DOI: 10.34172/mejdd.2022.251

Review Article 5

Gastrointestinal and Pancratohepatobiliary Cancers: A Comprehensive Review on Epidemiology and Risk Factors Worldwide

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Received: 11 Jun. 2021
Accepted: 01 Nov. 2021
Publieshed: 30 Jan. 2022

ABSTRACT

A significant number of cancer cases are afflicted by gastrointestinal cancers annually. Lifestyle and nutrition have a huge effect on gastrointestinal function, and unhealthy habits have become quite widespread in recent decades, culminating in the rapid growth of gastrointestinal cancers. The most prevalent cancers are lip and mouth cancer, esophageal cancer, gastric cancer, liver and bile duct cancer, pancreatic cancer, and colorectal cancer. Risk factors such as red meat consumption, alcohol consumption, tea, rice, viruses such as *Helicobacter pylori* and *Ebstein Bar Virus (EBV)*, along with reduced physical activity, predispose the gastrointestinal tract to damage and cause cancer. According to the rapid increase of cancer incidence and late diagnosis of gastrointestinal malignancies, further epidemiological researches remain necessary in order to make appropriate population-based preventive policies.

In this study, we reviewed clinical symptoms, risk factors, preventative measures, as well as incidence and mortality rates of gastrointestinal malignancies worldwide with focus on Iranian population.

KEYWORDS:
Epidemiology; Gastrointestinal cancer; Lifestyle; Mortality

Please cite this paper as:
Hormati A, Hajrezaei Z, Jazi K, Aslani Kolur Z, Rezvan S, Ahmadpour S. Gastrointestinal and Pancratohepatobiliary Cancers : A Comprehensive Review on Epidemiology and Risk Factors Worldwide. *Middle East J Dig Dis* 2022; 14:5-23. doi: 10.34172/mejdd.2022.251.

INTRODUCTION

In recent decades, lifestyle has changed significantly, and while technology has facilitated the diagnosis process, gastrointestinal cancers are yet diagnosed at end stages of the disease leading to high rates of mortality and morbidity Today's lifestyle can lead to cancer and various diseases in the future. There are several various lifestyle influences in which diet plays an important role in causing diseases, including gastrointestinal diseases.[1] Red meat, hot tea or coffee, few physical activities, reduced physical activity, preserved food, smoking, and alcohol consumption are the most common cancerous risk factors that are merged to our lives.[2] In general, not only the incidence and mortality of gastrointestinal cancers has increased in the last decade but also the estimations showed an increasing pattern in both mortality and incidence rates by 2040

worldwide.[3]

Global Cancer Incidence, Mortality and Prevalence database (GLOBOCAN) release epidemiological statistics for the most common gastrointestinal tract organs annually: lip and oral cancer, esophageal cancer, abdominal cancer, liver and bile duct cancer, gallbladder cancer, pancreatic cancer, and colorectal cancer. Meanwhile, Asia has a substantial number of people with gastrointestinal cancers. Iranian population follows the same increasing pattern of incidence and mortality. During the last decade, there has been a substantial rise in the number of cases of gastrointestinal cancer in Iran of which 10.2% are colorectal cancer, and 6.7% are gastric cancer, out of 28,927,690 total cancer cases in Iran.[4]

Late diagnosis of gastrointestinal cancers, highlights the importance of epidemiological studies and preventive policies. Here in, we reviewed clinical symptoms, risk factors, and preventative measures of the most prevalent gastrointestinal cancers by searching PubMed, Medline, and Scopus databases, as well as the Cochrane Library. Furthermore, we investigated GLOBOCAN 2020 database for incidence and mortality rates worldwide with focus on Iranian population.

METHODS

Clinical symptoms, risk factors, and preventative measures were found in the PubMed, Medline, and Scopus databases, as well as the Cochrane Library, while incidence rates and age-standardized rates were found in the GLOBOCON database. The age-standardized rate (ASR) of occurrence in Iran in 2020 (according to GLOBOCAN estimation) was used for this review article.

LIP AND ORAL CAVITY

Head and neck cancers (HNC) constitute malignancies observed in the larynx, tongue, tonsils, lips, pharynx, nasopharynx, gum, and other oral cavities. Lip cancers account for about 10-12% of HNC and is assumed more curable in comparison with other HNC. The leading type of malignancy associated with the lower and upper lip is squamous cell carcinoma (SCC) and basal cell carcinoma (BCC).[5] Of note, lower lip SCC is considered the most frequent malignancy explained by lower lips more exposure to the sun. Lip malignancies are of cancers of old ages, which means that patients are mostly over 50 years when presented.[5, 6]

Ultraviolet radiation (UV) and betel quid exposure are the most considerable risk factors of external lip malignancy, whereas internal lip cancer is majorly due to tobacco smoking, alcohol and hydrochlorothiazide use, as well as a high dose of azathioprine, cyclosporine prescription in transplant recipients. According to potential risk factors, men are found more susceptible than women as a result of further smoking and alcohol drinking.[7-10]

Oral cancers are malignancies, two of five of which are considered as having a poor prognosis.[11] In addition to tobacco and alcohol use, oral mucosal lesions, betel quid, gurtka, *human papilloma virus (HPV)*, and graft-versus-host-disease (GVHD) are also announced as potential risk factors for oral malignancies.[11-13] Noteworthy, alcohol in mouthwash liquids is not yet proven as a potential risk factor.[14]

According to the recent GLOBOCAN 2020 study, lip and oral cavity cancer is known to be the 17th predominant cancer worldwide with age-standardized prevalence rates of 4.1 per 100 000 and 377713 new cases. The highest occurrence is found in India (36%), China (8%), the United States of America (6.5%), Pakistan (4.5%), and Bangladesh (3.7%) and Iran is the 36th.

Of all the recent cases estimated for lip and oral cavity cancer, 264,211 were men (6 out of 100 000), and 113,502 were women (2.3 of 100 000). Lip and oral cavity cancer were internationally observed to have a 2-3 times higher prevalence in men than women, ranked 11th and 18th respectively, on par with other gastrointestinal malignancies.

The incidence of lip and oral cavity cancer in the Iranian population is 1.3 per 100 000, and 0.87% of all cancers diagnosed in 2020 were reported to be lip and oral cavity cancer. 1,139 new cases, of which 607 (1.4 per 100 000) are male and 532 (1.3 per 100 000) are female, indicate that in accordance with global estimates, Iranian men are more likely to be affected than women. Remarkably, lip and oral cavity cancer are the 20th most prevalent cancers in Iran, with a combined risk of 0.144.[1-3] 177757 people are estimated to have died of lip and oral cavity cancer with 1.9 per 100 000 age-standardized mortality rates, including 125,022 (2.8 per 100 000) men and 52,735 (1.0 per 100 000) women.

Countries representing the top five age-standardized

mortality rates for both sexes are India (42.4%), China (8.3%), Pakistan (6%), Bangladesh (4.6%), and Russian Federation (3.2%). Additionally, Iran is estimated to rank 43rd country with age-standardized mortality rates. As stated by GLOBOCAN 2020, 390 cancer-related deaths in Iran (0.4% of all) are caused by lip and oral cavity cancer, which is considered 21st cancer in Iran after thyroid cancer. The age-standardized mortality rate is 0.44 per 100 000 along with a cumulative risk of 0.05. 158 (0.41 per 100 000) Iranian men and 175 (0.37 per 100 000) women, on par with the predominance of global men's mortality rates. The partial similarity in mortality and incidence patterns is explained by the poor prognosis of lip and oral cavity cancer mentioned in both global and national statistics.

The overall burden of lip and oral cavity cancer is increasing over time. Further to statistics reported in the past year, the global new cases are estimated to reach 1,403,985, presenting 55% increase in incidence rate. Among the male and female population, 53% and 59.7% elevation is estimated, respectively, which predict the number of new cases to reach 967,326 in men and 436658 in women. Mortality rates are also predicted to increase 56.4% globally by the next 20 years, representing 1298600 new cases, which include 891485 men (54.4% increase) and 407115 women (61.1% increase).

The Iranian population is expected to have a 101.3% growth compared to 2 293 new cases, of which 1,173 are men (93.2% increase), and 1,120 are women, compared to 2040 projections and 2020 recorded cases (110.5% increase). The number of additional deaths will be 973, posing an unprecedented 114.3% rise in annual rates. It is projected that 439 (90.9% increase) Iranian men and 533 (137.9% increase) women will die by 2040 due to lip and oral cavity cancer.[15]

ESOPHAGUS

Esophageal cancer (EC) is the 8th most common cancer worldwide, according to the GLOBOCAN 2020 survey, with age-standardized prevalence rates of 6.3 per 100,000 and 604,100 new cases. The highest number of occurrences can be found in China (53.7%), India (10.5%), Japan (4.3%), Bangladesh (3.6%), and the United States of America (3%) as the top five countries with the highest age-standardized incidence rates, respectively. 9.3 of 100,000 men and 3.6 out of 100,000 women were reported to develop EC worldwide.[4] 9% of all cancers and 27% of GI-related cancers were esophageal carcinomas. The male to female ratio was 1.71. EC is found highly prevalent in north and northeast of Iran. The incidence of EC is 4.1 per 100000, and EC new cases are expected to account for 2.6% of all malignancies diagnosed in 2020 among Iranian population, comprising 1,981 (2.8 per 100 000) men and 1,438 (2.4 per 100 000) women.[4]

Surprisingly, EC is Iran's 12th most common cancer. EC caused the death of 79,136 persons, with a 3.7 per 100 000 age-standardized mortality rate, including 1,790 (3.9 per 100 000) men and 1,310 (4.0 per 100 000) women. China (53.3%), India (10.7%), Bangladesh (3.7%), the United States of America (3%), and Japan are the countries with the highest age-standardized death rates for both sexes (2.3%).[6] Iran is also ranked 15th in the world in terms of age-standardized death rates. With a cumulative risk of 0.68, the age-standardized death rate is 5.6 per 100 000.

According to 2040 estimations, the Iranian population is predicted to grow by 118.7%, with 7,476 new cases, of which 4,189 are male (111.5% increase) and 3,287 are female (128.6% increase). The additional deaths will be totally 7,077, resulting in an annual rate increase of 128.3%, which is unparalleled. 3,798 (112.2% increase) Iranian men and 3,279 (15% increase) Iranian women are expected.

EC, a deadly malignancy with destitute guess, shows critical varieties within the frequency, mortality, and histopathology based on geographic districts.[7] Gigantic topographical variety is an epidemiological characteristic of (EC), with the most noteworthy frequency rates seen in Eastern Asia, Eastern and Southern Africa comparing to Western Africa representing the lowest rates.[8]

A study on Iranian population revealed that the restricted changes in treatment results given by customary treatments have incited us to look for imaginative techniques for treating this cancer.[9] Early organized mucosal infection (recognized by screening endoscopies, for the most part within the Distant East) is overseen by mucosal resections and endoscopic treatments. However, multimodality administration counting surgery, chemotherapy, and radiotherapy, is the key to treat locally progressed infections as threatening complications.[10] The onset of dysphagia is related to progressed illness, which includes the survival of 5 years in lower than 15%.

