



TRENDS OF NON-HODGKIN LYMPHOMA CANCER DEATH RATES WITH ADJUSTING THE EFFECT OF THE HUMAN DEVELOPMENT INDEX: THE GLOBAL ASSESSMENT IN 1990-2015

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Abstract – Objective: The transition of the countries to higher levels of Human Development Index (HDI) can affect the trend of cancer deaths. In recent years, Non-Hodgkin Lymphoma (NHL) cancer death has increased compared with death caused by all other cancers. The aim of this study was to investigate the association between NHL cancer death rates and HDI. Furthermore, the trend of NHL cancer death rates has been clustered with considering the effect of HDI during 1990-2015.

Materials and Methods: The data of NHL cancer death rates of 188 countries were obtained from the Global Burden of Disease's database between the years 1990-2015 (in 5-year intervals). First, the relationship between HDI and cancer death rates was assessed using the correlation coefficient. Then, the linear mixed model with a discrete random intercept was used to cluster the trends of death rates.

Results: There was a significant correlation between NHL cancer death rates and HDI during 1990-2005 (0.228, 0.274, 0.245, and 0.154, respectively). Three groups of death rates' trends were observed. Group 1 with lowest death rates includes countries with low death rates as well as low/moderate HDI. Countries with death rates similar to world's average and high/very high HDI have been clustered in group 2. Countries in Group 3 with the highest death rates had low/medium HDI with high death rates.

Conclusions: The strength of the relationship between NHL cancer death rates and HDI decreased after 1995, so that this relationship was no longer significant between the years 2010 and 2015. According to the results of clustering, most of the countries with low/medium HDI had a slowly increasing trend of NHL cancer death rates.

KEYWORDS: Death rates, Cancer, Non-Hodgkin Lymphoma, Trends, HDI, Clustering.

INTRODUCTION

Over the last few years, the incidence and prevalence of death due to cancer have increased worldwide¹. Therefore, cancer is one of the major public health problems in many countries². The lymphomas represent a heterogeneous group of disorders and account for up to 3% of all malignancies³. Non-Hodgkin Lymphoma (NHL) with various clinical and biolog-

ical features is derived from lymphoid tissue⁴. NHL was the 13th and 11th leading cause of death among all deaths due to cancers in years 2012 and 2015, respectively^{5,6}. Also, there were 386000 new cases (2.7% of all cancers) of NHL and 200000 deaths (2.4% of all deaths) from NHL worldwide in 2012⁵.

The incidence of NHL and death due to this cancer vary across geographic regions^{7,8}. The age-standardized rates (ASRs) of incidence were



the highest in North America (ASR 14.6 and 10.2 per 100000 in men and women, respectively) and in Australia/New Zealand (14.3 and 10.1). The lowest rates were estimated in South-Central Asia (3.3 in males and 1.8 in females) and Western Africa (3.7 and 2.5)^{5,6}. Also, ASRs of death were the highest in Northern Africa (5.4 and 3.7) and Western Asia (4.9 and 3.3). The lowest death rates were observed in South-Central Asia (3.3 in males and 1.8 in females), Eastern Asia (2.3 and 1.4) and Central America (2.40 and 1.90)⁵.

The highly unequal distribution of cancer risk factors in the world can cause differences in cancer incidence and death in diverse geographic regions. Development of countries is one of the risk factors for increasing or decreasing the incidence and death rate of cancer⁹. The Human Development Index (HDI) is one of the indicators associated with the development of countries. This index, which ranges from zero to one, is a composite of life expectancy, education, and income indices. Some studies have examined the association of HDI with the incidence and death rates of cancers such as brain and central nervous system¹⁰, pancreatic¹¹, kidney¹², prostate¹³, breast^{14,15}, ovarian¹⁶ and bladder¹⁷. The death rates due to some of these cancers were significantly different in more and less developed countries¹⁸.

