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Evolving Cancer Paradigms: Contrasting Cancer Incidence, Mortality and Survival in Wealthy and Less Privileged Countries - 2012

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Abstract

While cancer survival rates continue to decrease in countries of sustained medium-high to high economic development as a result of the inception of novel diagnostic techniques and therapies, cancer incidence and mortality rates continue to grow in all parts of the world. Population expansion and aging, increasing exposure to environmental carcinogens, adoption of westernized diets based on highly processed foods, and an assortment of other factors contribute to the increasing figures. In addition, several underdeveloped countries are undergoing an epidemiologic transition from transmissible diseases to non-transmissible malaise including cancer, as their economic models evolve toward industrial development. Large data collection programs including Global Burden of Disease Collaboration, GLOBOCAN-2012, and CONCORD-3, in addition to the United Nations Development Program data, have been used here to provide a basis for discussing cancer rate differences in diverse areas of the world. Sharply contrasting cancer incidence and mortality rates emerge. Two indexes are suggested in an attempt to better comprehend the data and provide a measure of dependability in the collected registries.

Keywords: Cancer Paradigms; Contrasting Cancer Incidence; Mortality

Abbrevations: LDC: Less Developed Countries; ET: Epidemiologic Transition; HDI: Human Development Index; CTSI: Cancer Treatment Success Index; POPs: Persistent Organic Pollutants.

Introduction

If it is highly likely that readers of this article will have passed away by the end of this century, it is also reasonable to suppose that cancer as a global disease will continue to affect millions of people across the world in the next several decades. This situation will be particularly callous in the majority of less developed countries (LDC) and poor zones of the industrial world (IC). Governments will find it increasingly difficult to put together public resources needed for bolstering local cancer research, adopting modern advances in prevention and early detection reaching the underprivileged, and providing adequate care to malignancies-stricken people

while enforcing education policies aimed at changing harmful living habits.

This dispiriting picture emerges from extrapolation of the course of the world's cancer burden in the past 20 years [1-3]. On the positive side there are encouraging trends of 5-year survival rates recorded in several countries, all cancers taken together, e.g. 1.5% increase per year between 2003 and 2012 in the United States [4]. This is the result of a continuous flow of novel therapies available to the public and the discovery of molecular mechanisms involved in tumor progression as currently understood in the 'hallmarks of cancer' framework, the tissue organization field theory and the metabolic disruption views [5,6]. In spite of this, the global death toll continues to grow in all major cancers with few exceptions. By 1990 cancer-related fatalities amounted to 12% of all deaths rising to 15% in 2013. It is expected to grow further in the next decade, jumping from 14 million cancer patients in 2012 to 21,6 million cases by 2030 [7,8].

Cancer Morbidity Contrast between High Income and Low Income Countries

There are great disparities in morbidity and mortality of all cancers between LDCs and ICs. By 2000, of the 10 million new cases and 7 million deaths from cancer, there was an almost equal share from either model of society: 53% and 56% for incidence and mortality from LDCs. By 2013, new cases had risen globally to 14.9 million and 8.2 million deaths. However, incidence was greater in IC: for every 246 cases per 100K in developed countries, there were 148 per 100K in developing countries [9]. Whether this is the result of the deployment of new diagnostic techniques using expensive equipment such as PET- CT scans, breast magnetic resonance imaging and other analytical techniques, is not clear. Citizens in ICs are more cancer-conscious and educated than in LDCs. The latter countries support notorious health budget restrictions, and their disease profiles are different.

Primary data sources are created by each country under their own restrictions and paradigms. Such variety of scenarios creates considerable difficulty when comparing global figures from different sources, cultures and methods as the GLOBOCAN 2012 intends to do [10]. This is the best tool available today, however, and important conclusions can be drawn. But great difficulties persist by considering the very nature of cancer.

