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Abstract: Background
The global economic crisis has been associated with increased unemployment and reduced public-sector expenditure on healthcare (PEH). We estimated the effects of changes in unemployment and PEH on cancer mortality, and identified how universal healthcare coverage (UHC) influenced the change.

Methods
Data were obtained from the World Bank and WHO (1990-2010). Mortality data from female breast, prostate, and colorectal cancers, which have survival rates that exceed 50%, were aggregated into a 'treatable' cancer class. Lung and pancreatic cancers, which have five-year survival rates <10%, were likewise aggregated to give an 'untreatable' cancer category. Multivariable regression analysis was used, controlling for country-specific demographics and infrastructure, with time-lag analyses and robustness checks to explore the relationship between unemployment and PEH on cancer mortality, with and without UHC. Trend analysis was used to project mortality rates based on trends prior to the sharp unemployment rise experienced by many countries from 2008 to 2010, and compare them with observed rates.

Results
Data were available for 75 countries (unemployment analysis) and 79 countries (PEH analysis). Unemployment rises were significantly associated with an increase in all-cancer mortality and all specific cancers save for female-lung cancer. Untreatable cancer mortality by contrast was not significantly linked with changes in unemployment. Lag analyses showed significant associations remained five years after unemployment increases for the treatable cancer class. Re-running analyses while accounting for UHC status removed the significant associations. All-cancer, treatable cancer, and specific cancer mortalities significantly decreased as PEH increased. Associations held over a five-year period regardless of whether UHC was present. Time-series analysis found just over 40 000 estimated excess deaths due to a subset of treatable cancers from 2008-2010 based on 2000-2007 trends. The great majority of these deaths were from non-UHC countries.

Interpretation
Unemployment increases are associated with cancer mortality increases. There is evidence that UHC protects against mortality increases associated with rises in unemployment, while PEH increases are associated with reduced cancer mortality. Reduced access to healthcare may underlie these associations.

Funding
None.

Economic downturns, universal healthcare coverage, and cancer mortality in high- and middle-income countries, 1990–2010

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SUMMARY

Background

The global economic crisis has been associated with increased unemployment and reduced public-sector expenditure on healthcare (PEH). We estimated the effects of changes in unemployment and PEH on cancer mortality, and identified how universal healthcare coverage (UHC) influenced the change.

Methods

Data were obtained from the World Bank and WHO (1990–2010). Mortality data from female breast, prostate, and colorectal cancers, which have survival rates that exceed 50%, were aggregated into a 'treatable' cancer class. Lung and pancreatic cancers, which have five-year survival rates <10%, were likewise aggregated to give an 'untreatable' cancer category. Multivariable regression analysis was used, controlling for country-specific demographics and infrastructure, with time-lag analyses and robustness checks to explore the relationship between unemployment and PEH on cancer mortality, with and without UHC. Trend analysis was used to project mortality rates based on trends prior to the sharp unemployment rise experienced by many countries from 2008 to 2010, and compare them with observed rates.

Results

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Unemployment increases are associated with cancer mortality increases. There is evidence that UHC protects against mortality increases associated with rises in unemployment, while PEH increases are associated with reduced cancer mortality. Reduced access to healthcare may underlie these associations.

Funding

None.

Key words: cancer; government spending; health economics; mortality; public health; unemployment; universal healthcare coverage.

INTRODUCTION

The global economic crisis, which began in 2008, compelled many countries to cut public spending in order to reduce public-sector borrowing.[1] These spending cuts often entailed either reductions or a flattening in public-sector jobs and public-sector expenditure on healthcare (PEH).[2,3] Thirty three of 53 WHO European region countries underwent no change in PEH between 2008 and 2009, while six experienced a reduction in PEH,[4] which have prompted concerns about the possible negative effects on public health. Studies have demonstrated that long-term unemployment leads to increased suicide rates and reduced healthcare access.[5,6]

Ecological studies exploring health-economic trends in the short run (separate from residual or secular trends) have thus far focused on macroeconomic changes and outcome indicators, such as suicide rates, cardiovascular disease incidence, all-cause mortality, and specific forms of cancer, but not cancer *per se*.[3,7–15] These potential associations may predominantly be explained by behavioural, mental, or stress-related changes with direct and immediate effects, whether, as in the case of suicides, they are counter-cyclical associations linked to the direct psychological and financial impact of job loss,[16] or pro-cyclical associations linked to reduced injury-related work and lifestyle activities in the case of all-cause mortality.[9] Few studies, however, have analysed the relationship between economic downturns and cancer especially in countries that may be more susceptible to economic shocks due to limited social security and healthcare systems.

Establishing a causal relationship between an economic change, such as aggregate unemployment, on cancer mortality is challenging, as downstream effects of unemployment-induced behavioural changes on lifestyle-related cancers manifest much later (20–30 years) than, for example, suicide or acute, stress-related cardiovascular events. However, access to healthcare and PEH may act as mediating factors with more immediate effects on health outcomes. One study on the Great Depression found deaths from cancer correlated with reduced income,[17] although the lack of treatment options for patients presenting with late-stage disease meant that the effect of the economic downturn on reduced healthcare access and mortality could not be as strongly demonstrated as it could in an era where systemic treatment is now available.

Cancer is one of the leading causes of death worldwide, accounting for 8.2 million deaths in 2012, with estimates suggesting a rise in annual cancer cases from 14 million in 2012 to 22 million by 2030.[18] Hence an understanding of the effects of macroeconomic changes on cancer outcomes worldwide is important.

We examined the association between changes in aggregate unemployment and PEH with deaths due to specific cancers, groups of cancers, and all cancers for countries where data was available and deemed of sufficient quality (1990–2010). Mortality was considered a more reliable measure of health outcomes than incidence due to the susceptibility of the latter to artificial rises following the adoption of improved means of diagnosis. We chose unemployment due to its ability to capture changes in individuals' circumstances, especially in the lower-income strata of societies. Given the recent drive, in many countries, to implement universal healthcare coverage (UHC),[19] we explored whether UHC conferred a protective effect. We also estimated the difference between the actual numbers of cancer-related deaths during and after the recent economic downturn and the expected numbers based on prior trends. For convenience, we have used the term 'excess deaths' to denote those estimated differences for which the number of deaths was higher than expected.

METHODS

Data sources

Economic data were obtained from the World Bank's Development Indicators & Global Development Finance 2013 edition datasets.[20] Unemployment (World Bank data code: SL.UEM.TOTL.ZS) was defined as the share of the labour force without work but available and seeking employment.[20] PEH (World Bank data code: SH.XPD.PUBL.ZS) was measured as a percentage of gross domestic product (GDP) at purchasing power parity (PPP); it was defined by the World Bank as including all rent and capital spending from government budgets (central and local), external borrowings and grants (including donations from international agencies and non-governmental organisations), and social (or compulsory) health insurance funds. Unemployment and cancer mortality (see below) data for 1990 to 2010 were available for 75 countries and data on PEH and cancer mortality for 1990 to 2009 were available for four additional countries (table 1), representing, as of 2009, 2.106 billion and 2.156 billion people in each dataset, respectively.[20] Classification of countries into high- and middle-income was done according to the World Bank's Atlas Method.[21] In brief, middle-income countries are those with a gross national income per capita of more than $1 045 but less than $12 736, whereas high-income economies are those with a gross national income per capita of $12 736 or more. Countries were classified into those with very high or high human development indices (HDI) according to the UN's Human Development Programme.[22]

Cancer mortality data (deaths per 100 000) for 1990 to 2010 for the countries in the unemployment and PEH datasets were obtained from the World Health Organisation (WHO) mortality database.[23] These data are based on death certification and updated annually from civil registration systems of WHO member states. Mortality data for prostate (ICD-10 C61), female-breast (ICD-10 C50), lung (male and female; ICD-10 C33–C34), colorectal (male and female; ICD-10 C18–C21) cancers and all cancers were extracted. Female breast, prostate and colorectal cancers have survival rates that exceed 50%.[24] Notably, at the time data were collected, complete cancer mortality data were unavailable for China, India, and countries from sub-Saharan Africa. We therefore aggregated the mortality data for these tumour types into a 'treatable' cancer class. Lung and pancreatic cancers (male and female; ICD-10 C25), which have five-year survival rates <10%, were likewise aggregated to give an 'untreatable' cancer category.[24] Age-standardised death rates (ASDRs), accounting for age distribution differences in populations, were extracted for all ages and ages 0–84 for both sexes and each sex separately. For age-specific cancer mortality rates, we aggregated crude rates (per 100 000 people) for each sex and country by 10-year age groups except for the youngest age group (0–34), which was combined to reduce the influence of age groups with fewer observations. These crude rates were defined as the number of deaths during a calendar year for a particular age group divided by the age group's mid-year population.

Multivariable regression analysis

We used multivariable regression analysis to assess the relationship between mortality rates for each cancer subtype, treatable cancers, untreatable cancers, and all cancers (response variable), and unemployment or PEH (predictor variable). Due to incomplete cancer mortality data for many of the 75 countries in the unemployment dataset, observations for the year 2010 were excluded from the analysis. To ensure that results were not driven by uncontrollable inter-country variations, we used fixed effects in the regression models, including one dummy variable for each country in each dataset excluding a reference group (i.e. 74 dummy variables for the unemployment dataset and 78 for the PEH dataset; table 2). This meant that the regression models evaluated mortality changes within individual countries while holding constant time-invariant differences between countries, including higher predispositions to cancer as well as political, healthcare, cultural, and structural differences. Multivariable regression with fixed effects was used since this methodology has been widely employed in similar studies, and is regarded as statistically robust and conservative.[25] The population structure of each country was also controlled for by incorporating total population size and demographic structure (the percentage of the population over 65 years and less than 15 years old) into the model (table 2). Further details of the model are provided in appendix S2.

We conducted 1-, 2-, 3-, 4-, and 5-year time-lag analyses. For both datasets, we then classified countries into those with UHC and those without, and re-ran the analyses using UHC status as a robustness check. Countries were considered to have UHC if all of the following previously described criteria were met: legislation mandating UHC; >90% of the population with access to some form of healthcare insurance; and >90% of the population with access to skilled birth attendance. The latter criterion was used to ensure the implementation of UHC met minimum performance standards expected of a functioning healthcare system. To test the sensitivity of our results to this definition, we re-ran the analysis using an alternative performance criterion, details of which are included in appendix S1 in the Supplementary Material (table S1). Robustness checks are detailed in table 2 and appendix S2.

Trend analysis

For the all-cancer mortality trend projection analysis, we set strict country inclusion criteria to ensure that only high quality data were used. We therefore excluded countries with civil registration coverage of cause-of-death less than 90% for the study period,[23] eliminating in the process 26 countries from the 61 for which all-cancer mortality data were complete for 2000 to 2010 (figure 1). In order to limit the effect of miscoding and comorbidity (frequent for older population groups), we excluded the 85+ age group, and to further ensure robustness in cross-country comparisons, we excluded age groups with fewer than 20 deaths in any calendar year. Details of the models used are provided in appendix S3.

Multivariable regression analyses were conducted using Stata SE version 12 (Stata Corporation, Texas, USA). Time-series analyses were conducted in R version 2.14.1 (http://www.r-project.org).

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for submitting the manuscript for publication.

RESULTS

Unemployment

A 1% unemployment rise was associated with a statistically significant increase in mortality for all but one of the six cancer sub-types studied: prostate (regression coefficient (R)=0.0981, 95% CI 0.0353–0.1609; p=0.0022), female-breast (R=0.1583, 95% CI 0.1110–0.2056; p<0.0001), male-lung (R=0.2260, 95% CI 0.1216–0.3304; p<0.0001), male-colorectal (R=0.0596, 95% CI 0.0188–0.1003; p=0.0042), and female-colorectal (R=0.0676, 95% CI 0.0362–0.099; p<0.0001) (figures 2A-E, figure S1A, table S2). The association for female-lung cancer mortality with unemployment was negative (R= –0.0593, 95% CI –0.1013 to 0.0172; p=0.0058; figure 2F, table S2). Whereas treatable cancer mortality was significantly linked with unemployment (R=0.1256, 95% CI 0.0148–0.2364; p=0.0265) (figure 2G, table S2), no such significance was observed for untreatable cancers (R=0.082, 95% CI -0.041–0.205; p=0.1919) (figure 2H, table S2). The strongest associations were found in the all-cancer data (R=0.3745, 95% CI 0.1939–0.5551; p=0.0001; figure 2I, table S2). Lag analysis showed that these results remained through to five years after unemployment increases (figure 2I). These associations held and remained significant in the robustness checks performed (tables S3–S9).

On accounting for the UHC status of countries, we found no significant association between unemployment and cancer mortality within the first year of unemployment rising (table 3, figures S1B-C). The results were unaffected by country classifications according to an alternative definition for UHC (appendix S1).

Trend analysis

For the trend analysis, population-weighted mean values of the projected age-specific rates and ASDRs for each year and sex were obtained. Globally (for the 35 countries selected), we observed significant deviations in the projected ASDR from the observed ASDR for both male all cancer mortality (figure 3A, table S10) and female all cancer mortality (figure 3B, table S10) with the 2010 predicted ASDR – 3 years after the unemployment rise in 2007 – deviating the most from the observed ASDR (males: rate ratio 1.0362, 95% CI 1.0209–1.052; p<0.0001; females: rate ratio 1.0428, 95% CI 1.0254–1.0607; p<0.0001). This corresponded to 55 434 (95% CI 32 439–78 428) excess deaths among men and 53 573 (95% CI 32 386–74 759) excess deaths among women in 2010 alone. Summing the point estimates for males and females from 2008 to 2010 yielded 252,199 excess deaths (figure 3A). This finding was recapitulated upon confinement of our analysis to treatable cancers (rate ratio 1.0362, 95% CI 1.0225–1.0502; p<0.0001; figure 3C, table S10) resulting in 22 977 (95% CI 14 482-31 472) excess deaths in 2010. By contrast, for untreatable cancers, the deviation between predicted and observed ASDR was not significant in 2008, 2009, or 2010 (figure 3D, table S10).

