

EPIDEMIOLOGICAL TRENDS IN DIGESTIVE CANCERS IN ROMANIA, 1955-2012, COMPARED TO ALCOHOL CONSUMPTION. CORRELATION OR COINCIDENCE?

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Abstract

Background and aims. Cancer has emerged as the leading cause of death in human populations. The contribution of alcohol has been highly suspected. The purpose of this paper was to analyze the time trend of digestive cancers in Romania, in terms of mortality rates (1955-2012), and incidence rates (2008-2012), and the alcohol consumption data (1961-2010), aiming to find out if there is any association.

Methods. The data on six more common digestive cancers mortality rates (1955-2012) and incidence rates (2008-2012) were obtained from the historical and recent country statistics and publications of International Agency for Research on Cancer (IARC)/ World Health Organisation (WHO), as age-standardized rate expressed per 100,000 population (ASRw). Data on alcohol consumption were obtained from the statistics and publications of WHO and United European Gastroenterology (UEG), as liters of pure alcohol/year.

Results. Between 1955-2012, the ASRw of mortality registered an increase of the cancers of the esophagus in M (from 2.03 to 3.90), and of colorectal cancer in both sexes (from 4.65 to 18.20 in M, and from 4.57 to 9.70 in F). Between 1980-2012, an increasing trend of mortality was registered, in both sexes, for the cancers of the pancreas (from 5.50 to 9.30 in M and from 2.92 to 5.10 in F) and liver (from 1.77 to 11.00, in M, and from 0.83 to 4.20 in F). In terms of incidence, between 2008-2012, an increasing trend of ASRw was registered for the cancers of the esophagus in M (from 3.90 to 4.30), gastric cancer in M (from 15.90 to 16.30), colorectal cancer in both sexes (from 27.60 to 34.50 in M and from 19.00 to 20.20 in F), pancreatic cancer in F (from 5.20 to 5.90), and liver cancer in M (from 8.10 to 9.20). Alcohol consumption per capita (liters pure alcohol/year) increased in the same period, from an average of 5 in 1961, to 12.8 in 2003-2005, and to 14.4 in 2008-2010.

Conclusions. Given the parallel increase of some digestive cancers and alcohol consumption registered in our area, alcohol could represent more than a coincidence.

Keywords: alcohol behavior, digestive cancers, risk factor, time trend

Background and aims

Cancer has emerged as the leading cause of death in human populations [1-3]. Epidemiological studies emphasized the role of life style and of environmental factors in promoting the risk for digestive cancers. The contribution of alcohol was highly suspected. Even for digestive cancers with dominant infection etiology, like liver cancer and gastric cancer, the contribution of alcohol should be assessed. At population level there is a need to compare trends in epidemiological data of gastrointestinal cancers and data on alcohol consumption, in order to

extrapolate any causative relationship.

Digestive cancers, taken together, predominated as incidence and mortality rates, worldwide [4,5]. In 2012, six cancers represented 55% of the global incidence burden, and three of them were digestive cancers, namely colorectal, stomach and liver cancers [6]. Care for digestive malignancies remained apparently suboptimal, as compared to other cancers [1,7-10].

The relative role of lifestyle vs environmental vs host factors as causes of cancer continued to be intensively studied [11]. Migrant studies suggested the role of environmental factors in promoting the risk for different diseases, including digestive cancers [1,12]. The role of infection was confirmed for certain digestive cancers [13]. Life style was also involved

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in oncogenesis. Alcohol is an oncogene [14]. Alcohol consumption, in terms of quantity and quality, could be a contributory risk factor to the development of preneoplastic lesions at the level of the digestive tract and, eventually, to digestive cancers, by indirect and direct effects [15-18]. Individual predisposition and genetics of cancers represent the most recent evaluations used for the estimation of the final mechanisms of the diseases [12]. Alcohol consumption increased in recent decades worldwide, also in Romania, where the alcohol consumption is one of the highest in the world, according to WHO estimates [16].

Given that the incidence of most digestive cancers changed in the last decades as well, we looked for the association between alcohol consumption and digestive cancers. We analyzed the total data and also the gender differences. The purpose of this paper is to analyze the time trend of digestive cancers in Romania, in terms of mortality rates (between 1955-2012), and incidence rates (between 2008-2012), in males (M) and females (F), in association with the time trend in alcohol consumption (between 1961-2010).

Materials and methods

The data on six more common digestive cancers mortality rates (1955-2012) and incidence rates (2008-2012) in M and F, were obtained from the historical and recent country statistics and publications of IARC/WHO, as ASRw (age-standardized rate expressed per 100,000 population, World Standard Population) (Tables I-III) [19-24]. The six cancers studied were: esophageal, gastric, colorectal, pancreatic, hepatic, gallbladder. Data on alcohol consumption were obtained from the statistics and publications of WHO [16] and UEG [17], as liters of pure alcohol/year. We compared the curves of evolution of most common digestive cancers during this time span with the evolution of alcohol consumption in the same country and time interval. We selected these data sources because they are reliable and open access. Some of the previous digestive cancer observatory studies for our country were also based on country statistics and publications of IARC/WHO/Globocan [25-28] and represented local reports.

