewer considered the risk of key biases within the study and made a determination that this was 'low', 'medium', or 'high'.

2.6. Meta-analysis

For our quantitative assessment of the impact of rurality on cancer mortality, we selected the final fully-adjusted statistical model from each article. Fully adjusted models considered a variety of confounding factors. A pre-requisite for this review was that the model contained SES, which we considered to be a key confounding factor. Outcome data (e.g., hazard ratios) from included studies were entered into Review Manager Version 5.3. Studies which reported hazard ratios

(HR) were combined in a meta-analysis. If HRs were not provided, they were calculated manually from relevant information e.g., estimate (beta), standard error, or confidence intervals. Missing standard errors (that could not be calculated from a given confidence interval) were imputed with the weighted average of all SEs in available studies.

Meta-analyses were performed on the log hazards of the rural to urban comparison to provide the overall hazard ratio (HR) and confidence interval (CI). Urban category was taken as the reference. Statistical heterogeneity was assessed through I^2 and a random effects model was utilized. Where heterogeneity was present, we carried out sensitivity analyses by excluding studies with results that were highly dissimilar to overall meta-analysis results.

In addition, if studies provided risk ratios rather than HR, we undertook a sensitivity analysis which included these studies in with those which used HR (Supplementary Table 1) (Ahrens and Pigeot, 2005).

2.7. Narrative synthesis

Our meta-analysis aggregated results which considered rurality as a binary variable. A number of studies classified rurality using multiple (> 2) categories, but there was insufficient comparable data to conduct separate meta-analysis for these studies. These studies were described narratively. We also characterised and synthesised proposed mechanisms of urban-rural survival differences proposed by the study authors by stratifying the various levels at which mechanisms operated and the extent to which they were supported by evidence. This was conducted by extracting relevant quotes (and their associated justifications) from the original studies using a bespoke data extraction form. We aimed to synthesise common themes, recurrent ideas and implicit concepts in order to create an explanatory framework (Vaismoradi et al., 2013).

3. Results

Database searches returned 4283 titles. One hundred and sixty seven full text articles were assessed, of which, 55 were analysed in full-text for eligibility. 39 satisfied the eligibility criteria and were included in the systematic review and narrative synthesis (Fig. 1).

3.1. Characteristics of included studies

There were 39 included studies (Table 1) predominantly conducted in developed western countries; 17 in the United States or Canada, four in the United Kingdom, four in the rest of Europe and 14 in Australia or New Zealand. A variety of cancer types were studied; four breast, eight colorectal, five lung, three pancreatic, three prostate, two neuroendocrine; and one each of bone and joint sarcoma, cervical, endometrial, oesophageal, and hepatocellular cancers. A further nine studies evaluated multiple cancer types.

3.2. Narrative summary of study findings

Of 39 studies included in this review, 30 reported a clear survival disadvantage for non-metropolitan patients. Five studies on single cancer types, two from the USA, two from Australia and one from New Zealand (Bennett et al., 2007; Chow et al., 2015; Modesitt et al., 2006; Shugarman et al., 2008; Singla et al., 2014), found no difference in cancer survival between urban and rural patients. Two studies (Hagedoorn et al., 2016; Sankaranarayanan et al., 2014a), the first in Belgian lung cancer patients, the second in US colorectal cancer patients reported a rural survival advantage. Two studies (Horner and Chirikos, 1987; O'Reilly et al., 2007), one from the US and one from Northern Ireland UK exploring multiple health conditions suggested a mixed effect, with outcomes worse for some cancers and better for others in rural areas. Overall, rurality appears to confer inferior cancer survival outcomes worldwide. However, studies reporting conflicting results also merit close consideration as their context, focus or

participants may point to the key remediable mechanisms of rural cancer disadvantage because of their rural health infrastructures.

3.3. Definitions of geographical location

Multiple definitions of geographical location were used (Table 2). 18 used a binary urban/rural categorisation, while others ($n = 21$) used urban/rural categorisations with up to 8 categories. Some studies assessed accessibility by road to health service centres, treatment centres, and GP services using distance or time variables. Other studies used population density (Bennett et al., 2007; Brewer et al., 2009), or settlement size to define the urbanicity of a region. Variables such as the ZIP code or domicile code were also used to define the urban and rural differences. Individuals that were furthest from service or treatment centres and GPs located within a city were assumed to be rural simply by distance travelled. Less frequently used definitions of rurality included: access to local transportation (Jones et al., 2008b) focused on straight-line distance to nearest cancer centre.

3.4. Definitions of socioeconomic status

Socioeconomic indicators ranged from a standard measurement provided by a government database (e.g., Carstairs Deprivation Scale), individual information (e.g., Insurance status), or area level measures of deprivation (by postcode or regional prosperity) (Table 3). Nine studies used Australia's Index of Relative Socioeconomic Disadvantage (IRSD); 11 studies used income; five studies used bespoke deprivation scores; and five used insurance status. The remaining nine studies used bespoke measures such as car/home ownership or federal poverty levels.

3.5. Risk of bias

Each study was assessed for risk of bias by two reviewers and given a rating of low, medium or high. Raters agreed for 32 out of 39 studies, with 27 being given a low/low rating, two being given low/medium, five medium/low, and five given a medium/medium rating, between the two raters. A comparison of these ratings was undertaken, and the kappa statistic was in moderate agreement of 0.478.

3.6. Meta-analysis

3.6.1. Urban versus rural comparison: (Multiple cancers)

Eleven of the included studies used a binary urban-rural categorisation and were therefore eligible for our meta-analysis. All of these studies measured cancer-specific survival and adjusted for multiple variables including: age, sex, race/ethnicity, year of diagnosis, marital status, occupation, education, socioeconomic status, tumour site, tumour metastasis, tumour grade, and/or cancer stage.

The forest plot (Fig. 2) shows the individual study estimates from the meta-analysis, and in the majority of cases shows a survival advantage to urban residents. The main outlier was Kokabi et al. (2016) which looked at a relatively rare cancer (unresectable hepatocellular carcinoma (HCC)). The overall combined hazard ratio was 1.05 (95% CI 1.03–1.07) indicating a significantly greater hazard of cause-specific mortality in rural residents. The heterogeneity between studies was 81%. Given Kokabi was in a relatively rare cancer we removed this study in a sensitivity analysis and the overall estimate remained stable 1.09 (95% 1.05–1.12), but heterogeneity reduced to 43%.

