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DOI:

[10.1016/S0140-6736\(16\)00577-8](https://doi.org/10.1016/S0140-6736(16)00577-8)

Document Version

Peer reviewed version

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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](https://doi.org/10.1016/S0140-6736(16)00577-8)

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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 country-specific demographics and infrastructure, with time-lag analyses and robustness checks to explore the relationship between unemployment and PEH on cancer mortality, with and without UHC. Trend analysis was used to project mortality rates based on trends prior to the sharp unemployment rise experienced by many countries from 2008 to 2010, and compare them with observed rates.

Results

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

Interpretation

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

Funding

None.

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

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Word count (Introduction, Materials and Methods, Results, Discussion): 3,692

Number of references (excluding those cited only in the Research in Context panel): 42

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

41 ***Methods***

42 Data were obtained from the World Bank and WHO (1990–2010). Mortality data from female breast,
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*

70 None.

71

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

74

75 **INTRODUCTION**

76

77 The global economic crisis, which began in 2008, compelled many countries to cut public spending in
78 order to reduce public-sector borrowing.¹ These spending cuts often entailed either reductions or a
79 flattening in public-sector jobs and public-sector expenditure on healthcare (PEH).^{2,3} Thirty three of 53
80 WHO European region countries underwent no change in PEH between 2008 and 2009, while six
81 experienced a reduction in PEH,⁴ which have prompted concerns about the possible negative effects on
82 public health. Studies have demonstrated that long-term unemployment leads to increased suicide rates
83 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,
87 cardiovascular disease incidence, all-cause mortality, and specific forms of cancer, but not cancer *per*
88 *se*.^{3,7-15} These potential associations may predominantly be explained by behavioural, mental, or stress-
89 related changes with direct and immediate effects, whether, as in the case of suicides, they are counter-
90 cyclical associations linked to the direct psychological and financial impact of job loss,¹⁶ or pro-cyclical
91 associations linked to reduced injury-related work and lifestyle activities in the case of all-cause
92 mortality.⁹ Few studies, however, have analysed the relationship between economic downturns and
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
101 deaths from cancer correlated with reduced income,¹⁷ although the lack of treatment options for patients
102 presenting with late-stage disease meant that the effect of the economic downturn on reduced healthcare
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.

110

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
115 means of diagnosis. We chose unemployment due to its ability to capture changes in individuals’
116 circumstances, especially in the lower-income strata of societies. Given the recent drive, in many
117 countries, to implement universal healthcare coverage (UHC),¹⁹ we explored whether UHC conferred a
118 protective effect. We also estimated the difference between the actual numbers of cancer-related deaths
119 during and after the recent economic downturn and the expected numbers based on prior trends. For
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

123

124 **METHODS**

125

126 **Data sources**

127 Economic data were obtained from the World Bank's Development Indicators & Global Development
128 Finance 2013 edition datasets.²⁰ Unemployment (World Bank data code: SL.UEM.TOTL.ZS) was
129 defined as the share of the labour force without work but available and seeking employment.²⁰ PEH
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
133 (including donations from international agencies and non-governmental organisations), and social (or
134 compulsory) health insurance funds. Unemployment and cancer mortality (see below) data for 1990 to
135 2010 were available for 75 countries and data on PEH and cancer mortality for 1990 to 2009 were
136 available for four additional countries (table 1), representing, as of 2009, 2.106 billion and 2.156 billion
137 people in each dataset, respectively.²⁰ Classification of countries into high- and middle-income was
138 done according to the World Bank's Atlas Method.²¹ In brief, middle-income countries are those with a
139 gross national income per capita of more than \$1 045 but less than \$12 736, whereas high-income
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
142 Human Development Programme.²²

143

144 Cancer mortality data (deaths per 100 000) for 1990 to 2010 for the countries in the unemployment and
145 PEH datasets were obtained from the World Health Organisation (WHO) mortality database.²³ These
146 data are based on death certification and updated annually from civil registration systems of WHO
147 member states. Mortality data for prostate (ICD-10 C61), female-breast (ICD-10 C50), lung (male and
148 female; ICD-10 C33–C34), colorectal (male and female; ICD-10 C18–C21) cancers and all cancers
149 were extracted. Female breast, prostate and colorectal cancers have survival rates that exceed 50%.²⁴
150 Notably, at the time data were collected, complete cancer mortality data were unavailable for China,
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
153 C25), which have five-year survival rates <10%, were likewise aggregated to give an 'untreatable'
154 cancer category.²⁴ Age-standardised death rates (ASDRs), accounting for age distribution differences in
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
158 influence of age groups with fewer observations. These crude rates were defined as the number of

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**

162 We used multivariable regression analysis to assess the relationship between mortality rates for each
163 cancer subtype, treatable cancers, untreatable cancers, and all cancers (response variable), and
164 unemployment or PEH (predictor variable). Due to incomplete cancer mortality data for many of the 75
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
168 reference group (i.e. 74 dummy variables for the unemployment dataset and 78 for the PEH dataset;
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
172 fixed effects was used since this methodology has been widely employed in similar studies, and is
173 regarded as statistically robust and conservative.²⁵ The population structure of each country was also
174 controlled for by incorporating total population size and demographic structure (the percentage of the
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**

189 For the all-cancer mortality trend projection analysis, we set strict country inclusion criteria to ensure
190 that only high quality data were used. We therefore excluded countries with civil registration coverage
191 of cause-of-death less than 90% for the study period,²³ eliminating in the process 26 countries from the
192 61 for which all-cancer mortality data were complete for 2000 to 2010 (figure 1). In order to limit the
193 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–
209 0.1609; p=0.0022), female-breast (R=0.1583, 95% CI 0.1110–0.2056; p<0.0001), male-lung
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

221 On accounting for the UHC status of countries, we found no significant association between
222 unemployment and cancer mortality within the first year of unemployment rising (table 3, figures S1B-
223 C). The results were unaffected by country classifications according to an alternative definition for
224 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 – 3
231 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

241 We next asked whether these trends held among different groups of countries. To answer this, we
242 extracted ASDRs for the following: 26 countries with UHC implemented and 9 countries without UHC
243 as of 2008; 31 high-income countries and 4 middle-income countries as classified by the World Bank
244 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
248 significantly lower than the observed ASDRs for all 3 projected years (in 2010: rate ratio 1.0746, 95%
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

256 Stratifying countries by income using the World Bank's classification,²¹ yielded higher rate ratios
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 ($R = -$
269 0.0037 , 95% CI -0.0045 to -0.0028 ; $p < 0.0001$), male-colorectal ($R = -0.0011$, 95% CI -0.0016 to $-$
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 $-$
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

274 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)
279 but not at all with deaths from untreatable cancers (figure 4H). The same trends were found irrespective
280 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

297 In all analyses, we could not demonstrate an association to female-lung cancer unlike other cancers
298 (figures 2F and 4F). One plausible reason arising from our treatable versus untreatable cancer analysis
299 is that this discrepancy might have been the consequence of the survival rate for female lung cancer
300 being less than that for male; however, this hypothesis is not supported by evidence.²⁶ As such, this
301 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
314 other causes of death.²⁷ The chronological link between the unemployment rise due to the global
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

319 mortality is through reduced access to healthcare (figure 5), which may manifest as late-stage
320 diagnoses,^{28,29} and poor or delayed treatment.³⁰ Furthermore, unemployment has been found to correlate
321 with lower socioeconomic status (SES).^{31,32} In turn, there is substantial evidence linking lower SES to
322 lower cancer survival, with reduced access to treatment being a mediating cause,^{33,34} as well as lower
323 health-seeking behaviours.³⁵ Job loss is also strongly associated with mental health and behavioural
324 problems,⁵ and this may also have a negative impact on survival in cancer patients as a consequence of
325 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
328 across countries.³⁷ Integrated multidisciplinary care pathways for cancer involving screening,
329 radiotherapy, chemotherapy, and surgery, are costly but effective at reducing mortality. Changes in the
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
332 changes in PEH include changes in the number of healthcare professionals, with fewer healthcare
333 professionals likely to result in reduced quality of care if productivity gains are not made,³⁸ and changes
334 in the number of localised sites providing healthcare, with longer distances or travel times likely to
335 increase delays in presentation for diagnosis as well as adversely affect treatment.³⁹
336