Results

Mortality rates, for the cancers of the esophagus, stomach, colon and rectum, were available for a period of 57 years (1955-2012). Mortality rates for the cancers of the pancreas and liver were available for 32 years (1980-2012), and those of the gallbladder for 22 years (from 1990 to 2012). The incidence rates of the all six digestive cancers were available for 2008 and 2012. Even often truncated, they offered the possibility to compose a picture of the time trend evolution of digestive cancers in our country (Table I) [19-24], and to analyze some particular aspects, such as the rate of the increase/decrease/sex (Table II) [19-24], and the recent evolution in incidence/sex (Table III) [23,24]. For the most recent period of estimation, the year 2012, the

mortality-to-incidence ratio (M:I ratio) and the M/F ratio of incidence were calculated (Table IV) [24]. Data on alcohol consumption in Romania (Table V) were available for three periods of time (1961, 2003-2005, and 2008-2010), between 1961 and 2010 [16,17].

Esophageal cancer registered an inconstant, but slow increase, only in males (Tables I, II). In 2012, it was the 5th digestive cancer as incidence and mortality in males, and the 6th in females. (Table III). The M:I ratio was high, second only to liver cancer (Table IV). The M/F ratio of mortality highly increased, from 3.27/1 in 1955-59, to 7.80/1, in 2012 (Table I). M/F ratio of incidence was 8.60/1 in 2012, the highest among digestive cancers (Table IV).

Gastric cancer (GC) mortality registered a constant decrease in both sexes, higher in F (Tables I, II). Between 2008-2012, an increase in incidence was registered in M (Table III). In 2012, GC was still the 2nd digestive malignancy as incidence and the 2nd cause of mortality from digestive cancer in M, and the 3rd in F (Table III). The M:I ratio was higher only as compared only to CRC and gallbladder cancer (Table IV). The M/F ratio of mortality increased, from 1.76/1 in 1955-59, to 2.82/1 in 2012 (Table I). The M/F ratio of incidence was 2.81/1, in 2012 (Table IV).

Colorectal cancer (CRC) has emerged as the most frequent digestive malignancy in 2012, as incidence and mortality from digestive cancer (Table III), after a long time of constant increase (Tables I-II). In the same time, it had the lowest M:I ratio (of 0.52 in M and of 0.48 in F) (Table IV). The M/F ratio of mortality increased, from 1.01/1 in 1955-59, to 1.87/1 in 2012 (Table I). The M/F ratio of incidence was of 1.70/1, in 2012 (Table IV).

Pancreatic cancer also registered a constant increase (Tables I, II). In 2012, it was the 3rd digestive cancer as incidence, and the 4th digestive cancer as cause of mortality in M. In F, it was the 2nd digestive cancer as incidence and the 3rd cause of deaths from digestive cancer (Table III). The M:I ratio was high, being surpassed only by the mortality rates of liver and esophageal cancer (Table IV). The M/F ratio of mortality registered some decrease, from 1.88/1 in 1980-84, to 1.82/1 in 2012 (Table I). The M/F ratio of incidence was 1.74/1, in 2012 (Table IV).

Liver cancer registered the highest rate of increase of mortality (Tables I,II). In 2012, it was the 4th digestive cancer an incidence, but the 3rd digestive cancer as a cause of mortality (Table III). The mortality exceeded the incidence rates in 2012 (Table IV). The M/F ratio of mortality slightly increased, from 2.13/1 in 1980-84, to 2.61/1 in 2012 (Table I). The M/F ratio of incidence was of 3.06/1, in 2012 (Table IV).

Gallbladder incidence and mortality rates were apparently more stable in the period of observation, of 22 years (Tables I,II). In 2012, it was the 6th digestive cancer as incidence and mortality, in males. In females, it was the 5th digestive cancer as incidence and mortality. In females, only esophageal cancer was more rarely recorded as incidence (Table III). The M:I ratio was higher only

as regard to CRC (Table IV). The M/F ratio of mortality decreased, from 1.14/1 in 1990-94, to 1/1 in 2012 (Table I). M/F ratio of incidence was 1/1 in 2012 (Table IV).

Alcohol consumption per capita registered a historical increase in Romania (as estimated by the

Global report on alcohol and health - 2014 ed. Country profile: Romania, page:232) (Table V) [16]. The recorded/unrecorded alcohol consumption per capita (15+, in liters of pure alcohol) was estimated at average 8.8/4 in 2003-2005 and at 10.4/4 in 2008-2010) [16].

Table I. Digestive cancers in Romania – mortality rate time trends 1955-2012, in males and females (ASRw) [19-24].