Although the HDI is a predictor for the socioeconomic level of different countries, it is obvious that it may not explain the total differences between death rates of different countries. In addition to the geographical impact, factors such as sex, age, and race can affect the death rates due to cancer^{6,19-21}. On the other hand, we know that all effective factors across countries are not identifiable or even measurable. Therefore, a suitable statistical analysis is needed to consider the heterogeneity (intrinsic differences) among countries in assessing the rate of death through adjusting the effect of HDI. One of the common approaches is the linear mixed regression model²². Differences in death rates of countries can be due to the existence of groups with different trends of death rates. To achieve this goal, it is suitable to use the linear mixed model with discrete random intercept^{23,24}.

The trend and grouping the trends of NHL cancer death rates in different countries and their relationships with HDI have not been reported yet. Using death rates data from the Global Burden of Disease study (GBD) database, this study was conducted in order to evaluate the relationship between the trends of death rates due to NHL cancer and HDI. We also used the linear mixed model with a discrete random intercept to classify countries according to their NHL cancer death rates from 1990 to 2015 and assess the effect of HDI on NHL cancer death rates of each group.

MATERIAL AND METHODS

OUTCOME VARIABLE

Death rates of NHL cancer were obtained from the GBD database²⁵. The information includes age-standardized death rates (per 100000 populations) of NHL cancer in 188 countries from 1990 to 2015 (in 5-year intervals).

INDEPENDENT VARIABLE

The HDI data were extracted from the United Nations Development Program (UNDP) website for the same time intervals with cancer death rates (<http://hdr.undp.org/en/data/#>) that contains information about HDI for countries between years 1990-2017. The HDI values were classified into four categories: low (HDI less than 0.550), medium (HDI of 0.550–0.699), high (HDI of 0.700–0.799), and very high (HDI greater than 0.800).

STATISTICAL ANALYSIS

Firstly, the prevalence of HDI from 1990 to 2015 has been reported. In addition, the mean (SD) of NHL cancer death rates was presented across HDI categories and six different time points. Pearson correlation coefficient was used to evaluate the relationship between NHL cancer death rates and HDI. Also, the linear mixed model with the discrete random intercept was fitted for grouping trends of death rates with adjusting the effect of HDI²³.

In this model, random intercept is assumed to have k possible values with some probability π_i , where $\sum_{i=1}^k \pi_i = 1$ for $i=1, \dots, k$. Suppose $y_{j,t}$ denotes the death rate for country j ($j=1, \dots, 188$) at time t ($t=1, 2, \dots, 6$). The following linear mixed model was considered for the vector $y_j = (y_{j,1}, \dots, y_{j,6})^T$:

$$y_j = \theta_{i_0} + \theta_{i_1} \text{Medium HDI}_j + \theta_{i_2} \text{High HDI}_j + \theta_{i_3} \text{Very high HDI}_j + \varepsilon_{ij}$$

with random intercept θ_{i_0} , varying regression coefficients $\theta_{i_1}, \theta_{i_2}$ and θ_{i_3} across groups and multivariate normal residuals $\varepsilon_{ij} \sim (0, \Phi_i)$ that have varying temporal variance-covariance matrix across groups. The temporal matrix was modeled by generalized autoregressive process with order m ($m = 0, 1, \dots, T - 1$) which is equivalent to the modified Cholesky decomposition, $\Phi_i^{-1} = U_i^T D_i^{-1} U_i$. By considering homoscedastic or varying quantities of Φ_i across the groups, different sub-models can be defined as: VVA ($\Phi_i^{-1} = U_i^T D_i^{-1} U_i$), VEA ($U_i^T D_i^{-1} U_i$), EVA ($U_i^T D_i^{-1} U_i$), EEA ($U_i^T D_i^{-1} U_i$), VVI ($1/d_i U_i^T U_i$), VEI ($1/d_i U_i^T U_i$), EVI ($1/d_i U_i^T U_i$), and EEI ($1/d_i U_i^T U_i$). For more details please refer to McNicholas et al²⁴.