Populace screening by endoscopy is not cost-effective, but some elective imaging and cell examination innovations are under examination. Over the past ten years, a critical advance has been made in endoscopic conclusion and treatment of dysplasia (squamous and Barrett's), and early esophageal cancer utilizing resection and removal advances upheld by proving in randomized controlled trials.[11] Esophageal cancer is frequently analyzed amid its progressed stages, emphasizing the need for developing early-detection strategies. In an endeavor to improve the outcome of patients after surgery, such patients are regularly treated with neoadjuvant concurrent chemoradiotherapy (CCRT) to diminish tumor measures. In any case, CCRT may upgrade harmfulness levels and conceivably cause a delay in surgery for patients who react ineffectively to CCRT.[12] Squamous cell carcinoma and adenocarcinoma are the two transcendent histological subtypes with changing geological and racial dispersion. All-inclusive, SCC remains the foremost common histological type sort. In Western countries, in any case, adenocarcinoma has been the driving histological subtype, corresponding to a rise within the frequency of corpulence, gastroesophageal reflux disease, and Barrett's esophagus.[13]

SQUAMOUS CELL CARCINOMA

Esophageal squamous cell carcinoma (ESCC) is the 6th most common cancer worldwide. Because of challenges in early conclusion and destitute adequacy of treatment, the 5-year survival rate of ESCC is < 10%.[16] ESCC is commonly related to the mid-portion of the esophagus. ESCC accounts for approximately 90% of the 456,000 esophageal cancers each year. Although the rate of ESCC is increasing, its rates are diminishing within the USA and many European nations. Despite the rapid rise of adenocarcinoma frequency with in recent decades, squamous cell carcinoma remains the transcendent cell sort around the world.[17] ESCC is responsible for almost 90% of all esophageal cancers in Iran. The age-standardized rate of oesophageal SCC within the city of Gonbad (Golestan Territory, northeast of Iran) was found to have one of the most elevated rates for any single cancer that had been reported worldwide. In addition, authors indicated that the incidence of ESCC has decreased to less than 50% within years in relation to local economic development.[18] The etiology of ESCC is multifactorial and unequivocally population-dependent. A study in US reported that cigarette smoking, alcohol consumption, and low vegetable intake.[13] In addition, tobacco and liquor use are reported to be the two major dangerous components that increase the risk of developing ESCC.[17] Since these attitudes were generally more predominant in men than in women, men are more susceptible to develop ESCC than women.[15] Soscioeconimic status plays a significant role in ESCC development. Surprisingly, in countries with high income, Soscioeconimic status was proven to be a considerable risk factor for ESCC.[15, 19] Regardless of suspected etiological variables, hereditary changes are also firmly seen in ESCC which include (i) changes in tumor silencer qualities, particularly p53, resulting in abnormal DNA replication and repair and apoptosis; (ii) disturbance of the G1/S cell cycle checkpoint and misfortune of cell cycle control; Seropositive patients for p53 were more likely to safely respond to chemotherapy. Assessments determined that p53 may be a valuable molecular target both within the determination and within the treatment of ESCC.[20] A meta-analysis, of three randomized controlled trials and six reviews, comprising 1684 cases concluded that postoperative chemotherapy may general and disease free survival.[21] In addition to chemotherapy, endoscopic resection shows up to be a secure strategy to treat patients suffering high-grade intraepithelial neoplasia and mucosal squamous-cell carcinomas of the oesophagus.[22]

ADENOCARCINOMA

Esophageal adenocarcinoma (EAC) is the dysplastic esophageal epithelium mostly found in cardia and gastroesophageal intersection.[23] Barrett's esophagus could be a premalignant condition in which a change from metaplasia through low-grade dysplasia then eventually high-grade dysplasia and EAC are seen. However, multiple studies stated that most patients with Barrett esophagus do not develop EAC.[24]

The incidence of EAC is higher in men than in women. Gastroesophageal reflux, infection, Barrett's esophagus, corpulence, and tobacco smoking are main risk factors for EAC. Furthermore, less likely, hereditary variations have been associated in developing EAC.[25] Despite these known risk factors, most patients with EAC are diagnosed

with dysphagia from late-stage tumors and few number of patients are distinguished by screening and observation programs. Endoscopic ultrasonography is valuable to survey surrounding infection as well as the inclusion of territorial lymph nodes.[16] Gastroesophageal reflux infection (GERD) is a vital red flag figure for EAC. GERD could lead to erosive esophagitis and after an unsuccessful repair, it could turn to a metaplastic, specialized intestinal epithelium (ie Barrett's esophagus). Among the 6-14% of GERD patients who develop Barrett's esophagus, 0.5-1% will advance to adenocarcinoma. For patients with mucosal BC (Barrett's carcinoma), both surgery and ER (endoscopic resection) are successful treatment modalities.[26] Endoscopic resection led to favorable results for low-risk patients with early EAC.[27]

STOMACH

Gastric cancer (GC) is the second most frequent cancer across the world, however there is significant incidential geographical variation. Researches have shown that two strategies may help to reduce gastric cancer mortality rates: a) prevention b) personalized treatment.[28] Country and population are regarded as the most influential factors among sufferers. GC mostly affects lower socio-economical groups. Stomach cancer is the sixth most common cancer worldwide, according to the current GLOBOCAN 2020 survey, with age-standardized prevalence rates of 11.1 per 100 000 and 1 089 103 new cases. China (43.9%), Japan (12.7%), India (5.5%), Russian Federation (3.4%), and Republic of Korea (2.6%) are five countries with the highest age-standardized incidence rates, according to recent reports.[29] 10,065,305 males (15.8 of 100,000) and 9,227,484 women were among the recent GC cases estimated (7 out of 100,000).

Stomach has a prevalence of 17.5 per 100 000 in the Iranian population, and GC new cases are expected to account for 11.2 percent of all malignancies diagnosed in 2020, with 1,981 (22.8 per 100,000) men and 1,438 (12.5 per 100,000) women.

Interestingly, GC is Iran's second most common cancer. GC was responsible for the death of 12,994 individuals, with a 15.5 per 100 000 age-standardized rate, including 8,534 (19.9 per 100,000) men and 4,810 (11 per 100,000) women. China (48.6%), India (6.9%), Japan (6%), Russian Federation (3.6%), and Brazil (3.6%) are the countries with the highest age-standardized death rates for both sexes (2.1%). Furthermore, Iran is considered to be the seventh most populous country in the world, based on age-standardized death rates. With 12,994 new cases, the age-standardized death rate is 1.7 per 100 000.

Statistics demonstrated that gastric cancer mortality rate has never had been constant and its incidence has decreased over the past 60 years. Two third of cases are men, the blacks have a higher risk to get this cancer comparing to whites. The incidence of gastric cancer in cardiac has increased though rates have generally decreased.[30] 87.8% of patients were above 45 years and 12.2% of patients were under 45 years old, this research was conducted among the 1658 gastric cancer patients. Additionally, females are predominant in the young groups. The young are encounter severe advanced features.[31]

In comparison to 2040 predictions, the Iranian population is anticipated to expand by 122.8 percent, with 32 659 additional cases, of which 20 418 are male (112.7 percent increase) and 12 238 are female (142 percent increase). The total number of extra fatalities will be 28,982, resulting in an annual rate increase of 123 percent, which is unparalleled. Iranian males will number 18 070 (up 111.7 percent) while Iranian women will number 10 911 (up 111.7 percent).

In the north and northwest of Iran, this cancer has been the most prevalent due to environmental factors such as high prevalence helicobacter pylori, high dietary consumption of salt, and smoking.[32] Gastric cancer is anatomically divided into true gastric adenocarcinoma and gastro-esophageal-junction adenocarcinoma, and histologically into diffuse and intestinal types.[33] Base on the pattern of growth and invasiveness, pathological features of gastric carcinoma are divided into two types: a) expanding which grew mass, and also resulting tumor nodules, and b) infiltrative which tumor cells attacked individually. The degree of cell maturation varies while glands are much more common in expanding carcinoma.[34] Liver, peritoneum, lung, and bone were graded as the most common sites of metastasis. The commonplaces of metastasis in signet ring adenocarcinoma are peritoneum, bone, ovaries and less frequently to the lungs and liver compared whit generic adenocarcinoma. Metastases to the

lung frequently involve the liver while metastases to the liver and peritoneum often happen singly. Metastatic gastric cancer patients survive about 3 months but the patients with bone and liver metastases survive about 2 months.[35] Although weight loss and abdominal pain are often known as late signs of tumor progression, patients in early stages don't have any symptoms, therefore the diagnosis of GC is difficult. Some causes have been related to increasing the risk of gastric cancer such as chronic atrophic gastritis, helicobacter pylori infection, smoking, heavy alcohol use and severe dietary factors. Stomach cancer suspects should be evaluated by Esophagogastroduodenoscopy. To determine prognosis and also relevant treatment we should evaluate gastric wall invasion and lymph node involvement accurately. Consequently, endoscopic ultrasonography in combination with CT scanning and operative lymph node dissection may be practical in staging the tumor. Surgery alone possibly causes failure, similarly, chemotherapy and radiotherapy aren't capable of treating cases unless we combine them.[36] A team of professionals in different fields can be hope to treat this cancer. Circumstances of metastatic disease are poor, and they survive about 1 year. Target therapies such as trastuzumab, an antibody or peptide against HER2, and the VEGFR antibody, ramucirumab have been suggested to treat this cancer.[33] More than 50 % of the cases died during the first year after their diagnosis and almost all the other cases died in the second year.[37] Recently, radiolabeled compounds are of great interest as a new method in targeted therapy.[38, 39]

LIVER AND INTRAHEPATIC DUCTS

According to last GLOBOCAN reports on 2020, liver cancer (LC) with the age-standardized incidence rates of 9.5 per 100 000 and 905 677 new cases, is considered the sixth prevalent cancer worldwide.[15, 40] The highest incidence is found in eastern and south eastern Asia (17.7).[41] The first five countries with highest age-standardized incidence rates include Mongolia (85.6), Egypt (34.1), Lao (24.4), Cambodia (24.3) and Vietnam (23.0) and Iran is the 61st.

