

Environmental Factors Controlling Gastric Cancer

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BACKGROUND

Gastric cancer has been and still considered one of the most common causes of cancer-related death; it continues to be a major public health issue. However, studies showed that the incidence of gastric cancer varies in different spots of the world, and that high incidence rates were documented in Eastern Asia, Eastern Europe and South America, while low incidence was recorded in North America and Africa [1–3]. It has been found that 21,000 new cases of gastric cancer were diagnosed in the United States in 2010, where 50% of those diagnosed individuals died from the disease [4,5]. Gastric cancer is the third most frequently diagnosed cancer and the second leading cause of cancer deaths in Japan, with an estimated 102,040 new cases and 50,156 cancer deaths in 2008 [6]. In Brazil, Gastric cancer is the fourth most common cancer among men and sixth among women [7]. In 2013, gastric cancer accounts for 840,953 deaths globally for both sexes [8]. Evidence from ecological, case-control, and cohort studies have strongly suggested that the risk of gastric cancer is related with several factors; some are genetics, while other factors are related to the environment and life style; there are also geographic and ethnic differences in incidence of gastric cancer, all these factors showed good association with gastric cancer [1,9,10].

With this said, gastric cancer could be prevented by at least controlling the environmental factors and life style which seem to represent important factors in developing gastric cancer, and have a significant role in the diseases prevention [11–18]. However, it is still not clear which factor has the strongest impact on gastric cancer, and how those factors “together” can control the development of the disease. Therefore, this chapter is devoted to present the environmental factors that could have acute and chronic impact on developing gastric cancer; and present in, the studies that showed the role of those factors in controlling gastric cancer. This chapter sheds light on the gaps in this issue to guide researchers for further studies in this field to understanding the most important environmental factor(s) that play a strong role in gastric cancer onset and development. This will help in developing strategies whereby gastric cancer can be highly reduced.

GASTRIC CARCINOGENESIS

Gastric cancer has been considered a single heterogeneous disease with several epidemiologic and histopathologic characteristics [19–21]. Three subtypes of gastric cancer have been identified based on histopathologic and anatomic criteria, these are proximal, diffuse, and distal gastric cancer. These types showed a complex interaction between genetics, lifestyle and environmental factors [20,22,23]. There is a suggestion that the proximal gastric tumors have a worse prognosis, stage by stage compared with distal tumors [24]. Studies have shown that the onset of gastric cancer is strongly related to the chronic and acute gastritis which is not treated or controlled, and that the environmental factors are the main cause of gastritis. However, the most important and well-studied risk factor related gastritis which could develop to cancer is *Helicobacter pylori* (*H.Pylori*) infection [25–27]. This might interact or and be impacted by the environmental (e.g. smoking and occupational exposure) and nutritional factors [17,28–31]. Further studies are needed to understand the regional/type differences in gastric cancer onset related genetics and environmental factors.

ACUTE AND CHRONIC GASTRITIS

Gastritis is an inflammation, irritation or erosion of the lining of the stomach. Gastritis could be associated with some symptoms such as vomiting, pain, feel of fullness, dark stool; but in many cases people don't have any symptoms. Gastritis can occur suddenly (Acute), or gradually (chronic). Several factors can cause gastritis including alcohol consumption, bile reflux, long term use of certain medication (e.g. Ibuprofen and Aspirin), certain illness and viral infection (e.g. *H. Pylori*) [10,32–34]. However, factors including diet habit and lifestyle are found to play an important role in worsening or treatment of gastritis [10,35]. And because gastritis could be developed to gastric cancer [36,37], it is very critical to avoid the factors that can lead to gastritis including limit the consumptions of alcohol, tobacco, spicy food, fried and acidic food and reduce stress; and consume some specific herbs (e.g. berberine and clove), fruit, vegetables and green tea. However, it remains unclear which constituents in the fruit and vegetable play a significant role in the prevention of gastritis and thus gastric cancer. This subject is critical and need more studies. Identifying the strongest constituent in the food that can make change/treat the early

stages of gastritis is very critical to avoid the development of gastric cancer which will make a significant advance in this field.