For determining the best sub-model and the number of groups, the Bayesian Information Criteria (BIC) was calculated^{23,24}. Thus, the sub-model with minimum value of BIC was the best choice. R software was used for fitting the different sub-models.

TABLE 1. Frequency distribution of countries by HDI from 1990 to 2015 years.

HDI	Years					
	1990	1995	2000	2005	2010	2015
Low	74 (39.4)	68 (36.2)	61 (32.4)	55 (29.3)	50 (26.6)	42 (22.2)
Medium	63 (33.5)	71 (37.8)	65 (34.6)	54 (28.7)	37 (19.7)	41 (21.8)
High	40 (21.3)	28 (14.9)	31 (16.5)	40 (21.3)	54 (28.7)	54 (28.7)
Very High	11 (5.9)	21 (11.2)	31 (16.5)	39 (20.7)	47 (25.0)	51 (27.1)

TABLE 2. Mean (SD) NHL cancer death rates for different HDI categories from 1990 to 2015.

HDI	Years					
	1990	1995	2000	2005	2010	2015
Low	3.36 (1.28)	3.53 (1.36)	3.76 (1.50)	3.86 (1.62)	3.99 (1.67)	4.12 (1.72)
Medium	3.36 (1.61)	3.32 (1.55)	3.35 (1.73)	3.23 (1.31)	3.07 (1.05)	3.31 (1.30)
High	3.90 (1.43)	4.04 (1.29)	4.06 (1.16)	4.08 (2.11)	3.79 (1.96)	3.78 (1.96)
Very High	5.59 (1.11)	5.74 (1.04)	5.17 (1.34)	4.60 (1.16)	4.32 (0.99)	4.14 (1.03)
Total	3.61 (1.51)	3.77 (1.57)	3.90 (1.62)	3.88 (1.64)	3.84 (1.57)	3.85 (1.58)

ETHICS REVIEW

This study was approved by the Research Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (Approval Code: IR.SBMU.RETECH.REC1397.653).

RESULTS

Generally, 188 countries in the years 1990, 1995, 2000, 2005, 2010, and 2015 were studied. Table 1 shows the distribution of the frequency of HDI during the years in the study. As can be observed, countries' human development status has improved over time, which means the number of countries with low/medium HDI, decreased during these times (from 73% in 1990 to 24% in 2015). In contrast, the number of countries with high/very high HDI increased (from 27% in 1990 to 76% in 2015).

The mean of NHL cancer death rates was shown in Table 2. The death rates due to NHL cancer had a decreasing trend from 2005 to 2015 after an increasing trend from 1990 to 2000. In order to assess the effect of HDI on cancer death rates, we calculated the mean of NHL cancer death rates for different HDI categories (Table 2). Countries with medium and very high HDI had the lowest and highest mean cancer death rates, respectively. Correlation coefficients between HDI values and death rates were 0.228, 0.274, 0.245, 0.154, 0.089, and 0.039 from 1990 to 2015, respectively. This relationship was significant from 1990 to 2005.

For grouping the trend of death rates, considering the effect of HDI, the linear mixed model with the discrete random intercept was fitted for eight dif-

ferent temporal variance-covariance structures with different number of groups and different orders (the results were not shown here). The best fit of NHL cancer death rates data according to the BIC was VVA temporal structure with order 2 and 3 groups. The selected temporal pattern shows that the correlation structure between death rates at different time points, as well as the variability of these rates at each time point, was different in each group. According to the order 2 of temporal correlation, it can be said that the death rate at any time point depends on the death rate at the two previous time points.

Figure 1 gives a visual representation of the group means for NHL cancer death rates over time. The lowest and highest death rates were observed in groups 1 and 3, respectively, and countries of group 2 had an intermediate position comparing to others. Countries in group 1 had a slowly increasing trend.

