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Global Trends In Cancer Burden Based On Geographic Location, Socio-Economic Status And Demographic Shift

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GLOBAL TRENDS IN CANCER BURDEN BASED ON GEOGRAPHIC LOCATION, SOCIO-ECONOMIC STATUS AND DEMOGRAPHIC SHIFT

by

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The global burden of cancer is rising at an alarming rate. It remains as one of the top causes of morbidity and mortality worldwide. It is predicted that within 2020, there will be 15 million new cases of cancer in the world, with cancer-related deaths increasing to 12 million. According to the World Health Organization (WHO), the global cancer burden is expected to surge 57% worldwide in the next 20 years. A significant rise in cancer burden will occur in the low-income and middle-income (developing) countries not only due to demographic shifts, but also by the transition of risk factors due to globalization of economies and behavioral patterns mirroring high-income economies (developed countries). The rise in global cancer burden and the urgency to fight against cancer has lead to cancer control being termed as a “global health priority. This alarming rise in cancer burden will require a renewed attention for control, prevention and early detection of cancer that can complement the improved treatments. The understanding of the global trends and regional and socio-economic variations of cancer incidence and mortality would help global health workforce design strategies for prevention, early detection and develop unified global and region-specific plans to coordinate and improve health care environment and patient health.

To

Aparajita, Anisha and Arjun

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Most importantly, none of this would have been possible without the love and patience of my family. My wife, to whom this thesis is dedicated to, has been a constant source of love, support and strength all these years. Her aid in raising our children Anisha and Arjun was fundamental for the completion of my research. Finally, my special thanks to the persons whom I owe everything I am today, my parents Lakshmi and Bikash Chowdhury and my brother Chandan.

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Chapter I

INTRODUCTION

An overview of global cancer burden as a global health priority

According to the World Health Organization (WHO), the global cancer burden is expected to surge 57% worldwide in the next 20 years. This alarming rise in cancer burden will require a renewed attention for control, prevention and early detection of cancer that can complement the improved treatments. The rise in global cancer burden and the urgency to fight against cancer has lead to cancer control being termed as a "global health priority". [1-5]

The total number of deaths associated with cancer reached 8 million in 2010, which correlates to about 15% of all deaths worldwide.[6] It has been estimated that 33% to 50% of cancers can be prevented through control or avoidance of known risk factors.[7] Additionally, a significant proportion of the remaining 50% of cancer related deaths could be prevented through early detection and effective treatment strategies. Therefore as noted by Drs. Ilbawi and Anderson[2], it is critical to prioritize cancer interventions in the global health agenda in which non-communicable diseases (NCDs) including cancer receive less than 3% of the total donor development assistance for health ($503 Million out of $22 Billion per year).[2] Epidemiological data obtained from developed (higher-income) countries indicate that the prevention and early detection programs have been somewhat successful at decreasing cancer deaths.[8] However, the real challenge and difficulty has been the translation of these prevention and early detection programs to less developed (low-and middle-income) countries. Some of the major hurdles faced in these countries include less effective health care system and lack of cancer awareness, competing health priorities, use of carcinogens, low funding for health care reforms and limited health care workforce with specialized training.[9] In the less developed nations, 65% of the cancer-related deaths occur annually, however the global health resources directed towards these countries constitute only about 5%.

Global heath priority of cancer control is designed towards three primary goals: i) prevention of preventable cancer ii) cure of curable cancer and iii) palliate cancers for which prevention and/or cure is not achieved.[2] Cancer affects all regions and communities worldwide. However, the prevalence and type of cancer shows marked variation among communities. As discussed above, the total burden of cancer remains highest in the affluent countries, but the low-and middle-income countries are narrowing that gap at a very rapid pace. As the low-and middle-income countries succeed in attaining the lifestyle of higher-income countries, they will face with increased cancer burden.

It is important for global health workforce to understand the global burden of cancer. Several factors lead to the "globalization" of cancer.[10] The rapid aging of population is increasing the cancer burden. Other critical factors include diet, tobacco and use of harmful substances and infectious agents. The understanding of the global trends and regional and socio-economic variations would help global health leadership design strategies for prevention, early detection and develop unified global and region-specific strategies to coordinate and improve health care environment and patient health. The Human Development Index (HDI) is an important classifier for the globalization of cancer.[11] The HDI takes into account education, life expectancy and national income to categories countries into one of four levels of human development: low, medium, high and very high. It is well known that the communicable diseases and nutrition related disorders are still the most common causes of death in low-HDI countries. However, the projections are that NCDs, including cancer, will overtake the communicable diseases and nutrition related diseases by 2030.[12] The projected increase in global cancer burden—from 12·7 million new cases in 2008, to 22·2 million by 2030 —indicates population growth and an evolving age distribution together with other important changes in underlying incidence, allied to the prevalence and distribution of risk factors.

The key points related to the global cancer burden is highlighted below:

- In 2012, there were >14 million new cancer cases and >8 million cancer deaths. Figures 1, 2 and 3 shows the worldwide distribution of incidence, mortality and prevalence of cancer. Table 1 lists the global cancer burden with the current incidence and mortality rates for all cancers across the world. Table 2a,b shows the global burden of different cancers for both sexes, all ages combined. Table 3 shows the global cancer burden (incidence and mortality) for all cancers across the world and the more developed and less developed regions of the world. It is observed that the more developed regions have higher cancer burden compared to less developed regions.
- For women, breast cancer was the leading cancer globally and in developed and developing countries.
- For men, lung cancer was the leading cancer globally and in developed and developing countries.
- For men, incident cases have increased the most for prostate cancer at the global setting and in developed and developing countries.
- For women at the global level, incident cases have increased the most for non-Hodgkin lymphoma; in developed countries, incident cases have increased the most for kidney cancer; in developing countries, incident cases have increased the most for breast cancer.
- More developed regions have higher incidence of cancer compared to less developed regions.

In the following chapters, we will discuss prediction or time trends in pancreatic and liver cancer with respect to geographic locations; socio-economic status and demographic shift using the well-defined predictions from GLOBOCAN 2012 across geographical and socio-economical divide. Pancreatic cancer (PC) is a lethal malignancy that accounts for about 4% of cancer-related deaths in both males and females worldwide.[13-24] In the United States, PC accounts for about 2.7% of all new cancer cases and is projected to become the second largest cause of cancer-related deaths by 2030.[25] Liver cancer (LC) is fast developing into a global medical crisis[26]. Historically, LC has been most prevalent in the developing regions of Southeast Asia and Africa. This high burden of LC in these developing regions has been mainly attributed to Hepatitis B virus (HBV) and exposure to aflotoxin[27]. However, in recent years, developed Western countries have witnessed an alarming rise in LC partly due to increased Hepatitis C virus (HCV) infection and non-communicable diseases (NCD) associated with alcohol use and non-alcoholic steatohepatitis (NASH)[26]. LC is the fifth most common cancer and the third leading cause of cancer-related deaths globally[26,27]. Although the trends in the incidence and mortality of PC and LC are well studied in the United States and some Western European countries, the same cannot be said for the rest of the world. There are few publications on PC and LC originating from regions of low incidence or resource-poor areas of the world.[28] Similarly, there is a scarcity of reports describing the overall global trends in the incidence and mortality of PC and LC across all regions of the world and encompassing all strata of socio-economic development.

Conclusion:

Prediction and time trends of the number of cases of incidence and mortality is quite relevant for health care planning purposes and allocation of available resources. The demographic shift towards elder age groups worldwide and select geographic regions over the next two decades is likely to contribute to an increase in cancer burden for many cancer sites.

Figure 1: Worldwide age-adjusted Incidence for all cancer excluding non-melanoma skin cancer for both sexes

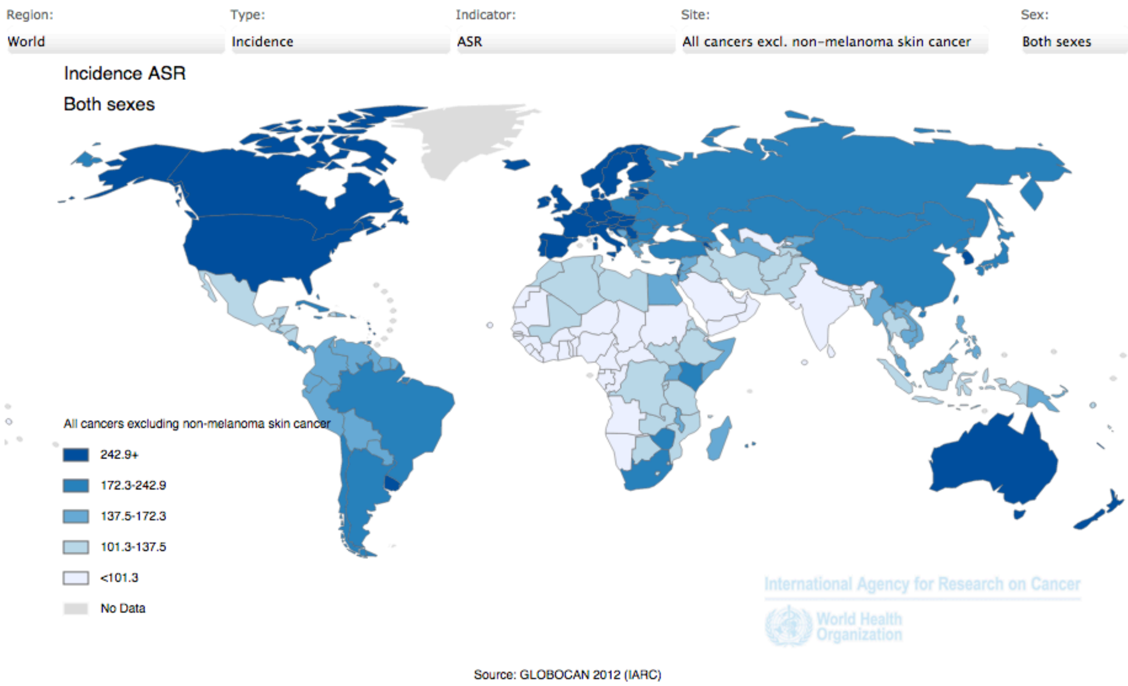


Figure 2: Worldwide age-adjusted mortality for all cancer excluding non-melanoma skin cancer for both sexes

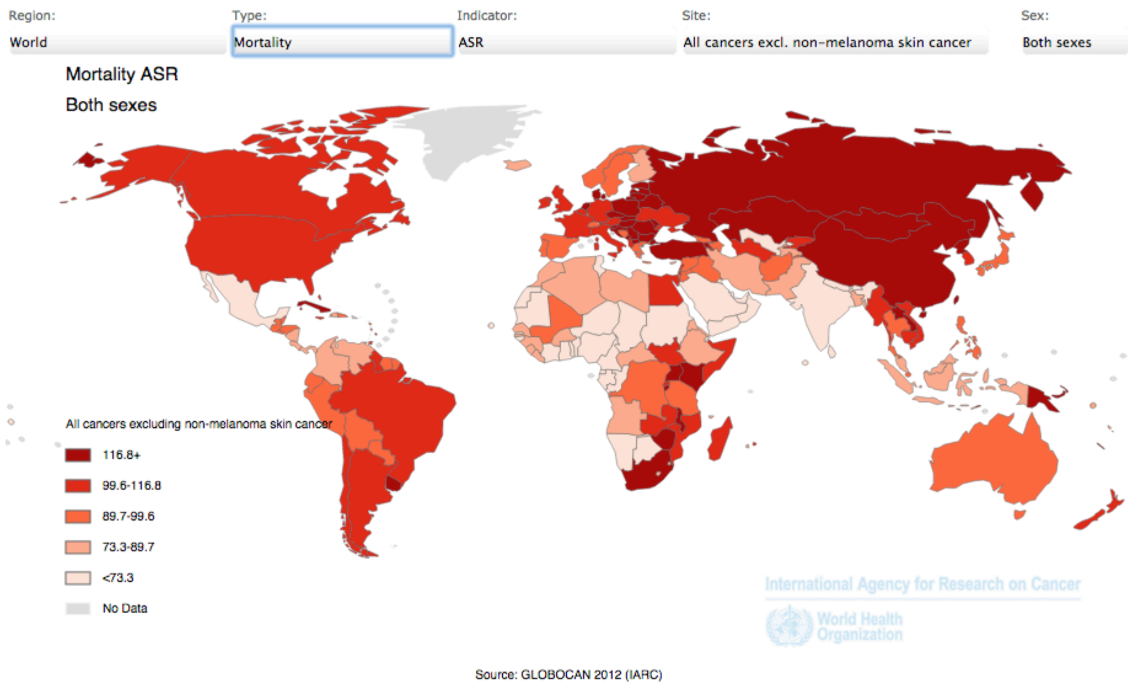


Figure 3: Worldwide age-adjusted prevalence for all cancer excluding non-melanoma skin cancer for both sexes

