

Obesity and the Incidence of Upper Gastrointestinal Cancers: An Ecological Approach to Examine Differences across Age and Sex

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Abstract

Background: Esophageal and gastric cancers differ in their epidemiology but have several risk factors in common. The aim of this study was to assess age and sex differences in the burden of esophageal and gastric cancers in the context of the global obesity epidemic.

Methods: Data from 50 countries were obtained from Cancer Incidence in Five Continents Volume X and GLOBOCAN 2012. Age-specific and age-standardized incidence rates of esophageal adenocarcinoma and squamous cell carcinoma (ESCC), as well as cardia (CGC) and noncardia (NCGC) gastric cancer, were estimated. Countries were grouped and analyzed according to their obesity prevalence.

Results: A gradient across quartiles of obesity prevalence was found for esophageal adenocarcinoma, with the highest incidence rates in high prevalence countries (ASR 3.0 vs. 0.8 per 100,000 in

highest vs. lowest obesity quartiles, males). In contrast, for ESCC as well as for CGC and NCGC the reverse was true, with the highest rates observed in countries with the lowest obesity prevalence (ESCC, 2.2 vs. 11.5; CGC, 2.8 vs. 7.8; NCGC, 3.9 vs. 17.4 in highest vs. lowest obesity quartiles, males). Although for esophageal adenocarcinoma, sex and age differences in incidence were most pronounced in countries with a high prevalence of obesity, these differences were much smaller for the other cancer sites assessed.

Conclusions: Variation in obesity prevalence may partly explain age and sex differences in the incidence of esophageal adenocarcinomas.

Impact: Ecologic studies can help assess relationships between risk factors and cancer, and generate new hypotheses that may be pursued through more directed research. *Cancer Epidemiol Biomarkers Prev*, 25(1): 90–97. ©2015 AACR.

Introduction

In 2012, worldwide almost 1.5 million people developed esophageal or gastric cancer (1). Although closely allied in terms of their anatomical location and shared exposures, incidence patterns and trends of the two cancers are very different. This observation has led to an increasing interest in the epidemiology of different subtypes or subsites of both malignancies in order to disentangle the possible contribution of risk factors and to plan appropriate cancer control strategies. Most esophageal cancers can be subdivided into two main histologic subtypes: esophageal adenocarcinomas and esophageal squamous cell carcinomas (ESCC). Whereas esophageal adenocarcinomas usually develop in the lower third of the esophagus, ESCC occurs mostly in the upper two thirds of the esophagus (2). Gastric cancers can generally be classified into two topographical categories: cardia

gastric cancers (CGC) arising from the area of the stomach adjoining the esophageal–gastric junction, and non-CGCs (NCGC) developing in more distal regions of the stomach.

Recent studies have highlighted the different epidemiologic profiles and incidence trends of esophageal and gastric cancer, respectively, by subtype and subsite. Although the incidence of esophageal adenocarcinoma is highest and has been increasing in Caucasian populations of high-income countries, ESCC is most common in Asian populations (3, 4). In contrast, the incidence of both gastric cancer subsites is highest in Eastern and South-Eastern Asia, although rates of CGC exceeded those of NCGC in North America and several European countries (3, 4). The underlying reasons for these patterns remain partly unexplained. Differences in the prevalence of risk factors have been suggested to contribute to this pattern. Although tobacco smoking is a stronger risk factor for ESCC (5) and both types of gastric cancer (6), it has also been shown to be associated with an increased risk of esophageal adenocarcinoma (7). Obesity, conversely, has been estimated to be responsible for a third of all global esophageal adenocarcinoma cases in males in 2012 (8), but has also been linked to CGC (9)—not only as an independent risk factor but also through its involvement in the development of gastro-esophageal reflux disease (GERD) and the metaplastic precursor of esophageal adenocarcinoma, Barrett's esophagus (10, 11). Moreover, although NCGC is strongly linked to *Helicobacter pylori* (*H. pylori*) infection (12, 13), inverse associations have been found for CGC and esophageal adenocarcinomas (14, 15). A similar relationship has also been observed for socioeconomic status, with clear gradients and the highest risks for NCGC and

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ESCC found with increasing deprivation but no clear associations for CGC and esophageal adenocarcinomas (16).