We next asked whether these trends held among different groups of countries. To answer this, we extracted ASDRs for the following: 26 countries with UHC implemented and 9 countries without UHC as of 2008; 31 high-income countries and 4 middle-income countries as classified by the World Bank using the Atlas Method;[21] and 22 very high HDI and 13 high HDI countries.[22]

For the UHC country group, no significant difference was found for treatable cancer ASDR (figure 3E, table S10). By contrast, for the non-UHC country group the predicted ASDRs for treatable cancers were significantly lower than the observed ASDRs for all 3 projected years (in 2010: rate ratio 1.0746, 95% CI 1.0417–1.11; $p<0.0001$), which equated to 21 241 (95% CI 12 244–30 238) excess deaths due to treatable cancers in 2010 (figure 3F, table S10). Differences between the actual and projected ASDR of untreatable cancer were non-significant for both UHC and non-UHC country groups in 2008 with a significantly lower-than-expected number of deaths in 2009 and 2010 for the UHC country group, and a marginally significant higher-than-expected number of deaths in 2010 for the non-UHC country group (table S10).

Stratifying countries by income using the World Bank's classification,[21] yielded higher rate ratios (indicating higher-than-expected numbers of deaths) for male, female and treatable cancers among middle-income countries than among high-income countries (table S10). For untreatable cancers, high-income countries experienced significantly lower-than expected numbers of deaths whereas middle-income countries experienced significantly higher-than-expected numbers of deaths (table S10). On dividing countries according to HDI, neither the very high nor high HDI groupings experienced higher-than-expected numbers of untreatable cancer deaths although significantly lower-than expected numbers across all years were only observed for the very high HDI group (table S10).

Public-sector expenditure on healthcare

Increases in PEH, as a proportion of GDP, were significantly associated with mortality reductions in seven of the nine cancer categories studied: prostate (R= –0.0013, 95% CI –0.0019 to –0.0008; $p<0.0001$), female-breast (R= –0.0023, 95% CI –0.0029 to –0.0017; $p<0.0001$), male-lung (R= –0.0037, 95% CI –0.0045 to –0.0028; $p<0.0001$), male-colorectal (R= –0.0011, 95% CI –0.0016 to –0.0007; $p<0.0001$), female-colorectal (R= –0.0011, 95% CI –0.0014 to –0.0008; $p<0.0001$), treatable (R= –0.006858, 95% CI –0.007532 to –0.006184; $p<0.0001$) and all-cancers (R= –0.0053, 95% CI –0.0070 to –0.0036; $p<0.0001$) (figure 4, table S11). Female-lung cancer mortality (R= 0.0007, 95% CI 0.0004 to 0.0011; $p=0.0001$) on the other hand was significantly positively associated with PEH while for mortality from untreatable cancers we observed no significant link (R= 0.0006, 95% CI –0.0002 to 0.0014; p=0.1492) (figures 4F and 4H, table S11).

Lag analysis showed that these results carried through to five years after increases in PEH (figure 4). Spending increases were associated with a slight increase in lung cancer mortality in women (figure 4F) but not at all with deaths from untreatable cancers (figure 4H). The same trends were found irrespective of UHC status (table 4). For the most part, these significant associations held in the robustness checks performed (tables S12–S18).

DISCUSSION

Our results suggest that increases in unemployment in 1990 to 2009 were associated with increased mortality of prostate, breast, male-lung, and colorectal cancers in a range of countries. Increases in unemployment were also associated with increased mortality due to a subset of treatable cancers as well as all cancers. Time-lag analyses indicated that these adverse effects persisted long after initial rises in unemployment. For the most part, these associations remained significant after controlling for economic, resource availability, infrastructure, and out-of-pocket spending indicators. UHC implementation, however, removed the association between changes in unemployment and cancer mortality implying that UHC could have had a protective effect against the possible impact of unemployment. Our findings also suggest that increased PEH (as a proportion of GDP) is associated with improved cancer mortality. This trend continued irrespective of UHC status.

In all analyses, we could not demonstrate an association to female-lung cancer unlike other cancers (figures 2F and 4F). One plausible reason arising from our treatable versus untreatable cancer analysis is that this discrepancy might have been the consequence of the survival rate for female lung cancer being less than that for male; however, this hypothesis is not supported by evidence.[26] As such, this remains a topic for future investigation.

The trend analysis studied a particular set of periods in order to obtain counter-factual results for 2008–2010 (the projection period), based on models of the mortality trends for 2000–2007 (the observation period), with the hypothesis that observation-period trends would continue for the projection period. These periods were chosen so as to correspond with the sharp upturn in unemployment observed from 2008 onwards (figure S2) during the global economic crisis, while limiting the effects of previous unemployment fluctuations and technical progress in cancer care, which may otherwise have influenced rates if the observation period had been extended further back than 2000. We found the strongest, most significant deviations between observed and projected rates to occur for the non-UHC country grouping, corroborating our multivariable regression analyses. Likewise, the difference between expected and actual all-cancer mortality rates in middle-income countries exceeded that between high-income countries, a finding that mirrors the variable influence that the income class of a country has on other causes of death.[27] The chronological link between the unemployment rise due to the global economic crisis and the subsequent change in cancer mortality, lends favour to a potentially causal link, rather than reverse causality or endogeneity.

The primary means by which increased unemployment is likely to have an adverse impact upon cancer mortality is through reduced access to healthcare (figure 5), which may manifest as late-stage diagnoses,[28,29] and poor or delayed treatment.[30] Furthermore, unemployment has been found to correlate with lower socioeconomic status (SES).[31,32] In turn, there is substantial evidence linking lower SES to lower cancer survival, with reduced access to treatment being a mediating cause,[33,34] as well as lower health-seeking behaviours.[35] Job loss is also strongly associated with mental health and behavioural problems,[5] and this may also have a negative impact on survival in cancer patients as a consequence of lower rates of treatment commencement following diagnosis or higher treatment discontinuation rates.[36]

Our results regarding PEH and cancer mortality are consistent with studies comparing spending levels across countries.[37] Integrated multidisciplinary care pathways for cancer involving screening, radiotherapy, chemotherapy, and surgery, are costly but effective at reducing mortality. Changes in the availability of healthcare resources – whether at the diagnosis or treatment stage – due to changes in spending, are likely to have an impact on health outcomes. Additionally, further consequences of changes in PEH include changes in the number of healthcare professionals, with fewer healthcare professionals likely to result in reduced quality of care if productivity gains are not made,[38] and changes in the number of localised sites providing healthcare, with longer distances or travel times likely to increase delays in presentation for diagnosis as well as adversely affect treatment.[39]

Our study has at least two major policy implications. First, it makes a strong case for UHC and its possible moderating effect on unemployed populations during economic downturns. In UHC countries where healthcare provision is meant to be equally accessible regardless of employment status, access to healthcare is less problematic than in non-UHC countries where access is often provided by means of an employment package. Second, amidst a background of rising healthcare costs, if spending restrictions are not accompanied by proportionate improvements in efficiency, worse quality of care and, in turn, higher mortality levels, may follow.

We note several limitations of our study. First, we evaluated population health outcomes and economic trends but did not account for variations at regional and sub-national levels. Second, for reasons of data availability and quality, we were unable to analyse the effects of the global economic crisis after 2010. However, in addition to the sizeable economic fluctuations that occurred during the period studied, our analysis was still able to capture the effects of the earlier stages of the crisis with the trend analysis, during which unemployment levels rose sharply and in some countries peaked. For the PEH dataset, we did not account for changes in efficiency; indeed, it is possible that a country spends less on healthcare but achieves greater outcomes due to the efficiency of its system. Linked to this, we acknowledge the reduced global reach of our study due to the lack of data for low-income countries as well as China and

India. Indeed, an examination of whether our findings hold in lower income countries where it is possible that mortality rates for certain cancer types have been rising rather than falling would offer valuable insight. Fourth, our study was retrospective and observational, limiting our ability to draw causal inferences. The possibility of residual confounding from social determinant and region-specific healthcare system variables also necessitates a comprehensive, longitudinal approach characterising trends and predictors of healthcare access and quality before and after significant economic changes to strengthen the case for any causative effect as well as clarifying the expected latency between cancer treatment and mortality. Finally, by employing a fixed-effects model, we assumed that any unobserved factors within each country were time-invariant and not correlated with our variables of interest, although the comprehensiveness of our robustness checks will have reduced the probability of this assumption affecting our findings.

Notwithstanding the limitations discussed, our findings suggest that both unemployment and PEH are significantly associated with cancer mortality, with associations lasting up to five years. We estimate that the 2008–2010 global economic crisis may have been associated with up to 250 000 excess cancer-related deaths. Our analysis also suggests that UHC may remove the association between unemployment and cancer mortality, lending evidence in favour of healthcare system reforms aimed at providing UHC, particularly among middle-income countries.

AUTHORS' CONTRIBUTIONS

MM, JW, AMN and CW compiled the data. MM conceived and designed the study with input from JW, RaA, RS, TZ, and RiA. MM and JW conducted the statistical analysis, and wrote the first draft of the manuscript. AMN, CW, RaA, RS, TZ and RiA helped interpret the findings, and provided input to subsequent drafts of the manuscript. All authors have seen and approved the final version of the report. MM and JW contributed equally.

CONFLICTS OF INTEREST

None to declare.

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ETHICS COMMITTEE APPROVAL

Ethics approval was not applicable for this study.

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RESEARCH IN CONTEXT

Evidence before this study

We searched the literature to identify articles that quantitatively estimated either the effect of both unemployment and healthcare spending (public or otherwise) on cancer mortality, or the effect of universal healthcare coverage on cancer mortality. We searched PubMed for publications up to and including May 31 2015 using the following combinations of search terms: (i) unemployment AND cancer AND mortalit* AND (spending OR expenditure); (ii) cancer AND mortalit* AND ("universal health coverage" OR "universal healthcare coverage"). Search combination (i) yielded seven publications, and combination (ii) yielded one publication. With respect to search combination (i), one study used a time-trend analysis to examine the relationship between unemployment and mortality in Scotland, and included specific causes of death such as lung cancer.[40] A second study simply used Pearson's correlation rather than a panel-based fixed effects model to find an association between all-cancer mortality, and healthcare expenditure (negative) and unemployment (positive) in European countries.[41] The authors were therefore unable to control for potential confounding variables. The study periods for both these publications ended before the 2008 economic recession. Three further studies investigated a substantially narrower geographical region and outcome than the present study. The first study examined the relationship between spending, unemployment and breast cancer mortality in the European Union only,[14] the second examined the relationship between unemployment and stomach cancer mortality again in the European Union only,[15] while the third examined prostate cancer mortality in countries belonging to the Organisation for Economic Co-operation and Development.[42] The remaining two studies were not considered relevant, as they did not quantify the relationship between the macroeconomic indicators and cancer mortality. The study extracted from search combination (ii) was also irrelevant in that again it did not seek to quantify the influence of coverage on mortality.

Added value of this study

The study presented here is the first global analysis of the impact of unemployment and public healthcare spending on mortality due to all cancers, "treatable" cancers, "untreatable" cancers and specific forms of cancer. In using a conservative, fixed-effects regression analysis model to ascertain the existence of an association and quantify any associations combined with robustness checks, this study accounts for criticisms levelled at other studies looking at the relationship between health outcomes and unemployment, namely, the omission of potential confounding variables likely to be correlated with both unemployment rates (or public healthcare spending) and cancer mortality rates. In using a panel-data approach for the multivariable regression analysis to compare unemployment rates (or public healthcare spending) at intervals of one year for each year after the increase in unemployment (or public healthcare spending) with the mortality rates in each country, we controlled for time-invariant heterogeneity between countries. Finally, we combined the above with a time-trend analysis, to provide a rigorous characterisation of the associations between unemployment, public healthcare spending, universal healthcare coverage, income, and cancer mortality. The major findings from these complementary approaches are that unemployment increases are associated with rises in cancer mortality, with universal healthcare coverage protecting against this phenomenon. Consideration of certain types of cancer as either treatable or untreatable revealed that significantly higher-than-expected numbers of deaths were only observed for treatable cancers. In contrast to unemployment, public healthcare spending increases are associated with reductions in cancer mortality with a recapitulation of the divergent findings between treatable and untreatable cancers. Whether or not a country has implemented universal healthcare coverage does not significantly alter the strength of this relationship.

Implications of all the available evidence

Policies that maintain spending and hence access to and quality of healthcare in the face of economic downturns especially among cancers that are considered treatable may offset some of the negative effects of such periods on health outcomes. Furthermore, the findings of our study add to the existing body of evidence in favour of universal healthcare coverage.

FIGURE LEGENDS

Figure 1. **Cohort selection diagram for the trend prediction analysis**

Cohort selection with final aggregation by UHC status. The first step involves selecting only those countries with complete consecutive mortality data from 2000 to 2010. The second filters out countries with civil registration coverage of cause-of-death of <90%. Next, the over-85 age group and age groups with fewer than 20 deaths in any calendar year were excluded. The first row of boxes at the end of the workflow shows the categorisation of countries by UHC status (as determined by skilled birth attendance). The second row of boxes at the end of the workflow shows the categorisation of countries by income status. The third row shows the categorisation of countries by HDI. Cancer mortality data (deaths per 100 000) were obtained from the World Health Organisation Mortality Database 2013.[23] HDI categories were obtained from the United Nations Development Programme website.[22] HDI, Human development index, UHC, Universal healthcare coverage.

