Title: Cancer mortality-to-incidence ratio as an indicator of cancer management outcomes in OECD countries

Running Title: Cancer mortality-to-incidence ratio

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Abstract

PURPOSE: Assessing long-term success and efficiency is essential to evaluate cancer control programs. Mortality-to-incidence ratio (MIR) can serve as an insightful indicator of cancer management outcomes for individual nations. Calculating MIRs for the top five cancers among Organization for Economic Cooperation and Development (OECD) countries, the current study attempted to outline the outcomes of national cancer management policies according to the health system ranking of each country.

METHODS: The MIRs for the five most burdensome cancers globally (lung, colorectum, prostate, stomach, and breast) were calculated for all 34 OECD countries using 2012 GLOBOCAN incidence and mortality statistics. Health system rankings reported by the World Health Organization in 2000 were updated with relevant information when possible. A linear regression model was fit by taking MIRs as a dependent variable and health system rankings as the independent variable.

RESULTS: The linear relationships between MIR and health system rankings for the five cancers were significant, with coefficients of determination ranging from 49% to 75% without outliers. A clear outlier, Korea reported lower-than-predicted MIRs for stomach and colorectal cancer, reflecting its strong national cancer control policies, especially on cancer screening, for these cancers.

CONCLUSIONS: MIR was found to be a practical measure for evaluating the long-term success of cancer surveillance and the efficacy of cancer control programs, especially cancer screening. Extending the use of MIRs to evaluate other cancers may also prove useful.

KEY WORDS: Neoplasms, Early Detection of Cancer, Incidence, Mortality, Delivery of Health Care
INTRODUCTION

Cancer is a leading cause of death in both more and less economically developed countries. In 2012, there were 14.1 million new cancer cases and 8.2 million cancer deaths worldwide; 57% (8 million) of new cancer cases and 65% (5.3 million) of cancer deaths occurred in less developed regions [1]. Due to the growth and aging of populations, cancer burden is expected to grow worldwide. The five most frequently observed cancers (lung, breast, colorectal, prostate, and stomach) in both sexes account for nearly half of all cancer cases. Lung and breast cancer are the most frequently diagnosed cancers, and the leading causes of cancer death in men and women, respectively, both overall and in less developed countries [2]. In general, cancer incidence rates are higher in more developed regions with longer life expectancies. Actually, incidence rates for all cancers combined are twice as high for more developed countries than for less developed countries. Meanwhile, however, mortality rates for all cancers are only 8% to 15% higher in more developed countries [2]. This disparity primarily reflects differences in cancer case mix, which is affected by risk factors and detection practices, and/or in the availability of treatment.

A substantial portion of cancer cases and deaths could be prevented by broadly applying effective prevention measures, such as tobacco control, vaccination, and the use of early detection tests. Thus, the implementation of cancer control programs has been recommended as a means to effectively reduce cancer incidence and mortality; national cancer control programs have been developed in several countries [3]. Nonetheless, assessing the long-term success and efficiency of these programs is essential. The mortality-to-incidence ratio (MIR) provides an alternative means to assess the burden of a disease by presenting mortality after accounting for incidence. In prior studies, MIR was found to be a simple and insightful measure of the efficacy of cancer control programs [4, 5]. The ratio identifies whether a
country has a higher or lower mortality, compared to its incidence. To determine the causes of
differences in mortality and incidence, other information should be gathered. Previously, the
MIR statistic has been used to demonstrate racial disparities in cancers [6], as well as to
examine relationships between health care systems and cancer outcomes in the U.S. [7] and
worldwide [8]. Recently, Vasu Sunkara demonstrated a strong association between MIRs for
colorectal cancer and health care systems [8]. The author suggested that MIR could be useful
as an indicator for identifying disparities in cancer screening and treatment internationally.

