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Insights Concerning Gender-Related Gastric Cancer Differences - 2018

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Abstract

The human stomach receives several metric tons of food in a person's life. During every gastric digestion cycle, the residence time of solid food in the stomach varies from 30 min to 4 hours. Food particles undergo hydrodynamic mixing, mechanical disintegration, enzyme/acid chemical attack and partial degradation, thereby releasing thoroughly nutrients and other chemicals. During gastric residence, nano- and micromolar concentrations of food/beverage genotoxins, if present, may overcome the gastric mucus protection and enter into direct contact with epithelial cells, particularly in cases of atrophic gastritis, pathological or aging-related achlorhydria and advanced *Helicobacter pylori* (Hp) infection, thus increasing the risk of developing gastric cancer (GC). Frequent intake of high-risk foods and beverages maintains a continuous flow and exposure of gastrointestinal tissues to harmful materials, as indicated by the environmental association of certain GC types with diet. Individuals respond differently to procarcinogenic aggression, according to a variety of determinants, among which gender is prominent. Thus, GC incidence among adult males is 1.5 – 2 times greater than females in most countries. Reasons for this disparity are not fully understood. This review focuses on epidemiological and cohort studies aimed at solving this long-standing question, by examining differences in consumption habits between males and females. Alcohol beverages in combination with Hp prevalence and impaction in both genders is emphasized, as well as gender-dependent differences in response to Hp eradication and aging. Recent advances in sex hormone involvement in the genesis of, or protection against, the development of GC are discussed.

Keywords: Gastric cancer; Gender; Alcohol abuse; *Helicobacter pylori*; Sex hormones; Estrogen receptors; Progesterone receptors; Epidemiology

Introduction

During the average lifetime of a healthy, normal person, the amount of edible solids processed by the gastrointestinal system is in the range of 40 to 60 metric tons, in addition to about two- thirds that weight of liquids. These victuals carry countless organic, inorganic, and biochemical compounds, either natural or transformed during processing and cooking. In addition, there are about 2500 food additives and another 12 000 substances unintentionally entering the food chain via environmental contamination [1]. A number of these compounds are potentially free radical chain initiators, they can be mutagenic and genotoxic and/or cause epigenetic alterations (e.g. aberrant DNA methylation/oxidation, DNA fragmentation, histone modification). Free radicals also elicit transcriptome responses also with possible impacts on the genesis of cancer [2]. Crosstalk between food genotoxins acting as agonists, synergists or antagonists is an increasing possibility in the tumorigenesis of digestive organs [3].

Despite the protective shield provided by the mucus lining the gastric epithelium, the stomach is especially vulnerable to food toxins because their stationary residence time in this organ is significantly longer than their transit time through the esophagus, small and large intestines unless undue retentions occur. Exceptions are the mouth to some degree during mastication or food residues remaining there, and the sigmoid-rectal region where feces accumulate for several hours or even days during episodes of constipation. Prolonged contact with DNA-reactive and ROS products from food and beverages contributes to the long established influences of diet on gastric cancer (GC) prevention and genesis [1,4,5] and the various responses to diet influenced by genetic variations among consumers [6].

Overall, it is not surprising that GC is one of the most frequent and high mortality malignancies in the world today, despite the vast number of studies devoted to understanding its pathology, molecular biology and etiology [7-12]. Globally, GC incidence ranks fifth among the most frequent cancers, but this ranking depends on several factors. The socioeconomic and educational status measured by the United Nations Human Development Index (HDI), prominently influences the incidence pattern of most frequent cancers (Figure 1) [13,14]. A country's HDI takes into account life quality of citizens according to the combined effect of life expectancy at birth, years of schooling, and gross national income. Four levels result from this assessment, very high (VHHD), high (HHD), medium (MHD) and low (LHD) human development indexes. These four levels share public life in most countries but their proportions vary within and between nations.

Paradoxically, the incidence of breast, prostate, colo-rectal and lung cancers is particularly severe and much higher in VHHD and HHD groups than lower HD societies. This trend also occurs in GC in which low HD nations appear less affected relative to higher HD

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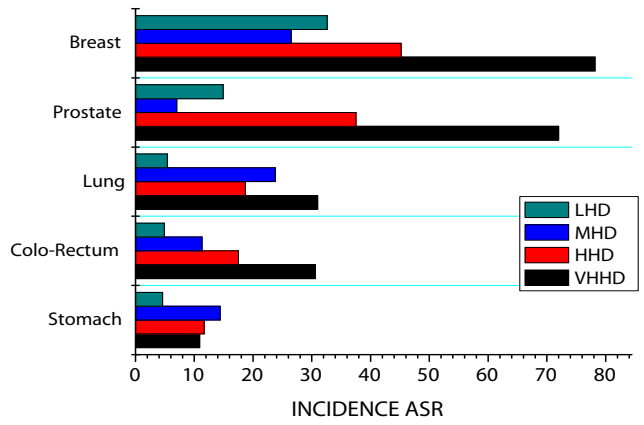

Figure 1: World age-adjusted incidence rates of major cancers in 2012 in relation to the Human Development Index devised by the United Nations Development Program [14]: VHHD, Very high human development; HHD, high human development; MHHD, medium-high human development; LHD, low human development. Data combined from [13] and [14].

groups. Results at country level may not convey the actual situation of specific communities within the same country or state. A striking example is the inordinately high age-adjusted mortality ratios of various cancer types among Australian aborigines, a presumably LHD group, compared with the average population of New South Wales State (NSW), which ranks 2nd in the world as a VHHD group [15]. Stomach cancer among Aboriginal males was more than twice that of the NSW population. Also in some mountain districts of the Venezuelan Andes, GC is the first cause of cancer-derived mortality in males and the ASMRs are among the highest in the South American continent [16]. By contrast, GC is the fifth frequent malignancy in the rest of the country.

The global appraisal depicted in Figure 1 suggests that the current lifestyle habits and the associated environmental factors that result in HDI status strongly influence the cancer outcomes. Encouraging healthier habits in the population should have a positive impact on reducing the cancer trends in the future. However, cancer incidence rates in local human groups call for additional control strategies.

