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## **Rural-urban residence and cancer survival in high-income countries: a systematic review**

**Running Title:** Residential location and cancer survival

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**Precis:** In this systematic review of 45 observational studies, the authors found that cancer patients living in rural areas generally had worse survival than their urban counterparts. The most consistent evidence, observed across several studies, was for colorectal, lung and prostate cancer. Identifying the underlying mechanisms of survival disadvantage for rural cancer patients may help to establish effective interventions and improve survival for all patients.

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## **Abstract**

There is some evidence that place of residence is associated with cancer survival, but findings are inconsistent, and the underlying mechanisms by which residential location might affect survival are not well understood. We conducted a systematic review of observational studies investigating the association of rural versus urban residence with cancer survival in high-income countries. We searched Ovid Medline, EMBASE and CINAHL up to 31 May 2016. Forty-five studies published between 1984 and 2016 were included. We extracted unadjusted and adjusted relative risk estimates with the corresponding 95% confidence intervals (CIs). Most studies reported worse survival for cancer patients living in rural areas than those in urban regions. The most consistent evidence, observed across several studies, was for colorectal, lung and prostate cancer. Of the included studies, eighteen did not account for socio-economic position. Lower survival for more disadvantaged patients is well documented; therefore, it could be beneficial for future research to take socio-economic factors into consideration when assessing rural/urban differences in cancer survival. Some studies cited differential stage at diagnosis and treatment modalities as major contributing factors to regional inequalities in cancer survival. Further research is needed to disentangle the mediating effects of these factors, which may help to establish effective interventions to improve survival for patients living outside major cities.

**Keywords:** Neoplasms; cancer survival; remoteness; urban; rural; systematic review

## 1. Introduction

The potential influence of patients' place of residence on survival from cancer has come to the attention of many researchers, as it may highlight where health care resources need to be allocated to reduce the burden of cancer and improve cancer outcomes.<sup>1,2</sup>

Several studies have investigated the association between area of residence and cancer survival, the vast majority of them conducted in high-income countries, but findings have been inconsistent.<sup>3-8</sup> Furthermore, the potential roles of stage at cancer diagnosis, co-morbidity, treatment, and health-related lifestyle factors in rural/urban differences in cancer outcomes have not been fully explored. A review conducted in 1992 of patterns of cancer mortality and survival in rural and urban regions suggested that residents of rural areas were more likely to be diagnosed at advanced stage compared with those living in urban communities.<sup>1</sup> Some studies have proposed that people in rural areas have limited access to diagnostic and treatment services.<sup>9-11</sup> A more recent systematic review found that rural patients had worse prognosis and quality of life; travel distance was reported as a significant barrier to early diagnosis, receiving optimal cancer treatment and compliance to prescribed treatment.<sup>12</sup>

The purpose of this review was to systematically summarise the published literature on the association between rural/urban residence and cancer survival. We focused on high-income countries only, as residents of low- and middle-income countries have less access to adequate health care services. In addition, we evaluated the current evidence in relation to the underlying reasons for rural/urban inequalities in cancer survival.

## 2. Methods

### 2.1. Search strategy

We systematically searched Ovid Medline, EMBASE and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) to identify observational studies published in English up to 31 May 2016 that investigated the association between place of residence defined as rural or urban and cancer survival in high-income countries (the search strategy is provided in Supplementary Table 1). The World Bank Data-2014 was used to identify high-income nations.<sup>13</sup> We expanded our search by reviewing the bibliographies of all eligible studies and related reviews.<sup>1,12,14,15</sup> We also conducted a search using Google Scholar to identify potentially eligible studies that might not have been detected through the above process. This systematic review was planned and carried out in adherence to the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) guidelines.<sup>16</sup> The review protocol was registered with PROSPERO (International Prospective Register Of Systematic Reviews), reference number CRD42016039228, which is accessible from [[http://www.crd.york.ac.uk/PROSPERO/display\\_record.php?ID=CRD42016039228](http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42016039228)].

### 2.2. Eligibility criteria

Studies were eligible if they met the following criteria: (i) observational study; (ii) written in English and published in a peer-reviewed journal; (iii) included people diagnosed with cancer at age ≥15 years in a high-income country; (iv) compared rural with urban areas; (v) outcome of interest was death from any cause or death from a specific type of cancer; (vi) reported estimates of a hazard ratio (HR), odds ratio (OR) or excess mortality rate ratio (EMRR) derived from relative survival analysis with a corresponding 95% confidence interval (CI) or standard error. Eligible abstracts that did not have full text available were excluded. We included the most comprehensive version of a report if multiple publications from a study were available.

### 2.3. Screening and data extraction

N.A. performed the literature search and excluded studies based on the titles and abstracts. Full reports of selected articles were imported to Covidence, a web-based program for conducting systematic reviews, for detailed, independent screening according to the eligibility criteria by N.A. and R.L.M. Discrepancies were discussed and resolved by consulting with D.R.E. Information from the identified studies was extracted by N.A. with assistance from R.L.M. The following data were extracted from each study: the first author's last name, publication year, country where the study was conducted, data sources, sample size, years of cancer diagnosis, range of age at diagnosis, cancer types, measure and categories of area of residence, statistical methods, measures of association and their 95% CI, and covariates used for adjustment. All information regarding factors that might explain rural and urban differences in cancer survival were also extracted.

#### **2.4. Assessment of risk of bias**

The risk of bias of individual studies was appraised by N.A. and checked by R.L.M. using the domains of bias from the ROBINS-E (Risk Of Bias In Non-randomized Studies – of Exposures) tool obtained from [<https://www.bristol.ac.uk/population-health-sciences/centres/cresyda/barr/riskofbias/robins-e/>]. The following areas were assessed for risk of bias: confounding, selection of participants into the study, classification of the exposure, inappropriate adjustment for potential mediators, extent of missing data, measurement of the outcome, and reporting of results.