Of all new cases estimated to have been diagnosed with LC, 632,320 were men (14.1 of 100,000) and 273,357 were women (5.2 of 100,000). In line with most of gastrointestinal malignancies, LC is globally found 2-3 higher incidence among men than women, which ranks 5th and 9th respectively.[40, 41]

The incidence of LC through Iranian population is 6.8 per 100 000 and 4.3% of all cancers diagnosed in 2020, were estimated to be LC. 5 701 new cases out of which 3210 (7.5 per 100,000) are men and 2,491 (6.4 out of 100,000) are females, represent that Iranian men are more susceptible to be affected than women, in consistent with global assessments. Noteworthy, LC stands in the 8th place among common cancers in Iran with cumulative risk of 0.68.[15]

Although LC was the fourth cause of cancer-associated-death in the world in 2018, it is established the second after lung cancer in 2020, rating 8.3% of all cancer associated deaths. 830,180 people estimated to have been died of LC with 8.7 per 100,000 age-standardized mortality rates, including 577,522 (12.9 per 100 000) men and 252,658 (4.8 per 100 000) women.[15]

Countries representing the highest age-standardized mortality rates for both sexes are Mongolia (80.6%), Egypt (32.5%), Cambodia (22.9%), Lao (22.9%) and Thailand (22.1%). Additionally, Iran is estimated to rank 57th country with age-standardized mortality rates.[15]

As stated by GLOBOCAN 2020, 5,324 cancer-related-deaths in Iran (6.7% of all) is caused by LC which is considered the third fatal cancer in Iran after stomach and lung cancer in respect. Age-standardized mortality rate is calculated 6.4 per 100,000 along with cumulative risk of 0.63. The past year, 3,004 (7.0 per 100,000) Iranian men and 2,320 (5.7 per 100,000) women, on par with predominance of global men's mortality rates.[15]

Partial similarity in mortality and incidence patterns is explained by poor prognosis of LC, mentioned in both global and national statistics.[41]

The overall burden of LC is increasing overtime. Further to statistics reported in the past year, the global new cases is estimated to reach 1 403 985, presenting 55% increase in incidence rate. Among male and female population in respect, 53% and 59.7% elevation is estimated which predict number of new cases to reach 967,326 men and 436,658 women. Mortality rates are also predicted to increase 56.4% globally by the next 20 years, representing 1,298,600 new cases which include 891 485 men (54.4% increase) and 407,115 women (61.1% increase).[15]

Table 1: The incidence rate of gastrointestinal cancer rate at top 5 countries with highest incidence (%)

Iran (th)	Top 5 countries with highest incidence (%)					Cancer
36th	Bangladesh (3.7)	Pakistan (4.5)	USA (6.5)	China (8)	India (36)	Lip and Oral Cavity
14th	United States of America (3)	Bangladesh (3.6)	Japan (4.3)	India (10.5)	China (53.7)	Esophagus
10th	Republic of Korea (2.6)	Russian Federation (3.4)	India (5.5)	Japan (12.7)	China (43.9)	Stomach
61th	Vietnam (23.0)	Cambodia (24.3)	Lao (24.4)	Egypt (34.1)	Mongolia (85.6)	Liver and Intrahepatic Ducts
98th	Korea (2.9)	Nepal (4.1)	Bangladesh (4.9)	Chile (5.6)	Bolivia (8.5)	Gallbladder cancer
25th	Russian (4.2%)	Germany (4.3%)	Japan (8.9%)	USA (11.4%)	China (25.2)	Pancreas
29th	Germany (3.1%)	Russian (3.9%)	Japan (8%)	USA (16.6%)	China (28.2%)	Colorectal

Considerably, comparing 2040 estimations and 2020 reported cases, Iranian population is likely to experience 120.7% increase along 12,581 new cases of which 6,682 are male (108.2% increase) and 5,699 are female (136.8% increase). Number of new cases of death would be 11,760, presenting 120.9% estimated increase in annual rates. 6 220 (107.1% increase) Iranian men and 5 538 (138.8% increase) women are estimated to be died due to LC by 2040. Shadmani et al. reported that Iran statistical analysis appears to show an increased rate of LC-related incidence and mortality by 2040, both rate higher in women than men which requires more significant attention to reduce probable incoming damages.[4]

2019 WHO classification of tumors of digestive system, indicates that primary LC is divided to two major types; HepatocellularCarcinoma,IntrahepaticCholangiocarcinoma. Other rare subdivisions are Hepatoblastoma, Extrahepatic Cholangiocarcinoma (ECC), Mucin Cystic Neoplasms (MCN) and Mesenchymal tumors.[42, 43]

Following, we explained common types of LC, with focus on risk factors and epidemiology. In addition, national and global features are compared.

HEPATOCELLULAR CARCINOMA (HCC)

HCC, which accounts for 75 percent to 85 percent of all LC cases, is the fourth leading cause of cancer-related death worldwide in 2018, with a low prognosis. The global prevalence of HCC is heterogeneous due to the broad geographical range of risk factors. However, Asia accounts for 72% of events, Europe for 10%, Africa for 7.8%, North America for 5.1 percent, and Latin America for 4.6 percent.[44] Incidence rates are reported increasing in western countries but in contrast, stable or decreasing in Asia.[45]

Studies stated the incidence and mortality rate of 1.66 and 1.9 per 100,000 persons in Iran respectively, which determines lower incidence rates among Iranian men in comparison to global trends in respect to higher prevalence in men rather than women.[46] In a cohort study from September 2007 for 10 years, conducted by Sarveazad et al. 227, HCC patients were assessed to evaluate their 5-years survival rate. As the result of 14.3 months follow up and 208 of patients' expiry, 5-years survival of HCC patients in Iran was announced 8.37%. Poor prognostic predictions were strictly associated with metastasis, number of lymph nodes involvements, tumor size, type of therapy and hepatitis type.[47] Hassanipour et al. indicated Semnan province as the highest and Fars province having the lowest incidence rate of HCC in Iran.[46]

According to Moghadam et al., the annual incident rate of HCC per 100,000 people in Kerman was 0.522 in 2010. In addition, when age and gender were taken into account, the annual occurrence rates of HCC in Kerman were 0.7 per 100,000 people and 0.7 per 100,000 people, respectively. The authors also claimed that patients in Kerman were on average 5.5 years younger than those in other areas of Iran (56.17 18.32 years vs. 61.68 14.62 years).[48]

HCC tumor, associated with chronic liver disease as cirrhosis, is one of tumors that are diagnosed without need of histopathology examination and radiological investigations in cirrhotic trustfully confirm the state of suffering. In appreciation to early detection of HCC, patient survival is significantly augmented. Summarise of

the incidence rate of gastrointestinal cancer rate at top 5 countries with highest incidence are given in Table 1.

RISK FACTORS

Age and Sex: Age at diagnosis differ geographically, for instance, in Japan, north America and Europe, age of onset is above 60 but in parts of Asia including Iran and north Africa, age at diagnosis is estimated 30-60.[46, 49, 50] Onset at<40 years of age was mostly reported in west and east Africa.[50] Despite the fact that a few nations, such as Ecuador and Colombia, have similar or comparable occurrence rates for men and women, Iran and other countries have 2 to 4 times higher rates in men than in women.[49]

Race: The highest incidence rate is found in Indian-Alaskan natives.[49] and to our knowledge, no similar study about race based incidence is conducted in Iran, likely due to no significant race diversity in population. Demographic characteristics and differences in lifestyle thoroughly explains low incidence rates of HCC in Fars province of Iran.[46]

Hepatitis B (HBV) and Hepatitis C viruses (HCV): HCC, an infection-related cancer, is mainly induced by chronic HBV and HCV infections in lower outcome countries. HBV, a DNA virus, is the main responsible for infection in Eastern Asian and most African countries, except for northern Africa with highest prevalence of HCV.[50, 51] HBV is transmitted vertically and the risk of cancer developing among HBV carriers in the world ranges from 10-25%.[49, 50, 52] Acute hepatitis, chronic hepatitis, cirrhosis, and HCC caused by HBV are expected to cause 20 million deaths between 2015 and 2030, with 5 million deaths from HCC alone.[53]

HCV, unlike HBV, is an RNA virus that is spread by infected blood and medical facilities and causes tumors by repeated destruction, regeneration, and fibrosis.[49, 52] HCV infection that is chronic According to estimates, 10-20% of the 57 million people infected with HCV will experience liver problems, including HCC, by 2030.[54] HCV is the most common virus-related cause of HCC in North America, Europe, Asia, the Middle East, and Northern Africa, especially Egypt.[55]

Reported frequent etiologies in Iran are chronic hepatitis B, chronic hepatitis C and NASH.[56] Various studies approved the relation of HBV genotype D infection and HCC incidence among Iranian patients and small cell changes, low-grade dysplastic nodules, and high-grade dysplastic nodules were found precursors of HCC in livers infected with HBV.[57, 58] HBV infection is seen in 80% of cases of developed HCC; this virus appears to be the most frequent source of HCC in Iran.[59] The prevalence of HBV infection in the Iranian population was estimated to be between 1.7 and 5%, with a substantial decrease to 1.3 percent thanks to successful vaccination.[56,60] Highest prevalence is reported from Golestan province and the lowest from Kermanshah, 8.9% and 0.7% respectively. According to studies, the prevalence of HCV in Iran varies by province: 15.6 percent in Fars, 44.3 percent in Kerman, 29.6 percent in Zahedan, 59.1 percent in Hamadan, 71.3 percent in Gilan, and 76.7 percent in the north-west of the country.[61] In Iran, HBV and HCV infection were found to be major risk factors for HCC, with incidence rates of 52.1 percent and 8.5 percent, respectively. Due to HBV vaccines and removal strategies, HCV is expected to overtake HBV as a major risk factor for HCC in Iran by 2020,[62] while HBV infection will still be the most significant risk factor for HCC in Iran.[63] HBV and HCV infection, as well as the high prevalence of other risk factors such as liver cirrhosis, explain the high incidence rate of HCC in Semnan province, according to Hassanipour et al. According to other reports, the highest rates of liver cancer were found in Ardebil, Semnan, Fars, and Khuzestan. Contrary, old and inadequate epidemiological studies, shows that Iran require more recent systematic studies in order to apply effective elimination and preventive strategies for infectious HCC development.

Alcohol: Alcohol, which the International Agency for Research on Cancer classifies as a Group 1 carcinogen, has been linked to the growth of fatty liver, acute/chronic hepatitis, cirrhosis, and hepatocellular carcinoma.[64] In America and Europe, excessive alcohol consumption is the second most common risk factor for HCC production, although lower intakes have not been linked to the development of HCC.[49, 50] Studies state that light drinking (<3 drinks/day) was responsible for a 34% reduced risk among non-Asian populations but no significant relationship was found in Asian societies.[65] According to religious and legal prohibition of alcohol consumption in

Iran, reliable high-quality population-based studies are lacking. However, available alcohol sustaining drinks in black markets, counts for less than 5 per 100,000 in Iranian population as a minor risk factor comparing to Europe and USA and 2.8% of HCC patients were presented with history of excess alcohol consumption.[66]

Nonalcoholic Fatty Liver Disease (NAFLD), Diabetes, and Obesity: In the United States, 32.8 % of people have NAFLD, which varies by sex (34.7 % for men, 31.0 % for women) and race (Mexican- Americans 41.2 %; whites 32.5 %; blacks 29.1.[66] NAFLD from simple steatosis to non-alcoholic steatohepatitis (NASH) is considered responsible for approximately 10-12% and 1-6% of HCC incidence in Western and Asian population respectively and is reported to be more common among old-age patients. In comparison to 4% prevalence of viral-HCC, incidence of NASH-related HCC is low (2.6%), however, according to related studies, it is estimated to increase in Asian population.[67] A 35.2 % prevalence of NAFLD was found in Iranian adults in a cluster random sampling sample, and central obesity was found to have a greater correlation with NAFLD than BMI per se. However, to our knowledge, reliable studies are required in Iran to demonstrate the exact relationship between NAFLD and HCC.