GC is an intricate heterogeneous, multistep and multifactorial malignancy of greater molecular complexity in the genetic and epigenetic landscapes than previously anticipated [17-19]. Advances in the understanding of GC need frequent updates as a stream of molecular breakthroughs, early detection technologies, surgical methods, adjuvant and neoadjuvant therapies together with a stream of antineoplastic compounds, become accessible to oncologists [20]. This is a taxing endeavor. In the last 20 years a collection of over 40 thousand articles devoted to GC in the Web of Science database (keys: gastric cancer, science journals) have been published, 4103 in 2017 alone and growing. Nearly 11 000 entries deal with cell molecular mechanisms, over 4000 are review articles and 243 contend with protective measures, including prevention through lifestyle and diet, early diagnosis, and GC deterrent strategies.

These advances are becoming steadily more available to an increasing number of citizens, either during prevention programs or to those already affected by GC. Nevertheless, the global GC burden remains high. In 2012 [13] there were 952.000 cases and 723.000 deaths (i.e. 76% of cases worldwide), giving a clear indication of GC lethality. Also in less developed countries, GC can be the primary cause of cancer-related deaths among males and the third most common among females after tumors of breast and cervix-endometrium.

GC incidence is declining in economically advanced countries of Asia and the West as a result of better food quality and preservation without salting [11,21,22], advanced early diagnostics technologies applied over an expanding number of people [23,24], extensive surveys, and eradication therapies for *Helicobacter pylori* (Hp) [25,26]. Results vary widely, however. For example, Korea, a highly industrialized country, maintained high GC incidence rates until recently when a decrease from 41.2 - 44.4 per 100 000 (1999–2011) to 35.8 in 2014 was recorded [27].

Other less developed countries such as a few in Central and South America also report declining GC incidence per year, most notably Costa Rica [males/females (%)], -4.4/-3.5; Chile, -4.2/-3.4; Brazil, -3.9/-2.2 during 1998-2007 [28]. Mortality rates improved among males but not females in this geographical area for reasons not well established. The gross statistical records, therefore, do not depict an accurate portrayal of the GC status since most registries in developing countries do not differentiate between GC types. While in some parts of the world non-cardia intestinal-type neoplasias are clearly declining in parallel with better control of Hp infection, cardia and corpus cancer rates are increasing because these cancer types respond to different etiologies [29]. Unfortunately, other regions of the world and many small socioeconomically deprived communities still endure undue incidence and mortality figures [30].

GC offers many challenges and unsolved issues. At the onset, comparison between GC epidemiology studies is only possible on very basic grounds as few of these account for specific cancer types among the variety of accepted cancer classifications, be these morphological, clinical, pathological, or molecular [19,31,32]. Most studies scrutinize GC cases without further description, while detailed cancer registries in some countries do provide more precise data, but frequently only on a fraction of the country's population. It is the classical histological GC landscape of intestinal and diffuse types as well as distal, proximal, or cardia and non-cardia cancers at the gastroesophageal junction, which configures different cause-effect relationships, profiles of people at risk, therapies and their outcomes, and long-term trends [33,34]. Compared with the decrease of distal cancer incidence in most industrial societies, tumors in the proximal gastric area are increasingly frequent, and clinical symptoms appear at a younger age, [35,36]. More than 90% of gastric malignancies are adenocarcinomas of the chronically inflamed and atrophic gastric epithelium, in which several cytokines are involved [37-38]. The GC scenario is also compounded by poorly understood carcinoid neuroendocrine tumors, rare as they are at present but increasing in incidence [39,40]. Gastric neuroendocrine tumors may also occur in the upper duodenal epithelium as well as duodenal gastrinomas that are possibly linked to gastro-duodenal Hp infection but are not yet satisfactorily understood [41]. These and other knowledge gaps are enticing opportunities for new avenues of research and in need of renewed paradigms applicable to GC.

Prominent among these obscure issues are the lack of explanations for differences in age-adjusted incidence rates (ASR) between males

and females, and the precise food chemistry and molecular biology beyond the very basic free radical suppression and moderate anti-inflammatory effects. The protective value of fruits, vegetables, and some spices is largely based on these grounds but their explicit impact on the accepted hallmarks of cancer, whether descriptive, genetic, epigenetic, metabolic or otherwise remains largely incomplete [42-45]. Curcumin, the active component of turmeric, is a most notable exception. This phenolic derivative of ferulic acid shows activity against cancer cell proliferation, tumor growth, metastasis, angiogenesis and disruption of malignant cell metabolism at the low microgram L^{-1} level, in addition to its anti-inflammatory and antioxidant effects [46-49]. Current research focuses on the antitumor activity of curcumin and synthetic analogs in gastric malignancies both *in vitro* and *in vivo* models [50,51]. In addition to inhibiting free radical oxygen species (ROS), other natural products in food (nutraceuticals) modulate or restrain a series of transcription factors and signaling cascades including STAT-3, AP-1, NF-κB, NRF2, Hedgehog, PPARγ, HIF and β-catenin/wnt pathways which are involved in chronic inflammation and cancer [4,52]. Resveratrol and anthocyanin pigments seem to follow similar patterns.

Edible and medicinal plants with anticancer potential known through folk healing traditions and advances in molecular networks are currently more developed in the diet–colon cancer relationship than in the GC arena [53]. This review updates progress up to March 2018 in GC epidemiological studies, particularly those exploring the great differences in GC ASR between men and women. Issues about the carcinogenicity of alcohol beverage consumption patterns and in combination with Hp infection, as well as sex hormone involvement are emphasized.

Gender Contrasts in GC and Other Major Diseases

Relative to females, age-adjusted mortality rates (ASMR) for men are 43% greater for the principal 15 causes of death, including the major cancers. Similarly, the male/female malignant neoplasms ASMR ratio is 1.5 in the United States [54,55]. These events suggest important biological differences between sexes in the response to disease [56]. Most women react with stronger immune and inflammatory reactions than men, partly through the enhanced influence of effector glucocorticoid hormones [57], cell autophagy [58], and other cell mechanism disparities [59].

