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DOI: 10.1016/S0140-6736(16)00577-8

Document Version Peer reviewed version

Link to publication record in King's Research Portal

Citation for published version (APA):

Maruthappu, M., Watkins, J., Noor, A. M., Williams, C., Ali, R., Sullivan, R., Zeltner, T., & Atun, R. (2016). Economic downturns, universal health coverage, and cancer mortality in high-income and middle-income countries, 1990–2010: a longitudinal analysis. *Lancet*. Advance online publication. https://doi.org/10.1016/S0140-6736(16)00577-8

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Elsevier Editorial System(tm) for The Lancet Manuscript Draft

Manuscript Number: THELANCET-D-15-05399R2

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

Article Type: Article

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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 countryspecific 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. *Manuscript (clean)

1	Economic downturns, universal healthcare coverage, and cancer
2	mortality in high- and middle-income countries, 1990–2010
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31	Word count (Introduction, Materials and Methods, Results, Discussion): 3,692
32	Number of references (excluding those cited only in the Research in Context panel): 42
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34 SUMMARY

35

36 Background

37 The global economic crisis has been associated with increased unemployment and reduced public-38 sector expenditure on healthcare (PEH). We estimated the effects of changes in unemployment and PEH 39 on cancer mortality, and identified how universal healthcare coverage (UHC) influenced the change. 40

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41 *Methods*

Data were obtained from the World Bank and WHO (1990-2010). Mortality data from female breast, 42 43 prostate, and colorectal cancers, which have survival rates that exceed 50%, were aggregated into a 44 'treatable' cancer class. Lung and pancreatic cancers, which have five-year survival rates <10%, were 45 likewise aggregated to give an 'untreatable' cancer category. Multivariable regression analysis was 46 used, controlling for country-specific demographics and infrastructure, with time-lag analyses and 47 robustness checks to explore the relationship between unemployment and PEH on cancer mortality, 48 with and without UHC. Trend analysis was used to project mortality rates based on trends prior to the 49 sharp unemployment rise experienced by many countries from 2008 to 2010, and compare them with 50 observed rates.

51

52 **Results**

53 Data were available for 75 countries (unemployment analysis) and 79 countries (PEH analysis). 54 Unemployment rises were significantly associated with an increase in all-cancer mortality and all 55 specific cancers save for female-lung cancer. Untreatable cancer mortality by contrast was not 56 significantly linked with changes in unemployment. Lag analyses showed significant associations 57 remained five years after unemployment increases for the treatable cancer class. Re-running analyses 58 while accounting for UHC status removed the significant associations. All-cancer, treatable cancer, and 59 specific cancer mortalities significantly decreased as PEH increased. Associations held over a five-year 60 period regardless of whether UHC was present. Time-series analysis found just over 40 000 estimated 61 excess deaths due to a subset of treatable cancers from 2008–2010 based on 2000–2007 trends. The 62 great majority of these deaths were from non-UHC countries.

63

64 Interpretation

65 Unemployment increases are associated with cancer mortality increases. There is evidence that UHC 66 protects against mortality increases associated with rises in unemployment, while PEH increases are 67 associated with reduced cancer mortality. Reduced access to healthcare may underlie these associations. 68

69 Funding	;
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70 None.

71

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

75 **INTRODUCTION**

76

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}

84

85 Ecological studies exploring health-economic trends in the short run (separate from residual or secular 86 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 87 se.^{3,7–15} These potential associations may predominantly be explained by behavioural, mental, or stress-88 89 related changes with direct and immediate effects, whether, as in the case of suicides, they are countercyclical associations linked to the direct psychological and financial impact of job loss,¹⁶ or pro-cyclical 90 91 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 92 93 cancer especially in countries that may be more susceptible to economic shocks due to limited social 94 security and healthcare systems.

95

96 Establishing a causal relationship between an economic change, such as aggregate unemployment, on 97 cancer mortality is challenging, as downstream effects of unemployment-induced behavioural changes 98 on lifestyle-related cancers manifest much later (20-30 years) than, for example, suicide or acute, 99 stress-related cardiovascular events. However, access to healthcare and PEH may act as mediating 100 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 101 presenting with late-stage disease meant that the effect of the economic downturn on reduced healthcare 102 103 access and mortality could not be as strongly demonstrated as it could in an era where systemic 104 treatment is now available.

105

106 Cancer is one of the leading causes of death worldwide, accounting for 8.2 million deaths in 2012, with
 107 estimates suggesting a rise in annual cancer cases from 14 million in 2012 to 22 million by 2030.¹⁸
 108 Hence an understanding of the effects of macroeconomic changes on cancer outcomes worldwide is
 109 important.

- 111 We examined the association between changes in aggregate unemployment and PEH with deaths due to 112 specific cancers, groups of cancers, and all cancers for countries where data was available and deemed 113 of sufficient quality (1990–2010). Mortality was considered a more reliable measure of health outcomes 114 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' 115 116 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 117 protective effect. We also estimated the difference between the actual numbers of cancer-related deaths 118 during and after the recent economic downturn and the expected numbers based on prior trends. For 119 120 convenience, we have used the term 'excess deaths' to denote those estimated differences for which the 121 number of deaths was higher than expected.
- 122

124 METHODS

125

126 Data sources

127 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 128 defined as the share of the labour force without work but available and seeking employment.²⁰ PEH 129 130 (World Bank data code: SH.XPD.PUBL.ZS) was measured as a percentage of gross domestic product 131 (GDP) at purchasing power parity (PPP); it was defined by the World Bank as including all rent and 132 capital spending from government budgets (central and local), external borrowings and grants (including donations from international agencies and non-governmental organisations), and social (or 133 134 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 135 136 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 137 done according to the World Bank's Atlas Method.²¹ In brief, middle-income countries are those with a 138 gross national income per capita of more than \$1 045 but less than \$12 736, whereas high-income 139 140 economies are those with a gross national income per capita of \$12 736 or more. Countries were 141 classified into those with very high or high human development indices (HDI) according to the UN's Human Development Programme.²² 142

143

Cancer mortality data (deaths per 100 000) for 1990 to 2010 for the countries in the unemployment and 144 PEH datasets were obtained from the World Health Organisation (WHO) mortality database.²³ These 145 data are based on death certification and updated annually from civil registration systems of WHO 146 147 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 148 were extracted. Female breast, prostate and colorectal cancers have survival rates that exceed 50%.²⁴ 149 Notably, at the time data were collected, complete cancer mortality data were unavailable for China, 150 151 India, and countries from sub-Saharan Africa. We therefore aggregated the mortality data for these 152 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' 153 cancer category.²⁴ Age-standardised death rates (ASDRs), accounting for age distribution differences in 154 155 populations, were extracted for all ages and ages 0–84 for both sexes and each sex separately. For age-156 specific cancer mortality rates, we aggregated crude rates (per 100 000 people) for each sex and country 157 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 158

