Lessons Learned from the Epidemiology of Colorectal, Lung, and Stomach Cancer

Hanwen Mickle Ma*
Shanghai Shangde Experimental School, Shanghai, China.

* Corresponding author. email: 3320513353@qq.com
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Abstract: Cancer is a leading cause of death worldwide in recent years. Up until 2020, new cancer cases reached approximately 19.3 million with 10 million deaths. New cases of colorectal cancer reached 1.93 million cases, lung cancer to 2.21 million cases and stomach cancer to 1.09 million cases, which are three of the most common types of cancer in 2020. In this review, with the aid of data from World Health Organization, colon, lung, and stomach cancers were discussed from an epidemiological point of view, addressing both epidemiological distribution and determinants in addition to a brief biological background. In colon cancer, Ras mutations and mutations in DNA repair genes such as MLH1, MSH2 are shown to be common. Obesity was shown to increase the risk of development of colon cancer by 30-70% as studies suggest. Therefore, prevalence of obesity in Europe, Australia and United States was suggested to be highly attributable to high incidence rates of colon cancer in these regions. Looking at lung cancer, several studies showed that mutations /aberrant expression of oncogenes like cyclin D1, KRAS, and c-MYC are commonly found to be involved. From epidemiological perspective, industrialized Asian countries were found to be affected the most by lung cancer, where smoking, air pollution and poor diet are the major risk factors. Regarding stomach cancer, excessive alcohol consumption, chronic inflammations in the inner lining of the stomach caused by different diseases as in chronic atrophic gastritis, and other factors were found to be major risk factors. Asia and Russia were shown to be the most affected by stomach cancer. Towards the end, the paper suggested a variety of measures to be taken to minimize the incidence rates of different types of cancer. Realistic restrictions on smoking and alcohol consumption were suggested to minimize their negative effects. Moreover, and most importantly, making healthy lifestyle accessible and affordable in underprivileged areas is strongly recommended to address the prevalence of cancer.

Key words: oncology, cancer distribution data, risk factors, WHO statistics.

1. Introduction

Cancer is a disease in which a group of cells grows beyond regulation due to expanded proliferative activity, which creates a large quantity of cells called tumors. Normal cells accumulate enough mutations quantitatively and qualitatively of different signaling proteins and then become cancerous, while most of them will involve cell proliferation. Cancer cells tend to invade into adjacent tissues through the blood stream and generate new tumors in their new locations. At an advanced stage of cancer, tumors intervene with the functionality of different organs, leading to death if not successfully treated.

In 2019, cancer was the 2nd leading cause of death in the United States as per the Center for Disease Control and Prevention (CDC). The World Health Organization (WHO) has also reported that lung cancer is 6th

amongst main causes of death globally. Moreover, stomach cancer is one of the most 10 leading causes of death in upper-middle-income countries. In high-income-countries, colon and rectum cancer lies 7th amongst the leading causes of death.

Since cancer occurs due to the accumulation of genetic mutations leading to an exaggerated proliferation, it is impossible to pinpoint one avoidable cause of cancer as in viral or bacterial infections. However, there are different "risk factors" that are correlated with different types of cancer incidences. Although it is known to the public that obesity, excessive consumption of alcohol, smoking, and certain types of infection are among the risk factors of cancers, it is useful for policy makers in each region to determine the risk factors correlated with the common types of cancers locally.

Epidemiology is one branch of medicine in biology that refers to the study of distribution, causes and risk factors related to diseases at the population level. This paper will focus on analyzing and exploring the latest epidemiological distribution of stomach, lung, and colon cancer with the aid of graphs, statistics from World Health Organization. More importantly, the paper will address the potential epidemiological determinants of these types of cancer from published data.

1.1. General distribution of cancer

The incidence rate of all cancers was found to be extremely high in Europe, North America and Japan in Asia (Fig. 1). The main factor is high proportion aging groups in population of these highly developed countries. Epidemiologic studies show that 11% of the world's population is over 60 years of age and is expected to increase by 2050, to reach 22% of the population which the main countries are United States and Japan [1]. In 2050, the population that aged 65 and over is predicted to be 83.7 million, almost double its estimated population of 43.1 million in 2012 in United States [2]. Therefore, aging populations in these countries may lead to high incidence rate of cancers. According to statistics from the National Cancer Institute Surveillance, Epidemiology, and End Results Program in 5 years from 1998 to 2002, revealing that 56% of all newly diagnosed cancer patients and 71% of cancer deaths are aged 65 or older [3]. Identical trend is also revealed in Europe and Japan, approximately 50% of all neoplasms occur in the 12% of the population aged 65 years and older, and this percentage will continue to grow with the increasing older population [4].

