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Global Cancer Mortality: National Healthcare System Resources And Surivival From Cancer

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Abstract

Global Cancer Mortality: National Healthcare System Resources and Survival from Cancer

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Cancer continues to rise steadily as a contributor to premature death in the developing world. Despite this, little is known about what aspects of national healthcare systems are associated with reduced mortality from cancer. Thus, we aimed to investigate the relationship between national healthcare system resources and cancer mortality. The most recent estimates of cancer incidence and deaths were obtained for the 85 countries with reliable data. We defined cancer mortality to incidence ratio as deaths per year divided by incidence per year for a given cancer. Countries were categorized according to high (GDP>$15,000) or low-income (GDP<$15,000), and a multivariate linear regression model was used to determine the association between healthcare system indicators and cancer-specific mortality to survival ratio. Indicators studied included per capita gross domestic product (GDP), overall healthcare expenditure, health expenditure as a proportion of GDP, total external beam radiotherapy devices per capita (TEBD), physician density, and the year 2000 World Health Organization (WHO) healthcare system rankings.

The overall cancer mortality to survival ratio in high income countries (47%) was significantly lower than that of low income countries (64%), with a $p<0.0001$. In high income countries, GDP, health expenditure and TEBD showed significant inverse correlations with overall cancer mortality to survival ratio, with health expenditure (overall and as a proportion of GDP) showing the strongest relationship. For overall cancer, a $3,040 increase in GDP ($p=0.004$), a $379 increase in THE ($p<0.0001$), a 0.75% increase in THE per GDP ($p<0.001$) or an increase of 0.59 TEBD 100,000 population ($p=0.027$) were all associated with a 1% decrease in mortality to survival ratio. In low income countries, only WHO score correlated with decreased overall cancer mortality to survival ratio ($p=0.022$).

Our analysis suggests that WHO healthcare score is associated with improved cancer outcomes in low income countries while absolute levels of financial resources and infrastructure play a more important role in high income countries.

Acknowledgments

I would like to thank the Universe for allowing such a miracle as this moment to happen.

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Introduction

Cancer is an important global problem, especially in the developing world. Greater than half of cancer cases worldwide arise in developing countries, and this proportion is expected to rise to 70% by 2020 (1). As cancer incidence and mortality rates increase in the developing world on a yearly basis (2), the United Nations and WHO have placed greater emphasis on its treatment and prevention. September 2011 marked the first ever High-Level Meeting of the United Nations on non-communicable diseases, where researchers and policy makers united to forge new policies to tackle the growing worldwide epidemic of chronic disease. This meeting will took place without essential data on the specific aspects of national healthcare systems that are associated with the variation of cancer mortality worldwide.

Given the cultural, socioeconomic, and environmental factors that can influence cancer outcomes, it is unclear whether and to what extent healthcare expenditure, infrastructure and organization are associated with cancer mortality rates. Assessing overall health expenditure is perhaps the simplest method to measure a country's commitment to healthcare. Studies have shown weak but significant relationships between healthcare spending and improved cancer mortality in particular subsets of developed countries (3) (4), but this association is unexplored in the developing world.

In addition to being associated with overall expenditure, cancer mortality may be affected by the specific aspects of healthcare infrastructure towards which spending is geared. Healthcare infrastructure can be measured in several ways. In the developed world, the number of doctors per capita has been found to be associated with cancer mortality in some studies (3) but not in others (4). In addition to physician density, a useful measure of healthcare infrastructure is access to radiation therapy (5). Radiation therapy is often underutilized in developing countries due to the up-front expense of required machines and facilities. In fact, 22 countries in Africa and Asia have no radiation therapy facilities at all, with many more having only a fraction of the machines required by their populations (6). However, it is unclear whether access to radiation oncology facilities actually correlates with reduced cancer mortality worldwide.

The overall functionality of a national healthcare system is another factor that could potentially affect cancer mortality. The year 2000 World Health Organization (WHO) overall healthcare system rankings for example provided a systematically derived, quantifiable measure of healthcare system fairness and effectiveness. The rankings aimed to use available data from around the world to assess the effectiveness of 191 countries in "Improving health, reducing health disparities, protecting households from impoverishment due to medical expenses, and providing responsive services that respect the dignity of patients," (7). The ranking was a complex indicator that was based on the following factors: healthcare system responsiveness (based on overall patient satisfaction and the ability of a system to act promptly and effectively), the distribution of responsiveness (e.g. in rich vs. poor), overall level of health (measured by average disability adjusted life years), the distribution of health, and finally, the fairness of distribution of the financial burden of a system. Interestingly, they ranked the USA, the nation spending the highest amount of money per capita on healthcare at the time, 37^{th} (8). As a result of this surprising finding as well as debate within the scientific and political community regarding the methodology and utility of the rankings, little research has been done to see the effectiveness of the rankings in predicting national health outcomes. Indeed, no study to date has measured the association between these rankings and cancer mortality.

Statement of Purpose

The goal of this study was two-fold: to see the extent to which cancer mortality varied throughout the world and to identify the relation between healthcare system factors and cancer outcomes in both developed and developing countries. Broadly, we assessed three categories of variables with cancer mortality: overall monetary resources, healthcare system infrastructure, and the WHO's overall healthcare system score. Due to the vast disparities in resources, healthcare systems and disease burdens in the developed vs. developing world, we hypothesized that factors affecting outcomes in low income countries would differ from those in high income countries. Thus we assessed the healthcare system correlates of cancer mortality in each group separately.