In the remaining 27 studies, other measure of geographical location were used. Despite a differing categorisation, among the 27, 18 found a significant survival disadvantage for the most remote patients. The remaining articles found no differing survival outcomes between their urban and rural patients.



PRISMA 2009 Flow Diagram

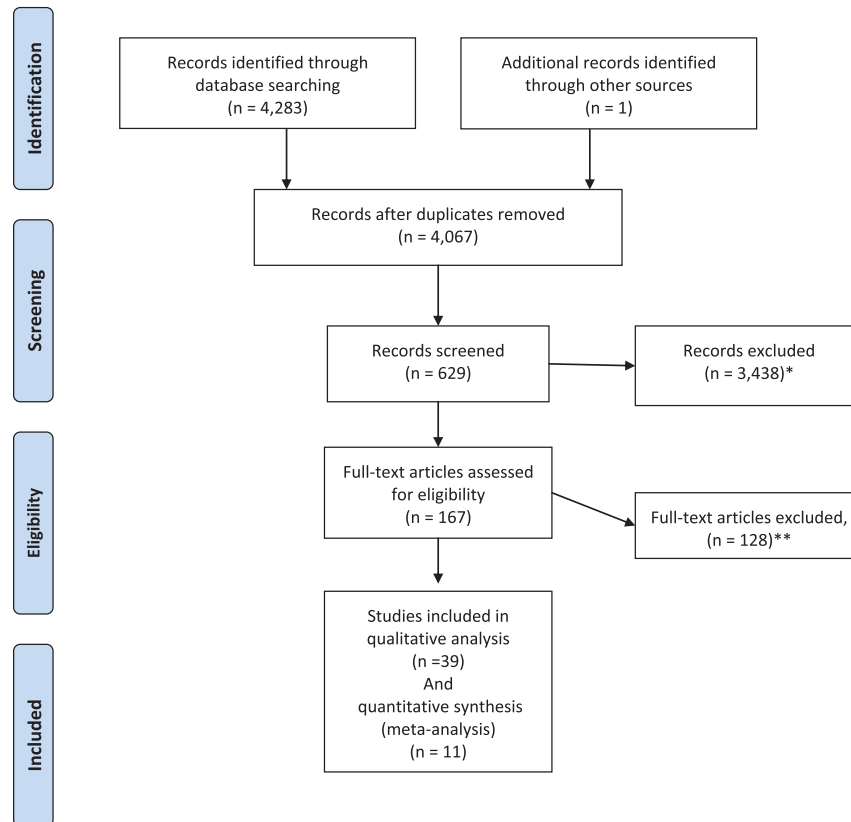


Fig. 1. PRISMA 2009 flow diagram. *Studies did not fit inclusion criteria (e.g., did not compare rural vs urban, no consideration of socioeconomic status). **Studies did not adopt a multivariate analytical approach.

Table 2
Rurality measurements.

Rurality measurement	Studies
Accessibility/Remoteness Index of Australia (ARIA)	(Baade et al., 2011; O'Reilly et al., 2007; Haggart et al., 2013; Brewer et al., 2009; Hall et al., 2004; Kokabi et al., 2016; Hall et al., 2005a, 2005b; Desoubeaux et al., 1997; Hall et al., 2005b; Cheung, 2013a; Stavrou et al., 2009; Raju et al., 2015)
Australian Standard Geographic Classification Remoteness Structure (ASGC)	(Denton et al., 2017; Cheung, 2013b; Papa et al., 2014; Hallet et al., 2015; Singla et al., 2014; Modesitt et al., 2006; Yu et al., 2014; Richard et al., 2011; Yu et al., 2015; Cheung, 2013c)
County of residence	(Cheung, 2013b; Haggart et al., 2013; Horner and Chirikos, 1987; Hagedoorn et al., 2016)
Distance	(Jones et al., 2008a, 2008b; Shuang et al., 2014; Turner et al., 2017; Turner et al., 2017; Van Hooijdonk et al., 2008; Stavrou et al., 2009)
Metropolitan and non-metropolitan	(Klein et al., 2011; Van Hooijdonk et al., 2008)
National Inpatient Sample (NIS)	(Markin et al., 2012; Davis and Bartlett, 2008)
National Institute of Statistics and Economic Studies (INSEE)	(Desoubeaux et al., 1997; Lindley and Oyana, 2016)
Office of Management and Budget (OMB) metropolitan and nonmetropolitan classifications of 2003	(Sankaranarayanan et al., 2014b; Cohen et al., 2017)
Patient's medical service study area	(Chow et al., 2015; Ahrens and Pigeot, 2005)
Population density	(Hagedoorn et al., 2016; Shugarman et al., 2008; O'Reilly et al., 2007; Sankaranarayanan et al., 2014a; Westeel et al., 2007; Westeel et al., 2007)
Postal code	(Bennett et al., 2007; Murage et al., 2017; Brewer et al., 2009; Horner and Chirikos, 1987; Campbell et al., 2000; Bonett et al., 1990; Markossian et al., 2016; Papa et al., 2014; Raju et al., 2015; Yu et al., 2015)
Proximity to rural areas and proximity to geographic clusters	(Lindley and Oyana, 2016; Yu et al., 2014)
Registered Persons Database (RPDB)	(Hallet et al., 2015; Baade et al., 2011)
Rural-Urban Commuting Area (RUCA)	(Hines et al., 2014; Markin et al., 2012; Markossian et al., 2016; Papa et al., 2014; Shugarman et al., 2008; Chow et al., 2015)
Rural urban continuum code	(Cheung, 2013a, 2013b; Markossian et al., 2016; Cheung, 2013a; Denton et al., 2017; Cheung, 2013b; Haggart et al., 2013; Kokabi et al., 2016; Hall et al., 2004; Modesitt et al., 2006; Vaismoradi et al., 2013; Panchal et al., 2016; Hall et al., 2005a)
Statistical Local Areas (SLAs)	(Dasgupta et al., 2012; Bennett et al., 2007)

Table 3
Socioeconomic measurements.