Year	Esophagus	Stomach	Colon & rectum	Pancreas	Liver	Gallbladder
1955-59 [19]	2.03/0.62	33.14/18.77	4.65/4.57			
1960-64 [19]	1.86/0.58	37.26/20.29	6.10/6.02			
1965-69 [19]	1.96/0.51	32.61/16.32	8.61/5.55			
1970-74 [19]	1.75/0.56	30.06/13.92	6.59/6.20			
1974-79 [19]	1.65/0.52	27.65/12.56	7.45/6.46			
1980-84 [19]	1.56/0.43	22.36/9.39	8.65/6.84	5.50/2.92	1.77/0.83	
1985-89 [20]	1.70/0.40	19.40/7.70	9.60/7.30	6.00/3.10	2.01/1.00	
1990-92 [21]	1.80/0.40	17.70/7.00	10.10/7.40	6.40/3.20	3.30/1.50	
1990-94 [22]	2.04/0.41	17.81/6.91	10.56/7.59	6.61/3.31	4.34/1.99	1.26/1.10
2008 [23]	3.50/0.40	15.20/5.40	16.70/9.70	9.40/4.70	10.50/4.00	1.20/1.10
2012 [24]	3.90/0.50	13.00/4.60	18.20/9.70	9.30/5.10	11.00/4.20	1.10/1.10

Table II. Digestive cancers in Romania – mortality rate time trends 1955-2012, in males and females (ASRw), and the rate of increase/decrease [19-24].

	Esophagus	Stomach	Colon & rectum	Pancreas	Liver	Gallbladder
Years	1955-2012	1955-2012	1955-2012	1980-2012	1980-2012	1990-2012
Mortality rate M/F	2.03/0.62-3.90/0.50	33.14/18.77-13.00/4.60	4.65/4.57-18.20/9.70	5.50/2.92-9.30/5.10	1.77/0.83-11.00/4.20	1.26/1.10-1.10/1.10
Rate of increase/Decrease						
Males	+1.92	-2.54	+3.97	+1.89	+6.21	-1.14
Females	-.124	-4.08	+2.12	+1.74	+5.06	1

Table III. Digestive cancers in Romania - incidence and mortality rates in males and females (ASRw), in 2008 and 2012 [23,24].

Cancer	2008				2012			
	Incidence		Mortality		Incidence		Mortality	
	M	F	M	F	M	F	M	F
Esophagus	3.90	0.50	3.50	0.40	4.30	0.50	3.90	0.50
Stomach	15.90	5.80	15.20	5.40	16.30	5.80	13.00	4.60
Colon & rectum	27.60	19.00	16.70	9.70	34.50	20.20	18.20	9.70
Pancreas	10.30	5.20	9.40	4.70	10.30	5.90	9.30	5.10
Liver	8.10	3.00	10.50	4.00	9.20	3.00	11.00	4.20
Gallbladder	1.70	1.60	1.20	1.10	1.50	1.50	1.10	1.10

Table IV. Digestive cancers in Romania – incidence, mortality, M/F ratio of incidence, and mortality-to-incidence ratio, 2012 [24].

Cancer	Incidence		Mortality		M/F ratio of incidence	M:I ratio
	M	F	M	F		
Esophagus	4.30	0.50	3.90	0.50	8.60/1	M: 0.90 F: 1.00
Stomach	16.30	5.80	13.00	4.60	2.81/1	M: 0.79 F: 0.79
Colon & rectum	34.50	20.20	18.20	9.70	1.70/1	M: 0.52 F: 0.48
Pancreas	10.30	5.90	9.30	5.10	1.74/1	M: 0.90 F: 0.86
Liver	9.20	3.00	11.00	4.20	3.06/1	M: 1.19 F: 1.40
Gallbladder	1.50	1.50	1.10	1.10	1/1	M: 0.73 F: 0.73

Table V. Alcohol consumption in Romania. Data compiled from the Global status report on alcohol and health- 2014 edition, Country profile: Romania, page: 232 [16].

Alcohol consumption per capita, (15+years), (liters pure alcohol)/year	Average 1961	Average 2003-2005	Average 2008-2010	Change
Total	5	12.8	14.4	↑

