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Mortality in Digestive Cancers, 2012: International Data and Data from Romania

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ABSTRACT

We aimed to compare the difference in case fatality rate between more developed and very high Human Development Index (HDI) regions, less developed and low HDI regions, and Romania. The incidence and mortality rates for digestive cancers were obtained from the IARC/WHO 2012 database. World mean mortality-to-incidence ratios registered the highest values in pancreatic cancer (0.97/0.94), and liver cancer (0.93/0.96) in males/females, respectively. The lowest values were recorded in colorectal cancer (0.48 in both sexes). Mortality-to-incidence ratios were generally higher in less developed areas, low HDI populations, and in Romania. The difference in case fatality rate between different areas showed higher variations for colorectal, gastric and gallbladder cancers, and smaller variations for esophageal, liver, and pancreatic cancers. In summary, mortality-to-incidence ratios of digestive cancers were high in 2012; higher values were registered in less developed and low HDI regions, and in Romania. Mortality-to-incidence ratios were similar in both sexes, even though the incidence was generally higher in men. Digestive cancer mortality variation suggests the necessity of finding better strategies for prevention, early diagnosis and treatment of digestive cancers.

Key words: digestive cancers – mortality-to-incidence ratio – world area – Human Development Index– Romania.

Abbreviations: ASRWs: age-standardized rate (World Standard Population) per 100,000 population; CRC: colorectal cancer; GC: gastric cancer; HDI: Human Development Index; HCC: hepatocellular carcinoma; IARC: International Agency for Research on Cancer; MIR: mortality-to-incidence ratio; WHO: World Health Organization.

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INTRODUCTION

Cancer has emerged as the leading cause of death in human populations, according to recent estimations [1]. The predicted global cancer burden is expected to increase [1]. Countries with medium and low Human Development Index (HDI) will experience the highest increase in the future cancer burden [1-3]. At the same time, the rates of death from specific cancers have begun to fall in many western countries [4-11].

Taken together, digestive cancers predominated as incidence and mortality rates worldwide [12, 13]. Care for digestive malignancies remained suboptimal, as compared to other cancers. Poor adherence to established guidelines, even in developed and HDI areas could be an explanation [1, 2, 14-16]. At the population level, much discrepancy existed with regard to preventive strategies, diagnostic and therapeutic resources [1-3,17-19]. An inverse correlation between HDI and mortality-to-incidence ratio (MRI) was revealed [13]. The MIR could represent an approximate case fatality ratio for a given cancer [20].

The aim of our study was to evaluate the MIRs in males (M) and females (F) for six digestive cancers (esophagus, stomach, colon and rectum, liver, gallbladder and pancreas) in different areas/populations of the world, and also in Romania.

METHOD

The incidence and mortality rates of the six digestive cancers, estimated as age-standardized rates by world population (ASRWs), were identified from the IARC/WHO/GLOBOCAN statistics 2012 [21]. The studied categories were the international population categories defined by IARC/WGO/GLOBOCAN 2012: world, more developed regions, very

high HDI regions, less developed regions and low HDI regions, and Romania [21]. According to the Human Development Report 2013, Romania HDI value for 2012 was 0.786, in the HDI category, the 56th position out of 187 countries and territories [22].

The MIRs of digestive cancers, as well as the differences (%) in the case fatality rate in the different parts of the world were estimated and compared with those in Romania.

RESULTS

The world estimated MIRs of esophageal cancer in M/F were 0.85/0.87 (Table I), an intermediate value as compared to the other digestive cancers (Tables II-VI). The M/F ratio was 2.9/1, higher in more developed and very high HDI regions and lower in less developed and low HDI regions. The MIRs were similar in both genders. In M, a difference of 9.0% was found in MIRs between less/more developed regions, and of 17.2% between low/high HDI populations; in F, the differences were 13.8%, and 18.2%, respectively (Table VII). In Romania, the MIRs of esophageal cancer were higher as compared to world estimates, and more similar to the low HDI populations; the M/F ratio had higher values (8.6/1) (Table I). The mortality rates of esophageal cancer were lower only compared to low HDI regions, and only in M (Table VIII).