#### **2.5. Evidence synthesis**

Meta-analyses across studies were not performed because of the diversity of definitions of urban versus rural residence and outcome (overall versus cancer-specific survival). We used fixed-effects meta-analysis to combine results from the same study for remote and very remote areas as well as by disease stage. Forest plots of study-specific results are presented. We considered the strength of association weak if the relative risk (RR) was  $<1.05$ , moderate if  $RR\ 1.05-1.20$  and strong if  $RR > 1.20$ . Caution should be used when interpreting the various measures of RR. The EMRR based on relative survival analysis and hazard ratios from an analysis of cause-specific survival or overall survival are not equivalent. A hazard ratio of 1.15 comparing the overall survival of rural versus urban patients indicates that rural patients had a death rate from any cause that was 1.15 times that of urban patients; this hazard ratio is usually derived from a Cox regression analysis with death from any cause as the outcome. A hazard ratio of 1.15 for cause-specific survival (derived from a Cox regression analysis with death from the cancer as the outcome) indicates that rural patients had a death rate from the cancer under study that was 1.15 times higher than that of urban patients. The EMRR is derived from a model in which the total hazard of death is composed of the sum of the expected hazard based on population mortality rates (usually accounting for age, sex and calendar period) and an additional component (excess mortality) due to the cancer. An EMRR of 1.15 indicates that the excess mortality due to the cancer for rural patients is 1.15 times higher than that for urban patients.

### **3. Results**

#### **3.1. Study selection**

We identified 1,771 articles via Ovid Medline, EMBASE and CINAHL. Of these, 599 duplicate citations were removed, and an additional 1,090 articles were excluded based on their title and abstract, leaving 82 articles for further evaluation. After full-text screening, we excluded a further 37 studies. Therefore, 45 articles were eligible for inclusion in

the systematic review. The reasons for excluding articles are shown in Figure 1; 65% of the excluded studies did not assess urban and rural differences in cancer survival and 24% were conference abstracts without full text.

### 3.2. Study characteristics

Supplementary Table 2 summarises the characteristics of the eligible studies and the estimates with corresponding 95% confidence intervals (CIs) for the association between place of residence and overall or cancer-specific survival. We considered the following categorisations, hereafter referred to as ‘urban’, as reference: ‘metropolitan’, ‘major or capital city’, ‘inner, main or large urban’, ‘city core’, ‘large or big metro’ and ‘very or highly accessible’. We treated ‘inner regional’, ‘outer regional’, ‘remote/very remote’, ‘large, small or isolated rural’, ‘country area’, ‘outer urban’, ‘suburban’, ‘small cities or towns’, ‘densely populated outer’, ‘rural outer’, ‘non-metropolitan counties’, ‘non-urban’, ‘less urban’, ‘small urban’, and ‘moderately accessible’ as the other category, ‘rural’.

Seventeen studies were conducted in Australia,<sup>8,11,17-31</sup> sixteen in the United States of America (US),<sup>7,32-46</sup> six in Europe,<sup>10,47-51</sup> four in Canada<sup>52-55</sup> and two in New Zealand.<sup>56,57</sup> These studies investigated several neoplasms including female breast,<sup>24,27,31,40,42,47,49,52,56</sup> male breast,<sup>38</sup> cervix,<sup>34,57</sup> colorectum,<sup>8,19,20,25,32,35,36,45,46</sup> endometrium,<sup>43</sup> oesophagus and stomach,<sup>7</sup> liver (intrahepatic cholangiocarcinoma),<sup>39</sup> lung,<sup>33,37,48,51</sup> melanoma,<sup>23</sup> neuroendocrine tumours,<sup>53</sup> non-Hodgkin lymphoma,<sup>50, 54</sup> ovary,<sup>17,44</sup> pancreas,<sup>41,55</sup> prostate,<sup>18,28,30</sup> and selected groups of cancers.<sup>10,11,21,22,26,29</sup> Most studies used only population-based cancer registry data, while others used data from a range of sources including hospitals,<sup>26,51</sup> academic medical centres,<sup>41</sup> or treatment services or registries;<sup>28,29,44,45</sup> others used population-based cancer registries linked with public and private hospitals and treatment datasets.<sup>20,25, 49,53,55</sup> Twenty-one studies reported overall survival (*i.e.*, death from any cause).<sup>8,17,18,25,26,29,33,35-39,41,42,46,48,51-53,55,56</sup> The remaining studies presented cancer-specific or relative survival, which estimate effects on death due to the cancer under study only.<sup>7,10,11,19-24,27,28,30-32,34,40,43-45,47,49,50,54,57</sup>

There were differences in the definition of rural and urban residence across studies. Several used standard measures of geographical classification. Most Australian studies used the Accessibility/ Remoteness Index of Australia (ARIA/ARIA+),<sup>11,17,19,20,22,24,25</sup> or the Australian Standard Geographic Classification – Remoteness Areas (ASGC–RA) to define place of residence,<sup>8,18,28-31</sup> while most US studies applied the Rural/Urban Continuum Codes (RUCC),<sup>7,33,40,42,43,45</sup> the Rural/Urban Commuting Area (RUCA),<sup>36,37,41</sup> or Census Tracts (CTs) classifications.<sup>34,48</sup> Others defined rural/urban residence based on population size or density, local government area or distance from treatment centres.<sup>10,23,35,38,39,46,52-54,56,57</sup> Some studies defined location based on the patients’ medical service study area, address, residential postcode or main income sources for the municipality;<sup>26,27,32,44,47,49,51,55</sup> One Australian study simply compared metropolitan versus other residence<sup>21</sup> and one study did not provide detailed information on how rural and urban were defined.<sup>50</sup>