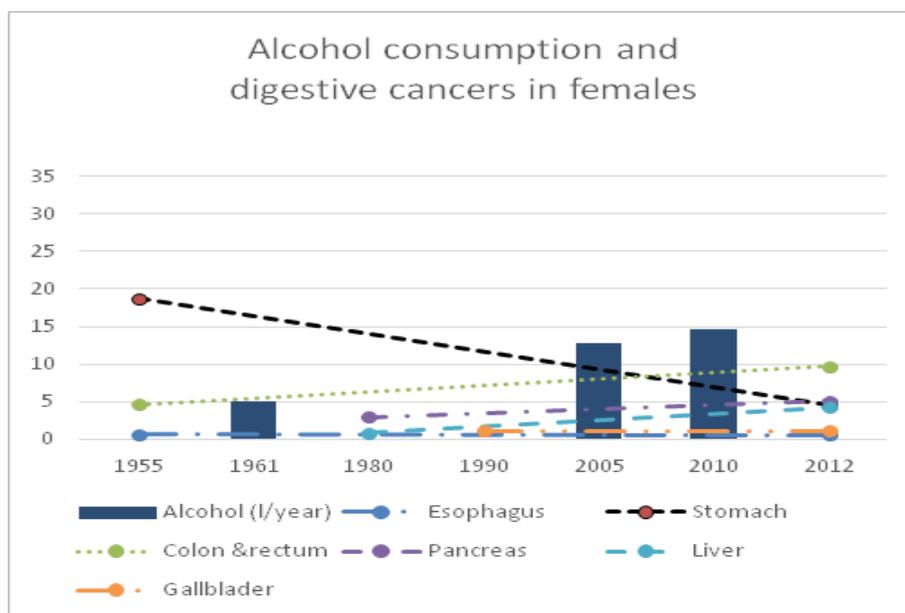


Figure 1.a. Alcohol consumption and digestive cancers in females.

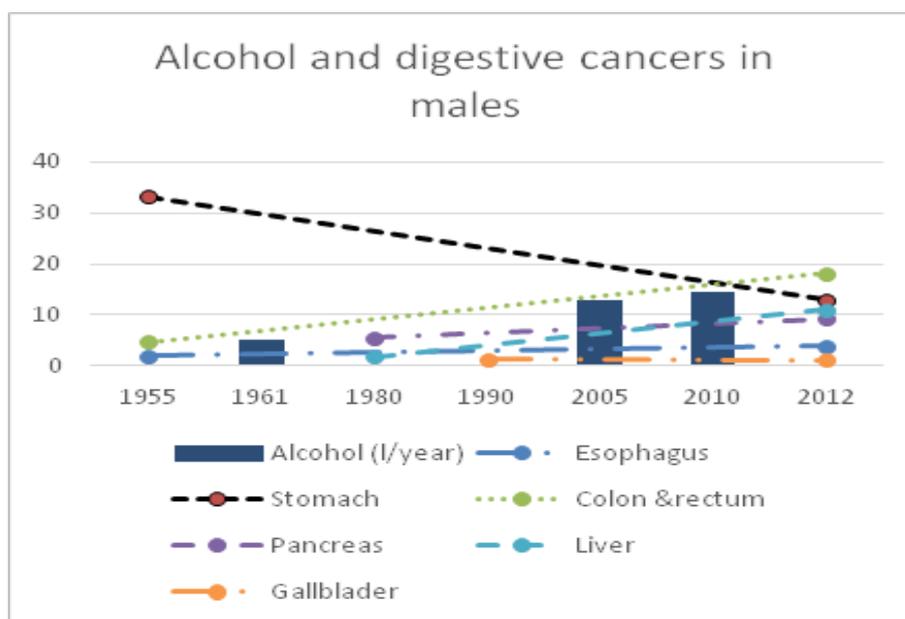


Figure 1.b. Alcohol consumption and digestive cancers in males.

The trend of increasing alcohol consumptions and the main 6 digestive cancers is displayed in Figure 1. In Figure 1.a the data of digestive cancers are for females, in Figure 1.b the data are for cancers in males. Of course, the alcohol consumption data cannot be broken according to the gender.

Discussion

Time trends 1955-2012 of digestive cancers in Romania

Our analysis compared the parallel time trend in alcohol consumption evolution and six most common

digestive cancers. We aimed to detect a possible correlation between the increase in incidence of these neoplasia and the increase in alcohol consumption at populational level.

With regard to mortality, in the period of observation, an increasing trend was registered for the cancers of the colon and rectum (CRC), pancreas and liver in both sexes. A decreasing trend was registered in esophageal cancer in F and of gastric cancer (GC) in both genders. Gallbladder cancer has shown an apparently more stable status of mortality rate (Tables I, II). For cancers showing an increasing trend of mortality, the rate of increase was generally higher in males. For GC

mortality, the decreasing trend was higher in F (Table II).

With regard to the incidence, between 2008-2012 an increasing trend was registered for the cancers of the esophagus (in M), GC (in M), CRC (in both sexes, but higher in M), pancreas (in F), and liver (in M). Cancers showing a stable evolution were esophageal cancer (in F), GC (in F), pancreatic cancer (in M), and liver cancer (in F). A declining trend was registered in gallbladder cancer (in both sexes) (Table III). Given the short period of the estimation of incidence rate, of four years, the data offered a possible epidemiologic orientation, and suggested the need of further surveillance. It is a problem of discussion if the increasing trends in incidence registered in recent times of some digestive cancers represent a real phenomenon, or the result of improved methods of diagnosis [1-7,12].

As a result of the long time evolution of digestive cancers in our country, a new hierarchy was established as incidence and mortality rates (Tables I-III) [19-24]. In 2012, the most frequent recorded digestive malignancies as incidence were CRC, GC and pancreatic cancer. As mortality, the most frequent malignancies were CRC, GC and liver cancer (Table III) [24].