The world MIRs of gastric cancer (GC) in M/F were 0.73/0.76 (Table II), which was an intermediate value as compared to the other digestive cancers. The M/F ratio was similar for more developed, very high HDI and less developed regions. It was lower in low HDI populations. The MIRs were similar in both genders. In M, a difference of 26.6% was found in MIRs between less/more developed regions, and a difference of 48.9% between low/high HDI populations; in F, the differences were 25.3% and 44.6%, respectively (Table VII). In Romania, the MIRs of GC were higher (0.79) as compared to world mean values, and also higher than in more developed and very high HDI regions (Table II). The M/F ratio had higher values (2.8/1). The mortality rates of GC were lower only as compared to low HDI (in both sexes) and less developed regions (in F) (Table VIII).

The world MIRs of colorectal cancer (CRC) in M/F were 0.48/0.48 (Table III). This was the lowest mortality rate as compared to other digestive cancers. The M/F ratio was 1.4/1, with small differences between regions. The MIRs were similar in both genders (Table III). In M, a difference of 29.9% was recorded in MIRs between less/more developed regions, and of 53.9% between low/high HDI populations; in F, the differences were of 31.5% and 55.7%, respectively (Table VII). In Romania, the MIRs of CRC were more similar to the mean world estimates (0.52/0.48) (Table III). The M/F ratio was higher (1.7/1). The mortality rates of CRC were in both sexes lower compared to the less developed and low HDI regions (Table VIII).

The world MIRs of liver cancer in M/F were 0.93/0.96 (Table IV), and these were very high values, comparable only with those of pancreatic cancer. The M/F ratio was 2.8/1, which was higher in more developed and very high HDI regions, and lower in less developed and low HDI regions. The MIRs were similar in both genders. In M, a difference of 13.7% was recorded in MIRs between less/more developed regions, and of 17.9% between low/high HDI populations; in F, the differences were of 4.1% and 13.6%, respectively (Table VII). The MIRs of liver cancer were higher in Romania (1.19 in M and 1.4 in F). The M/F ratio was 3.0/1. The mortality rates of liver cancer were higher in both sexes as compared to all the studied regions and populations (Table VIII).

Table I. Mortality to incidence ratios of esophageal cancer and their relationship to regions and the HDI

Cancer	Incidence		Mortality		M/F ratio	Mortality/incidence
	M	F	M	F		
World	9.0	3.1	7.7	2.7	2.9/1	M: 0.85 F: 0.87
More developed regions	6.4	1.2	5.2	0.9	5.3/1	M: 0.81 F: 0.75
Very high HDI	6.7	1.3	5.2	1.0	5.1/1	M: 0.77 F: 0.76
Less developed regions	10.1	4.1	9.0	3.6	2.4/1	M: 0.89 F: 0.87
Low HDI	7.6	4.9	7.1	4.6	1.5/1	M: 0.93 F: 0.93
Romania	4.3	0.5	3.9	0.5	8.6/1	M: 0.90 F: 1.00

Table II. Mortality-to-incidence ratios of gastric cancer and their relationship to regions and the HDI

Cancer	Incidence		Mortality		M/F ratio	Mortality/incidence
	M	F	M	F		
World	17.4	7.5	12.8	5.7	2.3/1	M: 0.73 F: 0.76
More developed regions	15.6	6.7	9.1	4.2	2.3/1	M: 0.58 F: 0.62
Very high HDI	16.0	6.7	7.9	3.5	2.3/1	M: 0.49 F: 0.52
Less developed regions	18.1	7.8	14.4	6.5	2.3/1	M: 0.79 F: 0.83
Low HDI	5.6	3.7	5.4	3.5	1.5/1	M: 0.96 F: 0.94
Romania	16.3	5.8	13.0	4.6	2.8/1	M: 0.79 F: 0.79