337 Our study has at least two major policy implications. First, it makes a strong case for UHC and its
338 possible moderating effect on unemployed populations during economic downturns. In UHC countries
339 where healthcare provision is meant to be equally accessible regardless of employment status, access to
340 healthcare is less problematic than in non-UHC countries where access is often provided by means of
341 an employment package. Second, amidst a background of rising healthcare costs, if spending
342 restrictions are not accompanied by proportionate improvements in efficiency, worse quality of care
343 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

354 India. Indeed, an examination of whether our findings hold in lower income countries where it is
355 possible that mortality rates for certain cancer types have been rising rather than falling would offer
356 valuable insight. Fourth, our study was retrospective and observational, limiting our ability to draw
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,
363 although the comprehensiveness of our robustness checks will have reduced the probability of this
364 assumption affecting our findings.

365

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

372

373

374 **AUTHORS' CONTRIBUTIONS**

375

376 MM, JW, AMN and CW compiled the data. MM conceived and designed the study with input from JW,
377 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**

499 We searched the literature to identify articles that quantitatively estimated either the effect of both
500 unemployment and healthcare spending (public or otherwise) on cancer mortality, or the effect of
501 universal healthcare coverage on cancer mortality. We searched PubMed for publications up to and
502 including May 31 2015 using the following combinations of search terms: (i) unemployment AND
503 cancer AND mortalit* AND (spending OR expenditure); (ii) cancer AND mortalit* AND ("universal
504 health coverage" OR "universal healthcare coverage"). Search combination (i) yielded seven
505 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
507 mortality in Scotland, and included specific causes of death such as lung cancer.⁴⁰ A second study
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
510 European countries.⁴¹ The authors were therefore unable to control for potential confounding variables.
511 The study periods for both these publications ended before the 2008 economic recession. Three further
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
514 in the European Union only,¹⁴ the second examined the relationship between unemployment and
515 stomach cancer mortality again in the European Union only,¹⁵ while the third examined prostate cancer
516 mortality in countries belonging to the Organisation for Economic Co-operation and Development.⁴²
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
524 healthcare spending on mortality due to all cancers, "treatable" cancers, "untreatable" cancers and
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

531 (or public healthcare spending) at intervals of one year for each year after the increase in unemployment
532 (or public healthcare spending) with the mortality rates in each country, we controlled for time-invariant
533 heterogeneity between countries. Finally, we combined the above with a time-trend analysis, to provide
534 a rigorous characterisation of the associations between unemployment, public healthcare spending,
535 universal healthcare coverage, income, and cancer mortality. The major findings from these
536 complementary approaches are that unemployment increases are associated with rises in cancer
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.

549

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
560 (deaths per 100 000) were obtained from the World Health Organisation Mortality Database 2013.²³
561 HDI categories were obtained from the United Nations Development Programme website.²² HDI,
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 time-
572 lag analyses. Economic data were obtained from the World Bank.²⁵ Cancer mortality data (deaths per
573 100 000) were obtained from the World Health Organisation Mortality Database 2013.²³ * p<0.05; **
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)

584 countries. ASDRs were extracted from the World Health Organisation Mortality Database 2013.²³ *
585 $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

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
596 5-year time-lag analyses. Economic data were obtained from the World Bank.²⁵ Cancer mortality data
597 (deaths per 100 000) were obtained from the World Health Organisation Mortality Database 2013.²³ *
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

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

605 **Table 1: Population estimates of countries included in multiple regression and time-series**
606 **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
Unemployment dataset (75 countries)	Population size Proportion of population less than 15 years of age Proportion of population over 65 years of age	Economic	Inflation GDP per capita changes Base interest rates	80
		Resource availability	Number of physicians per 100 000 population; Number of hospital beds per 100 000 population	79
		Infrastructure	Urbanisation; Access to water; Calorie intake	80
		Out-of-pocket spending	Out-of-pocket expenditure	78
		WHO data quality check	N/A (Re-run analysis using data classified as Level 1 or Level 2 in quality by the WHO)	77
		Income	(2 categories coded into 1 dummy variable)	78
		Human development index	(3 categories coded into 2 dummy variables)	79
PEH dataset (79 countries)	Population size Proportion of population less than 15 years of age Proportion of population over 65 years of age	Economic	Inflation; GDP per capita changes; Base interest rates	84
		Resource availability	Number of physicians per 100 000 population; Number of hospital beds per 100 000 population	83
		Infrastructure	Urbanisation; Access to water; Calorie intake	84
		Out-of-pocket spending	Out-of-pocket expenditure	82
		WHO data quality check	N/A (Re-run analysis using data classified as Level 1 or Level 2 in quality by the WHO)	81
		Income	(2 categories coded into 1 dummy variable)	82
		Human development index	(3 categories coded into 2 dummy variables)	83

610

611 **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.

613

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

614

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.

619

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

621

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
624 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

627

1 **Economic downturns, universal healthcare coverage, and cancer**
2 **mortality: a global analysis in high- and middle-income countries,**
3 **1990–2010**

4
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31
32 **Word count** (Introduction, Materials and Methods, Results, Discussion): 3,565,692

33 **Number of references** (excluding those cited only in the Research in Context panel): 4042

35 **SUMMARY**

36

37 ***Background***

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

41

42 ***Methods***

43 Data were obtained from the World Bank and WHO (1990–2010). Mortality data from female breast,
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 from~~in~~ 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
56 specific cancers save for female-lung cancer. Untreatable cancer mortality by contrast was not
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***

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

69

70 *Funding*

71 None.

72

73 **Key words:** cancer; government spending; health economics; mortality; public health; unemployment;

74 | universal healthcare coverage.

75

76 **INTRODUCTION**

77

78 The global economic crisis, which began in 2008, compelled many countries to cut public spending in
79 order to reduce public-sector borrowing.¹ These spending cuts often entailed either reductions or a
80 flattening in public-sector jobs and public-sector expenditure on healthcare (PEH).^{2,3} ~~Indeed, 33~~ Thirty
81 three of 53 WHO European region countries underwent no change in PEH between 2008 and 2009,
82 while six experienced a reduction in PEH,⁴ which have prompted concerns about the possible negative
83 effects on public health. Studies have demonstrated that long-term unemployment leads to increased
84 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*
89 *se*.^{3,7-15} These potential associations may predominantly be explained by behavioural, mental, or stress-
90 related changes with direct and immediate effects, whether, as in the case of suicides, they are counter-
91 cyclical associations linked to the direct psychological and financial impact of job loss,¹⁶ or pro-cyclical
92 associations linked to reduced injury-related work and lifestyle activities in the case of all-cause
93 mortality.⁹ Few studies, however, have analysed the relationship between economic downturns and
94 cancer especially in countries that ~~are~~ may be more susceptible to economic shocks due to ~~less-~~
95 ~~developed~~ limited 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
102 cancer correlated with reduced income,¹⁷ although the lack of treatment options for patients presenting
103 with late-stage disease meant that the effect of the economic downturn on reduced healthcare access and
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.