Early epidemiological studies revealed even more dramatic differences in the number of GC cases between males and females. These disparities persist to this day despite profound changes in lifestyle, food habits and the relative affluence of the general population over the past several decades, the growing strengthening of the female fraction of the working force, the enhancement of their relative economic independence and impacts on living conditions. Global figures for 2012 show that males were nearly twice more affected by GC (631.000 new cases, 66%) than females (320.000 new cases, 34%). Similar figures are recorded for 5-year failed recovery after undergoing GC tumor surgical resection (male deaths: 469.000, 65%; females: 254.000; 35%) [13]. However, GC death rates relative to incidence were similar in both sexes, suggesting that gender differences influence GC before or during very early malignant events. As generally recorded for both sexes, female GC is age-related

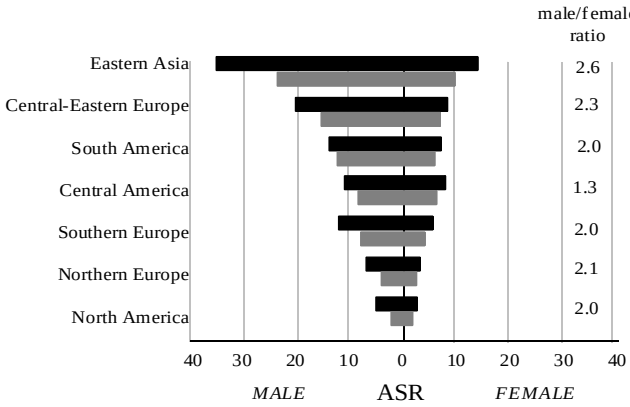

Figure 2: Age-standardized incidence rates (ASR) of gastric cancer in males and females (black bars), mortality (gray bars) and male/female ratios in selected regions of the world. Data from [13].

with 85% of deaths occurring in the 55-85+ age group.

Analogous cancer incidence male/female disparities are also recorded for neoplasms of the esophagus, with more than twice the 5-year prevalence figures among males than females. General GC ASMR male to female ratios in the 1.5–2.8 range are also observed in other regions of the industrialized and developing world [28,60]. Figure 2 illustrates these gender differences in GC rates in selected countries.

Three contrasting points stand out from Figure 2 plot: 1) Incidence and mortality rates are much higher for males everywhere, independently of GC total rates. 2) Gender differences are more pronounced in Eastern Asia, East-central Europe, and Southern Europe. 3) GC rates vary geographically, implying a gamut of etiological factors prominently related to environmental influences, be these food habits, infection patterns, natural or man-made chemicals or a combination of these, in addition to genetic implications of racial or ethnic types.

These broad-spectrum features suggest that females appear less exposed than males to GC risk factors or are protected by peculiar characteristics of their gender and/or dissimilar living habits from males in many societal groups across the world, considering that one third of common cancers are related to lifestyle [61,62], including GC [63]. Gender-specific daily habits either in a single family or in a community may be different enough, e.g. individual diet, alcohol consumption, leisure time exercise, to significantly influence cancer outcomes [64,65]. Gender-specific responses to alimentary aggression and sex hormone disparities may be summarized as follows:

- Does the apparent protection of females emerge from a distinctively greater prevalence of frequent and heavy drinking among men than women?
- Does binge alcohol drinking enhance the Hp insult to the gastric epithelium and thus create better conditions for developing carcinomas?
- Is the female stomach more susceptible to Hp pathological outcomes than that of males?
- Do female sex hormones play a role in delaying

tumorigenesis?

- Is this the result of a distinct natural physiological condition, susceptibility or a response of the upper alimentary tract to carcinogenic chemicals in foods and beverages?

With these questions in mind, the following issues are reviewed.

Alcohol Abuse and GC

Alcohol consumption patterns among men and women differ more or less universally, although drinking habits vary from one place to another and are currently on the increase for both sexes in some countries. The disparity in long-time drinking prototypes may be associated with gender-related pathology outcomes including cancer of digestive organs.

Excess alcohol exposure on the gastrointestinal function

The impact of alcohol consumption on gastrointestinal (GI) dysfunction has been studied for a long time [66,67]. Among other effects, superficial and chronic gastritis and mucosal hemorrhagic damage occur in heavy drinkers; there is a loss of mucosal integrity, microbial overgrowth, and dysbiosis. Alcohol impact may progress to liver dysfunction via endotoxin leakage through the gastric epithelium and portal transport [68]. Although the molecular mechanisms are not yet completely understood, there is evidence that heavy alcohol consumption creates conditions for altering the expression of antimicrobial peptides (AMPs) formed in epithelial Paneth cells [69]. These cells are normally found in the small intestine as part of the innate immune defense but may occur also in the pyloric region in cases of gastric and intestinal-type metaplasias in precancerous and GC patients [70,71].

Ethanol in alcoholic beverages is classified by the International Agency of Research on Cancer (IARC) as Group I carcinogen to humans [72], affecting mouth, throat, esophagus, colo-rectal, liver, and breast [73]. GC was excluded at that time by IARC (2006) as epidemiological studies concerning alcohol – GC associations were not conclusive, but left the way open for further research on this subject. The current consensus is that ethanol itself is neither carcinogenic nor mutagenic, but as a chemically active compound, it is linked to a variety of cancer-related molecular events [74]. As a solvent of lower polarity than water, ethanol may operate as a carrier of lipophilic mutagens in food and beverages and enhance their bioavailability. The same solvent effect operates in the disruption of epithelial cell membranes and intercell tight junctions by coupling to membrane phospholipids via phospholipase D. As a result, membrane phosphatidylcholine, a highly polar ionic compound, is converted to the much less polar phosphatidylethanol (PPE), changing the intermolecular interaction properties and membrane functions [75]. PPE has been found in all organs and blood of human alcoholics [76] and could be a potential biomarker for preventing cancers of the GI tract. Additionally, perturbation of intracell tight junctions elicits β-catenin translocation which has been associated with the migration and invasion of colon cancer cells and may also occur during GC cell invasion and metastasis [77]. Ethanol induction of angiogenesis has been reported *in vitro* in umbilical vein endothelium and arsenic-promoted colon cancer cell tumor models [78,79].

Chronic ethanol exposure also markedly increases proinflammatory cytokines IL-1α, IL-6 and TNFα, and key chemokines in colonic mucosa [80]. Proinflammatory transcription factors leading to enhanced COX-2 and iNOS expression are induced by ethanol, which taken together engenders a chronic inflammatory, procarcinogenic framework in GI tract tissues exposed to binge and frequent heavy intakes of alcohol. While similar outcomes might be expected in the gastric mucosa, reports in this area are scant.

Alcohol contact time in gastrointestinal tract tissues

Contact effects of ethanol are compounded by gastric residence time and absorption in stomach and duodenum. Alcohol is slowly absorbed in the stomach and much faster in the small intestine [81]. The contact time of ethanol in the gastric zone is contingent upon the rate of gastric emptying. In healthy adults, emptying is estimated at 1–4 kcal/min of partially digested chime and occurs in spurts [82]. Emptying is nonetheless highly variable between individuals or even in the same person and with food nutrients [83]. High alcohol concentrations delay gastric motility, thereby extending contact time with the gastric mucosa [84]. All facts considered, the effects of ethanol contact on GI epithelia are exceedingly unpredictable. Determinant causes include nutritional composition and consistency of food being digested, age, stomach health score, post prandial glycemia and insulin levels, gastric hormonal interplay, exercise score and eating habits, including amount and frequency between meals. With so many factors at play, this creates a very complex scenario for predicting ethanol contact time in the gastric milieu and thus the extent of its damaging effects.