The development of gastric cancer could highly be impacted by the additive influences of the risk factors; risk factors could have different effects on the onset and the evolution of gastric cancer. Therefore, studies are needed to understand how these factors work “individually and together” to develop gastric cancer. That way, information about the most important factors “together” that can accelerate the risk of gastric cancer could be disseminated for further studies and outreach.

ENVIRONMENTAL RISK FACTORS

The environmental factors and the exposure to high level of carcinogens have been found to be a strong factor in developing gastric cancer [8,16,38]. However, the onset and the evolution of gastric cancer could be impacted by several risk factors with almost an additive effect of these factors. Moreover, some factors could play a major role in this process; however, this information is still missing, along with the limited treatment options, make gastric cancer still represents the major health problem worldwide. To date, it is not clear how the exposure to the well-defined risk factors including tobacco use, diet, environmental and occupational exposure contribute to the onset and the development of the gastric cancer. It seems that the exposure to each risk factor could contribute distinctly to the development of gastric cancer and that each risk factor could trigger a specific toxicity pathway that contributes to the onset and the evolution of the cancer. Despite the efforts that have been made to understand the most important factor or contributor to gastric cancer, it has become more clear that gastric cancer just like other cancers, evolves through a complicated web of multiple causes; and that is not only pointless but also counterproductive, to assign certain exposures a certain role in causing cancer. It is however, cleared from scientific research that the preventable environmental and the occupational exposures are very critical and fueling excess cancer cases and deaths.

Figure 1 shows that the exposure routs to different factors during the life time, and how they interact to contribute “in general” to cancer. The term exposome comprises every exposure [39]. Three main categories of exposures/factors should be considered when study the risk factors that controlling gastric cancer; these are *internal factors* (ex. Metabolism, endogenous circulating hormones, body morphology, physical activity, gut microbiota, inflammation, and aging), *specific external* (ex. radiation, infections, chemical contaminants/ pollutants, diet, lifestyle factors (e.g., tobacco, alcohol) and *general external factors* (ex. social capital, education, financial status, psychological stress, urban-rural environment and climate)[39]. However, the interaction between these factors, make it difficult to make decision on which factor could be the major cause of gastric cancer. Therefore, future studies should focus on the major risk factors based geographic and ethnic or a specific-major risk factor population, taking into account other factors that might interact with this factor and have additive and /or synergistic effect. There might be a factor(s) that have an antagonistic effect that could give valuable information to treat

and reduce the incidence of disease. However, at this point, the only effective means of reducing the incidence and mortality of gastric cancer is to prevent the risk factors. Here in this section, the major *preventable environmental risk factors* are presented referring to the studies that have been done before, and shedding light on the gaps in this regard.