Methods

Outcome Variable

Age standardized cancer incidence and death rates were obtained from the International Agency for Research on Cancer's Globocan 2008 database, which included the most recent data from each country worldwide. While incidence data was available for a majority of countries, only 85 countries had recent (post 2005) non-estimated mortality data and were thus included for analysis. Of these 85 countries, 41 were in Europe, 24 in the Americas, 17 in Asia, 2 in Oceania and only 1 in Africa. Data were stratified by cancer type, sex, and age, with groupings from 0-14 years, 15-39 years, 10 year groups until age 70, and 70+ years. As there are no standard international definitions of race and ethnicity, data were not stratified by race. There were 28 different cancer types reported, 26 in women and 24 in men. However, data from Kaposi Sarcoma was excluded from the evaluation as only two countries included this data, leading to a total of 27 cancer types analyzed, 25 in women and 24 in men. Additionally, each country had a summary measure for all cancers excluding non-melanoma skin cancer (overall cancer). The mortality to incidence ratio (M/I) was determined by dividing a given year' s mortality for a cancer by the cancer' s incidence in that year. While this is not an exact measure of survival, since being diagnosed with cancer in one year can lead to mortality in a different year, and incidence can change significantly from year to year, it is a simple and straightforward approximation that is useful for large datasets.

While a very broad range of countries from all continents are included, the poorest of poor countries, including all countries with GDPs of less than $1,690, were not included due to their lack proper and accurate cancer incidence and mortality databases. This list of excluded countries consists of all but one country in Africa, as well as many countries across Asia and Latin America.

Table 1. Variables Used in Regression model

Independent Variable	Source	Description
WHO healthcare system score (overall and responsiveness)	WHO World Health Report 2000	The score was based on a system's responsiveness to patients, the fairness of financial distribution, the overall national level of health, and the distribution of health
Physician Density	WHO Global Atlas of the Health Workforce 2008	Estimated number of physicians per 100,000 population
Gross Domestic Product (GDP)	World Development Indicators database, World Bank (2007)	Estimated purchasing parity gross domestic product per capita in US$
Total Health Expenditure (THE)	World Development Indicators database, World Bank (2007)	Estimated total (government and private) health expenditure per capita in US$
THE per GDP	World Development Indicators database, World Bank (2007)	Estimated percent of THE as a proportion of GDP
Radiation Therapy	International Atomic Energy Agency's	total external beam radiotherapy devices per capita

	Directory for Radiotherapy 2010	(TEBD)
Control Variable	**Source**	**Description**
HIV rate	CIA World Factbook 2003-2008	Estimated percent of population infected by HIV
Rural population	UN World Urbanization Prospects (2007)	Estimated percent of population that live in rural area
Ethanol consumption	WHO Core Health Indicators 2003	Estimated per capita liters of ethanol consumed
Male smoking rate	WHO Report on the Global Tobacco Epidemic 2007	Estimated percent of men who smoke tobacco regularly
Female smoking rate	WHO Report on the Global Tobacco Epidemic 2008	Estimated percent of women who smoke tobacco regularly
Male obesity rate	WHO Global Database on BMI (2008)	Estimated percent of men who have a BMI>30
Female obesity rate	WHO Global Database on BMI (2008)	Estimated percent of women who have a BMI > 30

Table 1 shows the independent variables and control variables that were used in the regression model, as well as the source and description of each variable.

Table 2. Summary statistics by region for high and low income countries

Category	Variable	Region							
	High Income Countries	Eastern Europe	Western Europe	North America	Eastern Asia	Western Asia	Oceania		Overall
	Countries	12	18	5	5	2	2		44
	Mortality	55%	40%	50%	49%	49%	39%		47%
Organization	WHO Rank	61	16	55	29	37	37		36
Financial Resources	GDP	$21,043	$38,612	$31,212	$38,197	$42,393	$32,569		$32,418
	THE	$1,174	$4,451	$2,989	$1,552	$1,397	$3,388		$2,824
	THE per GDP	5.30%	11.40%	8.20%	4.60%	4.10%	10.40%		8.10%
Healthcare Infrastructure	TEBD	3.4	6	5.9	2	2.5	5.8		4.7
	Physician Density	322	347	150	159	274	230		284

	Low Income Countries	Eastern Europe	North America	Central America	South America	Eastern Asia	Western Asia	Africa	Overall
	Countries	11	1	6	12	4	6	1	41
	Mortality	65%	61%	62%	59%	68%	73%	70%	64%
Organization	WHO Rank	76	61	77	72	99	121	175	92
Financial Resources	GDP	$8,951	$12,447	$7,340	$9,397	$4,893	$5,616	$10,632	$7,543
	THE	$387	$564	$257	$406	$93	$126	$497	$269
	THE per GDP	4.10%	4.50%	3.40%	4.10%	2.00%	2.10%	4.70%	3.40%
Healthcare Infrastructure	TEBD	1.6	1	0.8	1.7	0.8	1.1	1.2	1.2
	Physician Density	210	198	106	202	139	241	77	215

Table 2 shows the mean for each variable used in the regression model (excluding controls) by region and income category. High income countries had a GDP > $15,000 while low income countries' were below $15,000. All variables varied widely by region and income category. Overall, low income countries also had lower levels of resources and higher mortality than high income countries. Within high income countries, E. Europe had the worst mortality at 55% while Oceania and W. Europe had the best at 39-40%. (p=0.006). Within low income countries, The Americas had lower mortalities than E. Europe and Asia . W. Asia, composed of former soviet states, had the highest mortality of any region at 73%. (Mortality = Overall cancer mortality, GDP = Gross Domestic Product per capita, WHO = World Health Organization, THE = total health expenditure per capita, TEBD = Total external beam radiation devices per 100,000 population, Physician Density = Physicians per 100,000 population)

Independent Variables:

As previously mentioned, the markers chosen to correlate with cancer survival were World Health Organization (WHO) overall healthcare system score and system responsiveness score, physician density, per capita Gross Domestic Product (GDP), per capita total healthcare expenditure (THE), access to radiation oncology (measured by total external beam devices (TEBD) per capita) and THE per GDP. Table 1 lists all indepndent variables as well as all control variables used in the study, with a listing of each variable's source. Table 2 shows the mean and ranges for the above variables overall and by region for both low and high income countries.

