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Inequalities in cancer incidence and mortality across medium to highly developed countries in the 21st century

Melina Arnold¹, Elisenda Rentería¹, David I Conway², Freddie Bray¹, Tom Van Ourti³, Isabelle Soerjomataram¹

¹ Section of Cancer Surveillance, International Agency for Research on Cancer, 150 Cours Albert Thomas, 69008 Lyon, France.

² School of Medicine, Dentistry, and Nursing, College of Medical, Veterinary and Life Sciences, University of Glasgow, 378 Sauchiehall Street, Glasgow G2 3JZ, United Kingdom.

³ Erasmus School of Economics, University of Rotterdam, Burgemeester Oudlaan 50, PO Box 1738 3000 DR Rotterdam, The Netherlands; and Tinbergen Institute.

Corresponding author:

Melina Arnold, PhD
Section of Cancer Surveillance
International Agency for Research on Cancer
150 Cours Albert Thomas
69008 Lyon
FRANCE
Phone: +33 (0)4 7273 8400
Fax: +33 (0)4 7273 8696
Mail: arnoldm@iarc.fr

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Abstract (250 words)

Purpose: Inequalities in the burden of cancer have been well-documented and a variety of measures exist to analyse disease disparities. While previous studies have focused on inequalities within countries, the aim of the present study was to quantify existing inequalities in cancer incidence and mortality between countries.

Methods: Data on total and site-specific cancer incidence and mortality in 2003-2007 were obtained for 43 countries with medium to high levels of human development via Cancer Incidence in Five Continents Vol. X and the WHO Mortality Database. We calculated the concentration index as a summary measure of socioeconomic-related inequality between countries.

Results: Inequalities in cancer burden differed markedly by site; the concentration index for all sites combined was 0.03 for incidence and 0.02 for mortality, pointing towards a slightly higher burden in countries with higher levels of the Human Development Index (HDI). For both incidence and mortality, this pattern was most pronounced for melanoma. In contrast, the burden of cervical cancer was disproportionately high in countries with lower HDI levels. Prostate, lung and breast cancer contributed most to inequalities in overall cancer incidence in countries with higher HDI levels, while for mortality these were mostly driven by lung cancer in higher HDI countries and stomach cancer in countries with lower HDI levels.

Conclusion: Global inequalities in the burden of cancer remain evident at the beginning of the 21st century: with a disproportionate burden of lifestyle-related cancers in countries classified as high HDI, while infection-related cancers continue to predominate in transitioning countries with lower levels of HDI.

Keywords: socioeconomic inequalities; concentration curve; global; cancer incidence; cancer mortality

INTRODUCTION

Cancer cases and deaths are not equally distributed across populations. In 2012, more than half of all new cancer cases and two thirds of all cancer deaths occurred in less developed regions. (1) Although differences may be partly attributed to demographic structure, population size and stages of epidemiologic transition, much of the observed disparities remain unexplained. (2, 3) It therefore remains open to discussion whether these inequalities are avoidable.

Quantifying, understanding and reducing inequalities has become a strategic priority in global policy making and represents one of the 17 sustainable development goals released by the United Nations. (3) Previous studies have documented the degree to which inequalities in the burden of disease and mortality are linked to socioeconomic status within countries or regions. (4, 5) In view of the rising burden of cancer worldwide and on-going changes in cancer patterns and profiles across human development levels, it is equally important to gain further insights into the distribution of cancer cases and deaths across levels of human development as an indication of between country inequalities (6). Yet, this knowledge remains scarce and a global quantification of inequalities in cancer burden is still lacking.

Therefore in this study, we aimed to quantify and assess inequalities in site-specific cancer burden across 43 countries (from medium to high HDI level countries determined by data availability). By linking the human development index (HDI) (7) with cancer incidence and mortality, we were able to compute the concentration index – a summary measure of the magnitude of socioeconomic-related inequality.