Ethanol and acetaldehyde

The cancer risks of heavy alcohol beverage consumption are enhanced by the enzymatic oxidation of ethanol to acetaldehyde. This compound is a type 2B carcinogen per se (possibly carcinogenic to humans) but becomes an aggressive type-1 human carcinogen when associated with consumption of alcoholic beverages [85] and a key player in gastric and oesophageal cancers [86-88]. Other cohort studies, however, could not confirm the acetaldehyde – GC association in heavy wine drinkers [89]. Acetaldehyde is known to be DNA-reactive with consequences for molecular events leading to cancers of the upper alimentary tract [90,91].

Acetaldehyde occurs naturally in alcoholic beverages at a concentration of 0.112mg/kg body weight/day at average European consumer levels. These levels of consumption increase the overall lifetime risk of developing cancers well above the risk posed by environmental substances [86]. Substantial concentrations of acetaldehyde have been detected in spirits derived from sugar cane in Guatemala and Brazil, agave liquors from Mexico, and other liquors from China and some European countries [86]. Thus, acetaldehyde in these popular alcoholic beverages may be instrumental in the high GC incidence rates recorded in these countries.

The biochemical conversion of ethanol to acetaldehyde during the human digestive process has been established [90]. Alcohol dehydrogenase (ADH)-catalyzed oxidation occurs rapidly in mouth and throat due to Candida yeasts and other species of the microbiota in the upper gastrointestinal (GI) tract of people with poor mouth hygiene. Additional oxidation takes place on account of catalase and cytochrome p450 2E1 enzymes during GI digestion. Oxidation by microsomal P450 2E1 yields reactive oxygen species (ROS) such

as hydrogen peroxide, oxygen superoxide, ethanol ($CH_3CH_2O\bullet$) and 1-hydroxyethyl radicals ($CH_3CH^{\bullet}OH$) [92,93]. These species contribute to lipid peroxidation, oxidative DNA damage and cause DNA strand breaks, according to a rat liver model *in vivo* [94,95].

Normally, acetaldehyde does not accumulate in the stomach or small intestine as it is rapidly oxidized further to acetate by aldehyde dehydrogenases, grouped under the ALDH denomination. This reaction, however, is accompanied by additional ROS formation and further potential cell damage. ALDH2 is the major enzyme in acetaldehyde oxidation. A point mutation in position 487 of this protein with the replacement of glutamate by lysine renders ALDH2 inactive. The ALDH2 genotype is stable and occurs in ethnic populations in differing proportions chiefly affecting East Asians. The incidence of GI tract cancers is especially high in this area [96]. Polymorphism of certain ALDHs strongly influences the GC risk in heavy drinkers [97]. The debate over food and drink-derived acetaldehyde as mouth-throat and stomach cancer promoter continues to this date [98].

Low, heavy and binge drinking standards

Surprisingly, there is no international consensus to define the limits of heavy and binge drinking, hence each study needs to establish its own standards. Frequently, heavy drinking consists of consuming more than 5 drinks in a single episode on more than 5 days in a single month, without reference to the type of alcoholic beverage or alcohol content in it and impact on blood concentration of ethanol. Others define binge drinking when plasma ethanol concentration surpasses 0.08g/dL [99]. This ethanol level results from more than 5 drinks in adult males and four in adult females but no reference is made to alcohol retention in the stomach or from what derivation (i.e. whether fermented, distilled or particular source). Prospective surveys and case-control studies generally ignore the plasma or breath ethanol concentration of participants, and therefore, gender-specific responses to ethanol intake have not been established in this context.

Alcohol intake, GC and gender differences

With these methodological shortcomings, notwithstanding, review and meta-analysis studies on large cohorts in China and Europe published after the 2010 IARC report give credit to the hypothesis that heavy alcohol beverage intake is indeed a GC risk factor [100-102]. These insights are re-enforced by the fact that heavy drinking is more prevalent among men than women in all countries [103], and may thus contribute to gender differences in GC incidence.

A recent meta-analysis was conducted including nearly six million participants and 22,545 GC cases from the United States, Europe, and Asia [104]. Light alcohol consumption was associated with a *lower* risk of developing GC in females relative to non-drinkers [RR=0.74 (95% confidence interval 95% CI 0.57-0.98)]. On the other hand, heavy alcohol intake for many years by people of both sexes was associated with a significantly higher risk of developing GC, regardless of country and therefore ethnicity and ethical standards. Importantly, males and females showed different sensitivity. For a maximum level of 60g of alcohol per week, overall GC incidence RR in males was 1.18 (95% CI 1.08-1.29) in comparison with non-drinkers, after adjustments for educational level, body mass index, tobacco smoking and physical activity. Meanwhile, among females the RR was 20% higher (RR=1.33 (95% CI 0.79-2.24) than males [RR = 1.13 (95% CI 1.06-1.22)]. Similar conclusions were reached from an independent meta-analysis [105]. Additionally, RR is positively associated with the amount of alcohol as shown by another cohort and 30-year follow-up study from Lithuania on 7,150 individuals [89]. Incidence GC ASRs in Lithuania (males: 33.8, females 14.4/100 K people) doubles the GC average of 27 European Union countries (males: 16.7, females 7.8/100 K people, data for 2008) [60]. In the latter study both alcohol intake and the type of beverage (beer, wine, and vodka) were accounted for. Using the consumption of 0.1–9.9 g of ethanol per week as reference, there was a dose-response alcohol - GC association in the 30-year follow-up of the cohort: RR=1.90 (95% CI 1.13–3.18) for a >100g/week consumption level, after adjustment was made for smoking, education level, body mass index, and age.

As regards to beverage type, using low volume consumption as reference (beer: <1L per occasion, wine: <0.5L, and vodka : <200g of alcohol), non-drinkers of the latter two beverages were at higher risk [RR=1.50 (95% CI 0.89–2.53) versus RR=1.22 (95% CI 0.65-2.30), respectively] while heavy drinking of wine (>0.5L/occasion) or vodka (>200g/occasion) increased the relative GC risk selectively: RR(wine)=2.95 (95% CI 1.30–6.98); RR(vodka)=1.51 (95% CI 0.52–4.36). By contrast, beer intake of 1L or more per occasion, was moderately protective: RR(beer)=0.83 (95% CI0.58–1.18). Other studies report disparate results and regard beer as a GC risk factor, whereas wine may even prevent GC development [106,107]. These conflicting reports demand further studies in several other populations and ethnicities. Both wine and beer are derivatives of natural products and their chemical composition may vary considerably.

