

The Role of Environmental Factors in Digestive Cancer

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Abstract

The risk of digestive cancer in each country is analyzed in cancer registries for Incidence and Mortality. Survival is estimated from registries with a correct follow-up. Estimated values of Incidence and Mortality, expressed as an age standardized rate (ASR) for 100 000 persons, for all the population of a country are also found in the WHO-IARC database Globocan, recently edited for the year 2008. At each site of digestive tumors, the variations between countries, in cancer incidence, mortality and survival, depend on the resources and the global health status of the country. Indeed environmental causal factors linked to lifestyle may have an increasing or decreasing impact on the risk of cancer. Such factors are classified on 3 categories: 1- nutrition plays a determinant role in colorectal cancer with a higher risk in countries with more resources and more calories in the diet. 2- Toxic agents like alcohol and tobacco increase the risk at all sites of digestive cancer; their role is preponderant in esophageal cancer. Aflatoxin, a food contaminant in tropical, less developed countries, increases the risk of liver cancer. 3 – Infectious agents play a major role with the Bacteria *H.pylori* for stomach cancer over the world, and the Hepatitis virus B and C for liver cancer in less developed countries of Africa and Asia. The control of carcinogenic causal environmental factors is included in the primary prevention of digestive cancer.

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Introduction

In a small (5%) percentage of cases, cancer occurs through the transmission of a dominant gene by one ascendant; the development of this hereditary cancer occurs independently of any causal factor. Sporadic cancer corresponds to the majority of cases; here the development of the tumor may result, in connection to environment and lifestyle, of a prolonged abnormal exposure to toxic or infectious factors. The susceptibility to these causal factors varies with the genetic profile of the concerned person, justifying the occurrence of familial, but not hereditary, cancer, i.e. cases of sporadic cancer occurring in first degree parents, exposed to similar risk factors in their family.

The role of environmental factors linked to lifestyle has been exposed in multiple publications.⁽¹⁻⁸⁾ Particularly D.M. Parkin wrote a complete special issue of the *British Journal of Cancer* on this topic in 2011,⁽⁸⁾ analysing the role of 14 distinct toxic or infectious factors with a carcinogen impact, on 18 sites of cancer, out of which 7 were located in the digestive system. The study concerned only the

population of England in 2010, a country with a westernised lifestyle. In synthesis in this European country, non optimal exposure to one, or too many, of these carcinogenic factors, occurred in 42.7% of the incident cases in the year 2010. Cancer prevention aims to reduce cancer mortality through early detection and appropriate treatment of the tumor at a curable stage. This strategy, called secondary prevention is often developed through screening in asymptomatic persons. Cancer prevention also occurs through the identification and elimination of these causal factors linked to lifestyle and environment: their control is primary prevention of cancer.

The worldwide risk of digestive cancer

Population based cancer registries give for most countries very precise information of the annual burden of cancer at each site. Annual incidence and mortality are displayed there. Cancer survival is estimated from registries with a continuous follow-up of cases included, at each successive year. Cancer registries produce observed values of incidence and mortality, but in many countries this only applies

to a fraction of the population. Estimated values of incidence and mortality in all the population of a country and at each tumor site are also found in the WHO-IARC database GLOBOCAN, recently re-edited for the year 2008.⁽⁹⁾

In each cancer population based registry and for each tumor site, the yearly number of new cases occurring in 100,000 persons of the concerned population, is the crude rate of incidence. The figure is influenced by the distribution of age classes in this population; therefore for comparison of the risk between different countries, the figures refer to a standard of population. The age standardised rate (ASR) of incidence per 100,000 persons refers to the repartition of age classes in the world population in 1960, and is adopted in the listing of registries edited at intervals by the WHO International Agency for Research on Cancer in Lyon; in the most recent edition, the data are listed from 225 registries in 60 distinct countries, for the period 1998-2002.⁽¹⁰⁾

In each cancer registry and at each tumor site, the annual number of deaths by cancer is displayed in the corresponding population. The crude mortality rate is the annual number of deaths per 100,000 persons of the concerned population occurring in a year. The mortality is also expressed as an ASR mortality per 100,000 persons.

