Original article

Delayed rise in incidence of gastric cancer in females results in unique sex ratio (M/F) pattern: etiologic hypothesis

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Abstract

Background. The age-standardized and cumulative incidence rates of gastric cancer (GCA) are twice as high in males as in females.

Methods. Based on age-group-specific (5-year age groups) annual incidence data of GCA among males and females published by 18 cancer registries worldwide, and on a consecutive series of 938 GCAs from Finland, we explored how the male predominance of GCA has changed over the decades and how this male predominance may possibly vary worldwide between populations with high and low gastric cancer incidence.

Results. It appeared that the age-group-specific male-to-female (M/F) ratio of the annual GCA incidence is not constant but increases with age, reaches a peak at age around 60, and decreases thereafter. This special form of the M/F curve is not seen in other gastrointestinal (GI) cancer types (colon, rectum, pancreas). This “low-high-low” form of the M/F curve is related to a 10- to 15-year delay in the appearance and onset of GCA of the intestinal type in females compared with males. The age-group-specific M/F ratio rises as the GCA of the intestinal subtype prevails in males and is rare in females before age 60 and starts to decrease after age 60 as the GCA of the intestinal subtype begins to be common also in females. This special form of the M/F curve is globally consistent and similar in countries or populations of high and low GCA incidence. The data from the Finnish Cancer Registry indicate that the age group-specific M/F curve of the annual GCA incidence has, in addition, remained unchanged over the decades (from the 1950s) in spite of a decrease in the annual GCA incidence of more than 70%. In order to examine the role of gastritis-related diseases as a cause of the sex difference in GCA, 1700 consecutive endoscoped outpatients were studied in Finland. In this series, the age-group-specific prevalences of *Helicobacter pylori* gastritis, atrophic gastritis, or intestinal metaplasia were proportionally as common in males as in females in all age groups except for the youngest one (20–49 years), in which *H. pylori* nonatrophic gastritis was slightly more common in males than in females.

Conclusion. The male predominance of GCA is a global phenomenon, and is similar in populations with high and low GCA incidence, and this predominance is related to a 10- to 15-year delay in the appearance and onset of GCA of the intestinal subtype in females compared with males. It is suggested that sex hormones (estrogens) protect women against GCA, and that GCA begins to be as prevalent in females as in males only after the menopausal age. Another possibility is that a later acquisition of *H. pylori* gastritis in females than in males causes the relative delay in the appearance and onset of new GCA cases in females compared with males.

Key words Gastric cancer · Estrogens · Trefoil factor · *H. pylori*

Introduction

Age-standardized and cumulative incidence rates of gastric cancer (GCA) in males are approximately double those in females. For example, the annual age-standardized (world population 1982–1986) incidence rates in Cali, Colombia, were 36.3 per 100 000 males and 19.9 per 100 000 females; the cumulative rates being 4.45 and 2.36 respectively, for age up to 74 years [1]. In Finland, the corresponding age-standardized rates were 20.3 for males and 11.2 for females, and the cumulative rates were 2.27 and 1.17, respectively [1]. The sex ratio of the incidence rates varies, however, with age, forming a “low-high-low” pattern, which seems to be unique to stomach cancer [1].

It is postulated that the specific pattern in the M/F ratio of the annual GCA incidence is related to a dissimilar timing in the appearance (incidence) of new GCA cases between males and females. This hypothesis was tested by studying the statistics on GCA published by cancer registries and the International Agency for Research on Cancer (IARC) world-wide, the results of which are presented in this report.

The etiology of GCA is considered to be multifactorial. It has been recognized by the IARC that infection with *Helicobacter pylori* plays a causal role [2]. Therefore, the possible etiologic implications of *H. pylori* gastritis and sex hormones on the differences of GCA between males and females are also discussed.

Subjects and methods

Data on the annual incidence of GCA were obtained from the IARC publication *Cancer in five continents, Vol. VI* [1]. Additionally, statistics for Finland over the decades (1955–1990) were obtained from the official publications of the Finnish Cancer Registry [3,4]. Data on cancer incidences were accepted and analyzed in the present study only from registries from which there were more than 500 observations during the recording period.

The age-group-specific annual incidence rates of different subtypes of GCA (intestinal, diffuse, unclassified) for Finland were obtained by applying the proportions of the GCA subtypes in different age groups in a series of 938 consecutive cancer cases (Table 1), including all those diagnosed by endoscopy, surgery, and/or autopsy at the Helsinki District University Central Hospital (HUCH)-Jorvi Hospital, Espoo, Finland. The HUCH-Jorvi Hospital, represents the population of Finland, especially the urban south of the country. The histologic classification was based on the criteria of Laurén [5].