111

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
116 means of diagnosis. We chose unemployment due to its ability to capture changes in individuals’
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~~
119 ~~(UHC) conferred a protective effect, hypothesising that UHC would enable the unemployed to access~~
120 ~~healthcare, especially as many countries progress towards UHC systems.~~¹⁹ we explored whether UHC
121 conferred a protective effect. We also estimated the difference between the actual numbers of cancer-
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
124 for which the number of deaths was higher than expected. ~~We estimated additional cancer-related deaths~~
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
132 Finance 2013 edition datasets.²⁰ Unemployment (World Bank data code: SL.UEM.TOTL.ZS) was
133 defined as the share of the labour force without work but available and seeking employment.²⁰ PEH
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
137 (including donations from international agencies and non-governmental organisations), and social (or
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
141 dataset, respectively.²⁰ Classification of countries into high- and middle-income was done according to
142 the World Bank's Atlas Method.²¹ In brief, middle-income countries are those with a gross national
143 income per capita of more than \$1 045 but less than \$12 736, whereas high-income economies are those
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
146 Programme.²²

147

148 Cancer mortality data (deaths per 100 000) for 1990 to 2010 for the countries in the unemployment and
149 PEH datasets were obtained from the World Health Organisation (WHO) mortality database.²³ These
150 data are based on death certification and updated annually from civil registration systems of WHO
151 member states. Mortality data for prostate (ICD-10 C61), female-breast (ICD-10 C50), lung (male and
152 female; ICD-10 C33–C34), colorectal (male and female; ICD-10 C18–C21) cancers and all cancers
153 were extracted. Female breast, prostate and colorectal cancers have survival rates that exceed 50%.²⁴
154 We therefore aggregated the mortality data for these tumour types into a 'treatable' cancer class. Lung
155 and pancreatic cancers (male and female; ICD-10 C25), which have five-year survival rates <10%, were
156 likewise aggregated to give an 'untreatable' cancer category.²⁴ Notably, at the time data were collected,
157 complete cancer mortality data were unavailable for China, India, and countries from sub-Saharan
158 Africa. Age-standardised death rates (ASDRs), accounting for age distribution differences in
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
162 influence of age groups with fewer observations. These crude rates were defined as the number of

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**

166 We used multivariable regression analysis to assess the relationship between mortality rates for each
167 cancer subtype, treatable cancers, untreatable cancers and all cancers (response variable), and
168 unemployment or PEH (predictor variable). Due to incomplete cancer mortality data for many of the 75
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
176 fixed effects was used since this methodology has been widely employed in similar studies, and is
177 regarded as statistically robust and conservative.²⁵ The population structure of each country was also
178 controlled for by incorporating total population size and demographic structure (the percentage of the
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**

193 For the all-cancer mortality trend projection analysis, we set strict country inclusion criteria to ensure
194 that only high quality data were used. We therefore excluded countries with civil registration coverage
195 of cause-of-death less than 90% for the study period,²³ eliminating in the process 26 countries from the
196 61 for which all-cancer mortality data were complete for 2000 to 2010 (figure 1). In order to limit the
197 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–
213 0.1609; p=0.0022), female-breast (R=0.1583, 95% CI 0.1110–0.2056; p<0.0001), male-lung
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

225 On accounting for the UHC status of countries, we found no significant association between
226 unemployment and cancer mortality within the first year of unemployment rising (table 3, figures S1B-
227 C). The results were unaffected by country classifications according to an alternative definition for
228 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 – 3
235 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
240 finding was recapitulated upon confinement of our analysis to treatable cancers (rate ratio 1.0362, 95%
241 CI 1.0225–1.0502; p<0.0001; figure 3C, table S10) resulting in 22 977 (95% CI 14 482-31 472) excess
242 deaths in 2010. By contrast, for untreatable cancers, the deviation between predicted and observed

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

244

245 We next asked whether these trends held among different groups of countries. To answer this, we
246 extracted ASDRs for the following: 26 countries with UHC implemented and 9 countries without UHC
247 as of 2008; 31 high-income countries and 4 middle-income countries as classified by the World Bank
248 [using the Atlas Method](#);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
265 dividing countries according to HDI, neither the very high nor high HDI groupings experienced higher-
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 $-$
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

278 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

281 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
284 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

301 In all analyses, we could not demonstrate an association to female-lung cancer unlike other cancers
302 (figures 2F and 4F). One plausible reason arising from our treatable versus untreatable cancer analysis
303 is that this discrepancy might have been the consequence of the survival rate for female lung cancer
304 being less than that for male; however, this hypothesis is not supported by evidence.²⁶ As such, this
305 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
318 other causes of death.²⁷ The chronological link between the unemployment rise due to the global
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

323 mortality is through reduced access to healthcare (figure 5), which may manifest as late-stage
324 diagnoses,^{28,29} and poor or delayed treatment.³⁰ Furthermore, unemployment has been found to correlate
325 with lower socioeconomic status (SES).^{31,32} In turn, there is substantial evidence linking lower SES to
326 lower cancer survival, with reduced access to treatment being a mediating cause,^{33,34} as well as lower
327 health-seeking behaviours.³⁵ Job loss is also strongly associated with mental health and behavioural
328 problems,⁵ and this may also have a negative impact on survival in cancer patients as a consequence of
329 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
332 across countries.³⁷ Integrated multidisciplinary care pathways for cancer involving screening,
333 radiotherapy, chemotherapy, and surgery, are costly but effective at reducing mortality. Changes in the
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
336 changes in PEH include changes in the number of healthcare professionals, with fewer healthcare
337 professionals likely to result in reduced quality of care if productivity gains are not made,³⁸ and changes
338 in the number of localised sites providing healthcare, with longer distances or travel times likely to
339 increase delays in presentation for diagnosis as well as adversely affect treatment.³⁹

340

341 Our study has three at least two major policy implications. First, it makes a strong case for UHC and its
342 possible moderating effect on unemployed populations during economic downturns. In UHC countries
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
347 ameliorating them. Some have advocated that to reduce adverse effects, government policy should seek
348 to actively maintain aggregate employment levels;²⁵ the implication being that, from a public health
349 perspective, expansionary fiscal policy is the optimal response to the slumps in aggregate demand and
350 concomitant private sector unemployment seen during economic downturns. Similarly, it is reasonable
351 to propose that if governments fail not just to maintain PEH but also to maintain levels of total
352 healthcare expenditure by not compensating for reduced private sector and private household spending
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.

357

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
360 availability and quality, we were unable to analyse the effects of the global economic crisis after 2010.
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,
363 during which unemployment levels rose sharply and in some countries peaked. For the PEH dataset, we
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
367 India. Indeed, an examination of whether our findings hold in lower income countries where it is
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
379 Notwithstanding the limitations discussed, our findings suggest that both unemployment and PEH are
380 significantly associated with cancer mortality, with associations lasting up to five years. We estimate
381 that the 2008–2010 global economic crisis may have been associated with up to ~~100-250,000~~ **additional**
382 **excess** cancer-related deaths. Our analysis also suggests that UHC **may** ~~removes~~ the association
383 between unemployment and cancer mortality, lending evidence in favour of healthcare system reforms
384 aimed at providing UHC, particularly among middle-income countries.

385
386

387 **AUTHORS' CONTRIBUTIONS**

388

389 MM, JW, AMN and CW compiled the data. MM conceived and designed the study with input from JW,
390 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
520 causes of death such as lung cancer.⁴⁰ A second study simply used Pearson's correlation rather than a
521 panel-based fixed effects model to find an association between all-cancer mortality, and healthcare
522 expenditure (negative) and unemployment (positive) in European countries.⁴¹ The authors were
523 therefore unable to control for potential confounding variables. The study periods for both these
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
526 examined the relationship between spending, unemployment and breast cancer mortality in the
527 European Union only,¹⁴ the second examined the relationship between unemployment and stomach
528 cancer mortality again in the European Union only,¹⁵ while the third examined prostate cancer mortality
529 in countries belonging to the Organisation for Economic Co-operation and Development.⁴² The
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
546 a rigorous characterisation of the associations between unemployment, public healthcare spending,
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.