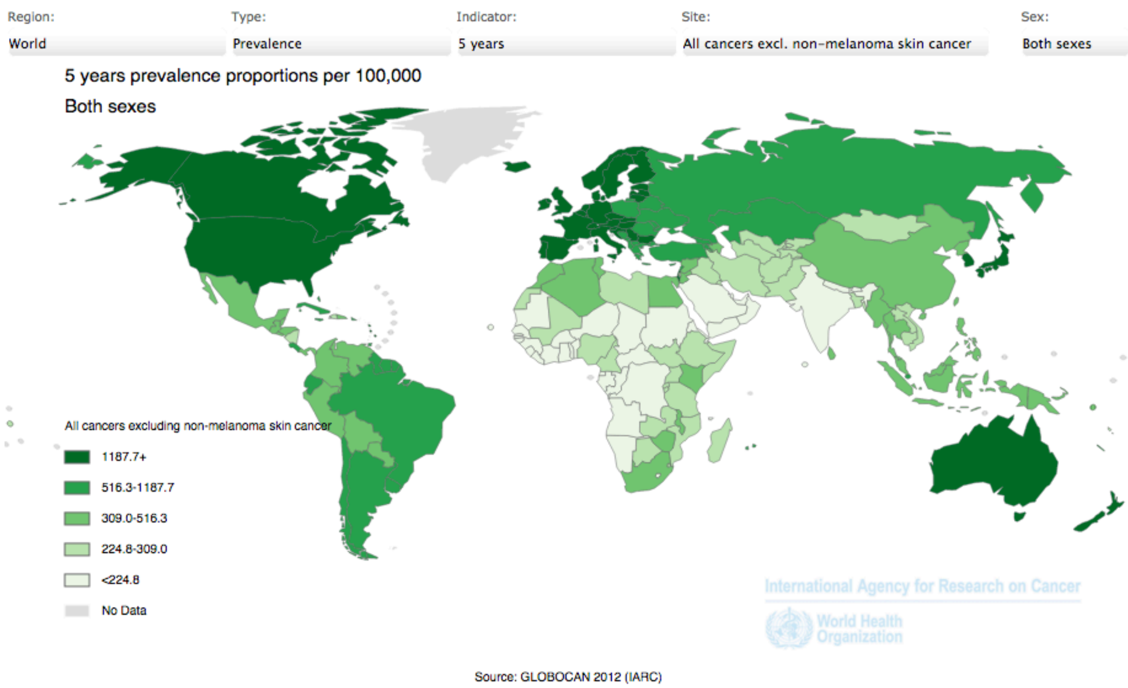


Table 1 below shows the global cancer burden with the current incidence and mortality rates for all cancers across the world.

Summary statistics (2012)

WORLD	Male	Female	Both sexes
Population (thousands)	3557717	3496728	7054446
Number of new cancer cases (thousands)	7410.4	6657.5	14067.9
Age-standardised rate (W)	204.9	165.2	182.0
Risk of getting cancer before age 75 (%)	21.0	16.4	18.5
Number of cancer deaths (thousands)	4653.4	3548.2	8201.6
Age-standardised rate (W)	126.3	82.9	102.4
Risk of dying from cancer before age 75 (%)	12.7	8.4	10.5
5-year prevalent cases, adult population (thousands)	15296.1	17159.1	32455.2
Proportion (per 100,000)	589.4	660.5	625.0
5 most frequent cancers (ranking defined by total number of cases)			
	Lung	Breast	Lung
	Prostate	Colorectum	Breast
	Colorectum	Lung	Colorectum
	Stomach	Cervix uteri	Prostate
	Liver	Stomach	Stomach

Data sources and methods

Incidence

Method: Population weighted average of the area-specific rates applied to the 2012 area population.

Mortality

Method: Population weighted average of the area-specific rates applied to the 2012 area population.

Prevalence

Sum of area-specific prevalent cases

Glossary

Age-standardised rate (W):
A rate is the number of new cases or deaths per 100 000 persons per year. An age-standardised rate is the rate that a population would have if it had a standard age structure. Standardization is necessary when comparing several populations that differ with respect to age because age has a powerful influence on the risk of cancer.

Risk of getting or dying from the disease before age 75 (%):
The probability or risk of individuals getting/dying from cancer. It is expressed as the number of new born children (out of 100) who would be expected to develop/die from cancer before the age of 75 if they had cancer rates (in the absence of other causes of death).

Table 2(a-b) below shows the global burden of different cancers for both sexes, all ages combined.

Table 2a:

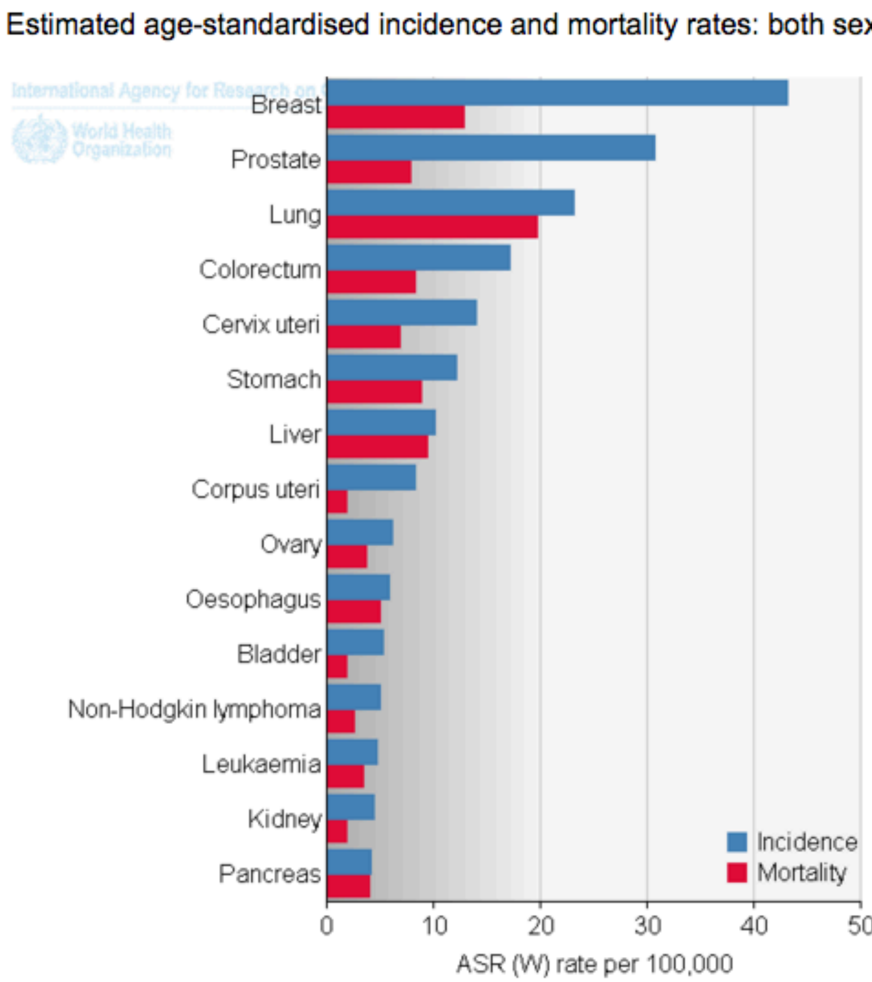


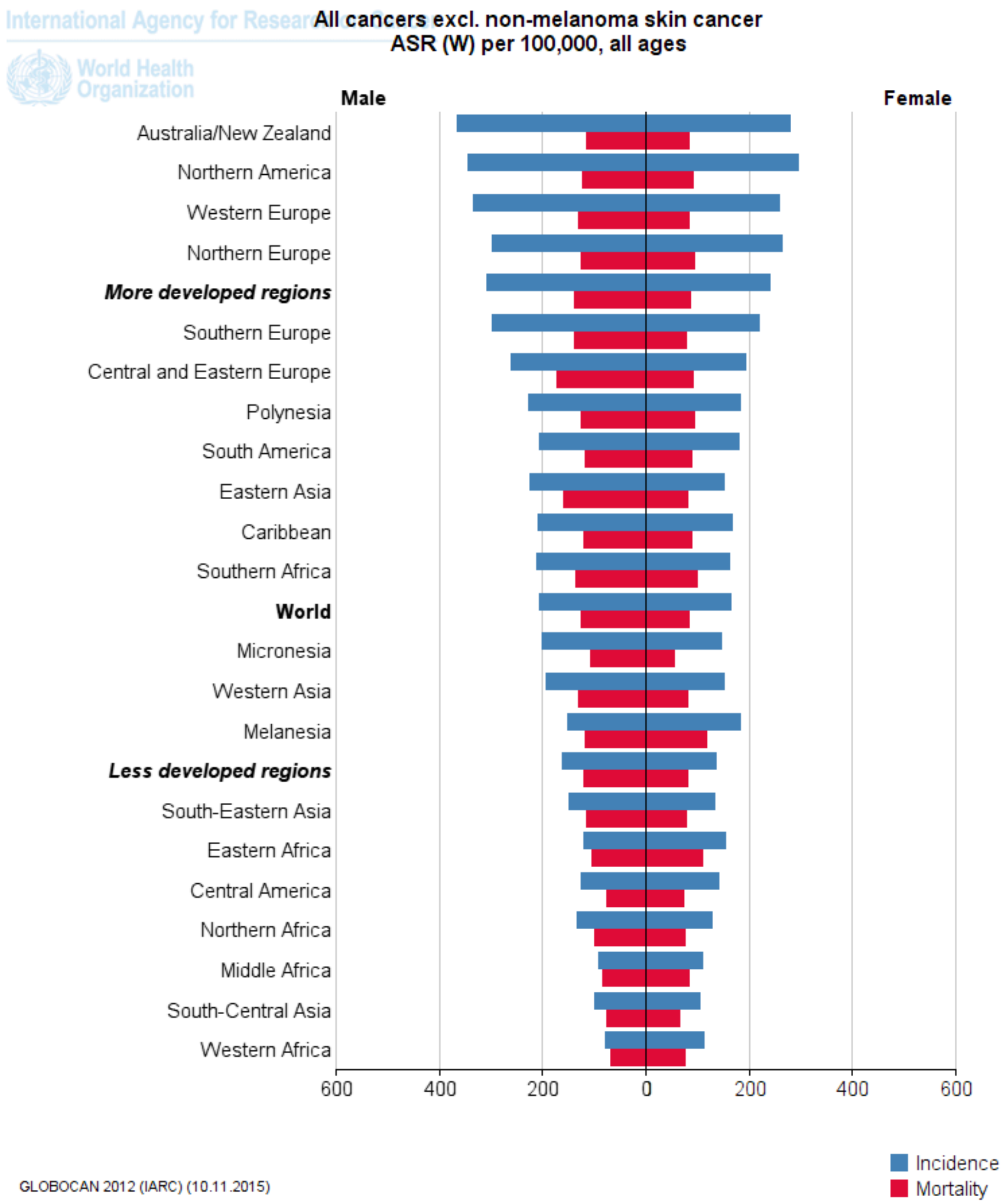
Table 2b:

Estimated incidence, mortality and 5-year prevalence: both sexes

Cancer	Incidence			Mortality			5-year prevalence		
	Number	(%)	ASR (W)	Number	(%)	ASR (W)	Number	(%)	Prop.
Lip, oral cavity	300373	2.1	4.0	145353	1.8	1.9	702149	2.2	13.5
Nasopharynx	86691	0.6	1.2	50831	0.6	0.7	228698	0.7	4.4
Other pharynx	142387	1.0	1.9	96105	1.2	1.3	309991	1.0	6.0
Oesophagus	455784	3.2	5.9	400169	4.9	5.0	464063	1.4	8.9
Stomach	951594	6.8	12.1	723073	8.8	8.9	1538127	4.7	29.6
Colorectum	1360602	9.7	17.2	693933	8.5	8.4	3543582	10.9	68.2
Liver	782451	5.6	10.1	745533	9.1	9.5	633170	2.0	12.2
Gallbladder	178101	1.3	2.2	142823	1.7	1.7	205646	0.6	4.0
Pancreas	337872	2.4	4.2	330391	4.0	4.1	211544	0.7	4.1
Larynx	156877	1.1	2.1	83376	1.0	1.1	441675	1.4	8.5
Lung	1824701	13.0	23.1	1589925	19.4	19.7	1893078	5.8	36.5
Melanoma of skin	232130	1.7	3.0	55488	0.7	0.7	869754	2.7	16.8
Kaposi sarcoma	44247	0.3	0.6	26974	0.3	0.3	80395	0.2	1.5
Breast	1671149	11.9	43.1	521907	6.4	12.9	6232108	19.2	239.9
Cervix uteri	527624	3.8	14.0	265672	3.2	6.8	1547161	4.8	59.6
Corpus uteri	319605	2.3	8.3	76160	0.9	1.8	1216504	3.7	46.8
Ovary	238719	1.7	6.1	151917	1.9	3.8	586624	1.8	22.6
Prostate	1094916	7.8	30.7	307481	3.7	7.8	3857500	11.9	148.6
Testis	55266	0.4	1.5	10351	0.1	0.3	214666	0.7	8.3
Kidney	337860	2.4	4.4	143406	1.7	1.8	906746	2.8	17.5
Bladder	429793	3.1	5.3	165084	2.0	1.9	1319749	4.1	25.4
Brain, nervous system	256213	1.8	3.4	189382	2.3	2.5	342914	1.1	6.6
Thyroid	298102	2.1	4.0	39771	0.5	0.5	1206075	3.7	23.2
Hodgkin lymphoma	65950	0.5	0.9	25469	0.3	0.3	188538	0.6	3.6
Non-Hodgkin lymphoma	385741	2.7	5.1	199670	2.4	2.5	832843	2.6	16.0
Multiple myeloma	114251	0.8	1.5	80019	1.0	1.0	229468	0.7	4.4
Leukaemia	351965	2.5	4.7	265471	3.2	3.4	500934	1.5	9.6
All cancers excl. non-melanoma skin cancer	14067894	100.0	182.0	8201575	100.0	102.4	32455179	100.0	625.0

Incidence and mortality data for all ages. 5-year prevalence for adult population only.
ASR (W) and proportions per 100,000.