Body mass index (BMI) was assessed in order to find the relation between obesity and incidence and mortality rate of HCC. A population-based cohort study on 1.2 million men, confirmed the association of high BMI in late adolescence and the augmented risk of developing HCC, similar to another study announcing 86-119% increase.[68, 69] Further research revealed an 87 % increased risk of liver cancer with a typical BMI, as well as a 66 % increased risk of liver cancer-related mortality,[70] which suggested examinations of waist and hip circumference to capture abdominal and gluteofemoral adiposity as important elements of obesity, in this regard, a twofold increase in risk of HCC development was reported.[71, 72] To date, we didn't find appropriate reports on association between obesity and HCC in Iran which is of high importance and need to be taken for granted.

Diabetes mellitus is considered a twofold to threefold elevating risk of HCC with gradual increase by longer duration of the disease while the association with diabetes severity or blood sugar control remains vague.[73]

Aflatoxin (AF) and aristolochic acid: AF contamination, mycotoxin produced by fungi of Aspergillus is commonly found widespread in countries with warm and humid environments and AFB1 type is particularly engaged. AFB1 is a carcinogen factor counted responsible for 50-90% of mutations found is HCC as a group one carcinogen. The comorbidity of HBV and AF exposure contributes to the increase of HCC incidence risk by 54-fold (6-fold AFB alone and 11-fold for HBV alone). Aflatoxin exposure in Iran was reported in Kerman province where more than 60% of Iranian produced pistachios.[48, 49, 59]

Tobacco smoking: According to recent studies, current smoking had correlations with 47-86% increase in HCC risk and mortality, additionally, patients who quit smoking over 30 years ago the risk of HCC was approximately equivalent to non-smokers. We didn't find any data presenting the relation between smoking and liver cancer in Iranian population.[73]

Despite the fact that the prevalence of LC in Iran is smaller than in other nations, new cases are expected to emerge due to the epidemiological transformation, which includes increased life expectancy, population ageing, and increased exposure to risk factors.[46] More high-quality studies are required to reveal the most important province-based risk factors and promote the elimination and preventing strategies.[74]

CHOLANGIOCARCINOMA (CCA)

CCA refers to a variety of malignancies found in biliary tree. According to anatomical site of the tumor origin, CCA is divided to three groups; intrahepatic (iCCA or ICC) and extrahepatic which is divided to perihilar (pCCA) and distal (dCCA).[75] Symptoms commonly presented are painless jaundice (190, 66.9%), abdominal pain (77, 27%), and pruritus 133 (46.8%) and weight loss (169, 59.5%).[76]

Although iCCAs, emerging above the second-order bile ducts, is the least common form of cholangiocarcinoma, it is considered the second most prevalent hepatic malignancy after HCC, representing approximately 10-15% of LC cases, with incidence and mortality rates of 0.3-6 and 1-6 per 100,000 per year respectively. CCA mortality, like all gastrointestinal cancers, is higher in men than in women

around the world, and in Asian countries than Western countries. In addition, South Korea, China, and Thailand recorded incident rates of over 6 per 100,000 persons, with Thailand reporting the highest rate of 96 cases per 100,000 men, reflecting a global increase in addition to the annual mortality rate of over 4 deaths per 100,000.[77] A cross-sectional epidemiological study on patients above 18, suffering CCA was performed in Ahvaz hospital from 2014 to 2017, in Iran. Results revealed a 6.8 per 1000 incidence rate, whereas another study on outpatient's clinic visits during 2000 to 2004 in Tehran, reported 0.2 of all liver diseases as CCA, indicating a significant increase in incidence rate.[77] In addition, authors contributed that CCA is the 9th common inpatient gastrointestinal diagnosis in Tehran. According to some estimates, men are more likely than women to develop cholangiocarcinoma, both internationally and in the Iranian community.[78]

With a median lifespan of less than 24 months, iCCA's node metastasis and vascular invasions confirm a poor prognosis. The 5-year survival rate is about 5%, depending on the tumor's stage and histological type. In a survey of 283 CCA patients in Iran, Alizadeh et al. recorded a mean survival period of 7.42±5.76 months, confirming previous research and global sources.[77]

70% of CCA occur sporadically without any apparent cause. However, several risk factors have been identified, which vary geographically.

RISK FACTORS

Parasitic Infections (Biliary Liver Flukes): Biliary liver flukes, which raise the risk of CCA fivefold, are widespread in East Asia, where eating raw or undercooked fish is a cultural practice.[79, 80] Both Opisthorchis viverrine, which is found in northeast Thailand and Cambodia, and Clonorchis sinensis, which is found in China, Taiwan, Korea, and Vietnam, are linked to an increased risk of CCA.[81, 82] While Iran is not considered to be a Clonorchis endemic region, Heidarpour et al. have confirmed a case of cholangiocarcinoma in a 55-year-old woman from the south shores of Iran, Genaveh harbor, raising concerns about an old silent carcinogen.[83]

Primary Sclerosing Cholangitis (PSC) is an infectious condition that affects the intrahepatic and extrahepatic bile duct systems.[84] PSC is linked to a 400- to 1500-fold higher lifetime risk of CCA, with annual incidences ranging from 0.5 to 1.5 % and a lifetime risk of 20%.[85-87] PSC was recently identified as the most important risk factor for CCA[88] in a case-control survey of 2,395 CCA, and the prevalence of CCA in PSC was found to be 8.3% in a major multinational multicenter cohort study in 37 countries.[89] Patients with PSC present with CCA in their forties and older, whereas CCA is usually diagnosed in the seventh decade of life.[90]

Cholelithiasis: Cholelithiasis, the fourth most common inpatient gastrointestinal diagnosis in Tehran, can be divided into hepatolithiasis, choledocholithiasis, and cholecystolithiasis. cholecystolithiasis or choledocholithiasis are at an increased risk of developing eCCA, followed by increase in the size of gallstones, calcification of epithelium, and duration of disease.[91] Hepatolithiasis is a condition in which gallstones form in the intrahepatic bile ducts and is thought to be a risk factor for CCA. The prevalence of iCCA in patients with hepatolithiasis has been estimated to be 4-11 %, with chronic cholangitis being the most common cause.[92-94] Likewise, another study in Ahvaz, established smoking, diabetes and the history of gallstones as threemost common risk factors for developing CCA in south Iranian population. The mean age among patients with both cholelithiasis and CCA, was 57.7 years found higher in women (61%). Smoking, having a family history of cancer, having an appendectomy before the age of 20, and having symptoms for more than ten years were all risk factors for the occurrence of ICC in hepatolithiasis.[95]

Hepatitis B and C: Chronic inflammation and increased cell proliferation in viral hepatitis-associated cholangiocarcinogenesis varies geographically in contribution to HBV and HCV prevalence.[96-98] Studies from Western countries established HCV as a potential risk factor, meanwhile HBV-induced-iCCA is frequently reported from Asian countries.[99-101]

Patients with hepatitis B virus-associated iCCA were younger, had a higher percentage of male patients, had a higher level of serum alpha-fetoprotein, and had a lower rate of lymph node metastasis.[102]

Diabetes, obesity, alcohol intake, and smoking are considered the most important risk factors in the development of CCA, and they need to be analyzed more

thoroughly.[103]

A meta-analysis evaluated the association between overweight or obesity and the incidence of CCA. According to ten studies faced the inclusion criteria, being overweight, obesity and excess body weight were all firmly associated with CCA.[104] The worldwide obesity epidemic, as well as metabolic syndrome and/or the presence of nonalcoholic fatty liver disease as risk factors, must be taken into consideration in the future.[105]

Saengboonmee et al. in consistent with previous studies approving association between Diabetes and CCA incidence, suggested likely associations between high mortality and O. viverrini associated CCA.[106]

Ever, former and current smoking found to be associated with increased eCCA, additionally, current smoking and smoking intensity was reported to increase the risk of iCCA. The former study also illustrated that alcohol consumption could be responsible for iCCA.[107] A cross-sectional epidemiological study on patients above 18, suffering CCA, performed in Ahvaz hospital from 2014 to 2017, confirmed previous data about smoking (25%), drug abuse (9%) and diabetes (29.5%) association with augmentation of incidence of CCA. Noteworthy, due to prohibition of alcohol consumption in Iran, the association with CCA could not be well established. In another study, regarding to 120 of 283 (42.3%) patients smoking, it was found to be the most common risk factor for CCA were.[76]

GALLBLADDER CANCER

Gallbladder cancer (GBC) is an infrequent but highly fatal malignancy, mostly found incidentally during diagnostic procedures for cholelithiasis.

Incidence, Mortality and Trends

According to GLOBOCAN, in 2020, 115 949 people estimated to have been diagnosed with GBC, indicating 1.2 per 100 000 of all cancer diagnoses worldwide. GBC ranked 24th cancer in the world by representing 0.6% of all cancer cases and cumulative risk of 0.13%. Bolivia stands top in the world in terms of ASR rate in GBC, with 8.5, followed by China with 5.6, Bangladesh with 4.9, Nepal with 4.1, and the Republic of Korea with 2.9, with Iran at 96th place.[15]

GBC is the only gastrointestinal cancer representing the predominance of women affection; 41 062 cases were men (0.89%) and 74,887 were females (1.4%).[108] This discrepancy is well defined not only by women's longer life expectancy, but also higher levels of estrogen hormone in females is believed to increase the risk of gallstones by augmenting the saturation of cholesterol in bile.

GLOBOCAN 2020 estimated 561 Iranian individuals to have been confirmed with GBC, ranking it 24th (0.43 %) out of 35 frequent malignancies in Iran, with a 0.07 % cumulative risk. According to 2020 data, Iranian women are more prone to GBC than men; 253 cases were men (0.59 %) and 308 cases were females (0.75 %).[109] Few cancers such GBC represent higher proportions of mortality than incidence in the world. Late diagnosis, anatomical position of gallbladder and vagueness of symptoms, explains poor prognosis of GBC and median survival for advanced age cancer is reported no more than a year.[108]

Few cancers such GBC represent higher proportions of mortality than incidence in the world. Late diagnosis, anatomical position of gallbladder and vagueness of symptoms, explains poor prognosis of GBC and median survival for advanced age cancer is reported no more than a year.[108]

GBC mortality accounted for 0.85% of all cancer deaths, ranked 21st out of all cancer deaths and represented a 0.09% cumulative risk in the past year. In 2020, 84,675 people were died due to GBC, establishing 0.84 per 100000 age-standardized mortality rates GBC ASB Mortality Bolivia tops the list with 5.8, followed by Bangladesh (3.9), China (3.5), Nepal (3.1), and the Republic of Korea (2.3). In addition, Iran is placed 91st.