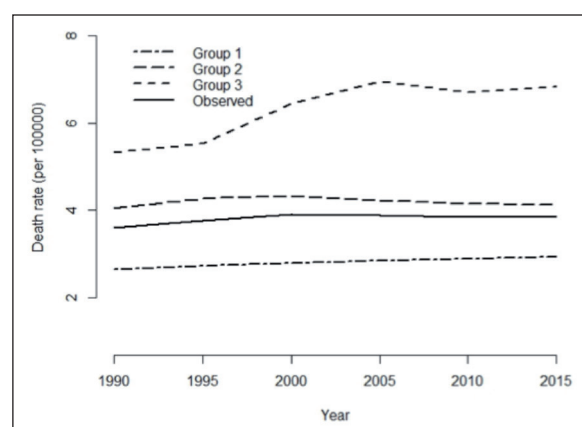


Fig. 1. Mean plot NHL cancer death rates according to group memberships.

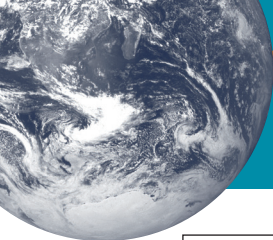


Fig. 2. Mapping of NHL cancer death rates from 188 countries based on results from fitting the linear mixed model with the discrete random intercept.

Group 2 included countries with a decreasing trend between years 1995-2015 after an increasing trend. Countries in group 3 had a sharp increasing trend (with the exception in 2010). Countries included in all three groups are mapped in Figure 2.

Table 3 contains the regression coefficient estimates. As shown, the HDI had a significant effect on NHL cancer death rates in groups 1 and 3. In group 1, the mean of death rates in countries with very high HDI were less than the mean of death rates in countries with low HDI ($p = 0.022$). Also, in group 3, the mean of death rates in countries with medium, high or very high HDI were less than the mean of death rates in countries with low HDI ($p = 0.001$, $p < 0.001$, and $p < 0.001$, respectively). Thus, in each group, the effect of HDI on death rates was relatively different.

For further insight, the HDI frequency distribution of each group was represented in Figure 3. Countries of group 1 had the lowest prevalence rate of high/very high HDI comparing to low/medium HDI categories. Also, the highest prevalence rate of high/very high HDI was shown in countries of group 2. Most countries in group 3 had low/medium HDI.

For describing general countries' status in each group, the frequency distributions of different groups were presented separately considering seven different super-regions GBD: Southeast Asia, East Asia, and Oceania; Central Europe, Eastern Europe, and Central Asia; High-income; Latin America and Caribbean; North Africa and Middle East; South Asia and Sub-Saharan Africa (Table 4). Most of the countries of Sub-Saharan Africa and South Asia were in group 1 and all the countries of High Income region were in group 2. Group 3 includes only a few countries from the Latin America and Caribbean, North Africa and Middle East and Sub-Saharan Africa regions.

DISCUSSION

Cancer is one of the most important health issues in the world. Due to the rapid growth of population and aging, the importance of study on cancers is increasing tremendously. Moreover, the progress of HDI to higher levels leads to changes in people's lifestyle. These changes can have a profound impact on can-

TABLE 3. Regression coefficient estimates and standard errors (S.E) of the model for NHL cancer death rates in each group.

HDI	Group 1			Group 2			Group 3		
	Estimates	S.E	p-value	Estimates	S.E	p-value	Estimates	S.E	p-value
Low	0	—	—	0	—	—	0	—	—
Medium	-0.008	0.031	0.795	0.004	0.082	0.959	-0.263	0.081	0.001
High	-0.039	0.045	0.392	-0.008	0.116	0.942	-0.455	0.133	<0.001
Very High	-0.060	0.026	0.022	0.023	0.233	0.921	-0.473	0.126	<0.001