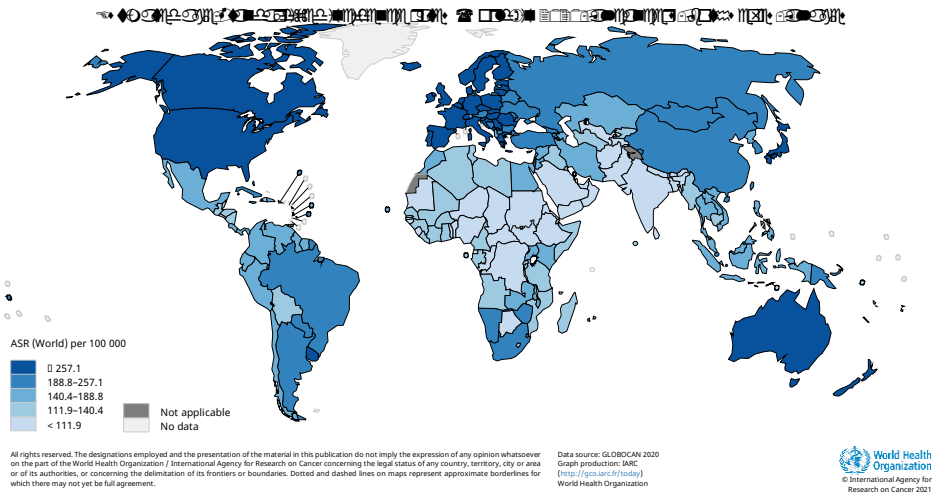


Fig. 1. Cancer incidents distribution over the world map.

As shown in the figure (Fig. 1), darker blue refers to higher incidences while lighter blue refers to lower rates. The figure is generated by the WHO Global Cancer Observatory tool.

Since it has been consistently shown that cancer is strongly correlated with aging [5] for various reasons, including age-related degenerative diseases [6], accumulation of DNA changes with aging [7], [8] and age-related increase in inflammatory activity [9], [10], the strong correlation between aging populations like in Europe, United States and Japan and high rates of cancer incidences is fairly understandable. However, the mortality rate of these three countries is low (Fig. 2) due to improved public health measures and medical standards [11]. For instance, the widely using of organized mammographic screening programs in Europe contributes to a reduction in breast cancer mortality rate. Moreover, screening for colorectal cancer has been confirmed to be effective [11]. All of these increasing medical programs promoted in Europe, United States and Japan will lead to lower mortality rate of cancers.

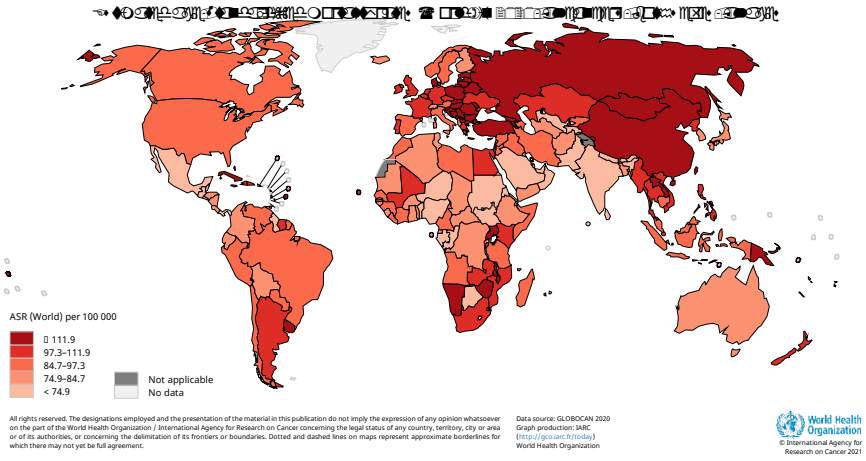


Fig. 2. Estimated age-standardized mortality rates.

Fig. 2 Estimated age-standardized mortality rates caused by cancers in worldwide in 2020 with both sexes and all ages. Darker red represents higher mortality rates of cancer, while lighter red refers to lower rates. The figure is generated by the WHO Global Cancer Observatory tool.

1.2. Colon, Lung, and Stomach Cancer

Colon, lung, and stomach cancers were reported to be among the highest 5 types of cancer in terms of incident rates in 2020 (Fig. 3).

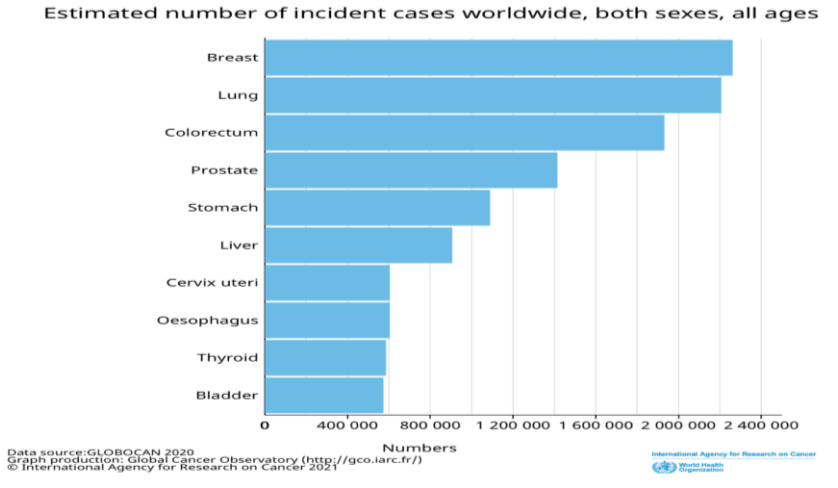


Fig. 3. The estimated number of cancer cases globally in all sexes and ages.