METHODS

Data sources

Data on cancer incidence between 2003 and 2007 were extracted from Cancer Incidence in Five Continents Volume X (CI5X). (8) These are the most recent data from high-quality population-based cancer registries, with detailed assessment of the comparability, completeness, and validity. Data from national registries were available for the majority of countries (25 countries). If nationwide data were absent, cases from regional registries in the same country were pooled to obtain an estimate of the national incident cancer burden (18 countries). Data on cancer mortality were obtained from the WHO Mortality Database for the years 2003-2007. (9) To ensure data quality, we only included data from countries where previous data quality assessments indicated at least medium quality data. (10) For mortality, all datasets represented a nationwide registration of cancer deaths by cause. For both incidence and mortality, the following most commonly diagnosed cancer sites were included: all sites excluding non-melanoma skin (ICD-10:C00-96 excl. C44), oesophagus (C15), stomach (C16), colorectum (C18-21), pancreas (C25), trachea, bronchus and lung (C33-34), melanoma of skin (C43), female breast (C50), cervix uteri (C53), prostate (C61), kidney (64) and leukaemia (C91-95). In addition, cancers of the head and neck (C00-14) and testis (C62) were included because of their known or suspected link with socioeconomic status (11, 12).

Population data by country, sex and age were obtained from the United Nations (UN), world population prospects, for the year 2005. (13) Estimates of HDI and its components (life expectancy, education and gross domestic product (GDP) per capita) by country for the year 2005 were available from the United Nations Development Programme. (7) Age-standardized incidence and mortality rates were calculated using the world standard population. In this study, we included countries where both good quality incidence and mortality data were available, resulting in a total of 43 medium to highly developed countries with an HDI ranging from 0.771 (the Philippines) to 0.968 (Iceland and Norway) (**Annex Table 1**).

Statistical analysis

In order to assess inequality in the burden of cancer across levels of human development, we first compared the overall population size to the number of cases or deaths by cancer site for each tertile of HDI. In a second step, concentration curves were drawn and concentration indices calculated by cancer site for incidence and mortality. (14)

The concentration curve provides a graphical representation of inequality. It plots the cumulative cancer incidence or mortality rate against the cumulative proportion of the population ranked by each country's HDI (from lowest to highest, left to right). When it coincides with the diagonal, the line of perfect equality, there is no association between the incidence or mortality rates across countries and HDI. In contrast, the further the curve lies above (or below) the diagonal, the greater the concentration of cases among those countries with lower (or higher) levels of HDI.

The concentration index is directly related to the concentration curve and provides a summary measure of the deviation from the line of perfect equality. It has been developed by health economists, [10] and used to measure and compare the degree of socioeconomic inequality, for instance in child mortality (15), adult health (16), access to health care (17) or lifestyle factors such as physical activity or obesity. (18) It is closely related to the relative index of inequality, (19) and proportional to the association between each country's share in the total cancer burden and the population-weighted rank of human development (20).

The concentration index ranges from -1 to 1. (14, 21) It takes a value of zero if the concentration curve coincides with the diagonal or if the concentration of cases among countries with lower levels of HDI is equal to the concentration of cases among countries with higher HDI levels (in which case the curve is not equal to the line of perfect inequality). A concentration index greater than zero indicates that the cancer cases or deaths are disproportionately concentrated in higher HDI countries (the concentration curve lies below the diagonal), while a value below zero points towards a higher burden in countries with lower levels of HDI (the concentration curve lies above the diagonal). Point estimates, standard errors and corresponding 95% confidence intervals for the concentration index were computed using the *conindex*, and existing command from the statistical software package Stata. (20) As the concentration index is a function of the covariance of HDI rank and incidence or mortality shares, it can easily be decomposed into the contributions of each cancer site to the overall inequalities. The contribution of each cancer site consists of the product of the HDI-related inequality in this cancer site and its weight in the total of cancer cases and deaths. (22, 23)

As patterns were similar for males and females, no sex-specific results (except for sex-specific tumours) were presented. Stata 13 was used for all analyses.