Table III. Mortality-to-incidence ratios of colorectal cancer and their relationship to regions and human development

Cancer	Incidence		Mortality		M/F ratio	Mortality/incidence
	M	F	M	F		
World	20.6	14.3	10.0	6.9	1.4/1	M: 0.48 F: 0.48
More developed regions	36.3	23.6	14.7	9.3	1.5/1	M: 0.40 F: 0.39
Very high HDI	37.9	24.4	13.9	8.7	1.5/1	M: 0.36 F: 0.35
Less developed regions	13.6	9.8	7.8	5.6	1.3/1	M: 0.57 F: 0.57
Low HDI	5.5	4.4	4.3	3.5	1.2/1	M: 0.78 F: 0.79
Romania	34.5	20.2	18.2	9.7	1.7/1	M: 0.52 F: 0.48

Table IV. Mortality-to-incidence ratios of liver cancer and their relationship to regions and human development

Cancer	Incidence		Mortality		M/F ratio	Mortality/incidence
	M	F	M	F		
World	15.3	5.3	14.3	5.1	2.8/1	M: 0.93 F: 0.96
More developed regions	8.6	2.7	7.1	2.5	3.1/1	M: 0.82 F: 0.92
Very high HDI	11.0	3.5	8.6	2.9	3.1/1	M: 0.78 F: 0.82
Less developed regions	17.8	6.6	17.0	6.4	2.6/1	M: 0.95 F: 0.96
Low HDI	8.1	4.4	7.7	4.2	1.8/1	M: 0.95 F: 0.95
Romania	9.2	3.0	11.0	4.2	3.0/1	M: 1.19 F: 1.4

The world MIRs of gallbladder cancer in M/F were intermediate (0.76/0.78) (Table V) as compared to the other digestive cancers. The M/F ratio was 0.8/1, confirming the global predominance of gallbladder cancer in F. In less developed and low HDI regions, the F predominance of gallbladder cancer was evident. It was slightly higher in M in more developed and in very high HDI regions. The MIRs were similar in both genders. In M, a difference of 18.7% was recorded in MIRs between less/more developed regions, and of 25.0% between low/high HDI populations; in F, the differences were of 15.6% and 32.0%, respectively (Table VII). In Romania, the MIR of gallbladder cancer was lower (0.73 in both sexes) as compared to the mean world values (Table V). The M/F ratio was similar for both sexes. The mortality rates of gallbladder cancer were lowest in both sexes than in all world regions (Table VIII).

The world MIRs of pancreatic cancer in M/F were 0.97/0.94 (Table VI), values very high and comparable only with those of liver cancer (Tables I-V). The M/F ratio was 1.3/1, which was similar to that of other regions (Table VI). The MIRs

Table V. Mortality-to-incidence ratios of gallbladder cancer and their relationship to regions and human development

Cancer	Incidence		Mortality		M/F ratio	Mortality/incidence
	M	F	M	F		
World	2.1	2.3	1.6	1.8	0.8/1	M: 0.76 F: 0.78
More developed regions	2.3	2.0	1.5	1.4	1.1/1	M: 0.65 F: 0.70
Very high HDI	2.7	2.5	1.8	1.7	1.08/1	M: 0.66 F: 0.68
Less developed regions	2.0	2.4	1.6	2.0	0.8/1	M: 0.80 F: 0.83
Low HDI	0.9	1.9	0.8	1.9	0.4/1	M: 0.88 F: 1.00
Romania	1.5	1.5	1.1	1.1	1/1	M: 0.73 F: 0.73

Table VI. Mortality-to-incidence ratios of pancreatic cancer and their relationship to regions and human development