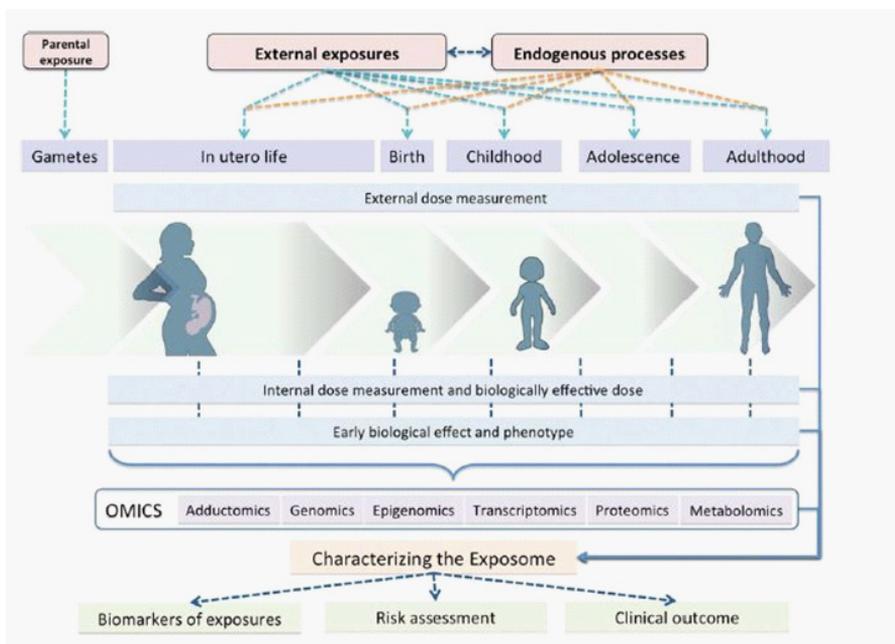


Figure1: Characterizing the exposome. The exposome comprises every exposure to which an individual is subjected over a lifetime. Exposures arise from two broad categories: external and internal sources. The external exposures include different environmental and lifestyle factors (e.g., chemicals, infectious agents, diet, tobacco, alcohol), and the internal exposures include endogenous processes (e.g., metabolism, hormones, inflammation, gut microflora) [39].

Preventable Risk Factors

Diet

Differences in diet have been shown to be an important factor in explaining variation in gastric cancer. Evidence suggested that high salt intake or salted food increase the risk of gastric carcinogenesis (Figure 2). A high salt concentration in stomach destroys the mucosal barrier which could contribute to inflammation and damage (i.e. diffuse erosion and degradation); it is therefore, plausible that high salt intake increases the risk of gastric cancer in humans [37,40–42]. Dietary sources of N-nitroso compounds such as preserved and smoked food are also associated with gastric cancer [43,44]. In addition, pickled food or dried fish and meat increase the risk of developing gastric cancer [10,19]. High consumption of refined carbohydrates, saturated fat and cholesterol have also enhanced the risk of cancer for intestinal type gastric cancer [45,46]. Moreover, data obtained from 21 studies involving a total of 1,652,231 individuals, followed for

period ranging between 3.3 to 25 years showed significant increase in risk cancer associated with high intake of total carbohydrates, salted fish, processed meat, refined grains and saturated fat [47].

However, the risk of the consumption of food that implicated in developing gastric cancer increase when an interaction with other factors occurs [48]. As there are foods that contribute to gastric cancer, other type of food showed inverse association with gastric cancer such as green tea, fruit and vegetables; the positive effect of the fresh fruit and vegetables on the mucosa of gastrointestinal tract is due mainly to the antioxidant properties of the micronutrients [31,49]. Onion, red grapes, nuts and green tea were found to have an ability to reduce gastric cancer incidence in population studies, which shown to be likely due to their ability to induce apoptosis and inhibit neoangio genesis [50–53]. Moreover, components in other food such as oleocanthal in olive oil, and polyphenol in apple were found to play a vital role in inhibit the biological process that lead to gastric cancer [54,55]. Owing to the reactive compounds/constituents that are found in the food and contributed to the evolution or the reduction of gastric cancer, it is very critical to identify the most important constituents-based food which can inhibit the toxicity pathways that contribute to gastric cancer development. This could be based on studies devoted to extract the “good” and “bad” compounds and determine how they might interact when they come together? What is the impact of these constituents-based food on the major toxicity pathways-related gastric cancer development? When people consume the “good” food, what kind of food has a strong impact than others which can give notable change in the biological pathways-related cancer? It is also critical to identify the harmful food that has a strong effect in triggering the toxicity pathways-related gastric cancer. These findings will help in framing the strategy whereby the treatment of gastric cancer can be easier and faster, especially in the early stages of gastric cancer development.