The vertical axis represents different types of cancers, and the horizontal axis represents the total number of incident cases. The figure is generated by the WHO Global Cancer Observatory tool. In this section, the background and epidemiology of the 3 aforementioned types of cancer will be reviewed.

2. Colon Cancer

Colon cancer, also known as colorectal cancer, mostly grows at the large intestine and the rectum [Fig. 4 (A)]. The distal colon which is the left side of the large intestine usually derives a high incidence rate compares to the proximal colon which is the right side of large intestine. According to the statistics from American Cancer Society, the incidence rate of distal colon is approximately about 51%, in contrast, the proximal colon is about 42%. Accompanied by the rearrangement and management of the data, the incidence rates were displayed to vary proportionally on age and sex of the patients during diagnosis phase, the increased age is connected with higher susceptibility to colon cancer and females are more likely to develop colorectal cancer at the right side of the colon than males [12]. Both Inherited gene mutations and acquired gene mutation would lead to colon cancers. For inherited mutations, such as Familial Adenomatous Polyposis, Gardner syndrome, and attenuated FAP are caused by genetic change on APC gene [13]. The gene of adenomatous polyposis coli is a tumor suppressor gene that is mainly responsible for controlling the growth of cells, while the genetic changes of APC gene in human body will block or repress cell growth and contribute to formation of numerous colorectal polyps. The functional incapacitation in adenomatous polyposis coli gene triggers molecular and histological changes in chains [14]. LCRC has been shown to be prevalent in patients with FAP. In adults, over 1000 of the genes correlated with CRC are already expressed differently between proximal and distal colon before development of cancer. 70% of these genes are upregulated at the distal colon and 30% at the proximal colon, explaining the differences in features between LCRC and RCC [15].

According to the data from WHO (2012), a highly attributable factor that leads to high incidence rate of colorectal cancer in Europe, North America and Oceania is high obesity rate in these countries [Fig. 4 (B)]. Data from previous epidemiological studies showed that obesity increases the chance to develop CRC by 30%-70%, assuming that an obese subject is one with BMI of ≥30 kg/m2.

For Europe, the general prevalence of overweight was approximately exceeding 60% and keep constant from 2005 to 2013. Meanwhile, the rate of obesity increased significantly which is about 17.5% from 2005 to 2013 [22]. According to another article which is about forecasting future trends of obesity in Europe, the results show that obesity is expected to rise gradually in 44 countries in Europe. If current trends remain the same, then 33 of the 53 countries will be predicted to have an increment in obesity prevalence of 20% or even more [23]. The highest prevalence is Ireland which can reach 43% [24].

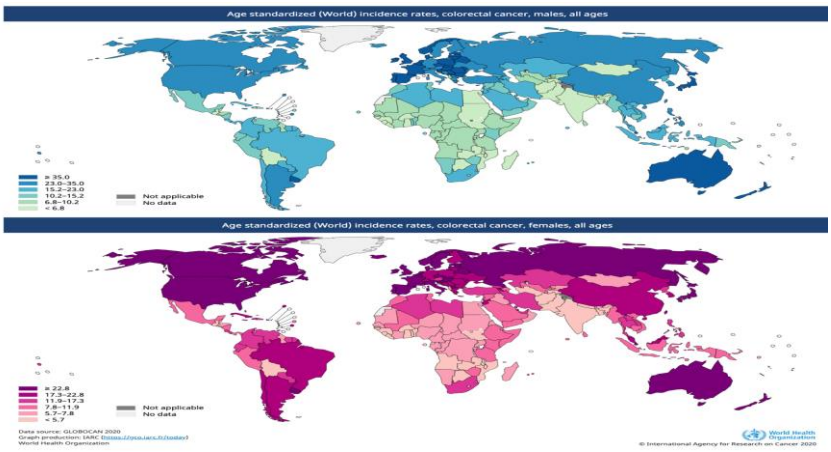


Fig. 4. (A) The global distribution of age-standardized incidence rates of colon cancer in both sexes.