Cancer survival is usually expressed at each tumor site in percent as a crude 5 years survival. The 5 years relative survival refers to survival rate taking into account the comparison with persons of same sex and age, not suffering from this cancer. Survival analysed in cancer registries is also estimated at each stage of the detected tumor, for 'localised' to 'distant' cancer.

Sites of digestive cancer considered in this review are listed according to their code in the International Classification of Diseases (ICD10). The tumor sites in the digestive tract include cancer in the esophagus (C-15), stomach (C-16), colon and rectum (C-18 to C-21). Outside of the digestive tract the major sites include cancer in the liver (C-22), gallbladder and biliary tract (C-23 and C-24), and pancreas (C-25). The frequency of digestive cancer is confirmed by the worldwide numbers of incident cases and of deaths by cancer which are estimated and displayed in the database GLOBOCAN 2008.⁽⁹⁾ Globally they represent around 30% of incident cancer at all sites

and 37% of the total number of deaths by cancer at all sites, as shown in Table 1. Other digestive tumors not considered in this review include cancer in the lips, mouth and tongue (C-00 to C-06), oropharynx (C10), pharynx and hypopharynx (C-12 to C14).

	N° incident cases in 2008	N° deaths in 2008
All cancers	12 661 000	7 564 000
Esophagus Ca.	481 000	406 000
Stomach Ca.	998 000	736 000
Colon, Rectum Ca.	1 234 000	608 000
Liver Ca.	749 000	695 000
Gallbladder Ca.	145 000	109 000
Pancreas Ca.	278 600	266 600

Table 1: Estimated Worldwide burden of digestive cancer in 2008 according to GLOBOCAN.⁽⁹⁾ At each site, both sexes are included in the annual numbers of incident cases and of death by cancer. The global burden of digestive cancer - 3,885,600 cases and 2,820,600 deaths - amounts to 30.6% of the incident cases of cancer at all sites and 37.2% of mortality by all cancers.

Classification of countries through development

The countries of the world are classified in large geographic areas. The more developed countries, in their majority, are located in North America, Europe plus Australia and Japan. On the other hand, less developed countries are concentrated in Asia, Africa, Central and South America. Some countries, which are not yet classified as completely developed, like Brazil, Russia, India, and China, have a very fast improvement of their resources and are called "emerging" countries. The World Bank⁽¹¹⁾ is publishing a very precise list of the countries resources classified in 4 categories, with yearly revision of the figures. The list is based on the annual "per capita" income classified as Low, Middle-lower, Middle upper and High. The annual income per person is expressed in

Dollars, and the data for 2011 are given in Table 2.

Category of the country	GNI per capita
Low	\$1005 or less
Lower middle	\$1006 to \$3975
Upper middle	\$3976 to \$12,975
High	\$13,976 or more

Table 2: Amount in Dollars of the annual income per person (GNI per capita) in the population of a country for the year 2011, according to the listing of the World Bank. ⁽¹¹⁾ Countries are distributed in 4 categories according to individual income.

At each site of digestive tumors there are considerable variations in the risk for incidence, mortality and survival between countries at different levels of development. The variation is a consequence of the relationship between the resources of a country and the global health status of the respective population. First, this applies to the role of causal factors of digestive cancer in relation to lifestyle and resources of the persons. Causal factors may have an impact on the risk of cancer with an increase or a decrease, depending on the tumor site and type. Second, the proportion of cases detected early, at a curable stage depends on the diffusion of screening strategies in the corresponding country. Indeed there are considerable variations in the survival of colorectal cancer according to its stage at detection. In the SEER registries of the USA ⁽¹²⁻¹⁴⁾ the 5 years survival is as high as 96% for stage I (localized) and as low as 6% for stage IV (distant). Third, the quality of an adapted treatment, particularly for endoscopic and surgical procedures, depends on the level of development. In the same registries, the 5 years survival increased at all sites of digestive cancer during two decades of progression in early detection and treatment, as shown in Table 3.