WHO rankings

The first variable of interest was the year 2000 WHO overall healthcare system rankings (OHS), which ranked the USA, the nation spending the highest amount of money per capita on healthcare at the time, 37th (8). As previously mentioned, the ranking itself was derived from a score based on several variables: the system's responsiveness to patients, the fairness of financial distribution, the overall national level of health, and the distribution of health. The responsiveness measure included two major components: respect for persons and client orientation. Fairness of financial distribution measured the relative out of pocket amount paid by the rich and poor. The overall national level of health was counted as the average disability adjusted life expectancy (DALE) of the nation. The distribution of health was concerned with the variance of DALE around the mean. Our study took into account the overall healthcare system ranking as well as the specific measure of responsiveness to patients, as this measure was most likely to affect prompt diagnosis and treatment of malignancies. For statistical reasons, the absolute scores on which the ranks were based were used in the analysis.

Physician Density

In addition to overall healthcare system scores, physician density plays a potentially important role in health outcomes. Theoretically, a greater number of physicians per capita would result in an increase of access of a population to physicians, and thus potentially earlier and more effective treatment of cancer. Previous studies on the subject have been equivocal. Or 2001 found that an increase in physicians per capita in 29 Organization for Economic Cooperation and Development (OECD) countries was associated with a significant reduction in potential years of life lost by cancer mortality in women, but not in men (3). Quaglia et al. 2005 on the other hand found that in 23 European countries, the density of healthcare employees did not correlate with improved cancer survival among the elderly (4). Thus the question still remains as to whether, globally, there is an association between physician density and cancer survival. Our study used the measure of physicians per 100,000 population as recorded in the WHO Global Atlas of the Health Workforce (9).

GDP, THE & THE per GDP

Greater human resources are not the only part of a healthcare system that could provide improved outcomes. More financial resources on a national level theoretically allow for improved cancer prevention and treatment. Or 2001 showed a significant inverse relationship between GDP and years of life lost by cancer mortality in OECD countries (3). Quaglia et al. 2005 showed a significant positive correlation between both GDP and THE and cancer survival in European elderly (4). However, both studies only included a small cohort of countries and in the latter, a specific age population. This study aimed to see whether these trends hold on a more global scale. Per capita GDP and THE were based on 2007 World Bank estimates (10). Additionally, this study aimed to measure whether the importance of healthcare in a given society, as measured by the percent of GDP spent on THE (THE per GDP), correlated with cancer survival separate from either THE or GDP alone.

Radiation Therapy

With the question of cancer, not only are the number of physicians and the amount of spending on treatment potentially important to outcomes, but also where that spending goes. The three most common treatment modalities for any carcinoma are chemotherapy, surgery, and radiation therapy, with each type of carcinoma more responsive to one particular or a specific combination of treatments. Radiation therapy (RT) in particular has often been severely underutilized in developing countries, in large part due to the up-front expense of required machines and facilities. As such, 22 countries in Africa and Asia have no RT facilities at all, with many more having far fewer machines than required by their populations (6). In Africa for example, the supply of megavoltage radiation therapy machines was 18% of the estimated need (6). Despite large startup costs however, external beam radiation therapy in the long term is one of the most effective and cost effective cancer treatments (5). The speed and ease of treatment as well as the lack of need for expensive chemotherapeutic agents or dangerous surgeries make this a potentially excellent option for cancer treatment in developing countries. However, no study has been done to show whether access to radiation oncology facilities actually correlates to improved health outcomes and improved cancer survival. Our study aimed to correlate survival with total external beam devices per capita (TEBD), both Linear Accelerators and Cobalt machines. TEBD data was obtained from the International Atomic Energy Agency’s Directory for Radiotherapy Centers, a detailed list of radiation therapy resources by country.

Data Analysis

Multivariate regression modeling was performed using Stata version IC10 with the response variable of age standardized M/I. Three separate models were created for each cancer and predictor variable combination: one for males, one for females and one for both sexes combined. As this study aimed to assess predictors of overall cancer care, the summary measure of overall cancer M/I was the variable of greatest interest. However, analysis was done on all cancers individually as well to see whether any results found for overall cancers held for individual cancers. This step was performed to mitigate the potential confound caused by some countries having a higher incidence of more deadly cancers as a proportion of overall cancer incidence than others, thus artificially increasing their M/I. Each model included adjustments for the behavioral, demographic and environmental risk factors listed in Table 1. Since GDP, THE and TEBD were collinear variables (pearson correlation coefficient>0.7 or < -0.7), they were not included in each other's models. However, physician density was included in all models as a control, as it was not collinear with the other predictor variables. See Table 3 for correlations between all predictor and control variables.

It was hypothesized that the relationship between predictor variables and M/I would be different in lower vs. higher income countries, thus the 85 countries were split roughly in half at the GDP point of $15,000 and the above regressions were repeated for the high and low GDP categories. Further breakdown into smaller GDP categories was not performed due to diminishing power. Correlation coefficients, regression coefficients and p-values were recorded for each regression equation. The amount of change needed in a given predictor variable to cause a 1% decrease in M/I was calculated by dividing 0.01 by the regression coefficient.