The age-group-specific prevalences of chronic gastritis and atrophic gastritis in males and females were examined by a cross-sectional survey of 1700 consecutive outpatients endoscoped at HUCH-Jorvi Hospital for dyspeptic symptoms in 1986–1991. In all, at least two biopsies from antrum and corpus were available and analyzed.

Incidence and incidence rate

The terms “age-group-specific incidence” and “incidence rate” are used in the present study. They refer to the number of new cancer cases diagnosed annually in a standardized population (per 100 000 males or females) in different age groups (5-year age groups) as expressed in the official publications of the cancer registries and IARC.

Results

The male-to-female ratio (M/F ratio) of the annual incidence rates of GCA in different age groups for eight 5-year time periods (1955 to 1990) in Finland is depicted

Fig. 1. The “low-high-low” form of the curve of the the male-to-female (M/F) ratio of the annual incidence of gastric cancer in 5-year age groups. Data of the Finnish Cancer Registry from different time periods (1955–1990). The arrow indicates the age of the highest M/F ratio

in Fig. 1. The ratio is approximately 1 in young age groups (20–39 years) but rises thereafter and reaches a peak of 2 to 2.5 in age groups around 60, after which it decreases and reaches levels only slightly higher (around 1.5) than those observed in young age groups. This special “low-high-low” form of the M/F curve over the age groups was constantly observed and was similar (Fig. 1) at all chronologic time periods (from the 1950s to the 1990s), even though the age-adjusted incidence of gastric cancer in Finland had decreased by 77% in males and 76% in females from 1953 to 1995 [4].

The age-group-specific M/F ratios of the annual GCA incidence in populations (countries) with high, intermediate, or low incidence, published in *Cancer in five continents, Vol VI* [1], are shown in Fig. 2. Again, the special “low-high-low” form of the M/F curve is observed, with ratios close to 1 in young age groups, close to 2.5 around age 60, and 1.5 to 2 in old age groups. Furthermore, a similar form of the M/F ratio was also observed when the incidence rates of GCA in different birth cohorts from Finland were looked at (data not shown). Such patterns are not found for other cancers, as shown for colon and pancreas cancers in Figs. 3 and 4.

In order to examine differences in the GCA incidence between males and females more closely, we explored more deeply the data published by the Finnish Cancer Registry in 1986. The age-group-specific annual incidence rates for all GCAs in males and females in 1986 are shown in Fig. 5 and those for the intestinal and diffuse types in Fig. 6. These latter incidence rates were derived by calculation of the proportions of GCAs of

Fig. 2. The age-group-specific M/F ratios of the annual gastric cancer incidence from 18 cancer registries representing countries with low, intermediate, and high cancer incidence during the time period 1986–1990. The arrow indicates the age of the highest M/F ratio

Fig. 3. The age-group-specific M/F ratios of the annual colon cancer incidence from 12 cancer registries with more than 500 observations (years 1986–1990)

the intestinal and diffuse subtypes in different 5-year age groups in a consecutive series of 938 stomach cancers (Table 1) from Southern Finland in 1976–1995 and by applying these proportions to the cancer incidence data from Finland in 1986. It appears that the “low-high-low” pattern of the M/F ratio for GCA is related to differences in age-group-specific incidences of GCA between males and females, particularly with those of the intestinal type. GCA of the intestinal subtype seems to appear 10 to 15 years earlier in men than in women, and GCA of the intestinal subtype is rare in

Fig. 4. The age-group-specific M/F ratios of the annual pancreatic cancer incidence from 12 cancer registries with more than 100 observations (years 1986–1990)

Fig. 5. Annual age-group-specific incidences of gastric cancer among males and females. Data from Finnish Cancer registry in 1986

females before age 60 (Fig. 6). The age-specific M/F ratio rises and is high in young age groups when the appearance and onset of new cases of the intestinal type of GCA is more frequent in males than in females, and decreases in old age groups, in which the appearance and onset of GCA becomes more and more frequent also in females.