Socioeconomic measurement	Studies
Index of relative socioeconomic Disadvantage (IRSD) (Australia)	(Baade et al., 2011; O'Reilly et al., 2007; Dasgupta et al., 2012; Bennett et al., 2007; Hagggar et al., 2013; Brewer et al., 2009; Hall et al., 2004; Kokabi et al., 2016; Hall et al., 2005a, 2005b; Hall et al., 2005b; Desoubeaux et al., 1997; Stavrou et al., 2009; Raju et al., 2015; Yu et al., 2014; Richard et al., 2011; Yu et al., 2015; Cheung, 2013b) (Bennett et al., 2007; Murage et al., 2017; Brewer et al., 2009; Horner and Chirikos, 1987; Campbell et al., 2000; Bonett et al., 1990; Jones et al., 2008a, 2008b; Shuang et al., 2014; Turner et al., 2017; Turner et al., 2017)
Deprivation score	(Cheung, 2013a, 2013b; Markossian et al., 2016; Cheung, 2013a; Denton et al., 2017; Cheung, 2013b; Hagggar et al., 2013; Hallet et al., 2015; Baade et al., 2011; Horner and Chirikos, 1987; Hagedoorn et al., 2016; Klein et al., 2011; Van Hooijdonk et al., 2008; Markin et al., 2012; Davis and Bartlett, 2008; Raju et al., 2015; Yu et al., 2015; Shugarman et al., 2008; Chow et al., 2015; Van Hooijdonk et al., 2008; Hallet et al., 2015; Westeel et al., 2007; Westeel et al., 2007; Cheung, 2013a, 2013b; Markossian et al., 2016; Cheung, 2013a; Denton et al., 2017; Cheung, 2013b; Hagggar et al., 2013; Hallet et al., 2015; Baade et al., 2011; Horner and Chirikos, 1987; Hagedoorn et al., 2016; Klein et al., 2011; Van Hooijdonk et al., 2008)
Income	(Chow et al., 2015; Ahrens and Pigeot, 2005; Kokabi et al., 2016; Hall et al., 2004; Lindley and Oyana, 2016; Yu et al., 2014; Modesitt et al., 2006; Vaismoradi et al., 2013; Sankaranarayanan et al., 2014b; Cohen et al., 2017)
Insurance	(Denton et al., 2017; Cheung, 2013b; Papa et al., 2014; Hallet et al., 2015; Singla et al., 2014; Modesitt et al., 2006)
Socio-economic indexes for areas 2011 (SEIFA) (Australia)	(Desoubeaux et al., 1997; Lindley and Oyana, 2016)
French Institut National de la Statistique et des Etudes Economiques (INSEE)	
Other (e.g., car/home ownership or Federal poverty level (FPL))	(Markossian et al., 2016; Papa et al., 2014; O'Reilly et al., 2007; Sankaranarayanan et al., 2014a)

3.7. Urban vs rural: comparisons by cancer type

We explored whether the overall association between rurality and cancer survival was present for specific cancers. Chow et al. (2015) and Desoubeaux et al. (1997) both investigated colorectal cancer survival and a meta-analysis of these two studies gave combined HR of 1.12 [95% CI 0.92–1.37] and I² of 73%, indicating non-significant worse survival for rural colorectal cancer patients. Cheung (2013a) and Raju et al. (2015) both studied pancreatic cancer with combined HR of 1.06 [95% 1.03–1.09] from a two study meta-analysis, indicating a significantly worse survival outcome in rural patients. Cheung (2013b) and Hallet et al. (2015) looked at neuroendocrine cancer and in the combined meta-analysis HR of 1.14 [95% CI 1.06, 1.22] again showing a significantly poorer outcome for rural patients.

3.8. Narrative synthesis of all studies

Having established that there is a rural disadvantage in cancer survival, we analysed the 39 studies for the authors' own explanations of this difference. Thematic synthesis was conducted. Mechanisms of rural survival disadvantage fitted thematically within a social ecological model (Richard et al., 2011). This is a theory-based framework for understanding the multifaceted and interactive effects of personal and environmental factors and how they may determine behaviours and outcomes. The model can be used to suggest organizational leverage

points at which geographical cancer outcomes could be made more equitable in future. The model in Fig. 3 describes an influential continuum of individual patient characteristics; the effect of community, culture and environment, healthcare institutions all influenced by the overarching policy and service organization context.

At the level of the individual patient, it seems that rural communities can have a concentration of people with demographic factors which predict poor cancer outcomes, such as ethnicity, age and poverty. Additionally, it seems likely that rural residence can compound the deleterious impact of such factors on cancer outcomes by, for example, interacting with travel burden to health services (Hagedoorn et al., 2016; Sankaranarayanan et al., 2014a; Horner and Chirikos, 1987; Brewer et al., 2009; Cheung, 2013a, 2013b; Cheung, 2013; Markossian et al., 2016; Stavrou et al., 2009; Van Hooijdonk et al., 2008).

Aspects of the rural community, culture and environment may also interact with individual characteristics. Subjective norms around health behaviours could impact screening uptake, symptom evaluation and medical help-seeking with clear implications for late presentation, diagnosis and treatment. Campbell et al. (2000) findings of better outcomes for villagers rather than lone rural-dwellers is of particular interest in this context. Within the rural environment there is a strong suggestion that transport infrastructure can influence help-seeking behaviours. If patients have poor access to public transport in rural settings or do not own a vehicle, they may not seek medical help in a timely manner. Another contributing factor was limited health literacy