Figure 2. **Time-lag analyses of changes in unemployment on cancer mortality.**

Multivariable regression analysis was conducted on data for 75 countries from 1990 to 2009 to assess the relationship between unemployment, and prostate cancer mortality (A), breast cancer mortality (B), male colorectal cancer mortality (C), female colorectal cancer mortality (D), male lung cancer mortality (E), female lung cancer mortality (F), treatable cancer mortality (G), untreatable cancer mortality (H) and all-cancer mortality (I). Analyses were conducting with controls for population size, population structure (proportion of population below 14 years of age and above 65 years of age), and country-specific differences in healthcare infrastructure. Data are also shown for 1-, 2-, 3-, 4-, and 5-year time-lag analyses. Economic data were obtained from the World Bank.[25] Cancer mortality data (deaths per 100 000) were obtained from the World Health Organisation Mortality Database 2013. [23] * $p<0.05$; ** $p<0.01$; *** $p<0.001$.

Figure 3. **Predicted cancer-related mortality rate and number of deaths, 2008–2010, based on 2000–2007 observation base.**

Projections of age-standardised cancer-related mortality rates per 100 000 (ASDR) for 35 countries from 2008 to 2010 were made based upon ASDRs observed from 2000 to 2007, and compared with those observed from 2008 to 2010. The number of excess deaths due to male cancers (A), female cancers (B), treatable cancers (female breast, prostate and colorectal) (C), and untreatable cancers (lung and pancreatic) (D) were estimated by comparing 2008-2010 projected rates with 2008-2010 observed rates. The projections of ASDRs for treatable cancers are also shown for UHC (E) and non-UHC (F) countries. ASDRs were extracted from the World Health Organisation Mortality Database 2013.[23] * $p<0.05$; ** $p<0.01$; *** $p<0.001$.

Figure 4. **Time-lag analyses of changes in public-sector healthcare expenditure on cancer mortality.**

Multivariable regression analysis was conducted on data for 79 countries from 1990 to 2009 to assess the relationship between public-sector healthcare expenditure, and prostate cancer mortality (A), breast cancer mortality (B), male colorectal cancer mortality (C), female colorectal cancer mortality (D), male lung cancer mortality (E), female lung cancer mortality (F), treatable cancer mortality (G), untreatable cancer mortality (H), and all-cancer mortality (I). Analyses were conducted with controls for population size, population structure (proportion of population below 14 years of age and above 65 years of age), and country-specific differences in healthcare infrastructure. Data are also shown for 1-, 2-, 3-, 4-, and 5-year time-lag analyses. Economic data were obtained from the World Bank.[25] Cancer mortality data (deaths per 100 000) were obtained from the World Health Organisation Mortality Database 2013.[23] * $p<0.05$; ** $p<0.01$; *** $p<0.001$.

Figure 5. **Possible causal pathways for the observed associations**

PEH, Public-sector expenditure on healthcare; SES, Socioeconomic status.

TABLES

Country/Grouping	Population 2009	Country/Grouping	Population 2009
Albania	3 151 185	Luxembourg	497 783
Argentina	40 023 641	Macedonia	2 100 558
Armenia	2 968 154	Malta	413 991
Australia	21 778 800	Mauritius	1 275 032
Austria	8 365 275	Mexico	116 815 612
Azerbaijan	8 947 243	Moldova	3 565 603
Barbados	279 006	Netherlands	16 530 388
Belgium	10 796 493	New Zealand	4 315 800
Belize	301 016	Nicaragua	5 743 329
Brazil	193 490 922	Norway	4 828 726
Bulgaria	7 585 131	Panama	3 615 846
Canada	33 726 915	Paraguay	6 347 383
Chile	16 991 729	Peru	28 934 303
Colombia	45 802 561	Philippines	91 886 400
Costa Rica	4 601 424	Poland	38 151 603
Croatia	4 429 000	Portugal	10 632 482
Cuba	11 288 826	Romania	21 480 401
Czech Republic	10 487 178	Russian Federation	141 910 000
Denmark	5 523 095	Serbia	7 320 807
Dominican Republic	9 884 265	Singapore	4 987 600
Ecuador	14 756 424	Slovak Republic	5 418 590
Egypt	76 775 023	Slovenia	2 039 669
El Salvador	6 183 484	Spain	45 908 594
Estonia	1 340 271	Suriname	520 173
Finland	5 338 871	Sweden	9 298 515
France	64 702 921	Switzerland	7 743 831
Georgia	4 410 900	Tajikistan	7 447 396
Germany	81 902 307	Thailand	66 277 335
Greece	11 282 760	Trinidad and Tobago	1 322 518
Guatemala	13 988 988	Turkmenistan	4 978 962
Hungary	10 022 650	Ukraine	46 053 300
Iceland	318 499	United Kingdom	61 811 027
Republic of Ireland	4 458 942	United States	306 771 529
Israel	7 485 600	Uruguay	3 360 431
Italy	60 192 698	Uzbekistan	27 767 400
Japan	127 557 958	Venezuela	28 583 040
Kazakhstan	16 093 481	High-income	1 066 391 720
Republic of Korea	49 182 000	Middle-income	188 342 304
Kuwait	2 850 102	UHC	641 437 562
Kyrgyz Republic	5 383 300	Non-UHC	613 296 462
Latvia	2 254 834	Very high human development index	849 195 806
Lithuania	3 339 456	High human development index	405 538 218

***Table 1:* Population estimates of countries included in multiple regression and time-series analyses, 2009.** Population estimates were obtained from the World Bank (data code: SP.POP.TOTL).[20] For country groupings, populations are calculated only for those countries

included in the time-series analysis as per figure 1. UHC, Universal healthcare coverage.

	Common controls	**Robustness check control**	**Particular control**	**Total number of controls**
Unemployment dataset (75 countries)	Population size Proportion of population less than 15 years of age Proportion of population over 65 years of age	Economic	Inflation GDP per capita changes Base interest rates	80
		Resource availability	Number of physicians per 100 000 population; Number of hospital beds per 100 000 population	79
		Infrastructure	Urbanisation; Access to water; Calorie intake	80
		Out-of-pocket spending	Out-of-pocket expenditure	78
		WHO data quality check	N/A (Re-run analysis using data classified as Level 1 or Level 2 in quality by the WHO)	77
		Income	(2 categories coded into 1 dummy variable)	78
		Human development index	(3 categories coded into 2 dummy variables)	79
PEH dataset (79 countries)	Population size Proportion of population less than 15 years of age Proportion of population over 65 years of age	Economic	Inflation; GDP per capita changes; Base interest rates	84
		Resource availability	Number of physicians per 100 000 population; Number of hospital beds per 100 000 population	83
		Infrastructure	Urbanisation; Access to water; Calorie intake	84
		Out-of-pocket spending	Out-of-pocket expenditure	82
		WHO data quality check	N/A (Re-run analysis using data classified as Level 1 or Level 2 in quality by the WHO)	81
		Income	(2 categories coded into 1 dummy variable)	82
		Human development index	(3 categories coded into 2 dummy variables)	83

Table 2: **Controls used in multiple regression and sensitivity analyses.** Data were obtained from the World Bank.[20] PEH, Public-sector expenditure on healthcare.

Cancer mortality in year of unemployment rise (deaths per 100 000)	Co-efficient	Robust standard error	p Value	Lower confidence interval (95%)	Upper confidence interval (95%)
Prostate cancer	0.0975	(0.1025)	0.3422	–0.1042	0.2992
Breast (female) cancer	0.0802	(0.0763)	0.2939	–0.0699	0.2302
Colorectal (male) cancer	–0.0679	(0.0589)	0.2495	–0.1838	0.0479
Colorectal (female) cancer	–0.0306	(0.0384)	0.4263	–0.1062	0.0450
Lung (male) cancer	–0.0126	(0.1753)	0.9428	–0.3575	0.3324
Lung (female) cancer	–0.0143	(0.0454)	0.7534	–0.1035	0.0750
Treatable cancers	0.0319	(0.0692)	0.6449	–0.1037	0.1675
Untreatable cancers	0.0758	(0.061)	0.2142	-0.0437	0.1952
All cancers	0.0525	(0.1778)	0.7679	–0.2970	0.4019

Table 3: **Unemployment and cancer mortality rates controlling for universal healthcare coverage.**

Countries were classified as universal healthcare coverage (UHC) countries according to whether they were assessed to have met all of the following previously described conditions: legislation mandating UHC; >90% healthcare coverage; and >90% skilled birth attendance.

Cancer mortality in year of PEH rise (deaths per 100 000)	Co-efficient	Robust standard error	p Value	Lower confidence interval (95%)	Upper confidence interval (95%)
Prostate cancer	–0.0009	(0.0001)	1.052×10^{-10}***	–0.0011	–0.0006
Breast (female) cancer	–0.0009	(0.0001)	1.013×10^{-10}***	–0.0012	–0.0007
Colorectal (male) cancer	-3×10^{-5}	(0.0003)	0.9126	–0.0006	0.0006
Colorectal (female) cancer	–0.0004	(0.0001)	1.04×10^{-5}***	–0.0011	–0.0002
Lung (male) cancer	–0.0007	(0.0003)	0.0087**	–0.0012	–0.0002
Lung (female) cancer	0.0005	(0.0001)	2.19×10^{-5}***	0.0003	0.0007
Treatable cancers	–0.0022	(0.0005)	8.074×10^{-6}***	–0.0032	–0.0012
Untreatable cancers	0.0008	(0.0004)	0.0341*	0.0001	0.0016
All cancers	–0.0016	(0.0005)	1.7×10^{-6}***	–0.0026	–0.0006

Table 4: **PEH and cancer mortality rates controlling for universal healthcare coverage.**

Countries were classified as universal healthcare coverage (UHC) countries according to whether they were assessed to have met all of the following previously described conditions: legislation mandating UHC; >90% healthcare coverage; and >90% skilled birth attendance. PEH, Public-sector expenditure on healthcare. * p<0.05; ** p<0.01; *** p<0.001

Economic downturns, universal healthcare coverage, and cancer mortality~~: a global analysis~~ in high- and middle-income countries, 1990–2010

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SUMMARY

Background

The global economic crisis has been associated with increased unemployment and reduced public-sector expenditure on healthcare (PEH). We estimated the effects of changes in unemployment and PEH on cancer mortality, and identified how universal healthcare coverage (UHC) influenced the change.

Methods

Data were obtained from the World Bank and WHO (1990–2010). Mortality data from female breast, prostate and colorectal cancers, which have survival rates that exceed 50%, were aggregated into a 'treatable' cancer class. Lung and pancreatic cancers, which have five-year survival rates <10%, were likewise aggregated to give an 'untreatable' cancer category. Multivariable regression analysis was used, controlling for country-specific demographics and infrastructure, with time-lag analyses and robustness checks to explore the relationship between unemployment and PEH on cancer mortality, with and without UHC. Trend analysis was used to project mortality rates based on trends prior to the sharp unemployment rise experienced by many countries from~~in~~ 2008 to 2010, and compare them with observed rates.

Results

Data were available for 75 countries (unemployment analysis) and 79 countries (PEH analysis). Unemployment rises were significantly associated with an increase in all-cancer mortality and all specific cancers save for female-lung cancer. Untreatable cancer mortality by contrast was not significantly linked with changes in unemployment. Lag analyses showed significant associations remained five years after unemployment increases for the treatable cancer class. Re-running analyses while accounting for UHC status removed the significant associations. All-cancer, treatable cancer and specific cancer mortalities significantly decreased as PEH increased. Associations held over a five-year period regardless of whether UHC was present. Time-series analysis found just over 40 000 estimated excess deaths due to a subset of treatable cancers from 2008-2010 based on 2000-2007 trends. The great majority of these deaths were from non-UHC countries.

Interpretation

Unemployment increases are associated with cancer mortality increases. There is evidence that UHC protects against mortality increases associated with rises in unemployment, while PEH increases are associated with reduced cancer mortality. Reduced access to healthcare may underlie these associations.

Funding

None.

Key words: cancer; government spending; health economics; mortality; public health; unemployment; universal healthcare coverage.

INTRODUCTION

The global economic crisis, which began in 2008, compelled many countries to cut public spending in order to reduce public-sector borrowing.[1] These spending cuts often entailed either reductions or a flattening in public-sector jobs and public-sector expenditure on healthcare (PEH).[2,3] ~~Indeed, 33~~Thirty three of 53 WHO European region countries underwent no change in PEH between 2008 and 2009, while six experienced a reduction in PEH,[4] which have prompted concerns about the possible negative effects on public health. Studies have demonstrated that long-term unemployment leads to increased suicide rates and reduced healthcare access.[5,6]

Ecological studies exploring health-economic trends in the short run (separate from residual or secular trends) have thus far focused on macroeconomic changes and outcome indicators, such as suicide rates, cardiovascular disease incidence, all-cause mortality and specific forms of cancer, but not cancer *per se*.[3,7–15] These potential associations may predominantly be explained by behavioural, mental, or stress-related changes with direct and immediate effects, whether, as in the case of suicides, they are counter-cyclical associations linked to the direct psychological and financial impact of job loss,[16] or pro-cyclical associations linked to reduced injury-related work and lifestyle activities in the case of all-cause mortality.[9] Few studies, however, have analysed the relationship between economic downturns and cancer especially in countries that ~~are~~ may be more susceptible to economic shocks due to l~~ess-developed~~imited social security and healthcare systems.