Because it is well known that the intestinal type of gastric cancer is the last stage in a series of neoplastic transformations of the inflamed mucosa and *H. pylori* gastritis [2], we also investigated whether there were any sex differences in the prevalence of GCA precursor conditions, i.e., chronic gastritis, gastric atrophy, and intestinal metaplasia. Table 2 presents data on these

Fig. 6a,b. Annual age-group-specific incidences of gastric cancer of **a** the intestinal (*IGCA*) type and **b** diffuse (*DGCA*) type in males and females. The incidences were obtained by calculating the proportions of gastric cancers of the intestinal and diffuse subtypes in 5-year age groups in a consecutive series of 938 gastric cancer patients and by applying these proportions to the gastric cancer incidence data (Finnish Cancer Registry in 1986)

Table 1. Demographics of gastric cancer. A consecutive series of cancers diagnosed by endoscopy, surgery, or autopsy at the Helsinki District University Central Hospital (HUCH)-Jorvi Hospital from 1976–1995

Subtype	Total no.	Age (years; mean $\pm$ SD)	Males, percent share	Proximal (angulus or above), percent share
Intestinal	434	70 $\pm$ 10	62%	60%
Diffuse	371	58 $\pm$ 13	46%	71%
Unclassified	133	68 $\pm$ 12	62%	66%
Total	938	65 $\pm$ 13	55%	65%

Table 2. Prevalence of chronic gastritis, atrophic gastritis of any grade, and advanced (moderate or severe) atrophic gastritis in consecutive outpatients endoscoped in 1986–1991

	Total No.	Chronic gastritis No. % (95% CI)	Atrophic gastritis No. % (95% CI)	Advanced atrophic gastritis No. % (95% CI)
Age group 20–49				
Males	431	239 55% (51–60)	46 11% (8–14)	17 4% (2–6)
Females	381	136 36% (31–41)	49 13% (9–16)	21 6% (3–8)
Age group 50–59				
Males	162	127 78% (72–85)	46 28% (21–35)	16 10% (5–14)
Females	239	177 74% (69–80)	72 30% (24–36)	34 14% (10–19)
Age group 60–79				
Males	194	166 86% (81–91)	91 47% (40–54)	52 27% (21–33)
Females	293	236 81% (76–85)	137 47% (41–52)	66 23% (18–27)

95% Confidence intervals (95% CIs) are indicated in parentheses

prevalences in Finland from a survey of a consecutive series of 1700 outpatients endoscoped during 1986–1991. No sex differences were found after age 50 in the prevalence of gastritis, atrophic gastritis, or intestinal

metaplasia. In younger patients (age group, 20–49 years), however, the prevalence of nonatrophic gastritis was slightly higher in males than in females, at 55% in males and 36% in females ($P < 0.05$; χ^2 test).

Discussion

This study indicates that the male predominance of GCA is related to a delay in the “timing” of the appearance and onset of GCA of the intestinal type in females relative to males. It opposes the view that the risk of GCA is simply higher in men than women. In fact, it seems that the incidence of GCA increases progressively with age quite equally in both sexes, but that this progression begins 10–15 years earlier in males than in females. Because of the limited lifetime, this difference in “timing” results in a false impression that GCA is, in general, more common in males than in females.

The difference in the timing of the appearance of GCA between the sexes is well demonstrated with the age group-specific M/F ratio of GCA incidence. In relation to age, the M/F ratio forms a curve with a “low-high-low” pattern in which the peak is reached at the age of 60 years. This age point seems to indicate an age period during which the rise of the annual GCA incidence in females proportionally exceeds that in males. A surprising finding is that this “peak” of the M/F curve is always at age 60, in all countries from which reliable statistics on GCA incidence are available. The “low-high-low” pattern of the M/F ratio has also remained unchanged over the decades, from the 1950s, in Finland, even though the incidence of gastric cancer has markedly decreased in both sexes, by approximately 70% [4]. The “low-high-low” pattern also seems to be similar all over the world, being unrelated to the incidence of the GCA, ethnicity, or socioeconomics, and is similar in all birth cohorts.

This globality and consistency of the age-specific pattern of the M/F curve firmly suggests some globality and consistency in the pathogenesis of GCA in general; i.e., the pathogenesis of GCA must include similar intrinsic mechanisms all over the world, even though the incidence varies a lot. The global consistency of the M/F pattern suggests, further, that the differences in the pathogenesis of GCA between males and females are based on some basic biological differences between the sexes, rather than being simply a result of environmental factors alone. In this respect, two options are conceivable. First, male sex is somehow linked to an inherent susceptibility to gastric cancer, or, alternatively, female sex, i.e., female hormones, are protective. The second option (or possibility) is that sex differences interact with environmental influences, and this determines the risk. In this respect, the characteristics of *H. pylori* infection are to be considered in particular, because this infection is the main cause of chronic gastritis, the forerunner of gastric cancer in most of the cases.

The present results exclude neither of the above two possibilities. The hormonal hypothesis is supported by the present observation that females seem to be “pro-

tected” from GCA of the intestinal type up to menopausal age, after which the GCA incidence begins to increase among the women as well. After the menopause, this increase is similar to that in males, or it may even occur more rapidly, as evidenced by a decrease in the M/F ratio pattern in old age. This inevitably raises the hypothesis that female sex hormones, i.e., estrogens, have a potency to prevent or inhibit the genesis of GCA of the intestinal type.