Fewer studies have been conducted in developing countries concerning the alcohol consumption-GC connection, in spite of high gastric malignancy rates among the less privileged, and where alcohol consumption rates are also high. A case-control study on 220 GC cases with defined histology and 752 healthy controls selected from the Mexico City population reported a markedly higher risk among consumers of more than 5g per day of ethanol [age-sex-adjusted odds ratio (OR) 1.95 (95% CI 1.00-3.71)] [108]. There was a positive association between the OR and the daily uptake of distilled alcoholic beverages (tequila, brandy, rum) of up to 14g of ethanol compared with abstainers, confirming other similar reports. By contrast, one beer a day, equivalent to 13g of ethanol, the maximum dose studied, had no effect on GC OR in the study group. A much higher OR was nevertheless found for wine consumption of comparable alcohol levels of 60mL a day containing 9.6g of ethanol (no specific wine characteristics were reported); OR: 2.93 (95% CI 1.27–6.75) relative to non-wine consumers. This result (~70g/week) is in line with the impact of red wine on GC at an intake rate of 560g per week [OR: 2.61 (95% CI 1.01–6.78)] recorded in a Portuguese population [109]. Therefore, it appears that ethanol by itself does not initiate all the proneoplastic effects required for tumorigenesis unless other specific beverage constituents are present.

Paradoxically, resveratrol in red wine is reportedly protective against GC cell growth acting via cell cycle arrest, DNA antioxidant protection and potentially other mechanisms which support the healthy role of red wine as part of the Mediterranean diet [110-112]. Of special interest was the ORs for specific histological types resulting

from wine drinking; these ORs were intestinal type: 2.16 (95% CI 0.68–6.92) and diffuse type: 4.48 (95% CI 1.44–13.94), other factors being equal in this Mexican study [108]. Other dietary variables were included in the questionnaires to volunteers but no interaction between alcohol intake and consumption of fruits, vegetables, chili pepper and processed meats was observed. Unfortunately, gender responses were not accounted for.

Taken together, these investigations lead to the conclusion that females are more sensitive to developing GC insofar as heavy alcohol drinking is involved. Elsewhere, however, females are less prone to developing GC. The answer to this paradox may lie in the differences in alcohol intake levels, beverage types and constituents, and habits between male and female consumers.

Male vs. female alcohol beverage consumption

A few years ago a multinational study brought together systematic evidence to show that the higher consumption of alcohol beverages among males relative to females was a generalized problem across cultures [113]. Alcohol intake was highest in the oldest age group of men in English speaking communities from a sample of 35 countries surveyed in the period 1997-2007 [113], confirming results from the few studies published from developing countries and elsewhere [115]. Surveys show that alcohol abstainers are much more frequent among females (32.4%) than males (8.7%) in a sample of 1.464 households monitored in Sao Paulo, Brazil. Heavy drinking, three or more times a week, was recorded in 26.3% of males and only 10.9% of females [115].

However, there is evidence that the biological and psycho-social consequences of heavy alcohol consumption lead to different disorders and more medical problems in women than in men. Women develop higher blood ethanol concentrations after drinking similar doses of alcohol per kg of body weight [116]. For women younger than 50 years, a decreased activity of gastric mucosal alcohol dehydrogenase by 41% and a 42% slower alcohol gastric emptying compared with men has been reported [116,117]. Higher blood levels of alcohol may contribute to the enhanced vulnerability of women to alcohol-related diseases in a shorter time span than men, including some cancers [118]. Different rates of metabolism and sex hormones participate to an undetermined extent in the deleterious mechanisms of alcohol abuse. Alcohol-induced changes in life habits possibly related to cancer development also take place in very complex ways [119]; the problem being compounded by a contemporary increase in alcohol abuse and collective binge drinking among young women, which is predicted to exacerbate health disorders in the future, in addition to the significantly higher incidence of alcohol-linked cancers to that found in men [120].

Male versus Female Susceptibility to *Helicobacter Pylori* Gastric Insult

Hp etiology has been studied extensively and infection routes are many, including direct intrafamilial, person to person intercourse in populous or isolated communities, mother-child contact, water and food, basically from direct or indirect fecal-oral transmission [121-123]. Considering the diversity of infection vehicles, exposure risks should be similar for males and females but Hp colonization is not.

According to large population prospective studies with medium to high Hp seroprevalence measured as immunoglobulin G (IgG) response, a moderately higher fraction of middle-aged males were infected with this bacterium relative to age-matched females irrespective of the Hp prevalence in the population [124]. Among Korean adults comprising a sample of 5732 healthy and asymptomatic individuals, the male/female ratio was 1.11 (69.4% of males, 62.4% of females) [124]. Somewhat higher ratios, calculated as male/female relative risk in two age-matched 1201 healthy volunteer populations of Western Venezuela, selected among lowland and highland communities with contrasting GC death rates, were recorded in a IgG seroprevalence study ($RR_{(M/F)}$ lowlands: 1.17 95% CI 0.99-1.36, N= 601; $RR_{(M/F)}$ highlands: 1.16 95% CI 1.06-1.25, N = 600) [125].

Up to 2004, no studies had explored the differential response of males and females to Hp infection. Hp impact is customarily assessed using the Sydney System Score (SSS) grading. SSS focuses on four basic aspects: gastric *chronic inflammation* as seen by increases of lymphocytes and plasma cells in the lamina propria, neutrophil infiltration of surface epithelium and pits, *mucosal atrophy* with loss of specialized glands from antrum and corpus, and the occurrence and extension of *intestinal metaplasia*.