Site of cancer	Years 1980-84	Year 2002
Esophagus	6.9%	16.7%
Stomach	16.7%	25.7%
Colon & Rectum	53.9%	69.1%
Liver	3.8%	14.0%

Table 3: Increase in the 5 years relative survival from digestive cancer in both sexes during the period 1980-2000 in the USA in relation to development of screening and treatment at early stage, as shown in the SEER registries. ⁽¹⁴⁾

In the less developed Sub-Saharan countries of the African continent, early detection of a cancer is not frequent and the overall survival is very low for most tumors. Furthermore the organisation of the sanitary system in the less developed countries is not homogenous, and the healthcare is better in urban than in rural sectors, where it is still deficient. This heterogeneity in healthcare in urban and rural sectors often persists in emerging countries in spite of their rapid development. On the other hand in the more developed countries classified in the higher category of the World Bank listing, healthcare is homogeneously distributed with a generalised positive impact on cancer mortality and survival.

Environmental causal factors in digestive cancer

Causal factors promoting carcinogenesis are often present in the environment of the persons and their action occurs through modalities of the lifestyle. As a rule, lifestyle criteria correlate with economic resources and depend on the development in the concerned country which has a direct impact on the role of causal factors of cancer. Around the world the carcinogenic factors connected to lifestyle can be classified in 3 categories which may have an impact on the risk of digestive cancer:

- 1- Nutrition, with the quantitative and qualitative character of aliments absorbed in the diet, plays a determinant role in the risk for colorectal cancer.
- 2- Toxicity, with agents like alcohol and tobacco absorbed in complement to diet, increases the risk for digestive cancer at all sites. Toxic factors associated to tobacco and Betel Quid chewing, increase the risk of esophageal cancer. Aflatoxin as a food contaminant in the culture of corn in tropical and less developed countries specifically increases the risk for liver cancer.
- 3- Infection occurs by multiple modalities of contamination and is an important causal factor of digestive cancer. The infectious agents include for stomach cancer the bacteria *Helicobacter pylori*, for liver and biliary tract cancer with hepatocarcinoma and cholangiocarcinoma; the Hepatitis B and C Viruses, the infections by liver flukes like *Opistorchis viverrini*, and *Clonorchis sinensis*.

In a first analysis of the global burden of infection associated cancers in the year 2002,⁽⁷⁾ it was

that a complete prevention of infectious factors would decrease the number of incident cancers by 7.7% in developed countries and by 26.7% in less developed countries. In a more recent analysis⁽⁴⁾ of the global burden of cancers attributable to infections in 2008, infectious agents accounted for 16.1% of all cancers, i.e. 2,000,000 incident cases. The proportion was much higher in the less developed countries of Asia and Africa (22.9%), than in more developed countries of Europe and North America (7.4%). In the same analysis⁽⁴⁾ the most frequent infectious agents playing a role in digestive cancer were the bacteria *H. pylori* with an estimated number of incident cases in 2008 at 660,000 and the Hepatitis B and C viruses with an estimated number of incident cases in 2008 at 600,000.

For these environmental causal factors, the role played in the etiology of digestive cancer differs in each region of the world, showing quantitative variations in the impact on the incidence of cancer. In more developed countries the majority of causal factors belongs to nutrition and diet with absorption of an excessive amount of calories, or to toxic agents like alcohol and tobacco. The conclusions of the recent analysis of these factors conducted at all sites of cancer in England⁽⁸⁾ are also valid in the majority of developed countries in Europe and North America. On the other hand, infectious factors play a predominant role in less developed countries of the world, like *H. pylori* infection in Asia and Viral Hepatitis B in Africa.

A more or less important reduction in the risk of cancer may be obtained by the control of the causal factors linked to lifestyle of the population; this is primary prevention of cancer. The strategy of primary prevention and its efficacy varies of course with the nature of the causal factor and with the style of life in this country. The efficacy of primary prevention through control of noxious environmental factors depends of course on the level of healthcare and economic resources in the concerned country, it also depends on its interaction with the lifestyle of the persons. The generalised practice of a vegetarian diet in India achieves an effective and spontaneous primary prevention of colorectal cancer. In opposition the prevention of hepatocarcinoma in Africa requires a complex and diffuse intervention of vaccination against hepatitis Virus B in the population.