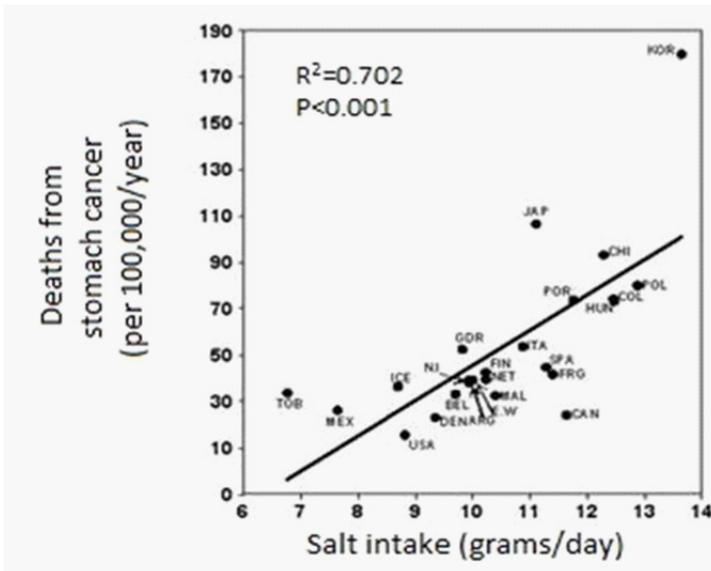


Figure 2: Salt and stomach cancer [41].

HELICOBACTER PYLORI INFECTION (H. PYLORI)

H. Pylori infection is the most important etiological factor implicated in gastric carcinogenesis. *H. pylori* (also called *Campylobacter pyloridis*) was first identified in humans and cultured by Marshall and Warren a microaerophilic [56]; it is gram-negative bacterium, spiral-shaped with several polar flagella for mobility whose presence in the gastric environment is correlated with diseases such as gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue lymphoma, and gastric adeno carcinoma [57]. Although, *H. Pylori* has been classified by the International Agency Research on Cancer as group 1 human carcinogen [58]; however, most people infected with *H. Pylori* never develop ulcer related gastric cancer for unknown reasons [59]; the presence of *H. Pylori* is a common infection, but, it seems that the development of *H. Pylori* is other risk factors sensitive [60,61]. *H. Pylori* reside under micro aerobic conditions at a peri plasmic pH of 4.0-8.5, and grow at a peri plasmic pH of 6.0-8.5 (in a neutral microenvironment) between the mucus and the superficial epithelium of the stomach. *H. Pylori* stimulates cytokine production by epithelial cells that recruit immune and inflammatory cells [62]. The extent and severity of gastric mucosal inflammation, and the clinical outcome of the infection, depend on a number of factors including the virulence of the bacterium, host genetic susceptibility, immune response, age of initial infection and the exposure to toxicants in the environment “environmental pollutants” [62,63]. However, to date, *H. Pylori* is the only bacterium that recognized as a carcinogen; therefore, a significant research has been conducted to identify the bacterial factors and the toxicity pathways that are responsible for the progression to more severe disease status [64–66]. There are two main virulence factors are implicated in the progression and the severity of gastric cancer, these are Cytotoxin-Associated Gene A (**CagA**) and Vacuolating Cytotoxin A (**VacA**) which are injected and secreted by *H. Pylori*, respectively [67,68]. CagA, after injection, found to act directly in an unphosphorylated state to impact the cellular tight junction [69], cellular polarity [70], cellular proliferation and differentiation [71], cell scattering and induction of the inflammatory responses [72,73]. VacA, is another important factor, once secreted, VacA undergoes proteolytic cleavage to yield two smaller products, p33 and p55. However, the consequence of this cleavage is not understood [74]; moreover, VacA found to dissociate upon exposure to non-neutral environment (alkaline or acidic conditions) [75]. Also CagA and VacA toxins found to interact with each other and contribute to the severity of disease [76]. However, cagA was identified as a stronger risk than other factors and a marker for gastric cancer [77,78].