- 159 deaths during a calendar year for a particular age group divided by the age group's mid-year population.
- 160

161 Multivariable regression analysis

We used multivariable regression analysis to assess the relationship between mortality rates for each 162 163 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 75 164 165 countries in the unemployment dataset, observations for the year 2010 were excluded from the analysis. 166 To ensure that results were not driven by uncontrollable inter-country variations, we used fixed effects 167 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; 168 169 table 2). This meant that the regression models evaluated mortality changes within individual countries 170 while holding constant time-invariant differences between countries, including higher predispositions to 171 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 172 regarded as statistically robust and conservative.²⁵ The population structure of each country was also 173 controlled for by incorporating total population size and demographic structure (the percentage of the 174 175 population over 65 years and less than 15 years old) into the model (table 2). Further details of the 176 model are provided in appendix S2.

177

178 We conducted 1-, 2-, 3-, 4-, and 5-year time-lag analyses. For both datasets, we then classified countries 179 into those with UHC and those without, and re-ran the analyses using UHC status as a robustness 180 check. Countries were considered to have UHC if all of the following previously described criteria were 181 met: legislation mandating UHC; >90% of the population with access to some form of healthcare 182 insurance; and >90% of the population with access to skilled birth attendance. The latter criterion was 183 used to ensure the implementation of UHC met minimum performance standards expected of a 184 functioning healthcare system. To test the sensitivity of our results to this definition, we re-ran the 185 analysis using an alternative performance criterion, details of which are included in appendix S1 in the 186 Supplementary Material (table S1). Robustness checks are detailed in table 2 and appendix S2.

187

188 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 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

- 194 group, and to further ensure robustness in cross-country comparisons, we excluded age groups with
- 195 fewer than 20 deaths in any calendar year. Details of the models used are provided in appendix S3.
- 196
- 197 Multivariable regression analyses were conducted using Stata SE version 12 (Stata Corporation, Texas,
- 198 USA). Time-series analyses were conducted in R version 2.14.1 (http://www.r-project.org).
- 199

200 **Role of the funding source**

- 201 There was no funding source for this study. The corresponding author had full access to all the data in
- 202 the study and had final responsibility for submitting the manuscript for publication.
- 203

204 **RESULTS**

205

206 Unemployment

207 A 1% unemployment rise was associated with a statistically significant increase in mortality for all but 208 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 209 210 (R=0.2260, 95% CI 0.1216–0.3304; p<0.0001), male-colorectal (R=0.0596, 95% CI 0.0188–0.1003; 211 p=0.0042), and female-colorectal (R=0.0676, 95% CI 0.0362–0.099; p<0.0001) (figures 2A-E, figure 212 S1A, table S2). The association for female-lung cancer mortality with unemployment was negative (R= 213 -0.0593, 95% CI-0.1013 to 0.0172; p=0.0058; figure 2F, table S2). Whereas treatable cancer mortality 214 was significantly linked with unemployment (R=0.1256, 95% CI 0.0148-0.2364; p=0.0265) (figure 2G, 215 table S2), no such significance was observed for untreatable cancers (R=0.082, 95% CI -0.041–0.205; 216 p=0.1919) (figure 2H, table S2). The strongest associations were found in the all-cancer data 217 (R=0.3745, 95% CI 0.1939–0.5551; p=0.0001; figure 2I, table S2). Lag analysis showed that these 218 results remained through to five years after unemployment increases (figure 2I). These associations held 219 and remained significant in the robustness checks performed (tables S3–S9).

220

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 S1BC). The results were unaffected by country classifications according to an alternative definition for
UHC (appendix S1).

225

226 Trend analysis

227 For the trend analysis, population-weighted mean values of the projected age-specific rates and ASDRs 228 for each year and sex were obtained. Globally (for the 35 countries selected), we observed significant 229 deviations in the projected ASDR from the observed ASDR for both male all cancer mortality (figure 230 3A, table S10) and female all cancer mortality (figure 3B, table S10) with the 2010 predicted ASDR -3231 years after the unemployment rise in 2007 – deviating the most from the observed ASDR (males: rate 232 ratio 1.0362, 95% CI 1.0209–1.052; p<0.0001; females: rate ratio 1.0428, 95% CI 1.0254–1.0607; 233 p<0.0001). This corresponded to 55 434 (95% CI 32 439–78 428) excess deaths among men and 53 573 234 (95% CI 32 386–74 759) excess deaths among women in 2010 alone. Summing the point estimates for 235 males and females from 2008 to 2010 yielded 252,199 excess deaths (figure 3A). This finding was 236 recapitulated upon confinement of our analysis to treatable cancers (rate ratio 1.0362, 95% CI 1.0225-237 1.0502; p<0.0001; figure 3C, table S10) resulting in 22 977 (95% CI 14 482-31 472) excess deaths in 238 2010. By contrast, for untreatable cancers, the deviation between predicted and observed ASDR was not

- 239 significant in 2008, 2009, or 2010 (figure 3D, table S10).
- 240

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

245

246 For the UHC country group, no significant difference was found for treatable cancer ASDR (figure 3E, 247 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% 248 249 CI 1.0417–1.11; p<0.0001), which equated to 21 241 (95% CI 12 244–30 238) excess deaths due to 250 treatable cancers in 2010 (figure 3F, table S10). Differences between the actual and projected ASDR of 251 untreatable cancer were non-significant for both UHC and non-UHC country groups in 2008 with a 252 significantly lower-than-expected number of deaths in 2009 and 2010 for the UHC country group, and a 253 marginally significant higher-than-expected number of deaths in 2010 for the non-UHC country group 254 (table S10).

255

Stratifying countries by income using the World Bank's classification,²¹ yielded higher rate ratios 256 257 (indicating higher-than-expected numbers of deaths) for male, female and treatable cancers among 258 middle-income countries than among high-income countries (table S10). For untreatable cancers, high-259 income countries experienced significantly lower-than expected numbers of deaths whereas middle-260 income countries experienced significantly higher-than-expected numbers of deaths (table S10). On 261 dividing countries according to HDI, neither the very high nor high HDI groupings experienced higher-262 than-expected numbers of untreatable cancer deaths although significantly lower-than expected 263 numbers across all years were only observed for the very high HDI group (table S10).