Causal factors at each site of digestive cancer

Esophageal cancer

In GLOBOCAN,⁽⁹⁾ the worldwide number of incident cases of esophageal cancer occurring in 2008 was estimated for both sexes at 481,000, out of which 80,000 occurred in developed countries and 399,000 (83% of total) in developing countries. In the recent analysis⁽⁸⁾ of environmental factors associated to esophageal cancer in England, tobacco smoking or chewing is present in 65.5% of cases and alcohol drinking in 20.6% of cases. There are two distinct tumor types in the esophagus: squamous cell cancer and adenocarcinoma. The incidence of adenocarcinoma is much lower than that of squamous cell cancer, but it tends to increase. Squamous cell cancer is more frequent in developing countries of Asia; the tumor arises from the normal squamous epithelium of the esophageal mucosa; alcohol and tobacco are acknowledged as causal factors of squamous cell cancer, and their control is recommended for primary prevention of this tumor. Adenocarcinoma, developed in a metaplastic columnar epithelium, also called Barrett esophagus, is in relation to chronic inflammation through gastro-esophageal reflux and is more frequent in developed countries of North America and Europe with a higher risk in Caucasians. The risk for this tumor is increased by smoking and higher in persons with excess weight and obesity at a young age. In addition to the control of acid reflux by proton pump inhibitors in persons with gastro-esophageal reflux, the primary prevention of esophageal adenocarcinoma through control of environmental factors, relies on the control of smoking and reduction of calories in the diet to prevent obesity. Early detection of esophageal squamous cell cancer through population based screening trials is organized of high risk areas in China and Southern Brazil and based on a balloon or sponge scrapping of the esophageal mucosa, followed by upper GI endoscopy in persons positive to the test. For esophageal adenocarcinoma, organised screening endoscopic trials are not recommended.

Stomach cancer

In GLOBOCAN,⁽⁹⁾ the worldwide number of incident cases of stomach cancer occurring in 2008 was estimated for both sexes at 988,000, out of which 274,000 occurred in developed countries and 713,000

(70% of total) in developing countries. Gastric cancer, localised in the distal part of the stomach accounts for 80% of the cases, while proximal gastric cancer (also called cardia cancer) accounts for 20% of the cases. However in most countries, during the recent decades, the decreasing incidence of distal gastric cancer is in contrast with the increasing incidence of proximal gastric cancer at the cardia. In the analysis of the global burden of infection-associated cancers in 2002⁽⁷⁾ the proportion of gastric cancers attributable to *H. pylori* infection was estimated at 61.4% in developed countries and 64.4% in developing countries; the global numbers are shown in Table 4. Therefore gastric cancer is the tumor site more frequently associated to an infectious agent. In a more recent worldwide analysis, conducted in 2008⁽⁴⁾ the prevalence of the infectious agent in cases of non-cardia (distal) gastric cancer was estimated at 90% and 74.7% of incident cases of this tumor occurring in 2008 were classified as attributable to this infectious agent. In addition to infection of the gastric mucosa, nutritional factors such as a high intake of salt and nitrates and a low intake of fruit and vegetables, may increase the risk of cancer.

Countries	Sex	N° distal gastric cancer	N° attributable to <i>H. pylori</i> infection
Developed countries	Men	156 000	117 000
	Women	117 000	75 000
	Both	273 000	192 000
Developing countries	Men	324 000	254 000
	Women	187 000	146 000
	Both	511 000	400 000

Table 4: Estimation of the worldwide number of stomach cancer attributable to *H. pylori* infection in 2002 for developed and developing countries according to the worldwide analysis conducted by DM Parkin.⁽⁷⁾ The figures are based on the following assumption: the proportion of adult persons infected by the bacteria is 58% in developed countries and 74% in developing countries.

The sequence of gastric carcinogenesis in relation to *H. pylori* infection as a cause of atrophic gastritis, a pre-neoplastic condition, has been described by Correa in the gastric lumen: the increased pH causes

a growth of anaerobic bacteria with formation of carcinogenic compounds like the nitrosamines. The bacteria *H. pylori* has been classified as a carcinogen agent in a monography of the WHO-IARC agency in Lyon. Another infectious factor plays a role in addition to *H. pylori* in gastric carcinogenesis: Epstein-Barr virus is present in the tumor cells of about 10% of cases of gastric cancer.⁽¹⁵⁾ This agent accounts for around 80,000 cases annually. Until recently the role of *H. pylori* infection in gastric carcinogenesis was limited to distal gastric cancer. More recently a positive association with this infectious factor was observed both for proximal and distal gastric cancer. Indeed cancer associated to Epstein Barr virus shows a more frequent localisation in the proximal stomach with a high proportion of diffuse type of tumors.