Establishing a causal relationship between an economic change, such as aggregate unemployment, on cancer mortality is challenging, as downstream effects of unemployment-induced behavioural changes on lifestyle-related cancers manifest much later (20-30 years) than, for example, suicide or acute, stress-related cardiovascular events. However, access to healthcare and PEH may act as mediating factors with more immediate effects on health outcomes. One study on the Great Depression found deaths from cancer correlated with reduced income,[17] although the lack of treatment options for patients presenting with late-stage disease meant that the effect of the economic downturn on reduced healthcare access and mortality could not be as strongly demonstrated as it could in an era where systemic treatment is now available.

Cancer is one of the leading causes of death worldwide, accounting for 8.2 million deaths in 2012, with estimates suggesting a rise in annual cancer cases from 14 million in 2012 to 22 million by 2030.[18] Hence an understanding of the effects of macroeconomic changes on cancer outcomes worldwide is important.

We examined the association between changes in aggregate unemployment and PEH with deaths due to specific cancers, groups of cancers, and all cancers for countries where data was available and deemed of sufficient quality (1990–2010). Mortality was considered a more reliable measure of health outcomes than incidence due to the susceptibility of the latter to artificial rises following the adoption of improved means of diagnosis. We chose unemployment due to its ability to capture changes in individuals' circumstances, especially in lower-income strata of societies. Given the recent drive, in many countries, to implement universal healthcare coverage (UHC), ~~We explored whether universal healthcare coverage (UHC) conferred a protective effect, hypothesising that UHC would enable the unemployed to access healthcare, especially as many countries progress towards UHC systems.~~[19] we explored whether UHC conferred a protective effect. We also estimated the difference between the actual numbers of cancer-related deaths during and after the recent economic downturn and the expected numbers based on prior trends. For convenience, we have used the term 'excess deaths' to denote those estimated differences for which the number of deaths was higher than expected. ~~We estimated additional cancer-related deaths due to the recent economic downturn.~~

METHODS

Data sources

Economic data were obtained from the World Bank's Development Indicators & Global Development Finance 2013 edition datasets.[20] Unemployment (World Bank data code: SL.UEM.TOTL.ZS) was defined as the share of the labour force without work but available and seeking employment.[20] PEH (World Bank data code: SH.XPD.PUBL.ZS) was measured as a percentage of gross domestic product (GDP) at purchasing power parity (PPP); it was defined by the World Bank as including all rent and capital spending from government budgets (central and local), external borrowings and grants (including donations from international agencies and non-governmental organisations), and social (or compulsory) health insurance funds. Unemployment and cancer mortality (see below) data for 1990 to 2010 were available for 75 countries and data on PEH for 1990 to 2009 were available for four additional countries (table 1), representing, as of 2009, 2.106 billion and 2.156 billion people in each dataset, respectively.[20] Classification of countries into high- and middle-income was done according to the World Bank's Atlas Method.[21] In brief, middle-income countries are those with a gross national income per capita of more than $1 045 but less than $12 736, whereas high-income economies are those with a gross national income per capita of $12 736 or more. Countries were classified into those with very high or high human development indices (HDI) according to the UN's Human Development Programme.[22]

Cancer mortality data (deaths per 100 000) for 1990 to 2010 for the countries in the unemployment and PEH datasets were obtained from the World Health Organisation (WHO) mortality database.[23] These data are based on death certification and updated annually from civil registration systems of WHO member states. Mortality data for prostate (ICD-10 C61), female-breast (ICD-10 C50), lung (male and female; ICD-10 C33–C34), colorectal (male and female; ICD-10 C18–C21) cancers and all cancers were extracted. Female breast, prostate and colorectal cancers have survival rates that exceed 50%.[24] We therefore aggregated the mortality data for these tumour types into a 'treatable' cancer class. Lung and pancreatic cancers (male and female; ICD-10 C25), which have five-year survival rates <10%, were likewise aggregated to give an 'untreatable' cancer category.[24] Notably, at the time data were collected, complete cancer mortality data were unavailable for China, India, and countries from sub-Saharan Africa. Age-standardised death rates (ASDRs), accounting for age distribution differences in populations, were extracted for all ages and ages 0–84 for both sexes and each sex separately. For age-specific cancer mortality rates, we aggregated crude rates (per 100 000 people) for each sex and country by 10-year age groups except for the youngest age group (0–34), which was combined to reduce the influence of age groups with fewer observations. These crude rates were defined as the number of deaths during a calendar year for a particular age group divided by the age group's mid-year population.

Multivariable regression analysis

We used multivariable regression analysis to assess the relationship between mortality rates for each cancer subtype, treatable cancers, untreatable cancers and all cancers (response variable), and unemployment or PEH (predictor variable). Due to incomplete cancer mortality data for many of the 75 countries in the unemployment dataset, observations for the year 2010 were excluded from the analysis. To ensure that results were not driven by uncontrollable inter-country variations, we used fixed effects in the regression models, including one dummy variable for each country in each dataset excluding a reference group (i.e. 74 dummy variables for the unemployment dataset and 78 for the PEH dataset; table 2). This meant that the regression models evaluated mortality changes within individual countries while holding constant time-invariant differences between countries, including higher predispositions to cancer as well as political, healthcare, cultural, and structural differences. Multivariable regression with fixed effects was used since this methodology has been widely employed in similar studies, and is regarded as statistically robust and conservative.[25] The population structure of each country was also controlled for by incorporating total population size and demographic structure (the percentage of the population over 65 years and less than 15 years old) into the model (table 2). Further details of the model are provided in appendix S2.

We conducted 1-, 2-, 3-, 4-, and 5-year time-lag analyses. For both datasets, we then classified countries into those with UHC and those without, and re-ran the analyses using UHC status as a robustness check. Countries were considered to have UHC if all of the following previously described criteria were met: legislation mandating UHC; >90% of the population with access to some form of healthcare insurance; and >90% of the population with access to skilled birth attendance. The latter criterion was used to ensure the implementation of UHC met minimum performance standards expected of a functioning healthcare system. To test the sensitivity of our results to this definition, we re-ran the analysis using an alternative performance criterion, details of which are included in appendix S1 in the Supplementary Material (table S1). Robustness checks are detailed in table 2 and appendix S2.

Trend analysis

For the all-cancer mortality trend projection analysis, we set strict country inclusion criteria to ensure that only high quality data were used. We therefore excluded countries with civil registration coverage of cause-of-death less than 90% for the study period,[23] eliminating in the process 26 countries from the 61 for which all-cancer mortality data were complete for 2000 to 2010 (figure 1). In order to limit the effect of miscoding and comorbidity (frequent for older population groups), we excluded the 85+ age group, and to further ensure robustness in cross-country comparisons, we excluded age groups with fewer than 20 deaths in any calendar year. Details of the models used are provided in appendix S3.

Multivariable regression analyses were conducted using Stata SE version 12 (Stata Corporation, Texas, USA). Time-series analyses were conducted in R version 2.14.1 (http://www.r-project.org).

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for submitting the manuscript for publication.

RESULTS

Unemployment

A 1% unemployment rise was associated with a statistically significant increase in mortality for all but one of the six cancer sub-types studied: prostate (regression coefficient (R)=0.0981, 95% CI 0.0353–0.1609; p=0.0022), female-breast (R=0.1583, 95% CI 0.1110–0.2056; p<0.0001), male-lung (R=0.2260, 95% CI 0.1216–0.3304; p<0.0001), male-colorectal (R=0.0596, 95% CI 0.0188–0.1003; p=0.0042), and female-colorectal (R=0.0676, 95% CI 0.0362–0.099; p<0.0001) (figures 2A-E, figure S1A, table S2). The association for female-lung cancer mortality with unemployment was negative (R= –0.0593, 95% CI –0.1013 to 0.0172; p=0.0058; figure 2F, table S2). Whereas treatable cancer mortality was significantly linked with unemployment (R=0.1256, 95% CI 0.0148–0.2364; p=0.0265) (figure 2G, table S2), no such significance was observed for untreatable cancers (R=0.082, 95% CI -0.041–0.205; p=0.1919) (figure 2H, table S2). The strongest associations were found in the all-cancer data (R=0.3745, 95% CI 0.1939–0.5551; p=0.0001; figure 2I, table S2). Lag analysis showed that these results remained through to five years after unemployment increases (figure 2I). These associations held and remained significant in the robustness checks performed (tables S3–S9).

On accounting for the UHC status of countries, we found no significant association between unemployment and cancer mortality within the first year of unemployment rising (table 3, figures S1B-C). The results were unaffected by country classifications according to an alternative definition for UHC (appendix S1).

Trend analysis

For the trend analysis, population-weighted mean values of the projected age-specific rates and ASDRs for each year and sex were obtained. Globally (for the 35 countries selected), we observed significant deviations in the projected ASDR from the observed ASDR for both male all cancer mortality (figure 3A, table S10) and female all cancer mortality (figure 3B, table S10) with the 2010 predicted ASDR – 3 years after the unemployment rise in 2007 – deviating the most from the observed ASDR (males: rate ratio 1.0362, 95% CI 1.0209–1.052; p<0.0001; females: rate ratio 1.0428, 95% CI 1.0254–1.0607; p<0.0001). This corresponded to 55 434 (95% CI 32 439-78 428) excess deaths among men and 53 573 (95% CI 32 386-74 759) excess deaths among women in 2010 alone~~-~~. Summing the point estimates for males and females from 2008 to 2010 yielded 252 ~~,~~199 excess deaths (figure 3A)~~(figure 3A)~~. This finding was recapitulated upon confinement of our analysis to treatable cancers (rate ratio 1.0362, 95% CI 1.0225–1.0502; p<0.0001; figure 3C, table S10) resulting in 22 977 (95% CI 14 482-31 472) excess deaths in 2010. By contrast, for untreatable cancers, the deviation between predicted and observed

ASDR was not significant in 2008, 2009 or 2010 (figure 3D, table S10).

We next asked whether these trends held among different groups of countries. To answer this, we extracted ASDRs for the following: 26 countries with UHC implemented and 9 countries without UHC as of 2008; 31 high-income countries and 4 middle-income countries as classified by the World Bank using the Atlas Method;[21] and 22 very high HDI and 13 high HDI countries.[22]

For the UHC country group, no significant difference was found for treatable cancer ASDR (figure 3E, table S10). By contrast, for the non-UHC country group the predicted ASDRs for treatable cancers were significantly lower than the observed ASDRs for all 3 projected years (in 2010: rate ratio 1.0746, 95% CI 1.0417–1.11; p<0.0001), which equated to 21 241 (95% CI 12 244-30 238) excess deaths due to treatable cancers in 2010 (figure 3F, table S10). Differences between the actual and projected ASDR of untreatable cancer were non-significant for both UHC and non-UHC country groups in 2008 with a significantly lower-than-expected number of deaths in 2009 and 2010 for the UHC country group, and a marginally significant higher-than-expected number of deaths in 2010 for the non-UHC country group (table S10).

Stratifying countries by income using the World Bank's classification yielded higher rate ratios (indicating higher-than-expected numbers of deaths) for male, female and treatable cancers among middle-income countries than among high-income countries (table S10). For untreatable cancers, high-income countries experienced significantly lower-than expected numbers of deaths whereas middle-income countries experienced significantly higher-than-expected numbers of deaths (table S10). On dividing countries according to HDI, neither the very high nor high HDI groupings experienced higher-than-expected numbers of untreatable cancer deaths although significantly lower-than expected numbers across all years were only observed for the very high HDI group (table S10).

Public-sector expenditure on healthcare

Increases in PEH, as a proportion of GDP, were significantly associated with mortality reductions in seven of the nine cancer categories studied: prostate (R= –0.0013, 95% CI –0.0019 to –0.0008; p<0.0001), female-breast (R= –0.0023, 95% CI –0.0029 to –0.0017; p<0.0001), male-lung (R= –0.0037, 95% CI –0.0045 to –0.0028; p<0.0001), male-colorectal (R= –0.0011, 95% CI –0.0016 to –0.0007; p<0.0001), female-colorectal (R= –0.0011, 95% CI –0.0014 to –0.0008; p<0.0001), treatable (R= –0.006858, 95% CI –0.007532 to –0.006184; p<0.0001) and all-cancers (R= –0.0053, 95% CI –0.0070 to –0.0036; p<0.0001) (figure 4, table S11). Female-lung cancer mortality (R= 0.0007, 95% CI 0.0004 to 0.0011; p=0.0001) on the other hand was significantly positively associated with PEH while for mortality from untreatable cancers we observed no significant link (R= 0.0006, 95% CI –0.0002 to 0.0014; p=0.1492) (figures 4F and 4H, table S11).

Lag analysis showed that these results carried through to five years after increases in PEH (figure 4). Spending increases were associated with a slight increase in lung cancer mortality in women (figure 4F) but not at all with deaths from untreatable cancers (figure 4H). The same trends were found irrespective of UHC status (table 4). For the most part, these significant associations held in the robustness checks performed (tables S12–S18).

DISCUSSION

Our results suggest that increases in unemployment in 1990 to 2009 were associated with increased mortality of prostate, breast, male-lung, and colorectal cancers in a range of countries. Increases in unemployment were also associated with increased mortality due to a subset of treatable cancers as well as all cancers. Time-lag analyses indicated that these adverse effects persisted long after initial rises in unemployment. For the most part, these associations remained significant after controlling for economic, resource availability, infrastructure, and out-of-pocket spending indicators. UHC implementation, however, removed the association between changes in unemployment and cancer mortality implying that UHC could have had a protective effect against the possible impact of unemployment. Our findings also suggest that increased PEH (as a proportion of GDP) is associated with improved cancer mortality. This trend continued irrespective of UHC status.