### 3.3. Evidence of differences in cancer survival by rural and urban residence

Thirteen studies examined the association between place of residence and colorectal cancer survival: seven from Australia,<sup>8,11,19-22,25</sup> five from US<sup>32,35,36,45,46</sup> and one from Germany.<sup>10</sup> Three Australian<sup>19, 21, 25</sup> and a US study<sup>35</sup> found that living in outer regional, remote, rural and country areas was associated with 8–15% higher risk of death. In contrast, another US<sup>46</sup> study reported a moderate, inverse association between rural residence and overall survival (Figure 2). With respect to cancer-specific survival, a consistent pattern of worse survival outside major cities was noted in several studies from Australia<sup>11, 19, 22</sup> and the US,<sup>32,36</sup> although two Australian<sup>8,20</sup> and a US study<sup>45</sup> observed no significant rural

and urban differences in survival from colon or rectal cancer (Figure 2). In contrast, a German study found weak evidence of survival advantage among rural female patients with colorectal cancer relative to women living in the city.<sup>10</sup>

Of the 13 studies that investigated female breast cancer, three studies, from the US<sup>42</sup>, Australia<sup>21</sup> and New Zealand<sup>56</sup>, observed no differences in overall survival between rural and urban areas (Figure 3). Another Australian study<sup>27</sup> found strong evidence of worse survival for women living in rural areas (RR 1.84; 95% CI 1.28–2.64). In contrast, a Canadian study<sup>52</sup> reported higher overall survival for women residing in towns, villages and rural areas relative to their counterparts in urban areas; but this was not the case for women living in more remote areas. Regarding cancer-specific survival, studies from the US<sup>40,42</sup> reported no association between place of residence and survival from breast cancer, while studies from Australia<sup>11,24</sup> showed moderate association. Other studies conducted in Poland<sup>47</sup> and Australia<sup>22,31</sup> observed worse survival for patients residing in rural and outer regional regions (Figure 3). A German study<sup>10</sup> found 8% (95% CI 2 – 15%) higher risk of death due to breast cancer among women living in densely populated outer areas. Conversely, a study from Norway<sup>49</sup> (including 5,042 patients) observed higher breast cancer survival in rural than urban areas. The only study of male breast cancer (including 4,222 cases), conducted in the US, reported lower overall survival in non-metropolitan areas (RR 1.19; 95% CI 1.01–1.40).<sup>38</sup>

We identified only four studies<sup>11,18,28,30</sup> that compared rural and urban residence in relation to prostate cancer survival, all conducted in Australia. One study<sup>18</sup> showed lower overall survival for residents of regional and rural areas, with the RR estimates increased from 1.01; 95% CI 0.97–1.05 to 1.24; 95% CI 1.17–1.31 over time. Another study<sup>28</sup> found no significant evidence of survival inequalities between patients in major cities and those in regional or rural areas. The three studies that examined prostate-specific survival<sup>11,28,30</sup> all reported worse survival for men living outside urban areas with relative risk estimates in the larger study ranging from 1.31; 95% CI 1.22–1.41 to 1.61; 95% CI 1.46–1.77 (Figure 4).

Seven studies<sup>11,21,22,33,37,48,51</sup> assessed the association of area of residence with lung cancer survival (Figure 5). Of the five that investigated overall survival, studies from US<sup>33,37</sup> and France<sup>48</sup> observed moderate to strong association between place of residence and survival, while the remaining studies from Australia<sup>21</sup> and Poland<sup>51</sup> found no evident rural and urban differences in overall survival. Of the two Australian studies<sup>11,22</sup> that presented results for lung-specific survival, both found some evidence of worse survival among patients living in rural areas (Figure 5).

Figure 6 summarises the results from studies of female reproductive cancers. Of the seven studies<sup>11,17,21,22,34,44,57</sup> that investigated ovarian or cervical cancer, two Australian studies<sup>17,21</sup> reported worse overall survival in rural compared with urban areas, with RR estimates 1.20; 95% CI 1.01–1.42 and 1.53; 95% CI 1.05–2.23, respectively. With respect to cancer-specific survival, other studies from New Zealand<sup>57</sup>, Australia<sup>11</sup> and the US<sup>34</sup> found that rural residence was associated with lower survival from cervical and ovarian cancer. A fourth Australian study<sup>22</sup> reported worse survival from ovarian cancer among women living in inner or outer regional areas, while another study from US<sup>44</sup> found that residents of rural Northern California and Sacramento had more than two-times higher risk of death compared with patients living in San Francisco Bay (urban) area (Figure 6). A study conducted in Australia reported a strong association between rural residence and worse survival from uterine cancer.<sup>11</sup> The only relevant study of endometrial cancer found no differences in overall survival (RR 0.98; 95% CI 0.86–1.12), but higher cancer-specific survival among rural patients than their urban counterparts (RR 0.77; 95% CI 0.63–0.94).<sup>43</sup>

Of the remaining studies, three from the US or Australia assessing overall and cancer-specific survival from liver<sup>11,39</sup>, stomach and oesophagus<sup>7</sup> observed similar survival for rural and urban regions (Supplementary Table 2). An Australian study of 12,827 melanoma patients found survival disadvantage for rural (RR 1.20; 95% CI 1.02–1.43) but not

regional areas.<sup>23</sup> Another Australian study reported higher survival for individuals with melanoma living in accessible areas, while no differences were observed in moderately accessible and remote areas, relative to highly accessible regions.<sup>11</sup> A study from Canada found lower overall survival for rural residents diagnosed with neuroendocrine cancers (RR 1.16; 95% CI 1.04–1.30).<sup>53</sup> Of the three studies examining rural and urban differences in survival from non-Hodgkin lymphoma, a Canadian<sup>54</sup> and an Australian study<sup>11</sup> observed no significant differences in survival between rural and urban regions, while a study from France<sup>50</sup> reported that rural patients had two-times higher risk of death than urban cases. Lastly, an Australian study<sup>11</sup> reported similar survival experience from pancreatic cancer among patients living in rural and urban regions, while a US<sup>41</sup> and a Canadian<sup>55</sup> study found that rural residents with pancreatic cancer have worse overall survival than those living in urban areas, although the sample size in the US study was small (245 cases).