Using SSS, a pioneer case-control age-stratified study in search of gender response differences was conducted among Japanese patients of both sexes [126]. All participants showed benign stomach symptoms but were otherwise healthy, independently of their Hp infection status. They were distributed in groups according to Hp status: Hp(+) (574 cases) and Hp(-) (225 controls). As expected, inflammation and activity scores in the antrum were significantly higher in the Hp(+) than the Hp(-) group in both sexes of all ages between 30 and 70 years of age. Also predictably, SSS scores were undifferentiated between genders in the Hp(-) group and declined with age. Similar trends were recorded for inflammation and activity in the corpus. As regards to atrophy and intestinal metaplasia in the antrum, scores increased rapidly with age in both sexes but were more numerous and severe in men in the 50–70 years group. Of note, intestinal metaplasia followed similar trends in Hp(+) and Hp(-) elderly, postmenopausal women (>60). This feature suggested the involvement of sex hormones in protecting females against antrum intestinal metaplasia at a younger age. Supporting this tenet, the condition appeared much earlier among men (40y age group), both in antrum and corpus. Researchers also found an enhanced expression of inducible cyclooxygenase-2 (COX-2) in antrum biopsies of Hp(+) relative to Hp(-) male volunteers but there was no such response in the female groups [126]. COX-2 is expressed in inflammation and tumorigenic settings and it is induced by more than one cell signaling pathway elicited by Hp infection. It also influences the SSS outcomes. The mucosal response to Hp infection is thus gender-dependent and may contribute to an explanation of the recorded differences in GC incidence between males and females in Hp-related GC.

Augmented COX-2 expression conceals a paradox. This cyclooxygenase is the rate-limiting enzyme in the oxidation of arachidonic acid to prostaglandin E2. The prostaglandin lipid family enhances the gastric mucosal protection from irritating substances such as HCl/ethanol in heavy alcohol beverage drinkers, as well as against Hp-induced gastric preneoplasia, according to animal models [127-129]. This may constitute a feedback protective effect against the Hp negative impact but it is currently not well understood.

More recent research shows that the gastric immune response caused by Hp involves a richer series of cytokines. This depends on the pathological condition of the mucosa and varies between patients [130]. A much-expanded research and sample amplitude are needed to understand the mechanisms underlying the demonstrable gender response differences in Hp-elicited GC genesis.

Alcohol Intake and *Helicobacter Pylori* Connections?

Because GC is the result of multiple effectors and exposure to a very large number of victual and beverage components [131], individual factors by themselves may not be fully responsible for the complete development of the disease. This tenet is supported by the universally accepted role GC etiological agents such as Hp infection, whose impact on the gastric epithelium, however severe and instrumental for intestinal metaplasia, is not sufficient for the complete induction of intestinal-type adenocarcinomas [132]. We have proposed that Hp chemically modifies the gastric microenvironment as it moves across the mucus layer, thus gaining access and colonizing the epithelium and so facilitates entry of ingested carcinogens to the gastric cell surface that would otherwise be excluded from direct epithelial contact by the viscous and acidic mucus gel layer [133]. Atrophic gastritis caused by advanced and extended Hp infection and its accompanying well- known alterations of cell structure and function would be instrumental to the food procarcinogen-epithelium contact and so complete the Hp-carcinogenesis bridge. This proposal could provide a plausible explanation for contrasting GC death rates among people of both sexes and similar ethnic composition in communities located along an elevation gradient with a different phytogeographical distribution of toxic bracken ferns (*Pteridium* spp) which may find their way to the human diet in the Northern Andes of South America and elsewhere [16,125]. Ptaquiloside, a recognized sesquiterpenoid glycoside carcinogen produced by this fern, is transferred to milk of cows and goats upon feeding and is thus a potential dietary carcinogen for locals consuming milk and dairy products from these animals [134,135]. Ptaquiloside and its congener sesquiterpenoids are unstable in aqueous acid and would decompose rapidly to innocuous products in the gastric medium [136,137]. However, achlorhydria and advanced atrophic gastritis caused by Hp degradation of the gastric mucosa and secretion of ammonia by Hp urease increases the mucosal pH, thus permitting both the survival, activation and penetration of this water-soluble carcinogen into the gastric epithelium. Several other carcinogens entering the GI tract might follow the same access route, and thus become adjuvants to Hp procarcinogenic biochemistry.

Alcohol is a confounding factor in Hp–GC surveys, as heavy drinking is widespread among men, much less so in women in small communities. However, the Hp infection status among adults of both sexes is similar. Of interest is the bactericidal effect of wine reported against Hp *in vitro*, which has also been recorded for Chilean red wines and their nonalcoholic extracts [138,139]. Application of the *in vitro* observations to an adult population of both sexes in England, comparing wine with no wine drinkers (but moderate consumers of other spirits) and set against Hp active infection status (^{13}C urease test), resulted in a 17% reduced GC risk for moderate intakes of wine or beer (7 units/week) [OR=0.83 (95% CI 0.64–1.07)] [140]. Compounds in wine other than ethanol such as resveratrol could contribute to this bactericidal effect [139,141-143]. This feature is in line with the distribution of Hp populations in the human gastric milieu. The large majority of bacteria only colonize the mucus layer but a small fraction penetrates further into the epithelial cell layer [144]. Ethanol and other alcohols found in wine and spirits may diffuse into the mucus gel and partially kill the bacterial reservoir. This hypothesis has yet to be tested *in vivo*.

There have been a few studies of the possible etiological role of ethanol and Hp within the GC framework. Stratification of the infected sample of participants, adjustment of GC rates or discrimination of Hp(+) and Hp(-) cases in Russia, the European Union countries and Korea [101,145,146]. These studies were conducted using different methodologies and comparisons are thus difficult. Heavy alcohol intake (>60g/day) was again confirmed as a GC risk factor but there was no statistical difference between GC odds ratios reflecting the Hp(+/-) status; OR: 1.60 (95% CI 0.91 - 2.82) and OR: 1.65 (95% CI 1.06 - 2.58), for Hp(+) and Hp(-), respectively [101].

A study on a Moscow population showed a substantially raised OR for heavy vodka consumers relative to non drinkers but was nearly independent of Hp(+/-) status; OR, 2.0 (95% CI 1.2–3.1) and 2.3 (95% CI 1.4–3.7), respectively [145].

More recently, another survey was conducted in Korea, where the highest GC rates in the world are registered and intense GC research has been carried out in the past several years [146]. The Korean prospective study comprised 18 863 participants from multiple centers and identified 301 GC cases within this cohort in the period 1994–2004. Subcohorts with detailed data regarding Hp status, GC cases, and alcohol consumption patterns were included. In addition to assaying plasma immunoglobulin G (IgG) response to Hp, to indicate past as well as active infection of all common Hp strains in the population. Researchers also went a step further by testing the seroprevalence of virulent and GC-associated Hp strains: cytotoxin-associated gene A (CagA) and Vacuolating cytotoxin A protein (VacA) [147-149]. Blood samples were drawn and analyzed for Hp seroprevalence from 4% of the healthy volunteers (N=683) and serum from 266 GC cases selected during the 1994-2004 decade. Participants were recruited from both urban and rural areas and grouped according to their drinking habits of alcoholic beverages using standardized questionnaires: non-drinkers (<25g alcohol/occasion), heavy drinkers for 7 or more servings per week (<25–54.5 g alcohol/occasion), and binge drinkers for those who surpassed 55g alcohol intake per occasion. Sex differences in drinking habits followed separate protocol standards: <28g of alcohol for non-drinker men versus <4g for women, and >120g alcohol per occasion for heavy drinking males versus >29g for women.