Parallels in the epidemiology of esophageal and gastric cancers are also more evident when looking at incidence patterns across age and sex. Although males are at higher risk for all included cancers, this is particularly true for esophageal adenocarcinomas (male-to-female sex ratio, 4.4:1) and CGC (3.2:1; refs. 3, 4). These two cancer types are also referred to as cancers of the gastro-esophageal junction and are frequently considered one clinical entity (15). Males developing these junctional cancers are also more likely to present at younger ages than females (17). Understanding how risk factors are influencing these age and sex differences will facilitate the unraveling of underlying mechanisms in the etiology of these tumors.

In view of the global increase in obesity and its potential impact on the incidence of esophageal and gastric malignancies, we assessed this relationship with the aim to identify potential synergies and to increase the understanding of existing age and sex differences. Using an ecologic approach, we provide a wider view on obesity as a linking risk factor and the findings may generate new hypotheses in cancer epidemiology.

Materials and Methods

For all analyses, data from Cancer Incidence in Five Continents (CI5) Vol. X (18) and GLOBOCAN 2012 (1) were used. Both databases are governed by the International Agency for Research on Cancer but differ in their underlying data and purpose. CI5 provides high quality data on the incidence of cancer from cancer registries around the world and its Vol. X contains information from 290 cancer registries in 68 countries about cancers diagnosed from 2003 to 2007. The GLOBOCAN project provides estimates of the incidence of, mortality and prevalence from major cancer types at the national level, for 184 countries of the world, for the year 2012. These estimates are based on most recent data available and further details are provided elsewhere (19).

Using both data sources, age-specific and age-standardized incidence rates (ASR; world population, 1960) were estimated for esophageal cancer by histologic subtype (esophageal adenocarcinomas/ESCC) and gastric cancer by topographical subsite (CGC/NCGC) in 2012. The exact method and the resulting incidence rates have been described in more detail in Arnold and colleagues (3) and Colquhoun and colleagues (4). In brief, sex- and age-specific (<65; ≥65 years) proportions of esophageal adenocarcinomas/ESCC were computed for all countries included in CI5X except for those with no cases of esophageal adenocarcinomas/ESCC in one of four strata (male, female; <65, ≥65 years). Similarly, the proportions of CGC (C16.0) and NCGC (C16.1-6) cases out of all gastric cancers with known topography (C16.0-6) were calculated for each country included in CI5X and stratified by sex and the same broad age group, provided there were two or more cases of CGC and NCGC within each sex and age group stratification. Where data were available from multiple regional registries within a country, cases and populations were pooled to obtain national proportions. The histologic types of esophageal cancer and the topographical classification of gastric cancers were defined according to the third edition of the *International Classification of Diseases for Oncology* (ICD-O-3) as presented in Cancer Incidence in Five Continents Vol. IX (CI5IX; refs. 20, 21). For the current study, the age- and sex-specific proportions of CGC/NCGC and esophageal adenocarcinomas/

ESCC determined in the previous steps were then applied to the 2012 gastric and esophageal cancer incidence estimates in GLOBOCAN 2012 for 50 countries.

The prevalence of obesity, defined as a body mass index (BMI) ≥ 30 kg/m², by country and sex for the year 2008 was obtained from the Global Health Observatory (22). For this analysis, countries were grouped into quartiles of their obesity prevalence by sex. The quartiles of obesity prevalence were <16.5%, 16.5% to <21.4%, 21.4% to <24.6%, and $\geq 24.6%$ in males and <16.9%, 16.9% to <23.1%, 23.1% to <26.8%, and $\geq 26.8%$ in females. All included countries are listed by obesity quartiles in Supplementary Table S1. Age-specific and ASR were then calculated for each quartile and compared across cancer sites. Tests for linear trend were done by performing a linear regression treating obesity quartiles as a continuous variable. *P* values were considered statistically significant at the 0.05 level.