264

265 **Public-sector expenditure on healthcare**

266 Increases in PEH, as a proportion of GDP, were significantly associated with mortality reductions in 267 seven of the nine cancer categories studied: prostate (R = -0.0013, 95% CI -0.0019 to -0.0008; 268 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 -269 270 0.0007; p<0.0001), female-colorectal (R=-0.0011, 95% CI -0.0014 to -0.0008; p<0.0001), treatable 271 (R = -0.006858, 95% CI - 0.007532 to -0.006184; p < 0.0001) and all-cancers (R = -0.0053, 95% CI - 0.0053, 95% CI - 0.0053)272 0.0070 to -0.0036; p<0.0001) (figure 4, table S11). Female-lung cancer mortality (R=0.0007, 95% CI 273 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
- 275 0.0014; p=0.1492) (figures 4F and 4H, table S11).
- 276
- 277 Lag analysis showed that these results carried through to five years after increases in PEH (figure 4).
- 278 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
- 281 performed (tables S12–S18).
- 282
- 283

284 **DISCUSSION**

285

286 Our results suggest that increases in unemployment in 1990 to 2009 were associated with increased 287 mortality of prostate, breast, male-lung, and colorectal cancers in a range of countries. Increases in 288 unemployment were also associated with increased mortality due to a subset of treatable cancers as well 289 as all cancers. Time-lag analyses indicated that these adverse effects persisted long after initial rises in 290 unemployment. For the most part, these associations remained significant after controlling for 291 economic, resource availability, infrastructure, and out-of-pocket spending indicators. UHC 292 implementation, however, removed the association between changes in unemployment and cancer 293 mortality implying that UHC could have had a protective effect against the possible impact of 294 unemployment. Our findings also suggest that increased PEH (as a proportion of GDP) is associated 295 with improved cancer mortality. This trend continued irrespective of UHC status.

296

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.

302

303 The trend analysis studied a particular set of periods in order to obtain counter-factual results for 2008– 304 2010 (the projection period), based on models of the mortality trends for 2000–2007 (the observation 305 period), with the hypothesis that observation-period trends would continue for the projection period. 306 These periods were chosen so as to correspond with the sharp upturn in unemployment observed from 307 2008 onwards (figure S2) during the global economic crisis, while limiting the effects of previous 308 unemployment fluctuations and technical progress in cancer care, which may otherwise have influenced 309 rates if the observation period had been extended further back than 2000. We found the strongest, most 310 significant deviations between observed and projected rates to occur for the non-UHC country 311 grouping, corroborating our multivariable regression analyses. Likewise, the difference between 312 expected and actual all-cancer mortality rates in middle-income countries exceeded that between high-313 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 314 315 economic crisis and the subsequent change in cancer mortality, lends favour to a potentially causal link, 316 rather than reverse causality or endogeneity.

317

318 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

326

327 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, 328 radiotherapy, chemotherapy, and surgery, are costly but effective at reducing mortality. Changes in the 329 330 availability of healthcare resources – whether at the diagnosis or treatment stage – due to changes in 331 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 332 professionals likely to result in reduced quality of care if productivity gains are not made,³⁸ and changes 333 in the number of localised sites providing healthcare, with longer distances or travel times likely to 334 increase delays in presentation for diagnosis as well as adversely affect treatment.³⁹ 335

336

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.

344

345 We note several limitations of our study. First, we evaluated population health outcomes and economic 346 trends but did not account for variations at regional and sub-national levels. Second, for reasons of data 347 availability and quality, we were unable to analyse the effects of the global economic crisis after 2010. 348 However, in addition to the sizeable economic fluctuations that occurred during the period studied, our 349 analysis was still able to capture the effects of the earlier stages of the crisis with the trend analysis, 350 during which unemployment levels rose sharply and in some countries peaked. For the PEH dataset, we 351 did not account for changes in efficiency; indeed, it is possible that a country spends less on healthcare 352 but achieves greater outcomes due to the efficiency of its system. Linked to this, we acknowledge the 353 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 354 355 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 356 357 causal inferences. The possibility of residual confounding from social determinant and region-specific 358 healthcare system variables also necessitates a comprehensive, longitudinal approach characterising 359 trends and predictors of healthcare access and quality before and after significant economic changes to 360 strengthen the case for any causative effect as well as clarifying the expected latency between cancer 361 treatment and mortality. Finally, by employing a fixed-effects model, we assumed that any unobserved 362 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 363 364 assumption affecting our findings.

365

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 cancerrelated 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.

372

AUTHORS' CONTRIBUTIONS

- 376 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
 - 378 manuscript. AMN, CW, RaA, RS, TZ and RiA helped interpret the findings, and provided input to
 - 379 subsequent drafts of the manuscript. All authors have seen and approved the final version of the report.
 - 380 MM and JW contributed equally.
 - 381

382 CONFLICTS OF INTEREST

- 383
- 384 None to declare.
- 385

386 **ROLE OF FUNDING SOURCE**

- 387
- 388 No funding was received for this study.
- 389

390 ETHICS COMMITTEE APPROVAL

- 391
- 392 Ethics approval was not applicable for this study.

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- 494
- 495

496 **RESEARCH IN CONTEXT**

497

498 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),

506 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 507 508 simply used Pearson's correlation rather than a panel-based fixed effects model to find an association 509 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. 510 The study periods for both these publications ended before the 2008 economic recession. Three further 511 512 studies investigated a substantially narrower geographical region and outcome than the present study. 513 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 514 stomach cancer mortality again in the European Union only,¹⁵ while the third examined prostate cancer 515 mortality in countries belonging to the Organisation for Economic Co-operation and Development.⁴² 516 517 The remaining two studies were not considered relevant, as they did not quantify the relationship 518 between the macroeconomic indicators and cancer mortality. The study extracted from search 519 combination (ii) was also irrelevant in that again it did not seek to quantify the influence of coverage on 520 mortality.

521

522 Added value of this study

523 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 524 525 specific forms of cancer. In using a conservative, fixed-effects regression analysis model to ascertain 526 the existence of an association and quantify any associations combined with robustness checks, this 527 study accounts for criticisms levelled at other studies looking at the relationship between health 528 outcomes and unemployment, namely, the omission of potential confounding variables likely to be 529 correlated with both unemployment rates (or public healthcare spending) and cancer mortality rates. In 530 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 531 532 (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 533 534 a rigorous characterisation of the associations between unemployment, public healthcare spending, universal healthcare coverage, income, and cancer mortality. The major findings from these 535 complementary approaches are that unemployment increases are associated with rises in cancer 536 537 mortality, with universal healthcare coverage protecting against this phenomenon. Consideration of 538 certain types of cancer as either treatable or untreatable revealed that significantly higher-than-expected 539 numbers of deaths were only observed for treatable cancers. In contrast to unemployment, public 540 healthcare spending increases are associated with reductions in cancer mortality with a recapitulation of 541 the divergent findings between treatable and untreatable cancers. Whether or not a country has 542 implemented universal healthcare coverage does not significantly alter the strength of this relationship.