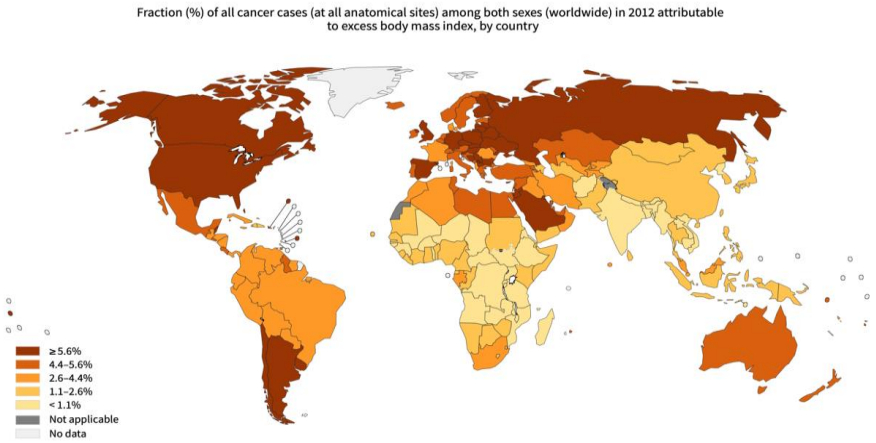


Fig. 4. (B) The global distribution of cancers triggered by obesity. The figure is generated by the WHO Global Cancer Observatory tool.

For United States, the obesity is more prevalent among children and teenagers. According to the data, White and Asian American children have significantly lower rates of obesity than African American children [25], and generally the obesity rate of children in US is higher than standard level, about 17% of the teen and kid population has confirmed to be obesity [26]. For adults, the prevalence of obesity is 39.8% in US from 2015 to 2016, this data is relatively lower than Europe and Australia, but still it's clear that the rate of obesity is increasing, which linked to risks of colon cancer [27].

3. Lung Cancer

Lung cancer is a type of cancer that origins from the lungs. It's one of the leading causes of cancer death in worldwide. There are different categories of lung cancers, such as non-small cell lung cancer (NSCLC) which includes adenocarcinoma, squamous cell carcinoma or small cell lung cancer which grows and spread more rapidly than NSCLC.

The related oncogenes that contribute to the pathogenesis of lung cancer include c-MYC, mutated KRAS, EGFR, cyclin D1, and BCL2 [28]. The cellular immortality of lung cancer cells is triggered by Telomerase RNA (hTR) and the catalytic component (hTERT) in nearly all lung cancers. Moreover, abnormalities in the function of FHIT, RASFF1A, and SEMA3B are linked in the pathogenesis of some lung cancers [29].

Tobacco consumption was shown to be significantly contributing to lung cancer incidence and mortality rates at the population level [30]. Other factors such as genetic susceptibility, poor diet, occupational exposure and air pollution were found to be -alone or in synergy with smoking- shaping the epidemiological distribution of lung cancer. However, although smoking is defined as the major risk factor of lung cancer, fairly preventable diseases are still contributing to this common and one of the deadliest of cancers [31].

From the world map (Fig. 6) and the pie charts (Fig. 5), generally, Asia has the highest incidence rate currently and 5-years prevalence. According to Reza Pakzad et al. 2015, a total of 1033881 incidences with 71.13% males and 28.87% females and 936051 mortalities with 71.45% males and 28.55% females recorded in Asian countries in 2012. Democratic Republic of Korea and China are two countries in Asia with the highest standardized incidence and mortality rates for lung cancers based on the statistics [32]. In Asia, the model of industrialized countries is being more common, such as in China (agriculture and industry), Japan, India and Korea which are the leading countries in industry. In most industrialized countries, lung cancer is the most common type of cancer at the population level. For both sexes, smoking behavior is one of the dominating factors [33]. While the pattern is different in two sexes in Asia, especially in China, where incidence rates of lung cancer in men reflect high smoking frequency but high rates among non-smoking women appear to be

related to other factors.

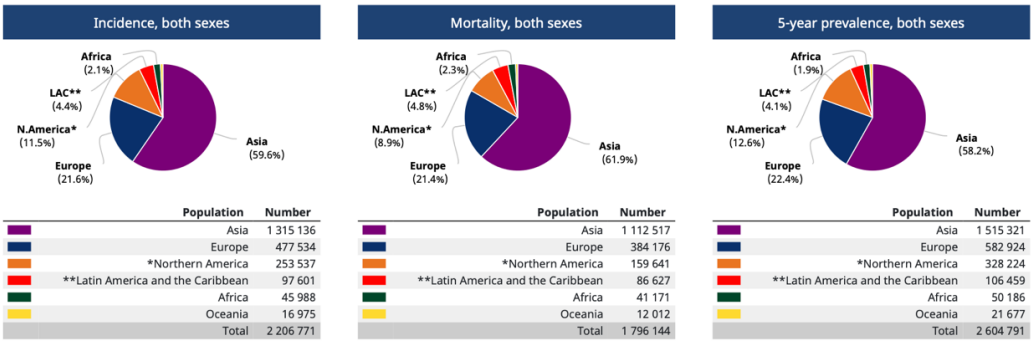


Fig.5. Pie charts show incidence, mortality and 5-year prevalence in different types of cancers. The figure is generated by the WHO Global Cancer Observatory tool.