Of the countries included in this study, China, Japan, and Republic of Korea have the highest burden of gastric cancer (1, 4). Diets high in salt as well as a high prevalence of *H. pylori* infection in those areas have been proposed to be the main drivers of the increased risk of NCGC (23, 24). In the past decades, there have been programs to increase awareness and implement early detection in these countries. This has led to increased cancer diagnosis, especially of small lesions, and hence increased cancer incidence (25). Such activities may obscure the apparent relationship with other risk factors and we therefore conducted a sensitivity analysis, excluding China, Japan, and Republic of Korea.

Given that tobacco smoking is another important risk factor for both esophageal and gastric cancer, the interaction between obesity prevalence and smoking was assessed for each cancer by reclassifying the included countries according to tertiles of obesity prevalence combined with tertiles of lung cancer mortality in 2012 obtained from the GLOBOCAN database (1), as a proxy for past smoking patterns (Supplementary Table S2a and S2b). ASR were calculated for each new exposure category by sex and cancer. Incidence rate ratios for each combined exposure category were then computed relative to the reference category (lowest obesity tertile and lowest lung cancer mortality tertile).

Stata 12 was used for data processing and analysis.

Results

Clear gradients in ASR were found across obesity quartiles in males (Fig. 1). Although the incidence of gastric cancer (both CGC and NCGC) and ESCC was highest in countries in the lowest quartile of obesity prevalence, the reverse was true for esophageal adenocarcinoma. For NCGC and ESCC, the incidence rate in the lowest obesity quartile was fivefold the rate in the highest obesity quartile (NCGC: ASR 17.4 and 3.9 per 100,000; ESCC: 11.5 and 2.2, respectively). The rates for esophageal adenocarcinoma between the highest and the lowest obesity quartiles differed by fourfold (ASR: 3.0 and 0.8). These patterns were less pronounced in females, where incidence rates were, in general, lower than males for all four cancers.

Age-specific incidence rates largely reflected similar patterns, increasing with age across cancers (Fig. 2). For ESCC, differences in incidence between lower and higher obesity quartiles increased with age: whereas the incidence rate of ESCC among 40 to 44 years old males was four times higher in countries in the lowest obesity quartile relative to countries in the highest