561

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
572 (deaths per 100 000) were obtained from the World Health Organisation Mortality Database 2013.²³
573 HDI categories were obtained from the United Nations Development Programme website.²² HDI,
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 time-
584 lag analyses. Economic data were obtained from the World Bank.²⁵ Cancer mortality data (deaths per
585 100 000) were obtained from the World Health Organisation Mortality Database 2013.²³ * p<0.05; **
586 p<0.01; *** p<0.001.

587
588 **Figure 3. Predicted cancer-related mortality rate and number of deaths, 2008–2010, based on**
589 **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
608 5-year time-lag analyses. Economic data were obtained from the World Bank.²⁵ Cancer mortality data
609 (deaths per 100 000) were obtained from the World Health Organisation Mortality Database 2013.²³ *
610 $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

611

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

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

614

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

617 **Table 1: Population estimates of countries included in multiple regression and time-series**
618 **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 healthcare coverage.

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

622

623 **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.

625

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

626

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.

631

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
636 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

639

17/02/2016

Laura Hart
Senior Editor
The Lancet

Dear Mrs Hart,

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

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

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

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

Yours sincerely

Mahiben Maruthappu & Johnathan Watkins

REVIEWER 4

Most reviewers' suggestions have been addressed.

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

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

“There is evidence that UHC protects against mortality increases associated with rises in unemployment...”

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

“...implying that UHC could have had a protective effect against the possible impact of unemployment.”

REVIEWER 5

General Comments

Overall this is a very well written manuscript!

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

Major comments

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

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

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

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

Minor comments

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

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

“Trend analysis was used to project mortality rates based on trends prior to the sharp unemployment rise experienced by many countries from 2008 to 2010...”

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

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

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

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

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

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

In the Methods:

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

In the Results:

“31 high-income countries and 4 middle-income countries as classified by the World Bank using the Atlas Method;²⁵”

and

“Stratifying countries by income using the World Bank’s classification...”

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

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

the Discussion as follows:

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

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

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

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

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

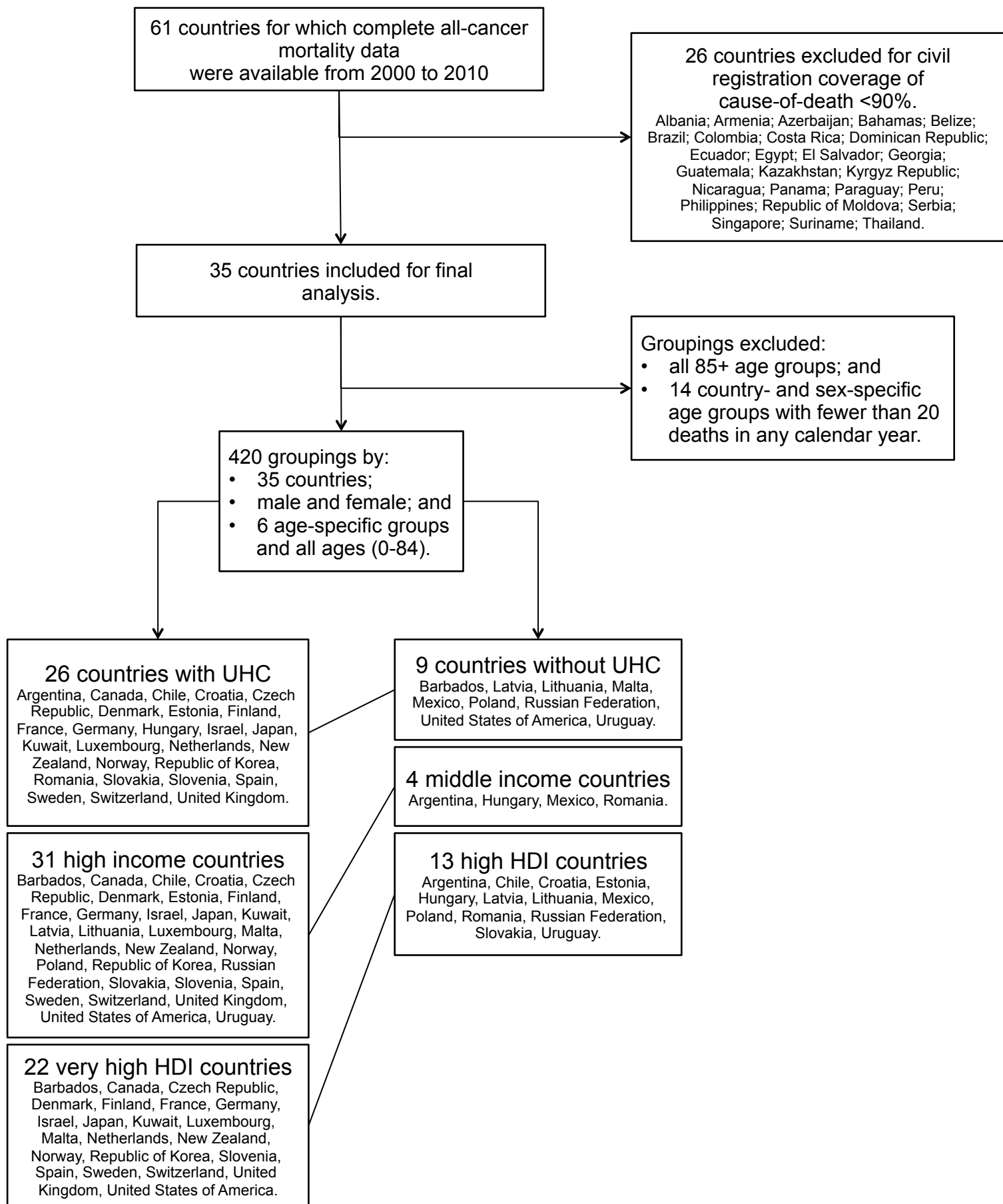


Figure 1

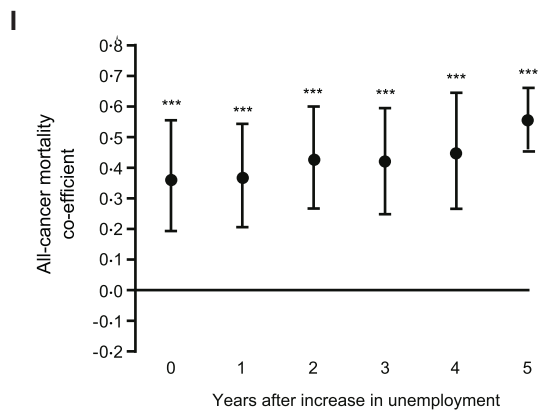
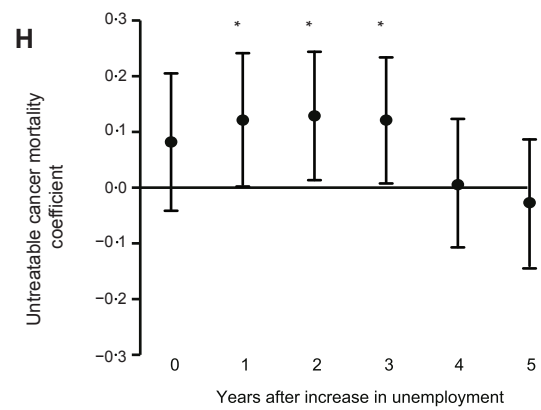
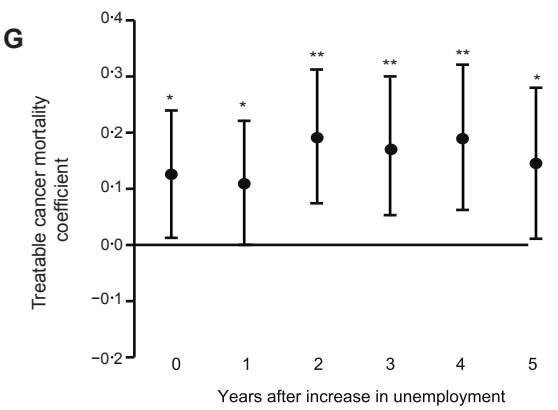
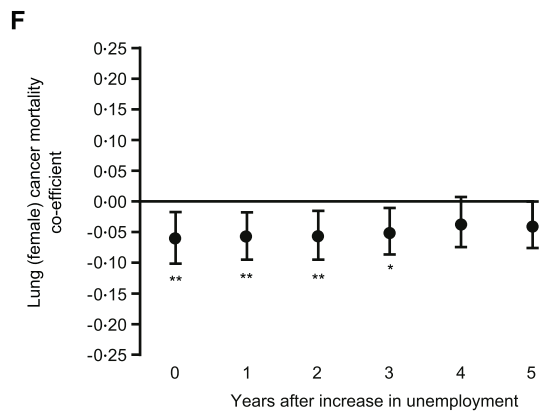
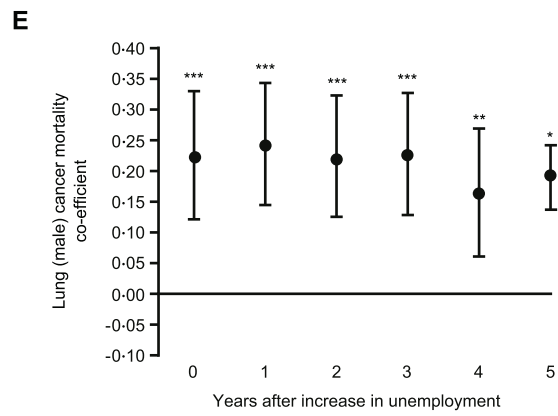
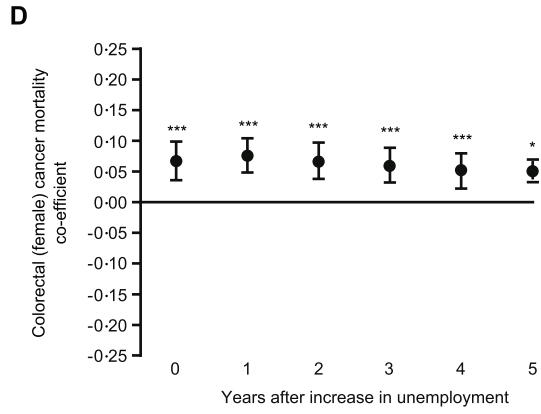
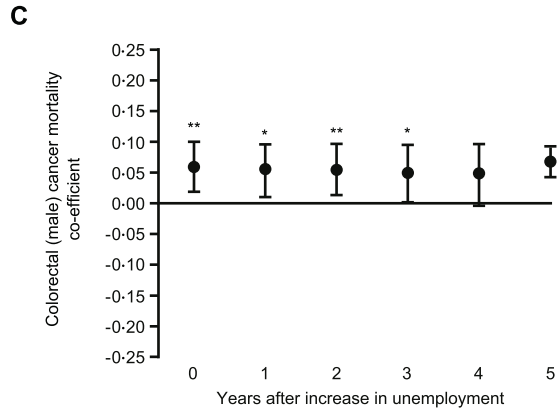
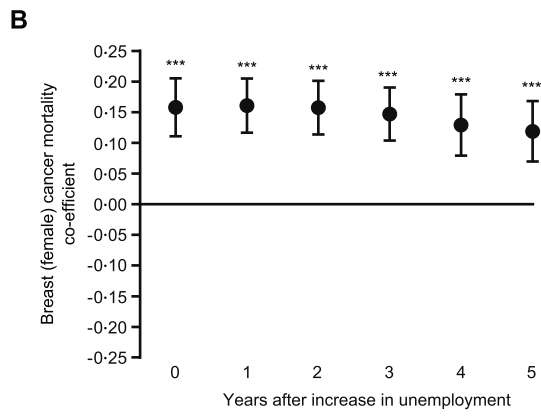
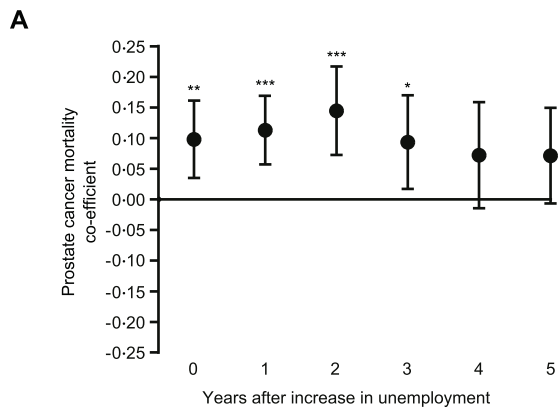