Therefore, in this study, we calculated MIRs for the five most common cancers for the 34
Organization for Economic Cooperation and Development (OECD) member countries in an
attempt to evaluate the outcomes of national cancer management policies according to the
performance of each country’s health systems. Only OECD member countries were chosen
because of their high quality health care-related data. In particular, this study aimed to assess
the outcomes of cancer control programs in Korea, as reflected by MIR, in comparison to
MIR values and health care system rankings across OECD countries. Also, we attempted to
identify factors that could potentially explain outliers in which MIRs were not well predicted
by regression models.
METHODS

Mortality and incidence rate data

Mortality and incidence rate data were derived from the GLOBOCAN 2012 database for all 34 OECD countries [1]. The GLOBOCAN database provides contemporary estimates of the incidence of, mortality and prevalence from major types of cancer, at national level, for 184 countries of the world. We collected age standardized rates per 100,000 population per year for lung, colorectum, prostate, stomach and breast, and calculated the MIRs thereof by dividing mortality rate by incidence rate. With GLOBOCAN data, it is recommended to report on the scope of the data sources and methods. Therein, the quality of data on incidence rate is graded from A (high quality) to G (no data), depending on the availability incidence data. For grade G country, GLOBOCAN estimate incidence rates using those of neighboring countries or registries in the same area [1]. Similarly, for mortality rate, data are scored from 1 (high quality, complete registration) to 6 (no data). In our data set of OECD countries, the mean grade of incidence rate data was grade B; only data for Greece and Hungary were given a grade of G. The mean score for availability of mortality data was 1.79 (from 1 to 6), with Mexico reporting the highest score of 5. Despite of poor quality of incidence or mortality data of Greece, Hungary, and Mexico, the methods used to estimate cancer incidence and mortality are well established and reported by the GLOBOCAN. Thus we included all these countries in the analysis to compare MIRs for the five most common cancers for the 34 OECD member countries. Further, the results are very similar, whether or not we contain the countries of poor quality of data (Mexico, Hungary & Greece) in the analysis.

Health system ranking

As an indicator of the quality of health systems, we adopted health system rankings
presented by the World Health Organization (WHO) in the year 2000 for 191 countries [9]. The health system ranking reflects five composite measures: overall health, health care financing, health inequality, health responsiveness, and distribution of health care services. Data for the five composite measures were derived from estimates for each country in 1997. Although the rankings have not been updated for a while due to criticisms about their efficacy [10], we valued the methodological framework and the thoroughness of the data with which the indicators were developed [11]. We decided to use the rankings after updating the composite measures when possible. Among the five composite measures, only overall health and health inequality were able to be updated. As overall health in the initial health ranking report was represented by health-adjusted life expectancy (HALE), we updated the measure with 2012 HALE data [12]. Health inequality was derived from calculations on child mortality [11]; therefore, we adopted 2011 OECD health data on child mortality. The other three measures of health care financing, health responsiveness, and distribution of health cancer services were not able to be updated due to inconsistencies in data availability for all OECD countries. Our updated version of the health system rankings reflected rankings similar to those originally reported, except for Austria, Portugal, Greece, Switzerland, Canada, Australia, New Zealand, and Korea.

Statistical analysis

A simple linear regression model was generated by taking MIR as a dependent variable and the updated health system rankings as independent variables. For the analysis, not exact values of each health system ranking for countries, but ranking number itself was used for the analysis, for previous literatures confirmed the linear association between MIR and health system ranking itself (8). The formula for this analysis was as follows: predicted MIR = health system ranking × beta + alpha. Then, divergent points were identified. Divergent
points were defined as countries whose residuals between their actual MIR and their predicted MIR determined by the regression model were greater or less than 0.07. After defining divergent points, we performed an additional simple linear regression analysis excluding divergent point countries. Statistical analyses were performed using STATA software (version 13; Stata Corp. L.P., College Station, TX), taking $p$-values less than 0.05 to indicate statistical significance.

**Ethical Issues**

This study was exempted from the institutional ethics review board, because it is not a human-subjects research and analyzed existing data.
RESULTS

Figures 1 to 5 depict scatter plots with predicted lines for lung, colorectal, prostate, stomach, and breast cancer. For all scatter plots, we detected significant linear relationships between MIR and the health system rankings with coefficients of determination ranging from 32% to 55%. These results demonstrated a positive association between lower health care system ranking (1-unit change) and higher MIR.