### 3.4. Risk of bias

The results from the assessment of the risk of bias of the included studies are shown in Supplementary Table 3. Almost all studies had low risk of bias with respect to classification and measurement of the exposure and the outcome, respectively. We considered age at diagnosis, sex (for non-sex-specific cancers), ethnicity/race (where applicable), and an individual-level measure of socio-economic position as important confounding domains that should be accounted for in the analyses (Supplementary Figure 1). In addition, studies that applied a relative survival framework to estimate EMRRs should have used region-specific population life-table. Of the six studies that reported EMRRs, three did not use appropriate population life-table.<sup>30, 31, 50</sup> With respect to confounding, about half of the included studies were at moderate risk of bias, mainly due to not accounting for socio-economic factors. Bias in the selection of participants into the study was determined to be low for most studies, except seven studies which were considered to be at high risk of this bias.<sup>26,28,29,41,44,45,51</sup> For the domain of bias due to selective reporting of results, all had a low risk of bias except two studies.<sup>10,22</sup> With respect to missing data and inappropriate adjustment for potential mediators, most studies were classified as having moderate to high risk of bias (Supplementary Table 3). We considered health-related lifestyle factors, screening participation, stage of cancer at diagnosis, co-morbidities and treatment modalities including surgery, chemotherapy and radiotherapy as potential mediators that should not have been adjusted for in the analyses.

Of the 45 studies included in the review, 18 did not adjust for measures of socio-economic position (SEP) or deprivation.<sup>7,10,11,17,18,22,23,26,27,33,39,42,47,48,50,51,52,54</sup> Most studies that adjusted for individual- or area-level measures of SEP or deprivation observed weak to moderate association between rural and urban residence and cancer survival. Of the six studies<sup>24,25,30,36,49,57</sup> that presented the results with and without adjustment for socio-economic deprivation, three found no significant differences in survival between rural and urban areas,<sup>24,25,57</sup> although adjustment for SEP decreased RR estimates. Of the remaining studies, one<sup>36</sup> found that an apparent worse survival observed in rural than urban areas disappeared after adjusting for SEP, while the survival gap persisted in the other two studies.<sup>30,49</sup>

We identified 35 studies that included covariates in multivariable analyses that are on the potential causal pathway between rural and urban residence and cancer survival (Supplementary Figure 1).<sup>7,8,10,11,17,19,20,23-25,27,28,30,32-34,36-38,40-50,53-57</sup> Of these, 15 studies that adjusted for at least one mediator did not report any significant differences in survival by area of residence,<sup>7,8,20,24,25,27,33,34,37,40,42,45,54,56,57</sup> while the remaining studies found evidence of association between rural and urban residence and cancer survival.<sup>10,11,17,19,23,28,30,32,36,38,41,43,44,46-50,53,55</sup> Of five studies that observed inequalities in survival and reported the results with and without including the mediator(s) in the models, three<sup>27,36,37</sup> suggested that treatment partially explained rural/urban differences in survival from colorectal, lung and breast cancer. The fourth study<sup>11</sup> found that stage of prostate and cervical cancer at diagnosis contributed in part to the observed worse

survival in rural areas, while the fifth study showed that stage at diagnosis and the treatment received did not explain better survival from colon cancer for rural regions.<sup>46</sup>

#### 4. Discussion

In this systematic review, the majority of studies reported worse survival for cancer patients living in rural and remote areas relative those living in urban regions. The most consistent evidence, observed across several studies, was for colorectal, lung and prostate cancer.

These findings are broadly in line with previous related reviews. A review examining the influence of travel burden on cancer outcomes found that cancer patients living in rural areas have poorer survival and a worse quality of life than their urban counterparts.<sup>12</sup> Further, a long travel distance to specialist hospital and treatment facilities appeared to negatively affect stage of cancer at diagnosis and receiving optimal treatment.<sup>12</sup> Another review of rural/urban differences in prostate cancer incidence and mortality reported higher risk of death among rural men in half of the studies, while the remaining did not show any differences;<sup>15</sup> the authors suggested that variations in rural/urban definitions and in accounting for ethnicity, sociodemographic characteristics, co-morbidities and stage at diagnosis may have contributed to inconsistent findings.<sup>15</sup> Some other studies have shown that rural men are more likely to be diagnosed at advanced stage of prostate cancer due to lower rates of PSA testing in rural areas.<sup>11,18</sup>

A systematic review of differences by place of residence in clinical management and outcomes for colorectal cancer patients in Australia found worse survival for those living outside major cities.<sup>14</sup> Some of the reviewed factors appeared to explain part of the observed differences in survival. For example, patients living in rural areas had more unhealthy behaviours and were less likely to participate in colorectal cancer screening; differences in stage at diagnosis, the prevalence of co-morbidities, and the treatment received, as well as access to oncology services and options for treatment, could also have contributed to lower survival from colorectal cancer in rural areas.<sup>14</sup> A US study showed that rural patients are less likely to receive information regarding participation in cancer treatment trials than urban residents, which may contribute to worse survival in rural and remote regions.<sup>58</sup>