In all analyses, we could not demonstrate an association to female-lung cancer unlike other cancers (figures 2F and 4F). One plausible reason arising from our treatable versus untreatable cancer analysis is that this discrepancy might have been the consequence of the survival rate for female lung cancer being less than that for male; however, this hypothesis is not supported by evidence.[26] As such, this remains a topic for future investigation.

The trend analysis studied a particular set of periods in order to obtain counter-factual results for 2008–2010 (the projection period), based on models of the mortality trends for 2000–2007 (the observation period), with the hypothesis that observation-period trends would continue for the projection period. These periods were chosen so as to correspond with the sharp upturn in unemployment observed from 2008 onwards (figure S2) during the global economic crisis, while limiting the effects of previous unemployment fluctuations and technical progress in cancer care, which may otherwise have influenced rates if the observation period had been extended further back than 2000. We found the strongest, most significant deviations between observed and projected rates to occur for the non-UHC country grouping, corroborating our multivariable regression analyses. Likewise, the difference between expected and actual all-cancer mortality rates in middle-income countries exceeded that between high-income countries, a finding that mirrors the variable influence that the income class of a country has on other causes of death.[27] The chronological link between the unemployment rise due to the global economic crisis and the subsequent change in cancer mortality, lends favour to a potentially causal link, rather than reverse causality or endogeneity.

The primary means by which increased unemployment is likely to have an adverse impact upon cancer mortality is through reduced access to healthcare (figure 5), which may manifest as late-stage diagnoses,[28,29] and poor or delayed treatment.[30] Furthermore, unemployment has been found to correlate with lower socioeconomic status (SES).[31,32] In turn, there is substantial evidence linking lower SES to lower cancer survival, with reduced access to treatment being a mediating cause,[33,34] as well as lower health-seeking behaviours.[35] Job loss is also strongly associated with mental health and behavioural problems,[5] and this may also have a negative impact on survival in cancer patients as a consequence of lower rates of treatment commencement following diagnosis or higher treatment discontinuation rates.[36]

Our results regarding PEH and cancer mortality are consistent with studies comparing spending levels across countries.[37] Integrated multidisciplinary care pathways for cancer involving screening, radiotherapy, chemotherapy, and surgery, are costly but effective at reducing mortality. Changes in the availability of healthcare resources – whether at the diagnosis or treatment stage – due to changes in spending, are likely to have an impact on health outcomes. Additionally, further consequences of changes in PEH include changes in the number of healthcare professionals, with fewer healthcare professionals likely to result in reduced quality of care if productivity gains are not made,[38] and changes in the number of localised sites providing healthcare, with longer distances or travel times likely to increase delays in presentation for diagnosis as well as adversely affect treatment.[39]

Our study has ~~three~~ at least two major policy implications. First, it makes a strong case for UHC and its possible moderating effect on unemployed populations during economic downturns. In UHC countries where healthcare provision is meant to be equally accessible regardless of employment status, access to healthcare is less problematic than in non-UHC countries where access is often provided by means of an employment package. Second, ~~fiscal consolidation measures introduced during the economic crisis are likely exacerbating the adverse health effects of the global economic downturn rather than ameliorating them. Some have advocated that to reduce adverse effects, government policy should seek to actively maintain aggregate employment levels;[25] the implication being that, from a public health perspective, expansionary fiscal policy is the optimal response to the slumps in aggregate demand and concomitant private-sector unemployment seen during economic downturns. Similarly, it is reasonable to propose that if governments fail not just to maintain PEH but also to maintain levels of total healthcare expenditure by not compensating for reduced private-sector and private-household spending in economic crises, then there may be considerable adverse consequences for public health. Third,~~ amidst a background of rising healthcare costs, if spending restrictions are not accompanied by proportionate improvements in efficiency, worse quality of care and, in turn, higher mortality levels, may follow.

We note several limitations of our study. First, we evaluated population health outcomes and economic trends but did not account for variations at regional and sub-national levels. Second, for reasons of data availability and quality, we were unable to analyse the effects of the global economic crisis after 2010. However, in addition to the sizeable economic fluctuations that occurred during the period studied, our analysis was still able to capture the effects of the earlier stages of the crisis with the trend analysis, during which unemployment levels rose sharply and in some countries peaked. For the PEH dataset, we did not account for changes in efficiency; indeed, it is possible that a country spends less on healthcare but achieves greater outcomes due to the efficiency of its system. Linked to this, we acknowledge the reduced global reach of our study due to the lack of data for low-income countries as well as China and India. Indeed, an examination of whether our findings hold in lower income countries where it is possible that mortality rates for certain cancer types have been rising rather than falling would offer valuable insight. Fourth, our study was retrospective and observational, limiting our ability to draw causal inferences. The possibility of residual confounding from social determinant and region-specific healthcare system variables also necessitates a comprehensive, longitudinal approach characterising trends and predictors of healthcare access and quality before and after significant economic changes to strengthen the case for any causative effect as well as clarifying the expected latency between cancer treatment and mortality. Finally, by employing a fixed-effects model, we assumed that any unobserved factors within each country were time-invariant and not correlated with our variables of interest, although the comprehensiveness of our robustness checks will have reduced the probability of this assumption affecting our findings.

Notwithstanding the limitations discussed, our findings suggest that both unemployment and PEH are significantly associated with cancer mortality, with associations lasting up to five years. We estimate that the 2008–2010 global economic crisis may have been associated with up to ~~100~~ 250 000 ~~additional~~ excess cancer-related deaths. Our analysis also suggests that UHC may remove~~s~~ the association between unemployment and cancer mortality, lending evidence in favour of healthcare system reforms aimed at providing UHC, particularly among middle-income countries.

AUTHORS' CONTRIBUTIONS

MM, JW, AMN and CW compiled the data. MM conceived and designed the study with input from JW, RaA, RS, TZ, and RiA. MM and JW conducted the statistical analysis, and wrote the first draft of the manuscript. AMN, CW, RaA, RS, TZ and RiA helped interpret the findings, and provided input to subsequent drafts of the manuscript. All authors have seen and approved the final version of the report. MM and JW contributed equally.

CONFLICTS OF INTEREST

None to declare.

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ETHICS COMMITTEE APPROVAL

Ethics approval was not applicable for this study.

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RESEARCH IN CONTEXT

Evidence before this study

We searched the literature to identify articles that quantitatively estimated either the effect of both unemployment and healthcare spending (public or otherwise) on cancer mortality, or the effect of universal healthcare coverage on cancer mortality. We searched PubMed for publications up to and including May 31 2015 using the following combinations of search terms: (i) unemployment AND cancer AND mortalit* AND (spending OR expenditure); (ii) cancer AND mortalit* AND "universal healthcare coverage". Search combination (i) yielded seven publications, and combination (ii) yielded one publication. With respect to search combination (i), one study used a time-trend analysis to examine the relationship between unemployment and mortality in Scotland, and included specific causes of death such as lung cancer.[40] A second study simply used Pearson's correlation rather than a panel-based fixed effects model to find an association between all-cancer mortality, and healthcare expenditure (negative) and unemployment (positive) in European countries.[41] The authors were therefore unable to control for potential confounding variables. The study periods for both these publications ended before the 2008 economic recession. Three further studies investigated a substantially narrower geographical region and outcome than the present study. The first study examined the relationship between spending, unemployment and breast cancer mortality in the European Union only,[14] the second examined the relationship between unemployment and stomach cancer mortality again in the European Union only,[15] while the third examined prostate cancer mortality in countries belonging to the Organisation for Economic Co-operation and Development.[42] The remaining two studies were not considered relevant, as they did not quantify the relationship between the macroeconomic indicators and cancer mortality. The study extracted from search combination (ii) was also irrelevant in that again it did not seek to quantify the influence of coverage on mortality.

Added value of this study

The study presented here is the first global analysis of the impact of unemployment and public healthcare spending on mortality due to all cancers, "treatable" cancers, "untreatable" cancers and specific forms of cancer. In using a conservative, fixed-effects regression analysis model to ascertain the existence of an association and quantify any associations combined with robustness checks, this study accounts for criticisms levelled at other studies looking at the relationship between health outcomes and unemployment, namely, the omission of potential confounding variables likely to be correlated with both unemployment rates (or public healthcare spending) and cancer mortality rates. In using a panel-data approach for the multivariable regression analysis to compare unemployment rates (or public healthcare spending) at intervals of one year for each year after the increase in unemployment (or public healthcare spending) with the mortality rates in each country, we controlled for time-invariant heterogeneity between countries. Finally, we combined the above with a time-trend analysis, to provide a rigorous characterisation of the associations between unemployment, public healthcare spending, universal healthcare coverage, income, and cancer mortality. The major findings from these complementary approaches are that unemployment increases are associated with rises in cancer mortality, with universal healthcare coverage protecting against this phenomenon. Consideration of certain types of cancer as either treatable or untreatable revealed that significantly higher-than-expected numbers of deaths were only observed for treatable cancers. In contrast to unemployment, public healthcare spending increases are associated with reductions in cancer mortality with a recapitulation of the divergent findings between treatable and untreatable cancers. Whether or not a country has implemented universal healthcare coverage does not significantly alter the strength of this relationship.

Implications of all the available evidence

Policies that maintain spending and hence access to and quality of healthcare in the face of economic downturns especially among cancers that are considered treatable may offset some of the negative effects of such periods on health outcomes. Furthermore, the findings of our study add to the existing body of evidence in favour of universal healthcare coverage.

FIGURE LEGENDS

Figure 1. **Cohort selection diagram for the trend prediction analysis**

Cohort selection with final aggregation by UHC status. The first step involves selecting only those countries with complete consecutive mortality data from 2000 to 2010. The second filters out countries with civil registration coverage of cause-of-death of <90%. Next, the over-85 age group and age groups with fewer than 20 deaths in any calendar year were excluded. The first row of boxes at the end of the workflow shows the categorisation of countries by UHC status (as determined by skilled birth attendance). The second row of boxes at the end of the workflow shows the categorisation of countries by income status. The third row shows the categorisation of countries by HDI. Cancer mortality data (deaths per 100 000) were obtained from the World Health Organisation Mortality Database 2013.[23] HDI categories were obtained from the United Nations Development Programme website.[22] HDI, Human development index, UHC, Universal healthcare coverage.

Figure 2. **Time-lag analyses of changes in unemployment on cancer mortality.**

Multivariable regression analysis was conducted on data for 75 countries from 1990 to 2009 to assess the relationship between unemployment, and prostate cancer mortality (A), breast cancer mortality (B), male colorectal cancer mortality (C), female colorectal cancer mortality (D), male lung cancer mortality (E), female lung cancer mortality (F), treatable cancer mortality (G), untreatable cancer mortality (H) and all-cancer mortality (I). Analyses were conducting with controls for population size, population structure (proportion of population below 14 years of age and above 65 years of age), and country-specific differences in healthcare infrastructure. Data are also shown for 1-, 2-, 3-, 4-, and 5-year time-lag analyses. Economic data were obtained from the World Bank.[25] Cancer mortality data (deaths per 100 000) were obtained from the World Health Organisation Mortality Database 2013. [23] * p<0.05; ** p<0.01; *** p<0.001.

Figure 3. **Predicted cancer-related mortality rate and number of deaths, 2008–2010, based on 2000–2007 observation base.**

Projections of age-standardised cancer-related mortality rates per 100 000 (ASDR) for 35 countries from 2008 to 2010 were made based upon ASDRs observed from 2000 to 2007, and compared with those observed from 2008 to 2010. The number of excess deaths due to male cancers (A), female cancers (B), treatable cancers (female breast, prostate and colorectal) (C), and untreatable cancers (lung and pancreatic) (D) were estimated by comparing 2008-2010 projected rates with 2008-2010 observed rates. The projections of ASDRs for treatable cancers are also shown for UHC (E) and non-UHC (F) countries. ASDRs were extracted from the World Health Organisation Mortality Database 2013.[23] * $p<0.05$; ** $p<0.01$; *** $p<0.001$.

Figure 4. **Time-lag analyses of changes in public-sector healthcare expenditure on cancer mortality.**

Multivariable regression analysis was conducted on data for 79 countries from 1990 to 2009 to assess the relationship between public-sector healthcare expenditure, and prostate cancer mortality (A), breast cancer mortality (B), male colorectal cancer mortality (C), female colorectal cancer mortality (D), male lung cancer mortality (E), female lung cancer mortality (F), treatable cancer mortality (G), untreatable cancer mortality (H), and all-cancer mortality (I). Analyses were conducted with controls for population size, population structure (proportion of population below 14 years of age and above 65 years of age), and country-specific differences in healthcare infrastructure. Data are also shown for 1-, 2-, 3-, 4-, and 5-year time-lag analyses. Economic data were obtained from the World Bank.[25] Cancer mortality data (deaths per 100 000) were obtained from the World Health Organisation Mortality Database 2013.[23] * $p<0.05$; ** $p<0.01$; *** $p<0.001$.

Figure 5. **Possible causal pathways for the observed associations**

PEH, Public-sector expenditure on healthcare; SES, Socioeconomic status.