Table 3 below shows the global cancer incidence and mortality rates for all cancers across the world and the more developed and less developed regions for both male and female.



Chapter II

METHODS

GLOBOCAN 2012

We utilized the GLOBOCAN 2012 database for obtaining data relating to the incidence and mortality for PC for all regions of the world. GLOBOCAN 2012 is a database that is maintained by the International Agency for Research on Cancer (IARC) that compiles estimates of incidence and mortality for 27 major types of cancer. This data includes information on all cancers that is stratified by gender for 184 countries and 30 world regions.[29]The detailed methodology used for the GLOBOCAN 2012 estimates can be accessed via GLOBOCAN webpage[30] and Ferlay et al (2015).[29]

World Health Organization (WHO) Regions

For the purposes of the study we utilized the geographic regions of the world described by the WHO. The six WHO regions are: The WHO African Region (AFRO; Region 1), WHO Region of the Americas (PAHO; Region 2), WHO Eastern Mediterranean Region (EMRO; Region 3), WHO European Region (EURO; Region 4), WHO South-East Asian Region (SEARO; Region 5), and WHO Western Pacific Region (WPRO; Region 6). Detailed information can be found at WHO website with alphabetical listing of the WHO Member States[31]

Human Development Index (HDI)

To account for the varying socio-economic standing of different countries/regions of the world we adhered to the model of Human Development Index. The HDI been developed by the United Nations Development Programme (UNDP) provides a summary measure of human development based on three fundamental areas of human development: 1) life expectancy at birth, 2) adult literacy rate and primary education to tertiary education enrolment rates, and 3) GDP per head adjusted for purchasing-power parity [US$]).[11] HDI uses complex statistical combinations to rank countries (187) into four tiers of human development (from 0 to 1).[11,32] The four tiers of human development include: countries with very high HDI (HDI≥0.800; VHHD), countries with a high HDI (HDI≥0.700; HHD), Medium HDI countries (HDI≥0.550; MHD), and countries with a low HDI (HDI<0.550; LHD).

Age Standardized Rate (ASR)

The Age Standardized Rate (ASR) is the measurement of the rate of distribution of population it would have if it had a standard age structure. The risk of developing cancer is highly influenced by age and therefore standardization is necessary when comparing several populations that differ with respect to age. The ASR data for all analysis were obtained from GLOBOCAN 2012 database.[29]

Demographic Shift

Demographic shift (also referred as population ageing) is the shift in the proportion of older population globally with the decline in fertility and increase in life expectancy.[33] This shift in population ageing is expected to have a profound effect on cancer burden.[29] The number of older persons (ages 60 and over) is the fastest growing globally and is projected to be approximately 1.4 billion by 2030.[33]

Statistical Analysis

R and SAS software (SAS Institute Inc., Cary, NC, USA) were used for statistical analysis. Linear regression was used to evaluate trends in total incidence and mortality for the world and by region from the prediction data obtained from GLOBOCAN 2012. For these models, time was modeled as 1, 2, 3, 4, and 5 corresponding to years 2010, 2015, 2020, 2025, 2030, so the slope of the regression line can be interpreted as a 5 year increase in the outcome variable.

Chapter III

Predictive global trends in the incidence and mortality of pancreatic cancer based on geographic location, socio-economic status and demographic shift

INTRODUCTION

In recent years, cancer control has been promoted as a global health priority.[1-5] The global cancer burden (GCB) is rising at an alarming rate and is expected to nearly double by 2030.[34-36] Pancreatic cancer (PC) is a lethal malignancy that accounts for about 4% of cancer-related deaths in both males and females worldwide.[13-24] In the United States, PC accounts for about 2.7% of all new cancer cases and is projected to become the second largest cause of cancer-related deaths by 2030.[25]

Although the trends in the incidence and mortality of PC are well studied in the United States and some Western European countries, the same cannot be said for the rest of the world. There are few publications on pancreatic cancer originating from regions of low incidence or resource-poor areas of the world.[28] Similarly, there is a scarcity of reports describing the overall global trends in the incidence and mortality of PC across all regions of the world and encompassing all strata of socio-economic development.

The aim of this study is to describe the influence of geography (based on World Health Organization [WHO] regional classification), socio-economic development (based on Human Development Index [HDI]) and demographic shift on the global trends in the incidence and mortality of PC. The intent of the study was not to develop an independent model for predicting global cancer burden. It was aimed to review the predictive global trends of pancreatic cancer based on the comprehensive data available in GLOBOCAN 2012 and present the results in a cogent fashion.

RESULTS

Global PC Incidence and Mortality (for 2012) based on geography: worldwide and WHO regions (Table 1)

The worldwide PC incidence including all ages and both sexes for 2012 is estimated at 337,872 with an age-standardized rate (ASR) of 4.2 per 100,000. The worldwide PC mortality including all ages and both sexes for 2012 is estimated at 330,391 with an ASR of 4.0 per 100,000. Among the different regions, the WHO region 6 (WPRO) is reported to have the highest incidence (113,015) whereas the highest mortality is noted in WHO region 4 (EURO- 111,029).

Global PC Incidence and Mortality (for 2012) based socio-economic development (HDI) (Table 1)

Comparison based on the four tier HDI model revealed striking differences in incidence and mortality rate between VHHD, HHD, MHD and LHD (Table 1). Both men and women from VHHD had much higher incidence and mortality (ASR) when compared to HHD, MHD and LHD regions.

Global trends (2010-2030) in PC Incidence based on geography: worldwide and WHO regions (Figure 1a)

Linear regression model was used to describe the trends in total PC incidence. We noted a statistically significant increase in incidence of PC for the entire world ($p<0.001$) with an average of 51,770 new cases every 5 years. Subset analysis for the WHO regions again revealed a statistically significant increase in the incidence for all six regions ($p<0.001$) with the most significant increases affecting region 6 (WPRO).

Global trends (2010-2035) in PC Mortality based on geography: worldwide and WHO regions (Figure 1 b)

We noted a statistically significant increase in PC mortality for the entire world ($p<0.001$) with an average of 50,519 deaths every 5 years. Subset analysis for the WHO regions also revealed a statistically significant increase in the PC-related mortality for all six regions ($p<0.001$) with the most significant increases affecting region 6 (WPRO). The prediction data used for the linear regression analysis were obtained from GLOBOCAN for the global trends in incidence and mortality of PC (2010 – 2030) and are included in Supplemental Table 1.

Effect of demographic change in PC incidence and mortality based on geography: for all WHO Regions (Figures 2a and 2b)

Figure 2a shows the estimated combined number of new cases for Regions 1-6 (for all ages; ages <65 and ages ≥ 65) for PC between 2012 and 2030. It is observed that the demographic shift in the total population will have a major influence on the projected incidence of PC in 2030 due to an increase in the number of adults 65 years and older. In addition to the rise in global PC incidence due to the demographic changes, we also observed a similar substantial increase in PC mortality due to the increase in the number of adults 65 years and older (Figures 2b).

Effect of demographic change in PC incidence and mortality based on socio-economic development (HDI) (Figures 3 and 4)

We determined the future burden of PC in 2030 by gender and demographics for the four levels of HDI on the basis of the rates in 2012. The Figures 3 and 4 and

Supplemental Table 2 provide trends of PC among VHHD, HDH, MDH and LHD. Overall, the highest incidence and mortality rates were observed for VHHD, followed by HDH, MDH and LDH.

The influence of demographic shift on PC incidence and mortality revealed striking findings for different HDI regions. The demographic shift contributed to a greater rise in PC incidence and mortality for ages > 65 years in the regions of VHHD, HHD and MHD. In contrast, although we noted a rise in the incidence and mortality in the region of LHD for all ages, the increase predominantly affected the younger age group (< 65 years of age).

DISCUSSION

The results of our study demonstrate that the global burden of PC is predicted to rise significantly over the next 15 years. This rise in the global burden of PC is noted in all geographic regions of the world. Similarly, the increase affects all regions of the world regardless of the socio-economic development as noted by the rise in the burden in all 4 HDI regions. This is alarming considering the progress in reducing the burden of many other cancers in some countries in the VHHD region.[37] Kohler et al analyzed the data for the major cancers in the US (1992-2011) and noted a significant decrease in the incidence of prostate cancer (-2.5 to -10.5%), breast cancer (-0.4% to -2.2%) lung cancer (-1.9 to 4.8% for men and -1.1 to 2.5 % for women) and colorectal cancer (-2.6 to 4.2% for men and -1.8% to -4.5%). Similarly, they noted a significant decrease in the mortality for several cancers such as lung (-1.1 to -2.9% for men and -0.8 to -1.9% for women), prostate (-0.5 to -4.1%), breast (-1.8 to -3.3%) and colorectum (-0.3 to -3.9% for men and -1 to -2.9% for women). The rise in the global burden of PC despite progress for other cancers in some parts of the world is a cause for concern.

We noted several points of interest in the rising global burden of PC. In 2012, region 6 (WPRO) and region 4 (EURO) accounted for the highest incidence and mortality. Over the next 15 years, although the incidence and mortality increases in all six regions, the rate of increase is not uniform. Whereas the PC related mortality is highest in region 4 (EURO) in 2012, this will be surpassed by region 6 (WPRO) over the next 15 years. The WPRO region with its 37 countries is home to nearly 1.8 billion people and consists of some of the world's least developed countries in addition to some of the most rapidly emerging economies. Advance knowledge of these figures can help public policy and debate to allocate resources to tackle this lethal malignancy in the least developed countries.

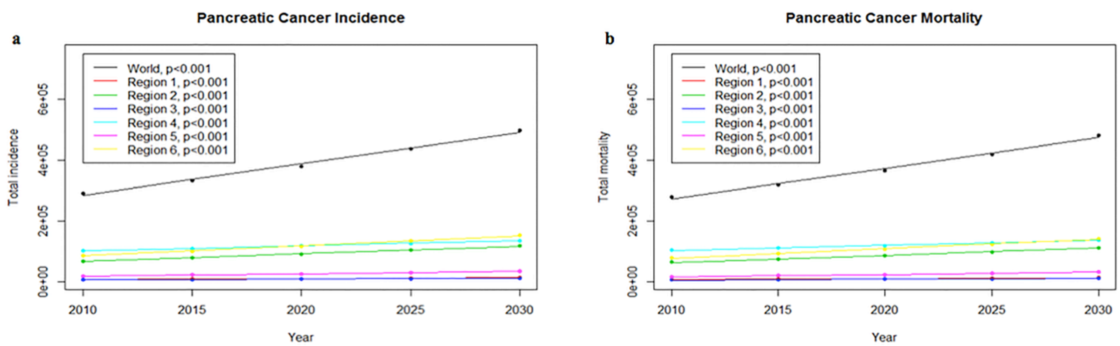
There was a significant association noted between PC and socio-economic status with the highest burden of PC seen in the VHHD countries. The ASR of PC incidence and mortality in VHHD countries is nearly six to seven fold higher than for the countries in the LHD strata. It is well known that there is a higher prevalence of the risk factors associated with PC (dietary and lifestyle choices) seen in the VHHD countries. It is likely that as more countries in the MHD and LHD regions transition to emerging economies with improving socio-economic conditions we may see a migration of these risk factors to those regions as well. Smoking, one of the most important risk factors for pancreatic cancer is on the rise in the developing countries which account for nearly 70% of the global consumption.[38] Obesity is another well-known risk factor for pancreatic cancer.[39,40] Countries in the economic transition phase are also known to go through a nutrition transition phase with a rise in the rates of obesity. Popkin et al noted that reduced physical activity and dietary changes in the 1990's have led to an increase in obesity rates in the developing countries.[41]

Kolkman et al performed a comparative study of the histo-pathologic type of esophageal cancer between a developed country (United States) and an emerging economy (India).[42] Although squamous cell carcinoma is the predominant type of cancer in India, they noted a gradual increase in the rate of adenocarcinoma to correlate with increase in risk factors specific for esophageal adenocarcinoma such as obesity. There are several countries in the world that are in the zone of economic improvement, which could be affected by rising burden of PC. Knowledge of the risk factors can help steer public health measures that focus on increasing awareness and prevention.