At one with incidence disparity, mortality rate is estimated higher in females; of number of deaths mentioned, 30,265 were men (0.65) and 54,439 were women (1.0). As already stated, few countries, consisting Japan and South Korea, reported a strong deviation from the norm of a female to male mortality ratio between 1.1 and 2.6.[110] GBC is the 23rd most lethal cancer in Iran (0.5 % of all cancer-related fatalities), with a 0.05 % cumulative risk of mortality. In 2020, 399 (0.48) patients were expected to die, with 175 (0.4) being males and 224 being women, in line with the global gender imbalance (0.55). From 1990 to 2015, the overall age-standardized

mortality rates of gallbladder and biliary tract cancer in Iran has been raised annually demonstrating a steep slope since the year 2000.[109] Similar patterns were reported for gender-specific trends with higher rates in females than in males. Correspondingly, authors claimed that the mean annual percent change of gallbladder and biliary tract cancer was 16.3% (95% CI: 15.9-16.7%) from 1990 to 2015.

Interestingly, comparing 2040 estimations and 2020 reported cases, global statistical analysis appears to show an increased rate of GBC-related incidence and mortality by 2040, both rate higher in men than women which requires more significant attention to reduce probable incoming damages. In accordance with global disparity, Iranian population projections for 2040 show that incidence and death rates are greater in women than males. Between 2001 and 2030, gallbladder cancer death rates in Iran are predicted to climb considerably in all regions, particularly in the north, west, southwest, east, and southeast.[34]

PANCREAS

Pancreatic cancer is a deadly disease with terrible prognosis and a rising incidence. Smoking, chronic pancreatitis, family history, diabetes, age 60 to 80, female gender, and chemical exposure are all risk factors for pancreatic cancer.

According to last GLOBOCAN reports on 2020, pancreas cancer (PC) with the age-standardized incidence rates of 4.9 per 100,000 and 495,773new cases, is considered the fifteenth prevalent cancer worldwide (15, 16). The highest incidence is found in eastern and eastern Asia (17.7). China has the greatest incidence of pancreatic cancer, with an ASR rate of 25.2 %, followed by the United States (11.4 %), Japan (8.9 %), Germany (4.3 %), and Russia (4.2 %). Iran is placed 25th as well.

Of all new cases estimated to have been diagnosed with PC, 262 865were men (5.7 of 100 000) and 232 908 were women (4.1 of 100 000). On par with most of gastrointestinal malignancies, PC is globally found 1.3 higher incidence among men than women, which ranks 12th and 11th respectively.[15, 17, 18]

The incidence of PC through Iranian population is 3.8 per 100 000 and 2.4% of all cancers diagnosed in 2020, were estimated to be PC, 3167 new cases out of which 2003 (4.7per 100 000) are males and 1164(2.9 per 100 000) are females, represent that According to worldwide evaluations, Iranian men are more vulnerable to the effects than women. Notably, PC ranks 14th among prevalent malignancies in Iran, with a cumulative risk of 0.41.[15,16,18] With 4.5 per 100,000 age-standardized mortality rates, 466,003 persons were projected to have died of PC, including 246,840 (5.3 per 100,000) men and 219,163 (3.8 per 100,000) females.

Pancreatic cancer death rates in the five countries with the greatest ASR are 26.1 % in China, 10.2 % in the United States, 8.7 % in Japan, and 4.4 % in Germany and Russia, respectively. It is ranked 27th as well.

As stated by GLOBOCAN 2020, 3 059 cancer-related-deaths in Iran (3.9% of all) is caused by PC which is considered the tenth fatal cancer in Iran after osephagus. Age-standardized mortality rate is PC calculated 3.7 per 100,000 along with cumulative risk of 0.40 (1). In 2020, 1,722 (4.0 per 100,000) Iranian men and 1 052 (2.5 per 100,000) women, on par with predominance of global men's mortality rates.[17]

Considerably, comparing 2040 estimations and 2020 reported cases, The Iranian people is expected to expand by 119.5 %, resulting in 6 950 additional instances, of which 4,161 are male (107.7 % increase) and 2,789 are female (139.6 % increase). The number of additional instances of death would be 6,736, representing a 120.2 % rise in yearly rates. By 2040, it is anticipated that 3,954 (108.1 % rise) Iranian males and 2,782 (140.0 % increase) Iranian women will have died as a result of PC. There are no notable environmental risk factors, although geographical diversity is lower than in other gastrointestinal cancers. Cigarette smoking tends to be the most important factor, with a risk ratio of around Alcohol and coffee intake have been listed as potential risks in some (but not all) research. Diet is most likely a major element, but it's impossible to quantify. Other possible correlations, such as diabetes, are unlikely to be important.[111] The induction of oncogenes, the inactivation of tumor suppressor genes, and the deregulation of several signaling pathways, including the EGFR, Akt, and NF-B pathways, have long been believed to play a role in the growth and progression of pancreatic cancer. As a result, techniques targeting EGFR, Akt, NF-

B, and their downstream signaling may be beneficial for pancreatic cancer prevention and/or treatment.[112]

COLORECTAL

Colorectal carcinoma is the most prevalent form of gastrointestinal cancer. After lung and breast cancer, it is the third most common cause.[113] Polyps are mucosal bumps that form on the gastrointestinal tract, urogenital tract, and respiratory tract. Colorectal polyps do not have a specific clinical manifestation unless they enlarge and block the lumen or cause bleeding. Colorectal polyps are seen histologically in four forms: neoplastic, hyperplastic, hamartoma, or inflammatory. Polyps are generally divided into two categories: neoplastic and non-neoplastic. Morphology and size are very important in differentiating polyps Neoplastic or adenomatous polyps are often seen as tubular and villous, with tubular size less than 1 cm and villous more than 3 cm.[114] Adenomatous tumors are usually benign but can lead to carcinoma if they develop some degree of dysplasia.[114, 115] On-neoplastic tumors can be hypo plastic, hamartomas, and inflammatory. These tumors are also called diminutive because they are less than 5 mm. On the one hand, because they do not have dysplasia, they do not have the risk of carcinoma, but on the other hand, in colonoscopy, they are sometimes indistinguishable from adenomatous polyps. Hamartoma polyps, also known as juvenile polyps, are more likely to bleed because they have more arteries. Inflammatory polyps are mainly found in cases of IBS and ulcerative colitis. These polyps are called pseudo-polyps because they occur in response to inflammation in the colon and rectum.[116] There are two pathways for carcinoma. The first pathway is the pathway seen in 70% of cases and seeks dysplasia in adenomatous polyps, in which a set of gene mutations and epigenetic changes are involved. In the second pathway are neoplasms that occur individually in the cells of the colon and rectum and cause inactivation of tumor suppressor genes. The most common of these mutations are RAS and RAF mutations.[117]

Colorectal cancer, like many cancers, is caused by both genetic and environmental causes. Of course, it is referred to as an environmental disease by some reports, which may be due to the fact that the role of environmental causes is more influential in causing this disease. Lynch syndrome occurs if the mutation is in the MLH1, MSH2, MSH6, PMS2 or chromosome, and if the mutation is in adenomatous polyposis coli (APC), hereditary adenomatous polyposis syndrome develops. Lifestyle-related causes such as smoking, heavy alcohol intake, red meat and refined food consumption, lowered and inactive diets, decreased high-fiber dietary use, and fruits and vegetables have a significant impact on colorectal cancer.[118]

Since the progression of colorectal cancer is long and time intensive, early diagnosis can be assisted by preventive processes. In the treatment and detection of polyps accompanied by adenoma tumors, gold colonoscopy is a standard that benefits. Various types of endoscopy, such as high-definition white-light endoscopy, chromo endoscopy, and magnification endoscopy, are also helpful in diagnosis. In its visualization of the rectum, sigmoid colon, and descending colon, sigmoidoscopy also reduces the risk of colorectal cancer.[119]

1,931,590 (10%) of the 1,929,279 cancer patients estimated to be in the world in 2020 have colorectal cancer, which is arguably the third most widespread. Of these, with a mortality rate of 4,614,226, 957,896 (51.8%) of them belong to Asia (52.4%).

According to the recent GLOBOCAN estimates for 2020, colorectal cancer (CC) is the fourth most common cancer worldwide, with age-standardized incidence rates of 19.5 per 100 000 and 1 931 590 new cases. The largest incidence is observed in Asia (51.8 percent). China (28.2 %), the United States of America (16.6 %), Japan (8 %), the Russian Federation (3.9 %), and Germany (3.1 %) are the top five nations with the highest age-standardized incidence rates, with Iran ranking 29th (0.5 %).[15, 17]

Of all the recent cases estimated to have been diagnosed with CC, 1 065 960 (23.4 out of 100 000) were male and 865 630 were female (16.2 of 100 000). CC is observed globally at 1.5 higher occurrence in males than females, ranked 3rd and 2nd respectively, on par with other gastrointestinal malignancies. In the Iranian population, the prevalence of CC is 13.9 per 100,000 people, and CC is anticipated to account for 10% of all malignancies diagnosed by 2020. 2 952 932 new cases, with 1 649 588 (10.9 %) males and 1 303 344 (9.5 %) females, indicate that, consistent with worldwide evaluations, Iranian males

are more likely to be afflicted than females. It should be noted that CC is the third most common cancer in Iran, with a total risk of 0.95[15]. While CC was the world's third cause of cancer-associated death in 2018, 9.4% of all cancer-associated fatalities are ranked as the second after lung cancer in 2020. 935 173 people with 9 per 100 000 age-standardized death rates, including 515 637 (11 per 100 000) males and 419 536 (7.2 per 100 000) females, were reported to have died of CC. China (30.6 percent), Japan (6.4 percent), the United States of America (5.8 percent), the Russian Federation (4.5 percent) and India are the countries with the top 5 age-standardized death rates for both sexes (4.1 percent). Furthermore, Iran is expected to rank 26th in terms of age-standardized death rates. According to GLOBOCAN 2020, CC is responsible for 3,964 cancer-related deaths in Iran (5 % of total), making it the seventh most lethal malignancy after prostate cancer. The age-standardized death rate is 8.6 per 100 000, with a cumulative chance of 0.899 per 100 000. It is predicted that by 2040, the number of new cases of colon cancer will increase 1,823,278 people, which is 961,222 men and 862,057 women, and 2,940,556 new cases of rectal cancer were registered, of which 678,274 men and 439,004 women. Mortality rate will be 58.58% in colon cancer and 6.52% in rectal cancer compared to 2020 in 2040. Of the 991,332 deaths from colon cancer by 2040, 519,715 will be male and 471,618 will be female, and of rectal cancer, 561,368 will be 339,031. They will be men and 222,338 of them will be women.[15]

Compared to 2040 predictions and 2020 reported cases, the Iranian population is predicted to expand by 104.1 % in CC, with 15,038 additional patients, of whom 8,302 are male (100.4 % increase) and 6,736 are female (108.8 % increase). The number of new fatalities will be 8,722, representing a 120% increase in yearly rates. By 2040, it is expected that 4 689 (a 105.5 % rise) Iranian men and 4 034 (a 139.8 % increase) Iranian females would die from colon cancer. Of the 8,661 new cases of rectal cancer, 5,072 were male and 3,589 were female, an increase of 97.5% from 2020. The worldwide mortality rate estimated for rectal cancer by 2040 is 4,566 per thousand, of whom 2,593 are male and 1,973 are female.