The M:I ratio registered the highest rates in liver, pancreatic and esophageal cancer. The M:F ratio of incidence registered an increasing trend in cancers of the esophagus, stomach, colon and rectum and liver ((Table IV).

Between 2008-2012, GC registered a divergent evolution of mortality and incidence. The mortality continued to decrease in both sexes, but the incidence increased in M and appeared to be stabilized in F (Table III). The continuing decreasing rate of mortality could be attributed to an earlier diagnosis, due to the wide spread of endoscopy, and, eventually, better therapeutic approaches. The increasing of incidence can be related to an insufficient control of the risk factors in our area and the lack of screening. The incidence rates depend essentially on the control of the risk factors and screening, with a special emphasis on the known preneoplastic lesions and their approaches. The mortality of digestive cancers is mainly related to early diagnosis and treatment strategy and armamentarium, that registered substantial improvements, worldwide [1-7,9,10,12].

CRC had the lowest M:I ratio, as compared to the other digestive cancers (Table IV). Our data on M:I ratio of colorectal cancer are comparable to the international records [6,7]. It could be related to a better diagnosis, favored by the use of colonoscopy, eventually earlier diagnosis and treatment efficacy. The strategy of CRC screening of persons beginning with 50 years of age and of endoscopic polypectomy of the adenomatous polyps of the colon, in order to prevent CRC, proved to be effective [2,3,6,7,10], and is applied in our practical medical activity too. The M/F ratio of mortality and incidence was the closest in all times (Tables I, IV), and that could suggest that M and F could share similar risk factors for this malignancy.

Liver cancer registered the highest and the more rapid rate of increase of mortality rates (Tables I, II). The mortality ratio exceeded the incidence rate in 2012, suggesting an under-diagnosis of the tumor (Table IV). This particular aspect was not unique to our area. It could be related to the historical difficulties registered in liver cancer diagnosis [8]. An improvement in liver cancer diagnosis, eventually early detection, could be expected from dedicated screening strategies for cancer and risk factors [8-10,12,13]. The M/F ratio of mortality slightly increased, and could suggest eventually that M share more risk factors for liver cancer.

Regarding pancreatic cancer, apart from its increasing trend and high mortality rate, a slight reduction in M/F ratio was registered in our population. It could eventually suggest that the exposition to risk factors could become more similar.

Time trends in alcohol consumption

Our data show that in Romania too some cancers where alcohol consumption is not involved, i.e. gastric cancer, decreased in incidence in both genders. In females all the other digestive cancers have increase in parallel to the increased alcohol consumption, except the esophageal cancer. Alcohol is a risk factor for esophageal cancer but we may assume that the alcohol use in females was not so important to determine an elevation of esophageal cancer rate. With regard to the males, beside the decrease of gastric cancer and the constant prevalence of gallbladder cancer (which is not so common in males), the other cancer had a higher frequency in the interval associated with increased alcohol consumption. Our data confirm that alcohol is an oncogenic factor and the cancer prevention should include the prevention of alcohol abuse.

The trend in alcohol consumption is universal. Indeed, the worldwide consumption in 2010 was equal to 6.2 litres of pure alcohol consumed per year, per person aged 15 years or older, which translated into 13.5 grams of pure alcohol per day [16]. High-income countries had, apparently, the highest alcohol per capita consumption (APC) and the highest prevalence of heavy episodic drinking among drinkers [16]. The most prevalent tendency worldwide was an increase in recorded alcohol per capita consumption [16]. The problem of the recorded/unrecorded alcohol consumption was also under survey [16,17]. Europe was registered as the region with the highest level of alcohol consumption [17]. The total alcohol consumption per capita per year (≥ 15 years of age) was near to 14 liters of pure alcohol in Romania in the period of estimation, second only to Lithuania, in Europe, in 2017 [17].

Alcohol consumption per capita registered a historical increase in Romania (as estimated by the Global report on alcohol and health - 2014 ed. Country profile: Romania, page:232) (Table V) [16]. Recorded/unrecorded alcohol consumption per capita (15+, in liters of pure alcohol) was estimated at average 8.8/4 in 2003-2005 and

at 10.4/4 in 2008-2010) [16]. The increase in total alcohol consumption paralleled the increase in some of the digestive cancers in our country (Tables I, II) [19-24].

Alcohol has been shown to have many disease associations, acute and chronic. Depending on the dose and the frequency of use, the exposure to alcohol appeared to have an effect on cancer promotion, too [29-33]. The differences among individuals in the way alcohol is metabolized may stem from differences in genetics, nutrition, and factors such as the exposure to other carcinogens [29-33]. There may be different biological pathways, depending on the anatomical site [30]. The population of study might be important, given the genetic susceptibility, in general, and, in particular, the genotype of the enzymes that metabolize alcohol, of the consumer [30]. Many studies tried to answer to the question of alcohol consumption, as an etiological factor for cancer/digestive cancer, with nuances, independent etiologic risk factor, or cofactor, or coincidence.