Cancer	Incidence		Mortality		M/F ratio	Mortality/incidence
	M	F	M	F		
World	4.9	3.6	4.8	3.4	1.3/1	M: 0.97 F: 0.94
More developed regions	8.6	5.9	8.3	5.5	1.4/1	M: 0.96 F: 0.93
Very high HDI	8.5	6.1	8.0	5.6	1.3/1	M: 0.94 F: 0.91
Less developed regions	3.3	2.4	3.2	2.3	1.3/1	M: 0.96 F: 0.95
Low HDI	1.4	1.1	1.3	1.1	1.2/1	M: 0.92 F: 1.00
Romania	10.3	5.9	9.3	5.1	1.7/1	M: 0.90 F: 0.86

were similar in both genders (Table VI). In M, no difference was recorded in MIRs between less/more developed regions; a difference of 2.1% was recorded between low/high HDI populations. In F, the differences were of 2.1% and 9.1%, respectively (Table VII). In Romania, the MIRs of pancreatic cancer were slightly lower than the mean world estimates (0.90/0.86) (Tab.VI). The M/F ratio was 1.7/1, higher than the international estimations. The mortality rates of pancreatic cancer were lower with regard to all the regions and populations under study, in both sexes (Table VIII).

The HDI and country development appeared to be relevant regarding the discrepancies observed in case fatality ratio of digestive cancers.

DISCUSSION

Based on the IARC/WHO statistics 2012, regarding the incidence and mortality of digestive cancers [21], our observations suggest the persistence of high MIRs and an important impact of socio-economic factors.

Mortality-to-incidence ratio of digestive cancers

Colorectal cancer registered the lowest value of MIR in all areas, including Romania. Lower values were registered in more developed and very high HDI regions. Pancreatic cancer registered high MIRs in all the regions and populations. Liver cancer also had high MIRs, higher in less developed and low HDI regions, as well as in Romania. The MIRs of liver cancer were better in more developed and high HDI regions. Esophageal, gastric and gallbladder cancers registered intermediate MIRs values.

In Romania, the MIRs of digestive cancers had intermediate values, with the notable exception of HCC. In the estimated period, HCC mortality exceeded the incidence, suggesting an under-diagnosis of this tumor. This aspect was found in other countries, too [23]. At the population level, much discrepancy existed regarding cancer incidence and mortality [1-3, 7-13, 23].

Mortality-to-incidence ratio and socio-economic factors

Cancer is a global problem, but not a uniform one. There are distinct patterns for cancers at regional and national level, reflecting the heterogeneity within the underlying risk factors [17]. The disparities in cancer incidence are multiplied by the disparities in cancer mortality rate. Historical studies and statistics on cancer incidence and mortality have suggested the role of socio-economic factors [1-3, 13, 17-19]. A comparison of regional cancer mortality distribution observed significant variations for some cancers (cancers of the bladder, breast, melanoma of the skin, prostate and hematological malignancies), and moderate variations for cancers of the colon, rectum and uterus. Cancers with very poor prognosis (lung, pancreas, liver) showed small variations. Variations in survival are likely to be due to differences in diagnosis and availability of appropriate treatment options [24]. An inverse correlation between HDI and MIR for gastrointestinal cancers, at regional and national level, was revealed, due to health inequality between different socio-economic levels [13].

The MIRs of all the digestive cancers were higher in less developed and low HDI regions. The difference (%) in case fatality rate for more developed and very high HDI regions, compared with less developed and low HDI regions, in M and F, showed higher percentages for CRC, GC and gallbladder cancer. The differences were lower for cancers with poorer prognosis, such as the liver, esophageal, and pancreatic cancer.

In Romania, only the MIR of CRC resembled with that of more developed and high HDI areas. The digestive cancer mortality was lower only as compared to low HDI areas (esophageal cancer in M) and less developed regions (GC, CRC and gallbladder cancers, in both sexes). In the period evaluated, liver and pancreatic cancer showed particular features that could be related to the existing problems in diagnosing these tumors. The liver cancer mortality was higher as compared to all the regions and populations, suggesting an under-diagnosis of the tumor. Such data were in keeping with those reported by other countries [23]. The pancreatic cancer mortality was lower than in all the regions and populations under study, suggesting an over-estimation of the diagnosis. Otherwise, both tumors are graved by high fatality, and the geographical patterns and mortality trends are very similar to those observed in incidence [25-28].