There are discrepancies between populations in the association of residential location with cancer stage at diagnosis. Several studies that have assessed rural/urban differences have found that rural patients present with more advanced disease stage.<sup>9,59-62</sup> In contrast, other studies have shown that rurality or travel distance have an inverse or no association with late diagnosis.<sup>6, 14, 63,64</sup>

In several countries, rural regions tend to have more socio-economic disadvantage than urban regions.<sup>65-67</sup> Moreover, other studies have found that rural regions have higher prevalence of physical inactivity, obesity, smoking, alcohol consumption and chronic diseases, often related to socio-economic deprivation.<sup>68-72</sup> We therefore assumed that SEP would confound associations between place of residence and cancer outcome, but we acknowledge that this assumption might not be correct, and that place of residence might also influence SEP. A review addressing the health disadvantage of rural and remote populations argued that worse cancer survival among rural patients is partially due to higher rates of poverty and lower levels of education and health literacy than for urban residents, which in turn affect health behaviours and the use of health care services in rural regions.<sup>73</sup> Another review of the association between co-morbidity and cancer survival found that individuals with psychiatric disorders or severe co-morbidities are more likely to be diagnosed at advanced stages, while people with chronic conditions tend to have early diagnosis due to regular medical check-ups.<sup>72</sup> Also, patients with co-morbid conditions are less likely to receive standard cancer treatment or adhere to prescribed treatment. It is not well understood whether undertreatment or noncompliance is associated with patient preferences or treatment side-effects and toxicity.<sup>72</sup>

## Limitations

This review has several limitations that should be considered when interpreting the findings. A significant limitation was the considerable variation in the criteria and methods used to define rural and urban regions. It is possible that screening participation for cancers such as breast, prostate and colorectal cancer, differs by place of residence. If so, this would affect comparisons of survival by place of residence because, even in the absence of effective treatment, screen-detected cancers will appear to have better survival due to lead time and length time bias and overdiagnosis. Therefore, it was challenging to make comparisons across included studies and draw conclusions. Moreover, many of the studies had an overall high risk of bias due to several factors such as confounding, missing data and inappropriate adjustment for mediators.

To investigate the underlying reasons for differences in cancer survival by place of residence, we extracted RR estimates adjusted for variables in the putative causal pathway. Unfortunately, most studies only reported fully adjusted estimates, which may have masked survival differences between rural and urban areas. Comparing results with and without accounting for mediators in the analyses, known as the difference method, is a common approach in epidemiological research which has some limitations. It fails when there are unmeasured mediator-outcome confounders or when multiple mediators of interest interact with each other.<sup>74</sup> Adjusting for mediators in these situations could yield misleading or biased results.<sup>74,75</sup> Thus, we could not draw definitive conclusions about whether stage at diagnosis and the treatment received explain part of the observed rural/urban differences in cancer outcomes.

Lastly, aggregated or composite indicators of socio-economic deprivation do not necessarily match with the individual measures;<sup>76</sup> therefore, it is not clear to what extent the observed inequalities in cancer survival between rural and urban area is influenced by patients' socio-economic position.

## Conclusions

In summary, rural cancer patients generally have worse survival relative to their urban counterparts. The lack of consistent findings across studies may arise from discrepancies in measurement and classifications of rural and urban regions and the covariates accounted for in multivariable analyses. This review highlights the importance of appropriate adjustment for prognostic factors when exploring differences in cancer survival by area of residence. The underlying mechanisms of survival disadvantage for rural patients are not well known; possible contenders include differences in health-related lifestyle behaviours, stage of cancer at diagnosis, co-morbid conditions and treatment modalities. Further research is required to unravel the potential mediating role of these factors, which may help to establish effective interventions to address inequalities and improve survival for all cancer patients.

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**Figure legends:**

**Figure 1.** Flow diagram describing selection of studies for inclusion in a systematic review of rural-urban residence and cancer survival in high-income countries

CINAHL, Cumulative Index to Nursing and Allied Health Literature.

**Figure 2.** Relative risk estimates for overall and cancer-specific survival comparing rural categories with urban areas  
CI, confidence interval; OR, odds ratio; HR, hazard ratio; EMRR, excess mortality rate ratio; USA, the United States of America

**Figure 3.** Relative risk estimates for overall and cancer-specific survival comparing rural categories with urban areas  
The results of an Australian study (Bonnet et al., 1984) are not shown as the authors did not report hazard ratios for breast cancer

CI, confidence interval; OR, odds ratio; HR, hazard ratio; EMRR, excess mortality rate ratio; USA, the United States of America