Some epidemiologic associations have been found between alcohol consumption and the risk of cancer, at various sites. The mechanisms implicated could be related to the effects of acetaldehyde, the effects of alcohol on carcinogen metabolism, the interaction with nutritional factors, the effects of alcohol on hormone levels, the physical effects of alcohol on tissues, the additional effects related to the compounds found in alcoholic beverages [29-34], eventually the modulation of cancer stem cells and underlying cellular/molecular mechanisms [35]. With regard to the role in the carcinogenesis of the upper gastrointestinal tract, the microbial metabolism of alcohol to acetaldehyde might have a particular importance as well as the direct contact with alcoholic beverages [29,33,34]. The solvent properties of alcohol may enhance the effects of carcinogen exposure [33]. Alcohol effects on membrane fluidity may affect the tissue [34].

As regard to cancers, alcohol consumption has been identified as carcinogenic for the following cancer categories: cancer of the mouth, nasopharynx, other pharynx and oropharynx, laryngeal cancer, oesophageal cancer, colon and rectum cancer, liver cancer and female breast cancer. In addition, alcohol consumption was considered to be a likely cause of pancreatic cancer too [16,17,29,30,36,37]. The higher the consumption, the greater the risk for these cancers [16-18,36,37]. A potential modifiable factor for cancer risk could be the alcohol control consumption [18]. Worldwide, 3.6% of all cancers (5.2 % in men and 1.7% in women) were attributable to alcohol drinking [36,37]. The Eastern Europe region appeared to experience the highest alcohol-attributable cancer burden, with 8.7 cancer deaths/100 000 people (12.9 in men and 5.7 in women) [30]. In 2012, about 5.9% of all global death (7.6% among males and 4.0% among females) were attributable to alcohol, as well as 5.1% of the global burden of disease [16].

Alcohol consumption and digestive cancers/site

Esophageal cancer and alcohol

Esophageal cancer was recorded as the 8th most common cancer worldwide, and the 6th most common cause of death in the last epidemiologic global estimation in 2012. Incidence rates (ASRw) were 9.0/100,000 population in M, and 3.1/100,000 population in F. Mortality rates were 7.7, and 2.7, respectively. These figures included both histological subtypes, esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC) [6]. Around 80% of the cases worldwide occurred in less developed regions. Global incidence rates were threefold higher in men, compared with women [6]. It had a very poor survival (M:I ratio of 0.88), and the geographical patterns of mortality were close to those of incidence [6]. Time trends of esophageal cancer have changed in western countries, where the EAC type registered a rapid increase in incidence, while the incidence of ESCC type has been relatively constant, or even declining [38].

Alcohol consumption appeared as a major risk factor for the ESCC type, and showed a dose-response risk [38]. The effects of alcohol were found to be stronger than tobacco, but the combined effect multiplied the risk [38]. Particular aspects were registered in some areas of the world, with the highest rates of the ESCC, like China and Iran, where alcohol and tobacco were not registered as major risk factors [38]. The relation of alcohol consumption with EAC type remained less characterized [38].

The synergy of alcohol consumption with other risk factors seemed to be important for the development of esophageal cancer [38,39]. Factors related to personal genetic susceptibility, and gene polymorphism of alcohol metabolizing enzymes of the consumer are non-modifiable risk factors. Other risk factors could be apparently modified. They include alcohol consumption (in terms of quantity, quality, the age of drinking initiation), and tobacco smoking. Particular aspects are related to infections agents (like HPV, Helicobacter pylori (Hp), oral microorganisms, nutritional deficiencies (like iron, folate, other micronutrients), medical conditions (like Barrett esophagus), obesity, medications (like antisecretory agents, and drugs that relax the gastroesophageal sphincter), that might be important [38].

Gastric cancer and alcohol

Gastric cancer (GC) registered a historical and universal trend to decrease [6,40-42]. The decreasing trend affected mainly the non-cardia type of GC. The cardia type of GC registered an increasing trend, or have been stable [40]. Gastric cancer was still the 5th most common malignancy worldwide (the 4th in males and the 5th in females), and represented 7% of the total new cancer cases and 9% of the total cancer death, in the last epidemiologic global estimation in 2012 [40]. The fatality rate was lower in countries with high levels of human development (M:I ratio, 0.65) as compared to countries at low or medium levels of human development (0.83) [40].

On the basis of most previous research, alcohol consumption seemed an unlikely cause of GC, although some results were partly contradictory [29,30,33,43]. Alcohol was suspected to be a greater risk factor for the cancer of the gastric cardia [44].