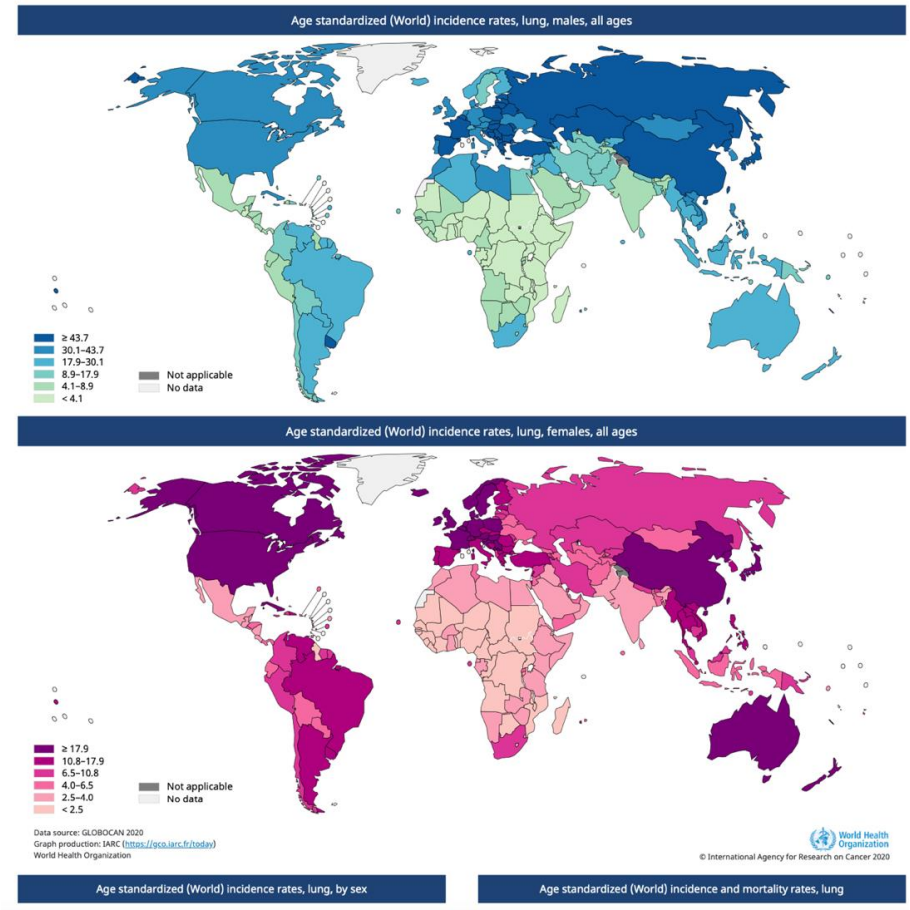


Fig. 6. The age standardized incidence rate of lung cancers in both sexes among all countries. According to the map, the darker color represents higher incidence rate of lung cancer.

Smoking can be classified into cigarette smoking, secondhand smoking and E-cigarette. Cigarette smoking is the most essential risk factor for lung cancer (Fig. 7). According to the surgeon general's report on smoking and health in 1964, approximately 52% of US males and 35% of US females were active smokers [34]. The statistical correlation remained solid when a decline in cigarettes consumption in US was followed with lower incidence rate of lung cancer after 1970s, compared to the trend in Asia. It's true that nicotine is not recognized as a carcinogenic substance, but more than 55 substances in cigarette are determined to be

carcinogenic by cancer research from the international agency, Journal of the National Cancer Institute. The polycyclic aromatic hydrocarbons are the main substance that can trigger multiple DNA changes causing higher risk of development of tumors [35]. The probability of smoking being a risk factor in lung cancer depends on the number of cigarettes being smoked daily and annually, therefore, the more you smoke, the higher the risk of being diagnosed with lung cancer later on [36]. Meanwhile, the cigar and pipe tobacco can also increase potential risks to develop lung cancer [37].