The correlation between age and PC burden showed mixed results. Advancing age (≥ 65) accounted for significant increases in PC incidence and mortality in VHHD, HHD and MHD countries. In contrast, the majority of the new cases and mortality related to PC in the LHD countries afflicts patients < 65 years of age and will continue to do so in the future. This age group in the LHD countries tends to be the main income earners and the rising PC burden in this segment can have significant adverse micro-economic and macro-economic consequences.

In summary, the results of our study demonstrate that the global burden of PC is expected to rise significantly over the next 15 years. Although some regions may experience a disproportionate increase, the rise was noted in all regions of the world regardless of the location socio-economic status, age and gender. We noted a definite association between pancreatic cancer and higher socio-economic status, which may contribute, to a rise in the future burden in countries with emerging economies. The predilection for pancreatic cancer to affect younger populations in LHD countries can have significant micro and macro-economic adverse consequences. Advance knowledge of this data can help formulate strategies to specifically target countries and populations and to also improvise public health policy to tackle this lethal disease on the global stage.

Figure 1: Trends in PC incidence (a) and mortality (b) based on worldwide and WHO regions 1-6. Time was modeled here as 1, 2, 3, 4, 5 corresponding to years 2010, 2015, 2020, 2025, 2030, so the slope of the regression line can be interpreted as a 5 year increase in the outcome variable.



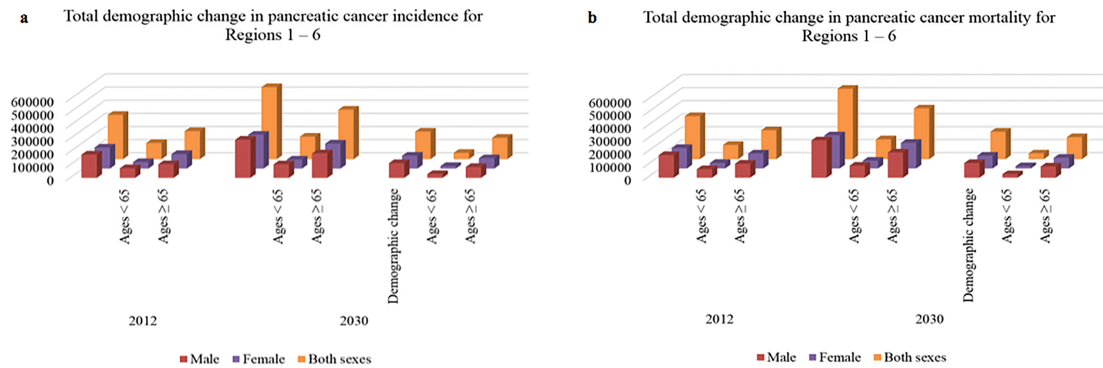
(a)

			Estimate	SE	t-value	p-value
World	Intercept		233042	8368	27.9	
	Time	5 year increase	51770	2523	20.5	0.000253
Region 1	Intercept		5358	319	16.8	
	Time	5 year increase	1477	96	15.3	0.000603
Region 2	Intercept		53984	1821	29.64	
	Time	5 year increase	12657	549	23.05	0.000179
Region 3	Intercept		4189	365	11.48	
	Time	5 year increase	1566	110	14.22	0.000753
Region 4	Intercept		93865	796	117.87	
	Time	5 year increase	8247	240	34.35	5.43E-05
Region 5	Intercept		14616	603	24.23	
	Time	5 year increase	3958	182	21.76	0.000212
Region 6	Intercept		68348	2248	30.4	
	Time	5 year increase	16791	678	24.77	0.000144

(b)

			Estimate	SE	t-value	p-value
World	Intercept		221493	8780	25.23	
	Time	5 year increase	50519	2647	19.08	0.000314
Region 1	Intercept		5234	315	16.59	
	Time	5 year increase	1451	95	15.26	0.000612
Region 2	Intercept		50411	1876	26.87	
	Time	5 year increase	12152	566	21.49	0.000221
Region 3	Intercept		4055	365	11.11	
	Time	5 year increase	1531	110	13.91	0.000804
Region 4	Intercept		94682	971	97.49	
	Time	5 year increase	8586	293	29.32	8.71E-05
Region 5	Intercept		12992	626	20.76	
	Time	5 year increase	3761	189	19.93	0.000276
Region 6	Intercept		61638	2379	25.91	
	Time	5 year increase	15766	717	21.98	0.000206

Figure 2. Effect of demographic change in PC incidence (a) and mortality (b) for combined WHO Regions 1-6.



Year	Estimated number of new cases (all ages)	Male	Female	Both sexes
2012		178135	159693	337828
	Ages < 65	74048	49139	123187
	Ages ≥ 65	104087	110554	214641
2030		290924	257755	548679
	Ages < 65	103347	68170	171517
	Ages ≥ 65	187577	189585	377162
	Demographic change	112789	98062	210851
	Ages < 65	29299	19031	48330
	Ages ≥ 65	83490	79031	162521

Year	Estimated number of cancer deaths (all ages)	Male	Female	Both sexes
2012		173802	156548	330350
	Ages < 65	66105	42102	108207
	Ages ≥ 65	107697	114446	222143
2030		286754	254762	541516
	Ages < 65	92715	58768	151483
	Ages ≥ 65	194039	195994	390033
	Demographic change	112952	98214	211166
	Ages < 65	26610	16666	43276
	Ages ≥ 65	86342	81548	167890

Figure 3. Effect of demographic change in PC incidence and mortality for VHHD (a-b) and HHD (c-d).

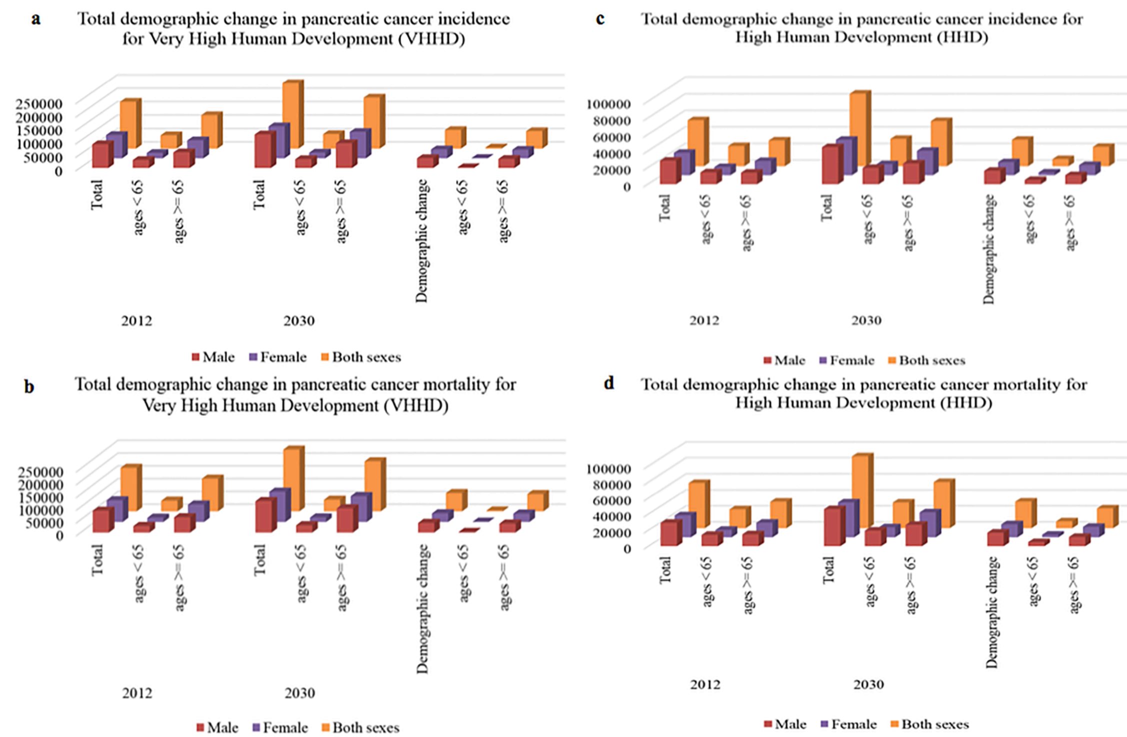


Figure 4. Effect of demographic change in PC incidence and mortality for MHD (a-b) and LHD (c-d).

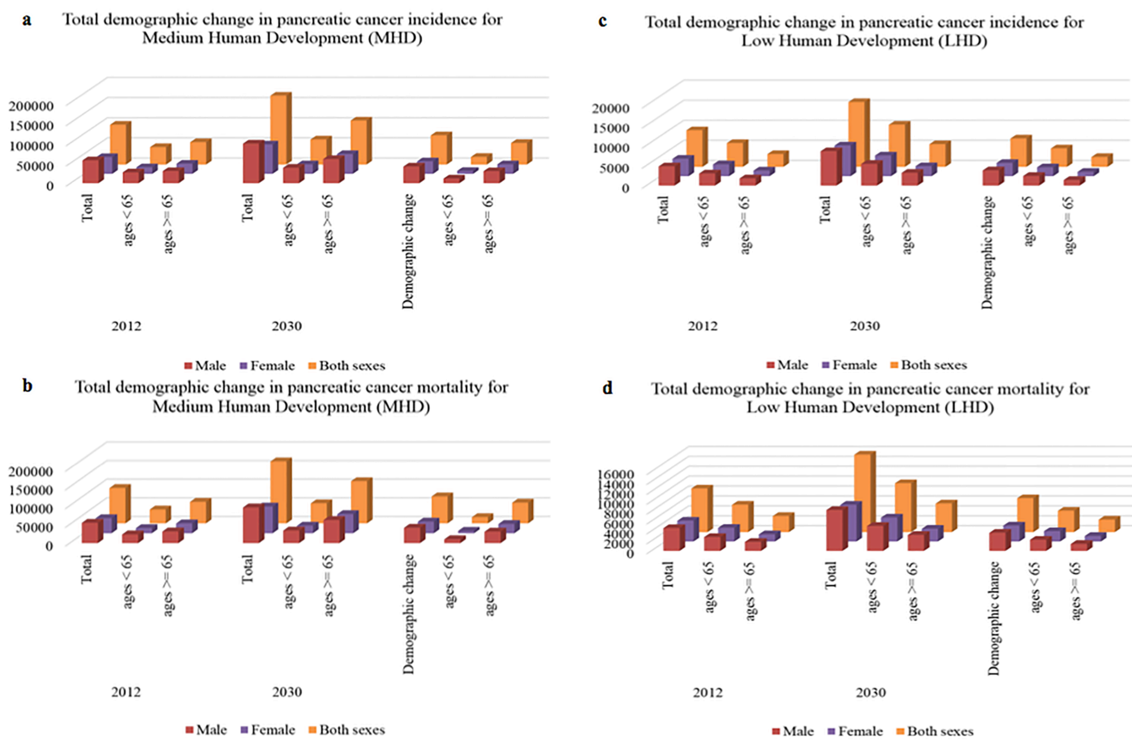


Table 1. PC incidence and mortality statistics for 2012 based on worldwide, WHO regions 1-6 and HDI.

