Male predominance of upper gastrointestinal adenocarcinoma cannot be explained by differences in tobacco smoking in men versus women

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Abstract

Background—Adenocarcinomas of the upper gastrointestinal tract (UGI) show remarkable male predominance. As smoking is a well-established risk factor, we investigated the role of tobacco smoking in the male predominance of UGI adenocarcinomas in the United States NIH-AARP Diet and Health study.

Method—A questionnaire was completed by 281,422 men and 186,133 women in 1995-1996 who were followed until Dec 31, 2003. Incident UGI adenocarcinomas were identified by linkage to state cancer registries. We present age-standardised cancer incidence rates per 100,000 person-years and Male/Female ratios (M/F) calculated from age-adjusted Cox proportional hazards models, both with 95% confidence intervals.

Results—After 2,013,142 person-years follow up, 338 adenocarcinomas of the oesophagus, 261 of gastric cardia, and 222 of gastric non-cardia occurred in men. In women, 23 tumours of oesophagus, 36 of gastric cardia, and 88 of gastric non-cardia occurred in 1,351,958 person-years follow up. The age-standardised incidence rate of all adenocarcinoma sites were 40.5 (37.8-43.3) and 11.0 (9.2-12.8) in men and women. Among smokers, the M/F of all UGI adenocarcinomas was 3.4 (2.7-4.1), with a M/F of 7.3 (4.6-11.7) for tumours in oesophagus, 3.7 (2.5-5.4) for gastric-cardia, and 1.7 (1.2-2.3) for gastric non-cardia. In non-smokers, M/F ratios were 14.2 (5.1-39.5) for oesophagus, 6.1 (2.6-14.7) for gastric cardia, 1.3 (0.8-2.0) for gastric non-cardia. The overall M/F ratio was 3.0 (2.2-4.3).

Conclusion—the male predominance was similar in smokers and non-smokers for these cancer sites. These results suggest that the male predominance of upper GI adenocarcinomas cannot be explained by differences in smoking histories.

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Keywords

oesophageal adenocarcinoma; gastric cancer; male predominance; smoking

INTRODUCTION

Adenocarcinomas of the upper gastrointestinal tract show remarkable male predominance that is evident in nearly all populations (1). It is well documented in a number of studies on European countries (2-5). Male gender is a well-established risk factor for oesophageal adenocarcinoma (6, 7). Male predominance of gastric cancer incidence also is an invariable observation reported from different populations. Global data suggests that the male predominance of upper gastrointestinal cancer is related to the anatomical location, being higher for proximal and lower for distal tumours (8). Recent data suggests that the male predominance is related to the histological type rather than anatomical location. Tumours with intestinal subtype showed similar male predominance of incidence irrespective of its anatomical location. Further analysis of the age-specific incidence curves indicated that the male predominance of intestinal subtype was due to a 17.3-year delay of development of this cancer in women (9).

The reason for the difference in the development of upper gastrointestinal cancer in women versus men is unclear and deserves further consideration and investigation. There are several possible mechanisms for a delay in development of the adenocarcinoma in females or facilitated development of those tumours in males. Protective effects of reproduction system components in females including oestrogen, progesterones and other hormones were main target of several investigations, but the results still remain inconsistent (10-12). Different body iron storage in men and women is another suspected risk factor. Biologically active iron components have been shown to be involved in many inflammatory and carcinogenic pathways (13-15). The role of mucosal iron radicals in Barrett's metaplasia and oesophageal adenocarcinoma is one of the new challenging fields of research and need to be elucidated.

Non-endogenous risk factors of oesophageal and gastric adenocarcinomas may also contribute to differences in cancer incidence by sex. H.pylori infection as the essential factor in the carcinogenic pathway of most gastric adenocarcinomas has a reasonably equal prevalence in men and women (16-18). In the same manner, gastro-oesophageal reflux disease, as the main risk factor of oesophageal adenocarcinoma, is unlikely to show dramatic differences in prevalence between men and women (19), although, there is no reliable data in this regard because of variable definitions of the disease. Dietary and other life style risk factors of gastric and oesophageal adenocarcinoma might be among suspected factors for these sex differences; however no current candidates can explain the difference in incidence.