TABLES

Country/Grouping	Population 2009	Country/Grouping	Population 2009
Albania	3 151 185	Luxembourg	497 783
Argentina	40 023 641	Macedonia	2 100 558
Armenia	2 968 154	Malta	413 991
Australia	21 778 800	Mauritius	1 275 032
Austria	8 365 275	Mexico	116 815 612
Azerbaijan	8 947 243	Moldova	3 565 603
Barbados	279 006	Netherlands	16 530 388
Belgium	10 796 493	New Zealand	4 315 800
Belize	301 016	Nicaragua	5 743 329
Brazil	193 490 922	Norway	4 828 726
Bulgaria	7 585 131	Panama	3 615 846
Canada	33 726 915	Paraguay	6 347 383
Chile	16 991 729	Peru	28 934 303
Colombia	45 802 561	Philippines	91 886 400
Costa Rica	4 601 424	Poland	38 151 603
Croatia	4 429 000	Portugal	10 632 482
Cuba	11 288 826	Romania	21 480 401
Czech Republic	10 487 178	Russian Federation	141 910 000
Denmark	5 523 095	Serbia	7 320 807
Dominican Republic	9 884 265	Singapore	4 987 600
Ecuador	14 756 424	Slovak Republic	5 418 590
Egypt	76 775 023	Slovenia	2 039 669
El Salvador	6 183 484	Spain	45 908 594
Estonia	1 340 271	Suriname	520 173
Finland	5 338 871	Sweden	9 298 515
France	64 702 921	Switzerland	7 743 831
Georgia	4 410 900	Tajikistan	7 447 396
Germany	81 902 307	Thailand	66 277 335
Greece	11 282 760	Trinidad and Tobago	1 322 518
Guatemala	13 988 988	Turkmenistan	4 978 962
Hungary	10 022 650	Ukraine	46 053 300
Iceland	318 499	United Kingdom	61 811 027
Republic of Ireland	4 458 942	United States	306 771 529
Israel	7 485 600	Uruguay	3 360 431
Italy	60 192 698	Uzbekistan	27 767 400
Japan	127 557 958	Venezuela	28 583 040
Kazakhstan	16 093 481	High-income	1 066 391 720
Republic of Korea	49 182 000	Middle-income	188 342 304
Kuwait	2 850 102	UHC	641 437 562
Kyrgyz Republic	5 383 300	Non-UHC	613 296 462
Latvia	2 254 834	Very high human development index	849 195 806
Lithuania	3 339 456	High human development index	405 538 218

***Table 1:* Population estimates of countries included in multiple regression and time-series analyses, 2009.** Population estimates were obtained from the World Bank (data code: SP.POP.TOTL).[20] For country groupings, populations are calculated only for those countries

included in the time-series analysis as per figure 1. UHC, Universal healthcare coverage.

	Common controls	**Robustness check control**	**Particular control**	**Total number of controls**
Unemployment dataset (75 countries)	Population size Proportion of population less than 15 years of age Proportion of population over 65 years of age	Economic	Inflation GDP per capita changes Base interest rates	80
		Resource availability	Number of physicians per 100 000 population; Number of hospital beds per 100 000 population	79
		Infrastructure	Urbanisation; Access to water; Calorie intake	80
		Out-of-pocket spending	Out-of-pocket expenditure	78
		WHO data quality check	N/A (Re-run analysis using data classified as Level 1 or Level 2 in quality by the WHO)	77
		Income	(2 categories coded into 1 dummy variable)	78
		Human development index	(3 categories coded into 2 dummy variables)	79
PEH dataset (79 countries)	Population size Proportion of population less than 15 years of age Proportion of population over 65 years of age	Economic	Inflation; GDP per capita changes; Base interest rates	84
		Resource availability	Number of physicians per 100 000 population; Number of hospital beds per 100 000 population	83
		Infrastructure	Urbanisation; Access to water; Calorie intake	84
		Out-of-pocket spending	Out-of-pocket expenditure	82
		WHO data quality check	N/A (Re-run analysis using data classified as Level 1 or Level 2 in quality by the WHO)	81
		Income	(2 categories coded into 1 dummy variable)	82
		Human development index	(3 categories coded into 2 dummy variables)	83

Table 2: **Controls used in multiple regression and sensitivity analyses.** Data were obtained from the World Bank.[20] PEH, Public-sector expenditure on healthcare.

Cancer mortality in year of unemployment rise (deaths per 100 000)	Co-efficient	Robust standard error	p Value	Lower confidence interval (95%)	Upper confidence interval (95%)
Prostate cancer	0.0975	(0.1025)	0.3422	–0.1042	0.2992
Breast (female) cancer	0.0802	(0.0763)	0.2939	–0.0699	0.2302
Colorectal (male) cancer	–0.0679	(0.0589)	0.2495	–0.1838	0.0479
Colorectal (female) cancer	–0.0306	(0.0384)	0.4263	–0.1062	0.0450
Lung (male) cancer	–0.0126	(0.1753)	0.9428	–0.3575	0.3324
Lung (female) cancer	–0.0143	(0.0454)	0.7534	–0.1035	0.0750
Treatable cancers	0.0319	(0.0692)	0.6449	–0.1037	0.1675
Untreatable cancers	0.0758	(0.061)	0.2142	-0.0437	0.1952
All cancers	0.0525	(0.1778)	0.7679	–0.2970	0.4019

***Table 3:* Unemployment and cancer mortality rates controlling for universal healthcare coverage.**

Countries were classified as universal healthcare coverage (UHC) countries according to whether they were assessed to have met all of the following previously described conditions: legislation mandating UHC; >90% healthcare coverage; and >90% skilled birth attendance.

Cancer mortality in year of PEH rise (deaths per 100 000)	Co-efficient	Robust standard error	p Value	Lower confidence interval (95%)	Upper confidence interval (95%)
Prostate cancer	–0.0009	(0.0001)	1.052×10^{-10}***	–0.0011	–0.0006
Breast (female) cancer	–0.0009	(0.0001)	1.013×10^{-10}***	–0.0012	–0.0007
Colorectal (male) cancer	-3×10^{-5}	(0.0003)	0.9126	–0.0006	0.0006
Colorectal (female) cancer	–0.0004	(0.0001)	1.04×10^{-5}***	–0.0011	–0.0002
Lung (male) cancer	–0.0007	(0.0003)	0.0087**	–0.0012	–0.0002
Lung (female) cancer	0.0005	(0.0001)	2.19×10^{-5}***	0.0003	0.0007
Treatable cancers	–0.0022	(0.0005)	8.074×10^{-6}***	–0.0032	–0.0012
Untreatable cancers	0.0008	(0.0004)	0.0341*	0.0001	0.0016
All cancers	–0.0016	(0.0005)	1.7×10^{-6}***	–0.0026	–0.0006

Table 4: **PEH and cancer mortality rates controlling for universal healthcare coverage.**

Countries were classified as universal healthcare coverage (UHC) countries according to whether they were assessed to have met all of the following previously described conditions: legislation mandating UHC; >90% healthcare coverage; and >90% skilled birth attendance. PEH, Public-sector expenditure on healthcare. * p<0.05; ** p<0.01; *** p<0.001

17/02/2016

Laura Hart
Senior Editor
The Lancet

Dear Mrs Hart,

RE: THELANCET-D-15-05399R1, Economic downturns, universal healthcare coverage, and cancer mortality in high- and middle-income countries, 1990-2010.

We would like to thank the editorial board and the referees for their contributions to and constructive comments on our manuscript. We have carefully considered the reviewers' comments and revised our manuscript accordingly. In particular, we would like to highlight the change in title to the manuscript from "*Economic downturns, universal health coverage, and cancer mortality: a global analysis, 1990-2010*" to "*Economic downturns, universal healthcare coverage, and cancer mortality in high- and middle-income countries, 1990–2010*" as suggested by one of the reviewers.

We have provided systematic responses to the reviewers' comments. Please note that amendments to the manuscript that are in response to the reviewers' comments are highlighted as tracked changes.

We hope we have clarified the points raised by the referees to your satisfaction and that you now consider the revised manuscript acceptable for publication.

Yours sincerely

Mahiben Maruthappu & Johnathan Watkins

REVIEWER 4

Most reviewers' suggestions have been addressed.

Given the correlational nature of the study, I would use an additionally cautious wording in the interpretation, but this is left to the authors' choice.

Our response > We have now amended the wording in the Interpretation in the Abstract to highlight the correlative nature of the study:

> ***"There is evidence that UHC protects against mortality increases associated with rises in unemployment…"***

In the Discussion section we also added an additional cautionary language:

> ***"…implying that UHC could have had a protective effect against the possible impact of unemployment."***

REVIEWER 5

General Comments

Overall this is a very well written manuscript!

The authors use data from SELECT high income and middle income countries to study the impact of macroeconomics variable (unemployment, public sector expenditure on health care, universal healthcare coverage and income, on cancer mortality.

Major comments

Comment #1: *Title: The title of the paper is a little mis-leading. It says "global analysis." With the exclusion of countries such as China, India and countries from Sub-Sahara Africa; the title should say something like "Economic downturns, universal health coverage, and cancer mortality in select high and middle income countries, 1990-2010"*

Our response > We agree with the reviewer's point and have amended the title of the paper to "*Economic downturns, universal healthcare coverage, and cancer mortality in high- and middle-income countries, 1990–2010*".

Comment #2: *There may be a different picture, if the analysis is stratified into high income, middle income and low-income countries.*

Our response > We acknowledge the absence of quality data for low-income countries. As such, we have confined our analyses examining the role of income to high- and middle-income economies. We conducted fixed-effect regressions using the income status of a country as a balancing variable. We refer the reviewer to Table S8 for the results of these. We also conducted time-series analyses for high- and middle-income groups of countries, the results for which we refer the reviewer to Table S10.

Minor comments

Comment #3: *Abstract (Method). Did all the countries included in the study experience sharp unemployment rise in between 2008 and 2010?*

Our response > We have now amended the text to point out that the sharp unemployment rise was experienced in many but not all countries.

> ***"Trend analysis was used to project mortality rates based on trends prior to the sharp unemployment rise experienced by many countries from 2008 to 2010…"***

Comment #4: *Methods: Need to indicate what criteria was used to classify countries into high and middle income. It is important to include the reason why India, China and countries from Sub-Saharan Africa (SSA) are not included in the analysis. Without India, China and countries from Low income countries (such as those in SSA), this can hardly be called a "global analysis."*

Our response > We have now highlighted the reason that data from China, India

and SSA countries were not included in the Methods section as follows:

> **"*Notably, at the time data were collected, complete cancer mortality data were unavailable for China, India, and countries from sub-Saharan Africa.*"**

Comment #5: *Results (Trend analysis). Brief mention is made of stratifying countries by income. This deserves more attention.*

Our response > We have now added notes to the Methods and the Results that income stratification was done based on the World Bank's Atlas method.

In the Methods:

> ***"Classification of countries into high- and middle-income was done according to the World Bank's Atlas Method.[25] In brief, middle-income countries are those with a gross national income per capita of more than $1 045 but less than $12 736, whereas high-income economies are those with a gross national income per capita of $12 736 or more."***

In the Results:

> ***"31 high-income countries and 4 middle-income countries as classified by the World Bank using the Atlas Method;[25]"***

and

> **"*Stratifying countries by income using the World Bank's classification*…"**

Comment #6: *Discussion (Limitation). Suggest mentioning that less than half of the countries in the world are included in this study. Highlight reasons why.*

Our response > We agree with the reviewer that this is an important point for the reader to appreciate. We have previously addressed a similar comment on

the Discussion as follows:

> ***"Linked to this, we acknowledge the reduced global reach of our study due to the lack of data for low-income countries as well as China and India. Indeed, an examination of whether our findings hold in lower income countries where it is possible that mortality rates for certain cancer types have been rising rather than falling would offer valuable insight."***

Comment #7: *Discussion. Figure S is mentioned, but I cannot find it.*

Our response > We believe the reviewer is referring to Figure S2 as mentioned in the following sentence:

> ***"These periods were chosen so as to correspond with the sharp upturn in unemployment observed from 2008 onwards (figure S2)."***

We have checked and can confirm that figure S2 was included in the revised submission, and will be included among the supplementary figures in this second revision.