Global pancreatic cancer burden based on geography: Worldwide and for the 6 WHO regions (2012)						
INCIDENCE						
Estimated incidence, all ages	**Population (all ages; both sex)**	**Population (all ages; male)**	**Population (all ages; female)**	**ASR (W) (all ages; both sex)**	**ASR (W) (all ages; male)**	**ASR (W) (all ages; female)**
World	337872	178161	159711	4.2	4.9	3.6
Region 1	8324	4304	4020	1.8	2.0	1.6
Region 2	75094	37016	38078	5.9	6.5	5.3
Region 3	7686	4503	3183	1.9	2.2	1.5
Region 4	110499	55795	54704	6.5	8.0	5.3
Region 5	23210	12401	10809	1.5	1.7	1.3
Region 6	113015	64116	48899	4.4	5.3	3.5
MORTALITY						
Estimated mortality, all ages	**Population (both sex)**	**Population (male)**	**Population (female)**	**ASR (W) (both sex)**	**ASR (W) (male)**	**ASR (W) (female)**
World	330391	173827	156564	4.0	4.7	3.4
Region 1	8048	4174	3874	1.7	2.0	1.5
Region 2	73751	36477	37274	5.6	6.4	5.0
Region 3	7440	4353	3087	1.8	2.1	1.5
Region 4	111029	56350	54679	6.4	7.9	5.1
Region 5	21638	11522	10116	1.4	1.5	1.2
Region 6	108444	60926	47518	4.1	5.0	3.3

<u>Global pancreatic cancer burden based on socio-economic development: For the 4 HDI regions (2012)</u>

INCIDENCE

Estimated incidence, all ages	**Population (all ages; both sex)**	**Population (all ages; male)**	**Population (all ages; female)**	**ASR (W) (all ages; both sex)**	**ASR (W) (all ages; male)**	**ASR (W) (all ages; female)**
Very High Human Development	174344	87924	86420	7.2	8.5	6.1
High Human Development	55638	28491	27147	4.6	5.4	3.9
Medium Human Development	98632	56902	41730	2.7	3.3	2.2
Low Human Development	9108	4767	4341	1.2	1.4	1.1

MORTALITY

Estimated incidence, all ages	**Population (all ages; both sex)**	**Population (all ages; male)**	**Population (all ages; female)**	**ASR (W) (all ages; both sex)**	**ASR (W) (all ages; male)**	**ASR (W) (all ages; female)**
Very High Human Development	170497	85643	84854	6.8	8.0	5.6
High Human Development	56474	29254	27220	4.6	5.6	3.8
Medium Human Development	94447	54242	40205	2.6	3.2	2.1
Low Human Development	8822	4610	4212	1.2	1.3	1.1

PC= Pancreatic cancer

ASR= Age standardized rate

Region 1= AFRO (Africa)

Region 2= PAHO (Americas)

Region 3= EMRO (Eastern Mediterranean)

Region 4= EURO (Europe)

Region 5= SEARO (South East Asia)

Region 6= WPRO (Western Pacific)

HDI= Human Development Index

Chapter IV

Global trends in liver cancer epidemiology based on geographic location, socio-economic status and demographic shift.

INTRODUCTION

Liver cancer (LC) is fast developing into a global medical crisis[26]. Historically, LC has been most prevalent in the developing regions of Southeast Asia and Africa. This high burden of LC in these developing regions has been mainly attributed to Hepatitis B virus (HBV) and exposure to aflotoxin[27]. However, in recent years, developed Western countries have witnessed an alarming rise in LC partly due to increased Hepatitis C virus (HCV) infection and non-communicable diseases (NCD) associated with alcohol use and non-alcoholic steatohepatitis (NASH)[26]. LC is the fifth most common cancer and the third leading cause of cancer-related deaths globally[26,27].

The trends in the incidence and mortality of LC have been well studied for certain developing regions of high incidence and few developed regions. However, there is scarcity of comprehensive reports unpinning the incidence and mortality trend for LC across all geographic regions and encompassing all strata of socio-economic development.

The aim of this epidemiological study is to critically dissect the influence of geography (based on World Health Organization [WHO] regional classification), socio-economic development (based on Human Development Index [HDI]) and demographic shift on the global trends in the incidence and mortality of LC.

RESULTS

Global LC Incidence and Mortality (for 2012) based on geography: worldwide and WHO regions (Figure 1a,b)

The worldwide LC incidence and mortality has been shown in Figure 1a. The global LC incidence including all ages and both sexes for 2012 is estimated at 782,451 with an age-standardized rate (ASR) of 10.1 per 100,000. The worldwide LC mortality including all ages and both sexes for 2012 is estimated at 745,533 with an ASR of 9.5 per 100,000. Among the different regions, the WHO region 6 (WPRO) is reported to have both the highest incidence (500,506) and mortality (476,692) accounting for about 64% of all LC incidence and mortality (Figure 1b).

Global LC Incidence and Mortality (for 2012) based socio-economic development (HDI) (Figure 1b)

Comparison based on the four tier HDI model revealed striking differences in incidence and mortality rate between VHHD, HHD, MHD and LHD (Figure 1b). The incidence and mortality of LC does not follow any particular socio-economic pattern. The MHD area has the highest incidence (531,931) and mortality (514,528) rates for all ages and both sexes combined. The VHHD areas are next with high incidence (153,946) and mortality (133,159) rates. The HHD and LHD areas have comparable incidence and mortality rates.

Supplemental Table 1 shows the estimated LC incidence and mortality (2012) for worldwide and WHO regions and HDI areas for all ages for both male and female. Overall, the LC incidence and mortality is higher in male than female.

Global LC 5-years prevalence (for 2012) based on geography: worldwide and WHO regions (Supplemental Figure 1a,b)

The worldwide LC 5-years prevalence (proportions per 100,000) for male and female population has been shown in Supplemental Figure 1a. The global LC 5-years prevalence for male is estimated at 453,345 (proportion = 17.5%). The global LC 5-years prevalence for female is estimated at 179,825 (proportion = 6.9%). Among the different regions, the WHO region 6 (WPRO) is reported to have both the highest 5-years prevalence for male (proportion = 41.9%) and female (proportion = 15.4%; Supplemental Figure 1b).

Global LC 5-years prevalence (for 2012) based socio-economic development (HDI) (Supplemental Figure 1b)

Comparison based on the four tier HDI model revealed an intriguing difference in the 5-years prevalence between VHHD, HHD, MHD and LHD (Supplemental Figure 1b). In contrast to the highest incidence and mortality rates discussed above for MHD area, the VHHD area has the highest 5-year prevalence for both male (proportion = 28.4%) and female (proportion = 11.7%). MHD area is second ranked with 5-year prevalence for both male (proportion = 20.7%) and female (proportion = 7.4%). The HHD and LHD areas have comparable 5-years prevalence rates.

Socio-economic variability within WPRO regional countries (Table 1, Supplemental Table 2a,b and Table 2)

Table 1 lists the estimated LC incidence and mortality (2012) for all WPRO regional countries (for all ages; both sexes). It is observed that China contributed to about 84.5% and 86.3% of all WPRO incidence and mortality respectively. However, the ASR (worldwide) is higher than China (22.3) for several other WPRO countries including Mongolia (78.1), Lao PDR (52.6), Viet Nam (24.6) and Republic of Korea (22.8).

Supplemental Table 2a shows the WPRO liver cancer estimates of incidence and mortality by different age groups. Interesting, the both male and female ages >= 75, the rate of mortality is higher compared to the incidence. Supplemental Table 2b shows the top 6 WPRO member states LC estimates by age. An alarming observation is the relatively early onset of LC incidence and mortality for Mongolia and Lao PDR.

Table 2 is the categorization of the different WPRO member states based on their HDI 2014 ranking, life expectancy, physician availability and health expenditure of the country. It is important to note that China as per Human Development Report 2014 is listed within the HHD category. China's HDI increased over the past three decades from 0.423 (1980) to 0.719 (2013). The GLOBOCAN 2012 estimates for incidence, mortality and trend predictions are based on data obtained prior to 2012 and have listed China within the MHD category. Within the WPRO countries, Australia and New Zealand are within the top 5 VHDD areas and has low incidence and mortality of LC [ASR(W) of 4.2 and 4.0 respectively]. While the health expenditure (as % of GDP) in Australia and New Zealand is an impressive 9.0 and 10.1 respectively, areas with high LC incidence and mortality like China (5.2%), Mongolia (5.3%), Republic of Korea (7.2%), Cambodia (5.7%) have moderate level of health expenditure. Lao PDR, a low human development area has the lowest health expenditure at 2.8% and shows high ASR(W) and early onset of LC incidence and mortality. It is also important to note that the life expectancy at birth is significantly different within these WPRO countries based on socio-economic status.

Global trends (2010-2030) in LC Incidence based on geography: worldwide and WHO regions (Figure 2a)

Linear regression model was used to determine the trends in total LC incidence. We noted a statistically significant increase in incidence of LC for the entire world ($p<0.0001$) with an average of 117,075 new cases every 5 years. Subset analysis for the

WHO regions again revealed a statistically significant increase in the incidence for all six regions with the most significant increases affecting region 6 (WPRO; $p<0.0001$).

Global trends (2010-2030) in LC Mortality based on geography: worldwide and WHO regions (Figure 2b)

We noted a statistically significant increase in LC mortality for the entire world ($p<0.0001$) with an average of 112,160 deaths every 5 years. Subset analysis for the WHO regions also revealed a statistically significant increase in the LC-related mortality for all six regions ($p<0.001$) with the most significant increases affecting region 6 (WPRO; $p<0.0001$).

Effect of demographic change in LC incidence and mortality in WPRO Region (Figures 3a,b)

Figure 3a shows the estimated number of new cases for WPRO Region (for all ages; ages < 65 and ages ≥ 65 years) for LC between 2012 and 2030. It is observed that the demographic shift in the total population will have a major influence on the projected incidence of LC in 2030 due to an increase in the number of adults 65 years and older. In addition to the rise in LC incidence due to the demographic changes, we also observed a similar substantial increase in LC mortality in WPRO Region due to the increase in the number of adults 65 years and older (Figures 3b). It is important to note that the number of LC incidence for 2012 was higher in the younger population ages < 65 years by more than 30,000. However, the predicted LC incidence is expected to shift towards the older population ages 65 years and older with an approximate increase of about 35,000 patients by 2030.

Effect of demographic change in LC incidence and mortality based on socio-economic development (HDI) (Supplemental Figures 2-5)

We determined the future burden of LC in 2030 by gender and demographics for the four levels of HDI on the basis of the rates in 2012. The Supplemental figures 2 to 5 provide trends of LC among VHHD, HHD, MHD and LHD. Overall, the highest incidence and mortality rates were observed for MHD, followed by VHDH, LDH and HDH. Thus, the demographic shift does not follow any particular socio-economic pattern.

The influence of demographic shift on LC incidence and mortality revealed striking findings for different HDI regions. The demographic shift predicts a greater rise in LC incidence (227,282) and mortality (236,431) for adults older than ages 65 years in the regions of MHD area compared to 111,212 and 102,316 for incidence and mortality respectively for ages < 65 years. In contrast, although we noted a rise in the incidence (36,984) and mortality (35,122) in the region of LHD for all ages, the increase predominantly affected the younger age group (< 65 years of age).

DISCUSSION

The global burden of cancer is rising at a precarious rate and has been the leading cause of death worldwide[1-5,34-36]. Intriguingly, LC has catapulted itself as one of the deadliest forms being the second most-common case of cancer-related death worldwide[26,27,29]. As per the American Cancer Society, the 5-year relative survival rate after diagnosis is approximately 28% for localized, 7% for regional and 2% for distant metastasis[43]. The combined 5-year relative survival rate from LC is about 15% in US and about 12% in Europe[43,44]. One of the challenges for LC patients and clinicians is that LC is not manifested during early stages and is often diagnosed at an advanced stage, thereby causing a poor 5-year relative survival rate.

The results of our study demonstrate that the global burden of LC is predicted to rise significantly over the next 15 years. This rise in the global burden of LC is noted in all geographic regions of the world. However, the highest rate of LC incidence and mortality is observed in WPRO region accounting for about 64% of all LC incidence and mortality. The LC burden was second highest in SEARO, followed by EURO, PAHO and AFRO regions. Similarly, the increase affects all regions of the world regardless of the socio-economic development as noted by the rise in the burden in all 4 HDI regions. The highest LC burden was observed in the MHD areas. However, an interesting finding in this study is that 5-years prevalence of LC is highest in VHHD area (28.4% and 11.7% for male and female) compared to MHD (20.7% for male and 7.4% for female). Therefore, the incidence of LC is increasing at a higher proportion for the more developed/VHHD countries. Considering the progress VHHD countries have made towards reducing the cancer burden for several types of cancer[37], the increase in the 5-years prevalence of LC for both men and women are alarming and needs detailed analysis. In the annual report on cancer burden for major cancer types in the US (1992-2011), Kohler et al noted a significant decrease in the incidence of prostate cancer (-2.5 to -10.5%), colorectal cancer (-2.6 to 4.2% for men and -1.8% to -4.5%), lung cancer (-1.9 to 4.8% for men and -1.1 to 2.5 % for women) and breast cancer (-0.4% to -2.2%). Similarly, they observed a significant decrease in the mortality for certain cancer types including breast (-1.8 to -3.3%), colorectum (-0.3 to -3.9% for men and -1 to -2.9% for women), lung (-1.1 to -2.9% for men and -0.8 to -1.9% for women) and prostate (-0.5 to -4.1%). Therefore, the rise in the LC burden despite progress for other cancers in some parts of the world is a cause for concern.