RESULTS

Cancer incidence

Overall, the number of new cancer cases was more concentrated in countries with higher levels of HDI. Countries within the highest HDI tertile had a slightly higher burden of all cancer sites combined; together they accounted for 44% of all cancer cases but only for 42% the total population considered (**Figure 1**). In contrast, countries in the lowest HDI tertile accounted for 34% of all cancer cases and comprised 37% of the total population. There was marked disparity for melanoma (60% of burden in highest vs. 18% in lowest HDI tertile), cancer of the bladder (50% vs. 23%), prostate (54% vs. 28%), lung (51% vs. 28%), testis (52% vs. 16%), kidney (55% vs. 18%), breast (48% vs. 31%), pancreas (46% vs. 32%), colorectum (45% vs. 32%) and leukaemia (46% vs. 33%). Conversely, countries within the lowest HDI tertile had a disproportionate burden of cervical (55% of burden in lowest vs. 28% in highest HDI tertile) cancer cases.

When summarizing this inequality for all cancer sites combined, the concentration index (C) was 0.03 (95%CI: 0.00, 0.06), pointing towards a slightly higher incidence burden in countries with higher HDI levels (**Figure 2**). This pattern was most pronounced for melanoma (C: 0.23; 95%CI: 0.11, 0.35), as well as for cancers of the bladder, prostate, lung, testis, kidney, breast, pancreas and colorectum, and leukaemia. The high burden of cervical cancer in countries with lower HDI levels was also confirmed using the concentration index (C: -0.21; 95%CI: -0.25, -0.17) and apparent in the concentration curve. Inequalities in incident cancer burden across HDI levels were statistically non-significant for cancers of the head and neck, oesophagus, stomach, and liver.

Table 1 also provides the results of the decomposition analysis, which quantifies each cancer site's contribution to the inequality in cancer incidence of all sites combined. According to this analysis, prostate, lung and breast cancer contribute most to the incident cancer burden in countries with high HDI levels, while cervical cancer contributed most to the cancer burden in countries with lower levels of HDI. Interestingly, the contribution of cervical cancer was much smaller in absolute value because its smaller weight in the total of cancer cases – despite being much more unequally distributed than lung, breast and prostate cancer.

Cancer mortality

Although overall cancer deaths were more equally distributed across HDI tertiles than incident cancer cases, this varied considerably by cancer site (**Figure 1**). While deaths from melanoma (50% of burden in highest vs. 28% in lowest HDI tertile), cancer of the pancreas (48% vs. 29%), lung (51% vs. 28%) and kidney (54% vs. 19%) as well as colorectum (44% vs. 33%), bladder (44% vs. 32%) and oesophagus (44% vs. 35%) were disproportionately higher in countries within the highest HDI tertile, the opposite was true for cancers of the cervix (23% vs. 62%), head and neck (32% vs. 50%), stomach (29% vs. 49%), and testis (38% vs. 39%). More than 60% of all cervical cancer deaths occurred in countries within the lowest HDI tertile, with an aggregated population comprising 38% of the total.

Table 1. Concentration indices (C)* and their 95% confidence intervals (95%CI) for site-specific cancer incidence and mortality using HDI as ranking variable