Non-cardia (distal) gastric cancer⁽¹⁶⁾ occurs all over the world but the incidence is higher in countries of Eastern Asia and in South America as shown in Table 5.

	Men	Women
North America		
USA : SEER 14 registries	7.2/100,000	3.4/100,000
South America		
Chile : Valdivia registry	43.1/100,000	16.0/100,000
Europe		
Denmark	7.1/100,000	3.2/100,000
Italy : Vénétie	15.7/100,000	7.3/100,000
Asia		
China : Shanghai registry	34.1/100,000	17.2/100,000
Japan : Osaka registry	51.3/100,000	19.8/100,000
Korea : Séoul registry	63.7/100,000	27.1/100,000

Table 5: The ASR incidence for gastric cancer in cancer registries from various countries for the period 1998-2002 according to 'Cancer Incidence in Five Continents'⁽¹⁰⁾

In Japan, this cancer accounts for a high proportion of cases at all tumor sites. Other regions at high risk of non-cardia gastric cancer include Eastern Europe and Western South America. The incidence of proximal gastric cancer is lower and the highest figures are

observed in North America and in Europe. Primary prevention of distal gastric cancer is focalised on the eradication of *H. pylori* infection at the individual scale in children. This is completed by the diffusion of a policy on healthy nutrition combining the reduction of salt and nitrites in the alimentation to an increased consumption of fruit and vegetables. This policy is currently applied in Japan, a country where the consumption of food preserved by salt was often combined with a low consumption of fruit, vegetables, and anti-oxidants. The changing style of life in nutrition in this country has a significant impact on the reduction of the risk. The preventive action of ascorbic acid, an anti-oxidant, is based on the inhibition of the endoluminal formation of carcinogens. Primary prevention of proximal (cardia) gastric cancer relies on the control of excess weight at a young age, to reduce gastro-esophageal reflux.

Secondary prevention of stomach cancer by organised screening for early detection at a curable stage is only justified in countries with a high incidence, like in Japan where there is a national screening policy. In this country the first test is photofluorography performed on seven small films easily swallowed, followed by gastroscopy in persons positive to the test.

Colorectal cancer

In GLOBOCAN,⁽⁹⁾ the worldwide number of incident cases of colorectal cancer occurring in 2008 was estimated for both sexes at 1,234,000, out of which 727,000 occurred in developed countries and 506,000 (41% of total) in developing countries. Worldwide, colorectal cancer is the third most common cancer in men, and the fourth in women. In 95% of cases colorectal cancer occurs as a sporadic disease in adults of both sexes, aged 50 years or more. The site of colon cancer is in the ascending segment, right angle, transverse segment, left angle and descending segment of the large bowel, while rectum cancer is in the most distal part of the large bowel between the recto-sigmoid junction and the anal margin. The proportion of colorectal cancer attributable to lifestyle and environmental factors in England for the year 2010 is estimated at 54%.⁽⁸⁾ These factors include a diet rich in calories of animal origin, with red and processed meat, overweight, inducing resistance to insulin and production of insulin-like growth factors like the IGF-1 which stimulates the proliferation of

intestinal cells. Aromatic polycyclic molecules with a carcinogenic impact, develop within meat directly grilled. Another causal factor is a sedentary mode of life with decreased physical activity. All these environmental factors are closely related to the development of resources and of urbanised life; therefore the incidence of cancer in the colon and cancer in the rectum is higher in countries classified in the Upper Middle and in the High Income categories for their GNI per capita, than in those classified in the Lower middle and Low Income categories, which account for 82% of the world population. Data on the incidence of cancer in the colon and in the rectum in Cancer Registries are displayed for the period 1998-2002 in the last edition of 'Cancer Incidence in Five Continents'.⁽¹⁰⁾ The ASR Incidence /100,000 of CRC for men is high in developed countries: 37.4 in Japan (Osaka registry), 38.4 in the USA (SEER 9 registries), 48.7 in France (Bas-Rhin registry). The figures for women are slightly lower but still high. Incidence is much lower, and under 10/100,000 in countries with low resources like in Zimbabwe (Harare registry) in Sub-Saharan Africa. Incidence of colorectal cancer increased in the two recent decades in urbanised areas of emerging countries like China and Brazil, reaching similar figures to those observed in the more developed countries.