We noted several points of interest in the rising global burden of LC in WPRO region. The WPRO region is consisting of 37 countries with a combined population of nearly 1.8 billion people. It consists of an mélange of world's least developed countries in addition to some of the most rapidly emerging economies. As noted in Table 2, the HDI rankings of the member countries within WPRO regions span across all 4 HDI areas and spreads across Australia (VVHD rank 2nd) to Solomon Islands and Papua New Guinea (LHD rank 157th). Therefore, advanced knowledge of these figures can help public policy and debate to allocate resources to tackle this lethal malignancy in the least developed countries.

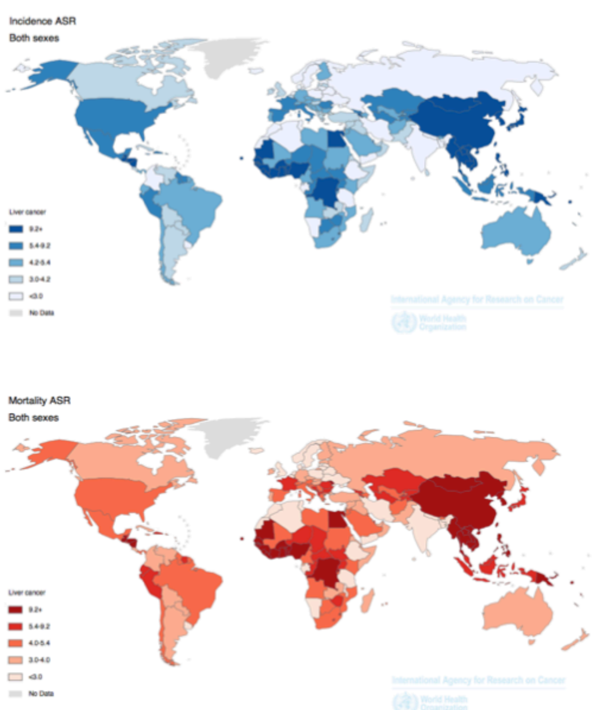
We did not observe a significant association between LC and socio-economic status with the highest burden of LC seen in the MHD countries. The ASR of LC incidence and mortality in MHD countries is > 2 fold greater than for the countries in the VHHD and LHD strata and >3 fold greater than HHD countries. It is well known that there is a higher prevalence of the risk factors associated with LC (dietary and lifestyle choices) seen in the MHD, HHD and VHHD countries. It is likely that as more countries in the LHD regions transition to emerging economies with improving socio-economic conditions we may see a migration of some of these risk factors to those regions as well. Chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) are the strongest risk factors for hepatocellular carcinoma (HCC), the histological type that is responsible for majority of LC worldwide. HCC can develop after many years of infection with either of these viruses. HBV and HCV are both highly contagious diseases that can be passed from person to person through blood (such as by sharing needles) or sexual contact. There is strong evidence of the association of obesity (high BMI), long term consumption of alcoholic drinks (three or more per day) and heavy exposure to aflatoxins (toxins secreted by certain fungi) with the development of LC. Aflatoxins are produced mainly due to improper storage of food in warmer climatic regions of the world. Major foods that are contaminated by aflatoxins include various types of nuts including peanuts, pistachios, and Brazil nuts. Other common contaminating food includes grains, chilies, black pepper and dry fruits. Aflatoxin exposure accentuates the development of HCC from HBV infection and has been partly contained with better storage of grains. Dietary and lifestyle modifications in several developing countries has been able to reduce obesity and diabetes, which are associated with HCV-infected population. As per the emerging 2015 reports from the World Cancer Research Fund International – Continuous Update Project (CUP), limited reports have shown that higher consumption of fish and regular physical activity decreases the risk of LC.

The correlation between age and LC burden showed mixed results. Advancing age (≥ 65) accounted for significant increases in LC incidence and mortality in MHD, HHD and VHHD countries. In contrast, the majority of the new cases and mortality related to LC in the LHD countries afflicts patients < 65 years of age and will continue to do so in the future. This age group in the LHD countries tends to be the main income earners and the rising LC burden in this segment can have significant adverse micro-economic and macro-economic consequences.

In summary, the results of our study demonstrate that the global burden of LC is expected to rise significantly over the next 15 years. Although the WPRO region may experience a disproportionate increase, the rise was noted in all regions of the world regardless of the location, socio-economic status, age and gender. We did not observe a definite association between LC and higher socio-economic status, which may be associated with variable risk factors. The predilection for LC to affect younger populations in LHD countries can have significant micro and macro-economic adverse consequences. Advance knowledge of this data can help formulate strategies to specifically target countries and populations and to also improvise public health policy to tackle this lethal disease on the global stage.

Figure 1: LC incidence and mortality worldwide by WHO and HDI classification (for all ages and both sexes)

a

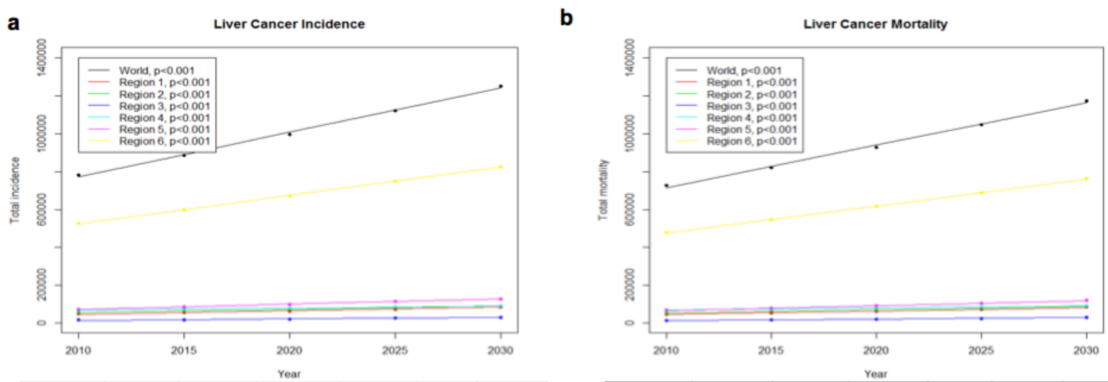


b

Liver - Estimated incidence, all ages: both sexes				
POPULATION	Numbers	Crude Rate	ASR (W)	Cumulative risk
World	782451	11.1	10.1	1.14
WHO Africa region (AFRO)	38823	4.4	7.3	0.81
WHO Americas region (PAHO)	63160	6.6	5.3	0.63
WHO East Mediterranean region (EMRO)	29367	4.7	7.1	0.87
WHO Europe region (EURO)	70576	7.8	4.3	0.52
WHO South-East Asia region (SEARO)	79962	4.3	5.1	0.60
WHO Western Pacific region (WPRO)	500506	27.2	20.4	2.21
Very High Human Development (VHHD)	153946	13.4	7.0	0.83
High Human Development (HHD)	46124	4.4	3.8	0.46
Medium Human Development (MHD)	531931	15.0	14.6	1.59
Low Human Development (LHD)	50292	3.9	6.2	0.70

Liver - Estimated mortality, all ages: both sexes				
POPULATION	Numbers	Crude Rate	ASR (W)	Cumulative risk
World	745533	10.6	9.5	1.04
WHO Africa region (AFRO)	37161	4.2	7.0	0.76
WHO Americas region (PAHO)	57884	6.1	4.6	0.54
WHO East Mediterranean region (EMRO)	27949	4.5	6.8	0.83
WHO Europe region (EURO)	69046	7.7	4.0	0.47
WHO South-East Asia region (SEARO)	76746	4.1	4.9	0.57
WHO Western Pacific region (WPRO)	476692	25.9	19.1	2.02
Very High Human Development (VHHD)	133159	11.6	5.5	0.64
High Human Development (HHD)	49711	4.8	4.1	0.48
Medium Human Development (MHD)	514528	14.5	14.1	1.50
Low Human Development (LHD)	47985	3.7	5.9	0.66

Figure 2a,b: Time Trend in liver cancer incidence and mortality for WHO regions 2010 – 2030. Time was modeled here as 1, 2, 3, 4, 5 corresponding to years 2010, 2015, 2020, 2025, 2030, so the slope of the regression line can be interpreted as a 5 year increase in the outcome variable.



a

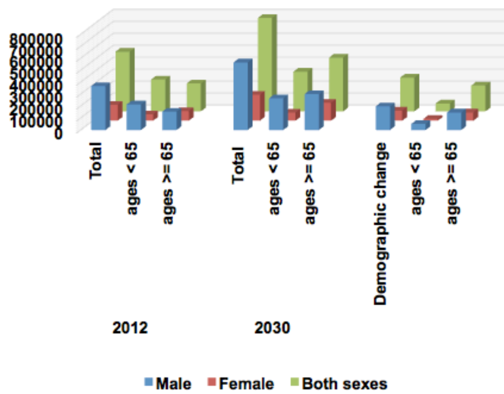
			Estimate	SE	t-value	p-value
World	Intercept		656898	11062	59.38	
	Time	5 year increase	117075	3335	35.1	<0.0001
Region 1	Intercept		35859.2	1821.7	19.68	
	Time	5 year increase	9298	549.3	16.93	0.0004
Region 2	Intercept		44781.2	963.6	46.47	
	Time	5 year increase	9179.2	290.5	31.59	<0.0001
Region 3	Intercept		10137.5	781.4	12.97	
	Time	5 year increase	3612.7	235.6	15.33	0.0006
Region 4	Intercept		61528.6	500	23.05	
	Time	5 year increase	5566.8	150.8	36.92	<0.0001
Region 5	Intercept		57160.2	1657.8	34.48	
	Time	5 year increase	13774	499.8	27.56	0.0001
Region 6	Intercept		450094	1148.2	392	
	Time	5 year increase	74898.2	346.2	216.3	<0.0001

b

			Estimate	SE	t-value	p-value
World	Intercept		604435	12454	48.53	
	Time	5 year increase	112160	3755	29.87	<0.0001
Region 1	Intercept		34863	1873	18.61	
	Time	5 year increase	9261	565	16.4	0.0005
Region 2	Intercept		42026	1129	37.23	
	Time	5 year increase	9152	340	26.89	0.0001
Region 3	Intercept		9741	794	12.26	
	Time	5 year increase	3593	240	15	0.0006
Region 4	Intercept		61881	691	89.56	
	Time	5 year increase	5838	208	28.02	<0.0001
Region 5	Intercept		51445	1869	27.53	
	Time	5 year increase	13109	563	23.27	0.0002
Region 6	Intercept		405635	2452	165.45	
	Time	5 year increase	71256	739	96.39	<0.0001

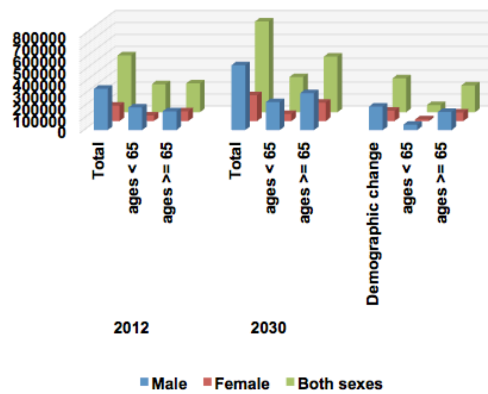
Figure 3a,b: Effect of demographic shift on the incidence (a) and mortality (b) rates in WPRO regions (2012 – 2030)

a



Year	Estimated number of new cancers (all ages)	Male	Female	Both sexes
2012	Total	367572	132934	500506
	ages < 65	213899	52784	266683
	ages >= 65	153673	80150	233823
2030	Total	565723	217507	783230
	ages < 65	265056	67824	332880
	ages >= 65	300667	149683	450350
	Demographic change	198151	84573	282724
	ages < 65	51157	15040	66197
	ages >= 65	146994	69533	216527

b



Year	Estimated number of cancer deaths (all ages)	Male	Female	Both sexes
2012	Total	347208	129484	476692
	ages < 65	188909	46166	235075
	ages >= 65	158299	83318	241617
2030	Total	544878	216105	760983
	ages < 65	234526	60469	294995
	ages >= 65	310352	155636	465988
	Demographic change	197670	86621	284291
	ages < 65	45617	14303	59920
	ages >= 65	152053	72318	224371