| Cancer site | Incidence | | | | | Mortality | | | | |
|-----------------------------|--------------------------|---------------|---------|---------|----------------|--------------------------|---------------|---------|---------|----------------|
| | Concentration index (C)* | 95%CI | p-value | Weight§ | contribution** | Concentration index (C)* | 95%CI | p-value | Weight§ | contribution** |
| All sites (C00-97, but C44) | 0.03 | (0.00,0.06) | 0.05 | | | 0.02 | (-0.00,0.05) | 0.06 | | |
| Head & Neck (C00-14) | -0.04 | (-0.09,0.02) | 0.18 | 0.03 | -0.001 | -0.13 | (-0.19,-0.08) | 0.00 | 0.03 | -0.003 |
| Oesophagus (C15) | 0.05 | (-0.02,0.12) | 0.16 | 0.01 | 0.001 | 0.05 | (-0.01,0.11) | 0.09 | 0.03 | 0.001 |
| Stomach (C16) | -0.01 | (-0.15,0.12) | 0.85 | 0.05 | -0.001 | -0.11 | (-0.22,0.01) | 0.08 | 0.07 | -0.008 |
| Colorectum (C18-21) | 0.06 | (0.04,0.09) | 0.00 | 0.10 | 0.007 | 0.06 | (0.01,0.10) | 0.03 | 0.10 | 0.006 |
| Liver (C22) # | 0.03 | (-0.12,0.18) | 0.73 | 0.02 | 0.001 | -0.04 | (-0.16,0.09) | 0.58 | 0.04 | -0.002 |
| Pancreas (C25) | 0.07 | (0.03,0.10) | 0.00 | 0.02 | 0.001 | 0.11 | (0.07,0.14) | 0.00 | 0.05 | 0.005 |
| Lung (C34) | 0.10 | (0.06,0.14) | 0.00 | 0.10 | 0.010 | 0.10 | (0.06,0.15) | 0.00 | 0.21 | 0.022 |
| Melanoma (C43) | 0.23 | (0.11,0.35) | 0.00 | 0.03 | 0.006 | 0.12 | (0.03,0.22) | 0.01 | 0.01 | 0.001 |
| Breast (C50) | 0.07 | (0.02,0.12) | 0.00 | 0.12 | 0.009 | 0.01 | (-0.03,0.05) | 0.70 | 0.07 | 0.001 |
| Cervix (C53) | -0.21 | (-0.25,-0.17) | 0.00 | 0.02 | -0.004 | -0.26 | (-0.33,-0.20) | 0.00 | 0.01 | -0.004 |
| Prostate (C61) | 0.11 | (0.03,0.19) | 0.01 | 0.12 | 0.013 | -0.01 | (-0.07,0.04) | 0.59 | 0.05 | -0.001 |
| Testis (C62) # | 0.10 | (-0.00,0.20) | 0.06 | 0.01 | 0.001 | -0.11 | (-0.21,-0.00) | 0.05 | 0.00 | 0.000 |
| Kidney (C64-66) # | 0.09 | (0.02,0.16) | 0.01 | 0.02 | 0.002 | 0.09 | (0.02,0.16) | 0.02 | 0.02 | 0.001 |
| Bladder (C67) | 0.12 | (0.05,0.19) | 0.00 | 0.03 | 0.004 | 0.06 | (-0.00,0.12) | 0.07 | 0.02 | 0.001 |
| Leukemia(C91-95) | 0.04 | (0.01,0.07) | 0.01 | 0.03 | 0.001 | 0.01 | (-0.01,0.04) | 0.34 | 0.03 | 0.000 |

* The concentration index (C) provides a summary measure of the deviation from the line of perfect equality (as shown in the concentration curves in Figure 2). C=0 indicates that the concentration of cases among countries with lower levels of HDI is equal to the concentration of cases among countries with higher HDI levels (=equality); C>0 indicates that cancer cases/deaths are disproportionately concentrated in high HDI countries (the concentration curve lies below the diagonal); C<0 indicates that cancer cases/deaths are disproportionately concentrated in countries with lower HDI countries (the concentration curve lies above the diagonal).

§ Weight equals the population weighted incidence/mortality rate of each cancer site.

**Contribution quantifies the contribution of each cancer site listed in the table, to the overall inequality of all-sites combined (C00-97 but C44). It is obtained as the concentration index multiplied by weight divided by the overall incidence or mortality rate (see Methods).

does not include data from Russia, Belarus, Ukraine and Switzerland

Concentration curves of cancer mortality were on average slightly closer to the line of perfect equality when compared to cancer incidence (**Figure 2**). While for all sites combined, the concentration index for mortality was very similar to that of cancer incidence, the countries with higher HDI levels were disproportionately affected by melanoma (C: 0.12; 95%CI: 0.03, 0.22), followed by cancer of the pancreas, lung, kidney, colorectum, bladder, and oesophagus. A disproportionately higher mortality in countries with lower HDI levels was most pronounced for cervical cancer (C: -0.26; 95%CI: -0.33, -0.20), but was also found for cancers of the head and neck, stomach and testis.