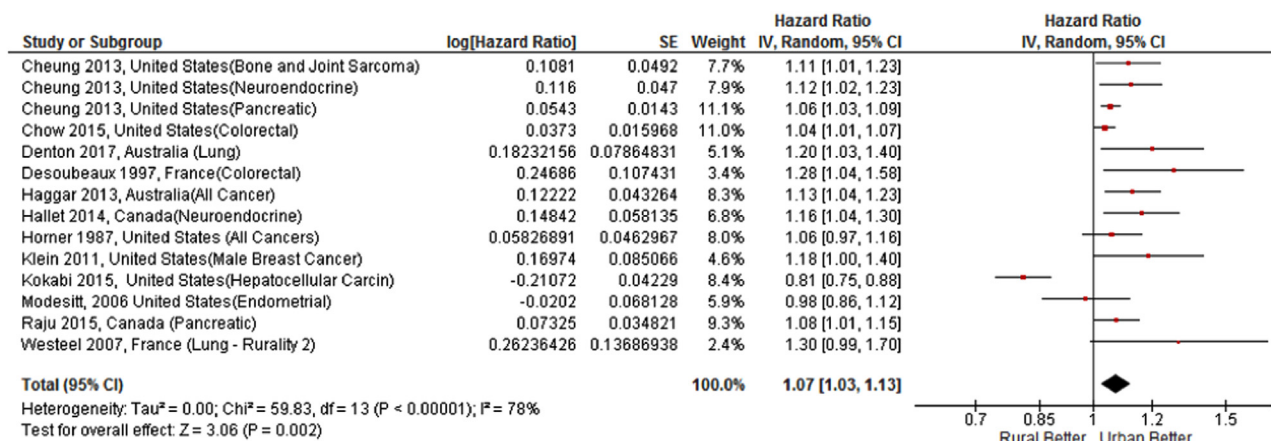


Fig. 2. Meta-analysis.

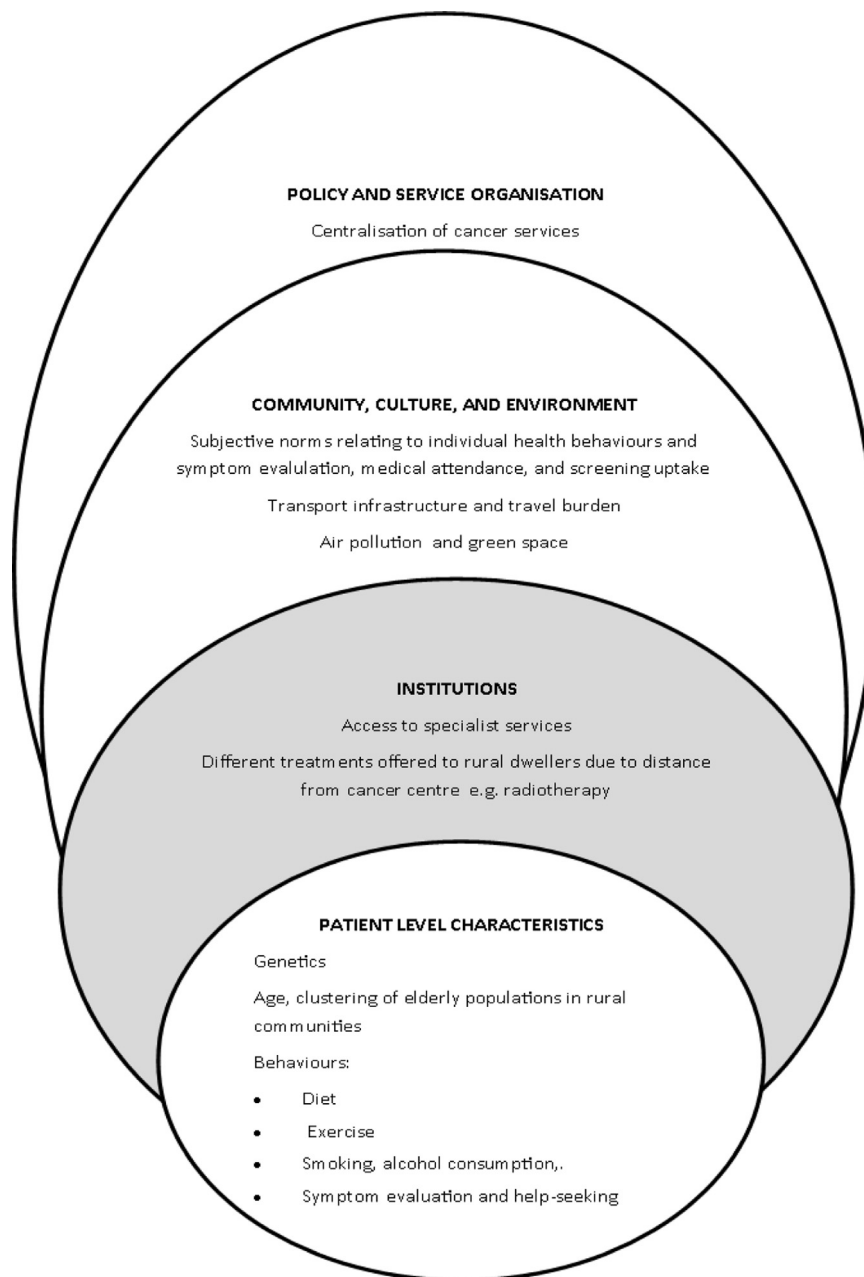


Fig. 3. Socioecological model.

or lack of employment, which can compound issues with transportation (private or public) (Davis and Bartlett, 2008). Other potentially important environmental factors include the nature of rural employment, pollutants and other environmental exposures (O'Reilly et al., 2007; Van Hooijdonk et al., 2008).

At the level of the healthcare institution, there was a clear sense that rural communities have fewer healthcare practitioners, who are often less specialized and have limited access to diagnostic technologies and cancer-specific treatments (Jones et al., 2008a; Westeel et al., 2007; Shugarman et al., 2008; Cheung, 2013a, 2013b; Hallet et al., 2015; Stavrou et al., 2009; Lindley and Oyana, 2016; Panchal et al., 2016; Papa et al., 2014; Yu et al., 2015, 2014; Baade et al., 2011).

Less dense provision of cancer services in rural populations increases the distance and journey time to specialist cancer centres. This means that rural communities across the world have poorer access to specialist services (Campbell et al., 2000; Turner et al., 2017; Dasgupta et al., 2012; Singla et al., 2014; Cheung, 2013a; Stavrou et al., 2009; Yu

et al., 2015; Baade et al., 2011; Markin et al., 2012; Denton et al., 2017; Haggart et al., 2013). Suggested resource limitations restricted the ability to attend with consequent treatment delays, as well as the impact of travel fatigue on the ability to fully benefit from therapy.