ACKNOWLEDGMENTS

The authors thank from the Qom University of Medical Sciences, Qom, Iran, for supporting of this article.

ETHICAL APPROVAL

There is nothing to be declared.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

REFERENCES

1. McCormack V, Boffetta P. Today's lifestyles, tomorrow's cancers: trends in lifestyle risk factors for cancer in low- and middle-income countries. *Ann Oncol* 2011;22:2349-57. doi:10.1093/annonc/mdq763
2. Abnet CC, Corley DA, Freedman ND, Kamangar F. Diet and upper gastrointestinal malignancies. *Gastroenterology* 2015;148:1234-43. e4. doi:10.1053/j.gastro.2015.02.007
3. Eijkelboom AH, Brouwer JG, Vasen HF, Bisseling TM, Koornstra JJ, Kampman E, et al. Diet quality and colorectal tumor risk in persons with Lynch syndrome. *Cancer Epidemiol* 2020;69:101809. doi:10.1016/j.canep.2020.101809
4. Shadmani FK, Farzadfar F, Yoosefi M, Mansori K, Shadman RK, Haghdoost A. Premature mortality of gastrointestinal cancer in Iran: trends and projections 2001–2030. *BMC Cancer* 2020;20:1-10. doi:10.1186/s12885-020-07132-5
5. Rettig EM, D'Souza G. Epidemiology of head and neck cancer. *Surg Oncol Clin* 2015;24:379-96. doi:10.1016/j.soc.2015.03.001
6. Bozan N, Kocak ÖF, Cankaya H, Kiroglu AF, Gur MH, Erten R. Lip cancer: A 16-year retrospective epidemiological study in Eastern part of Turkey. *J Pak Med Assoc* 2016;66:1433-5.
7. Tseng HW, Liou HH, Tsai KW, Ger LP, Shiue YL. Clinicopathological study of lip cancer: a retrospective hospital-based study in Taiwan. *APMIS* 2017;125:1007-16. doi:10.1111/apm.12751
8. Na R, Laaksonen MA, Grulich AE, Meagher NS, McCaughan GW, Keogh AM, et al. High azathioprine dose and lip cancer risk in liver, heart, and lung transplant recipients: a population-based cohort study. *J Am Acad Dermatol* 2016;74:1144-52. e6. doi:10.1016/j.jaad.2015.12.044
9. Laprise C, Cahoon EK, Lynch CF, Kahn AR, Copeland G, Gonsalves L, et al. Risk of lip cancer after solid organ transplantation in the United States. *Am J Transplant* 2019;19:227-37. doi:10.1111/ajt.15052
10. Pottegård A, Hallas J, Olesen M, Svendsen MT, Habel LA, Friedman GD, et al. Hydrochlorothiazide use is strongly associated with risk of lip cancer. *Intern Med J*

2017;282:322-31. doi:10.1111/joim.12629
11. Akinkugbe AA, Garcia DT, Brickhouse TH, Mosavel M. Lifestyle risk factor related disparities in oral cancer examination in the US: a population-based cross-sectional study. *BMC Public Health* 2020;20:1-11. doi:10.1186/s12889-020-8247-2
12. Ustrell-Borràs M, Traboulsi-Garet B, Gay-Escoda C. Alcohol-based mouthwash as a risk factor of oral cancer: A systematic review. *Med Oral Patol Oral Cir Bucal* 2020;25:e1. doi:10.4317/medoral.23085
13. Lalli A, Aldehlawi H, Buchanan J, Seoudi N, Fortune F, Waseem A. Screening for oral cancer utilising risk-factor analysis is ineffective in high-risk populations. *Br J Oral Maxillofac Surg* 2021;59:e17-e22. doi:10.1016/j.bjoms.2020.08.094
14. Prasetyaningtyas N, Jatiatmaja NA, Radithia D, Hendarti HT, Parmadiati AE, Hadi P, et al. The response of the tongue epithelial on cigarette smoke exposure as a risk factor for oral cancer development. *Eur J Dent* 2021;15:320-4. doi:10.1055/s-0040-1721312
15. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: Cancer J Clin* 2021;71:209-49. doi:10.3322/caac.21660
16. Nie Y, Liao J, Zhao X, Song Y, Yang G-y, Wang L-D, et al. Detection of multiple gene hypermethylation in the development of esophageal squamous cell carcinoma. *Carcinogenesis* 2002;23:1713-20. doi:10.1093/carcin/23.10.1713
17. Malhotra GK, Yanala U, Ravipati A, Follet M, Vijayakumar M, Are C. Global trends in esophageal cancer. *J Surg Oncol* 2017;115:564-79. doi:10.1002/jso.24592
18. Gupta B, Kumar N. Worldwide incidence, mortality and time trends for cancer of the oesophagus. *Eur J Cancer Prev* 2017;26:107-18. doi:10.1097/CEJ.0000000000000249
19. Ghavamzadeh A, Moussavi A, Jahani M, Rastegarpanah M, Iravani M, editors. Esophageal cancer in Iran. *Semin Oncol* 2001;28:153-7. doi:10.1016/s0093-7754(01)90086-7.
20. Baba Y, Iwatsuki M, Yoshida N, Watanabe M, Baba H. Review of the gut microbiome and esophageal cancer: Pathogenesis and potential clinical implications. *Ann Gastroenterol Surg* 2017;1:99-104. doi:10.1002/ags3.12014
21. Komal K, Chaudhary S, Yadav P, Parmanik R, Singh M. The therapeutic and preventive efficacy of curcumin and its derivatives in esophageal cancer. Asian Pac J Cancer Prev 2019;20:1329-37. doi:10.31557/APJCP.2019.20.5.1329
22. di Pietro M, Canto MI, Fitzgerald RC. Endoscopic management of early adenocarcinoma and squamous cell carcinoma of the esophagus: screening, diagnosis, and therapy. *Gastroenterology* 2018;154:421-36. doi:10.1053/j.gastro.2017.07.041
23. Huang F-L, Yu S-J. Esophageal cancer: risk factors, genetic association, and treatment. *Asian J Surg* 2018;41:210-5. doi:10.1016/j.asjsur.2016.10.005
24. Abbas G, Krasna M. Overview of esophageal cancer. *Ann Cardiothorac Surg* 2017;6:131-136. doi: 10.21037/acs.2017.03.03.
25. Greenstein AJ, Litle VR, Swanson SJ, Divino CM, Packer S, McGinn TG, et al. Racial disparities in esophageal cancer treatment and outcomes. *J Surg Oncol* 2008;15:881-8. doi:10.1245/s10434-007-9664-5
26. Abnet CC, Arnold M, Wei WQ. Epidemiology of esophageal squamous cell carcinoma. *Gastroenterology* 2018;154:360-73. doi:10.1053/j.gastro.2017.08.023
27. Christian C Abnet, Melina Arnold, Wen-Qiang Wei. Epidemiology of Esophageal Squamous Cell Carcinoma. *Gastroenterology* 2018;154:360-373. doi:10.1053/j.gastro.2017.08.023.
28. Stoner GD, Gupta A. Etiology and chemoprevention of esophageal squamous cell carcinoma. *Carcinogenesis* 2001;22:1737-46. doi:10.1093/carcin/22.11.1737
29. Shimada H. p53 molecular approach to diagnosis and treatment of esophageal squamous cell carcinoma. *Ann Gastroenterol Surg* 2018;2:266-73. doi:10.1002/ags3.12179
30. Wang Y, Zhu L, Xia W, Wu L, Wang F. The impact of adjuvant therapies on patient survival and the recurrence patterns for resected stage IIa–IVa lower thoracic oesophageal squamous cell carcinoma. *World J Surg Oncol* 2018;16:1-9. doi:10.1186/s12957-018-1516-1
31. Mönig S, Chevallay M, Niclauss N, Zilli T, Fang W, Bansal A, et al. Early esophageal cancer: the significance of surgery, endoscopy, and chemoradiation. *Ann N Y Acad Sci* 2018;1434:115-23. doi:10.1111/nyas.13955
32. Kalatskaya I. Overview of major molecular alterations during progression from Barrett's esophagus to esophageal adenocarcinoma. *Ann N Y Acad Sci* 2016;1381:74-91. doi:10.1111/nyas.13134
33. Öberg S, Wenner J, Johansson J, Walther B, Willén R. Barrett esophagus: risk factors for progression to dysplasia and adenocarcinoma. *Ann Surg* 2005;242:49. doi:10.1097/01.sla.0000167864.46462.9f
34. Coleman HG, Xie SH, Lagergren J. The epidemiology of esophageal adenocarcinoma. Gastroenterology 2018;154:390-405. doi:10.1053/j.gastro.2017.07.046
35. Wani S, Williams JL, Komanduri S, Muthusamy VR, Shaheen NJ. Over-utilization of repeat upper endoscopy in patients with non-dysplastic Barrett's esophagus: A quality registry study. *Am J Gastroenterol* 2019;114:1256-64. doi:10.14309/ajg.0000000000000184