Table 3. Correlation Coefficients Between All Variables

	WHO Overall Score	Responsiveness Score	Physician Density	GDP	THE	TEBD	THE per GDP	HIV Rate	Rural population	Ethanol Consumption	Male Smoking	Female Smoking	Male Obesity
Responsiveness Score	**0.68**												
Physician Density	**0.26**	**0.19**											
GDP	**0.68**	**0.75**	**0.24**										
THE	**0.63**	**0.71**	**0.36**	**0.83**									
TEBD	**0.63**	**0.70**	**0.42**	**0.70**	**0.87**								
THE per GDP	**0.63**	**0.66**	**0.40**	**0.66**	**0.93**	**0.87**							
HIV Rate	**-0.30**	**-0.06**	**-0.25**	**-0.08**	**-0.10**	**-0.12**	**-0.08**						
Rural population	**-0.50**	**-0.49**	**-0.24**	**-0.57**	**-0.45**	**-0.49**	**-0.44**	0.04					
Ethanol Consumption	**0.34**	**0.44**	**0.36**	**0.35**	**0.47**	**0.52**	**0.53**	**-0.03**	**-0.26**				
Male Smoking	**-0.22**	**-0.26**	**0.26**	**-0.14**	**-0.24**	**-0.21**	**-0.28**	**-0.14**	**0.16**	0.01			
Female Smoking	**0.45**	**0.37**	**0.47**	**0.36**	**0.44**	**0.46**	**0.51**	**-0.15**	**-0.43**	**0.57**	**0.15**		
Male Obesity	**0.42**	**0.30**	**0.09**	**0.32**	**0.30**	**0.34**	**0.32**	**-0.08**	**-0.39**	**0.22**	**-0.15**	**0.45**	
Female Smoking	0.02	**-0.13**	**-0.22**	**-0.08**	**-0.07**	-0.04	-0.04	**0.18**	**-0.16**	-0.03	**-0.09**	**0.11**	**0.58**

Table 3 Shows the correlation between all variables, independent and control, used in the regression models. Correlations that are shown in bold (the vast majority) are significant, while correlations that are underlined meet the criteria for colinearity (r>=0.70) and were thus not included in each other's linear regression models. GDP, THE, THE per GDP, TEBD and WHO responsiveness score all showed significant colinearity with each other.

Results

Overall monetary resources, healthcare system infrastructure, healthcare system organization and overall cancer mortality varied significantly between high and low income countries, and from region to region, even within income categories (Table 2). Overall, low income countries also had lower levels of financial resources and infrastructure, as well as lower WHO healthcare scores and higher mortality than high income countries ($p<0.0001$ for all variables studied). Within high income countries, E. Europe had the worst mortality at 55% while Oceania and W. Europe had the best at 39-40%. ($p=0.006$). Within low income countries, the Americas had lower mortalities (59-62%) than E. Europe and Asia. W. Asia, composed of former soviet states, had the highest mortality of any region at 73%. Figure 1 shows a map representation of the overall cancer mortality to incidence ratios. Many of the highest mortality rates are found in former or current communist countries in Eastern Europe and Western Asia. In low income countries, mortality ranged from a low of 56% in Costa Rica to a high of 78% in Armenia with a median of 64% in Guatemala. In high income countries mortality ranged from a low of 38%

in Australia to a high of 73% in Greece with a median of 50% in Sweden. The United States and Luxembourg, the two largest healthcare spenders globally, were tied for second at a 39% overall mortality rate. A list of all countries studied ranked by overall cancer mortality to incidence ratios is shown in Table 4.

Several variables correlated significantly with M/I in the regression models. The results for overall cancer are outlined in Table 5 and each variable is addressed individually below. It is interesting to note that for every variable that proved significant, the correlation was stronger (lower p-value) in men than in women, showing that all variables had greater predictive value in the former.

WHO Scores

For low income countries, only WHO overall score correlated significantly with overall cancer M/I, and only in the combined statistic for both sexes, but not in each sex individually. A 1% decrease in overall cancer mortality to incidence ratio correlated with a 7.0% increase in WHO overall healthcare system score (p=0.022). In high income countries, WHO overall score correlated with improved outcome in stomach, testicular and head and neck cancers only, but not overall cancer. WHO responsiveness score on the other hand, correlated poorly with M/I in low income countries. In high income countries, responsiveness score did correlate significantly with overall cancer rate in all three sex categories.