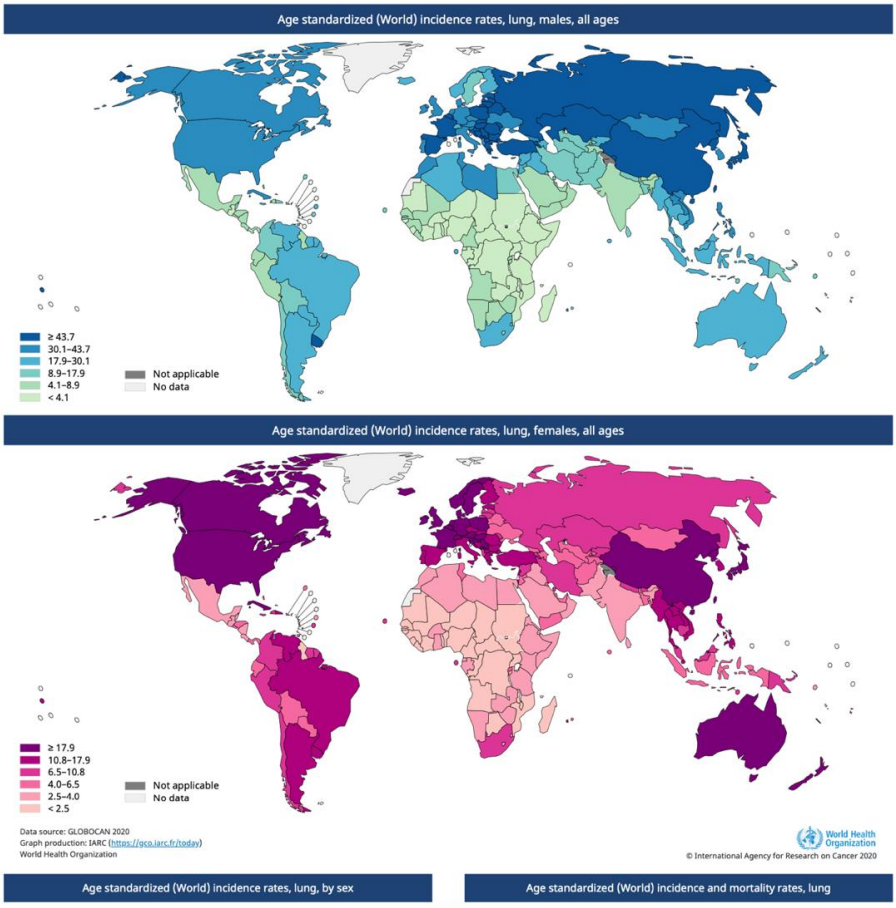


Fig. 7. The age standardized incidence rate of lung cancers in both sexes distributed in worldwide.

Secondhand smoking (i.e direct exposure to cigarette smoke) is also associated with the risk of lung cancer. [38], [39]. A study performed by Oberg et al. 2011 showed the impact of environmental tobacco exposure in 192 countries and concluded that 40% of children and 33% to 35% of non-smokers are exposed to secondhand smoke. The highest rates were identified in Europe, the western Pacific, and Southeast Asia which matches the distribution shown in figure 7, while the lowest rates were Africa.

Moreover, electronic cigarettes turned out to be risky as well in terms of contributing to development of lung cancer by long-term using [40]. The 2012 National Youth Tobacco Survey shows the frequency of ever-use of e-cigarettes in US's middle and high school students to be 6.8% [41], while prevalence among adults was 1.9% [42]. Although traditional cigarettes have a higher consumption rate which is 18%, the rate of E-cigarette consumption was shown to be increasing rapidly in recent years, especially among teenagers [43], [44]. More research has confirmed that E-cigarette caused an identical gene expression pattern in epithelial cells of human to cigarette smoking [45].

Beside tobacco smoking, some etiological factors have been shown to be risk factors for lung cancer, such as indoor exposure to environmental tobacco smoke, cooking oil vapor, burning of coal and radon, serious air

pollution and exposure to asbestos and other carcinogens during occupation periods [33]. Additionally, several articles have confirmed an increased lung cancer risk correlated with biomass fuels. A meta-analysis done in Europe, North America, and Asia has shown similar trends in lung cancer risk with exposure to coal, biomass, and mixed fuels [46]. Meanwhile, more studies have reported potential risk of lung cancer in bituminous smoky coal [47], [48].

Occupational exposure is another vital factor for triggering lung cancers, as the exposure to asbestos is one of the most recognizable occupational causes of lung cancer which is very common in Asia, Europe and United States. Workers who take job in asbestos mining, construction, shipbuilding, textiles, insulation, and vehicle repair are at the highest risk since there are several mechanisms present for carcinogenesis, such as abduction of oxidative damage and subsequent DNA reductions and somatic gene change [49]. Markowitz and other investigators analyzed data from a total of 2377 North American workers and found rising lung cancer risk related to asbestos exposure, giving similar effects of cigarette smoking [50], while exposure to diesel has also been concerned as a factor in developing lung cancer [51].

Moreover, recent researchers have found that dietary factors may be crucial, as the high consumption of vegetables and fruits can be protective against lung cancer, while excessive consumption of fatty food is one of the risk factors [33]. Some particular infections such as Mycobacterium tuberculosis, human papilloma virus and Microsporum Canis are also correlated with a high risk of lung cancer. For non-smokers, the factor of genetic predisposition in lung cancer which increasing the susceptibility of human to environmental carcinogens is currently being explored [52]. Among all the factors, pollution caused by factories, unprocessed biomass fuel exposure and high smoking rate and smoking exposure lead to the high incidence rate of lung cancers in Asia, North America, and parts of Europe [33], [53].