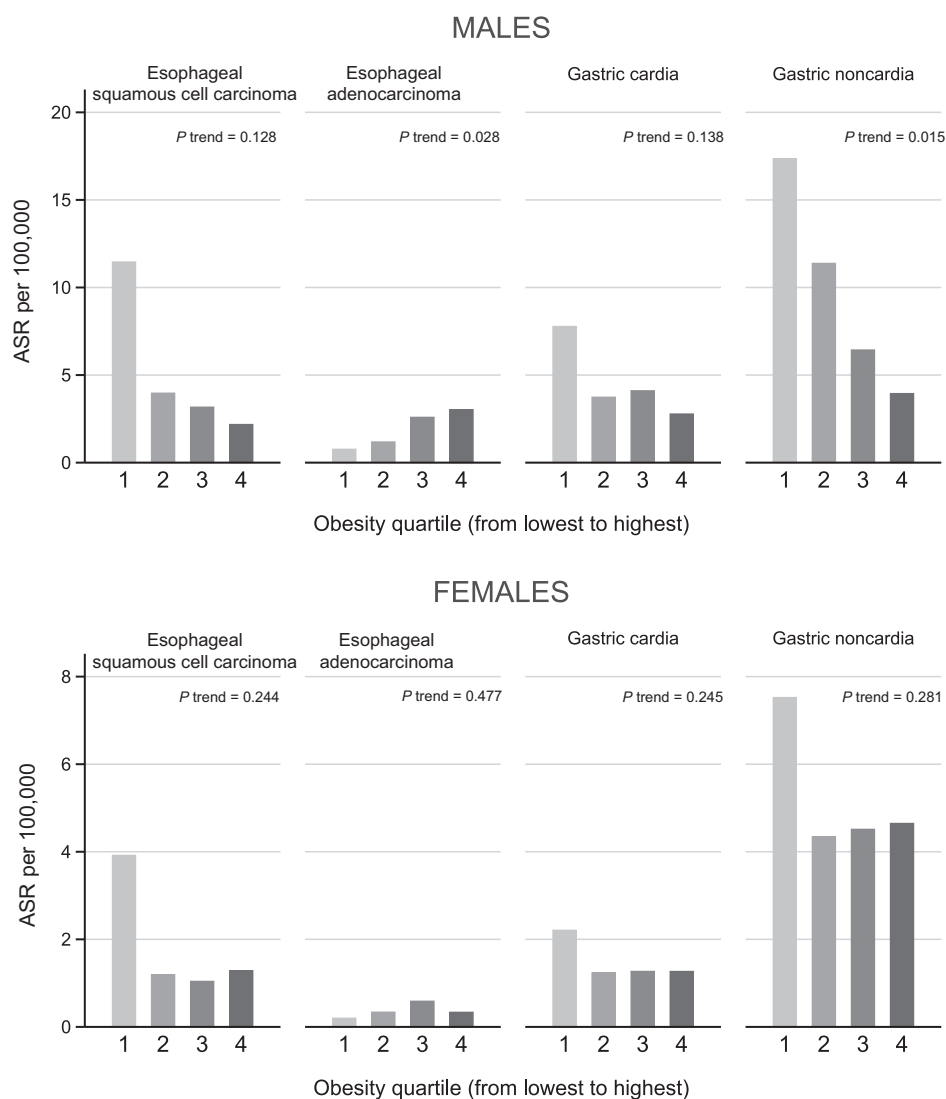


Figure 1. Age-standardized incidence rates (ASR) of esophageal and gastric cancers by sex and obesity quartile (proportion of body mass index ≥ 30 kg/m²).

quartile (ASR, 3.7 vs. 0.9, respectively), among the 75+ years old it was sevenfold higher (ASR, 117.8 vs. 17.7). In females, the differences in incidence between obesity groups across ages were smaller than in males, with the exception of the lowest quartile of obesity, which stood out for all cancer sites considered.

Male-female ratios in ASR were greatest for esophageal adenocarcinomas, ranging from a ratio of 9 in the highest obesity quartile to 3.8 in the lowest quartile. In contrast, the differences between male and female rates were smallest in the highest obesity quartile for all other sites (male-to-female ratio range for ESCC, 1.7–3.3; CGC, 2.2–3.5; NCGC, 0.9–2.6). Sex differences in incidence rates increased with age before leveling off after age 60 years for CGC, with no appreciable differences between obesity quartiles (Fig. 3). Large differences across sex and age were found for esophageal cancer with contrasting patterns for the two subtypes. Whereas male-female differences declined with increasing age for both sites, this was most pronounced in the two highest obesity quartiles in the case of esophageal adenocarcinomas, and in the second quartile for ESCC. For the latter site, the smallest

differences between sexes were observed in the highest obesity quartile with an opposing pattern across ages.

Excluding China, Japan, and Republic of Korea from the analyses resulted in slightly different patterns from those described above (Supplementary Figs. S1–S3). This was especially evident in females, where gradients in rates across obesity quartiles almost disappeared. In males, although patterns changed for the two gastric cancer subsites, gradients for both subtypes of esophageal cancer remained. In a second sensitivity analysis, we assessed the possible interaction between obesity and tobacco smoking for each cancer site and sex (Supplementary Table S3). An independent relation with obesity was observed for esophageal adenocarcinomas in males, where we found a gradually increasing risk with increasing obesity level at each population-level exposure of tobacco smoking. As for tobacco smoking, an independent effect was seen for ESCC where incidence rose by increasing smoking subgroup in all levels of obesity prevalence. Yet, although the risk of ESCC decreased with increasing obesity prevalence, this decrease was largest where tobacco smoking was highly prevalent.