Among oncologists it is generally accepted that malignant tissue tumors are first discovered in a patient when they reach 1 cm^3. This tissue mass may contain a billion cancerous cells by then, although disagreement as to actual figures has been put forward [11]. Precise numbers notwithstanding, such a mass of modified cells suggests that tumorigenesis started several years, even decades before the tumor was discovered. The distance between cause and effect is such and the number of intervening effectors to which people are exposed so large that establishing a relationship between cause and effect has been a very challenging enterprise.

Cancer and Epidemiologic Transition: The Case of Latin America

Among several others, a fundamental contributing factor is the spectrum of diseases in a given population and the manner in which these malaises change as the years pass. This is known as epidemiologic transition (ET) and affects cancer rates deeply. ET depends strongly on the relative socioeconomic development of the population as will be reviewed below. While most ICs have overcome tuberculosis, diphtheria, cholera, yellow fever and other bacterial plagues as main killers and an assortment of other infectious diseases that shortened the natural life expectancy of the population, several less developed countries continue to fight these ailments in addition to malaria and many other water-borne or insect transmitted parasites and viruses. These countries still endure inadequate sanitation and sub nutrition in substantial sections of their population, or the extremes of prolonged civil strife and war. These health issues take precedence over cancer in many parts of the LDCs world today.

Intimately associated with the local infectious bacterial panoply is the occurrence of malignancies caused by biological agents. It has been estimated that 16.1% of all cancer cases registered in 2008 (12.7 million) were attributable to infections [12]. In harmony with this finding, LDCs carried a higher proportion (22.9%) of infection-derived cancers than ICs (7.4%). While New Zealand rated 3.3% cancer cases due to infections, this figure climbed to 32.7% in Sub-Saharan Africa. Infection by aggressive strains of *Helicobacter pylory,* hepatitis B and C and human papilloma viruses, and *Ophistorchis viverrini* and *Clonorchis sinensis* liver flukes, have been linked to stomach and liver carcinomas, top killers in many LDCs. As well, *Schistosoma haematobium* worms have been linked to bladder cancer in parts of Asia, Africa and the Middle East. These infections are rare in ICs.

The progressive encroachment of economic globalization, the expansion of democratic principles

impinging on people's rights to healthy life conditions and rural migration to ever growing cities are creating new living conditions never seen before in many LDCs. These conditions may bring about, but not always, a more ample food offer, better sanitation, access to medical services and cultural exposure to westernized life styles and consumer patterns. ET at a large scale is taking place in many LDCs but large differences prevail as measured by prevalence of transmissible diseases (TD) [13]. Comparison of death statistics (1997) due to TD in four Latin American countries yielded 61% of all deaths for Guatemala, 22% in Mexico, 13% in Chile and only 7% in Uruguay [14]. At that time, Guatemala was in a state of pre-epidemiologic transition, Mexico fell in medium ET stage and Uruguay had practically completed this transition.

That the burden of TD and undernourishment-derived malaises are slowly being replaced by chronic, non-communicable diseases and age-related conditions is illustrated by the growing cancer rates of Uruguay, currently similar to those of Canada. Most importantly, both countries possess similar patterns of cancer types (Figure 1). This trend is reported also for other regions of the world in the middle of ET [15]. Meanwhile, to this date cancer incidence and mortality in Guatemala continue in the low range of Latin American countries, with gastric cancer as the most common malignancy. ET remains understudied in this area of the world and in the majority of LDCs. The question remains as to whether health authorities in LDCs undergoing ET are prepared for the challenges of new disease patterns in large sectors of the population in the coming years [16].

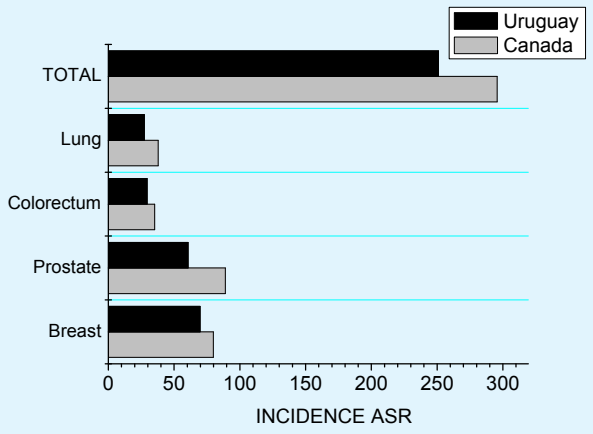

Figure 1: Comparison of age standardized incidence rates (ASR) of the most common cancers in Canada and Uruguay, suggesting the advanced epidemiological transition of the South American country. Data for 2012 from GLOBOCAN 2012.