For lung cancer (Fig. 1), with every 1-unit change in health system ranking, there was a 0.004 increment rise in MIR. Eight countries were identified as divergent points in the lung cancer model: Slovak Republic, Czech Republic, United States, and Australia demonstrated lower MIRs than predicted, whereas Sweden, Italy, Chile, and Estonia showed higher MIRs. Figure 2 revealed a 0.007 incremental change in MIR for colorectal cancer with a 1-unit change in health system ranking. Divergent points for this model included Denmark, Iceland, Korea, and Belgium, all of which had lower MIRs, and Spain, Poland, Japan, Turkey, Chile, and Greece, which had higher MIRs. In the prostate cancer model, a 1-unit change in health system ranking generated an increase in MIR of 0.007 units (Fig. 3). The United States, Czech Republic, Ireland, Estonia, Finland, Israel, and Portugal had lower MIRs, while Chile, Japan, Mexico, Greece, and Turkey had higher MIRs than predicted in this model. For stomach cancer (Fig. 4), every 1-unit change in health system ranking led to an increase in MIR of 0.008 units. Its divergent points for a lower-than-predicted MIR were Korea, Denmark, the United States, Czech Republic, Luxembourg, Japan, Slovak Republic, and Estonia; higher-than-predicted MIRs were found for Spain, Turkey, Poland, Switzerland, Greece, Italy, Sweden, and Chile. Finally, for breast cancer, a 1-unit change in health system ranking increased MIR by 0.004 units. Among divergent points for breast cancer, Czech Republic exhibited a lower MIR, while Turkey, Chile, and Greece showed higher MIRs than
predicted. Table S1 to S5 present full data on the updated health system rankings, mortality rates, incidence rates, actual MIRs, predicted MIRs, and residuals, alphabetically sorted by country name.

To eliminate the effect of divergent points, we excluded countries with residuals between their actual MIR and their predicted MIR that were greater or less than 0.07. Table 1 lists the coefficients of determination for the original model and the additional model devised after eliminating the divergent points. The $R^2$ value of lung cancer from the original model was 0.3168 (meaning that 31% of the total variability in MIR for lung cancer was explained by the model), and it increased to 0.4898 after removing outliers. The $R^2$ value of colorectal cancer increased from 0.5523 to 0.6784; the $R^2$ value of prostate cancer increased from 0.4129 to 0.7486; the $R^2$ value of stomach cancer increased from 0.3990 to 0.7264; and the $R^2$ value of breast cancer increased from 0.5077 to 0.5538.
DISCUSSION

In the present study, we demonstrated a significant positive linear relationship between MIR and the updated health care system rankings. After removing divergent points, we detected substantial increases in the coefficients of determination for each cancer model, up to 0.7486 for prostate cancer, meaning 74% of the total variability in MIRs across countries was explained by the updated health care system rankings. In the lung cancer model, however, the coefficient of determination remained only at 0.4898. Despite improvements in cancer treatment, the overall survival of lung cancer remains around 20% [13]. Additionally, although lung cancer screening with low-dose computed tomography is now recommended in several guidelines, researchers have yet to alleviate concerns about the test’s sensitivity [14]. Therefore, differences in MIR for lung cancer among OECD countries might not be clearly explained by differences in health systems.