36. Pech O, Bollschweiler E, Manner H, Leers J, Ell C, Hölscher AH. Comparison between endoscopic and surgical resection of mucosal esophageal adenocarcinoma in Barrett's esophagus at two high-volume centers. *Ann Surg* 2011;254:67-72. doi:10.1097/SLA.0b013e31821d4bf6
37. Ell C, May A, Pech O, Gossner L, Guenter E, Behrens A, et al. Curative endoscopic resection of early esophageal adenocarcinomas (Barrett's cancer). *Gastrointest Endosc* 2007;65:3-10. doi:10.1016/j.gie.2006.04.033
38. Ahmadpour S, Noaparast Z, Abedi SM, Hosseinimehr SJ. 99mTc-(tricine)-HYNIC-Lys-FROP peptide for breast tumor targeting. Anticancer Agents Med Chem 2018;18:1295-302. doi:10.2174/1871520618666180307142027
39. Aligholikhamseh N, Ahmadpour S, Khodadust F, Abedi SM, Hosseinimehr SJ. 99mTc-HYNIC-(Ser) 3-LTVPWY peptide bearing tricine as co-ligand for targeting and imaging of HER2 overexpression tumor. *Radiochim Acta* 2018;106:601-9. doi:10.1515/ract-2017-2868
40. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin D, Piñeros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer Res* 2019;144:1941-53. doi:10.1002/ijc.31937
41. Arnold M, Abnet CC, Neale RE, Vignat J, Giovannucci EL, McGlynn KA, et al. Global burden of 5 major types of gastrointestinal cancer. *Gastroenterology* 2020;159:335-49. e15. doi:10.1053/j.gastro.2020.02.068
42. M Laitio. Histogenesis of epithelial neoplasms of human gallbladder II. Classification of carcinoma on the basis of morphological features. *Patol Res Pract* 1983;178:57-66. doi:10.1016/S0344-0338(83)80086-7.
43. Klimstra D, Klöppel G, La Rosa S, Rindi G. Classification of neuroendocrine neoplasms of the digestive system. WHO Classification of tumours, 5th Edition Digestive system tumours. *Histopatology* 2020;76:182-188. doi:10.1111/his.13975
44. Singal AG, Lampertico P, Nahon P. Epidemiology and surveillance for hepatocellular carcinoma: New trends. *J Hepatol* 2020;72:250-61. doi:10.1016/j.jhep.2019.08.025
45. Dasgupta P, Henshaw C, Youlden DR, Clark PJ, Aitken JF, Baade PD. Global trends in incidence rates of primary adult liver cancers: A systematic review and meta-analysis. Front Oncol 2020;10:171. doi:10.3389/fonc.2020.00171
46. Hassanipour S, Mohammadzadeh M, Mansour-Ghanaei F, Fathalipour M, Joukar F, Salehiniya H, et al. The incidence of hepatocellular carcinoma in Iran from 1996 to 2016: a systematic review and meta-analysis. *J Gastrointest Cancer* 2019;50:193-200. doi:10.1007/s12029-019-00207-y
47. Sarveazad A, Agah S, Babahajian A, Amini N, Bahardoust M. Predictors of 5 year survival rate in hepatocellular carcinoma patients. Journal of research in medical sciences. *J Res Med Sci* 2019;24:86. doi: 10.4103/jrms.JRMS_1017_18. eCollection 2019.
48. Moghaddam SD, Haghdoost AA, Hoseini SH, Ramazani R, Rezazadehkermani M. Incidence of hepatocellular carcinoma in southeast iran. *Hepat Mon* 2010;10:270.
49. McGlynn KA, Petrick JL, El-Serag HB. Epidemiology of hepatocellular carcinoma. *Hepatology* 2021;73:4-13. doi:10.1002/hep.31288
50. Yang JD, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention and management. *Nat Rev Gastroenterol Hepatol* 2019;16:589-604. doi:10.1038/s41575-019-0186-y
51. Mohammadian M, Mahdavifar N, Mohammadian-Hafshejani A, Salehiniya H. Liver cancer in the world: epidemiology, incidence, mortality and risk factors. *WCRJ* 2018;5: e1082. doi :10.32113/wcrj_20186_1082
52. Tateishi R, Koike K. Changing etiology of hepatocellular carcinoma. *J Gastroenterol* 2020;55:125-6. doi:10.1007/s00535-019-01622-5
53. Ward JW, Hinman AR. What is needed to eliminate hepatitis B virus and hepatitis C virus as global health threats. *Gastroenterology* 2019;156:297-310. doi:10.1053/j.gastro.2018.10.048
54. Heffernan A, Cooke GS, Nayagam S, Thursz M, Hallett TB. Scaling up prevention and treatment towards the elimination of hepatitis C: a global mathematical model.*Lancet* 2019;393:1319-29. doi:10.1016/S0140-6736(18)32277-3
55. Akinyemiju T, Abera S, Ahmed M, Alam N, Alemayohu MA, Allen C, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the global burden of disease study 2015. *JAMA Oncol* 2017;3:1683-91. doi:10.1001/jamaoncol.2017.3055
56. Anushiravani A, Sepanlou SG. Burden of liver diseases: a review from Iran. *Mddle East J Dig Dis* 2019;11:189. doi:10.15171/mejdd.2019.147
57. Yazdanpanah S, Geramizadeh B, Nikeghbalian S, Malek-Hosseini SA. Hepatocellular Carcinoma and Its Precursors in 103 HBV-Related Cirrhotic Explanted Livers: A Study from South Iran. *Hepat Mon* 2016;16:e38584. doi:10.5812/hepatmon.38584
58. Abdolmohammadi R, Azar SS, Khosravi A, Shahbazi M. CCR5 polymorphism as a protective factor for hepatocellular carcinoma in hepatitis B virus-infected Iranian patients. Asian Pac J Cancer Prev 2016;17:4643. doi:10.22034/APJCP.2016.17.10.4643
59. Farhood B, Raei B, Malekzadeh R, Shirvani M, Najafi M, Mortezazadeh T. A review of incidence and mortality of colorectal, lung, liver, thyroid, and bladder cancers in

Iran and compared to other countries. *Contemp Oncol* 2019;23:7. doi:10.5114/wo.2019.84112
60. Makvandi M, Jelodar RS, Samarbafzadeh A, Neisi N, Sharifi Z, Gholampour A, et al. Natural history of chronic hepatitis B virus infection in Ahvaz City, Iran. Asian Pac J Cancer Prev 2018;19:2125. doi: 10.22034/APJCP.2018.19.8.2125
61. Smolle E, Zöhrer E, Bettermann K, Haybaeck J. Viral hepatitis induces hepatocellular cancer: what can we learn from epidemiology comparing iran and worldwide findings? *Hepat Mon* 2012;12(10 HCC):e7879. doi:10.5812/hepatmon.7879
62. Zidan A, Scheuerlein H, Schüle S, Settmacher U, Rauchfuss F. Epidemiological pattern of hepatitis B and hepatitis C as etiological agents for hepatocellular carcinoma in iran and worldwide. *Hepat Mon* 2012;12(10 HCC):e6894. doi:10.5812/hepatmon.6894
63. Madihi S, Syed H, Lazar F, Zyad A, Benani A. A Systematic Review of the current hepatitis B viral infection and hepatocellular carcinoma situation in Mediterranean countries. *Biomed Res Int* 2020;10;2020:7027169. doi:10.1155/2020/7027169.
64. Matsushita H, Takaki A. Alcohol and hepatocellular carcinoma. *BMJ Open Gastroenterol* 2019;6:e000260. doi:10.1136/bmjgast-2018-000260
65. Petrick JL, Campbell PT, Koshiol J, Thistle JE, Andreotti G, Beane-Freeman LE, et al. Tobacco, alcohol use and risk of hepatocellular carcinoma and intrahepatic cholangiocarcinoma: The Liver Cancer Pooling Project. *Br J Cancer* 2018;118:1005-12. doi:10.1038/s41416-018-0007-z
66. Alvarez C, Graubard B, Thistle J, Petrick J, McGlynn K. Attributable Fractions of NAFLD for Mortality in the United States: Results From NHANES III With 27 Years of Follow-up. *Hepatology* 2020;72:430-40. doi:10.1002/hep.31040.
67. Dhamija E, Paul SB, Kedia S. Non-alcoholic fatty liver disease associated with hepatocellular carcinoma: An increasing concern. *Indian J Med Res* 2019;149:9. doi:10.4103/ijmr.IJMR_1456_17
68. Murphy N, Jenab M, Gunter MJ. Adiposity and gastrointestinal cancers: epidemiology, mechanisms and future directions. *Nat Rev Gastroenterol Hepatol* 2018;15:659-70. doi:10.1038/s41575-018-0038-1
69. Hagström H, Tynelius P, Rasmussen F. High BMI in late adolescence predicts future severe liver disease and hepatocellular carcinoma: a national, population-based cohort study in 1.2 million men. *Gut* 2018;67:1536-42. doi:10.1136/gutjnl-2017-314259
70. Yang C, Lu Y, Xia H, Liu H, Pan D, Yang X, et al. Excess Body Weight and the Risk of Liver Cancer: Systematic Review and a Meta-Analysis of Cohort Studies. *Nutr Cancer* 2020;72:1085-97. doi:10.1080/01635581.2019.1664602
71. Florio AA, Campbell PT, Zhang X, Zeleniuch-Jacquotte A, Wactawski-Wende J, Smith-Warner SA, et al. Abdominal and gluteofemoral size and risk of liver cancer: The liver cancer pooling project. *Int J Cancer Res* 2020;147:675-85. doi:10.1002/ijc.32760
72. Rahmani J, Varkaneh HK, Kontogiannis V, Ryan PM, Bawadi H, Fatahi S, et al. Waist circumference and risk of liver cancer: a systematic review and meta-analysis of over 2 million cohort study participants. *Liver Cancer* 2020;9:6-14. doi:10.1159/000502478
73. Abdel-Rahman O, Helbling D, Schöb O, Eltobgy M, Mohamed H, Schmidt J, et al. Cigarette smoking as a risk factor for the development of and mortality from hepatocellular carcinoma: An updated systematic review of 81 epidemiological studies. J Evid Based Med 2017;10:245-54. doi:10.1111/jebm.12270
74. Hormati A, Ghadir MR, Zamani F, Khodadadi J, Khodadust F, Afifian M, et al. Are there any association between COVID-19 severity and immunosuppressive therapy? *Immunol Lett* 2020;224:12. doi: 10.1016/j.imlet.2020.05.002
75. Tavan Janvilisri, Kawin Leelawat, Sittiruk Roytrakul, Atchara Paemanee, Rutaiwan Tohtong. Novel Serum Biomarkers to Differentiate Cholangiocarcinoma from Benign Biliary Tract Diseases Using a Proteomic Approach. *Dis Markers* 2015;2015:105358. doi:10.1155/2015/105358.
76. Mohammad-Alizadeh AH, Ghobakhlou M, Shalmani HM, Zali MR. Cholangiocarcinoma: an-eight-year experience in a tertiary-center in Iran. Asian Pac J Cancer Prev 2012;13:5381-4. doi:10.7314/APJCP.2012.13.11.5381
77. Bertuccio P, Malvezzi M, Carioli G, Hashim D, Boffetta P, El-Serag HB, et al. Global trends in mortality from intrahepatic and extrahepatic cholangiocarcinoma. *J Hepatol* 2019;71:104-14. doi:10.1016/j.jhep.2019.03.013
78. Shaib YH, El-Serag HB, Davila JA, Morgan R, McGlynn KA. Risk factors of intrahepatic cholangiocarcinoma in the United States: a case-control study. *Gastroenterology* 2005;128:620-6. doi:10.1053/j.gastro.2004.12.048
79. Watanapa P, Watanapa W. Liver fluke-associated cholangiocarcinoma. *Br J Surg* 2002;89:962-70. doi:10.1046/j.1365-2168.2002.02143.
80. Steele J, Richter C, Saenna P, Stout V, Echaubard P, Wilcox BA. Thinking Beyond Opisthorchis viverrini Infection for Risk of Cholangiocarcinoma in the Lower Mekong Basin. *Infect Dis Poverty* 2018;7:44. doi: 10.1186/s40249-018-0434-3
81. Sithithaworn P, Yongvanit P, Duenngai K, Kiatsopit N, Pairojkul C. Roles of liver fluke infection as risk factor for cholangiocarcinoma. *J Hepatobiliary Pancreat Sci*