Once cancer patients reach services, their rural residence status can affect the quality, intensity, and timeliness of the care they receive. For example, patients commencing a course of chemotherapy or radiotherapy in a rural setting are less likely to complete those courses due to the repetitiveness of attendance culminated with the travel distance. Studies also found that aside from the inability to complete their treatments, rural patients received different courses of treatment and were less likely to receive the option of radiotherapy or surgery as their preliminary courses of treatment, therefore decreasing their chances of survival (Westeel et al., 2007; Chow et al., 2015; Sankaranarayanan et al., 2014a; Cheung, 2013a; Raju et al., 2015; Panchal et al., 2016; Denton et al., 2017; Hall et al., 2004, 2005a, 2005b; Hines et al., 2014; Klein et al., 2011).

Finally, the overall importance of healthcare policy and service organization was highlighted. In papers from Australia and New Zealand where no differences in rural-urban cancer survival was found, the authors concluded that this was largely the result of deliberate initiatives to counteract centralization, and also to improve rural cancer care provision by better equipping rural hospitals (Bennett et al., 2007; Dasgupta et al., 2012). Within Bennett's study, for example, they have a nationally coordinated breast screening programme that encourages screening for both urban and rural women, having mobile/outreach services and employing the same screening and treatment standards, no matter the location.

4. Discussion

4.1. Main findings

We have found strong evidence for an association between rural residence and poor cancer survival outcomes. In studies which adjusted for key confounders, including socioeconomic status, rural-dwellers were 5% less likely to survive cancer than urban counterparts. Despite the substantial heterogeneity among the included studies (in terms of geographic location and definition of rurality), 36 out of 39 studies found evidence of poorer cancer survival in rural areas. After aggregating results in our meta-analysis, we observed that rural-dwellers had poorer cancer survival overall with an overall HR of 1.05 (95% CI 1.02–1.07).

We have assessed observational research and found an association between rurality and poorer cancer survival. It is important to note that observational studies can only indicate associations rather than causation. The authors of the studies included in this review have proposed several mechanisms as potentially underlying their results. We found that the social ecological model was an effective way of grouping these potential mechanisms, and by adopting this theoretical model, we were able to identify commonalities between studies and clear evidence gaps which can guide future research. At the individual level research to compare urban and rural-dwellers with respect to health behaviours, exercise, occupation, and diet is needed. Similarly, research into the effects of service organization, placement and policy, where these differ between geographical regions, is also required.

4.2. Context within wider literature

Our results are consistent with the bulk of research evidence demonstrating an association between rurality and negative cancer survival outcomes. Furthermore, rural residence has been associated with poor outcomes in several other conditions, including: mental health, cardio-respiratory disease, maternity outcomes and trauma (Smith et al., 2008; Cohen et al., 2017). Studies from regions such as Southeast Asia and Africa were not included as data were typically incomplete, and socioeconomic status was not adjusted for (Sankaranarayanan, 2011; Sankaranarayanan et al., 2014b; Swaminathan et al., 2011). Nevertheless, these studies also observed a survival disadvantage among rural cancer patients in terms of care, screening, and timeliness of diagnosis (Swaminathan et al., 2011). Disparities within their urban-rural populations are not as well documented, but they are widely acknowledged (Semnani et al., 2016). A limitation to comparing studies of geographical impacts on health outcomes is that the varying scale of geography varies throughout the worldwide and the differing methods used by governments and academics to capture the concept of rurality (Berke et al., 2009; Halfacree, 2004).

Socioeconomic status was not assessed as a research question within this study, but when assessing the socio-ecological model, it is clear that socioeconomic status can impact survival on various levels. Socioeconomic status impacts individual lifestyle choices such as diet, exercise and occupation. Another factor influenced by SES is access or availability to the necessary health care systems for patients. There is a

clear interplay between SES and rurality, hence why we required included studies to adjust for SES in any models which looked at rurality.

We have based our analyses upon categorical definitions of rurality which compounds the problem of comparative geographical scale. It seems likely however, that major and continuing advances in geographical information systems (GIS) technology will offer future researchers ever more sophisticated methods to counteract this problem (Musa et al., 2013). In particular taking account of actual travel burden, in terms of time and distance, as well as precise information on access to different modes of transport and healthcare facilities will enable more illuminating research on the true importance of access to and positioning of healthcare facilities (Oladipo, 2014). Research in Northeast Scotland, for example, used geographic information systems (GIS) methods to accurately locate cancer patients with respect to health services and found that those most physically remote from hospital cancer centres were actually diagnosed and treated more quickly, challenging delay as one of the most commonly offered explanation for the rural cancer disadvantage (Turner et al., 2017). This review underlines the need for greater attention to the actual mechanisms underpinning the rural cancer disadvantage. These mechanisms are likely to be complex and multifactorial, with each region having unique mechanisms and solutions, but it should be possible to model these mechanisms and apply the most relevant parts of the model to local scenarios. Advancing GIS methods, in conjunction with innovative data science (using for example national census and social security data), may provide a platform for collaborative international research and synergistic learning (Connelly et al., 2016).

4.3. Strengths and limitations

This review took a global perspective and identified a large number of studies. Despite varying contexts and methodologies, we found a sufficient number of studies similar enough to conduct the first-ever international meta-analysis of the effect of rurality on cancer survival. Furthermore, we included studies that adjusted for socioeconomic status, crucial if the true impact of rurality is to be elucidated. We were able to effectively synthesise the mechanistic theories proposed by the authors of the included studies and craft a meaningful ecological model for future researchers and policy-makers. We have also highlighted the dearth of mechanistic evidence as to the causes of the global rural cancer disadvantage.