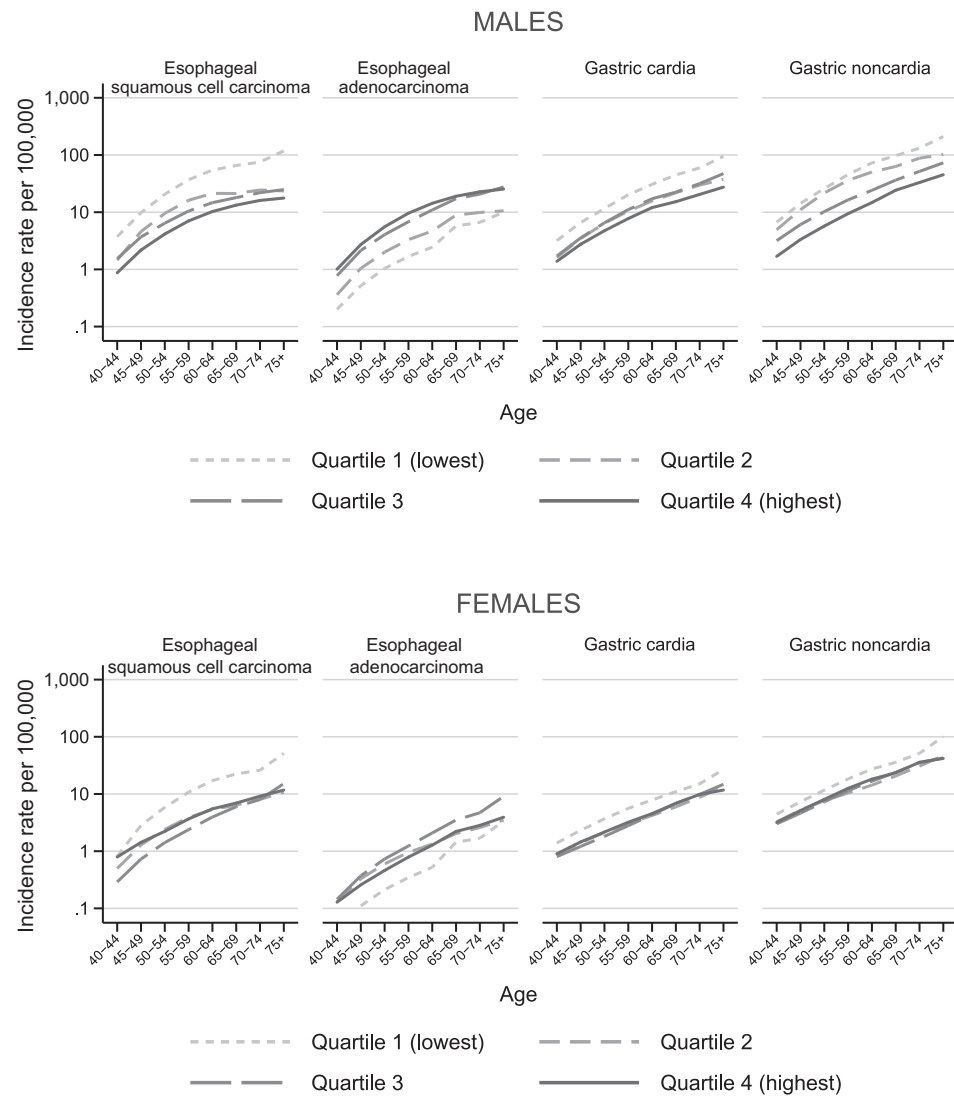


Figure 2. Age-specific incidence rates of esophageal and gastric cancers by sex and obesity quartile (proportion of body mass index ≥ 30 kg/m²).

Discussion

In this study, and for the first time, we assessed age and sex disparities in gastric and esophageal cancer incidence, respectively, by subsite and subtype, in the context of the global obesity epidemic. We showed that taking into account the major subsites and subtypes of both esophageal and gastric cancer is essential when trying to disentangle the potential impact of risk factors on their respective epidemiology. A gradient across obesity quartiles was found for esophageal adenocarcinomas, with the highest incidence rates occurring in countries with the highest prevalence of obesity, particularly for men. In contrast, for ESCC as well as for CGC and NCGC the gradient was reversed, with the highest rates observed in countries with the lowest obesity prevalence. Although for ESCC, differences in incidence between lower and higher obesity quartiles increased with age, differences in the incidence of esophageal adenocarcinomas across ages were most pronounced in countries with a high prevalence of obesity. This only partly applied to CGC and NCGC, where differences were greatest in low obesity countries. Sex differences were greatest for esophageal adenocarcinomas and most pronounced in the high-

est obesity quartile as well as before age 60. For all other sites, sex differences were smallest in the highest obesity quartile.