When the inequality in cancer mortality from all sites combined was decomposed into each cancer site's contribution, lung cancer was the main contributor to the cancer mortality burden in countries with higher HDI levels, while stomach cancer contributed most to corresponding inequalities in countries with lower HDI levels (**Table 1**). This reinforces the observation – as can be seen on comparison of the concentration indices for cancers of the cervix and stomach – that the site-specific contribution depends on the weight of total deaths as well as the extent of the inequality across levels of HDI.

DISCUSSION

This is the first investigation and visual representation of how inequalities in the cancer burden in the 21st century relate to human development. Marked inequalities in the cancer burden were found for both incidence and mortality; with differences across cancer sites. Whereas the burden from cancers such as prostate, breast and lung cancer was greater in countries with higher HDI levels and thus contributed most to overall inequalities in cancer incidence, cancer of the cervix represented a disproportionate burden in countries with lower HDI levels. Lung and stomach cancer were the main drivers of overall inequalities in cancer mortality in high and medium HDI countries. While previous studies have reported similar patterns (6, 24), our study confirmed and quantified these inequalities using the concentration index across a large number of countries internationally.

Lifestyle-related cancers represented the largest source of inequality in cancer incidence. Inequalities in kidney and lung cancer are likely related to past smoking patterns that translated into a high burden of smoking-related cancers in countries with higher HDI levels due to a long lag-time. In view of the shifting smoking epidemic towards an increasing prevalence in lower HDI countries (25, 26), inequalities in the burden of smoking-related cancers are likely to even out in the coming decades. Similar trends also apply to risk factors such as obesity and alcohol consumption, as well as diet and reproductive factors, which are assumed to be the main drivers of inequalities in lifestyle-related cancers in high HDI countries. Another cancer that was largely disproportionate in high HDI countries was Melanoma. It has been known to affect primarily fair-skinned, Caucasian populations and more highly developed countries. (27) Similarly, testicular cancer is much more common in countries with a high or very high HDI, with ongoing increases in incidence that largely remain unexplained. (28)

Lower socio-economic position has previously been linked to an increased risk of acquiring infection with human papillomavirus (HPV), *helicobacter pylori* (*H pylori*) and hepatitis B/C virus (29, 30), the main infectious agents that are linked to cancer. Also, the vast majority (80%) of all infection-related cancers occur in less developed regions of the world. (31) High-risk HPV types are considered a necessary cause for cervical cancer and accounted for half of all cancer cases attributable to infection in women in 2008. (31, 32) In addition, recent evidence suggested that about 89% of all (non-cardia) stomach cancers are attributable to *H pylori*. (33) In accordance with this, we found a disproportionate burden of cervical cancer incidence and mortality and stomach cancer mortality in lower HDI countries. Most notably, 55% of all new cervical cancer cases and more than 60% of cervical cancer deaths occurred in countries within the lowest HDI quartile, while accounting for only 38% of the total population considered. This points towards greater inequality in cancer mortality than in incidence for infection-related cancers and is in accordance with recent evidence suggesting that stomach and cervical cancer contributed most to disability-adjusted life-years lost from cancer and represent important causes of premature mortality in lower HDI regions. (34).

The incident burden of breast cancer was greater in countries with high HDI levels, which is probably related to lifestyle and reproductive factors, but might also reflect the impact of more active early detection of breast

cancer and differences in access to diagnostic services. In contrast, relative to the number of newly diagnosed breast cancers, fewer breast cancer deaths occurred in countries with high HDI levels. Differences between inequalities in cancer incidence and mortality might thus point towards differences in access to medical services and cancer treatment centres. Even within Europe, standards of care differ greatly between countries and variation in cancer survival has been associated with national wealth, investments in health technology and education. (35-37) In this study, in general we saw that in countries with higher HDI levels the proportion of new cancer cases was equal or greater than the proportion of cancer deaths from all included cancer sites. On the contrary the reverse was true for countries with lower HDI levels. This was particularly pronounced for testicular cancer, with 32% of all deaths but only 13% of all incident cases occurring in countries with lower HDI levels, but also true for other cancer sites such as cancer of the head and neck, stomach, liver, breast, prostate, bladder and melanoma.