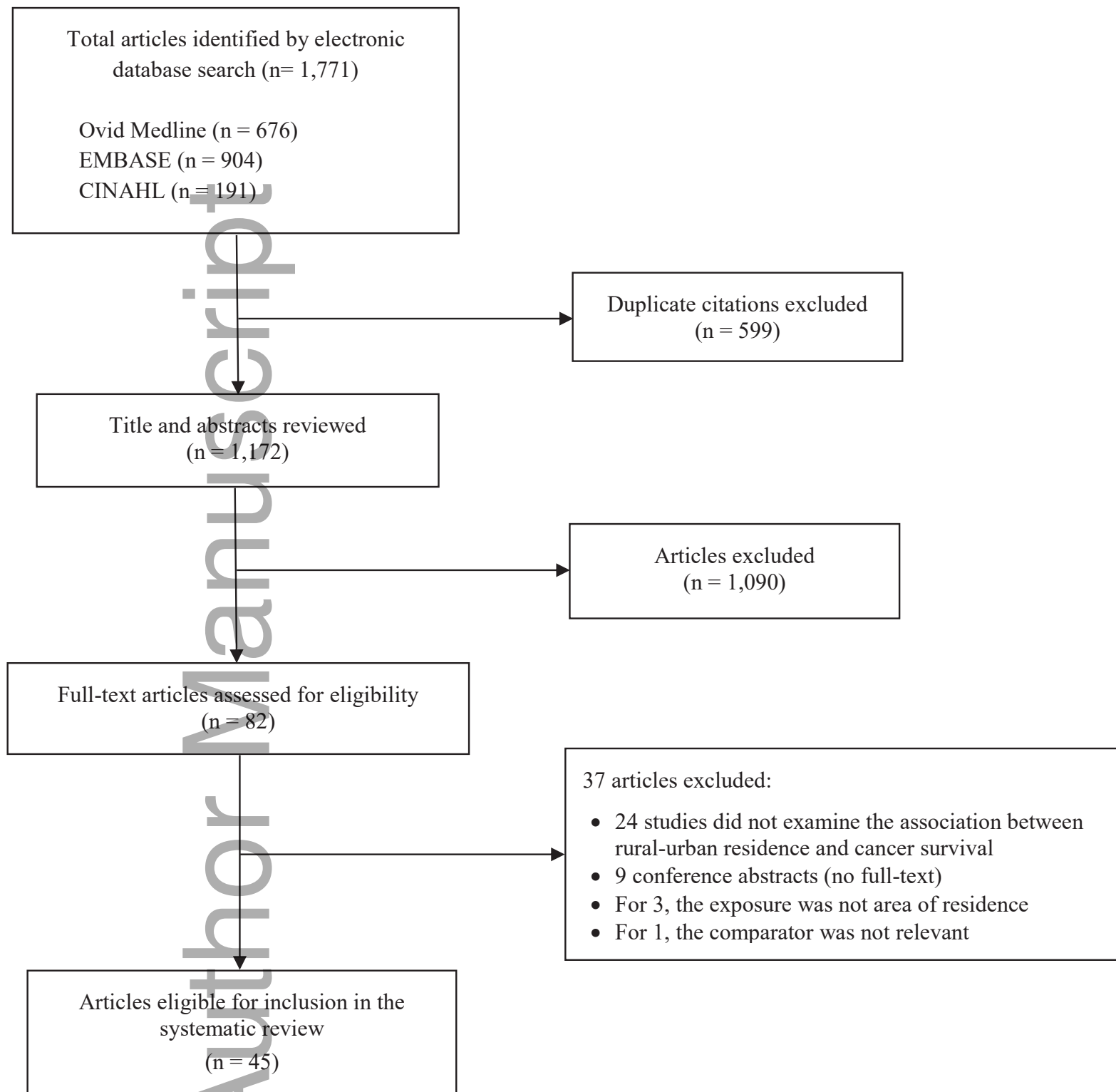
**Figure 4.** Relative risk estimates for overall and cancer-specific survival comparing rural categories with urban areas  
CI, confidence interval; OR, odds ratio; HR, hazard ratio; EMRR, excess mortality rate ratio

**Figure 5.** Relative risk estimates for overall and cancer-specific survival comparing rural categories with urban areas  
The results of an Australian study (Bonnet et al., 1984) are not shown as the authors did not report hazard ratios for lung cancer

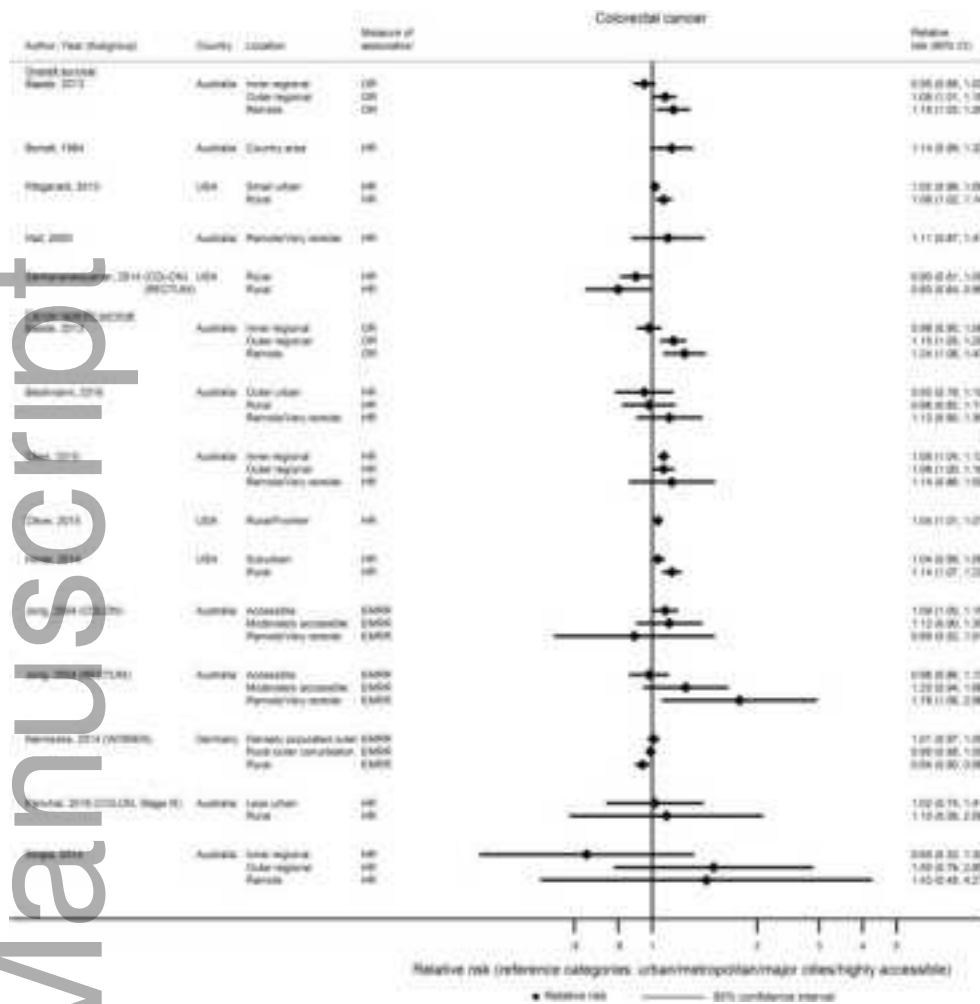
CI, confidence interval; OR, odds ratio; HR, hazard ratio; EMRR, excess mortality rate ratio