Figure 1. World Map By Age-adjusted Mortality to Incidence Ratios

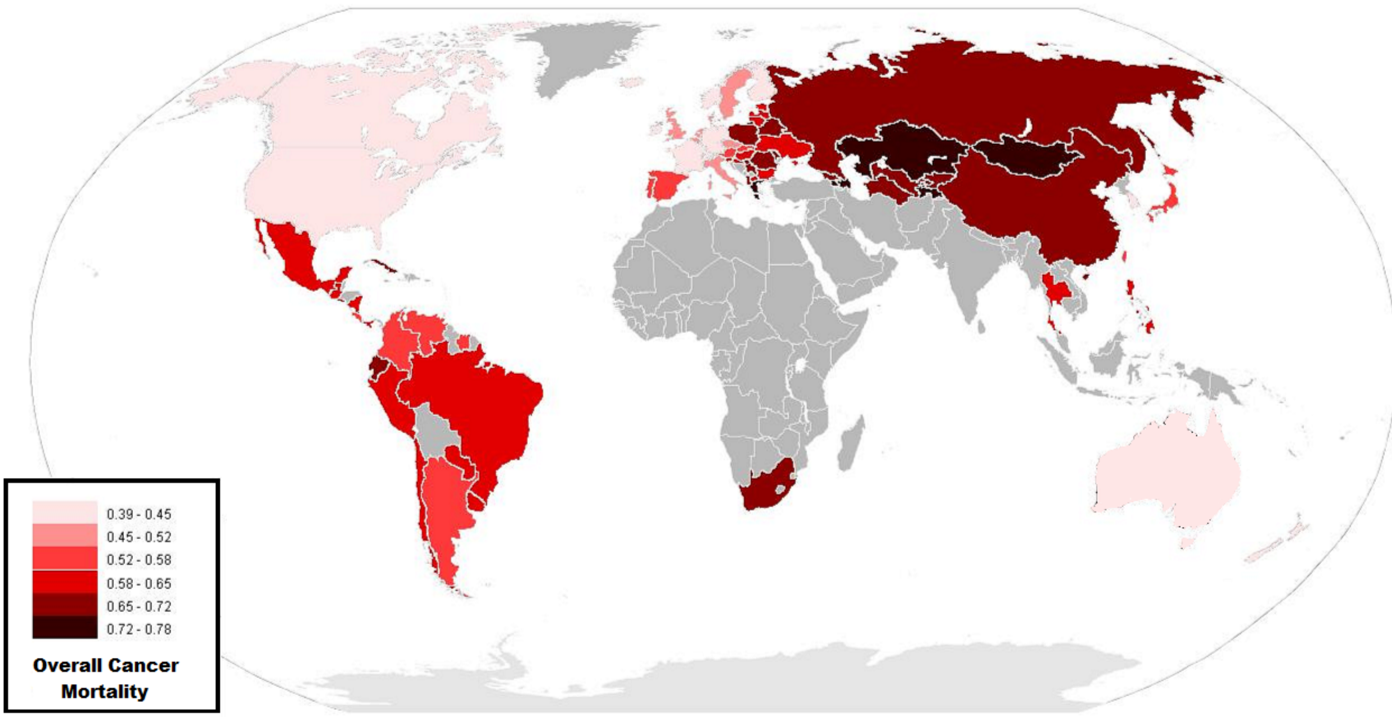

Figure 1 shows a color coded map of age-adjusted mortality to incidence ratios (M/I) for all cancers. Lighter colors correspond with lower mortality rates. As seen numerically in Table 2, Western Europe, Oceania and North America have the lowest M/I. In low income countries, Central and South America have lower M/I than much of Eastern Europe and Asia. Many of the highest M/I are found in former or currently communist countries in Eastern Europe and Western Asia.

Table 4. Ranking of Countries by Overall Cancer Mortality per Incidence

Rank	Country	M/I	Rank	Country	Mortality	Rank	Country	M/I
1	Australia	38.26%	30	Costa Rica	55.54%	59	Guatemala	64.41%
2	Luxembourg	38.61%	31	Suriname	55.58%	60	Hungary	64.61%
3	United States	39.37%	32	Japan	55.64%	61	El Salvador	64.95%
4	New Zealand	40.55%	33	Portugal	56.31%	62	Belize	65.07%
5	Ireland	40.61%	34	Brunei	56.69%	63	Moldova	65.25%
6	Israel	40.79%	35	Venezuela	57.51%	64	Trinidad and Tobego	65.27%
7	Republic of Korea	40.87%	36	Argentina	57.75%	65	Albania	65.69%
8	Iceland	42.48%	37	Bahamas	57.97%	66	Belarus	65.82%
9	Finland	42.78%	38	Colombia	58.14%	67	Ecuador	65.88%
10	Norway	42.97%	39	Bulgaria	58.41%	68	Poland	65.91%
11	Canada	43.64%	40	Slovenia	58.62%	69	Romania	66.12%
12	France	43.78%	41	Lithuania	59.23%	70	Russian Fed	66.38%
13	Kuwait	44.19%	42	Brazil	59.25%	71	Mauritius	66.57%
14	Germany	44.22%	43	Uruguay	59.31%	72	Cuba	67.34%
15	Switzerland	45.11%	44	Nicaragua	59.85%	73	South Africa	68.93%
16	Belgium	46.82%	45	Paraguay	60.09%	74	China	69.26%
17	Singapore	47.24%	46	Barbados	60.14%	75	Turkmenistan	69.93%
18	Cyprus	47.25%	47	FYR Macedonia	60.24%	76	Kyrgyzstan	70.21%
19	Italy	48.71%	48	Croatia	60.42%	77	Uzbekistan	70.40%
20	Denmark	48.89%	49	Dominican Republic	60.88%	78	Serbia	71.30%
21	Sweden	49.67%	50	Mexico	60.94%	79	Georgia	71.37%
22	The Netherlands	49.74%	51	Ukraine	61.14%	80	Mongolia	72.76%
23	Czech Republic	50.95%	52	Chile	61.39%	81	Tajikistan	72.87%
24	United Kingdom	51.42%	53	Thailand	62.53%	82	Greece	73.41%
25	Chinese Taipei	52.65%	54	Philippines	62.55%	83	Kazakhstan	74.00%
26	Spain	52.94%	55	Latvia	62.62%	84	Azerbaijan	77.20%
27	Malta	54.64%	56	Peru	63.18%	85	Armenia	78.17%
28	Austria	55.26%	57	Estonia	64.09%			
29	Slovakia	55.46%	58	Panama	64.40%			

Table 4 lists all countries included in the study ranked by Mortality to Incidence Ratio (M/I) as a percentage. Countries in red are high income as decided by the study parameter of GDP>$15,000 while countries in green are low income (GDP<$15,000). In general, high income countries have lower M/I when compared to their low income counterparts.