In this study, the most comprehensive, available and high quality data on cancer incidence and mortality were used, coming from two different sources. The selection criteria for incidence and mortality data restricted the final dataset to 43 countries. Our applied method, the concentration index, has the advantage of not only using information from the full HDI spectrum and accounting for population sizes of the set of countries included in the study, but also enabling the graphical depiction of inequality using the concentration curve. Despite this, the lack of data from low HDI settings and the data quality requirements for inclusion in this study led to an overrepresentation of highly developed countries. The results presented are thus predominantly relevant to high and very high HDI countries (see **Annex Table 1**) and are subject to some change were other datasets available and included. Restricting the analysis to only (very) high HDI countries, i.e. excluding Colombia, Ukraine and the Philippines, did not substantially alter the results and suggests that our findings also hold across high HDI countries. Including a larger set of countries, especially those of low and medium HDI, would assign more weight to these populations. This, in turn, might further emphasize inequalities in the burden of cancers that are more common in low HDI countries, notably infection- and poverty-related cancers.

Inequalities in cancer burden can be measured on different levels, using different indicators. The choice of the metric for quantifying inequalities can potentially lead to different results. (38) Using the current approach, we assessed inequalities in cancer incidence and mortality across HDI ranks – and not inequality *per se*. We repeated these analyses with the different components of HDI, i.e. education, life expectancy and gross domestic product, as rank measures and the results were very similar. On the other hand, summarizing the degree of inequality in a single number, the concentration index, enabled us to directly compare the degree of inequality across cancer sites. That the concentration index and curve can also be good temporal indicators of changes in disparities has previously been shown for breast cancer incidence and mortality in the United States. (39) Repeating and updating these analyses on the global level could potentially reveal important clues about transitions in disparities. Together with its visual representation, the concentration index offers a possibility to quantify inequalities and to identify the exact location of deviations from proportionality. By calculating the concentration index based on aggregated, country-level data (and not individual-level data),

within-country inequalities and regional variability were not considered; this analysis was beyond the scope of this work, while individual-level data are available in only a few countries.

Our study has shown that inequalities in the burden of cancer remain evident in the 21st century, even across medium to high HDI countries, and can be characterized by a disproportionate burden of lifestyle-related cancers in high HDI and infection-related cancers in lower HDI countries. Reducing the cancer burden from largely preventable and treatable cancers that are closely interrelated with inequalities must be priorities in cancer control. Yet, inequalities remain complex, require surveillance over time and must be used synergistically with other measures, including those that proxy within-country inequality. In future studies, incorporating data from countries undergoing developmental transition will be vital to better map global inequalities and better quantify the relative and absolute contribution of individual countries to these disparities.

Contributors

This study was conceived and designed by MA, TVO and IS. MA conducted the statistical analyses and wrote the first draft of the manuscript. All authors contributed to critical revisions of the manuscript and approved the final submitted version.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Figure legends