Figure 2

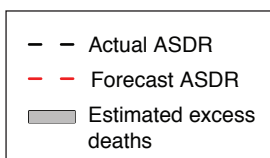
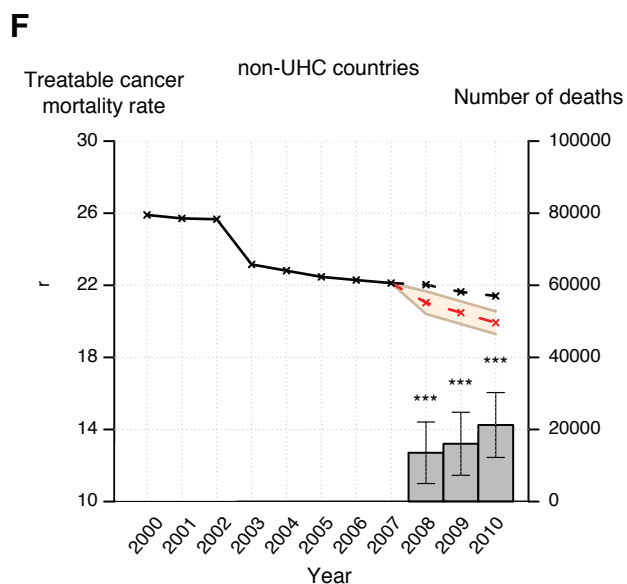
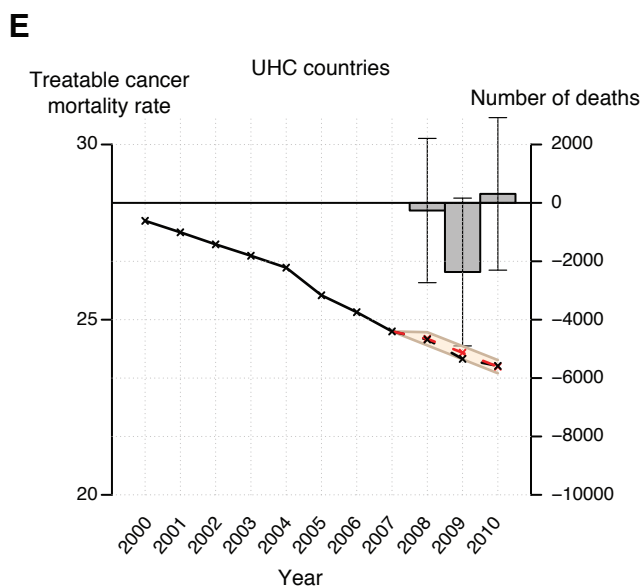
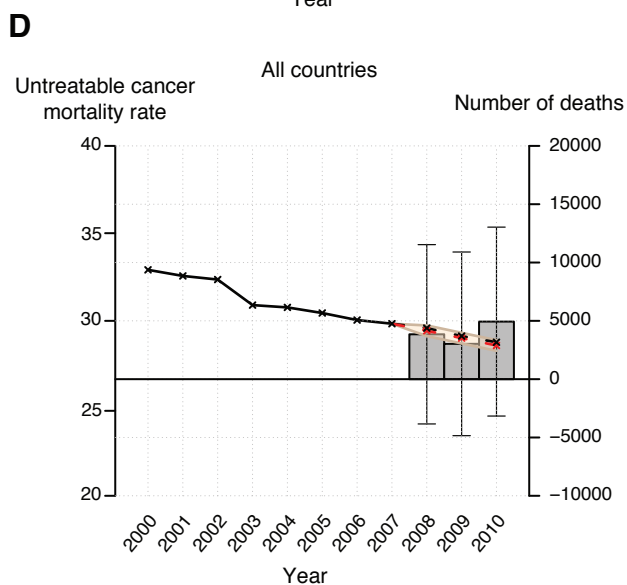
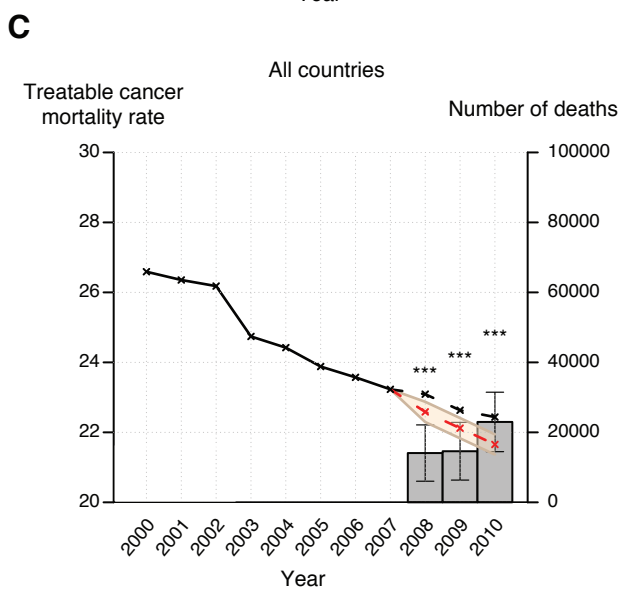
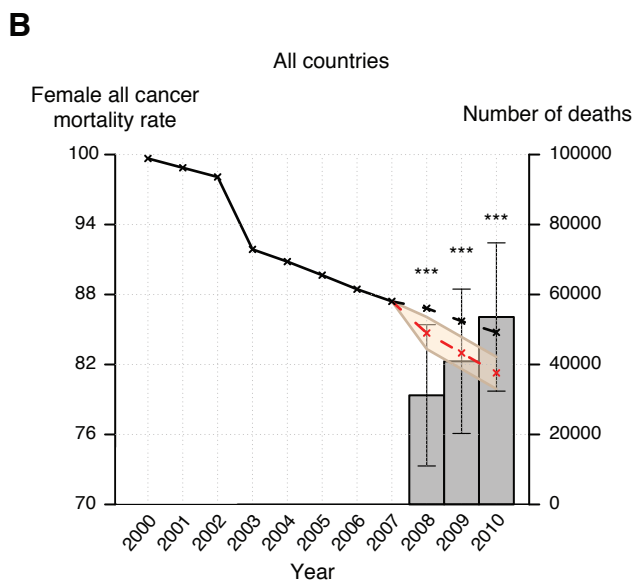
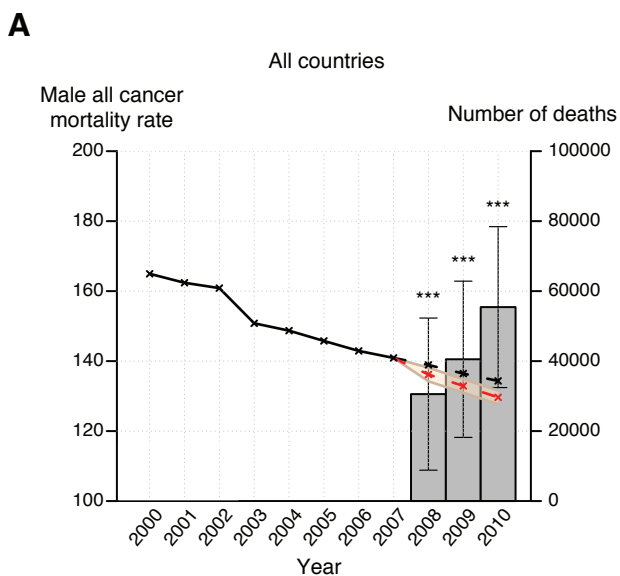


Figure 3

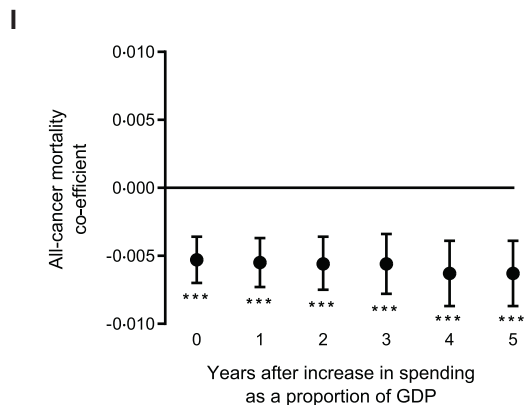
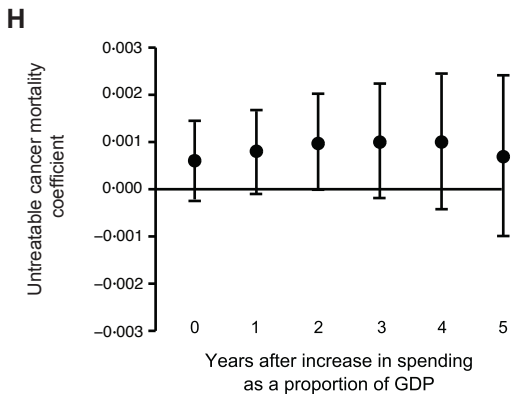
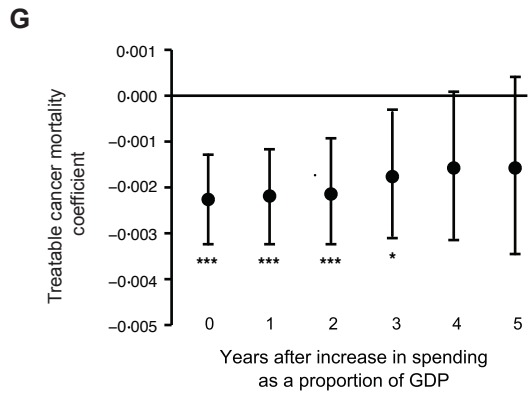
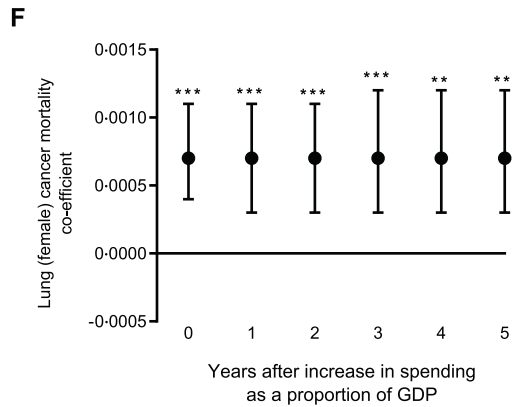
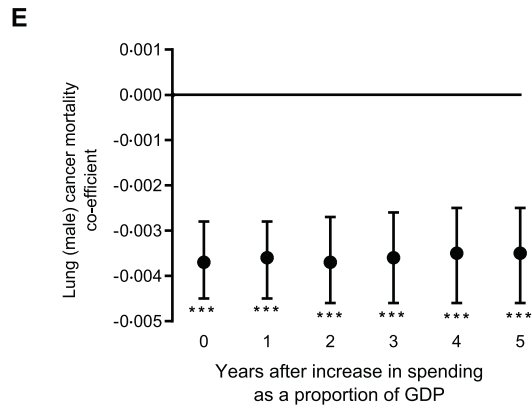
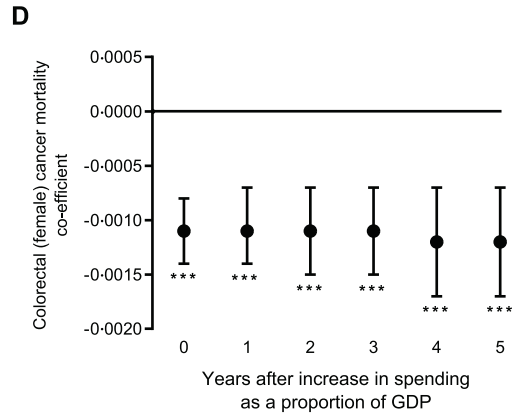
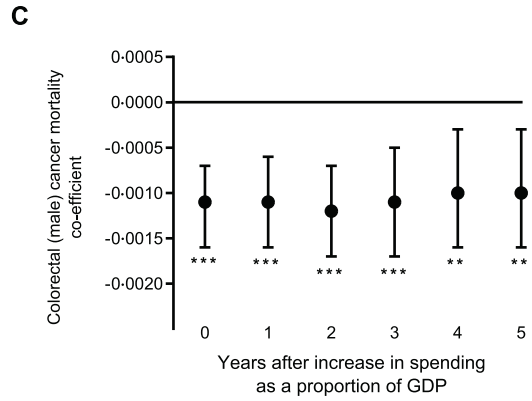
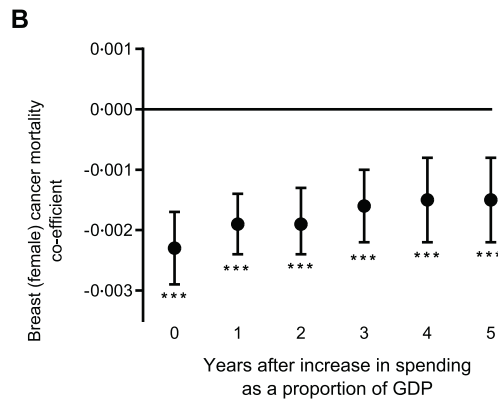
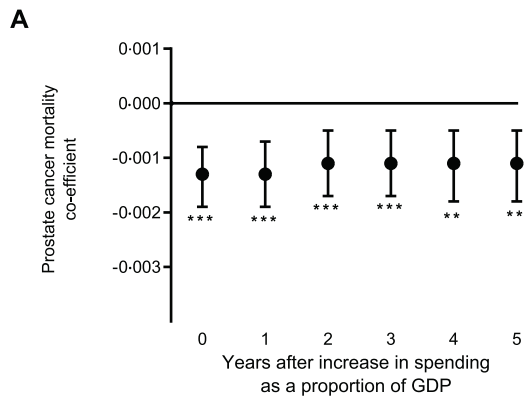