A large population based case-control study from Los Angeles County, has shown that the CagA-positive strain is related to intestinal type of gastric cancer [79]; in addition, pooled data showed that *H. pylori*-CagA positive strains are associated with gastric cancer [80]. In order to understand the environment in which the *H. Pylori* can be active or un-active, *H. pylori* activity in different environmental factors including pH, kind of food consumed, age, the consumption of alcohol, tobacco smoking and the exposure to toxicants, should be tested in all stages of *H. pylori*-based gastric cancer development. Although, excess intake of salt was found to be related to the

development of *H. pylori*, studies showed that increase the concentration of salt could inhibit the activity of *H. pylori* and affect the expression of a large number of genes due to changing environment-based osmotic stress. However, stressing bacteria could have negative impact on the diseases and might make the bacteria more aggressive; for this reason, careful is needed when *H. pylori* is treated in different environments, considering other risk factors [81, 82].

ALCOHOL CONSUMPTION AND TOBACCO SMOKING

Several experimental and epidemiological studies have linked the alcohol consumption and cigarette smoking to gastric cancer [20,83–86]; however, the effect of these factors in developing gastric cancer remains not clear. Alcohol is a gastric irritant, and can have harmful effect leads to gastritis which might contribute to gastric cancer taking into account other risk factors that might help in elevating the risk [87–89]. In addition, studies showed that alcohol should be consumed in a high quantity and for several days to have harmful effect [90]. However, other study showed that even at low level, alcohol can be harmful since it induces apoptosis and increase the expression of alcohol dehydrogenase of the gastric adenocarcinoma cell lines [91]. Other studies have also showed that alcohol consumption increase the expression of alcohol dehydrogenase, aldehyde dehydrogenase, cytochrome P450, and induce the production of reactive oxygen species and nitrogen species, the mechanisms by which alcohol consumption exerts its carcinogenic effect [36,92–94]. The metabolism of ethanol leads to the generation of Acetaldehyde (**AA**) and free radicals. Acetaldehyde is predominantly responsible for alcohol associated carcinogenesis; acetaldehyde is carcinogenic and mutagenic, binds to DNA and proteins, destructs folate and results in secondary hyper proliferation; acetaldehyde is also produced by tissue alcohol hydrogenases, cytochrome P 4502E1 and through bacterial oxidative metabolism in the upper and lower gastrointestinal tract [90,93,95]. Figure 3 shows the metabolism of alcohol, and how it contributes to cancer [93].

The risk of alcohol consumption in developing cancer is elevated when it combined with tobacco smoking; smoking changes the oral bacterial flora, also increases acetaldehyde. The association between tobacco smoking and gastric cancer has been investigated and confirmed by several studies [96–99], tobacco smoke has been found to have more than 5000 chemical compounds, of which about 93 compounds including PAHs, carbonyls, tobacco specific nitrosamines (e.g. NNN and NNK) and toxic metals, have been identified as harmful and potentially harmful compounds, and most of which are implicated in development of several kinds of cancers due to the activation of the toxicity pathways that lead to these cancers [86,100–103]. Recent study has shown association between hookah use and gastric cancer [104]. Thus, smokers are considered to have higher incidence of *H. pylori* infection compared to non-smokers [105].

The question now is, for how long we expect someone who drinks alcohol could have gastric cancer? And can we assess/predict the risk of alcohol consumption in developing cancer? And after how many years smokers could have cancer, considering the age and other risk factors? Also

how the gastric cancer incidence can be developed if tobacco smoking compounded with alcohol consumption? And can we use the biomarkers of alcohol drinking and tobacco smoking to clarify this issue?