In the models for stomach and colorectal cancer, Korea was a clear divergent point, with much lower-than-predicted MIRs. While the average MIR among all OECD countries was 0.63 for stomach cancer, Korea reported an MIR of 0.31. In the colorectal model, Korea’s MIR was 0.23, compared to the average MIR of 0.38. We suspect that the low MIRs for Korea reflect the nation’s strong national cancer control policies. In Korea, cancer is responsible for one in every four deaths [15]. In an effort to reduce an increasing cancer burden, the Korean government has supported cancer screening via the National Cancer Screening Program (NCSP) for the Korean population since 2002. Via the NCSP, Medical Aid enrollees and the lower 50% of National Health Insurance (NHI) beneficiaries are eligible for free-of-charge screening for stomach, breast, cervix, liver, and colorectal cancer. The upper 50% of NHI beneficiaries are eligible for screening with a co-payment of 10% of the uptake cost. For detecting stomach cancer, eligible participations over the age of 40 years
are invited biennially to undergo screening via upper endoscopy or upper gastrointestinal series (UGI). The total screening rate for stomach cancer was 73.6% in 2013 [16]. For colorectal cancer, individuals over 50 years are annually invited to undergo initial mass screening with fecal occult blood test, and further examination with colonoscopy or double-contrast barium enema is provided for those with positive results. The screening rate for colorectal screening was 55.6% in 2013 [16]. According to our results, we suggest that the nationwide cancer screening program in Korea appears to be associated with an MIR below the regression-predicted MIR.

Similar implications are also applicable for other divergent points in the regression models. In Japan, stomach cancer is a serious burden, accounting for 14.2% of all cancer deaths [17]. To reduce the burden, Japan has also conducted stomach cancer screening with photofluorography as part of a national program. Under the national health policy for the prevention of chronic diseases, stomach cancer screening has been promoted by providing financial support for cancer screenings. In the present study, Japan showed a lower-than-predicted MIR for stomach cancer of 0.41. In contrast, the higher-than-predicted MIRs among divergent nations may stem from a lack of appropriate cancer control programs. For example, Chile, which also reports some of the highest incidences of stomach cancer, lacks screening guidelines for stomach cancer, though it has implemented a national integrated non-communicable disease policy and action plans [8]. Likewise for colorectal cancer, Denmark, Iceland, and Belgium, which showed lower-than-predicted MIRs therefore, all have formal screening recommendations for colorectal cancer in place [18]. Meanwhile, countries with higher-than-predicted MIRs were less likely to have formal screening recommendations or have lower screening rates for colorectal screening [8].

Unexpectedly, Korea was not classified as a divergent nation in the breast cancer model, though it has provided biennial breast cancer screening with mammography for all women
over 40 years under the NCSP. For breast cancer, the majority of OECD countries have conducted mammography screening with relatively high screening rates. In addition, treatment of breast cancer has improved greatly with the introduction of multidisciplinary breast cancer care units, lessening the benefits from mammography screening. Still, Korea reported a lower actual MIR of 0.11 for breast cancer than its predicted MIR of 0.15, which was also lower than the average MIR across OECD countries of 0.20.

The NCSP in Korea does not provide nationwide screening for lung and prostate cancer. Nevertheless, the nation still recorded an actual MIR for lung cancer of 0.74, lower than its predicted value of 0.76 and lower than the average value for all OECD countries of 0.80. This might be explained by Korea’s comparably high 5-year survival rates for lung cancer. In comparison, Korea had a 5-year survival rate for lung cancer of 20.7%, the United States 16.6%, Canada 17%, and Japan 29.7% [15, 19, 20]. For prostate cancer, Korea reported a higher actual MIR of 0.15 than the predicted value of 0.11. In comparison, the actual MIR for prostate cancer in the United States was 0.10, the lowest among all OECD countries. In the United States, prostate cancer is the most common cancer and the second leading cause of death among men, according to National Cancer Institute Statistics [21]. To reduce cancer burden, prostate cancer screening is recommended by the American Cancer Society under informed consent, although the US Preventive Services Task Force warns against prostate cancer screening due to its outweighed harms compared to its benefits. Nevertheless, the guidelines and screening for prostate cancer proposed by the American Cancer Society seem to have helped effectively control prostate cancer, as reflected by its low MIR [22].