The major limitation of this review is the differing contexts in which the included studies have been conducted. The review has brought together research conducted in three continents and using differing definitions of rurality. Additionally, different data sources and methodological approaches were adopted. Both of these issues create issues around interpretation, but what is striking is the near unity of the findings, that rural residence leads to poorer cancer survival. A further limitation is that almost all of the studies identified are from the developed world. It seems likely that rural populations in developing countries will fare even worse, a point that future research needs to address. In terms of potential explanations for their observed results authors of individual studies are usually well-placed for insights into their study populations and regional health systems. On the other hand, their opinions about mechanisms are not necessarily correct and most studies to date have been seeking to describe, and not explain, epidemiological associations between urban and rural cancer patient outcomes.

5. Conclusions, implications and further research

In conclusion, there is strong evidence that worldwide rural-dwellers are less likely to survive cancer. In this meta-analysis rural-dwellers were 5% less likely to survive cancer than urban counterparts. However, the mechanisms accounting for this association have not been adequately explored. Causal mechanisms underlying the observed

association are likely to be multifactorial and exist at the level of individual patients, healthcare institutions, community, and public health policies that impact service organization. For this reason, it is vital that future rural-urban cancer research is multi-disciplinary with full engagement between epidemiologists, psychologists and anthropologists (Sperber, 1990). Future researchers should also establish common definitions of rurality and GIS assigned travel burden data is likely to be an effective approach.

Contributors

RA and RB did the literature search, data collection, and data extraction. RA, RB, PM, SF, and YO contributed to data collection, writing, and reviewing of the report. RC contributed to study design, data collection, data analyses, data interpretation, writing, and reviewing.

Declaration of interest

The authors of this publication have no personal, financial, or any other conflicts of interest. The first author would like to acknowledge Elphinstone scholars as the funding body for her studies.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.healthplace.2018.08.010.