The dependence of gastric carcinoma on sex hormones was suggested in some earlier studies. In a case-control study of 339 postmenopausal women with gastric cancer, Palli et al. [6] did find an inverse relation of GCA risk with the duration of fertility and lateness of the menopause. This was indicated to suggest that female hormones have a protective influence against stomach cancer.

The male predominance of GCA is also seen in laboratory animals [7]. Experimental gastric cancer is more frequently and more easily induced in male than in female animals. Castration and supplementation with estrogens lower the rate of experimental cancer, and a high cancer rate can again be achieved by stopping the application of estrogens, or by giving male sex hormones. Large epidemiological studies have further indicated that postmenopausal hormonal replacement therapy (HRT) lowers the overall rate of nongynecological cancer, including gastrointestinal cancers, colonic cancers in particular [8–12]. Correspondingly, it could be anticipated that HRT could also protect women from GCA, especially GCA of the intestinal type.

Estrogen receptors have been shown to occur in gastric epithelial cells [13–17]. In the gastrointestinal tract, including stomach, estrogens stimulate the expression of cysteine-rich trefoil peptides [18–23], which are expressed in mucin-producing cells and play a protective role in maintaining the integrity of the gastrointestinal mucosa and regulate the cell cycle, and may act as tumor suppressors [19–23].

H. pylori gastritis and atrophic gastritis are premalignant conditions, which raise the risk and initiate the pathogenesis of GCA [2]. *H. pylori* infection occurs in about 80–90% of GCA patients in the Western world and has to be, therefore, considered as a potential factor causing the differences in GCA between the sexes. *H. pylori* infection and gastritis are reported to occur equally often in both sexes, and this equality also seems to be the case concerning the occurrence of atrophic gastritis and intestinal metaplasia in males and females in the present survey.

A possibility, however, is that the timing (age) at the acquisition of the *H. pylori* infection also plays a role in the timing of the appearance of GCA of the intestinal type in old age [24]. This implies that boys may get *H.*

pylori gastritis at a younger age than girls; i.e., boys are infected earlier than girls in the same birth cohort. In the present study (Finland), the males in the youngest age group (20–49 years) had a higher prevalence of *H. pylori* gastritis than the females.

Some other studies have also reported a slight excess of nonatrophic gastritis in young males. In Nariño [25], a high-risk area for GCA in Colombian, 23.5% of men in the age group 25 to 44 years had *H. pylori* nonatrophic gastritis compared with 13.6% of females. Klein and co-workers [26] described the natural history of the infection in Peruvian children aged 6 to 30 months. The overall prevalence of the infection in infancy decreased from 71.4% to 47.9%, and a significant sex difference was found: boys, reduction from 63.6% to 55%; girls, reduction from 80% to 38.7% ($P = 0.03$). They concluded that, 18 months after birth, boys were more likely to acquire and less likely to clear the *H. pylori* infection than girls. In a community with a very high GCA risk in the Colombian Andes (Aldana, Nariño), boys from 3 to 9 years of age had a higher prevalence of the infection than girls: 76.7% vs 65.8% ($P = 0.015$) [27].

In a biracial rural community in Louisiana, in which gastric cancer rates in blacks are more than double those in whites, Malaty et al. [28] reported that, over a period of 12 years, 50% of white children lost their *H. pylori* infection, compared with only 4% of black children. The prevalence of infection was greater in boys than in girls. In addition, spontaneous elimination of the helicobacter infection from children has also been reported previously in developed countries [29,30]. No sex differences in those low-risk populations have been reported.

The age at first infection determines the length of time in which the infection has persisted as chronic gastritis. According to some views [24], an earlier age of *H. pylori* acquisition could result in earlier “timing” of the appearance of GCA in males compared with females. The situation has some similarities to the relationship between smoking and lung cancer. Doll and Peto [31] have estimated that a 10% excess prevalence of smoking around age 20 could lead to doubling of the rates of lung cancer around age 60. This may reflect carcinogenic forces produced by the constant inflammation of the bronchial mucosa which accumulates over decades of smoking. Doll and Peto [31] have further proposed mathematical formulas in which the time of exposure has the greatest influence on the outcome. The chronic inflammation of the gastric mucosa elicited by infection with *H. pylori* may exert a similar carcinogenic influence which can be accumulated over the years. In both mucosas, bronchial and gastric, sequential precancerous lesions have been identified.

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