Table 5. Significantly Correlating Variables by Sex and Income Category

		HIGH INCOME			*LOW INCOME*		
Sex	**Variable**	**1% change in M/I**	**95% Confidence Interval**	**p-value**	**1% change in M/I**	**95% Confidence Interval**	**p-value**
Male & Female	WHO Overall Score	-	-	-	7.0%	(3.8%, 44.4%)	0.022
	WHO Responsiveness Score	2.0%	(1.1%, 7.5%)	0.009	-	-	-
	GDP	$3,040	($1828, $9091)	0.004	-	-	-
	THE	$379	($248, $800)	<0.0001	-	-	-
	THE/GDP	0.75%	(0.46%, 1.95%)	<0.0001	-	-	-
	TEBD per 100,000	0.59	(0.31, 4.93)	0.027	-	-	-
	TEBD/THE	-0.031%	(-0.112%, -0.018%)	0.008	-	-	-
	Physicians per 100,000	-	-	-	-39	(-74, -26)	<0.001
Female	WHO Overall Score	-	-	-	-	-	-
	WHO Responsiveness Score	2.8%	(1.6%, 20.1%)	0.024	-	-	-
	GDP	$3,745	($2128, $15649)	0.012	-	-	-
	THE	$575	($333, $2105)	0.008	-	-	-
	THE/GDP	1.30%	(0.68%, 13.76%)	0.031	-	-	-
	TEBD per 100,000	-	-	-	-	-	-
	TEBD/THE	-0.037%	(-0.15%, -0.021%)	0.011	-	-	-
	Physicians per 100,000	-	-	-	-56	(-260, -31)	0.01
Male	WHO Overall Score	-	-	-	-	-	-
	WHO Responsiveness Score	1.7%	(1.0%, 5.3%)	0.005	-	-	-
	GDP	$2,667	($1642, $7092)	0.002	-	-	-
	THE	$358	($229, $820)	0.001	-	-	-
	THE/GDP	0.76%	(0.45%, 2.53%)	0.006	-	-	-
	TEBD per 100,000	0.54	(0.28, 6.4)	0.033	-	-	-
	TEBD/THE	-0.031%	(-0.118%, -0.018%)	0.009			
	Physicians per 100,000				-42	(-91, -27)	0.001

Table 5 shows significant correlates of overall cancer mortality to incidence ratio (M/I), as well as the increase in each variable needed to cause a 1% decrease in cancer mortality (1% change in M/I). For example, in high income countries, a $3,040 increase in GDP per capita is associated with a 1% decrease in overall cancer mortality (p=0.004). While GDP, THE, THE per GDP, WHO responsiveness score and TEBD all showed significant inverse correlations with mortality in high income countries, THE and THE per GDP showed the strongest correlations (highest R and lowest p-value). In low income countries, only WHO overall score correlated with decreased overall cancer mortality while physician density paradoxically correlated with increased mortality. (GDP = Gross Domestic Product per capita, WHO = World Health Organization, THE = total health expenditure per capita, TEBD = Total external beam radiation devices per 100,000 population, Physician Density = Physicians per 100,000 population)

A 1% decrease in overall cancer M/I correlated to a 2.0% increase in WHO responsiveness score (p=0.009). Specifically, improvement in WHO responsiveness score was associated with significant decrease in M/I of stomach, kidney, colon, breast, cervix, CNS, testis, non-Hogdkin lymphoma, and head and neck cancers.

GDP, THE and THE per GDP:

In low income countries, GDP, THE and THE per GDP did not correlate with overall cancer M/I in any sex category. Interestingly, M/I correlated positively with GDP for Lung, pancreas, stomach, and cervical cancer, meaning that as GDP increased in low income countries, survival decreased for these cancers. Only Hodgkin lymphoma had the expected inverse correlation with GDP. No individual cancer showed any significant correlation with THE, and only the M/I of gallbladder cancer in men showed a significant inverse correlation with THE.

In high income countries, GDP, THE and THE per GDP all correlated significantly with overall cancer M/I in all three sex categories. In both sexes combined, a 1% decrease in overall cancer mortality correlated with an increase of \$3,040 for GDP (p=0.004), \$379 for THE (p<0.0001) and 0.75% of GDP for THE per GDP (p<0.0001). The following cancers had a significant inverse correlation with all three variables: colorectal, breast, cervix, liver, CNS, kidney, stomach, testis, liver and head and neck. Non-Hodgkin lymphoma, lung and bladder cancer correlated with both THE and GDP but not THE per GDP, while a few cancers correlated only with each individual variable. For overall cancers, M/I correlated most significantly with THE, as evidenced by the fact that its p value was lowest in all three sex categories (See Table 5). Two of the three countries with the absolute lowest overall cancer M/I's, Luxembourg (0.386) and the United States(0.394), also had the highest THEs at $7439 and $7285 respectively.

TEBD and Physician Density

In low income countries, TEBD did not correlate significantly with overall cancer M/I. Physician density, surprisingly, showed a positive correlation in all three sex categories (p= 0.009), with an increase of 39 physicians per 100,000 leading to a 1% increase in overall cancer M/I for both sexes. Specifically, colorectal, Hodgkin lymphoma, head and neck, and ovarian cancer M/Is correlated significantly with physician density.

In high income countries, TEBD showed a significant inverse correlation with the M/I of overall cancers in men alone and both sexes combined

(0.027), but not in women alone. For overall cancer, a 1% decrease in M/I correlated with an increase of 0.59 external beam devices per 100,000 population. M/I of colorectal, CNS, stomach, liver, breast, lung, cervix, head and neck cancers correlated significantly with TEBD. Physician density on the other hand, correlated poorly with M/I in these countries.

Discussion:

Cancer mortality varied widely throughout the developed and developing world. Quantifiable measures of overall monetary resources, healthcare infrastructure, and healthcare system organization appeared to impact cancer mortality in different ways in higher vs. lower income countries. While financial resources and infrastructure showed significant correlations with overall cancer mortality in high income countries, low income countries showed correlations with none of these factors. This was not simply due to lack of power, as some measures of resources showed paradoxical weak (not statistically significant) positive correlations with mortality. For low income countries, WHO overall healthcare system score was the only variable strongly associated with improvement in overall cancer mortality. This score took into account not only general population health but also a system’s responsiveness to its patients and the equitable distribution of health and healthcare within a country. This finding suggests that for poor countries, increased healthcare expenditure may not significantly improve national cancer mortality in the presence of unequal distribution of healthcare resources. Indeed there may be a minimum threshold beyond which an increase in healthcare expenditure and infrastructure is associated with improved cancer mortality.