Cancer Rates and Human Development Index (HDI)

The HDI scale was devised by the United Nations Development Programme to estimate a country's citizen average well-being through the combined effect of three basic criteria: life expectancy at birth, expected and mean years of schooling, and gross national income per capita. Four levels result from this assessment, very high (VHHD), high (HHD), medium (MHD) and low (LHD) human development indexes [17]. When cancer incidence and mortality rates are applied to these groups a clear correlation appears (Table 1). Paradoxically, the more privileged groups endure the worse cancer incidence and mortality rates (ASR). Additional meaning to these rates can be extracted by estimating the predicted overall survival ratio (POSR) by way of equation 1:

$$POSR = [1 - ASR_{mortality},/ASR_{incidence}]$$

Human Development group	HDI	Incidence (ASR)	Mortality (ASR)	POSR
Very high human development	0.800-1.000	278.1	105.3	0.621
High human development	0.700-0.799	180.2	102.3	0.432
Medium human development	0.550-0.699	144.2	100.8	0.301
Low human development	0.352-0.549	112.8	86.7	0.231
Less developed regions - Mean	-	147.7	98.4	0.334

Table 1: Age standardized rates per 100.000 (ASR) of cancer incidence and mortality for both sexes and all ages in 2012 in selected human groups according to their Human Development Index (HDI), as estimated by the International Agency for Research on Cancer [GLOBOCAN 2012] and UNDP 2015. Predicted overall survival ratio (POSR) for all cancers included in surveys is calculated as $[1 - ASR_{mortality},/ASR_{incidence}]$.

POSR approaches the rough survival ratio, considering that deaths counts result from cancer incidence of previous years and assuming that incidence does not vary substantially in a five year period if the number of patients is sufficiently large. The higher POSR indicates a greater chance of survival and is a measure of the percentage of survival. Using this criterion (Table 1, right column) about 62% of all patients diagnosed with any type of cancer survive in the VHHDI group, whereas survival decreases to 43% in HHD and nearly 30% in MHD. Survival plunges to 23% or less in the LHD group.

These global figures are in agreement with 5-year survival rates for frequent cancers: breast neoplasms which have been widely researched and successful treatments are now available, show survival rates of about 90% in New Zealand and the United States for the 2010-2014 period but drops to 66% in India, according to the CONCORD-3 program [10]. Survival percentages of life-threatening cancers in children show similar disparities between IC and emerging economies: 80% in Scandinavian countries against 28.9% in Brazil.

In principle, VHHD citizens should have better access to cutting edge therapies and methods, as well as personal resources to surmount the cancer challenge, despite the high impact of cancer incidence in their society. The pattern of malignancies types in each HDI group is different (Table 2) and so strategies and priority approaches must be adapted to each reality. For example, breast, prostate and lung cancers incidence and mortality ASRs define a consistent pattern in VHHD and HHD groups, whereas stomach and liver tumors are prominent in MHD and LHD communities. In all cases across the HDI board, liver malignancies have very poor prognosis. Lung cancers presuppose additional complications as trends vary for men and women follow different figures and prognosis. Malignant neoplasms may occur in trachea, bronchus and lung spongy tissue giving rise to different clinical symptoms. In addition to the long latency of lung cancer after exposure to tobacco and other aggressive substances such as metal dusts, asbestos and some carcinogenic organic volatiles, many lung tumors are detected only after patients complain of symptoms when therapy is less effective, a general occurrence in most cancer cases. This is compounded by patients relative awareness of what cancer symptoms may feel like and physical or financial barriers to seeking medical help [18]. A particularly problematic situation in LDCs. This creates a complex scenario for predictions of survival chances.