Figures

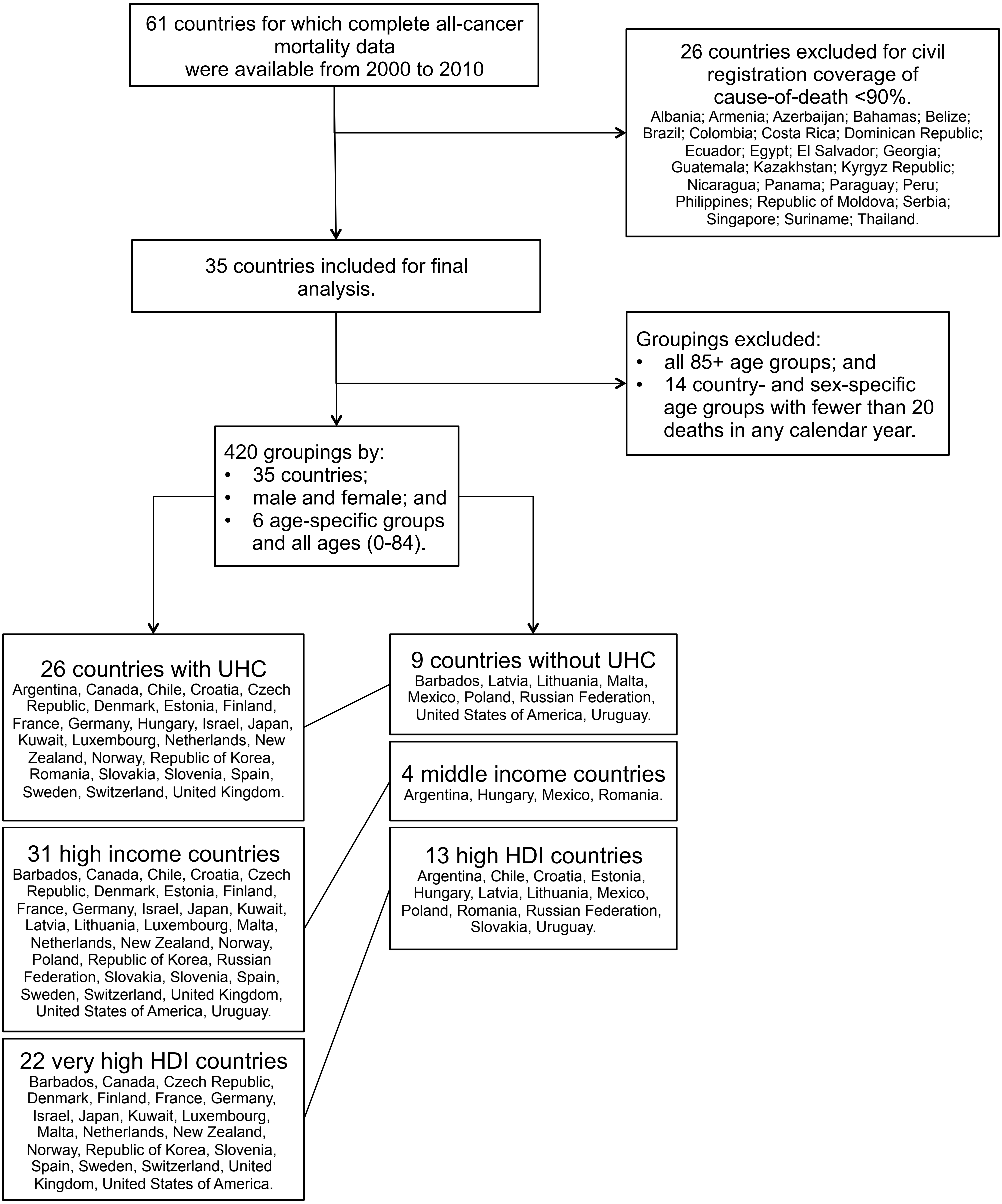

Figure 1

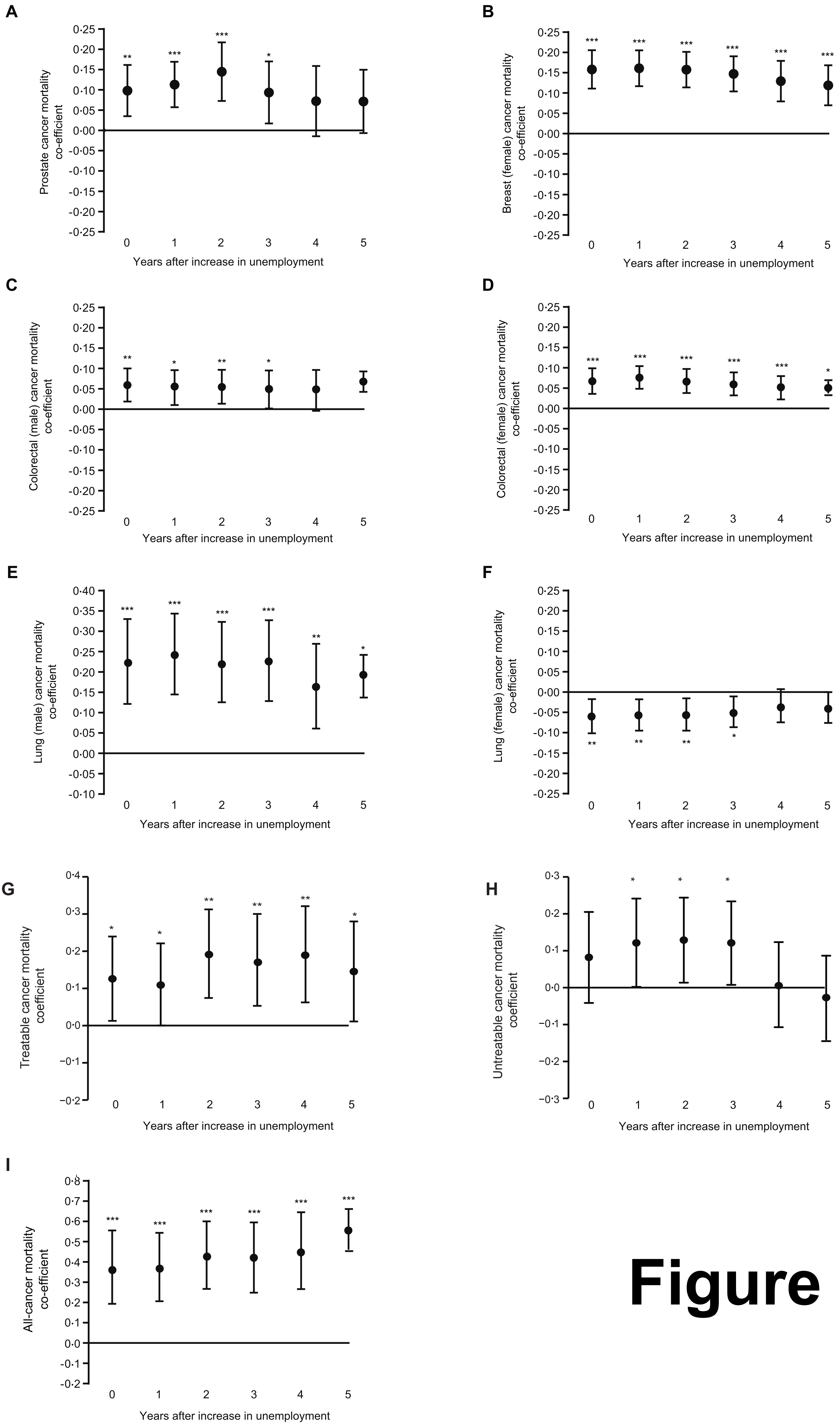
A
Prostate cancer mortality co-efficient
Years after increase in unemployment
B
Breast (female) cancer mortality co-efficient
Years after increase in unemployment
C
Colorectal (male) cancer mortality co-efficient
Years after increase in unemployment
D
Colorectal (female) cancer mortality co-efficient
Years after increase in unemployment
E
Lung (male) cancer mortality co-efficient
Years after increase in unemployment
F
Lung (female) cancer mortality co-efficient
Years after increase in unemployment
G
Treatable cancer mortality coefficient
Years after increase in unemployment
H
Untreatable cancer mortality coefficient
Years after increase in unemployment
I
All-cancer mortality co-efficient
Years after increase in unemployment

Figure 2

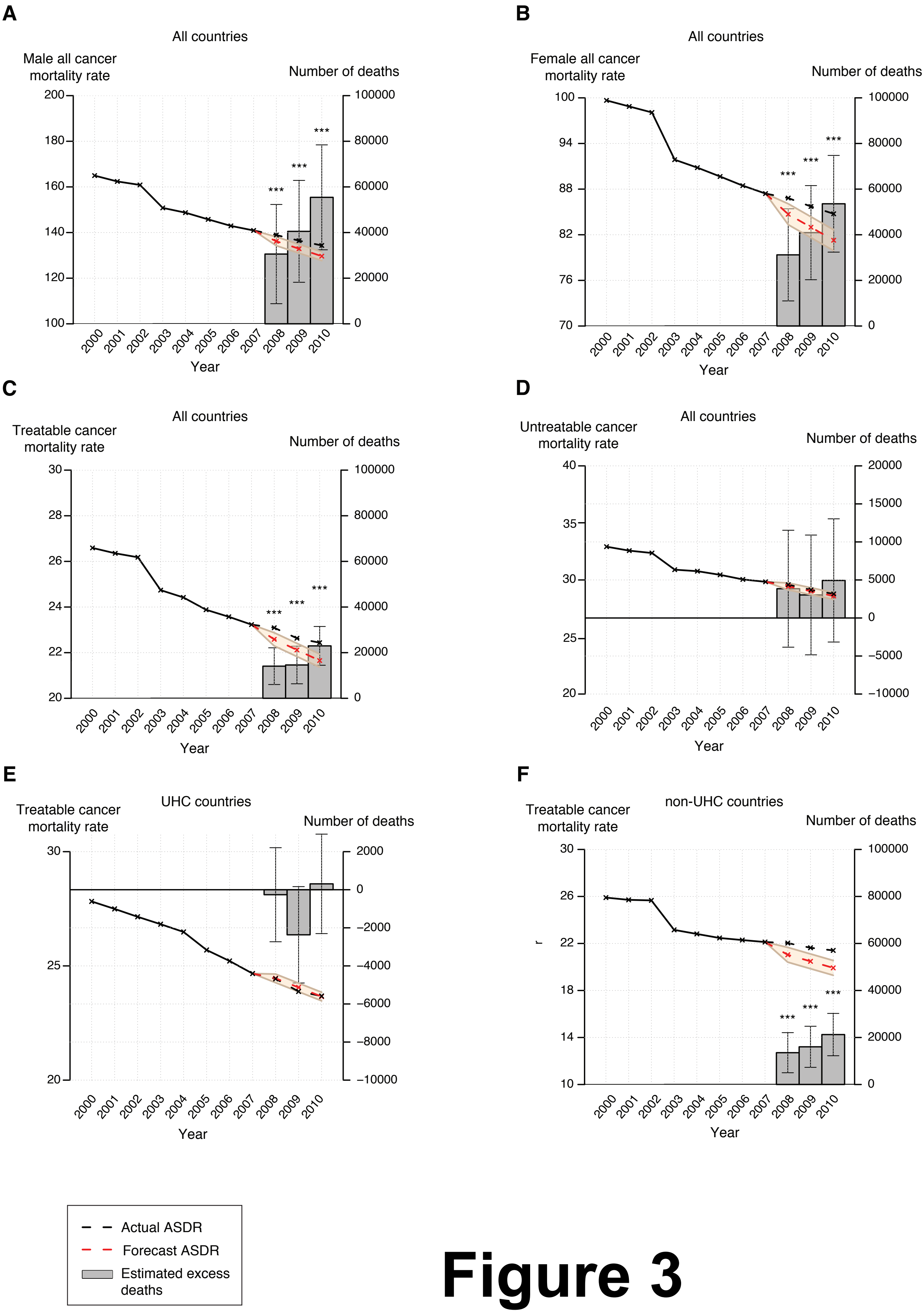
A
All countries
Male all cancer mortality rate
Number of deaths
B
All countries
Female all cancer mortality rate
Number of deaths
C
All countries
Treatable cancer mortality rate
Number of deaths
D
All countries
Untreatable cancer mortality rate
Number of deaths
E
UHC countries
Treatable cancer mortality rate
Number of deaths
F
non-UHC countries
Treatable cancer mortality rate
Number of deaths
Year
Actual ASDR
Forecast ASDR
Estimated excess deaths

Figure 3

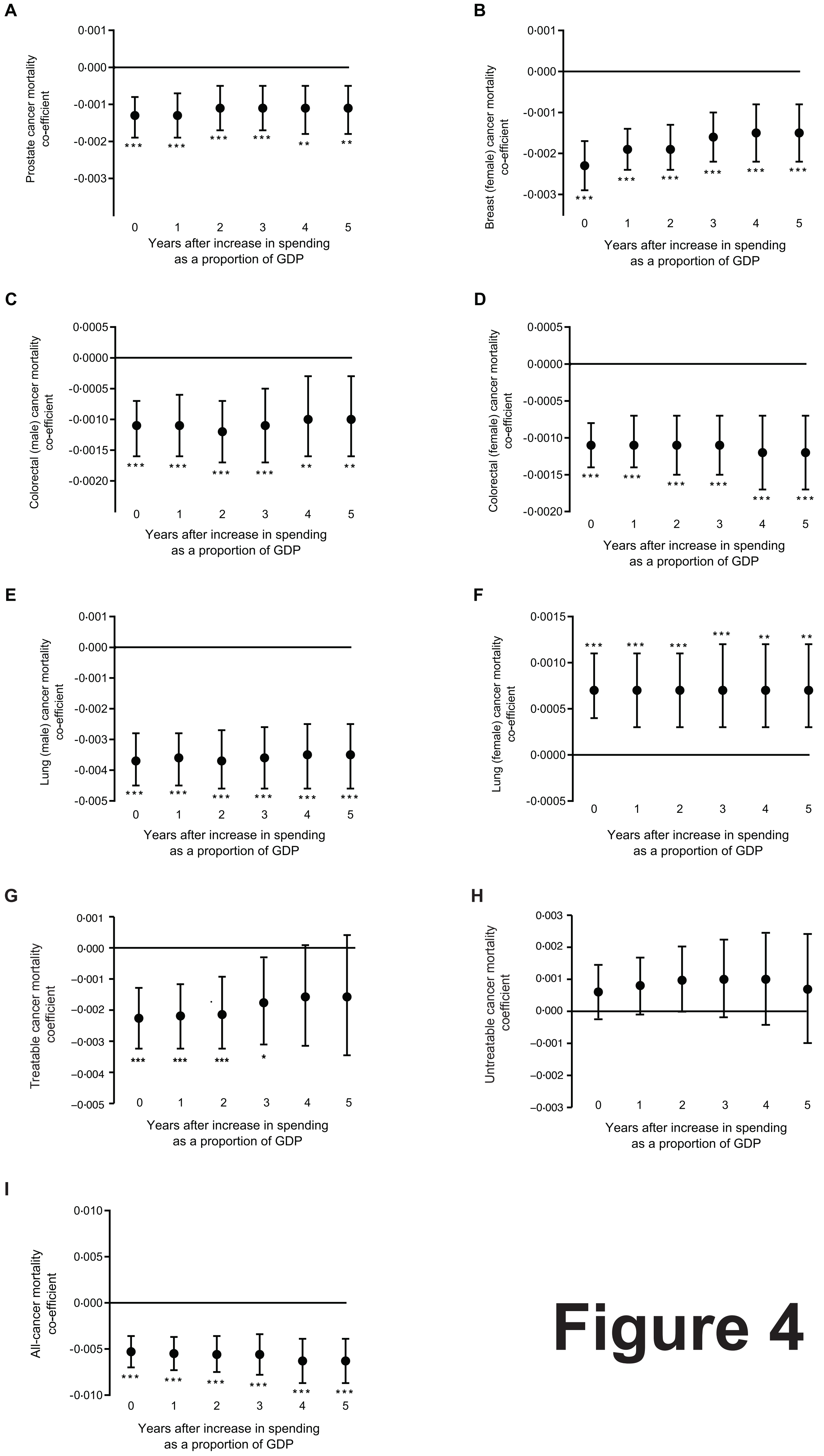
A
Prostate cancer mortality co-efficient
B
Breast (female) cancer mortality co-efficient
C
Colorectal (male) cancer mortality co-efficient
D
Colorectal (female) cancer mortality co-efficient
E
Lung (male) cancer mortality co-efficient
F
Lung (female) cancer mortality co-efficient
G
Treatable cancer mortality coefficient
H
Untreatable cancer mortality coefficient
I
All-cancer mortality co-efficient
Years after increase in spending as a proportion of GDP