References

- Ahrens, W., Pigeot, I., 2005. *Handbook of Epidemiology*. Springer, New York ISBN 9780387098333.
- Baade, P.D., Dasgupta, P., Aitken, J.F., Turrell, G., 2011. Distance to the closest radiotherapy facility and survival after a diagnosis of rectal cancer in Queensland: In reply. *Med. J. Aust.* 195 (11), 662.
- Bennett, H., Marshall, R., Campbell, I., Lawrenson, R., 2007. Women with breast cancer in Aotearoa New Zealand: the effect of urban versus rural residence on stage at diagnosis and survival. *N.Z. Med. J.* 120 (1266).
- Berke, E.M., West, A.N., Wallace, A.E., Weeks, W.B., 2009. Practical and policy implications of using different rural-urban classification systems: a case study of inpatient service utilization among veterans administration users. *J. Rural Health* 25 (3), 259–266.
- Bonett, A., Dorsch, M., Roder, D., Esterman, A., 1990. Infiltrating ductal carcinoma of the breast in South Australia. Implications of trends in tumour diameter, nodal status and case-survival rates for cancer control. *Med. J. Aust.* 152 (1), 19–23.
- Brewer, N., Pearce, N., Jeffrey, M., White, P., Ellison-Loschmann, L., 2009. Demographic differences in stage at diagnosis and cervical cancer survival in New Zealand, 1994–2005. *J. Women's Health* 18 (7), 955–963.
- Campbell, N.C., Elliott, A.M., Sharp, L., Ritchie, L.D., Cassidy, J., Little, J., 2000. Rural factors and survival from cancer: analysis of Scottish cancer registrations. *Br. J. Cancer* 82 (11), 1863–1866.
- Campbell, N.C., Elliott, A.M., Sharp, L., Ritchie, L.D., Cassidy, J., Little, J., 2002. Impact of deprivation and rural residence on treatment of colorectal and lung cancer. *Br. J. Cancer* 87 (6), 585–590.
- Cheung, M.R., 2013c. Low income and rural county of residence increase mortality from bone and joint sarcomas. *Asian Pac. J. Cancer Prev.* 14 (9), 5043–5047.
- Cheung, R., 2013a. Racial and social economic factors impact on the cause specific survival of pancreatic cancer: a SEER survey. *Asian Pac. J. Cancer Prev.* 14 (1), 159–163.
- Cheung, R., 2013b. Racial and socioeconomic disparities in malignant carcinoid cancer cause specific survival: analysis of the surveillance, epidemiology and end results national cancer registry. *Asian Pac. J. Cancer Prev.* 14 (12), 7117–7120.
- Chow, C.J., Al-Refaie, W.B., Abraham, A., Markin, A., Zhong, W., Rothenberger, D.A., et al., 2015. Does patient rurality predict quality colon cancer care?: a population-based study. *Dis. Colon Rectum* 58 (4), 415–422.
- Cohen, S.A., Cook, S.K., Sando, T.A., Sabik, N.J., 2017. What aspects of rural life contribute to rural-urban health disparities in older adults? Evidence from a national survey. *J. Rural Health* (n/a–n/a).
- Connelly, R., Playford, C.J., Gayle, V., Dibben, C., 2016. The role of administrative data in the big data revolution in social science research. *Soc. Sci. Res.* 59, 1–12.
- Coory, M., Smithers, M., Aitken, J., Baade, P., Ring, I., 2006. Urban-rural differences in survival from cutaneous melanoma in Queensland. *Aust. N.Z. J. Public Health* 30 (1), 71–74.
- Coughlin, S.S., Leadbetter, S., Richards, T., Sabatino, S.A., 2008. Contextual analysis of breast and cervical cancer screening and factors associated with health care access among United States women, 2002. *Soc. Sci. Med.* 66 (2), 260–275.
- Dasgupta, P., Baade, P.D., Aitken, J.F., Turrell, G., 2012. Multilevel determinants of breast cancer survival: association with geographic remoteness and area-level socioeconomic disadvantage. *Breast Cancer Res. Treat.* 132 (2), 701–710.
- Davis, S., Bartlett, H., 2008. Healthy ageing in rural Australia: issues and challenges. *Australas. J. Ageing* 27 (2), 56–60.
- Denton, E.J., Hart, D., Russell, P.A., Wright, G., Conron, M., 2017. Lung cancer and socioeconomic status: inextricably linked to place of residence. *Intern. Med. J.* 47 (5), 563–569.
- Desoubeaux, N., Herbert, C., Launoy, G., Maurel, J., Gignoux, M., 1997. Social environment and prognosis of colorectal cancer patients: a french population-based study. *Int. J. Cancer* 73 (3), 317–322.
- Hagedoorn, P., Vandenheede, H., Willaert, D., Vanthomme, K., Gadeyne, S., 2016. Regional inequalities in lung cancer mortality in Belgium at the beginning of the 21st century: the contribution of individual and area-level socioeconomic status and industrial exposure. *PLoS One* 11 (1).
- Haggart, F.A., Pereira, G., Preen, D.D., Holman, C.D.J., Einarsdottir, K., 2013. Cancer survival and excess mortality estimates among adolescents and young adults in Western Australia, 1982–2004: a population-based study. *PLoS One* 8 (2).
- Halfacree, K., 2004. Rethinking 'rurality'. In: Champion, T., Hugo, G. (Eds.), *New Forms of Urbanization: Beyond the Urban-Rural Dichotomy*. Ashgate, Aldershot, pp. 285–304.
- Hall, S., Holman, C.D., Sheiner, H., Hendrie, D., 2004. The influence of socio-economic and locational disadvantage on survival after a diagnosis of lung or breast cancer in Western Australia. *J. Health Serv. Res. Policy* 9 (Suppl. 2).
- Hall, S.E., Holman, C.D.J., Platell, C., Sheiner, H., Threlfall, T., Semmens, J., 2005a. Colorectal cancer surgical care and survival: do private health insurance, socioeconomic and locational status make a difference? *ANZ J. Surg.* 75 (11), 929–935.
- Hall, S.E., Holman, C.D.J., Wisniewski, Z.S., Semmens, J., 2005b. Prostate cancer: socioeconomic, geographical and private-health insurance effects on care and survival. *BJU Int.* 95 (1), 51–58.
- Hallet, J., Law, C.H.L., Karanickolas, P.J., Saskin, R., Liu, N., Singh, S., 2015. Rural-urban disparities in incidence and outcomes of neuroendocrine tumors: a population-based analysis of 6271 cases. *Cancer* 121 (13), 2214–2221.
- Hines, R., Markossian, T., Johnson, A., Dong, F., Bayakly, R., 2014. Geographic residency status and census tract socioeconomic status as determinants of colorectal cancer outcomes. *Am. J. Public Health* 104, 3.
- Horner, R.D., Chirikos, T.N., 1987. Survivorship differences in geographical comparisons of cancer mortality: an urban-rural analysis. *Int. J. Epidemiol.* 16 (2), 184–189.
- Jones, A.P., Haynes, R., Sauerzapf, V., Crawford, S.M., Zhao, H., Forman, D., 2008a. Travel time to hospital and treatment for breast, colon, rectum, lung, ovary and prostate cancer. *Eur. J. Cancer* 44 (7), 992–999.
- Jones, A.P., Haynes, R., Sauerzapf, V., Crawford, S.M., Zhao, H., Forman, D., 2008b. Travel times to health care and survival from cancers in Northern England. *Eur. J. Cancer* 44 (2), 269–274.
- Klein, J., Ji, M., Rea, N.K., Stoodt, G., 2011. Differences in male breast cancer stage, tumor size at diagnosis, and survival rate between metropolitan and nonmetropolitan regions. *Am. J. Men's Health* 5 (5), 430–437.
- Kokabi, N., Xing, M., Duszak, R., Howard, D.H., Applegate, K.E., Camacho, J.C., et al., 2016. Sociodemographic impact on survival in unresectable hepatocellular carcinoma: a survival epidemiology and end results study. *Future Oncol.* 12 (2), 183–198.
- Liff, J.M., Chow, W., Greenberg, R.S., 1991. Rural-urban differences in stage at diagnosis. Possible relationship to cancer screening. *Cancer* 67 (5), 1454–1459.
- Lin, C.C., Bruinooge, S.S., Kirkwood, M.K., Olsen, C., Jemal, A., Bajorin, D., et al., 2015. Association between geographic access to cancer care, insurance, and receipt of chemotherapy: geographic distribution of oncologists and travel distance. *J. Clin. Oncol.* 33 (28), 3177–3185.
- Lindley, L.C., Oyana, T.J., 2016. Geographic variation in mortality among children and adolescents diagnosed with cancer in Tennessee: does race matter? *J. Pediatr. Oncol. Nurs.* 33 (2), 129–136.
- Markin, A., Habermann, E.B., Chow, C.J., Zhu, Y., Vickers, S.M., Al-Refaie, W.B., 2012. Rurality and cancer surgery in the United States. *Am. J. Surg.* 204 (5), 569–573.
- Markossian, T.W., O'Neal, C., Senkowski, C., 2016. Geographic disparities in pancreatic cancer survival in a southeastern safety-net academic medical center. *Aust. J. Rural Health* 24 (2), 73–78.
- Modesitt, S.C., Huang, B., Shelton, B.J., Wyatt, S., 2006. Endometrial cancer in Kentucky: the impact of age, smoking status, and rural residence. *Gynecol. Oncol.* 103 (1), 300–306.
- Murage, P., Bachmann, M., Jones, A., Murchie, P., Crawford, M., 2017. Impact of travel time and rurality on presentation and outcomes of symptomatic colorectal cancer: a cross-sectional cohort study in primary care. *Br. J. Gen. Pract.* 67 (660), e460–e466.
- Musa, G.J., Chiang, P., Sytk, T., Bavley, R., Keating, W., Lakew, B., et al., 2013. Use of GIS mapping as a public health tool – from cholera to cancer. *Health Serv. Insights* 6 (HSI. S10471).
- Ngoma, T., Mandeli, J., Holland, J.F., 2016. Downstaging cancer in rural Africa. *Int. J. Cancer* 136 (12), 2875–2879.
- Obrien, E.D., Bailie, R.S., Jelfs, P.L., 2000. Cervical cancer mortality in Australia: contrasting risk by aboriginality, age and rurality. *Int. J. Epidemiol.* 29 (5), 813–816.
- Oladipo, J.A., 2014. Utilization of health care services in rural and urban areas: a determinant factor in planning and managing health care delivery systems. *Afr. Health Sci.* 14 (2), 322–333.
- O'Reilly, G., O'Reilly, D., Rosato, M., Connolly, S., 2007. Urban and rural variations in morbidity and mortality in Northern Ireland. *BMC Public Health* 7.
- Panchal, J.M., Lairson, D.R., Chan, W., Du, X.L., 2016. Geographic variation in oxaliplatin chemotherapy and survival in patients with colon cancer. *Am. J. Ther.* 23 (3), e720–e729.
- Papa, N., Lawrentschuk, N., Muller, D., Macinnis, R., Ta, A., Severi, G., et al., 2014. Rural residency and prostate cancer specific mortality: results from the Victorian Radical