Obesity is a known risk factor for various morbidities and mortality. Although wide variations exist in its prevalence, overweight (BMI ≥ 25 kg/m²) and obesity (BMI ≥ 30 kg/m²) have been increasing substantially on a global scale. Recent global statistics indicated that 35% of the adult population is overweight and 12% obese (22). Although increases in prevalence have affected both sexes, they have been more pronounced in females. Yet, in recent years, mean BMI of males exceeded that of females in several high-income countries (22, 26). Overweight and obesity prevalence commonly increases with age in females, although males are most likely to be overweight between ages 40 and 60 (27). Also, the prevalence of abdominal or android obesity, most commonly measured by waist circumference, is higher among males than among females (28). Obesity, especially abdominal fat, has been found to promote the development of gastroesophageal reflux and the metaplastic precursor of esophageal adenocarcinoma—Barrett's esophagus (10, 11). In addition, it also acts as an independent risk factor for esophageal adenocarcinoma (29, 30). Although high BMI has been estimated

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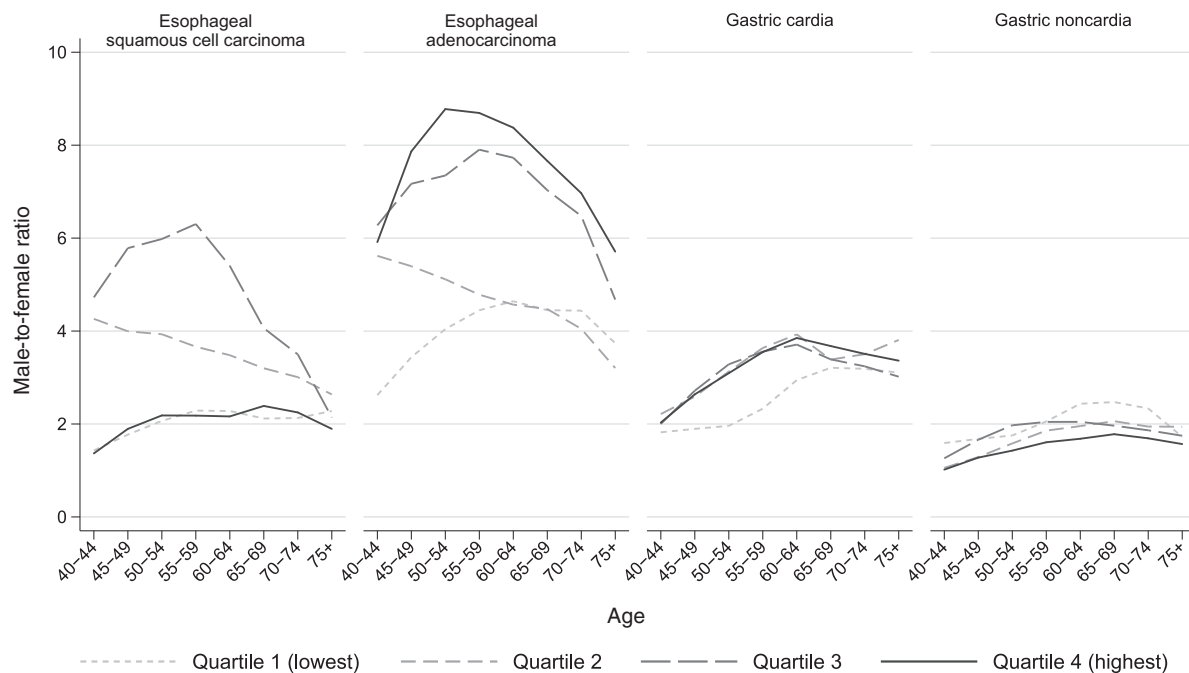


Figure 3.

Male-to-female ratios of esophageal and gastric cancers by age and obesity quartile (proportion of body mass index ≥ 30 kg/m²).

to increase the risk of esophageal adenocarcinoma by 52% (per 5 kg/m² increase in BMI) in males and 51% in females (31), studies looking at waist circumference have shown even stronger effects (32). In contrast, inverse associations for both high BMI and waist circumference have been described for ESCC (Supplementary Fig. S4), independent of smoking status (31, 33). Obesity has also been linked to gastric cancer, with different effects for the two subsites: although being overweight or obese was associated with a 55% increase in risk of CGC, no statistically significant association was observed for NCGC (9). This is consistent with what we found in this study, with the highest incidence rates of CGC, NCGC, and ESCC in the lowest obesity quartile and of esophageal adenocarcinomas in the highest obesity quartile. Yet, gradients were less clear for females, where differences in incidence rates were similar across obesity quartiles 2 to 4 for CGC, NCGC, and ESCC. This might be due to substantially lower rates of all four cancers in females and as to esophageal adenocarcinomas, possibly related to a lower waist circumference in females relative to males.