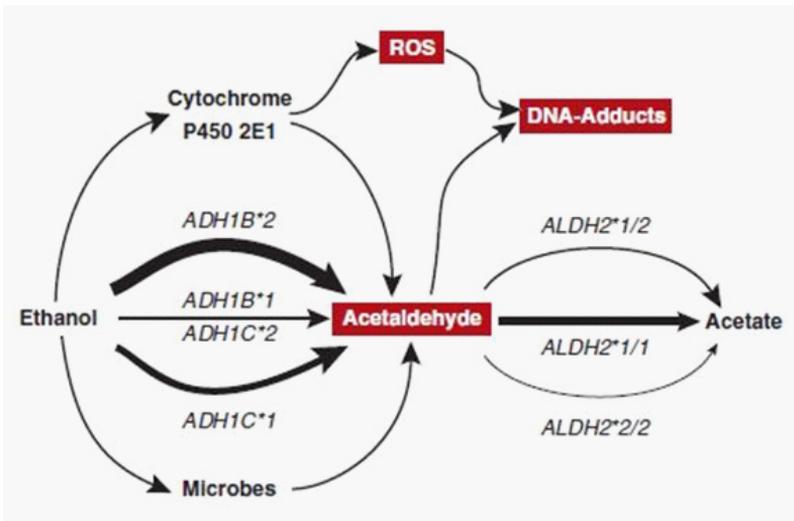


Figure 3: Pathways of ethanol metabolism and their role in carcinogenesis; Ethanol is oxidized to acetaldehyde through the actions of various Alcohol Dehydrogenase (ADH) enzymes (e.g., enzymes encoded by the ADH1B and ADH1C genes), through the microsomal enzyme Cytochrome P450 2E1 (CYP2E1), and by microbes living in the human gastrointestinal tract (e.g., mouth and colon). The relative contributions of these pathways and the differences in activity between enzymes encoded by different ADH1B and ADH1C alleles is represented by the thickness of the arrows. Acetaldehyde is oxidized to acetate primarily by the enzyme Aldehyde Dehydrogenase 2 (ALDH2). Again, the thickness of the arrows indicates the rate of acetaldehyde oxidation in people carrying two active ALDH2*1 alleles, one active ALDH2*1 and one inactive ALDH2*2 allele, or two inactive ALDH2*2 alleles respectively. Cancer-inducing substances (i.e., carcinogens) generated during the various pathways of alcohol metabolism are highlighted. These include acetaldehyde; highly reactive, oxygen-containing compounds (Reactive Oxygen Species [ROS]) generated by CYP2E1; and adducts formed by the interactions of acetaldehyde or ROS with DNA [93].

EXPOSURE TO TOXICANTS AND RADIATION

It has been found that the environmental exposure to toxicants is more important as a risk factor than genetic factor in developing gastric cancer [20,106]. Although the contribution of toxicants in the gastric cancer is not well understood in terms of the interaction with other risk factors (*H. Pylori*, salty food, smoked food.. etc), chronic inflammation and the increase of reactive oxygen and nitrogen production are the dominant reason of gastric cancer onset and development by destroying the DNA of the cells and triggering the gene expression [107–110]. Three types of exposures to toxicant were highlighted in relation to gastric cancer; these are organic compounds,

toxic metals and radiation [15,111–113]. Moreover, Local exposure to toxicants such as workers in coal, rubber and metal industries seem to have higher risk of gastric cancer [13,114,115]. Most of these finding are from meta-analysis and statistical models; while the implication of the environmental toxicants in gastric cancer needs an experimental analysis using *in vitro* and *in vivo* studies, in addition to the biomarkers of toxicants-related gastric cancer. The mechanisms by which the toxicants can trigger gastric cancer are explained (just like other cancers),by the activation of toxicity pathways (e.g. oxidative stress, genotoxicity and inflammation), and that these pathways contribute to cancer. However, several environmental studies used the simulated gastric fluid to understand the bioavailable fractions of these toxicants [116,117], recent study used the bioavailable toxic metals in stomach fluid to assess the risk of cancer after a specific time of exposure [118]. These kinds of studies are powerful to examine whether an occupational or environmental exposure to organics and toxic metals might or might not contribute to cancer, considering several risk factors which could highly impact the results. However, there are specific toxic metals (e.g. As and Cr) and organic compounds (e.g. Benzo a-Pyrene) are implicated in developing cancer [15,119,120].