A confirmation of the role of environmental factors linked to diet is shown by the stable and low incidence of colon cancer in India, a country where the diet is strictly vegetarian as a rule, during the same period; stability applies also to cancer at the rectum sub-site. The temporal trend for increasing incidence observed in North America, Europe, Japan and Australia in the period 1980-2000, is more marked for the colon than for the rectum sub-site. As an example, in Japan in the Osaka cancer registry⁽¹⁷⁾ the trend in incidence during the period 1974-2003, shows a topographic shift in the distribution of colorectal cancer towards proximal colon. In summary colorectal cancer is a frequent tumor, with an incidence rate higher in developed than in developing countries, as shown by the estimates of GLOBOCAN.⁽⁹⁾ In the year 2008 59% of cases occurred in developed countries which account for only 36% of the world population.

With respect to cancer survival, developing countries with low resources have not yet developed their National Health Care System and the efficacy in the diagnosis and treatment of colorectal cancer is

poor. Survival depends on the stage of the tumor at detection and is much higher for localised than for advanced cancer. The 5 years relative survival of colorectal cancer in registries from developed countries is displayed in the CONCORD study for the period 1990-94⁽¹⁸⁾: - for men the figures are: 51.9% in registries from USA, and 61.1% in registries from Japan. -for women the respective figures are 60.2%, and 77.3%. In registries from Europe slightly lower values are reported in the same study⁽¹⁸⁾ for men and women at the colon and rectum sub-sites; with almost similar results in the period 1995-99.⁽¹⁹⁾ In registries from Asia in the period 1990-2000⁽²⁰⁾ the 5 years relative survival from colon cancer is low at 32.3% in the Mumbai registry of India a country in the Lower middle category of the GNI per capita, and high at 65.7% in the Seoul registry of Korea, a country in the high category of the GNI per capita. An increase of the survival in the registries of 2 successive periods, suggests a progress in cancer prevention, either through early detection with more cases detected at stage I or II, or through improved treatment. In the period 1988-2001, the 5 years relative survival increased in the USA in relation to the progress in early detection and the figures in the SEER registries for both sexes at the colon and rectum sub-sites were 64.0% and 62.7% during the period 1988-2001.⁽¹²⁾ In the less developed countries of the world survival is much lower: the 5-year relative survival in the period 1990-2000 in Uganda, a sub-Saharan country,⁽³⁰⁾ is in the range 7 to 11%, because detection often occurs at an advanced stage. Emerging and developing countries with middle and higher resources, have already built structures of health care and cancer control in urbanized areas. In China in the period 1990-2000, the 5 years relative survival for cancer in the colon and rectum is higher in the urbanised district of Shanghai, than in the rural district of Qidong.⁽²⁰⁾ Cancer survival can reach the same level as in developed countries, in the urbanised sectors of developing countries with enough resources; however, heterogeneity persists with lower figures in rural areas. Multiple publications address to incidence, mortality and survival of this tumor.⁽²¹⁻³⁰⁾

Primary prevention of colorectal cancer is based on a reduction of the amount of calories, focused on proteins and fat and in increased physical activity and daily walking,⁽²³⁻³⁰⁾ in order to reduce excess weight and obesity. These prescriptions can be integrated in a national policy creating awareness among the

population on: 1 - restraining high consumption of sugar, and fat, 2 - increasing consumption of vegetal food including fruits, vegetables and whole grains, 3 - increased physical activity 4 - keeping an ideal bodyweight without obesity. An example of the impact of a spontaneous national primary prevention is given by India, an emerging country, where low incidence of colorectal cancer persists in spite of the development in urban districts, in relation to a generalised vegetarian alimentation.^(23,24,28,30) In India, the stable and low incidence of colon cancer during the period 1973-2002 in the urban registry of Mumbai, is in contrast with the increasing trend occurring in Japan and in China, as shown in Table 6.