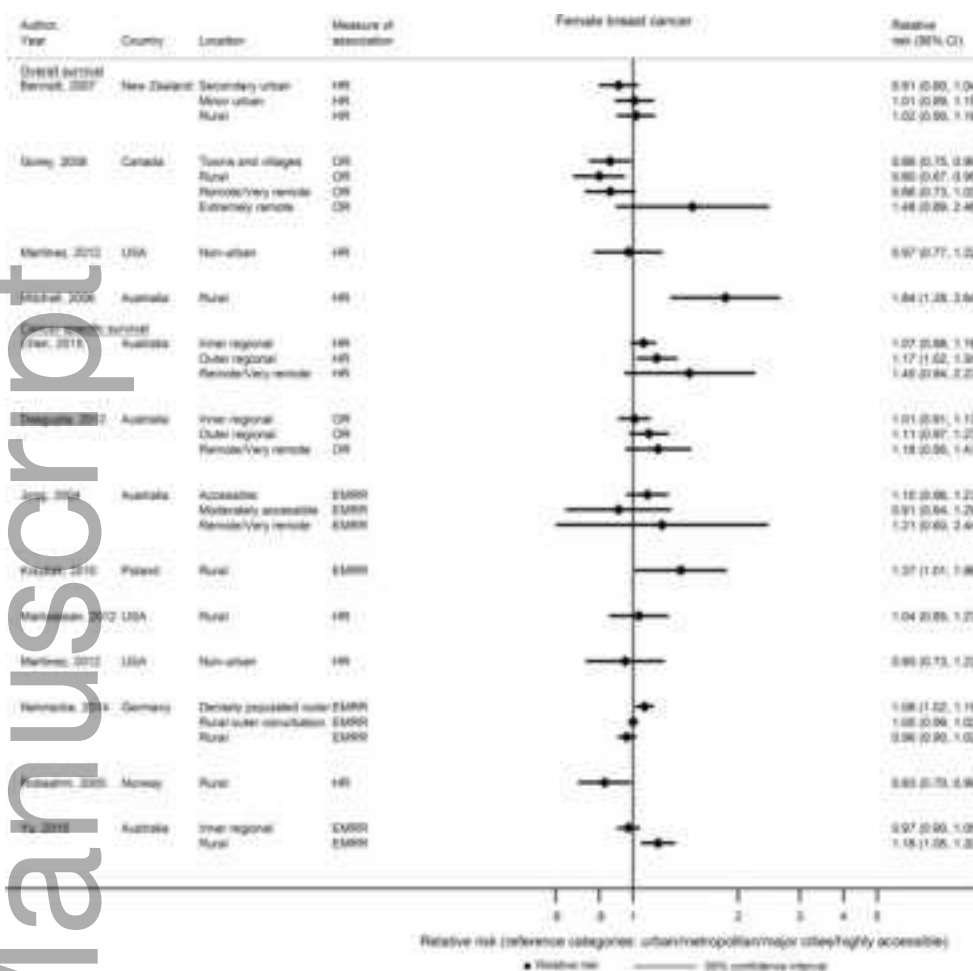
**Figure 6.** Relative risk estimates for overall and cancer-specific survival comparing rural categories with urban areas  
Rural Northern California and Sacramento were compared with San Francisco Bay (urban) area

CI, confidence interval; OR, odds ratio; HR, hazard ratio; EMRR, excess mortality rate ratio