Authors confirmed earlier results showing an increased GC risk for long-time drinking or heavy alcohol intake relative to the general population, in a dose-response manner [146]. Relative to non-drinkers, the age and sex-adjusted hazard risks (HR) were 1.49(95% CI 1.11-2.01) among alcohol consumers for more than 30 years and 1.50(95% CI 1.08-2.07) for those taking more than 7 alcoholic beverages per week. Unexpectedly, when considering Hp status, Hp(+) long time drinkers showed a *lower* hazard risk relative to non-drinkers (HR=1.17, 95% CI 0.80-1.70) as compared to Hp(-) heavy drinkers: (HR=1.65 95% CI 0.54-5.10). Even more surprising was

the inordinately high HR of Hp(-) heavy drinkers serving themselves >55g of alcohol seven or more times per week (HR=3.27, 95% CI 1.01–10.56) when compared with the same drinking group having Hp(+) status (HR=0.94, 95% CI 0.61–1.46). This paradoxical outcome, as mentioned earlier, may result from the antimicrobial effect of ethanol against Hp when ingested in large quantity. As regards to the expected impact of CagA(+) and VacA(+) Hp strains, there was no effect on GC hazard risk relative to CagA(-) and VacA(-) groups among moderate drinkers. However, for heavy drinkers infected with CagA(+)/VacA(+) Hp strains, GC hazard risk escalated to HR=11.31 (95% CI 1.45–87.92), both sexes taken together. Authors contend that gender discriminated records confirmed a moderately higher HR for men in most cases, but statistical significance relative to women was low or nil. It was thus concluded that, in the GC incidence context, there was no interaction between alcohol consumption and Hp status, independently of CagA/VacA status and gender.

Impact of *Helicobacter Pylori* Eradication on GC Risk and Gender

In the cancer domain, the germane clinical objective of Hp eradication is to substantially reduce the risk of GC genesis. The success of this therapy should be contingent upon the damage of the GI tract caused by Hp prior to eradication and the progress from metaplasia to dysplasia in the distal region that may have taken place by then. Pooled meta-analyzed data of Asian populations among asymptomatic Hp(+) participants of both sexes submitted to eradication therapy with a ten-year follow-up showed a significant reduction in GC risk relative to placebo or untreated controls: RR=0.66 (CI 95% 0.46–0.95) [150]. Nonetheless, there was no gender effect.

Shorter follow-up periods brought about conflicting results but partially confirmed previous studies. A cohort survey of nearly 20 thousand Hp(+) Swedes of both sexes submitted to Hp eradication therapy and with a 7 year follow-up period reported a large increase of developing gastric adenocarcinoma during the first three years post-treatment, relative to the expected GC cases in the Swedish population (15% Hp prevalence) [26]. Thereafter (7 years post treatment in both sexes), GC risk decreased sharply to RR=0.31 (CI 95% 0.11–0.67). This outcome is also in line with pooled data from Asian populations [150] but, as opposed to the Asian survey, a major gender effect was found. RR for GC manifestation 1–3 years after Hp eradication was nearly double that among females (RR=11.69, CI 95% 7.49–17.40) compared to males (RR=6.86 CI 95% 4.39–10.20) and then waned rapidly after the sixth year of eradication. No explanation was ventured for this gender difference in RR so soon after Hp treatment and the subject remains open to further research. However, it does offer a clinical perspective on what to expect from Hp eradication in the short term.

Age, Gender and GC Connections?

This question is not fully settled yet. A detailed GC epidemiological study comparing incidence rates in 5 year age groups found that the male to female ratio (M/F) was not consistent across all ages but increased with age [151]. Authors detected a 10-15 year delay to the time of diagnosis in females. GC incidence rates reached a maximum at 60 years of age and then decreased. Other gastrointestinal cancers such as colo-rectal and pancreas did not show the same trend. In addition, the intestinal type gastric adenocarcinoma was more common in males in all age groups but this type was much less frequent in females younger than 60 years who, in turn, endured increased rates of the diffuse type. GC incidence increased among elderly people of both sexes.

Notably, the bell-shaped M/F ratio curve remained constant irrespective of the decrease in the annual GC incidence, as authors in Finland recorded (70% reduction since 1950) [151]. It was also posited that the later acquisition of Hp infection by females leads to the delay of GC onset [151]. However, this circumstance is not as universal as the reported age-group M/F ratio suggests [152]. Hp infection starts in early childhood, largely before 10 years of age in both sexes in various parts of the world, including areas with contrasting GC incidence [153-155]. The crude incidence rate of Hp infection has been estimated at 1.4% per year, but in general decreases sharply after 15 years of age [155]. Additionally, there is no evidence that seroreversion following natural non-antibiotic Hp desertion is associated with gender.

Role of Sex Hormones in GC

The recorded delay of GC incidence in younger women and the less severe impact of Hp infection on their gastric mucosa evokes a protective role for sex hormones, but results are still controversial.

Early studies by a Japanese consortium explored the influence of female hormones on GC, based on the relationship of other sex hormone-dependent tumors such as prostate, breast, and endometrial malignancies, to hormone receptors for estrogen (ER), and progesterone (PgR) [156]. Occurrence and frequency of these receptors in gastric epithelium cells were tested. Gastric endoscopy resection samples were obtained from healthy and advanced GC patients of both sexes. However, an ER/PgR and gender association could not be firmly established since both receptors were found in a significant fraction of healthy individuals of either sex; males: 26.6% ER(+) and 19.8% PgR(+); females: 19.8% ER(+) and 14.0% PgR(+).The small sample size (52 males, 34 females) may have been a limitation in the design of this study. It was also found that only a small fraction of GC patients possessed both receptors simultaneously [156]. Nevertheless, the frequency of ER(+) and/or PgR(+) in gastric tissue was clearly associated with advanced cancers (Bormann stage IV), and also with the diffuse type, but not the more common intestinal type. However, conflicting results were reported later when the frequency of ER and PgR in gastric and colorectal adenocarcinomas and adjacent normal tissues were assayed [157]. Low levels of ERs were found in 62.5% of both, cancer and normal gastric tissue, whereas PgR figures were 75% and 50% respectively, suggesting that these receptors are native in the tissue and not the result of malignant processes. As regards to gender, no differences were apparent.