An improvement in cancer outcome could be realized, with appropriate resource allocation, at least for cancers having a better prognosis [24]. The HDI and country development appeared to be relevant regarding the discrepancies observed in the case fatality ratio of digestive cancers [13, 18, 19].

Mortality-to-incidence ratio of digestive cancers and gender

The incidence of digestive cancers predominated in M, with the notable exception of gallbladder cancer. The F prevalence of gallbladder cancer was evident on the global scale, and higher in less developed and low HDI regions.

The M/F ratio of cancer incidence registered the highest difference in esophageal cancer patients, particularly in more developed and high HDI areas, and in Romania. The lowest M/F ratio was observed in CRC patients. An even lower M/F ratio was registered in less developed regions. As a general observation, the M/F ratio showed more similar values for digestive cancer incidence in less developed areas and low HDI populations. The magnitude of the exposure to risk factors could be an explanation [29].

The digestive cancer mortality was similar in both sexes. The gender difference in the case fatality rate of digestive cancers appeared to be low in all the settings and all the areas under study. While digestive cancer incidence is mainly a problem of confrontation with the risk factors, cancer mortality depends on the diagnosis, time of diagnosis and treatment efficacy [29].

Decline of digestive cancer mortality attributed to screening/surveillance strategies

The early detection and treatment of cancer or precancerous lesions allowed substantial declines in cancer mortality in high-resource countries and could improve survival in low-resource countries [17]. Solid efficacy evidence of the

Table VII. Difference (%) in case fatality rates (MIR) for more developed regions and very high HDI compared with less developed regions and low HDI, in males and females

Cancer	Males	Males	Females	Females
	MIR more/less developed regions	MIR high/low HDI	MIR more/less developed regions	MIR high/low HDI
Esophagus	9.0%	17.2%	13.8%	18.2%
Stomach	26.6%	48.9%	25.3%	44.6%
Colorectum	29.9%	53.9%	31.5%	55.7%
Liver	13.7%	17.9%	4.1%	13.6%
Gallbladder	18.7%	25.0%	15.6%	32%
Pancreas	0	2.1%	2.1%	9.1%

screening programmes in reducing cancer mortality existed for three cancer sites: the cervix uteri, breast and colorectum [17, 30]. Several advances in recent years have led to improved screening/surveillance for early diagnosis of digestive cancers, and suggested an impact on cancer mortality [17, 30].

The incidence of CRC had a decreasing trend [31-36]. In the USA, a decrease by 30% in adults aged 50 years or older was found during 2001-2010 [36]. The dramatic declines in CRC incidence was attributed to the widespread colonoscopy screening. Colonoscopy screening increased from 19% (year 2000) to 55% in 2010 in adults aged 50 to 75 years [36]. Still, many concerns persist. An increase by 1.1% per year was found in the distal colon and rectum tumors in non-screened men and women, younger than 50 years, in the USA and Norway [36]. Other problems of concern are related to the long-term CRC mortality after adenoma removal [37, 38], the sessile serrated adenomas diagnosis and follow-up [39], the interval CRCs [40], the disease recurrence following primary therapy [41]. The tumor histopathologic and molecular characteristics, and the response to therapy could explain why CRC survival data do not add up [42-44].