	Period 1973 - 1977	Period 1998 - 2002
Japan, Myagi registry		
Men	8.3/100,000	36.0/100,000
Women	7.3/100,000	21.5/100,000
China, Shanghai registry		
Men	6.7/199,000	15.8/100,000
Women	6.0/100,000	14.6/100,000
India, Mumbai registry		
Men	3.5/100,000	3.0/100,000
Women	3.5/100,000	2.4/100,000

Table 6: The ASR Incidence of colon cancer in men and women in cancer registries of Asia in two periods 1973 to 1977 and 1998 to 2002. The incidence increases in relation to the progression of the development in Japan and in China, but not in India according to 'Cancer Incidence in Five Continents.'^(10, and previous editions)

Secondary prevention of colorectal cancer is based on screening trials which are often offered in developed countries of Europe, North America and in Japan. Mass screening is proposed to all persons in the age range 40 to 70 years and repeated at regular intervals of 2 to 5 years. The strategy of early detection and treatment is based on a filter test, the Guaiac or Immunologic Fecal Occult Blood Test; colonoscopy, the detection test, is performed only in persons found positive to the test.⁽³¹⁾ A 10% to 20% reduction in cancer mortality has been confirmed in the randomised trials conducted in the USA (Minnesota trial) and in Europe (Nottingham and Funen trials).

Countries	N° liver cancer	Attributable to HBV	Attributable to HCV	Attributable to HBV or HCV
Developed countries	119,800	26,000	22,000	48,000
Developing countries	515,000	393,000	172,000	475,000

Table 7: Estimation of the worldwide number of liver cancer, both sexes, attributable to infection by HBV and HCV in 2002 for developed and developing countries, according to a worldwide analysis.⁽⁷⁾ Globally 85.5% of hepatocarcinoma are attributable to viral hepatitis and 90% of cases occur in developing countries of Africa and Asia.

The reduction in incidence did not occur in the cost effective European trials in which the proportion of persons submitted to colonoscopy was small. Mass screening interventions addressed to the population of a country require an evaluation of the benefits and drawbacks. Benefits include a reduction in cancer mortality and increased survival.

Drawbacks include the morbidity of the endoscopic intervention and the inevitable over-detection of cancer in screened persons with a preclinical cancer, which would die from another cause. Non organized screening is also often proposed in developed countries to asymptomatic persons, in the age range 50-70 years; with the objective of early detection of cancer at a curable stage; this is called opportunistic screening. Primary colonoscopy is then directly performed, allowing also the detection and treatment of adenomatous premalignant lesions; then the development of colorectal cancer is prevented by the destruction of the precursors with an impact on cancer incidence. Indeed the trend to increased incidence of colorectal cancer in the USA during the last quarter of the XXth century is now inverted; a recent decline in incidence follows an increased endoscopic destruction of premalignant precursors.

Liver cancer

In GLOBOCAN,⁽⁹⁾ the worldwide number of incident cases of Liver cancer occurring in 2008 was estimated for both sexes at 749,000, out of which 122,000 occurred in developed countries and 625,000 (83% of total) in developing countries. Liver cancer develops in chronic cirrhosis; toxic and infectious environmental factors linked to lifestyle play a major role in the development of this tumor. Among toxic factors is alcohol consumption, at the origin of the liver cirrhosis,⁽³²⁾ tobacco smoking increases the risk of cancer and is a frequent associated factor. The

first step of alcohol toxicity on the liver is steatosis followed by fibrogenesis induced by acetaldehyde. Aflatoxin, a mycotoxin produced by *Aspergillus*, is present in the soil and contaminates the crops during farming in the south of China and in Sub-Saharan African countries. The necrosis produced in the liver is followed by development of an hepatocarcinoma. Infectious agents with a carcinogen activity are hepatitis viruses. In the review of infectious associated tumors conducted in 2002,⁽⁷⁾ the worldwide number of hepatocarcinomas attributable to virus B and C (HBV and HCV), is estimated at 340,000 for Hepatitis virus B, (54%) and at 195,000 for Hepatitis virus C (31%). The majority of the hepatocarcinomas (over 80%) attributable to viral hepatitis occurs in the less developed or developing countries, as shown in Table 7.