4. Stomach cancer

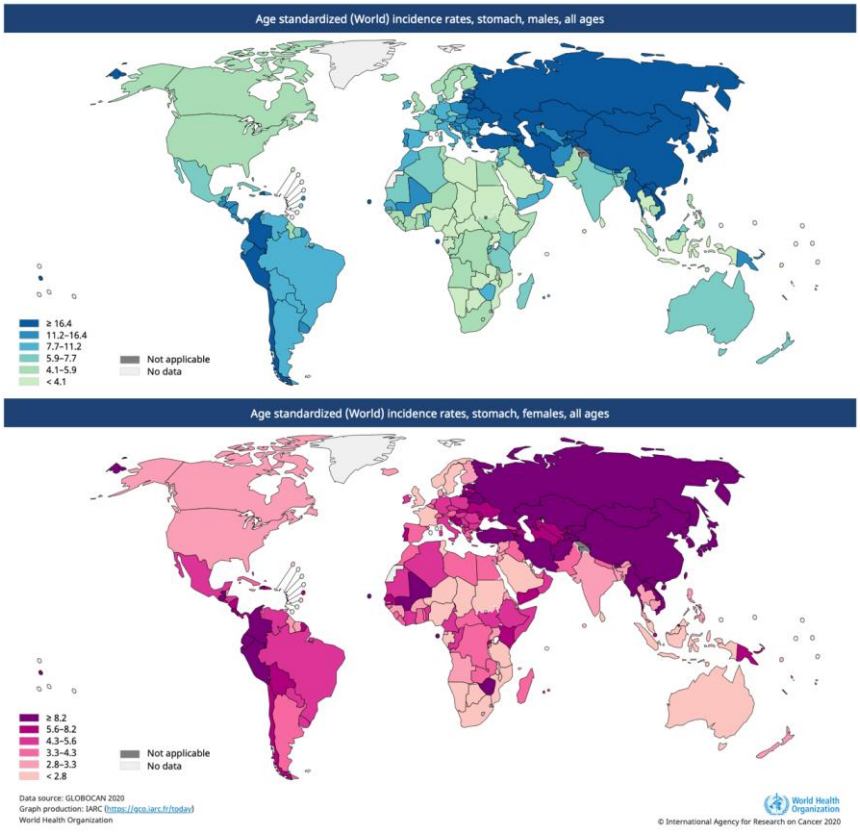
Stomach cancer which is also known as gastric cancer is an abnormal cell growth that starts in the stomach [Fig. 8 (A)] [54]. Such cancer can affect any parts or sections of the stomach. According to the statistics collected from world health organization, the stomach cancer will be more likely to affect the esophagus, more accurately at the gastroesophageal junction. [Fig. 8 (B)].

According to the American cancer society, the pre-cancerous changes in the stomach usually occur in the inner lining of the stomach. In atrophic gastritis, for example, stomach cells can be attacked by the immune system (autoimmune disease). The atrophic gastritis is often triggered by infection with helicobacter pylori or autoimmune reaction [55]. Patients with this condition may develop gastric cancers [55]. On the other hand, the precancerous lesion can also be intestinal metaplasia. In this situation, cells lined up in the stomach are replaced by cells that look like those normally lined up in the intestine. This disease will also cause people to have chronic atrophic gastritis and may also linked to helicobacter pylori infection. Therefore, both atrophic gastritis and intestinal metaplasia will lead to fewer glandular cells which are substances that secrete to help to conserve cells lining in the stomach. Then, when DNA damage emerge in these cells the results will be stunted growth where the cell size increases and look very abnormal. This is actually a sign for formation of gastric cancer and sometimes stunting can cause stomach cancer [56].

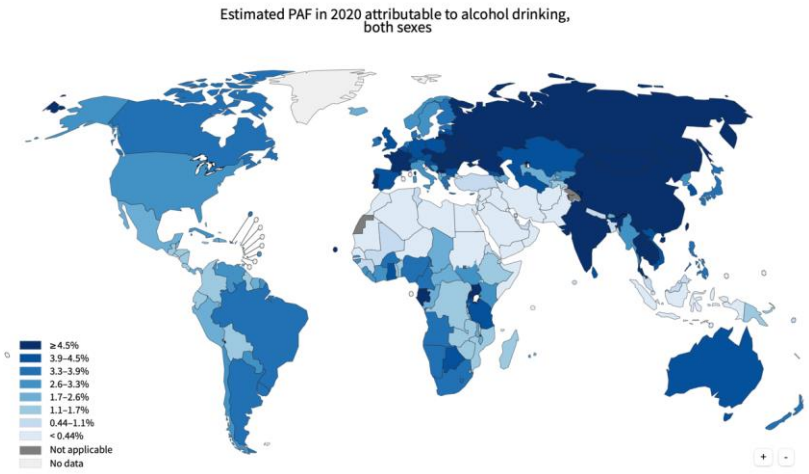
According to the map in Fig. 8, it's clearly identified that Asia and Russia have the highest incidence rates of stomach cancers. At the same time, North America and Australia have the lowest incidence rates of gastric cancer, and Africa has a kind of sporadic distribution of incidence rates in different areas.