Figure 4

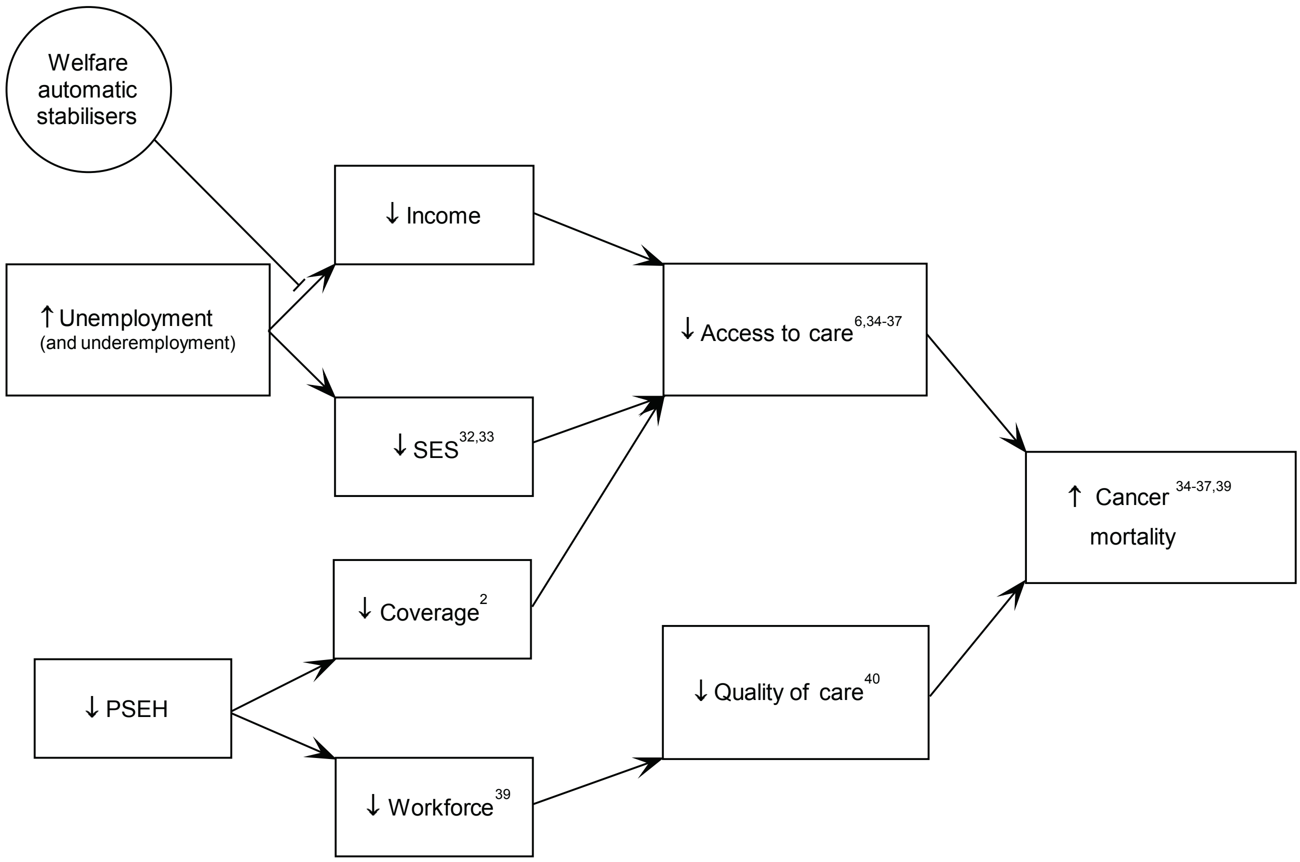
Welfare automatic stabilisers
↑Unemployment (and underemployment)
↓ Income
↓ SES[32,33]
↓ Access to care[6,34-37]
↑ Cancer[34-37,39] mortality
↓ Coverage[2]
↓ PSEH
↓ Workforce[39]
↓ Quality of care[40]

Figure 5

Supplementary Material including Tables
Click here to download Supplementary Material: REV2_AllCancer_Supp.doc

Supplementary Figures

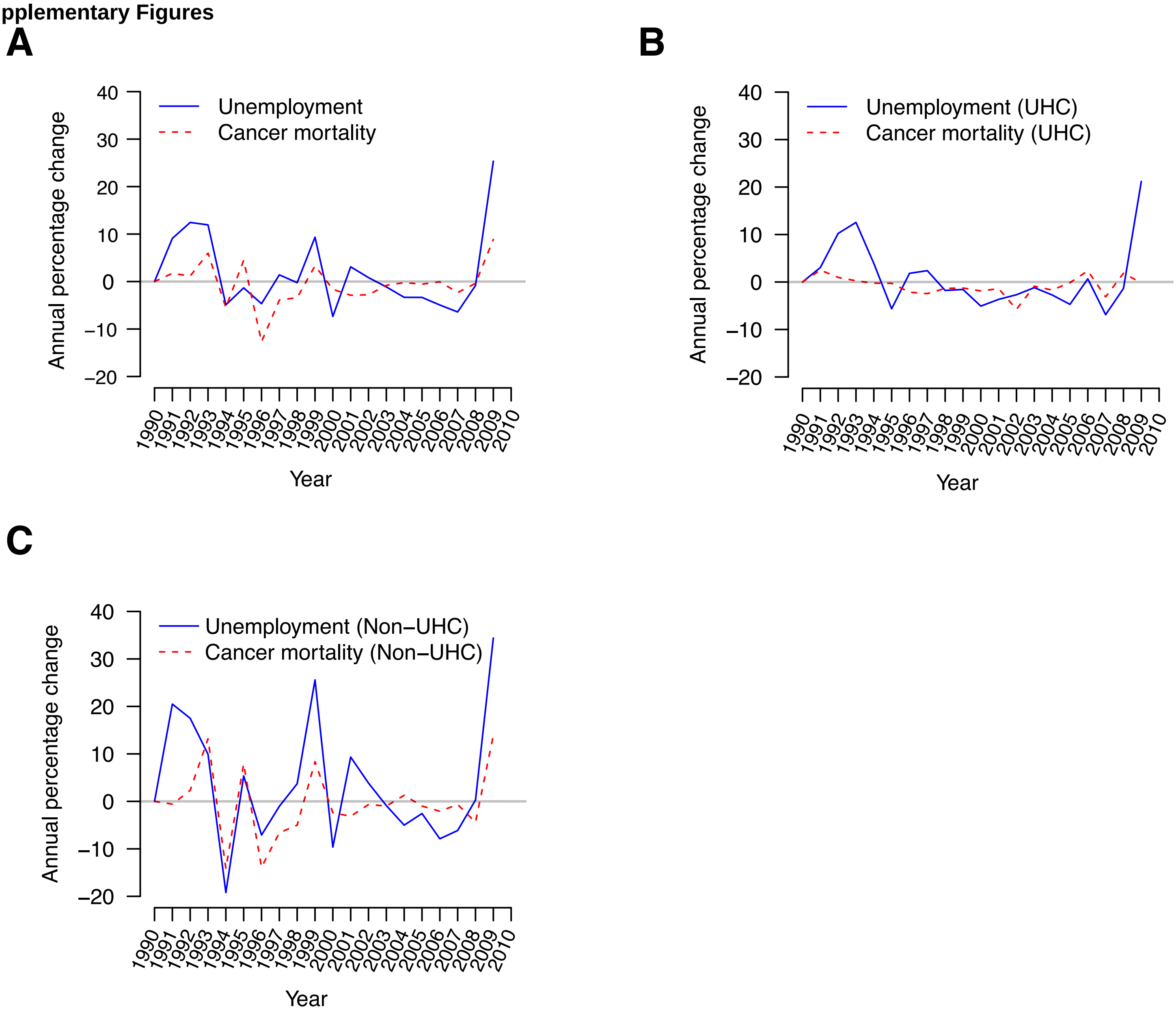

Figure S1

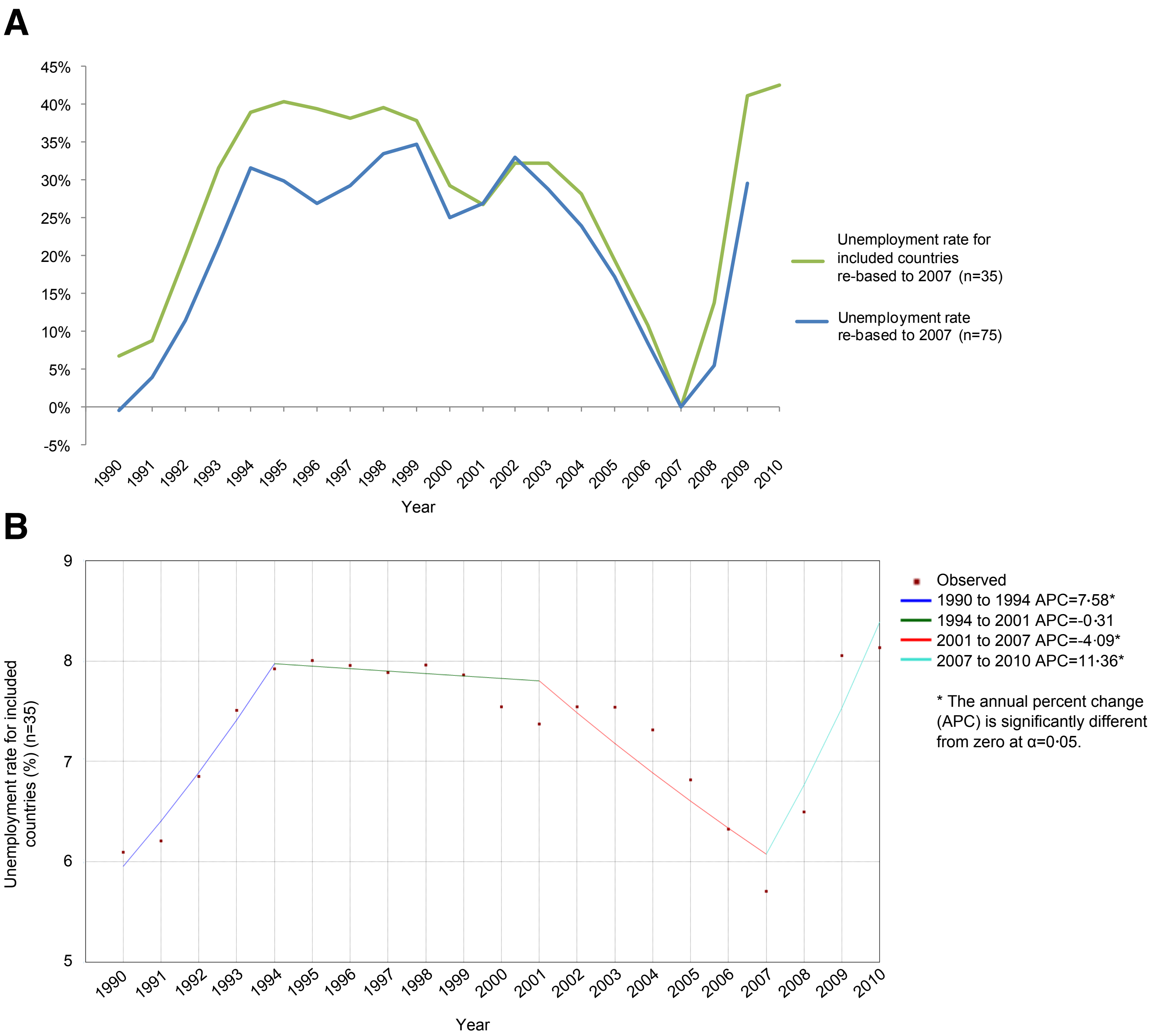
A
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
-5%
1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010
Year
Unemployment rate for included countries re-based to 2007 (n=35)
Unemployment rate re-based to 2007 (n=75)
B
Unemployment rate for included countries (%) (n=35)
9
8
7
6
5
Year
Observed
1990 to 1994 APC=7·58*
1994 to 2001 APC=-0·31
2001 to 2007 APC=-4·09*
2007 to 2010 APC=11·36*
* The annual percent change (APC) is significantly different from zero at α=0·05.

Figure S2