While WHO overall healthcare score was associated with improved cancer mortality in low income countries, no association was seen in high income countries. The differential results in high vs. low income countries at the same time validate and undermine the utility of the WHO score in assessing a healthcare system’s ability to treat cancer effectively. The score’s relationship with the end-measure of mortality depends on context. As noted previously, a large part of the WHO healthcare system score is based on the equality of health resources distribution. In the setting of relatively low national resources, equality is very important - to spread out the limited healthcare expenditure available so that everyone has access to the most basic cancer screening and treatment. In high income countries, because the most modern cancer treatment is so expensive (11), it may be difficult to provide the most technologically advanced treatments to every single person that needs it. More equitable high income nationalized systems may choose not to offer the most advanced treatments at all in order to limit costs and focus more on less expensive diseases. Thus, high income countries which offer the most advanced but expensive treatments to only a portion of the population, may have an edge in overall cure rates compared to their more equitable counterparts.

Among the variables chosen, the WHO score had particular drawbacks but also particular promise. A small portion of the score was based on national levels of health measured by disability adjusted life years lost to disease. As our dependent variable was cancer mortality, and higher cancer mortality within a country would potentially lead to poorer national levels of health, it was hypothesized that there could be the potential of testing a circular relationship. However, as this relationship was only a small part of the overall relationship being tested, it was decided to include the WHO score as a variable. The complexity of the score's algorithm, a source of much debate in the scientific community, was another reason the score was chosen. The score attempted the herculean task of quantifiably measuring the overall fairness and effectiveness of a healthcare system. Thus, in our model it served as a gestalt measure of a healthcare system's performance and organization to counterbalance the very specific measures of resources and infrastructure. While the merits and pitfalls of this score could be debated endlessly, the significant correlation between the score and overall cancer mortality in low income countries provides partial evidence in support of the score's utility. At the very least, this result should fuel further research on the relationship between the score and health outcomes.

The first question that arises from the above results is why do WHO overall healthcare system scores fail to predict cancer outcomes in high income countries? Cancer treatment is a resource intensive process. In the United States for example, the average cost of initial treatment for colorectal and lung cancer, two of the most common cancers worldwide, are between \$60,000 and \$75,000 per person (11). Expensive chemotherapeutic agents, surgeries and radiation treatments are required, often for only a small chance of improvement or cure. However, without these expensive and aggressive treatments, the chances of improvement or cure would be even less. A large part of the WHO overall healthcare system score is based on the equity of health resources distribution. In more equitable healthcare systems, which would gain a higher rank, there is more of a managed care approach; as such, expensive treatments with small chances of causing an improvement in survival are often not undertaken for financial reasons (12, 13). Thus, in high income countries, an improvement in WHO overall healthcare system rank would not necessarily lead to improved cancer survival, as a managed care or nationalized healthcare approach with more equitable distribution of resources would potentially limit the aggressiveness of treatment of patients with poorer prognoses and diseases that have very expensive treatments. On the contrary, in a less equitable system that has components which are fee for service, there is greater physician incentive for more costly and aggressive treatments, and less pressure to control costs (14). This more aggressive care could potentially result in improved cancer survival on the whole, albeit at high costs. Thus it is also not surprising that THE correlates so significantly with survival in high income countries.

In low income countries on the other hand, greater equity in access to healthcare and cost distribution means that at least the majority of the population have access to the most inexpensive cancer treatments. This explains why WHO overall healthcare rank correlates well with survival in low income countries. However, another question that arises is why do healthcare system resources such as THE or TEBD fail to predict outcomes in low income countries? One possible answer is that the variation in these indicators is too small in low income countries to show any predictive value. For example, the range of THE in low income countries is $634 ($29 in Tajikistan to $663 in Argentina), while it is $6,732 ($716 in Poland to $7439 in Luxembourg) in high income countries. Similar disparities in range exist for GDP, TEBD and THE per GPD. This finding suggests one of two things: that the variation in resources was too small in low income countries to show a statistically significant correlation with survival given the relatively small sample size, or, that there may be a threshold before which resources cannot cause an improvement in cancer survival. Further research is necessary to determine whether this threshold exists and what values of GDP, THE, THE per GDP or TEBD prove to be cutoff points before which significant improvement in cancer outcomes are not seen.

While GDP, overall healthcare expenditure, expenditure as a proportion of GDP, and access to radiation oncology were all significant inverse correlates of mortality in high income countries, the overall data suggests that overall healthcare expenditure showed the strongest correlation. Thus, in countries with a GDP>$15,000, healthcare spending truly does make a difference in fighting cancer, both as an absolute value, and as a proportion of a nation' s budget. The most significant difference is seen in the most treatment and screening sensitive cancers, namely breast and colorectal cancer. Access to radiation therapy (as measured by total external beam devices per capita) also has the strongest association with both of these cancers, where adjuvant radiation therapy is often the standard of care.

Limiting our study was the lack of data on the poorest of all countries, particularly those in Africa. African countries have a per capita GDP on average less than half of the next most resource limited continent, Asia. However, the burden of cancer is huge in Africa. For example, the risk of dying from cancer among African women is actually double that of developed countries (15). Thus, future research attempting to analyze correlates of cancer mortality in the poorest of poor countries is an absolute necessity. Another limitation was the potential impact of unmeasured variables on cancer outcomes. For example, expenditure on social welfare has been shown to be an independent correlate of general health outcomes in developed countries, even surpassing healthcare expenditure itself in some countries (7).