2014;21:301-8. doi:10.1002/jhbp.62
82. Shin HR, Oh JK, Masuyer E, Curado MP, Bouvard V, Fang YY, et al. Epidemiology of cholangiocarcinoma: an update focusing on risk factors. *Cancer Sci* 2010;101:579-85. doi:10.1111/j.1349-7006.2009.01458.x
83. Heidarpour M, Rajabi P, Pejhan S. Cholangiocarcinoma associated with liver fluke infection in an Iranian patient. *Iran J Pathol* 2007;2:74-6.
84. Kirstein MM, Vogel A. Epidemiology and risk factors of cholangiocarcinoma. *Visc Med* 2016;32:395-400. doi:10.1159/000453013
85. Ehlken H, Zenouzi R, Schramm C. Risk of cholangiocarcinoma in patients with primary sclerosing cholangitis: diagnosis and surveillance. *Curr Opin Gastroenterol* 2017;33:78-84. doi: 10.1097/MOG.0000000000000335
86. Takakura WR, Tabibian JH, Bowlus CL. The evolution of natural history of primary sclerosing cholangitis. *Curr Opin Gastroenterol* 2017;33:71-7. doi:10.1097/MOG.0000000000000333
87. Liang H, Manne S, Shick J, Lissoos T, Dolin P. Incidence, prevalence, and natural history of primary sclerosing cholangitis in the United Kingdom. *Medicine* 2017;96:e7116. doi: 10.1097/MD.0000000000007116
88. Choi J, Ghoz HM, Peeraphatdit T, Baichoo E, Addissie BD, Harmsen WS, et al. Aspirin use and the risk of cholangiocarcinoma. *Hepatology* 2016;64:785-96. doi:10.1002/hep.28529
89. Weismüller TJ, Trivedi PJ, Bergquist A, Imam M, Lenzen H, Ponsioen CY, et al. Patient age, sex, and inflammatory bowel disease phenotype associate with course of primary sclerosing cholangitis. *Gastroenterology* 2017;152:1975-84.e8. doi:10.1053/j.gastro.2017.02.038
90. Fung BM, Tabibian JH. Cholangiocarcinoma in patients with primary sclerosing cholangitis. *Curr Opin Gastroenterol* 2020;36:77-84. doi:10.1097/MOG.0000000000000616
91. Schottenfeld D, Beebe-Dimmer J. Chronic inflammation: a common and important factor in the pathogenesis of neoplasia. *CA: Cancer J Clin* 2006;56:69-83. doi:10.3322/canjclin.56.2.69
92. Sheen-Chen SM, Chou FF, Eng HL. Intrahepatic cholangiocarcinoma in hepatolithiasis: a frequently overlooked disease. *J Surg Oncol* 1991;47:131-5. doi:10.1002/jso.2930470213
93. Zen Y, Sasaki M, Fujii T, Chen T-C, Chen M-F, Yeh T-S, et al. Different expression patterns of mucin core proteins and cytokeratins during intrahepatic cholangiocarcinogenesis from biliary intraepithelial neoplasia and intraductal papillary neoplasm of the bile duct—an immunohistochemical study of 110 cases of hepatolithiasis. *J Hepatol* 2006;44:350-8. doi:10.1016/j.jhep.2005.09.025
94. Kim HJ, Kim JS, Joo MK, Lee BJ, Kim JH, Yeon JE, et al. Hepatolithiasis and intrahepatic cholangiocarcinoma: a review. *World J Gastroenterol* 2015;21:13418. doi:10.3748/wjg.v21.i48.13418
95. Liu ZY, Zhou YM, Shi LH, Yin ZF. Risk factors of intrahepatic cholangiocarcinoma in patients with hepatolithiasis: a case-control study. *Hepatobiliary Pancreat Dis Int* 2011;10:626-31. doi:10.1016/S1499-3872(11)60106-9
96. Ralphs S, Khan S. The role of the hepatitis viruses in cholangiocarcinoma. J Viral Hepat 2013;20:297-305. doi:10.1111/jvh.12093
97. Li H, Hu B, Zhou Z-Q, Guan J, Zhang Z-Y, Zhou G-W. Hepatitis C virus infection and the risk of intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma: evidence from a systematic review and meta-analysis of 16 case-control studies. *World J Surg Oncol* 2015;13:1-8. doi:10.1186/s12957-015-0583-9
98. Navas M-C, Glaser S, Dhruv H, Celinski S, Alpini G, Meng F. Hepatitis C virus infection and cholangiocarcinoma: an insight into epidemiologic evidences and hypothetical mechanisms of oncogenesis. *Am J Pathol* 2019;189:1122-32. doi:10.1016/j.ajpath.2019.01.018
99. Palmer WC, Patel T. Are common factors involved in the pathogenesis of primary liver cancers? A meta-analysis of risk factors for intrahepatic cholangiocarcinoma. *J Hepatol* 2012;57:69-76. doi:10.1016/j.jhep.2012.02.022
100. Zhou Y, Zhao Y, Li B, Huang J, Wu L, Xu D, et al. Hepatitis viruses infection and risk of intrahepatic cholangiocarcinoma: evidence from a meta-analysis. *BMC cancer* 2012;12:1-7. doi:10.1186/1471-2407-12-289
101. Mahale P, Torres HA, Kramer JR, Hwang LY, Li R, Brown EL, et al. Hepatitis C virus infection and the risk of cancer among elderly US adults: a registry-based case-control study. *Cancer* 2017;123:1202-11. doi:10.1002/cncr.30559
102. Jeong S, Tong Y, Sha M, Gu J, Xia Q. Hepatitis B virus-associated intrahepatic cholangiocarcinoma: a malignancy of distinctive characteristics between hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *Oncotarget* 2017;8:17292. doi:10.18632/oncotarget.14079
103. Li J, Han T, Xu L, Luan X. Diabetes mellitus and the risk of cholangiocarcinoma: an updated meta-analysis. *Prz Gastroenterol* 2015;10:108. doi:10.5114/pg.2015.49004
104. Li J-S, Han T-J, Jing N, Li L, Zhang X-H, Ma F-Z, et al. Obesity and the risk of cholangiocarcinoma: a meta-analysis. *Tumor Biol* 2014;35:6831-8. doi:10.1007/s13277-014-1939-4
105. Clements O, Eliahoo J, Kim JU, Taylor-Robinson SD, Khan SA. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma: a systematic review and meta-

analysis. *J Hepatol* 2020;72:95-103. doi:10.1016/j.jhep.2019.09.007
106. Saengboonmee C, Seubwai W, Wongkham C, Wongkham S. Diabetes mellitus: Possible risk and promoting factors of cholangiocarcinoma: Association of diabetes mellitus and cholangiocarcinoma. *Cancer Epidemiol* 2015;39:274-8. doi:10.1016/j.canep.2015.04.002
107. McGee EE, Jackson SS, Petrick JL, Van Dyke AL, Adami H-O, Albanes D, et al. Smoking, alcohol, and biliary tract cancer risk: a Pooling Project of 26 prospective studies. J Natl Cancer Inst 2019;111:1263-78. doi:10.1093/jnci/djz103
108. Rawla P, Sunkara T, Thandra KC, Barsouk A. Epidemiology of gallbladder cancer. *Int J Clin Exp Pathol* 2019;5:93. doi:10.5114/ceh.2019.85166
109. Salimzadeh H, Delavari F, Sauvaget C, Rezaee N, Delavari A, Kompani F, et al. Annual trends of gastrointestinal cancers mortality in Iran during 1990-2015; NASBOD study. *Arch Iran Med* 2018;21:46-55.
110. Torre LA, Siegel RL, Islami F, Bray F, Jemal A. Worldwide burden of and trends in mortality from gallbladder and other biliary tract cancers. *Clin Gastroenterol Hepatol* 2018;16:427-37. doi:10.1016/j.cgh.2017.08.017
111. Ghadirian P, Lynch H, Krewski D. Epidemiology of pancreatic cancer: an overview. *Cancer Detect Prev* 2003;27:87-93. doi:10.1016/S0361-090X(03)00002-3
112. Sarkar FH, Banerjee S, Li Y. Pancreatic cancer: pathogenesis, prevention and treatment. *Toxicol Appl Pharmacol* 2007;224:326-36. doi:10.1016/j.taap.2006.11.007
113. Karki S, Umar S, Kasi A. Treating Colorectal Cancer with Immunotherapy: Implications for Single Versus Combination Therapy. *Curr Colorectal Cancer Rep* 2020:1-11. doi:10.1007/s11888-020-00459-y
114. Pickhardt PJ, Pooler BD, Kim DH, Hassan C, Matkowskyj KA, Halberg RB. The natural history of colorectal polyps: overview of predictive static and dynamic features. *Gastroenterol Clin* 2018;47:515-36. doi:10.1016/j.gtc.2018.04.004
115. Amersi F, Agustin M, Ko CY. Colorectal cancer: epidemiology, risk factors, and health services. *Clin Colon Rectal Surg* 2005;18:133-40. doi:10.1055/s-2005-916274
116. Shussman N, Wexner SD. Colorectal polyps and polyposis syndromes. *Gastroenterol Rep* 2014;2:1-15. doi:10.1093/gastro/got041
117. Van Ta T, Nguyen QN, Chu HH, Truong V-L, Vuong LD. RAS/RAF mutations and their associations with epigenetic alterations for distinct pathways in Vietnamese colorectal cancer. *Pathol Res Pract* 2020;216:152898. doi:10.1016/j.prp.2020.152898
118. Johnson CM, Wei C, Ensor JE, Smolenski DJ, Amos CI, Levin B, et al. Meta-analyses of colorectal cancer risk factors. *Cancer Causes Control* 2013;24:1207-22. doi:10.1007/s10552-013-0201-5
119. Świderska M, Choromańska B, Dąbrowska E, Konarzewska-Duchnowska E, Choromańska K, Szczurko G, et al. The diagnostics of colorectal cancer. *Contemp Oncol* 2014;18:1. doi:10.5114/wo.2013.39995