The HBV is a DNA virus with distinct genotypes present in Asia and in Africa and Europe;⁽³³⁾ the contamination occurs through sex, or injections. The integration of the DNA virus, behaving as an oncogene in the genoma of the host cells, insures the chronicity of infection. The proportion of hepatocarcinomas with a positive HBV serology is above 50% in China, Taiwan, Korea and Thailand. HCV is a RNA virus with two distinct genotypes.⁽³⁴⁾ The virus is not an oncogene and is not impacted in the cell DNA and replication occurs in the cytoplasm, with an interference on the regulation of the cell cycle. Contamination by HCV occurs through the deficient asepsis of injections. The proportion of hepatocarcinomas positive for HCV is near to 70% in Japan and in Egypt.⁽³⁴⁾

Primary prevention of digestive cancer at all sites, including liver hepatocarcinoma, is possible worldwide through reduction of alcohol drinking and tobacco smoking or chewing. With respect to toxic factors like Aflatoxin, the prevention of the contamination of the crops of cereals and of milk of

animals is obtained through selection of the cultivar and pre-harvest treatments. Prevention against infectious agents is also a priority in Asia and in Africa, through vaccination against HBV. Concerning HCV, there is still no effective vaccine, but the use of safe blood products, disposable syringes and needles, and a strict asepsy for injections have dramatically reduced risk of infection.

Secondary prevention of liver hepatocarcinoma by screening asymptomatic persons or persons with chronic virus C Hepatitis is possible, using abdominal ultrasound and serum alpha-fetoprotein as filter tests.

Organized screening interventions have been successful in Japan and attempted in African countries. In persons with a positive filter test, confirmation of the diagnosis requires a tissue sampling by biopsy under ultrasound or CT scan. Conservative treatment of small tumors detected by screening is based on new techniques like radio-frequency or chemo-embolisation.

Gallbladder and biliary cancer

In GLOBOCAN,⁽⁹⁾ the worldwide number of incident cases of cancer in the gallbladder and biliary tract occurring in 2008 was estimated for both sexes at 145,000, out of which 60,000 occurred in developed countries and 85,000 (58% of total) in developing countries. The role of infectious agents in the risk of cholangiocarcinoma is considered. In the analysis of the global burden of infection-associated cancers in 2002⁽⁷⁾: in countries from Asia, liver flukes, which are endemic, may play a role: *Opisthorchis Viverrini* in China, Korea, Vietnam and *Opisthorchis felinus* in Thailand.

Pancreatic cancer

In GLOBOCAN,⁽⁹⁾ the worldwide number of incident cases of pancreatic cancer occurring in 2008 was estimated for both sexes at 278,700, out of which

166,000 occurred in developed countries and 112,000 (40% of total) in developing countries. Pancreatic cancer incidence and mortality are higher in developed Western countries and in Japan. In Europe, rates are highest in the Nordic countries. In the USA, rates are particularly high in native Hawaiians and in African Americans. In the special issue of the *British Journal of Cancer*,⁽⁸⁾ tobacco smoking is a significant environmental factor linked to the risk of pancreatic cancer. The presence of this toxic factor is acknowledged in 28.7% of the cases occurring in England. Another factor playing a role and linked to diet is the excess weight and obesity; sources of animal calories, proteins and fat, may play an important role in the etiology of pancreatic cancer. The presence of obesity is acknowledged in 12.2% of the cases occurring in England.

In conclusion

Environmental and preventable factors linked to lifestyle play a role in around 50% of digestive cancer at all sites. The burden of digestive cancer could be significantly reduced by an intervention on these factors. Toxic agents like alcohol and tobacco play a worldwide role. If they interfere with the risk of digestive cancer at all sites, their major promoting role is for esophageal cancer. Infectious agents like *H. pylori* for stomach cancer and Hepatitis B and C viruses for liver hepatocarcinoma, concern in priority the risk in regions of Asia and in Africa. Their role is more marked in the less developed countries.

There should be a joint action between policies of primary prevention and policies of secondary prevention. Both policies contribute to reduction of the risk and detection of cancer or precursors at an early curable stage, providing a safe and effective treatment. A good example is the role of colonoscopy in the prevention of colorectal cancer; this procedure offers a simple and non-aggressive treatment of the precursor adenomas and of superficial cancer detected in asymptomatic persons.

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