Figure 4

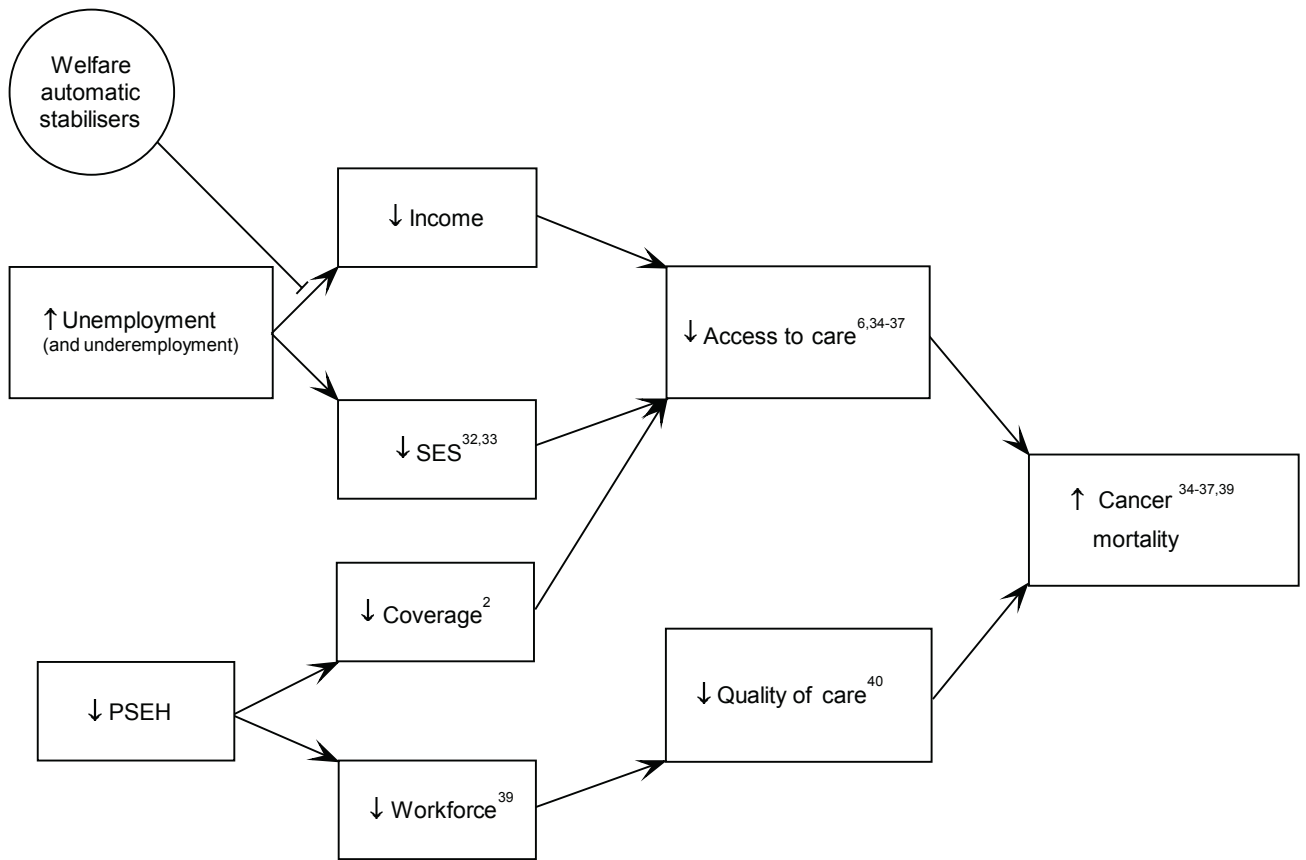
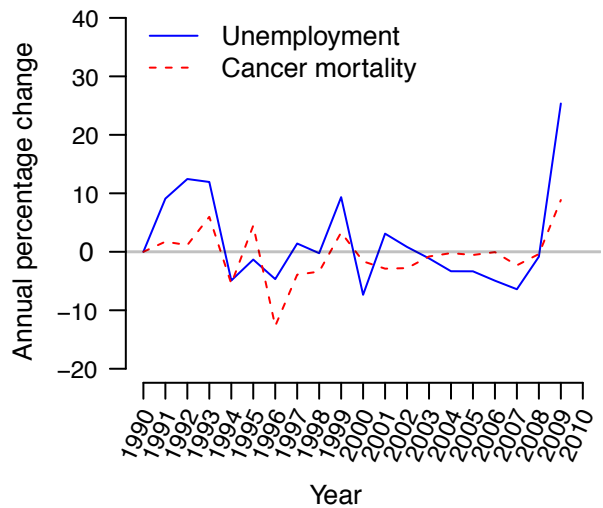