The fact that only 0.5% of the patients infected with Hp develop GC highly suggested the contribution of other risk factors [45]. A recent meta-analysis of 76 prospective cohort studies provided a comprehensive assessment of the association between diet, alcohol, and GC [45]. A concordant positive association between high-salt foods and GC was revealed. Elevated consumption of pickled vegetables, processed meat, salt fish, and salt were in relation to respectively 18%, 15%, 25%, and 11% greater risk of GC. Alcohol drinking was associated with a 15% increased GC risk when the highest reported intake was compared with the lowest. Dose-response analysis indicated that the risk of GC was increased by 12% per 5g/day increment of dietary salt intake or 5% per 10 g/day increment of alcohol consumption. A 100 g/day increment of fruit consumption was inversely associated with 5% reduction of GC risk [45].

A positive association of GC risk was found only with heavy alcohol drinking [46]. An absence of association was found between alcohol drinking and esophageal and gastric cardia adenocarcinoma risk, even at higher doses of consumption [47]. Alcohol consumption and cigarette smoking may exert independent effects on the development of GC in high-risk populations for this malignancy, like China [48]. A link between alcohol consumption and the development of GC was supported from a study in the Lithuanian population, with up to 30 years follow-up [49]. Light drinking including even one alcoholic drink a day was associated with increased risk of esophageal, gastric and colorectal cancer in South Korean population [50].

Gastric cancer related to Hp infection was estimated at 71-95% of cases [51]. The global prevalence of Hp infection in general population was more than 50% [52]. The prevalence of Hp in Eastern European adults was 70% [52]. In Romania, a prevalence of Hp infection of 62% was recorded in the period of estimation [53]. In a large cohort of symptomatic population of study, Hp infection was recorded in 63.67% of the patients, higher in younger patients (72.41% in patients aged less than 20 years old, and 66.22% in patients aged 20-29 years old), in the period of the estimation [54]. One study, dedicated to MicroRNAs (miRNAs) polymorphisms related to GC concluded that the four miRNAs investigated showed no association with GC risk [55].

Four potential areas of intervention to prevent GC mortality were emphasized: Hp eradication, early detection through screening by endoscopy, surveillance of premalignant lesions, and life style modifications [56]. Hp eradication is part of the world strategy to prevent GC [57]. The reduction in alcohol consumption could help the

strategy to prevent GC [16-18].

Colorectal cancer and alcohol

Colorectal cancer (CRC) represented 10% of the global cancer incidence burden in 2012 [6,58]. It was the 3rd most common cancer in men, and the 2nd in women [6,58]. Mortality was lower, and CRC was the 4th most common cause of death from cancer, worldwide [6,58]. Almost 55% of the cases were registered in more developed regions [6]. Time trend appeared to stabilize or declining in countries that attained the highest levels of human development [58].

CRC was considered a lifestyle disease. It is a matter of debate of how the multiple suggested factors contribute to the risk. CRC was added to the list of alcohol attributable cancers [16,17,29,58]. An association between high alcohol consumption (≥ 30 g/day) and colorectal cancer was observed [59]. The antagonist effect of alcohol on folate metabolism was suggested as a possible mechanism [15,59]. A strong evidence for an association between alcohol intake and CCR was found in two recent meta-analysis, that included articles published before 2011 [60], and before 2014 (61). The association of alcohol, as a risk factor, appeared to be evident for the proximal colon, distal colon and rectum [62]. The interaction of gut microbiota with diets and other lifestyle factors could affect the risk of CRC [63].

As regard to infections, papillomavirus (HPV) appeared as a major risk factor for perianal and anal cancers. For the cancers of the colon and rectum there existed no convincing evidence of the HPV involvement [13].

Pancreatic cancer and alcohol

Pancreatic cancer was estimated to be the 12th most common cancer in men, and the 11th most common cancer in women, as incidence, in the global 2012 record. In the same time, it was the 7th most common cause of death from cancer, in both sexes combined [6,16]. The majority of cases and death (55%) were registered in developed regions [6]. It had a poor prognosis, with a M:I ratio of 0.98 [6]. The sex ratio was close to one [6]. Trends of incidence and mortality rates in both sexes were rather stable over time [16].

Pancreatic cancer was added to the list of alcohol attributable cancers [16,17]. Alcohol could promote the development of pancreatic cancer through chronic high intake and via pancreatitis [64,65]. A synergistic effect with other risk factors was suggested (as metabolic risk factors and particular medical conditions, genetics, smoking, diet, working exposure) [65]. Only high alcohol intake appeared to be a significant risk factor for pancreatic cancer [66-69]. A case-control study suggested a non significant association between the risk of pancreatic cancer and alcohol, as either, the overall alcohol consumption or the type of alcohol consumed [70]. Given the histopathological diversity of pancreatic malignancies, the relation with the risk factors could be more complex [64,66].

Liver cancer and alcohol

On the global scale, the primary liver cancer was a

major contributor to both cancer incidence and mortality [6,71,72]. Liver cancer was the 5th most common cancer in men and the 9th in women, but the 2nd most common cause of death from cancer worldwide, in the last global estimation from 2012 [6,72]. Given the high fatality of liver cancer (overall mortality-to-incidence ratio, 0.95), the geographical patterns and trends for mortality were very similar to those observed in incidence [6,72].