Early diagnosis of GC was associated with a better survival [45-50]. Japan reported a 40-60% decrease in GC mortality in screened vs. unscreened subjects [48]. A 30% reduction of GC mortality by endoscopic screening, as compared to no screening, was also reported [49]. Screening by endoscopy appeared to be the most accurate method for the detection of early gastric cancer [49, 50]. A reduction of GC incidence after eradication of *H pylori* was also reported [51-58]. Consensus groups from Japan, Asia, Europe, and IARC/WHO recommended H pylori eradication as primary prevention of GC in high-risk areas [51, 52, 59, 60]. Areas of concern are multiple. An increasing trend of the incidence of cardia cancer was revealed (51, 61). Non-cardia GC increased in white people, aged 29-39 years, in the USA between 1977 and 2006 [51]. The age for screening and eradication of H pylori in high and low incidence areas of GC is a matter of debate [51, 60, 62]. The surveillance of pre-malignant gastric lesions can actually benefit from multiple methods, but their practical use is not yet standardized [63-66]. The screening/surveillance strategies for GC prevention and early diagnosis for global application are under study [67-70].

There are studies dedicated to HCC screening and its impact on early diagnosis, curability and survival [71-76]. The surveillance for HCC was associated with improvement of early tumor detection, prescription of curative therapies, and overall survival [71, 72]. In patients undergoing surveillance, the rate of early HCC was 70.9%, the rate of application of a treatment with potentially curative intention was 51.6%, and the 3-year survival rate was 50.8%. The comparative figures in patients symptomatic at presentation and/or those who were diagnosed incidentally were 29.9%, 23.7%, and 27.9%, respectively [71]. In Japan, about 80% of HCC cases were detected by screening, 71% of the patients were suitable for potentially curative treatment, and the survival was of 47

Table VIII. Difference (%) in case fatality ratio (MIR) for Romania (Ro) as compared to other regions and populations, in males and females

	Esophagus	Stomach	Colorectum	Liver	Gallbladder	Pancreas
Males						
World/Ro	5.6%	7.6%	7.7%	21.1%	4.0% (-)	7.3% (-)
More developed regions/Ro	10%	26.6%	31.1%	31.1%	11.0%	6.3% (-)
Very high HDI/Ro	14.5%	38%	30.8%	34.5%	9.6%	4.3% (-)
Less developed regions/Ro	1.2%	0	8.8% (-)	20.2%	8.8% (-)	6.3% (-)
Low HDI/Ro	3.3% (-)	17.8% (-)	33.4% (-)	20.2%	17.1% (-)	2.2% (-)
Females						
World/Ro	13%	3.8%	0	31.5%	6.5% (-)	8.6% (-)
More developed regions/Ro	25%	27.6%	18.5%	34.3%	4.2%	7.6% (-)
Very high HDI/Ro	24%	34.2%	27.1%	47.5%	6.9%	5.5% (-)
Less developed regions/Ro	13%	4.9% (-)	17.8% (-)	31.5%	12.1% (-)	9.5% (-)
Low HDI/Ro	7%	16% (-)	39.3% (-)	32.2%	27% (-)	14% (-)

(-): Lower mortality in Romania

months. The comparative figures for the UK were 15%, 37-38%, and 20 months, respectively; for Spain, 35%, 26-32% and 26 months, respectively; for Hong Kong, <10%, 8-16%, and 7 months, respectively [72]. Major concerns are related to poor adherence to the guidelines for HCC prevention and to low screening rates for known risk factors, poor adherence to surveillance strategies of patients at risk, and to intervention strategies [14, 73, 74, 77, 78] and disease recurrence.

In the future, primary and secondary prophylaxis of cancer, early diagnosis and multidisciplinary therapeutic approach could lead to the reduction of cancer morbidity and mortality. Several advances in recent years have led to improved screening/surveillance for early diagnosis, and treatment options for digestive cancers have multiplied. Advances in the molecular genetics of digestive cancers are expected to favorably influence the development of new therapies, and the identification of prognostic and predictive markers.

CONCLUSIONS

The digestive cancer mortality-to-incidence ratios in 2012 were high, and had even higher values in less developed and low HDI regions, and in Romania. Mortality-to-incidence ratio was similar in both sexes, even though the incidence was generally higher in men. Digestive cancer mortality variation suggests the necessity of better programs for interventions, for prevention, early diagnosis and therapy.

Conflicts of interest: None to declare.

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