543

544 Implications of all the available evidence

545 Policies that maintain spending and hence access to and quality of healthcare in the face of economic 546 downturns especially among cancers that are considered treatable may offset some of the negative 547 effects of such periods on health outcomes. Furthermore, the findings of our study add to the existing 548 body of evidence in favour of universal healthcare coverage.

550 FIGURE LEGENDS

551

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

553 Cohort selection with final aggregation by UHC status. The first step involves selecting only those 554 countries with complete consecutive mortality data from 2000 to 2010. The second filters out countries 555 with civil registration coverage of cause-of-death of <90%. Next, the over-85 age group and age groups 556 with fewer than 20 deaths in any calendar year were excluded. The first row of boxes at the end of the 557 workflow shows the categorisation of countries by UHC status (as determined by skilled birth 558 attendance). The second row of boxes at the end of the workflow shows the categorisation of countries 559 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 2013.²³ 560 HDI categories were obtained from the United Nations Development Programme website.²² HDI, 561 562 Human development index, UHC, Universal healthcare coverage.

563

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

565 Multivariable regression analysis was conducted on data for 75 countries from 1990 to 2009 to assess 566 the relationship between unemployment, and prostate cancer mortality (A), breast cancer mortality (B), 567 male colorectal cancer mortality (C), female colorectal cancer mortality (D), male lung cancer mortality 568 (E), female lung cancer mortality (F), treatable cancer mortality (G), untreatable cancer mortality (H) 569 and all-cancer mortality (I). Analyses were conducting with controls for population size, population 570 structure (proportion of population below 14 years of age and above 65 years of age), and country-571 specific differences in healthcare infrastructure. Data are also shown for 1-, 2-, 3-, 4-, and 5-year timelag analyses. Economic data were obtained from the World Bank.²⁵ Cancer mortality data (deaths per 572 100 000) were obtained from the World Health Organisation Mortality Database 2013.²³ * p<0.05; ** 573 574 p<0.01; *** p<0.001.

575

576 *Figure 3.* Predicted cancer-related mortality rate and number of deaths, 2008–2010, based on 577 2000–2007 observation base.

578 Projections of age-standardised cancer-related mortality rates per 100 000 (ASDR) for 35 countries 579 from 2008 to 2010 were made based upon ASDRs observed from 2000 to 2007, and compared with 580 those observed from 2008 to 2010. The number of excess deaths due to male cancers (A), female 581 cancers (B), treatable cancers (female breast, prostate and colorectal) (C), and untreatable cancers (lung 582 and pancreatic) (D) were estimated by comparing 2008-2010 projected rates with 2008-2010 observed 583 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.

586

587 *Figure 4.* Time-lag analyses of changes in public-sector healthcare expenditure on cancer 588 mortality.

589 Multivariable regression analysis was conducted on data for 79 countries from 1990 to 2009 to assess 590 the relationship between public-sector healthcare expenditure, and prostate cancer mortality (A), breast 591 cancer mortality (B), male colorectal cancer mortality (C), female colorectal cancer mortality (D), male 592 lung cancer mortality (E), female lung cancer mortality (F), treatable cancer mortality (G), untreatable 593 cancer mortality (H), and all-cancer mortality (I). Analyses were conducted with controls for population 594 size, population structure (proportion of population below 14 years of age and above 65 years of age), 595 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 596 (deaths per 100 000) were obtained from the World Health Organisation Mortality Database 2013.²³ * 597 598 p<0.05; ** p<0.01; *** p<0.001. 599

600 Figure 5. Possible causal pathways for the observed associations

- 601 PEH, Public-sector expenditure on healthcare; SES, Socioeconomic status.
- 602

603 **<u>TABLES</u>**

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 Renublic	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

605 *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:

607 SP.POP.TOTL).²⁰ For country groupings, populations are calculated only for those countries

608 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
		Economic	Inflation GDP per capita changes Base interest rates	80
Unormalorum	Population size Proportion of	Resource availability	Number of physicians per 100 000 population; Number of hospital beds per 100 000 population	79
ent dataset (75	15 years of age	Infrastructure	Urbanisation; Access to water; Calorie intake	80
countries)	rioportion over 65	Out-of-pocket spending	Out-of-pocket expenditure	78
	years of age	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
		Economic	Inflation; GDP per capita changes; Base interest rates	84
	Population size Proportion of population less than 15 years of age	Resource availability	Number of physicians per 100 000 population; Number of hospital beds per 100 000 population	83
PEH dataset (79 countries)		Infrastructure	Urbanisation; Access to water; Calorie intake	84
	rioportion over 65	Out-of-pocket spending	Out-of-pocket expenditure	82
	population over 65 - years of age	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

612 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

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

616 Countries were classified as universal healthcare coverage (UHC) countries according to whether they

617 were assessed to have met all of the following previously described conditions: legislation mandating

618 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

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

623 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

625 mandating UHC; >90% healthcare coverage; and >90% skilled birth attendance. PEH, Public-

626 sector expenditure on healthcare. * p<0.05; ** p<0.01; *** p<0.001

1	Economic downturns, universal health <u>care</u> coverage, and cancer
2	mortality : a global analysis in high- and middle-income countries,
3	1990–2010
4	
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33	Number of references (excluding those cited only in the Research in Context panel): 4042
34	

35 SUMMARY

36

37 Background

The global economic crisis has been associated with increased unemployment and reduced publicsector 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.

41

42 *Methods*

Data were obtained from the World Bank and WHO (1990-2010). Mortality data from female breast, 43 44 prostate and colorectal cancers, which have survival rates that exceed 50%, were aggregated into a 45 'treatable' cancer class. Lung and pancreatic cancers, which have five-year survival rates <10%, were 46 likewise aggregated to give an 'untreatable' cancer category. Multivariable regression analysis was 47 used, controlling for country-specific demographics and infrastructure, with time-lag analyses and 48 robustness checks to explore the relationship between unemployment and PEH on cancer mortality, 49 with and without UHC. Trend analysis was used to project mortality rates based on trends prior to the 50 sharp unemployment rise experienced by many countries fromin-2008 to 2010, and compare them with 51 observed rates.