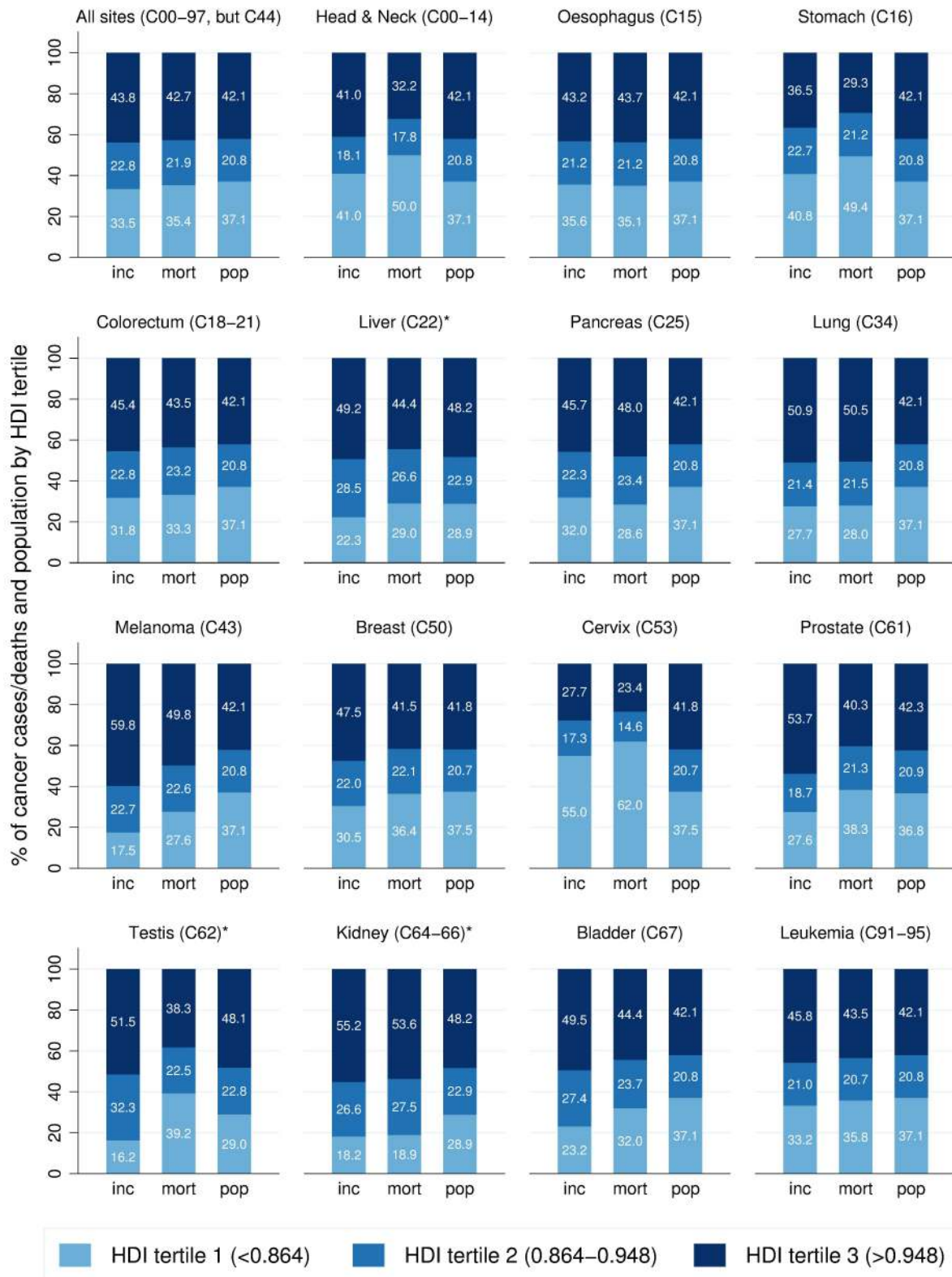
Figure 1. Proportion of cancer cases (inc), deaths (mort) and population (pop) by HDI tertile and cancer site

*results for kidney, liver and testicular cancer do not include data from Russia, Belarus, Ukraine and Switzerland