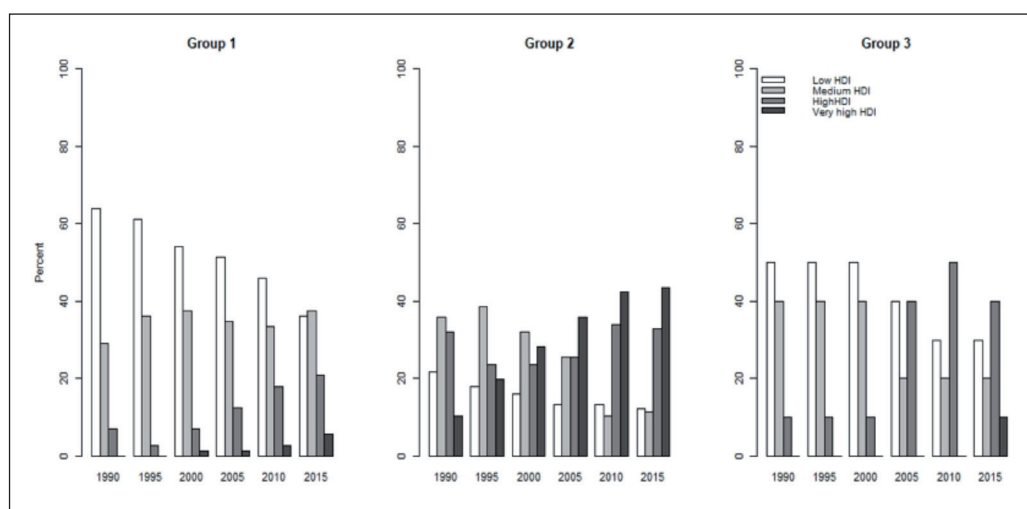


Fig. 3. Frequency distributions of HDI over time given group membership in NHL cancer death rates.

cer-related incidence and death²⁶. The proportion of death due to NHL cancer is increasing among all deaths due to cancers^{5,6}. Therefore, the aim of this study was to investigate the relation between the NHL cancer death rates and the country's HDI from 1990 to 2015, and also to cluster these death rates with adjusting the HDI effect.

The estimation of the global mortality rate due to NHL obtained from the GBD database showed that between years 1990 and 2000 there was an increasing trend (3.46, 3.66, 3.69, respectively per 100000 populations), and then from 2005 to 2015, there had been a decreasing trend (3.49, 3.53 and 3.36)²⁵. These numbers indicate stable death rates after 2005. Cancer death rates of different countries varied according to their socioeconomic status, which is determined through HDI. Therefore, countries with higher level of HDI between the years 1990 to 1995 had an increasing trend and then had a decreasing trend between 2000 and 2015, and countries with low HDI had an increasing trend from 1990 to 2015. In this study, there was a significant and direct correlation between the mortality rate and HDI from 1990 to 2005. The intensity of correlation declined from 1995 onward, so that the correlation between

2010 and 2015 was not significant. In other words, in the last decade, countries' HDI status did not indicate NHL cancer death rates.

In a study conducted in 2017, the association of the socio-demographic index with the incidence and mortality of 27 different types of cancers was examined using the data of GBD database. This index is a combination of *pro capita* income, education level, and fertility, which varies from zero to one. Value 1 represents the highest level of *pro capita* income and education and the lowest fertility rate. NHL in countries with high and low SDI was ranked 9th and 11th, respectively, among 27 different types of cancers. Thus, it can be concluded that with the improvement of the socioeconomic status, the death rate of this cancer increases, which is consistent with the results of our study²⁶.

In 2018, Khodamoradi et al²⁷ examined the association between Hodgkin lymphoma death rates and HDI and its components using data obtained from the Global Cancer Project database (2012). They concluded that ASR of death in countries with higher HDI was lower than that of countries with lower HDI. Therefore, the association between the Hodgkin lymphoma death rate and HDI was in contrast with the association between NHL and HDI.