52

53 Results

54 Data were available for 75 countries (unemployment analysis) and 79 countries (PEH analysis). 55 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 56 57 significantly linked with changes in unemployment. Lag analyses showed significant associations 58 remained five years after unemployment increases for the treatable cancer class. Re-running analyses 59 while accounting for UHC status removed the significant associations. All-cancer, treatable cancer and 60 specific cancer mortalities significantly decreased as PEH increased. Associations held over a five-year 61 period regardless of whether UHC was present. Time-series analysis found just over 40 000 estimated 62 excess deaths due to a subset of treatable cancers from 2008-2010 based on 2000-2007 trends. The great 63 majority of these deaths were from non-UHC countries.

64

65 Interpretation

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

70	Funding
10	1 anams

71 None.

- **Key words:** cancer; government spending; health economics; mortality; public health; unemployment;
- 74 universal health<u>care</u> coverage.

76 **INTRODUCTION**

77

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}

85

86 Ecological studies exploring health-economic trends in the short run (separate from residual or secular 87 trends) have thus far focused on macroeconomic changes and outcome indicators, such as suicide rates, 88 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-89 90 related changes with direct and immediate effects, whether, as in the case of suicides, they are countercyclical associations linked to the direct psychological and financial impact of job loss,¹⁶ or pro-cyclical 91 92 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 93 94 cancer especially in countries that are may be more susceptible to economic shocks due to less-95 developedimited social security and healthcare systems.

96

97 Establishing a causal relationship between an economic change, such as aggregate unemployment, on 98 cancer mortality is challenging, as downstream effects of unemployment-induced behavioural changes 99 on lifestyle-related cancers manifest much later (20-30 years) than, for example, suicide or acute, stress-100 related cardiovascular events. However, access to healthcare and PEH may act as mediating factors with 101 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 102 with late-stage disease meant that the effect of the economic downturn on reduced healthcare access and 103 104 mortality could not be as strongly demonstrated as it could in an era where systemic treatment is now 105 available.

106

107 Cancer is one of the leading causes of death worldwide, accounting for 8.2 million deaths in 2012, with
 108 estimates suggesting a rise in annual cancer cases from 14 million in 2012 to 22 million by 2030.¹⁸
 109 Hence an understanding of the effects of macroeconomic changes on cancer outcomes worldwide is
 110 important.

- 112 We examined the association between changes in aggregate unemployment and PEH with deaths due to 113 specific cancers, groups of cancers, and all cancers for countries where data was available and deemed 114 of sufficient quality (1990–2010). Mortality was considered a more reliable measure of health outcomes 115 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' 116 117 circumstances, especially in lower-income strata of societies. Given the recent drive, in many countries, 118 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 119 healthcare, especially as many countries progress towards UHC systems.¹⁹ we explored whether UHC 120 conferred a protective effect. We also estimated the difference between the actual numbers of cancer-121 122 related deaths during and after the recent economic downturn and the expected numbers based on prior 123 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 124 125 due to the recent economic downturn. 126
- 127

128 METHODS

129

130 Data sources

131 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 132 defined as the share of the labour force without work but available and seeking employment.²⁰ PEH 133 134 (World Bank data code: SH.XPD.PUBL.ZS) was measured as a percentage of gross domestic product 135 (GDP) at purchasing power parity (PPP); it was defined by the World Bank as including all rent and 136 capital spending from government budgets (central and local), external borrowings and grants (including donations from international agencies and non-governmental organisations), and social (or 137 138 compulsory) health insurance funds. Unemployment and cancer mortality (see below) data for 1990 to 139 2010 were available for 75 countries and data on PEH for 1990 to 2009 were available for four 140 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 141 the World Bank's Atlas Method.²¹ In brief, middle-income countries are those with a gross national 142 income per capita of more than \$1 045 but less than \$12 736, whereas high-income economies are those 143 144 with a gross national income per capita of \$12 736 or more. Countries were classified into those with 145 very high or high human development indices (HDI) according to the UN's Human Development Programme.²² 146

147

Cancer mortality data (deaths per 100 000) for 1990 to 2010 for the countries in the unemployment and 148 PEH datasets were obtained from the World Health Organisation (WHO) mortality database.²³ These 149 data are based on death certification and updated annually from civil registration systems of WHO 150 151 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 152 were extracted. Female breast, prostate and colorectal cancers have survival rates that exceed 50%.²⁴ 153 We therefore aggregated the mortality data for these tumour types into a 'treatable' cancer class. Lung 154 and pancreatic cancers (male and female; ICD-10 C25), which have five-year survival rates <10%, were 155 likewise aggregated to give an 'untreatable' cancer category.²⁴ Notably, at the time data were collected, 156 complete cancer mortality data were unavailable for China, India, and countries from sub-Saharan 157 Africa. Age-standardised death rates (ASDRs), accounting for age distribution differences in 158 159 populations, were extracted for all ages and ages 0–84 for both sexes and each sex separately. For age-160 specific cancer mortality rates, we aggregated crude rates (per 100 000 people) for each sex and country 161 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 162

- 163 deaths during a calendar year for a particular age group divided by the age group's mid-year population.
- 164

165 Multivariable regression analysis

We used multivariable regression analysis to assess the relationship between mortality rates for each 166 cancer subtype, treatable cancers, untreatable cancers and all cancers (response variable), and 167 unemployment or PEH (predictor variable). Due to incomplete cancer mortality data for many of the 75 168 169 countries in the unemployment dataset, observations for the year 2010 were excluded from the analysis. 170 To ensure that results were not driven by uncontrollable inter-country variations, we used fixed effects 171 in the regression models, including one dummy variable for each country in each dataset excluding a 172 reference group (i.e. 74 dummy variables for the unemployment dataset and 78 for the PEH dataset; 173 table 2). This meant that the regression models evaluated mortality changes within individual countries 174 while holding constant time-invariant differences between countries, including higher predispositions to 175 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 176 regarded as statistically robust and conservative.²⁵ The population structure of each country was also 177 controlled for by incorporating total population size and demographic structure (the percentage of the 178 179 population over 65 years and less than 15 years old) into the model (table 2). Further details of the 180 model are provided in appendix S2.