Early detection of gastric cancer is an important issue to avoid the development of the disease, which can be treated by surgery. However, several studies have been done to identify the gastric cancer at early stages or to predict the possibility of developing the disease; some used statistical models-based-levels of carcinogenesis [118,121], while others used the biomarkers related gastric cancer [122–124].

Radiation is another preventable factor; however, the result of the exposure to radiation takes a long time for chronic exposure, and the time might be reduced if the dose of exposure is high. Recent study showed that the radiation to the stomach had a dose-response association with higher risk of gastric cancer [125]. It is known that the time of exposure and the dose of radiation are two important factors by which the risk of cancer can be detected/ identified; however, little studies have been done in this regards, and more studies are needed to understand at which dose and what time the cancer could appear?

Last but not least, one approach could contribute significantly to gastric cancer prevention is by the determination of people at high risk, and then monthly/annually screening programs are applied especially for people with infection, work/live in a highly polluted area with carcinogens, have high body mass, alcohol users, tobacco smokers and/or have family history of gastric cancer; and an aggressive screening programs may be recommended for people based on the number of risk factors they exposed to [22].

INTERACTION WITH NON-PREVENTABLE RISK FACTORS

There are other important factors could interact with the preventable/ environmental factors which could worsen the diseases and contribute to the development of gastric cancer; these are mainly genetic factors, sex and age [22,84,106]. It was found that the incidence of gastric cancer increase with age [126]; and that man is more susceptible to the disease than women [127].

Regarding genetic factor, it was shown that only 1% to 3% of gastric cancer cases arise as a result of inherited syndrome [106]. However, the interaction of these factors with the environmental risk factors “discussed above” can magnify the risk and the incidence of gastric cancer. Therefore, the non-preventable factors should always be taken into account when study the onset and the development of gastric cancer to understand how these factors interact and maximize the effect of the environmental factors.

CONCLUSION AND RECOMMENDATIONS

Gastric cancer is a multifactorial disease, and there is a variety of environmental, infectious, and host-related factors that may interact favoring the development of the disease; some worthy of mention is the environmental factors which showed stronger implication in the development of gastric cancer compared to other non-preventable factors (e.g. genetic factors). Despite the decline in stomach cancer in many parts of the world, the non-cardia type of gastric cancer is the most type that was found to decrease compared to cardia type. It is believed that this is largely due to factors associated with the use of refrigerated foods, the availability of fresh vegetables and fruits and the decrease of using salt as a food preserver “the main risk factors implicated in the non-cardia type of gastric cancer”. However, the cardia type of gastric cancer showed arising in the last four decades, which could highly attributed to the increase in the populations with high body mass “a strong risk factor of cardia type of gastric cancer”. Meaning, food that we consume every day can either inhibit or induce gastric cancer. In addition, several environmental exposures have already been identified as risk factors for gastric cancer including smoking, bacterial infections and a variety of occupational exposures, which are identified to be a stronger risk factors compared to genetic factors. More studies are needed to understand the impact of each individual environmental risk factor related gastric cancer incidence, and how each factor interact with other factors, and which factors are more important. It is important to understand the relation between these factors with other non-preventable factors such as age, sex and genetic factors; for example, why men are more susceptible than women, is that related to other specific factors might be found in men and not women? The next adventure is to understand the nature and the nurture related gastric cancer, and how the risk factors together contribute to the onset and the development of this lethal cancer.

Screening is shown to be a vital approach to detect gastric cancer at its early stages. However, it has been found that the type and the incidence of gastric cancer are region-dependent and that there are significant regional differences in gastric cancer onset and development. This could be attributed to the differences in environmental factors such as nutrition, smoking and occupational exposure. Therefore, people/population with high incidence of gastric cancer may apply aggressive screening programs to prevent and to avoid the progression of the disease. And populations with low incidence of cancer may still need to use screening programs to avoid the disease.

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