Table 1: LC incidence and mortality in WPRO region 6 (for both sexes; all ages)

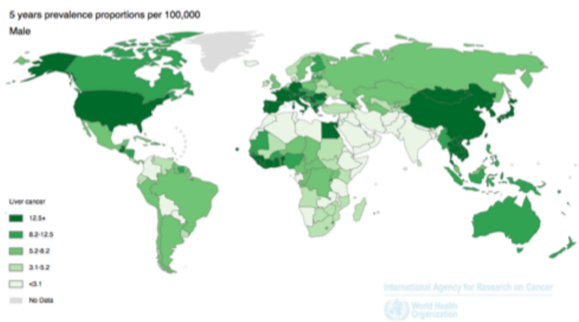
	Liver - Estimated incidence, all ages: both sexes				Liver - Estimated mortality, all ages: both sexes			
WPRO Countries	**Numbers**	**Crude Rate**	**ASR (W)**	**Cumulative risk**	**Numbers**	**Crude Rate**	**ASR (W)**	**Cumulative risk**
Eastern Asia	466336	29.4	**20.9**	2.26	443948	28.0	**19.6**	2.06
China	394770	29.0	**22.3**	2.37	383203	28.1	**21.4**	2.21
Japan	36168	28.6	**9.3**	1.08	32518	25.7	**7.7**	0.84
Korea, Republic of	16900	34.8	**22.8**	2.70	12275	25.3	**15.9**	1.87
Mongolia	1518	53.4	**78.1**	9.35	1345	47.3	**70.3**	8.51
South-Eastern Asia	79953	13.2	**14.2**	1.64	76357	12.6	**13.6**	1.56
Brunei	20	4.8	**7.0**	0.93	19	4.6	**6.8**	0.91
Cambodia	2264	15.6	**22.0**	2.60	2155	14.9	**21.5**	2.56
Lao PDR	2116	33.2	**52.6**	6.21	2022	31.7	**50.9**	5.97
Malaysia	1527	5.2	**6.0**	0.72	1750	6.0	**7.0**	0.82
Philippines	7734	8.0	**11.4**	1.32	7434	7.7	**11.4**	1.31
Singapore	763	14.5	**9.7**	1.17	747	14.2	**9.3**	1.05
Viet Nam	21997	24.5	**24.6**	2.72	20920	23.3	**23.7**	2.66
Oceania	2718	7.2	**5.4**	0.60	2515	6.7	**4.9**	0.53
Australia/New Zealand	1954	7.1	**4.2**	0.49	1774	6.5	**3.6**	0.41
Australia	1658	7.2	**4.2**	0.49	1538	6.7	**3.7**	0.43
New Zealand	296	6.6	**4.0**	0.48	236	5.3	**3.0**	0.35
Melanesia	706	7.7	**10.9**	1.17	674	7.4	**10.5**	1.14
Fiji	70	8.0	**8.9**	1.04	60	6.9	**7.8**	0.85
Papua New Guinea	543	7.6	**11.2**	1.16	521	7.3	**10.7**	1.11
Solomon Islands	41	7.2	**11.4**	1.32	39	6.9	**11.4**	1.36
Vanuatu	26	10.3	**15.1**	1.79	26	10.3	**15.1**	1.79
Micronesia	35	6.4	**7.0**	0.90	32	5.8	**6.5**	0.85
Samoa	4	2.2	**3.0**	0.33	4	2.2	**3.0**	0.33

Table 2: Categorization of WPRO regional members based on HDI rank, life expectancy, physicians and health expenditure.

HDI Rank	WPRO Member States	Human Development Index (HDI)	Life expectancy at birth	Physicians	Health expenditure
		Value	(years)	(per 10,000 people)	(as % of GDP)
		2013	2013	2003-2012	2011
Very High Human Development					
2	Australia	0.933	82.5	38.5	9.0
7	New Zealand	0.910	81.1	27.4	10.1
9	Singapore	0.901	82.3	19.2	4.6
15	Korea (Republic of)	0.891	81.5	20.2	7.2
17	Japan	0.890	83.6	21.4	9.3
30	Brunei Darussalam	0.852	78.5	13.6	2.5
High Human Development					
62	Malaysia	0.773	75.0	12.0	3.6
88	Fiji	0.724	69.8	4.3	3.8
91	China	0.719	75.3	14.6	5.2
Medium Human Development					
103	Mongolia	0.698	67.5	27.6	5.3
106	Samoa	0.694	73.2	4.8	7.0
121	Viet Nam	0.638	75.9	12.2	6.8
124	Micronesia (Federated States of)	0.630	69.0	1.8	13.4
131	Vanuatu	0.616	71.6	1.2	4.1
136	Cambodia	0.584	71.9	2.3	5.7
139	Lao People's Democratic Republic	0.569	68.3	1.9	2.8
Low Human Development					
157	Papua New Guinea	0.491	62.4	0.5	4.3
157	Solomon Islands	0.491	67.7	2.2	8.8

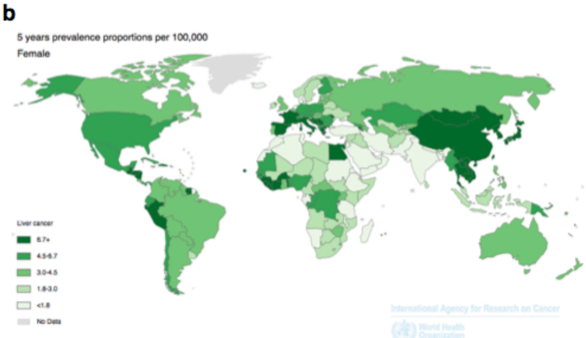
Supplemental Figure 1a,b: LC estimated incidence and 5-year prevalence (proportion) worldwide by WHO and HDI classification for male (a) and female (b) of all ages

a



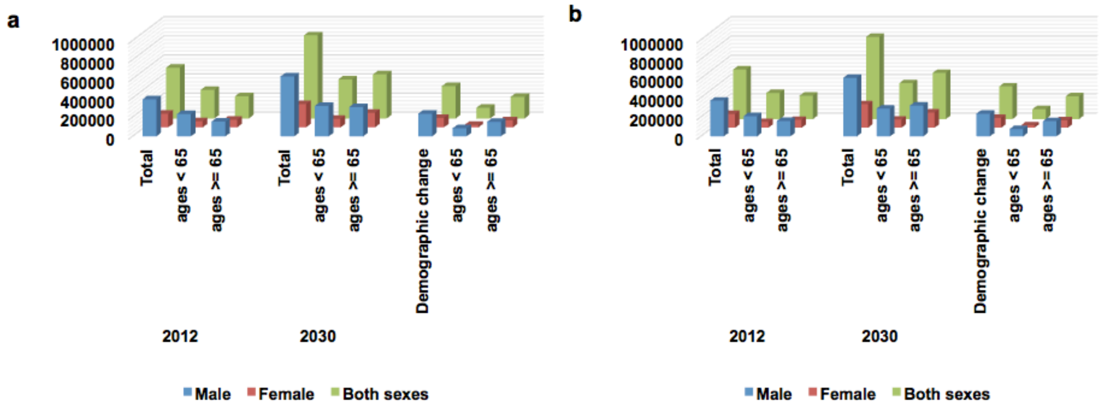
Liver - Estimated incidence and prevalence, adult population: male		
POPULATION	**Incidence**	**5-year (prop.)**
World	552118	453345 (17.5)
WHO Africa region (AFRO)	24418	17041 (6.7)
WHO Americas region (PAHO)	39968	35066 (9.9)
WHO East Mediterranean region (EMRO)	19652	11942 (5.6)
WHO Europe region (EURO)	46955	41823 (11.7)
WHO South-East Asia region (SEARO)	54136	33290 (5.0)
WHO Western Pacific region (WPRO)	366948	314160 (41.9)
Very High Human Development (VHHD)	107145	133002 (28.4)
High Human Development (HHD)	26294	20438 (5.3)
Medium Human Development (MHD)	386759	278467 (20.7)
Low Human Development (LHD)	31810	21438 (5.5)

b



Liver - Estimated incidence and prevalence, adult population: female		
POPULATION	**Incidence**	**5-year (prop.)**
World	226804	179825 (6.9)
WHO Africa region (AFRO)	13857	9413 (3.6)
WHO Americas region (PAHO)	22652	18402 (5.0)
WHO East Mediterranean region (EMRO)	9411	5600 (2.8)
WHO Europe region (EURO)	23292	19654 (5.1)
WHO South-East Asia region (SEARO)	25011	14554 (2.2)
WHO Western Pacific region (WPRO)	132565	112190 (15.4)
Very High Human Development (VHHD)	46341	57139 (11.7)
High Human Development (HHD)	19360	14876 (3.6)
Medium Human Development (MHD)	143157	95898 (7.4)
Low Human Development (LHD)	17898	11912 (3.0)

Supplemental Figure 2a,b: Effect of demographic shift on the incidence (a) and mortality (b) rates in MDH areas (2012 – 2030)

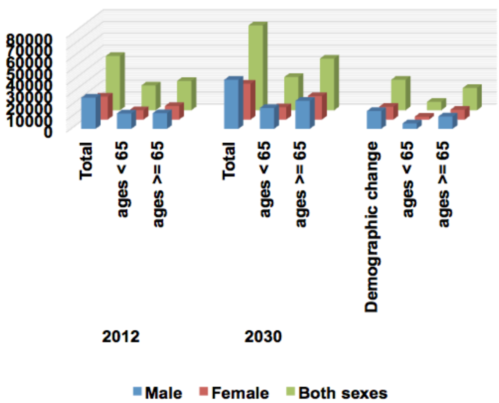


Year	Estimated number of new cancers (all ages)	Male	Female	Both sexes
2012	Total	388078	143853	531931
	ages < 65	233683	64611	298294
	ages >= 65	154395	79242	233637
2030	Total	626470	243955	870425
	ages < 65	318985	90521	409506
	ages >= 65	307485	153434	460919
	Demographic change	238392	100102	338494
	ages < 65	85302	25910	111212
	ages >= 65	153090	74192	227282

Year	Estimated number of cancer deaths (all ages)	Male	Female	Both sexes
2012	Total	372495	142033	514528
	ages < 65	211371	59647	271018
	ages >= 65	161124	82386	243510
2030	Total	609340	243935	853275
	ages < 65	288713	84621	373334
	ages >= 65	320627	159314	479941
	Demographic change	236845	101902	338747
	ages < 65	77342	24974	102316
	ages >= 65	159503	76928	236431

Supplemental Figure 3: Effect of demographic shift on the incidence and mortality rates in LDH areas (2012 – 2030)

a

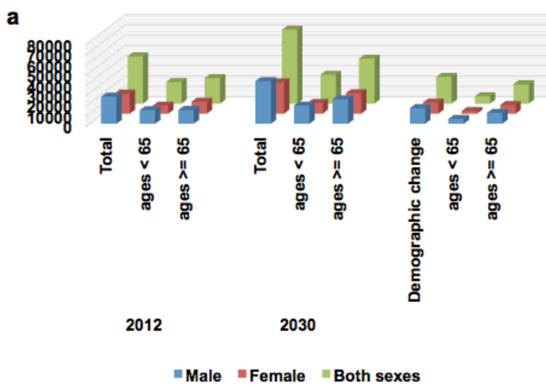


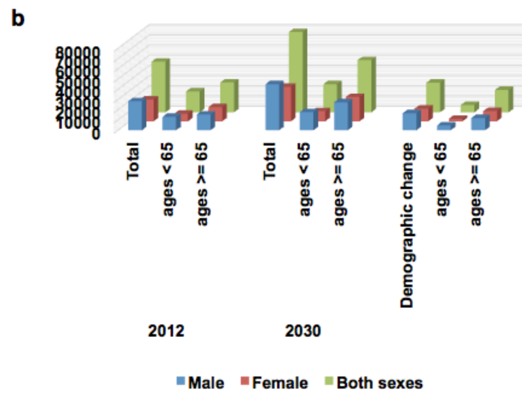
b

Year	Estimated number of new cancers (all ages)	Male	Female	Both sexes
2012	Total	26558	19566	46124
	ages < 65	13172	7949	21121
	ages >= 65	13386	11617	25003
2030	Total	41711	30464	72175
	ages < 65	17794	10453	28247
	ages >= 65	23917	20011	43928
	Demographic change	15153	10898	26051
	ages < 65	4622	2504	7126
	ages >= 65	10531	8394	18925