181

182 We conducted 1-, 2-, 3-, 4-, and 5-year time-lag analyses. For both datasets, we then classified countries 183 into those with UHC and those without, and re-ran the analyses using UHC status as a robustness 184 check. Countries were considered to have UHC if all of the following previously described criteria were 185 met: legislation mandating UHC; >90% of the population with access to some form of healthcare 186 insurance; and >90% of the population with access to skilled birth attendance. The latter criterion was 187 used to ensure the implementation of UHC met minimum performance standards expected of a 188 functioning healthcare system. To test the sensitivity of our results to this definition, we re-ran the 189 analysis using an alternative performance criterion, details of which are included in appendix S1 in the 190 Supplementary Material (table S1). Robustness checks are detailed in table 2 and appendix S2.

191

192 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

- 198 group, and to further ensure robustness in cross-country comparisons, we excluded age groups with
- 199 fewer than 20 deaths in any calendar year. Details of the models used are provided in appendix S3.
- 200
- 201 Multivariable regression analyses were conducted using Stata SE version 12 (Stata Corporation, Texas,
- 202 USA). Time-series analyses were conducted in R version 2.14.1 (http://www.r-project.org).
- 203

204 **Role of the funding source**

- 205 There was no funding source for this study. The corresponding author had full access to all the data in
- 206 the study and had final responsibility for submitting the manuscript for publication.
- 207

208 **RESULTS**

209

210 Unemployment

- 211 A 1% unemployment rise was associated with a statistically significant increase in mortality for all but 212 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 213 214 (R=0.2260, 95% CI 0.1216–0.3304; p<0.0001), male-colorectal (R=0.0596, 95% CI 0.0188–0.1003; 215 p=0.0042), and female-colorectal (R=0.0676, 95% CI 0.0362–0.099; p<0.0001) (figures 2A-E, figure 216 S1A, table S2). The association for female-lung cancer mortality with unemployment was negative (R= 217 -0.0593, 95% CI-0.1013 to 0.0172; p=0.0058; figure 2F, table S2). Whereas treatable cancer mortality 218 was significantly linked with unemployment (R=0.1256, 95% CI 0.0148-0.2364; p=0.0265) (figure 2G, 219 table S2), no such significance was observed for untreatable cancers (R=0.082, 95% CI -0.041–0.205; 220 p=0.1919) (figure 2H, table S2). The strongest associations were found in the all-cancer data 221 (R=0.3745, 95% CI 0.1939–0.5551; p=0.0001; figure 2I, table S2). Lag analysis showed that these 222 results remained through to five years after unemployment increases (figure 2I). These associations held 223 and remained significant in the robustness checks performed (tables S3–S9).
- 224

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 S1BC). The results were unaffected by country classifications according to an alternative definition for
UHC (appendix S1).

229

230 Trend analysis

231 For the trend analysis, population-weighted mean values of the projected age-specific rates and ASDRs 232 for each year and sex were obtained. Globally (for the 35 countries selected), we observed significant 233 deviations in the projected ASDR from the observed ASDR for both male all cancer mortality (figure 234 3A, table S10) and female all cancer mortality (figure 3B, table S10) with the 2010 predicted ASDR -3235 years after the unemployment rise in 2007 – deviating the most from the observed ASDR (males: rate 236 ratio 1.0362, 95% CI 1.0209–1.052; p<0.0001; females: rate ratio 1.0428, 95% CI 1.0254–1.0607; 237 p<0.0001). This corresponded to 55 434 (95% CI 32 439-78 428) excess deaths among men and 53 573 238 (95% CI 32 386-74 759) excess deaths among women in 2010 alone-. Summing the point estimates for 239 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% 240 CI 1.0225–1.0502; p<0.0001; figure 3C, table S10) resulting in 22 977 (95% CI 14 482-31 472) excess 241 242 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).
- 244

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 <u>using the Atlas Method</u>;²¹ and 22 very high HDI and 13 high HDI countries.²²

249

250 For the UHC country group, no significant difference was found for treatable cancer ASDR (figure 3E, 251 table S10). By contrast, for the non-UHC country group the predicted ASDRs for treatable cancers were 252 significantly lower than the observed ASDRs for all 3 projected years (in 2010: rate ratio 1.0746, 95% 253 CI 1.0417–1.11; p<0.0001), which equated to 21 241 (95% CI 12 244-30 238) excess deaths due to 254 treatable cancers in 2010 (figure 3F, table S10). Differences between the actual and projected ASDR of 255 untreatable cancer were non-significant for both UHC and non-UHC country groups in 2008 with a 256 significantly lower-than-expected number of deaths in 2009 and 2010 for the UHC country group, and a 257 marginally significant higher-than-expected number of deaths in 2010 for the non-UHC country group 258 (table S10).

259

260 Stratifying countries by income using the World Bank's classification yielded higher rate ratios 261 (indicating higher-than-expected numbers of deaths) for male, female and treatable cancers among 262 middle-income countries than among high-income countries (table S10). For untreatable cancers, high-263 income countries experienced significantly lower-than expected numbers of deaths whereas middle-264 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-265 266 than-expected numbers of untreatable cancer deaths although significantly lower-than expected 267 numbers across all years were only observed for the very high HDI group (table S10).

268

269 **Public-sector expenditure on healthcare**

270 Increases in PEH, as a proportion of GDP, were significantly associated with mortality reductions in 271 seven of the nine cancer categories studied: prostate (R = -0.0013, 95% CI -0.0019 to -0.0008; 272 p < 0.0001), female-breast (R= -0.0023, 95% CI -0.0029 to -0.0017; p < 0.0001), male-lung (R= -273 0.0037, 95% CI -0.0045 to -0.0028; p<0.0001), male-colorectal (R=-0.0011, 95% CI -0.0016 to -274 0.0007; p<0.0001), female-colorectal (R=-0.0011, 95% CI -0.0014 to -0.0008; p<0.0001), treatable 275 (R = -0.006858, 95% CI - 0.007532 to -0.006184; p < 0.0001) and all-cancers (R = -0.0053, 95% CI - 0.0053, 95% CI - 0.0053)276 0.0070 to -0.0036; p<0.0001) (figure 4, table S11). Female-lung cancer mortality (R=0.0007, 95% CI 277 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
- 279 0.0014; p=0.1492) (figures 4F and 4H, table S11).
- 280
- Lag analysis showed that these results carried through to five years after increases in PEH (figure 4).
- 282 Spending increases were associated with a slight increase in lung cancer mortality in women (figure 4F)
- 283 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
- 285 performed (tables S12–S18).
- 286
- 287

288 **DISCUSSION**

289

290 Our results suggest that increases in unemployment in 1990 to 2009 were associated with increased 291 mortality of prostate, breast, male-lung, and colorectal cancers in a range of countries. Increases in 292 unemployment were also associated with increased mortality due to a subset of treatable cancers as well 293 as all cancers. Time-lag analyses indicated that these adverse effects persisted long after initial rises in 294 unemployment. For the most part, these associations remained significant after controlling for 295 economic, resource availability, infrastructure, and out-of-pocket spending indicators. UHC 296 implementation, however, removed the association between changes in unemployment and cancer 297 mortality implying that UHC could have had a protective effect against the possible impact of 298 unemployment. Our findings also suggest that increased PEH (as a proportion of GDP) is associated 299 with improved cancer mortality. This trend continued irrespective of UHC status.