A changing of incidence rates of hepatocellular carcinoma was registered in different areas of the world, apparently reflecting the changing distribution of the predisposing risk factors [71,72]. A time trend to increase of the primary liver cancer incidence was registered in many areas of the world, known as to have had a low incidence previously (Northern and Southern Europe, North and South America, Oceania, India, Israel). In contrast, the incidence rates manifested a time trend to decrease in areas known as to have had a high incidence (East Asian countries – Japan, China, Singapore, and in Spain) [71,72]. Liver cancer death rates (liver and intrahepatic bile duct cancer) registered an increasing trend in the USA at a faster pace than any other cancer [73].

Alcohol is a recognized risk factor for chronic liver disease, including liver cancer, by indirect and direct effects. Excessive consumption of alcohol was associated to the development of alcoholic hepatitis in 30-35% of consumers, and of cirrhosis in 10-15 % [74,75]. On the global scale, the etiology of hepatocellular carcinoma (HCC) was dominated by the hepatitis viruses B (HBV) and C (HCV) in more than 80% of the cases [76-79]. The contribution of alcohol to HCC risk was estimated at 15%, higher in USA and Europe (20%), as compared to Japan, Asia and Africa (10%) [78]. In the period of the estimation, in the USA the proportion of HCC attributed to alcohol was 32%, as compared to HBV (16%) and HCV (22%) [80]. In Italy, the proportions were 18%, 13% and 61%, respectively, in the period of the estimation [81].

In Romania, 19.5% of cirrhosis had alcoholic etiology, 48.3% had viral etiology and 16.2% had double etiology, viral and alcoholic, in the period of the estimation [82]. The prevalence of both hepatitis viruses, B and C, was high, in the period of the estimation [83-86]. This aspect was considered particular for our country, at the time [83]. HBV infection had a mean prevalence of 5.6% [83] and the D genotype of HBV predominated [84]. HCV infection had a mean prevalence of 3.5% [83], and the infection proved to be replicative in 90% of the HCV-positive subjects [85]. The genotype 1 of HCV was almost exclusively recorded in our area [86]. Delta virus infection (HDV) associated to HBV was registered in a higher proportion in patients with cirrhosis as compared to patients with chronic hepatitis [87,88]. Alcohol contribution to chronic hepatopathies was well documented in our country, and should continue, including HCC, given the statistical data on alcohol consumption [16,17]. The fact that only 15-20% of alcohol

consumers developed terminal cirrhosis emphasized the importance of other contributing risk factors [89].

Gallbladder cancer and alcohol

Gallbladder cancer (GBC) accounted for 1.3% of the total new cases, and 1.7% of all cancer death. About 65% of the cases were recorded in less developed regions. It was one of the digestive malignancies that registered a higher incidence in females (M/F ratio of 0.76) [6]. The most important risk factor was considered to be represented by gallstones. As only 1-3% of patients with gallstones developed gallbladder cancer, other risk factors were proposed to play a role [90]. GBC was the most common malignancy of the biliary tract, representing 80-95% of the biliary tract cancers worldwide [91]. The incidence of GBC registered an increase in USA in recent times, concurrent with the increases in cholecystectomy rates. This increase was attributable in part to improved histopathological detection of carcinoma in cholecystectomy specimens, as well as laparoscopic advances. GBC was detected with a frequency of 0.2% to 3% of all cholecystectomies. Although less prevalent, GBC had an extremely poor prognosis [92].

Data on alcohol consumption and GBC were unclear [93-96]. Some studies suggested an inverse association between alcohol intake and gallstone disease [93]. Other studies suggested that alcohol consuming elevated the risk of GBC in men, while its effect in women remained unclear [96]. Smoking appeared as a risk factor for GBC [95,96], and gallstones [95].

The increasing trend of some digestive cancers and of alcohol consumption is not unique to our area. The increasing trend of incidence registered by some digestive cancers in our country could have multiple etiological connotations, as in other areas of the world. It could be associated with the alcohol consumption too, taking into account an historical appearance parallel in their time trend.

Conclusions

The data derived from the IARC/WHO country statistics of cancers, historical and recent, and of WHO/UEG country statistics for alcohol consumption, revealed a parallel increase.

In terms of mortality, an increasing trend was registered for the cancers of the esophagus (in men), and the cancers of colon and rectum, pancreas and liver, in both sexes. In terms of incidence, an increasing trend was registered for the cancers of the esophagus (in men), gastric cancer (in men), colorectal cancer (in both sexes), pancreas (in women), and liver (in men). Alcohol consumption increased in the same period.

Given the parallel increase of some digestive cancers and alcohol consumption registered in our area, alcohol could represent more than a coincidence. Alcohol could be a real risk factor/cofactor promoting the development of preneoplastic lesions of the gastrointestinal tract, and, eventually, of digestive cancers.

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