Tobacco smoking is a well-established risk factor for upper gastrointestinal cancers. Smoking is a modest but consistent risk factor for non-cardia gastric cancer in populations with different demographic and ethnic backgrounds (20-23). An association between smoking and oesophageal adenocarcinoma has been shown by several studies (21, 24, 25). The male predominance of some common cancers has been linked to different rates of smoking among males and females, as more men than women smoke in many different geographic parts of the world. For example, incidence rates of lung cancer have historically been higher in men than in women worldwide. Yet as the prevalence of smoking in men and women has become more similar, incidence rates of lung cancer in both sexes have also converged (26, 27). Data from large cohort studies indicate similar incidence rates of lung cancer in men and women with similar smoking histories (28, 29). Although the role of smoking in the development of upper gastrointestinal adenocarcinomas are not as large as of

those of lung, the potential role of tobacco smoking as an explanation for the predominance of these tumours in men has not been evaluated. The aim of the current study is to investigate the role of tobacco smoking in the male predominance of upper gastrointestinal adenocarcinomas in a well defined population of the prospective United States NIH-AARP Diet and Health Study.

METHOD & MATERIALS

The NIH-AARP Diet and Health study was initiated in 1995-1996 when a baseline questionnaire was mailed to 3.5 million AARP members aged 50-71 years who resided in eight states (California, Florida, Georgia, Louisiana, Michigan New Jersey, North Carolina, and Pennsylvania) (30). Questionnaires were completed by 617,119 individuals, 566,402 of these questionnaires were completed in satisfactory detail. We excluded respondents with prevalent cancer (except non-melanoma skin cancer, 51,205), subjects whose questionnaire was completed by proxies (15,760), those who died or who were diagnosed with cancer on the first day of follow-up. Respondents who failed to provide information about cigarette use (19,331) or cigar and pipe use (12,539) were also excluded. The analytic cohort included 281,422 men and 186,133 women. The NIH-AARP Diet and Health Study has been approved by the Special Studies Institutional Review Board of the U.S. National Cancer Institute (NCI).

Cohort follow-up

We ascertained vital status by annual linkage to the Social Security Administration Death Master File, questionnaire responses, and responses to other mailings. The addresses for cohort members were updated annually by matching to the United States Post office National Change of Address database, the Maximum Change of Address database (Anchor Computer), and responses to direct mailings.

Identification of cancer cases

Incident cancers were identified by linkage between the NIH-AARP cohort membership and 11 state cancer registry databases (8 states from baseline together with 3 most common states of relocation: Arizona, Nevada, and Texas). Approximately 90% of the cancers occurring in the cohort are detected by this approach (31). Incident adenocarcinomas of the oesophagus (C15.0–C15.9), gastric cardia (C16.0), and gastric non-cardia (C16.1-C16.9) were defined by International Classification of Diseases for Oncology, 3rd Edition codes as previously described (21).

Exposure Assessment

Tobacco use, along with alcohol intake, demographics, physical activity, and dietary intake were assessed via baseline questionaire. Previous validation studies indicate that questionnaires for tobacco use have high reproducibility (r =0.94) and validity (r =0.92 for women and r =0.90 for men relative to serum cotinine levels) (32, 33). Ever smokers had smoked more than 100 cigarettes during their lifetimes or had regularly smoked pipe or cigars for one year or longer.

Statistical Methods

We completed all analyses using SAS version 9.1. All tests were two sided and a significance level of 0.05 was used. Follow-up time started the date the questionnaire was returned (beginning October 25, 1995) and accumulated until diagnosis of UGI cancer, move out of the catchment area, date of death, or December 31, 2003. We calculated age-standardized incidence rates and 95% confidence intervals using five year age bands standardized to the entire NIH-AARP Diet and Health study population (34). For noted

analyses, incidence rates were standardized to the age and smoking use distribution of the entire NIH-AARP cohort using five year age bands and categories of cigarette dose (1-10 cigarettes per day, 11-20 cigarettes per day, 21-30 cigarettes per day, 31-40 cigarettes per day, and > 40 cigarettes per day) and cessation (current smokers, quit 1-4 years previously, quit 5-9 years previously, and quit 10 years previously). The relative risk and 95% confidence intervals for sex and ever smoking were calculated by Cox proportional hazards regression from age-adjusted models. We tested the proportional hazards assumption by modelling interaction terms of time and sex or time and cigarette use and found no significant deviations.