A recent meta-analysis of 14 independent studies in three continents (North America, Asia, and Europe) provides more refined leads. Individual reports were inconclusive but two protective factors in females emerged when these studies were taken together and meta-analyzed rigorously: longer years of fertility (RR=0.74, CI 95% 0.63-0.86) and hormone replacement therapy (RR=0.77, CI 95%

0.64–0.92) [158]. Other important features of women's reproductive life such as age at first menarche, age of first birth and time to menopause or oral contraceptive use had no influence on GC rates. Other studies, however, led to opposing conclusions in some crucial aspects of reproductive life: later age at menarche (>15y) relative to 12–13 y of age was a major GC risk factor later in life (OR=1.93, 95% CI 1.19-3.13) as well as normal aged menopause compared with premenopause (OR=1.99, 95% CI 0.98–4.05) [159]. Authors thus suggested that hormonal factors associated with greater and longer exposure to estrogen and/or progesterone may be protective against gastric adenocarcinoma in women.

In contrast to the results of Sipponen and Correa [151] who observed a 10-15 year delay to the time of diagnosis in females a recent retrospective analysis of 1586 female and 3136 male Korean GC patients reports that GC affects females at a younger age than males [152]. The fact that the Korean study also included the diffuse and poorly differentiated carcinoma, which is more prevalent among the young, may account for the disparate results of the two studies. Additionally, the frequency of poorly differentiated adenocarcinoma and signet ring cell carcinoma (SRC) was higher among Korean women and prognosis was poorer, particularly in advanced and SRC cases in young patients. These conflicting conclusions only serve to underline the increasing complexity of epidemiological studies as diagnostic methods become more sophisticated and preventive tests are performed on larger cohorts of the younger population.

Estrogen itself and ER–ligand complexes participate actively in the modulation of the ionic balance in the gastroduodenal region, which involve bicarbonate and chloride anions [160]. These secretions are believed to protect the gastric epithelial surface from luminal acid and peptic injury through localized pH control [161].

Interest in the role of estrogen in the GC genesis has been revitalized recently by a deeper study of ERs and PgRs in normal and cancerous gastric tissues and cells [162]. Two types of signaling pathways, genomic and non-genomic, are activated by ERs. The genomic pathway leads to the activation of the transcriptional domain, involving DNA transcription factors and a variety of mRNA expressions. The non-genomic pathway also modulates gene expression but through alternative transcription factors such as the AP1 activator protein, and the nuclear factor NF-κB [163]. In turn, the NF-κB family of transcription factors is linked to multiple signaling cascades and molecules, affecting the expression of more than 500 genes that include the modulation of inflammation, some chronic diseases, the immune response, cell survival and proliferation, the latter being of crucial importance to cancer progression [164,165]. According to a recent meta-analysis in which data were pooled from forty-four studies and 4418 cancer patients, overexpression of NF-κB is associated with poor overall survival of cancer patients three years after surgery of solid tumors, with much increased odds ratios (OR=3.40 95% CI=2.41–4.79) compared with healthy individuals [166].

Prominent among NF-κB-derived gene products are inflammatory and growth factors, tumor necrosis factor (TNF), cytokines, chemokines, antiapoptotic actuators, and angiogenesis regulators favoring tumor growth and carcinogenesis [37,165,167,168]. As a result, NF-κB has been a central target for a number of anti-inflammatory substances and potential cancer therapies [169-171]. Natural and synthetic compounds aimed at inhibiting NF-κB have been employed in breast and colo-rectal cancers, and constitute a major topic of research in GC today [172-177].

Importantly, ER activation contributes to tumor cell proliferation by integration of the two signaling pathways, in conjunction with the growth factor receptors EGR and IGR [178]. Two ERs have been identified, ER-α and ER-β. In contrast to ER-α, ER-β is localized in the cell nucleus forming part of transcription pathways and is widely distributed in animal and human tissue of both sexes, including the GI tract [179,180]. The ubiquitous occurrence of ER-β is of special relevance for estrogen mediation in a large number of physiological activities and clinical outcomes including cancer when ER dysregulation occurs.

In stomach pathology, both receptor types occur in normal and GC cells *in vitro* and have been found in endoscopic resections from healthy and GC patients of both sexes but in different proportions and GC type, as shown by immunochemical staining [162]. Of special note, ER-α could not be found in gastric adenocarcinomas of any type, whereas ER-β was expressed in 61.2% of male and 38.8% of female intestinal-type GCs across all ages, although this difference was not statistically significant (P=0.931), and was much less frequent in the diffuse type and signet ring cell carcinomas [162]. Other studies, however, do not concur; older (>50y) female patients showed a more frequent ER-β response (73.1%) than males (26.9%, P=0.027) [181]. Reports elsewhere account for ER-β mRNA expression in a greater proportion of GC patients [182]. Importantly, only 10.4% of ER-β(+) patients experienced GC recurrence and had an enhanced 3-year survival rate, whereas in ER-β(−) people GC recurrence was 32.1% and had a worse survival prognosis [162]. These results suggest that ER-β is involved more than ER-α in some form of inhibition of GC progression-invasion and improvement of patient survival chances, which could lead to GC therapies based on estrogen ER-β-ligand like substances. However, the mechanism of ER activation and the downstream effects on GC evolution still remains undetermined and the subject continues to be debated [183].

Novel Approaches and Future Directions

Motivated by the continuing prevalence and deadly outcome of GC, a flow of prevention strategies, recommendations and guidelines continue to appear in the literature, aiming to reach not only economically advanced societies with well structured public health programs but less developed regions of the world as well [184-188].

The gender connection with tumor genesis other than that for breast and female reproductive organs and the male to female differences in the incidence of malignancies need further research. As Hanahan and Weinberg [42] noted, the hallmarks of cancer evolves towards deeper molecular insights on cell signaling pathways, immune processes, genomics, and the metabolomics of cancer cells [19,32,189], as well as a more precise identification of factors protecting females more effectively than men against gastric tumorigenesis [190-193]. Cancer sciences will then have improved possibilities for developing novel strategies for individualized therapies and identification of predictive biomarkers for the earliest possible detection of gastric premalignancies, and thus eventually provide a global clinical solution to the continuing gastric cancer problem.

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