One very surprising result was that physician density not only failed to correlate with survival in high income countries, but it also had a significant inverse correlation with survival (direct correlation with M/I) in low income countries. This result ties in perfectly with geography and politics. Of the 18 low income countries with the highest physician density, 17 are current or former communist countries, including Cuba, former members of the Soviet Union and the Eastern Bloc. On the other hand, the vast majority of low income countries with the lowest physician densities are Latin American countries with no strong history of communism. This trend can easily be seen by looking at the color difference between Soviet and Eastern Bloc countries vs. Central and South American ones in Figure 1. It is understandable that countries with communist backgrounds employ more socialized healthcare systems with more centralized systems of physician training and higher physician densities (16). However, why do these countries also have poorer survival rates? This difference cannot fully be explained by economic factors as several of the countries in Latin America for example have equal or lower GDPs and THEs to those in Eastern Europe, but better survival rates. One possible explanation ties this result back to the previous comparison of managed care vs. fee for service based healthcare systems. Current or former communist countries are more likely to have a population-based approach to healthcare rather than an individual based approach, thus putting less emphasis on treating individuals with costly diseases than in treating cheaper diseases that are deemed treatment worthy by the state (17).

While GDP, THE, THE per GDP, TEBD and WHO responsiveness score were all significant positive correlates of survival in high income countries, the overall data suggests that THE is the strongest predictor. Due to the collinearity of the aforementioned variables, parsing out the importance of one over the other posed a significant challenge. The first and simplest way of comparing effects was to compare the p-value of each correlation. THE and THE per GDP had the lowest p-values at $p<0.0001$ in the both sexes category, while THE alone won the battle in each sex individually. Since THE per GDP is combination of THE and the inverse of GDP, it is a useful variable in assessing the relative strength of the two. Thus, the fact that THE per GDP showed a significant inverse correlation with M/I supports the hypothesis that THE has greater predictive value than GDP. It is also quite possible, that because all of the above variables are collinear, either a common underlying variable or THE alone is accountable for the correlations seen.

Considering the cost of modern cancer care, the apparent effect of THE on survival is not at all surprising. Any potential effect of THE on M/I will have to come through one of two routes: improved cancer screening leading to detection at earlier stages, or, improved treatment after detection. If the former were the case, the most common cancers for which there are widely established screening mechanisms (such as colon, breast and prostate cancer) and effective early stage treatment would be most affected by rising THE. If the latter were the case, THE's effects would be most pronounced in the most costly cancers to treat. Using recently published data from Mariotto et al. 2011 regarding the cost of treatment by cancer in the United States, as well as our global incidence and mortality data, we wished to see whether THE was more likely to correlate with the M/I for higher costing and more prevalent cancers (11). However, no relationship was found in either case. While it was true that the M/I of costly cancers (such as CNS cancers) and common treatable cancers (such as colorectal and breast cancer) correlated significantly with THE, so did several cancers that were relatively uncommon and inexpensive to treat. Thus the mechanism of any potential effect of THE on M/I remains uncertain.

In high income countries, every single significantly correlating variable (THE, GDP, THE/GDP, WHO responsiveness score, TEBD) showed a much stronger correlation with M/I in men than women (as evidenced by a lower p-value). This result held both for overall cancers and head to head comparisons of individual cancers. Such a finding would lead us to believe that improvements in healthcare system resources have a potentially stronger effect on men than women. But why would this be? Traditionally, women are seen as the sex that takes better care of their health and visits the doctor more frequently. Several studies have found that women have higher overall utilization of the healthcare system in the United States (18). So what exactly is it about cancer care that's different in men than women? A British study found that in a cohort of 5462 community members, men were significantly more likely to take part in colon cancer screenings than women (19). A Japanese study found that women with stomach cancer (the most common cancer in the country) presented at a significantly later stage than men, and consequently had decreased survival rates (20). Thus perhaps when it comes to certain common cancers, women are for some reason less likely to undergo screening, and more likely to present at later stages. This hypothesis would explain why improvement in healthcare systems and healthcare resources would have less of an effect on women than men.

In this paper, we have shown the importance of financial resources in predicting survival in high income countries compared to the primacy of healthcare system organization as determined by the WHO in low income countries. While we have shown differences in the strength of effect of each variable, it is difficult to be certain of how direct the effect is. As this is a retrospective correlational study, the potential covert effect of one or several unknown variables that dictates the above healthcare system indicators cannot be excluded. Additionally, despite efforts to separate the effects of each variable, a more complex interdependent relationship between all of the healthcare system indicators in predicting M/I is likely. This point is clearly evidenced in the above discussion regarding physician density in former Communist countries. It is also important to note the geographic limitations of this study. As the study was limited to countries with robust data collection mechanisms, the vast majority of Africa and a significant portion of Asia were excluded. Thus, the results cannot be extrapolated to these areas. That being said, the range of countries sampled was quite broad, with many countries having a THE that was greater than the entire GDP of their counterpart. The United States' THE of 7285 for example was four times the GDP of Turkmenistan.

This report opens up more questions than it answers, especially in regards to finding the optimal healthcare system for treating cancer. On some levels, our study provides justification for the seemingly astronomical costs of medical care in many developed countries such as the United States. The higher costs actually produce real improvements in cancer survival. Additionally, despite many concerns related to healthcare access and equitability in more complex fee for service systems such as that of the United States, such countries often outperform more equitable systems in cancer survival. However, as this was a correlational study, further analyses are required. Specifically, studies are necessary to find additional hidden factors that may predict cancer survival and parse out the extent and mechanism of influence of both known and unknown factors.

Conclusion

This paper serves as the first analysis to explore the relationship between healthcare system indicators and cancer outcomes across the globe. Cancer mortality varied widely throughout high and low income countries. While overall financial resources and healthcare infrastructure were strongly associated with cancer mortality in high income countries, the World health Organization's healthcare system score, a measure of healthcare system performance, organization and equality, was the only correlate of mortality in low income countries. This suggests a greater importance of healthcare system structure and equality in lower income countries vs. absolute levels of resources in higher income countries.

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