Human development group				
Organ	**VHHD**	**HHD**	**MHD**	**LHD**
Total	278.1(105.3)	180.2(102.3)	144.2(100.8)	112.8(86.7)
Breast	78.2(14.1)	45.2(14.6)	26.5(9.8)	32.6(17.0)
Prostate	72.0(9.7)	37.5(12.9)	7.0(3.8)	14.9(12.1)
Lung	31.0 (23.9)	18.7(16.4)	23.8(21.6)	5.4(4.8)
Colo-rectum	30.6(11.0)	17.5(10.0)	11.3(6.7)	4.9(3.9)
Cervix Uteri	8.5(2.7)	15.5(6.1)	13.8(7.1)	25.7(16.6)
Stomach	10.9(5.5)	11.7(9.5)	14.4(11.8)	4.6(4.4)
Bladder	9.7(2.4)	5.9(2.4)	2.9(1.4)	2.2(1.5)
Liver	7.0(5.5)	3.8(4.1)*	14.6(14.1)	6.2(5.9)

Table 2: Age standardized rates (ASR): incidence and (mortality) of major cancers as estimated by the International Agency for Research on Cancer [GLOBOCAN 2012], among selected human groups of both sexes and all ages, according to their Human Development Index.: very high human development; HHD: High human development; MHD: Medium human development; LHD: Low human development. Non-melanoma skin cancers have been excluded. VHHD

* Death rates can only be higher than incidence rates if there is a significant drop in incidence for the surveyed year or an undue number of deaths by this cause were registered on the same year. This is an unusual occurrence.

As a result, five-year survival rates vary in a wide range between countries [e.g. 6% (CL95% 6 – 7) in Bulgaria, a MHD country, 16% (16 – 17) and 30% (29 – 31) in Germany and Japan, respectively, both VHHD countries], or within the same country (Italy: Biella region 8% (5 – 11), Romagna region 19 (17 – 20) [19]. In turn, incidence and mortality of liver cancer, a more common neoplasm in MHD and LHD communities, is also increasing sharply in the United States in recent decades. Besides, it is not equally distributed among the population [Ryerson et al., 2016] as it occurs in other large countries.

Cancer, Location and Socioeconomic Status: The Latin American Position

It has long been established that cancer incidence is strongly contingent upon geographic location at the country level (Table 3). However, regional variations within the same country are frequently recorded but are

not reflected in world compendiums. Reports exist about highly contrasting rates in specific cancers found in areas only tens to a few hundred kilometers apart within the same country. Such differences may be linked to the uneven distribution of carcinogenic plants (Bracken ferns); [20] and local food habits [21,22]. Gastric cancer incidence and mortality are substantially higher among residents of high mountain elevations than coastal zones in most of Pacific Central and South America and Venezuela [23,24]. This feature is not reflected in GLOBOCAN-2012 studies but is a local relevant reality to devise effective control health policies [25].

Location	HDI	Incidence (ASR)	Mortality (ASR)	Survival ratio	CTSI
Northern Europe	-	277.4	108.2	0.61	*
Southern Europe	-	253.6	105.2	0.585	*
United States	0.92	318	105.8	0.667	0.573
Norway	0.941	318.3	99.3	0.688	0.688
Ireland	0.923	307.9	108.4	0.648	0.648
Korea (South)	0.901	307.8	100.3	0.674	0.674
France	0.897	303.5	107.9	0.644	0.14
Canada	0.92	295.7	103.2	0.651	0.498
UK	0.909	272.9	110	0.597	0.597
Sweden-Finland	0.913-0.895	265.1	90.1	0.66	0.65
Greece-Spain	0.866-0.884	231.5	98.2	0.575	0.117
Japan	0.903	217.1	93.8	0.568	0.243
China	0.738	174	122.2	0.297	0.007
C/South America	0.847-0.625	206.7	118	0.429	0.016
Brazil	0.754	231.6	123.8	0.465	0.001
Colombia	0.727	175.2	95.7	0.454	0.095
Argentina	0.827	230.4	141.7	0.385	0.09
Chile	0.847	195.3	120.4	0.384	0.052
Venezuela	0.767**	146.9	95.3	0.351	*
Uruguay	0.795	297.5	197.3	0.337	0.337
Paraguay	0.693	143.2	101.3	0.293	*
Guatemala	0.64	130.4	96.4	0.261	*
Sub-Saharan Africa	0.352-0.540	121	90.8	0.25	*
India	0.615	94	64.5	0.314	0
Nepal	0.558	85.2	67.7	0.205	*
Namibia	0.64	82.7	51.9	0.372	*