300

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.

306

307 The trend analysis studied a particular set of periods in order to obtain counter-factual results for 2008– 308 2010 (the projection period), based on models of the mortality trends for 2000–2007 (the observation 309 period), with the hypothesis that observation-period trends would continue for the projection period. 310 These periods were chosen so as to correspond with the sharp upturn in unemployment observed from 311 2008 onwards (figure S2) during the global economic crisis, while limiting the effects of previous 312 unemployment fluctuations and technical progress in cancer care, which may otherwise have influenced 313 rates if the observation period had been extended further back than 2000. We found the strongest, most 314 significant deviations between observed and projected rates to occur for the non-UHC country 315 grouping, corroborating our multivariable regression analyses. Likewise, the difference between 316 expected and actual all-cancer mortality rates in middle-income countries exceeded that between high-317 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 318 319 economic crisis and the subsequent change in cancer mortality, lends favour to a potentially causal link, 320 rather than reverse causality or endogeneity.

321

322 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

330

331 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, 332 radiotherapy, chemotherapy, and surgery, are costly but effective at reducing mortality. Changes in the 333 334 availability of healthcare resources – whether at the diagnosis or treatment stage – due to changes in 335 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 336 professionals likely to result in reduced quality of care if productivity gains are not made,³⁸ and changes 337 in the number of localised sites providing healthcare, with longer distances or travel times likely to 338 increase delays in presentation for diagnosis as well as adversely affect treatment.³⁹ 339

340

341 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 342 343 where healthcare provision is meant to be equally accessible regardless of employment status, access to 344 healthcare is less problematic than in non-UHC countries where access is often provided by means of 345 an employment package. Second, fiscal consolidation measures introduced during the economic crisis 346 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 347 to actively maintain aggregate employment levels;²⁵ the implication being that, from a public-health 348 perspective, expansionary fiscal policy is the optimal response to the slumps in aggregate demand and 349 350 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 351 healthcare expenditure by not compensating for reduced private sector and private household spending 352 353 in economic crises, then there may be considerable adverse consequences for public health. Third, 354 amidst a background of rising healthcare costs, if spending restrictions are not accompanied by 355 proportionate improvements in efficiency, worse quality of care and, in turn, higher mortality levels, 356 may follow.

358 We note several limitations of our study. First, we evaluated population health outcomes and economic 359 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. 360 361 However, in addition to the sizeable economic fluctuations that occurred during the period studied, our 362 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 363 364 did not account for changes in efficiency; indeed, it is possible that a country spends less on healthcare 365 but achieves greater outcomes due to the efficiency of its system. Linked to this, we acknowledge the 366 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 367 368 possible that mortality rates for certain cancer types have been rising rather than falling would offer 369 valuable insight. Fourth, our study was retrospective and observational, limiting our ability to draw 370 causal inferences. The possibility of residual confounding from social determinant and region-specific 371 healthcare system variables also necessitates a comprehensive, longitudinal approach characterising 372 trends and predictors of healthcare access and quality before and after significant economic changes to 373 strengthen the case for any causative effect as well as clarifying the expected latency between cancer 374 treatment and mortality. Finally, by employing a fixed-effects model, we assumed that any unobserved 375 factors within each country were time-invariant and not correlated with our variables of interest, 376 although the comprehensiveness of our robustness checks will have reduced the probability of this 377 assumption affecting our findings.

378

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 removes the association between unemployment and cancer mortality, lending evidence in favour of healthcare system reforms aimed at providing UHC, particularly among middle-income countries.

- 385
- 386

AUTHORS' CONTRIBUTIONS

- 389 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
 - 391 manuscript. AMN, CW, RaA, RS, TZ and RiA helped interpret the findings, and provided input to
 - 392 subsequent drafts of the manuscript. All authors have seen and approved the final version of the report.
 - 393 MM and JW contributed equally.
 - 394

395 CONFLICTS OF INTEREST

- 396
- 397 None to declare.
- 398

399 **ROLE OF FUNDING SOURCE**

- 400
- 401 No funding was received for this study.
- 402

403 ETHICS COMMITTEE APPROVAL

- 404
- 405 Ethics approval was not applicable for this study.

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- 507
- 508

509 **RESEARCH IN CONTEXT**

510

511 Evidence before this study

512 We searched the literature to identify articles that quantitatively estimated either the effect of both 513 unemployment and healthcare spending (public or otherwise) on cancer mortality, or the effect of 514 universal healthcare coverage on cancer mortality. We searched PubMed for publications up to and 515 including May 31 2015 using the following combinations of search terms: (i) unemployment AND 516 cancer AND mortalit* AND (spending OR expenditure); (ii) cancer AND mortalit* AND "universal 517 healthcare coverage". Search combination (i) yielded seven publications, and combination (ii) yielded 518 one publication. With respect to search combination (i), one study used a time-trend analysis to 519 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 520 521 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 522 therefore unable to control for potential confounding variables. The study periods for both these 523 524 publications ended before the 2008 economic recession. Three further studies investigated a 525 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 526 European Union only,¹⁴ the second examined the relationship between unemployment and stomach 527 cancer mortality again in the European Union only.¹⁵ while the third examined prostate cancer mortality 528 in countries belonging to the Organisation for Economic Co-operation and Development.⁴² The 529 530 remaining two studies were not considered relevant, as they did not quantify the relationship between 531 the macroeconomic indicators and cancer mortality. The study extracted from search combination (ii) 532 was also irrelevant in that again it did not seek to quantify the influence of coverage on mortality.