Figure 5

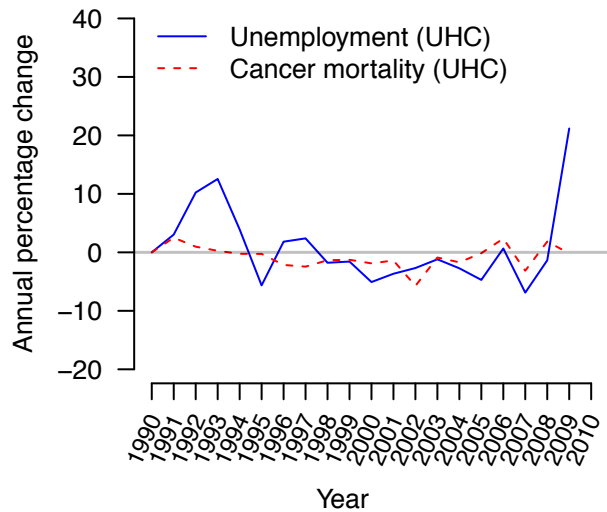
Supplementary Material including Tables

[Click here to download Supplementary Material: REV2_AllCancer_Supp.doc](#)

A



B



C

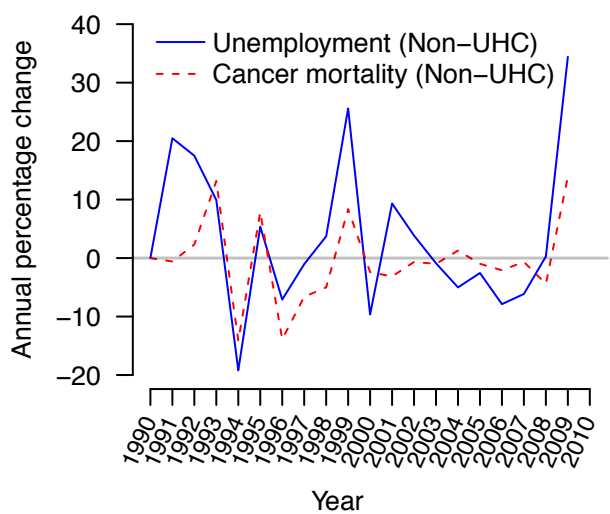
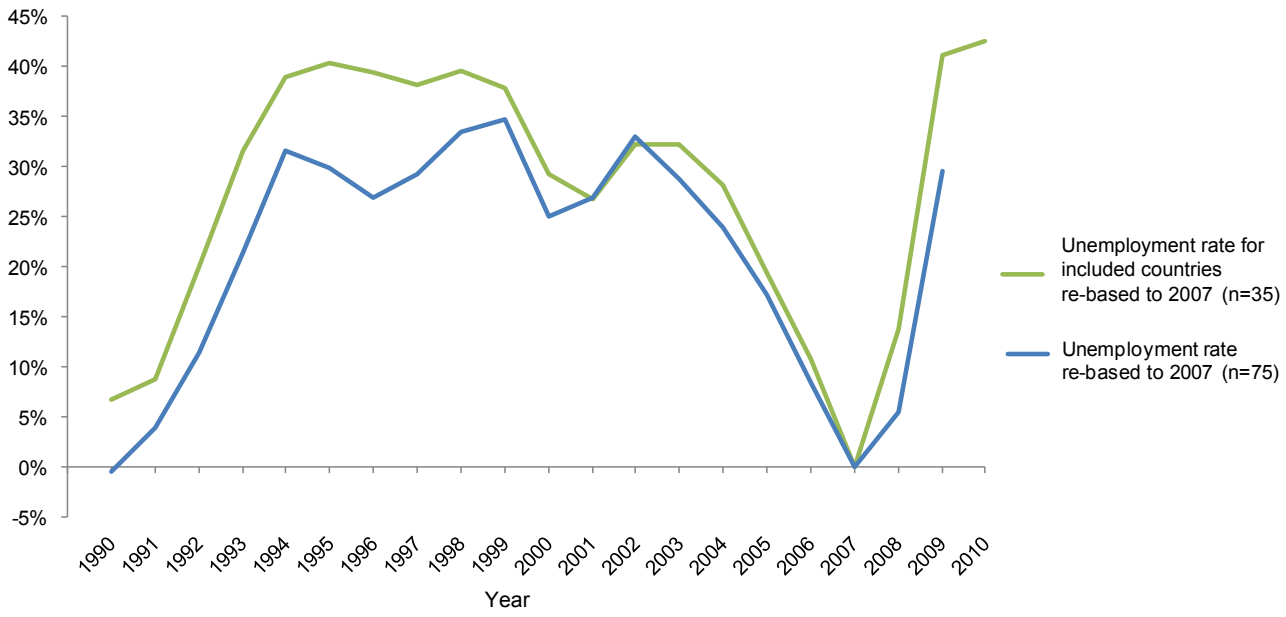
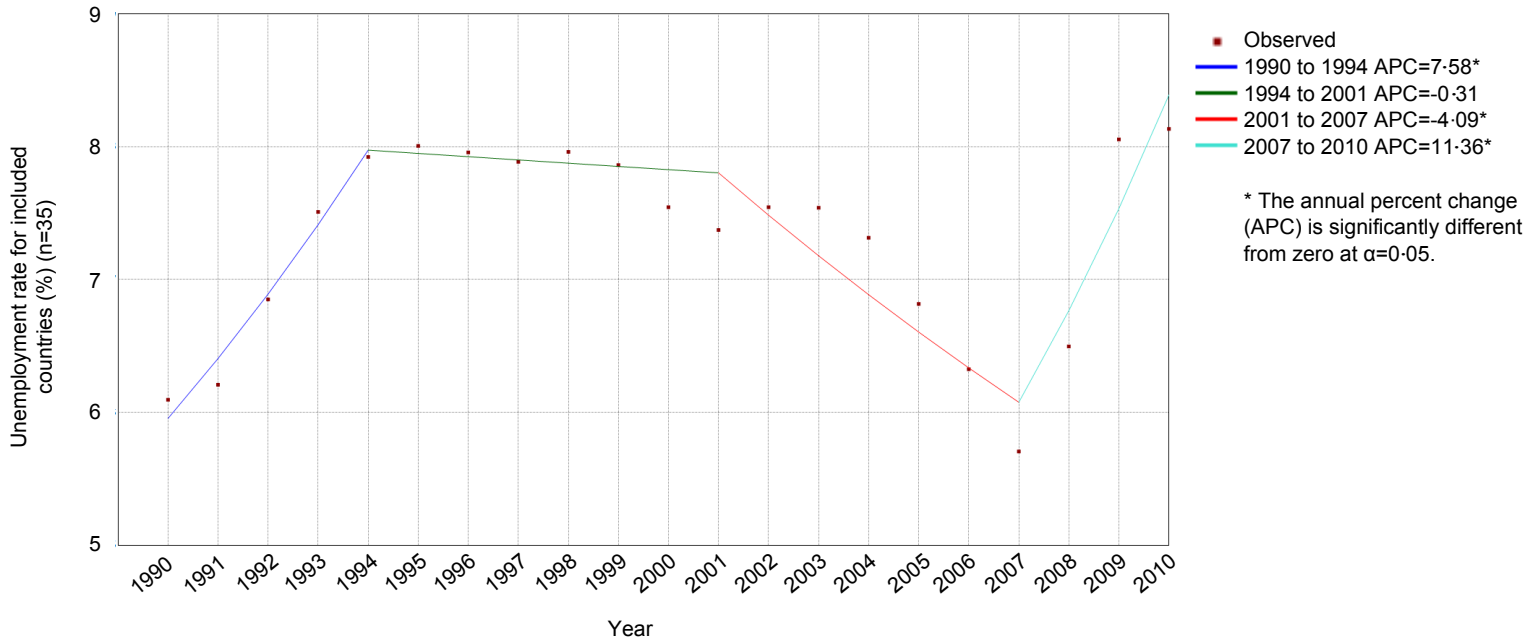


Figure S1

A**B****Figure S2**