Our study has several limitations that warrant consideration. First, our data focused completely on OECD countries, which generally have more sound health infrastructure. This, nevertheless, limits the generalization of our results for low-middle income countries lacking needed infrastructure. Second, there were inconsistencies in the data sources and methods for
determining cancer mortality and incidence rates from GLOBOCAN as described in the 
Methods section. Still, whether of inclusion or not inclusion of the limited quality of data in 
the analysis, we had consistent data results. Furthermore, updating data for the WHO 2000 
health system rankings was not fully achieved due to a lack of available data. Thus, our 
rankings may not exactly reflect the recent performances of each nation’s health care system. 

CONCLUSION

Herein, we found that lower MIR reflected the implementation of effective cancer control 
programs including cancer screening. In contrast, countries with higher-than-predicted MIRs 
often lacked proper health policies or recommendations for cancer control. For Korea, among 
the five cancers analyzed in this study, stomach and colorectal cancer had markedly lower 
MIRs, indicating effective cancer control, mainly as a result screening offered via the NCSP. 
Despite finding MIR to be an efficient and useful indicator of cancer control outcomes, 
studies on mortality rate reductions are required to confirm the effectiveness of cancer control. 
Notwithstanding, we favor extending the use of MIR for other cancers to assess the long term 
success of cancer screening programs thereof.
ACKNOWLEDGEMENTS

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CONFLICTS OF INTEREST

Conflicts of interest relevant to this article were not reported.

Supplementary material:

Table S1. Raw data and regression results for lung cancer based on mortality-to-incidence ratios for all OECD countries

Table S2. Raw data and regression results for colorectal cancer based on mortality-to-incidence ratios for all OECD countries

Table S3. Raw data and regression results for prostate cancer based on mortality-to-incidence ratios for all OECD countries

Table S4. Raw data and regression results for stomach cancer based on mortality-to-incidence ratios for all OECD countries

Table S5. Raw data and regression results for breast cancer based on mortality-to-incidence ratios for all OECD countries
References


Figure 1. Mortality-to-incidence ratio (MIR) for lung cancer versus health system ranking for all 34 OECD countries
Figure 2. Mortality-to-incidence ratio (MIR) for colorectal cancer versus health system ranking for all 34 OECD countries
Figure 3. Mortality-to-incidence ratio (MIR) for prostate cancer versus health system ranking for all 34 OECD countries
Figure 4. Mortality-to-incidence ratio (MIR) for stomach cancer versus health system ranking for all 34 OECD countries
Figure 5. Mortality-to-incidence ratio (MIR) for breast cancer versus health system ranking for all 34 OECD countries
Table 1. Coefficients of determination before and after removing outliers

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>$R^2$ in original models</th>
<th>$R^2$ without outliers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>0.3168</td>
<td>0.4898</td>
</tr>
<tr>
<td>Colorectum</td>
<td>0.5523</td>
<td>0.6784</td>
</tr>
<tr>
<td>Prostate</td>
<td>0.4129</td>
<td>0.7486</td>
</tr>
<tr>
<td>Stomach</td>
<td>0.399</td>
<td>0.7264</td>
</tr>
<tr>
<td>Breast</td>
<td>0.5077</td>
<td>0.5538</td>
</tr>
</tbody>
</table>
Figure 1. Mortality-to-incidence ratio (MIR) for lung cancer versus health system ranking for all 34 OECD countries

$y = 0.0037x + 0.7397$

R-squared = 0.3168
Figure 2. Mortality-to-incidence ratio (MIR) for colorectal cancer versus health system ranking for all 34 OECD countries.

Colorectal Cancer

\[ y = 0.0068x + 0.2658 \]

R-squared = 0.5523
Figure 3. Mortality-to-incidence ratio (MIR) for prostate cancer versus health system ranking for all 34 OECD countries.

Prostate Cancer

y = 0.0073x + 0.6320
R-squared = 0.4129
Figure 4. Mortality-to-incidence ratio (MIR) for stomach cancer versus health system ranking for all 34 OECD countries.
Figure 5. Mortality-to-incidence ratio (MIR) for breast cancer versus health system ranking for all 34 OECD countries.

\[ y = 0.0041x + 0.2658 \]

R-squared = 0.5077