The two other much discussed risk factors linked to gastric and esophageal cancer—and often mentioned in the context of obesity—are smoking and *H. pylori* infection. Recent evidence has suggested an inverse association of CGC and esophageal adenocarcinomas with *H. pylori* infection, which is most likely due to its potential to lower gastric acid secretion and reduce GERD (14, 15). A similar association has been found between *H. pylori* infection and the prevalence of overweight, where eradication of the bacterium was followed by a significant increase in body weight (34, 35). Gradual decreases in *H. pylori* prevalence, especially in younger birth cohorts, could thus be one of the reasons for the rising incidence of esophageal adenocarcinomas and CGC. Similarly, tobacco smoking is inversely associated with obesity

(32), but increases the risk of ESCC (5) and both types of gastric cancer (6). Recently, it has also been shown to be associated with an increased risk of esophageal adenocarcinomas (7). The combined effect of ongoing decreases in the prevalence of tobacco smoking and *H. pylori* infection has been found to be responsible for 47% of the observed decline in NCGC incidence in the U.S. (36). In our study, we assessed the interaction between smoking and obesity and found an interaction between the two factors for all four cancer sites studied: smoking and obesity clearly had independent effects on incidence of ESCC and esophageal adenocarcinomas, respectively. We also observed a seemingly protective effect of higher BMI on ESCC, which is consistent with previous reports and is thought to be due to reverse causation (33).

Strong male predominance is a well-known and often debated phenomenon in the epidemiology of both gastric and esophageal cancer (37, 38). Yet, the reasons underlying this pattern are still largely unknown. Although smoking did not offer an explanation for sex disparities in esophageal adenocarcinoma incidence (39), higher levels of adipokines such as leptin produced by visceral adipose tissue, which is more often observed in males, have been suggested to contribute to the marked sex differences (40). Patients with Barrett's esophagus were previously found to have a greater waist circumference than population controls, even within strata of BMI (41). This observation supports the hypothesis that central adiposity, rather than BMI, is a better predictor of esophageal adenocarcinoma risk. In general, males are more likely to have a larger waist circumference and develop Barrett's esophagus at younger ages than females (42, 43). This might explain some of our results showing larger sex disparities in the incidence of esophageal adenocarcinomas and CGC in younger age groups (17, 44).

The large sex disparities in esophageal adenocarcinoma incidence, which were most pronounced in countries with higher obesity levels, furthermore suggest that sex steroid hormones may influence this association. Hypotheses include a protective effect of estrogens, responsible for lower risks observed in females, and a positive association with free testosterone, elevating the risk in males. Increased levels of estrogen have been shown to be involved in the suppression of inflammatory responses and cytokine production in certain tissues (45). They could thus have a similar effect on reflux-induced inflammation of the gastro-esophageal junction. Obesity, in turn, increases the circulating levels of estrogen and may therefore protect females against some malignancies such as esophageal adenocarcinomas. Furthermore, breastfeeding has been found to decrease the risk for esophageal and gastric junction adenocarcinoma (46). In males, levels of free testosterone and dihydrotestosterone have been positively associated with an increased risk of Barrett's esophagus (47). The fact that total testosterone levels decrease with age and have been shown to be negatively related with obesity (48) is in line with our observation that sex disparities for both types of esophageal cancer were most pronounced at younger ages and progressively decreased after age 65 years—as opposed to sex differences in gastric cancer incidence, which increased until age 60 years before leveling off. In brief, high levels of testosterone in males, concurring with the protective effect of estrogen in females, could thus partly explain the large difference in incidence of esophageal adenocarcinomas between sexes at younger ages.