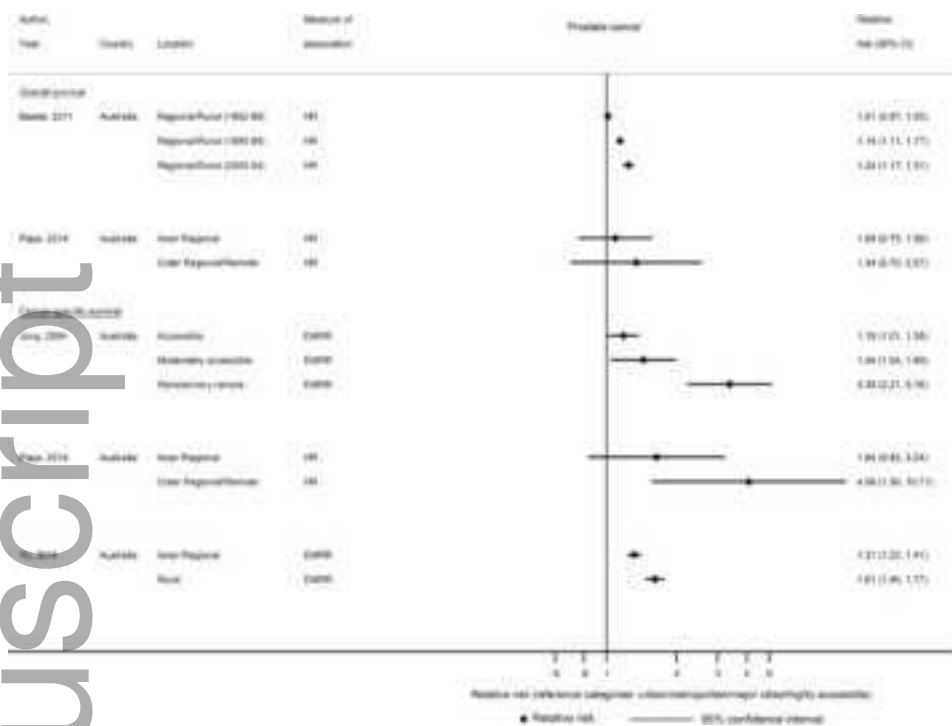


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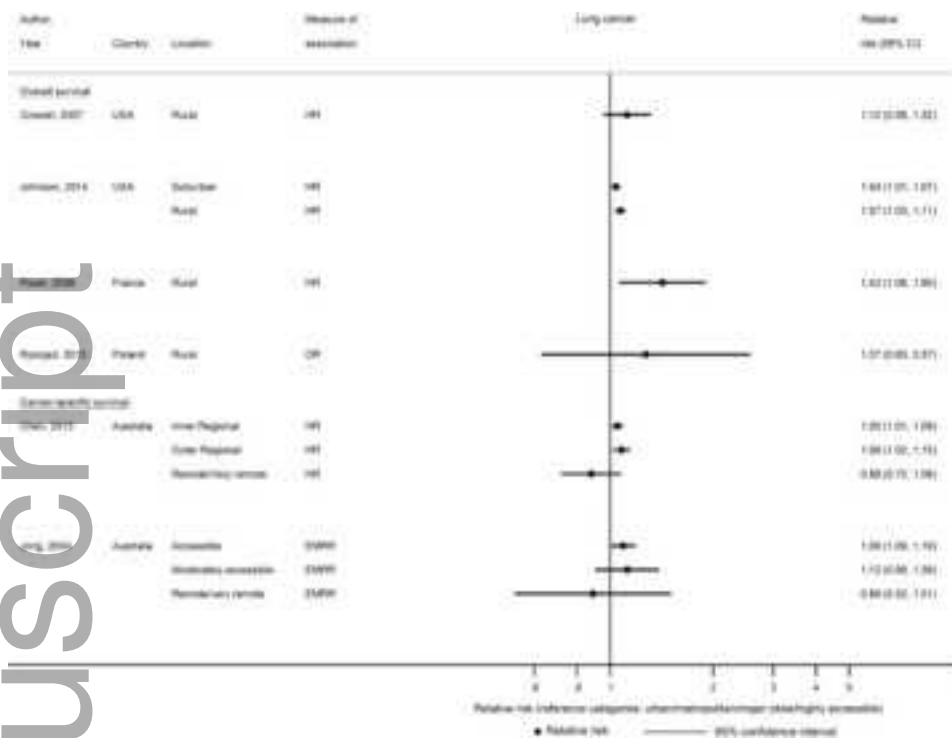




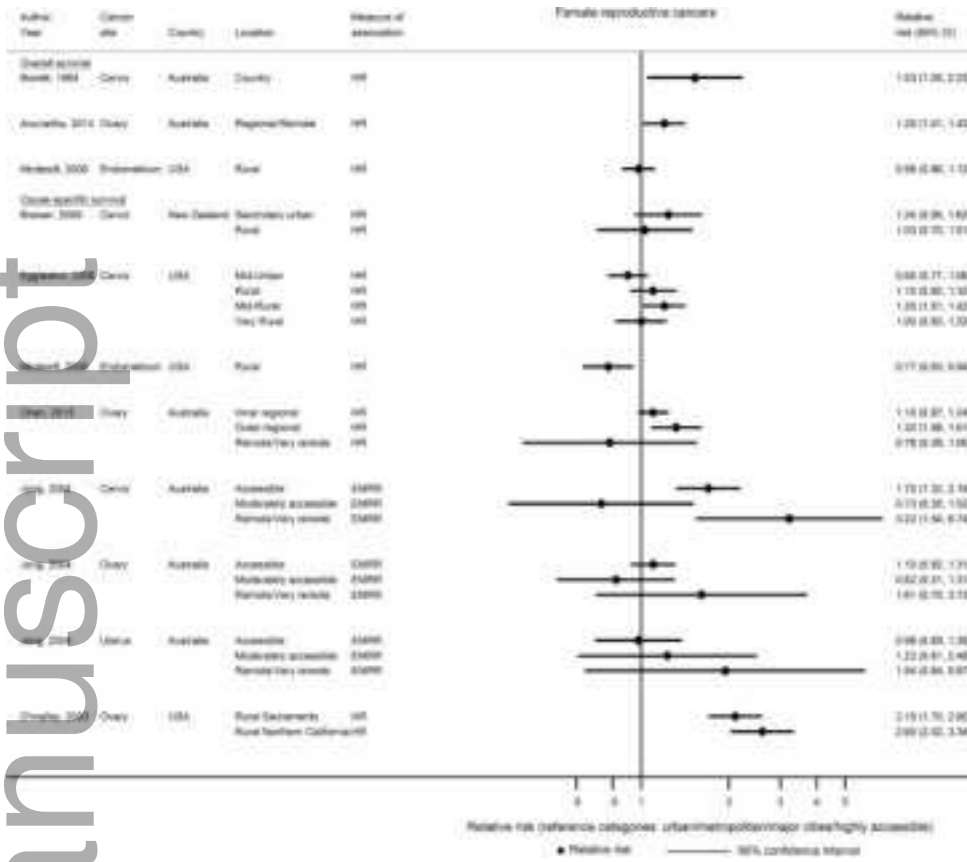
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