TABLE 4. Frequency distribution of groups' of NHL cancer death rates considering seven different super-regions GBD.

Super-regions GBD	Group 1	Group 2	Group 3
Central Europe, Eastern Europe, and Central Asia	10 (13.9)	19 (17.9)	0 (0)
High Income	0 (0)	33 (31.1)	0 (0)
Latin America and Caribbean	7 (9.7)	19 (17.9)	3 (30)
North Africa and Middle East	8 (11.1)	10 (9.4)	3 (30)
South Asia	4 (5.5)	1 (0.9)	0 (0)
Sub-Saharan Africa	28 (38.9)	14 (13.2)	4 (40)
Southeast Asia, East Asia, and Oceania	15 (20.8)	10 (9.4)	0 (0)
Total	72 (100)	106 (100)	10 (100)



The relationship between death rate due to different cancers and HDI has been investigated in several studies. It has been shown that the death rates due to brain, nervous system¹⁰, breast^{14,15} and pancreatic cancers¹¹ are positively correlated with HDI. However, a negative and significant correlation between the death rate due to kidney cancer¹² and prostate cancer¹³ with HDI was observed. Moreover, there was no significant relation between the death rate due to ovarian¹⁶ and bladder cancers¹⁷ with HDI. In all of these studies, these relationships have been studied at a specific time point, so the trend of changes was not evaluated over the years.

Some studies^{28,29} have examined the relationship between death due to NHL and proximity to industrial areas and exposure to chemical substances and industrial solvents. Ramis et al³⁰ investigated the association between death due to NHL and industrial pollution such as energy, metal, mineral, organic chemicals waste, paper, food, and use of solvents in Spain. The results showed that there was an increased risk of death due to NHL among populations adjacent to the contamination caused by the paper and pulp industries. In another study in Brazil, there was a significant correlation between the death rate and the use of pesticides³¹. Hence, industrial and chemical pollution may be a reason for high death rates in countries with very high HDI.

The death rate due to NHL varied in different countries, and can be justified by their HDI status. It is clear that the HDI status does not explain all differences between death rates. The linear mixed regression model with the discrete random intercept is a suitable approach to deal with this heterogeneity^{23,24}. Through this approach, countries are placed in homogeneous groups with the same trend. The results showed that there were three groups of death rates due to NHL cancer between 1990 and 2015.

Group 1, which includes mostly Sub-Saharan Africa and Southeast Asia, East Asia, and Oceania, had a very slow progress throughout the study period. Many of these countries had low/medium HDI and very few had high/very high HDI. In other words, this group includes countries with low death rates as well as low/moderate HDI between 1990 and 2015. Moreover, there were countries in this group with high/very high HDI that had lower death rates in comparison to other countries with similar HDI. Thus, in this group, death rates in countries with high HDI were lower than those with low HDI, which was significant.

The second group includes countries with the similar death rates to the global average. All High Income countries and more than 2/3 of Central Europe, Eastern Europe, Central Asia, and Latin America and Caribbean were in this group. As shown in Figure 2, this group mostly includes countries with high/very

high HDI. In addition, there was no significant difference between the mean death rates of countries with different HDI. Countries in Group 3 had often low/medium HDI with high death rates. These countries had an increasing trend from 1990 to 2015, with the exception in 2010. Countries with low HDI in this group had higher mean death rates than other countries, and these differences were significant.

CONCLUSIONS

The results of grouping of NHL cancer death rates showed that death rates of countries that are in transition to the higher levels of human development were increasing, and more developed countries had a declining trend in recent years, despite having a higher death rate. Therefore, the epidemiology of this cancer should be investigated in developing countries. Also, in future studies, the investigation of association between death rates due to NHL cancer and other indicators such as social exclusion index, urbanization percent, gender ratio, healthcare system indicators, and pollution index is suggested. Mortality-to-incidence can also be used instead of death rates.

CONFLICT OF INTEREST

The authors declare no conflict of interest

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