Table 3: Cancer incidence and mortality age standardized rates (ASR) recoreded by the International Agency for Research on Cancer [GLOBOCAN 2012] ,for selected countries along the Human Development Index (HDI) scale. Survival ratio was calculated from incidence and mortality ratios as per equation 1, and the Cancer Treatment Success Index (CTSI) by means of equation 2.

* The percentage of the national population included in cancer registries was not specified, thus CTSI cannot be calculated.

**HD Index for 2014, previous to the serious sociopolitical conflict and economic downturn 2015-2018.

This feature also implies a strong environmental element in cell tumorigenic evolution as part of the multifactorial equation of cancer induction [26,27]. Environmental chemicals including persistent organic pollutants (POPs) play a worrisome role as they penetrate deep into the organism at low dose affecting key cancer hallmark steps, causing genome instability and reaching the tumor microenvironment itself [28-32].

Putting together cancer incidence and mortality numbers encompassing entire countries organized according to wealth or industrial development gives rise

to a general pattern in which the top ranking HDI countries occupy the higher echelons and the LDCs the lower ranks (Table 3). As expected, data runs in parallel with HDI records of Table 1 as well as incidence of cancer types.

Data Dependability and Novel Risk Factors

Because cancer etiology includes a large number of components and the disease progress may take many years before tumors are detected, (with some exceptions), one can only speculate which factors intervene more prominently in the onset of cancer to feed the data except for the very obvious and well studied such as tobacco smoking, areca chewing, long exposure to sunlight and to carcinogenic chemicals, chronic inflammation of specific organs, and high risk foods which sum up to healthy or unhealthy lifestyles with impact on cancer formation [33,34]. New research encompassing large cohorts and longer periods of follow-up time is revealing novel risk factors associated with environmental components. As regards to other variable factors and living habits that may prevent neoplasm arrival (e.g. diet, control of obesity, physical activity, recognition of risk groups and their regular check-ups) that imply a geographical territory or community size, their identification may be hampered by the myriad of food ingredients in the ample gamut of dietary choices and unidentified confounding factors. The sum of these pro- and anti-carcinogenic components creates a great deal of uncertainty as to the statistical strength of national incidence-mortality-survival figures produced by local official health authorities frequently surpassed in their capacity by other serious community health issues in LDCs and political interest to present a country's health condition better than it really is.

Cancer Treatment Success Index (CTSI)

In an attempt to improve the assessment of the global epidemiological numbers from so many different sources and methods, we have devised a Cancer Treatment Success Confidence Index (CTSI), here introduced for the first time. CTSI is defined as the product of POSR (first term of equation 2) and the percentage of the surveyed population by cancer registries in each country within a period of time.