RESULTS

After 2,013,142 person-years follow up, there were 821 new upper gastrointestinal adenocarcinomas, comprising 338 of the oesophagus, 261 of the gastric cardia, and 222 of the gastric non-cardia in men. In women, after 1,351,958 person-years follow up, there were 147 new adenocarcinomas, which included 23 of the oesophagus, 36 of the gastric cardia, and 88 of the gastric non-cardia. The age-standardised incidence rate (cases/100,000 person years) of all adenocarcinoma sites were 40.5 (95%CI: 37.8-43.3) and 11.0 (9.2-12.8) in men and women, respectively, representing of M/F ratio of 3.7 (95%CI: 3.1-4.4). With respect to the different anatomical sites, oesophageal adenocarcinoma showed the highest M/F ratio of 9.7 (95%CI: 6.4-14.8), and more distal locations of cardia and non-cardia sub-sites showed lower M/F ratios, being 4.8 (95%CI: 3.4-6.8) and 1.7 (95%CI: 1.3-2.1), respectively (Table 1).

Next, we examined the incidence of upper gastrointestinal adenocarcinoma in smokers and non-smokers. As previously shown (21), smoking was positively associated with risk for adenocarcinomas of the oesophagus, gastric cardia, and gastric non-cardia in both men and women (Table 2). The male predominance persisted among both smokers and non-smokers. Among smokers, the M/F ratio of all UGI adenocarcinomas was 3.4 (95%CI: 2.7-4.1), with a M/F ratio of 7.3 (95%CI: 4.6-11.7) for tumours in the oesophagus, 3.7 (95%CI: 2.5-5.4) for tumours in the gastric-cardia, and 1.7 (95%CI: 1.2-2.3) for tumours in the gastric non-cardia. For non-smokers, the overall M/F ratio was 3.0 (95%CI 2.2-4.3) in non-smokers. Male to female ratios for individual sites were 14.2 (95%CI: 5.1-39.5) for the oesophagus, 6.1 (95%CI: 2.6-14.7) for the gastric cardia, and 1.3 (95%CI: 0.8-2.0) for the gastric non-cardia.

In further analysis, we calculated the incidence rate and related M/F ratios before and after adjustment for typical smoking dose and for former smokers, age at cessation (Table 3). The similarity of male predominance before and after adjustment for smoking was evident for all sites. The M/F ratio for oesophageal adenocarcinoma before and after adjustment was 9.9 (95%CI: 6.5-15.1) and 8.7 (95%CI: 5.7-13.4). Male to female ratios of cardia and non-cardia locations were 4.9 vs. 4.2 and 1.7 vs.1.7, respectively. The overall M/F ratio for all sites before and after adjustment for smoking was also similar (3.8 vs. 3.4).

DISCUSSION

We investigated whether the male predominance of upper GI adenocarcinoma could be explained by differences in tobacco smoking histories by sex. We found that the male predominance was similar in smokers and non-smokers overall and for oesophageal, gastric cardia and gastric non-cardia sub-sites. Our results suggest that the male predominance of upper GI adenocarcinomas cannot be explained by differences in smoking histories or by differing risks for the association between smoking and risk of these cancers in men and

women. In fact, the male predominance persisted among never smokers and this strongly argues that the difference in incidence rates cannot be explained by tobacco use.

Our study confirms the long recognised male predominance of upper gastrointestinal adenocarcinoma (35, 36). It also highlights the fact that the degree of male predominance increases on moving from the distal stomach to the cardia and to the oesophagus (8). The more marked male predominance at the more proximal sites may be largely explained by the fact that the proportion of tumours of the intestinal histological subtype of adenocarcinoma is highest in the oesophagus, less at the cardia and least in the distal stomach and it is this subtype which is influenced by gender (9).