Year	Estimated number of cancer deaths (all ages)	Male	Female	Both sexes
2012	Total	30707	17278	47985
	ages < 65	22156	11975	34131
	ages >= 65	8551	5303	13854
2030	Total	53113	29994	83107
	ages < 65	38021	20594	58615
	ages >= 65	15092	9400	24492
	Demographic change	22406	12716	35122
	ages < 65	15865	8619	24484
	ages >= 65	6541	4097	10638

Supplemental Figure 4a,b: Effect of demographic shift on the incidence (a) and mortality (b) rates in VHHD areas (2012 – 2030)

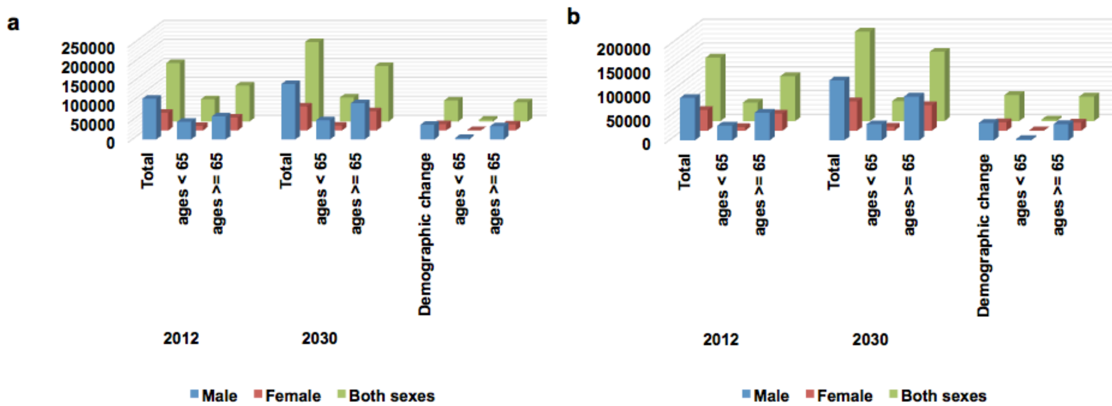




Year	Estimated number of new cancers (all ages)	Male	Female	Both sexes
2012	Total	26558	19566	46124
	ages < 65	13172	7949	21121
	ages >= 65	13386	11617	25003
2030	Total	41711	30464	72175
	ages < 65	17794	10453	28247
	ages >= 65	23917	20011	43928
	Demographic change	15153	10898	26051
	ages < 65	4622	2504	7126
	ages >= 65	10531	8394	18925

Year	Estimated number of cancer deaths (all ages)	Male	Female	Both sexes
2012	Total	28399	21312	49711
	ages < 65	13029	7425	20454
	ages >= 65	15370	13887	29257
2030	Total	45076	33646	78722
	ages < 65	17699	9847	27546
	ages >= 65	27377	23799	51176
	Demographic change	16677	12334	29011
	ages < 65	4670	2422	7092
	ages >= 65	12007	9912	21919

Supplemental Figure 5a,b: Effect of demographic shift on the incidence (a) and mortality (b) rates in HHD areas (2012 – 2030)



Year	Estimated number of new cancers (all ages)	Male	Female	Both sexes
2012	Total	107433	46513	153946
	ages < 65	46649	12100	58749
	ages >= 65	60784	34413	95197
2030	Total	146126	63496	209622
	ages < 65	50679	12801	63480
	ages >= 65	95447	50695	146142
	Demographic change	38693	16983	55676
	ages < 65	4030	701	4731
	ages >= 65	34663	16282	50945

Year	Estimated number of cancer deaths (all ages)	Male	Female	Both sexes
2012	Total	89339	43820	133159
	ages < 65	31100	7769	38869
	ages >= 65	58239	36051	94290
2030	Total	126329	61627	187956
	ages < 65	33985	8288	42273
	ages >= 65	92344	53339	145683
	Demographic change	36990	17807	54797
	ages < 65	2885	519	3404
	ages >= 65	34105	17288	51393

Supplemental Table 1: LC incidence and mortality worldwide by WHO and HDI classification (for male and female; all ages)

	Liver – Estimated incidence, all ages: male				Liver - Estimated mortality, all ages: male			
POPULATION	Numbers	Crude Rate	ASR (W)	Cumulative risk	Numbers	Crude Rate	ASR (W)	Cumulative risk
World	554369	15.6	15.3	1.72	521041	14.6	14.3	1.57
WHO Africa region (AFRO)	24791	5.6	9.8	1.07	23758	5.4	9.3	1.01
WHO Americas region (PAHO)	40288	8.6	7.4	0.88	34704	7.4	6.2	0.73
WHO East Mediterranean region (EMRO)	19844	6.2	9.7	1.19	18893	5.9	9.3	1.15
WHO Europe region (EURO)	47155	10.8	6.8	0.83	44087	10.1	6.1	0.73
WHO South-East Asia region (SEARO)	54678	5.8	7.2	0.86	52351	5.5	6.9	0.81
WHO Western Pacific region (WPRO)	367572	38.9	31.2	3.36	347208	36.7	29.2	3.09
Very High Human Development (VHHD)	107433	18.9	11.0	1.31	89339	15.7	8.6	1.00
High Human Development (HHD)	26558	5.2	5.1	0.61	28399	5.5	5.4	0.65
Medium Human Development (MHD)	388078	21.3	22.0	2.40	372495	20.5	21.2	2.26
Low Human Development (LHD)	32190	4.9	8.1	0.91	30707	4.7	7.7	0.87
	Liver - Estimated incidence, all ages: female				Liver - Estimated mortality, all ages: female			
POPULATION	Numbers	Crude Rate	ASR (W)	Cumulative risk	Numbers	Crude Rate	ASR (W)	Cumulative risk
World	228082	6.5	5.4	0.59	224492	6.4	5.1	0.55
WHO Africa region (AFRO)	14032	3.2	5.2	0.58	13403	3.1	4.9	0.54
WHO Americas region (PAHO)	22872	4.7	3.4	0.40	23180	4.8	3.3	0.38
WHO East Mediterranean region (EMRO)	9523	3.1	4.5	0.54	9056	3.0	4.4	0.52
WHO Europe region (EURO)	23421	5.0	2.4	0.27	24959	5.4	2.3	0.26
WHO South-East Asia region (SEARO)	25284	2.8	3.1	0.35	24395	2.7	3.0	0.34
WHO Western Pacific region (WPRO)	132934	14.8	10.0	1.06	129484	14.4	9.4	0.96
Very High Human Development (VHHD)	46513	8.0	3.5	0.39	43820	7.5	2.9	0.31
High Human Development (HHD)	19566	3.7	2.8	0.33	21312	4.0	3.0	0.35
Medium Human Development (MHD)	143853	8.3	7.6	0.81	142033	8.2	7.4	0.76
Low Human Development (LHD)	18102	2.8	4.4	0.50	17278	2.7	4.2	0.48

Supplemental Table 2a,b: LC incidence and mortality in WPRO region 6 by age (for male and female) (a). LC incidence and mortality in TOP 6 WPRO member states by age (for both sexes) (b)

A

WPRO liver cancer estimated incidence and mortality by age

	Total	0-14	15-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+	Crude	ASR (W)	Cum. [0-74]
Incidence - Male	367572	0.3	6	30.1	47.9	68.6	90.9	106.4	131.7	177.3	269	38.9	**31.2**	**3.4**
Mortality - Male	347208	0.3	5.2	26.9	41.9	59.9	81.6	94.6	120.2	175.3	298.3	36.7	**29.2**	**3.1**
Incidence - Female	132934	0.2	1.2	5.9	10.5	17	25.9	32.6	45.4	70.3	127.1	14.8	**10**	**1.1**
Mortality - Female	129484	0.1	0.8	5.1	8.8	14.2	22.4	32.7	42	64.2	141.4	14.4	**9.4**	**1.0**
Incidence – both sexes	500506	0.3	3.7	18.2	29.5	43.2	59	69.6	87.7	121.4	187	27.2	**20.4**	**2.2**
Mortality – both sexes	476692	0.2	3.1	16.2	25.6	37.4	52.6	63.7	80.3	117.3	207.7	25.9	**19.1**	**2.0**

B

Top 6 WPRO member states liver cancer estimated incidence and mortality by age

	Liver Cancer, both sexes	Total	0-14	15-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+	Crude	ASR (W)	Cum. [0-74]
China	Incidence	394770	0.3	4.1	19.3	30.8	45	61.7	73	93.9	134.1	226	29	22.3	2.4
	Mortality	383203	0.2	3.5	17.7	27.6	40.5	56.8	69.2	87.9	130	252.5	28.1	21.4	2.2
Mongolia	Incidence	1518	-	1.8	38	91.9	173.3	268.4	365.6	465.5	552.4	528.3	53.4	78.1	9.4
	Mortality	1345	-	1.6	29.1	72.4	140	230.9	335.4	441.5	521.5	514	47.3	70.3	8.5
Republic of Korea	Incidence	16900	0.3	2.4	19.1	34.3	54.3	79.1	102.8	117.4	126.8	128.2	34.8	22.8	2.7
	Mortality	12275	*0.1*	1.2	9.8	19.3	31.8	45.9	65.6	88.6	110.5	137.8	25.3	15.9	1.9
Cambodia	Incidence	2264	0.5	1.7	17.1	31.5	52.2	76	97.4	115.4	128.3	135.6	15.6	22	2.6
	Mortality	2155	0.4	1.3	14.1	26.2	43.6	66	92.2	120.3	148.6	173	14.9	21.5	2.6
Lao PDR	Incidence	2116	*0.3*	2.6	32.2	64.1	117.6	182	241.7	292.4	337.8	369.2	33.2	52.6	6.2
	Mortality	2022	*0.3*	1.9	26.7	53.5	96.4	153.1	219.5	292.4	378.5	460.4	31.7	50.9	6.0
Viet Nam	Incidence	21997	0.3	5.5	34.1	56.3	77	87.1	89.7	89.4	88.5	83.7	24.5	24.6	2.7
	Mortality	20920	0.3	4.5	29.1	47.3	65.2	79.8	89.8	97.7	106.6	111.8	23.3	23.7	2.7

Chapter V

Summary

The time trends in cancer incidence and mortality vary substantially for different countries. The cancer transition in low-and medium-HDI countries combined with growing and ageing population means that many countries are facing a double burden of cancer – that is the burden associated with infectious agents combined with an increasingly westernized lifestyle. The global cancer burden is expected to increase in all countries due to population growth, aging, and an increasing prevalence of certain risk factors. This outstanding global health concern has been well responded by the health community through the endorsement of the “25 by 25” strategy as part of the NCD Global Monitoring Framework. The goal of the NCD Global Health Framework is to reduce avoidable mortality from NCDs by 25% by 2025 through the support and active participation from all levels of society.[45] The “25 by 25” strategy would be expected to represent a decrease of 25% premature cancer deaths each year by 2025 (a reduction of 1.5 Million from a predicted 6 Million premature cancer deaths in people aged 30-69 years). The achievement of the 25% reduction in premature cancer deaths will need more effective prevention, to reduce incidence, and more effective health systems, to improve survival. As aptly put forth by Drs. Paolo Vineis and Christopher P Wild, “Cancer is a global and growing, but not uniform, problem.”[7] The primary prevention of cancer is the effective and cost-effective way to fight the war against cancer with 33% to 50% of cancers that are preventable. The progress of cancer control strongly depends on the complementation of cancer prevention with early detection and effective treatments. Unfortunately, the current socio-economic trends globally do not promote prevention since it takes time to manifest and lacks strong leadership/policy advocates.

Final thoughts

A topic of continuous global health debate is the usefulness to identify differences in cancer incidence and mortality trends between countries, between regions within a country, or between populations defined by racial or ethnic group or socio-economic status. The concern put forth is that whether the differences noted above have any effect on the health policy or the public especially because the countries being compared have widely different economic development, some of them extremely poor, others with civil conflicts. Anderson and colleagues[1] have put forth hypothesis that the information on the global trends and disparities in cancer burden can help focus debate on reducing geographical, racial and/or ethnic disparities. Groundbreaking research by Bray and colleagues[46] have demonstrated that long term surveillance of worldwide trends in cancer incidence has provided data for causal research and the basis for prevention and screening. It is expected that the continuous global surveillance of cancer would provide an impetus for alteration in healthcare policy and healthcare systems and serve as a key metric for the global cancer control.

Chapter VI

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