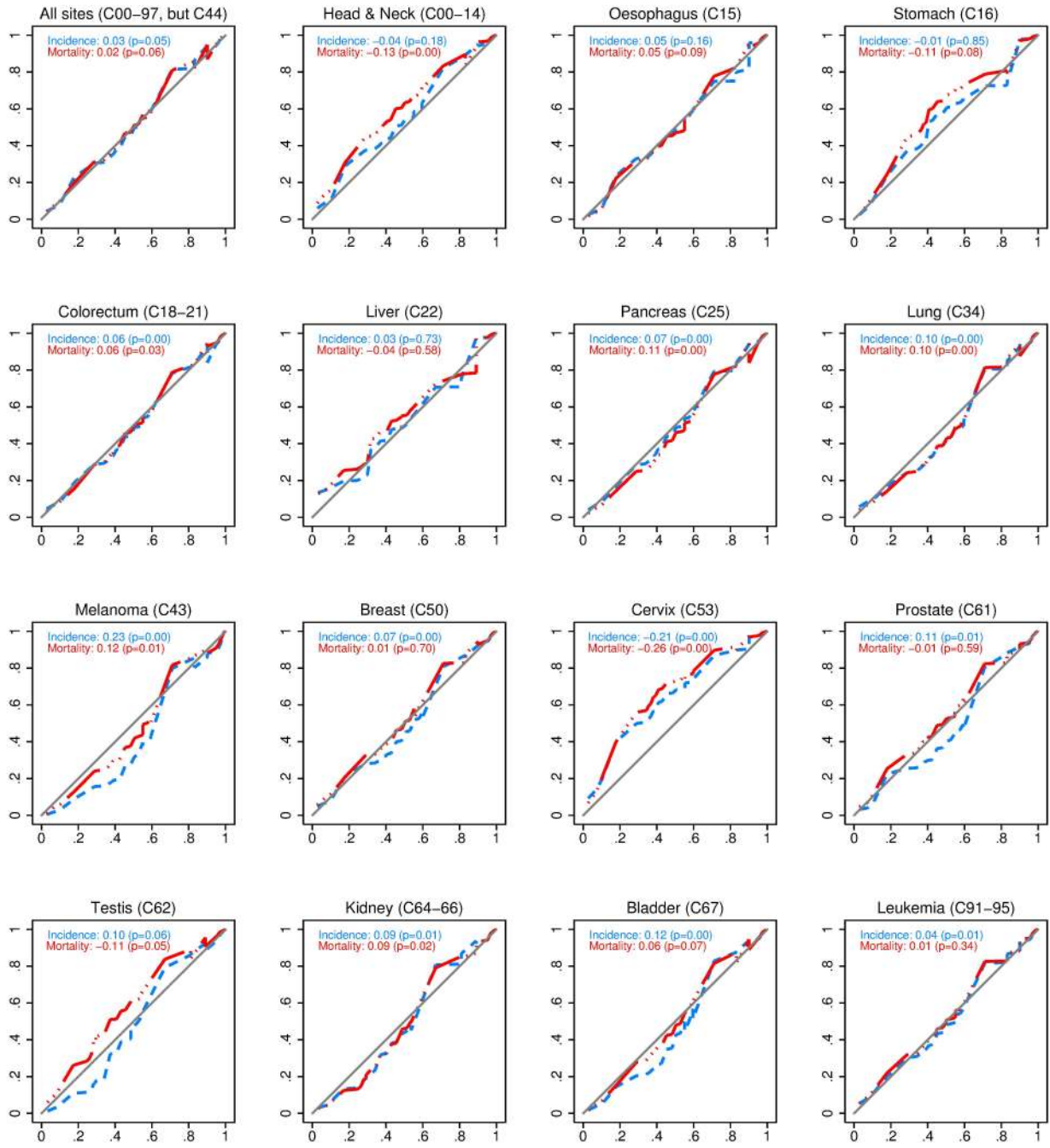
Figure 2. Concentration curves and indices for site-specific cancer incidence and mortality using HDI as ranking variable *

*results for kidney, liver and testicular cancer do not include data from Russia, Belarus, Ukraine and Switzerland

The concentration index (C) provides a summary measure of the deviation from the line of perfect equality as indicated by the concentration curves. $C=0$ indicates that the concentration of cases among countries with lower levels of HDI is equal to the concentration of cases among countries with higher HDI levels (=equality); $C>0$ indicates that cancer cases/deaths are disproportionately concentrated in high HDI countries (the concentration curve lies below the diagonal); $C<0$ indicates that cancer cases/deaths are disproportionately concentrated in countries with lower HDI countries (the concentration curve lies above the diagonal)



Cancer incidence/mortality (cumulative)



Country-level population gradient defined by HDI

Incidence (CI5X) Mortality (WHO)