533

534 Added value of this study

535 The study presented here is the first global analysis of the impact of unemployment and public 536 healthcare spending on mortality due to all cancers, "treatable" cancers, "untreatable" cancers and 537 specific forms of cancer. In using a conservative, fixed-effects regression analysis model to ascertain 538 the existence of an association and quantify any associations combined with robustness checks, this 539 study accounts for criticisms levelled at other studies looking at the relationship between health 540 outcomes and unemployment, namely, the omission of potential confounding variables likely to be 541 correlated with both unemployment rates (or public healthcare spending) and cancer mortality rates. In 542 using a panel-data approach for the multivariable regression analysis to compare unemployment rates 543 (or public healthcare spending) at intervals of one year for each year after the increase in unemployment 544 (or public healthcare spending) with the mortality rates in each country, we controlled for time-invariant 545 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, 546 547 universal healthcare coverage, income, and cancer mortality. The major findings from these 548 complementary approaches are that unemployment increases are associated with rises in cancer 549 mortality, with universal healthcare coverage protecting against this phenomenon. Consideration of 550 certain types of cancer as either treatable or untreatable revealed that significantly higher-than-expected 551 numbers of deaths were only observed for treatable cancers. In contrast to unemployment, public 552 healthcare spending increases are associated with reductions in cancer mortality with a recapitulation of 553 the divergent findings between treatable and untreatable cancers. Whether or not a country has 554 implemented universal healthcare coverage does not significantly alter the strength of this relationship.

555

556 Implications of all the available evidence

557 Policies that maintain spending and hence access to and quality of healthcare in the face of economic 558 downturns especially among cancers that are considered treatable may offset some of the negative 559 effects of such periods on health outcomes. Furthermore, the findings of our study add to the existing 560 body of evidence in favour of universal healthcare coverage.

562 **FIGURE LEGENDS**

563

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

565 Cohort selection with final aggregation by UHC status. The first step involves selecting only those 566 countries with complete consecutive mortality data from 2000 to 2010. The second filters out countries 567 with civil registration coverage of cause-of-death of <90%. Next, the over-85 age group and age groups 568 with fewer than 20 deaths in any calendar year were excluded. The first row of boxes at the end of the 569 workflow shows the categorisation of countries by UHC status (as determined by skilled birth 570 attendance). The second row of boxes at the end of the workflow shows the categorisation of countries 571 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 2013.²³ 572 HDI categories were obtained from the United Nations Development Programme website.²² HDI, 573 574 Human development index, UHC, Universal healthcare coverage.

575

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

577 Multivariable regression analysis was conducted on data for 75 countries from 1990 to 2009 to assess 578 the relationship between unemployment, and prostate cancer mortality (A), breast cancer mortality (B), 579 male colorectal cancer mortality (C), female colorectal cancer mortality (D), male lung cancer mortality 580 (E), female lung cancer mortality (F), treatable cancer mortality (G), untreatable cancer mortality (H) 581 and all-cancer mortality (I). Analyses were conducting with controls for population size, population 582 structure (proportion of population below 14 years of age and above 65 years of age), and country-583 specific differences in healthcare infrastructure. Data are also shown for 1-, 2-, 3-, 4-, and 5-year timelag analyses. Economic data were obtained from the World Bank.²⁵ Cancer mortality data (deaths per 584 100 000) were obtained from the World Health Organisation Mortality Database 2013.²³ * p<0.05; ** 585 p<0.01; *** p<0.001. 586

587

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

590 Projections of age-standardised cancer-related mortality rates per 100 000 (ASDR) for 35 countries 591 from 2008 to 2010 were made based upon ASDRs observed from 2000 to 2007, and compared with 592 those observed from 2008 to 2010. The number of excess deaths due to male cancers (A), female 593 cancers (B), treatable cancers (female breast, prostate and colorectal) (C), and untreatable cancers (lung 594 and pancreatic) (D) were estimated by comparing 2008-2010 projected rates with 2008-2010 observed 595 rates. The projections of ASDRs for treatable cancers are also shown for UHC (E) and non-UHC (F) 596 countries. ASDRs were extracted from the World Health Organisation Mortality Database 2013.²³ * 597 p<0.05; ** p<0.01; *** p<0.001.

598

599 *Figure 4.* Time-lag analyses of changes in public-sector healthcare expenditure on cancer 600 mortality.

601 Multivariable regression analysis was conducted on data for 79 countries from 1990 to 2009 to assess 602 the relationship between public-sector healthcare expenditure, and prostate cancer mortality (A), breast 603 cancer mortality (B), male colorectal cancer mortality (C), female colorectal cancer mortality (D), male 604 lung cancer mortality (E), female lung cancer mortality (F), treatable cancer mortality (G), untreatable 605 cancer mortality (H), and all-cancer mortality (I). Analyses were conducted with controls for population 606 size, population structure (proportion of population below 14 years of age and above 65 years of age), 607 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 608 (deaths per 100 000) were obtained from the World Health Organisation Mortality Database 2013.²³ * 609 p<0.05; ** p<0.01; *** p<0.001. 610

611

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

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

<u>TABLES</u>

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	Uruguav	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:

619 SP.POP.TOTL).²⁰ For country groupings, populations are calculated only for those countries

620 included in the time-series analysis as per figure 1. UHC, Universal health<u>care</u> coverage.

621		

	Common controls	Robustness check control	Particular control	Total number of controls
		Economic	Inflation GDP per capita changes Base interest rates	80
Unamploym	Population size Proportion of	Resource availability	Number of physicians per 100 000 population; Number of hospital beds per 100 000 population	79
ent dataset (75	15 years of age	Infrastructure	Urbanisation; Access to water; Calorie intake	80
countries)	nopulation over 65	Out-of-pocket spending	Out-of-pocket expenditure	78
	years of age	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
		Economic	Inflation; GDP per capita changes; Base interest rates	84
	Population size Proportion of population less than 15 years of age	Resource availability	Number of physicians per 100 000 population; Number of hospital beds per 100 000 population	83
PEH dataset (79 countries)		Infrastructure	Urbanisation; Access to water; Calorie intake	84
	population over 65	Out-of-pocket spending	Out-of-pocket expenditure	82
	population over 65 years of age	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

624 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

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

628 Countries were classified as universal healthcare coverage (UHC) countries according to whether they

629 were assessed to have met all of the following previously described conditions: legislation mandating

630 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

633

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

635 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

637 mandating UHC; >90% healthcare coverage; and >90% skilled birth attendance. PEH, Public-

638 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 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:

"<u>There is evidence that</u> UHC protects against mortality increases <u>associated</u> 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 <u>possible</u> 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 <u>experienced by many countries</u> 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:

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

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:

"<u>Classification of countries into high- and middle-income was done</u> 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 <u>using the Atlas Method;</u>²⁵<i>"

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.





Years after increase in unemployment



Α

All countries





All countries



Ε





В

All countries













Years after increase in spending as a proportion of GDP





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

40 Unemployment Annual percentage change Cancer mortality 30 20 10 0 -10 -20 \square 1 0 3 ດ້ ~~~~~~ റ് ດ້ à Year









В



Figure S2