An investigation performed by Yuko Minami shows that cigarettes and alcohol consumption may be risk factors of stomach cancer. The paper investigated the association between alcohol consumption rate and the risk of deaths due to stomach cancer among 1576 patients with histologically recorded stomach cancer diagnosed from 1997 to 2010 at a single hospital in Japan. Patients were followed until December 31, 2013.

The results showed that among all the patients, alcohol consumption was largely associated with an increased risk of all types of cancers, not with stomach cancer deaths alone. Meantime, a positive linear correlation between the frequency/amount of alcohol consumed per day and the risk of death of all cancers. In contrast, in patients who underwent curative resection, there was a positive association between alcohol consumption before receiving treatment and surviving stomach cancer [57].



(A)



(B)

Fig. 8. (A) Age-standardized incidence rates of stomach cancer in males and females across the world. (B) Population attributable fraction of alcohol drinking showing strong association between alcohol consumption and stomach cancer.

5. Discussion and Concluding Remarks

This paper focused on three specific types of cancers: colorectal, lung and stomach cancers. First, the paper discussed the risk factors and the biological context of these three cancers. Regarding colon cancer, the risk factors include inherited mutations such as FAP and APC gene, mutation in DNA repair genes. For lung cancer, tobacco smoking and other etiological factors were found to be major risk factors. Different oncogenes and tumor suppressor genes were also found to be involved as expected and as common in many types of cancer. Finally, in stomach cancer, chronic inflammations in the inner lining of the stomach as in several autoimmune diseases or bacterial infections, were of the common risk factors involved.

The epidemiological distribution and determinants of these three cancers were discussed from different perspectives, showing the epidemiological distribution from the latest WHO data and discussing possible risk factors. First, the paper showed the general epidemiology of all cancers worldwide. Lung cancer was then reviewed where it was found to have the highest incidence rate in Asia, and relatively high rates in The United States, Europe and Australia. Smoking, biomass fuel exposure, occupational fuel, air pollution, dietary factors and infections were all identified as risk factors for lung cancer among these countries. Next, according to the world map distribution, obesity was shown to be highly correlated with incidence rate of colon cancer among Australia, Europe and United States. Ultimately, the distribution alcohol consumption rates were shown to be highly attributable in stomach cancer according to the WHO data. An investigation from further confirmed alcohol as a risk factor for stomach cancer in Asia, since Asia has the highest incidence rate of stomach cancer.

Therefore, in order to reduce the incidence and mortality rate of colorectal, lung and stomach cancers, both individuals and governments are encouraged to take some new measures to minimize the risk of cancer prevalence. For Asia, incidence rates of lung cancer (which is highly associated with tobacco consumption) can be reduced by carrying out measures to control tobacco consumption, targeting low-income and low-to-middle income Asian countries. The tobacco control measures can include encouraging tobacco farmers and workers to work on alternative yields, or applying high taxation schemes on the whole production line of cigarettes. Moreover, health education, multisectoral activities to the public can be a tool to raise the public awareness among Asian population of risks of tobacco smoking on triggering lung cancer [58]-[60]. On the other hand, popularizing and promoting screening programs is crucial, as screening can effectively reduce incidence rates of colon cancer [60]-[64]. The positive impact of mammography screening has been confirmed in high-income countries from Asia. According to the data, survival rates of breast cancers are 70-85% when diagnosed at stages 1 and 2 [65]-[67]. However, in order to provide screening of cancer in large population, health services and infrastructure are vital, therefore, lack of screening will remain an issue among low-income countries [67]. Moreover, for stomach cancer prevention, increased frequency in physical activities, adequate intake of fresh vegetables and fruit and maintaining a healthy diet can be effective in protecting against of stomach and colon cancer [67].

In Europe and North America, the epidemiology shows that there's a correlation between obesity and colon cancer, thus, it's necessary to fight obesity as a main measure against colon cancer [67]. The potential prevention solutions for obesity that governments can implement are to a) promote physical activities (by making gyms/clubs/pools etc. more affordable, accessible, and abundant); b) enhance abilities of low-income population to purchase nutritious food, increase awareness about healthy diet and lifestyle; c) make medical help available for obese individuals through healthcare services and education sites.

To sum up, government of different countries should take action in minimizing prevalence of colon, lung and stomach cancer based on epidemiological data. Reducing the rate of these three types of cancers are difficult to achieve on the short-term, which poses a need of long-term and sustainable measures. Additionally, collaboration among countries/societies can be a key element in minimizing prevalence of cancers to aid societies with low-to-middle income. These countries/societies cannot afford advanced healthcare services

and/or maintain healthy activities. Hence, subsidies and aid from other highly-developed countries such as can help reduce prevalence of cancer in other underprivileged regions.

Conflict of Interest

The author declares no conflict of interest.

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