Equation 2

$$CTSI = \left[1 - \frac{ASR[mortality]}{ASR[incidence]}\right] x \left[\frac{\%\ Pop\ covered}{100}\right]$$

The fraction of surveyed people varies within an ample range in most regions of the world, independently of their per capita national gross product. For example, countries as diverse as Costa Rica, Mongolia and Denmark all include 100% of the national population in the registries of 10 major cancers. By contrast, Italian, German and French registries survey 57.7, 36.8 and 21.7% of the population, respectively. Others encompass smaller contingents of people relative to their population such as Colombia (9.0%), Brazil (7.7%), Iran (2.4%) and India (0.1%), or a fraction of one city only, e.g. Lima (Peru), 24.4%, and Casablanca (Morocco), 12.7%. In some cases these reduced contingents of people may be assumed to be statistically representative of the entire population but this criterion may be challenged. Deviations of the cancer status among the non surveyed groups are likely to be substantial from registered records, since these other communities may be subject to carcinogenic determinants away from the surveyed public, and be distributed in culturally and genetically heterogeneous communities. Also different is their exposure to a variety of environmental impacts, genetics, racial composition, local living styles and food profiles. These elements create a degree of uncertainty in the data that CTSI pursues to reflect through the second term of equation 2.

Theoretically, CTSI fluctuates between zero for the least dependable and worse cancer survival-treatment scenario and 1.0 for the best situation in which 100% of the population is surveyed for cancer and the ASR mortality/incidence ratio = zero (no cancer-related deaths). CTSI values were calculated for selected countries participating in GLOBOCAN 2012 study and exposed in the right column of Table 3. Pertinence of this index is discussed below.

The general trend of cancer incidence and mortality exposed for groups of people according to their Human Development Index (HDI) (Table 1) are reproduced by highly developed countries, the United States, Norway, Ireland and South Korea. It will be difficult, however, to find a common ground between the first two of these countries to justify their position in the cancer incidence scale. These rates decrease as the HDI drops until the lowest echelons in the scale, Nepal and Namibia.

The mortality/incidence ratio is quite conservative for most countries or regions: among the highly developed countries, this ratio goes from a comforting 0.688 in Norway, suggesting that nearly 70% of diagnosed cancer cases do not feed the mortality statistics, to a more preoccupying 0.568 in Japan. Contrasts also exist between Northern (0.610) and Southern Europe (0.585). Survival

rates have been improving in the United States in recent years jumping to 68% as CTSI suggests, since cutting-edge treatments seem to find their way to the general public more rapidly than in other societies.

Overall figures based on Government surveys put the South American continent in a lower success position (0.469). This average number for the sub-continent is not representative of national results as these vary broadly: 45% survival rates in Brazil and Colombia in the surveyed fraction of cancer patients to less than 30% in Paraguay. These figures correlate well with the HDI of each country giving additional credit to this association.

Application of this index to the data in Table 3 gives a measure of dependability of reported results. CTSI strongly depends on the size of the surveyed cancer patient cohort relative to the percentage of censored people. Most dependable values are found in countries censoring 100% of citizens as in Norway, Ireland, South Korea and Costa Rica. Among the ICs, CTSI drops sharply in France, because of the smaller fraction of censored people available for survival. CTSI falls to minimum values in India where the study was performed on only 4882 cancer patients in the 2000-2014 period covered by the registry. An incidence ASR per 100K people of 94.0 would predict 940.000 new cases per year in the 10^9 territorial population of India. Thus, the study comprised only 0.52 % of expected cases. Efforts to increase the CTSI or equivalent indexes should be conducted to face the cancer threat.

Transfer of Oncology Knowledge and Resources

The annotated disparities in POSR between countries and its correlation with relative well being of their citizens suggests that the transfer of modern technology for treatment of malignancies should be improved through internationally coordinated efforts. LDCs by themselves may not be able to put forward the necessary resources and specialized doctors in sufficient numbers to cope with their local cancer-affected collectives.

Conclusions

The cancer burden will continue to grow at a global scale in the next decades as a result of population expansion and aging, and insufficient personal or institutional resources needed to pay for growingly demanding therapy budgets. As the epidemiological transition from major death causes due to transmissible diseases and sub nutrition evolve towards higher prevalence of non-transmissible illnesses in developing countries, cancer profiles will change to resemble those currently prevailing in wealthier societies. However, it is not clear whether this transition will be accompanied by a technology transfer from high ranking cancer research and therapy centers in advanced economies to less resourceful countries, necessary to surmount the expected growth in cancer incidence in the underprivileged regions of the world.

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