Strengths and limitations

To ensure the validity of our approach, we used only high quality data (including only registries that have been selected for CI5) to estimate incidence rates of esophageal and gastric cancers. This was done by applying country-, age-, and sex-specific proportions of esophageal and gastric cancers by subtype/-site obtained from CI5X to GLOBOCAN 2012 estimates. Hence, these rates represent estimates of the true incidence within each country and should be interpreted with caution.

We only included countries represented in CI5X in our analyses, resulting in a selection of 50 mostly high-income countries, which may not be representative on the global level. As a consequence, the obesity groupings and the respective incidence rates depend on the countries included and can potentially change if other countries were included. It is also possible that misclassification of the different cancers has affected our results. This is rather unlikely in the case of ESCC because its histologic appearance is quite distinct from that of esophageal adenocarcinomas. However, misclassification of cancers of the gastro-esophageal junction could have led to an under- or overestimation of both esophageal adenocarcinoma and CGC incidences, with potentially varying effects across countries (15, 49). This might have influenced our results in a way that true patterns for esophageal adenocarcinomas and CGC might be even more distinct than what we found. In our study, we have seen some similarities in the epidemiology of esophageal adenocarcinomas and CGC, which have been argued to represent one clinical entity (15). Adenocarcinomas of the gastro-esophageal junction are thus thought to be a mixed group composed of tumors originating either from the stomach or the lower esophagus. This is why tumors of the gastric cardia are assumed to share risk factors with both NCGC and esophageal adenocarcinomas. The similar sex disparities of

esophageal adenocarcinoma incidence and CGC incidence have been suggested to be related to the intestinal histologic subtype rather than tumor location (17).

Data on obesity prevalence were used for the year 2008 and thus preceded the cancer data, which is biologically plausible and in line with evidence from other studies, even though the precise lag time between the exposure to obesity and the occurrence of cancer is not well established (50). We used an ecologic study design and the results can serve to generate new hypotheses surrounding the relationship between obesity and the different esophageal and gastric cancers. Using this approach, we compared groups of persons and countries with different levels of obesity, including persons both with and without cancer, in order to make inferences about the relationship between obesity and cancer on the individual level. Given the evidence that already exists on the individual level, for example, between esophageal adenocarcinoma and obesity, we do not believe that our results are due to an ecologic fallacy. Furthermore, in this type of study design it is difficult to control for confounding variables, but we did attempt to assess the role of an important confounder such as smoking by including a proxy country-level smoking variable (lung cancer mortality rates) in our sensitivity analyses. The temporal sequence between outcome and exposure is another critical point often ascribed to ecologic studies. In view of large increases in the incidence of esophageal adenocarcinoma among white Caucasian populations in high-income countries, the rising prevalence of obesity has been discussed as the central driver of this development, although some controversy exists around this hypothesis with regard to the temporality of both epidemics (51, 52). Assessing trends in incidence and obesity prevalence, as well as differences across age, cohorts, sex, and subsite/-type could provide further insights into the etiology of those tumors and should be pursued in the future.

Conclusion

In this study, and for the first time, we have assessed age and sex disparities in esophageal and gastric cancer incidence, respectively, by subtype and subsite, in the context of the global obesity epidemic. Obesity had been associated with rises in the incidence of both esophageal adenocarcinoma and CGC and might act in conjunction with sex hormones and potential effect modification of smoking as well as declines in the prevalence of *H. pylori* infection. Higher rates for esophageal adenocarcinomas and CGC in males could be explained by a higher prevalence of abdominal obesity, which is the most metabolically active, and increases the risk of reflux. Considering the different subtypes and subsites of both esophageal and gastric cancer is vital when trying to disentangle the potential impact of risk factors. Ecologic studies as this one can help generate new hypotheses in this field; yet potentially causal associations need to be confirmed using other study designs.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: M. Arnold, A. Colquhoun, D. Forman, I. Soerjomataram

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. Ferlay, I. Soerjomataram
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M. Arnold, A. Colquhoun, M.B. Cook, I. Soerjomataram
Writing, review, and/or revision of the manuscript: M. Arnold, A. Colquhoun, M.B. Cook, J. Ferlay, D. Forman, I. Soerjomataram
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J. Ferlay
Study supervision: I. Soerjomataram

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