- Prostatectomy Register. *Aust. N.Z. J. Public Health* 38 (5), 449–454.
- Peng, Z., Wei, J., Lu, X., Zheng, H., Zhong, X., Gao, W., et al., 2016. Diagnosis and treatment pattern among rural and urban breast cancer patients in Southwest China from 2005 to 2009. *Oncotarget* 7 (47), 78168–78179.
- Pozet, A., Westeel, V., Berion, P., Danzon, A., Debieuvre, D., Breton, J., et al., 2008. Rurality and survival differences in lung cancer: a large population-based multivariate analysis. *Lung Cancer* 59 (3), 291–300.
- Raju, R.S., Coburn, N.G., Liu, N., Porter, J.M., Seung, S.J., Cheung, M.C., et al., 2015. A population-based study of the epidemiology of pancreatic cancer: a brief report. *Curr. Oncol.* 22 (6), e478–e484.
- Reijneveld, S.A., Verheij, R.A., De Bakker, D.H., 2000. The impact of area deprivation on differences in health: does the choice of the geographical classification matter? *J. Epidemiol. Community Health* 54 (4), 306–313.
- Richard, L., Gauvin, L., Raine, K., 2011. Ecological models revisited: their uses and evolution in health promotion over two decades. *Annu. Rev. Public Health* 32, 307–326.
- Sankaranarayanan, J., Qiu, F., Watanabe-Galloway, S., 2014a. A registry study of the association of patient's residence and age with colorectal cancer survival. *Expert Rev. Pharm. Outcomes Res.* 14 (2), 301–313.
- Sankaranarayanan, R., 2011. Cancer survival in Africa, Asia, the Caribbean and Central America. Introduction. *IARC Sci. Publ.* (162), 1–5.
- Sankaranarayanan, R., Ramadas, K., Qiao, Y., 2014b. Managing the changing burden of cancer in Asia. *BMC Med.* 12 (1).
- Semnani, S., Noorafkan, Z., Aryaie, M., Sedaghat, S., Moghaddami, A., Kazemnejhad, V., et al., 2016. Determinants of healthcare utilisation and predictors of outcome in colorectal cancer patients from Northern Iran. *Eur. J. Cancer Care* 25 (2), 318–323.
- Shuang F., Hou S., Zhu J., Ren D., Cao Z., Tang J., 2014. **Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.**
- Shugarman, L.R., Sorbero, M.E.S., Tian, H., Jain, A.K., Ashwood, J.S., 2008. An exploration of urban and rural differences in lung cancer survival among medicare beneficiaries. *Am. J. Public Health* 98 (7), 1280–1287.
- Singer, B.H., Ryff, C.D., 2001. National Research Council. **The Influence of Inequality on Health Outcomes.**
- Singla, A., Broadbridge, V., Mittinty, M., Beeke, C., Maddern, G.J., 2014. Rural populations have equal surgical and survival outcomes in metastatic colorectal cancer. *Aust. J. Rural Health* 22 (5), 249–256.
- Smith, K.B., Humphreys, J.S., Wilson, M.G.A., 2008. Addressing the health disadvantage of rural populations: how does epidemiological evidence inform rural health policies and research? *Aust. J. Rural Health* 16 (2), 56–66.
- Sperber, D., 1990. *The Epidemiology of Beliefs.*
- Stavrou, E.P., McElroy, H.J., Baker, D.F., Smith, G., Bishop, J.F., 2009. Adenocarcinoma of the oesophagus: incidence and survival rates in New South Wales, 1972–2005. *Med. J. Aust.* 191 (6), 310–314.
- Swaminathan, R., Lucas, E., Sankaranarayanan, R., 2011. Cancer survival in Africa, Asia, the Caribbean and Central America: database and attributes. *IARC Sci. Publ.* 162, 23–31.
- Turner, M., Fielding, S., Ong, Y., Dibben, C., Feng, Z., Brewster, D.H., et al., 2017. A cancer geography paradox? Poorer cancer outcomes with longer travelling times to healthcare facilities despite prompter diagnosis and treatment: a data-linkage study. *Br. J. Cancer* 117 (3), 439–449.
- Underhill, C.R., Goldstein, D., Grogan, P.B., 2006. Inequity in rural cancer survival in Australia is not an insurmountable problem. *Med. J. Aust.* 185 (9), 479–480.
- Vaismoradi, M., Turunen, H., Bondas, T., 2013. Content analysis and thematic analysis: implications for conducting a qualitative descriptive study. *Nurs. Health Sci.* 15 (3), 398–405.
- Van Hooijdonk, C., Droomers, M., Deerenberg, I.M., Mackenbach, J.P., Kunst, A.E., 2008. Higher mortality in urban neighbourhoods in the Netherlands: who is at risk? *J. Epidemiol. Community Health* 62 (6), 499–505.
- Westeel, V., Pitard, A., Martin, M., Thaon, I., Depierre, A., Dalphin, J., et al., 2007. Negative impact of rurality on lung cancer survival in a population-based study. *J. Thorac. Oncol.* 2 (7), 613–618.
- Yu, X.Q., Luo, Q., Smith, D.P., O'Connell, D.L., Baade, P.D., 2014. Geographic variation in prostate cancer survival in new south wales. *Med. J. Aust.* 200 (10), 586–590.
- Yu, X.Q., Luo, Q., Kahn, C., O'Connell, D.L., Houssami, N., 2015. Temporal trends show improved breast cancer survival in Australia but widening urban-rural differences. *Breast* 24 (4), 524–527.