As in previous studies, we found that smoking was associated with an increased incidence of upper GI adenocarcinomas. In men, smoking is associated with an approximately two-fold increased risk of adenocarcinoma at each of the three anatomical subtypes. In women, smoking was associated with an increased risk of oesophageal and cardia adenocarcinoma and the effect was at least as great as that observed in men. Point estimates for the association of smoking and gastric non-cardia cancer were elevated but not significant. These results are consistent with previous studies (37-39).

Our study had several limitations. First, we used self-reported smoking history and sex differences in reporting could bias our results. However, previous validation studies suggest that Caucasian men and women, who constitute 93% of the cohort, recall smoking use with similar accuracy (32, 40). Second, there may be unaccounted for differences in smoking histories between males and females, such as males smoking more at a younger age when it might have more damaging effects. But, as previously shown (29), the median age at smoking initiation was 17 in both men and women in a subset of this cohort that completed a more detailed follow-up questionnaire. Also, we lacked information on the distal or intestinal histological subtype.

Strengths of our study include use of a prospective cohort where smoking use was assessed prior to cancer diagnosis and this also allowed us to calculate incidence rates rather than only relative differences in disease risk. Men and women also completed the same questionnaire allowing direct comparisons within the same cohort population.

In conclusion, in our cohort the marked male predominance of upper GI adenocarcinoma is not due to tobacco smoking. Other possible environmental factors which might be related to gender need to be considered. Our results suggest that the marked difference in incidence of upper GI adenocarcinoma in males than females is likely related to endogenous factors, such as reproductive hormones, differences in the prevalence of central obesity between males and females, or differences in pre-menopausal iron status.

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Table 1

Age standardized incidence rates per 100,000 person-years of selected cancers in the NIH-AARP cohort, aged 50+ years at baseline.

Cancer type	Men			Women			M/F Ratio[†] (95%CI)
	Years of follow-up	Cases	Rate* (95% CI)	Years of follow-up	Cases	Rate* (95% CI)	
Oesophageal AD	2,013,142	338	16.7 (14.9-18.5)	1,351,958	23	1.7 (1.0-2.4)	9.7 (6.4-14.8)
Gastric Cardia AD	2,013,142	261	12.9 (11.3-14.5)	1,351,958	36	2.7 (1.8-3.6)	4.8 (3.4-6.8)
Gastric non-cardia AD	2,013,142	222	11.0 (9.5-12.4)	1,351,958	88	6.6 (5.2-8.0)	1.7 (1.3-2.1)
All Adenocarcinomas	2,013,142	821	40.5 (37.8-43.3)	1,351,958	147	11.0 (9.2-12.8)	3.7 (3.1-4.4)

*
Age standardised incidence rate per 100,000 person years.

[†]
Risk estimate for sex from age-adjusted Cox proportional hazards models.

Table 2

Age standardized incidence rates per 100,000 person-years of selected cancers in non- smokers and smokers of cigarettes, pipes, or cigars in the NIH-AARP cohort, aged 50+ years at baseline.

UGI Site	Smoking status	Men				Women				M/F ratio[‡] (95%CI)
		Years of follow-up	Cases	Rate[*] (95% CI)	RR[†] for smoking	Years of follow-up	Cases	Rate[*] (95% CI)	RR[†] for smoking	
Oesophagus	Never	500,801	46	9.3 (6.6-12.1)	1.00 (ref)	602,930	4	0.7 (0 -1.3)	1.00 (ref)	14.2 (5.1-39.5)
	Ever	1,512,341	292	19.1 (16.9-21.3)	2.0 (1.5-2.7)	749,028	19	2.6 (1.4-3.8)	3.9 (1.3-11.5)	7.3 (4.6-11.7)
Gastric Cardia	Never	500,801	30	6.0 (3.9-8.2)	1.00 (ref)	602,930	6	1.0 (0.2-1.7)	1.00 (ref)	6.1 (2.6-14.7)
	Ever	1,512,341	231	15.1 (13.2-17.1)	2.4 (1.7-3.4)	749,028	30	4.0 (2.6-5.5)	4.1 (1.7-9.9)	3.7 (2.5-5.4)
Gastric non-cardia	Never	500,801	38	7.7 (5.3-10.2)	1.00 (ref)	602,930	37	6.0 (4.1-7.9)	1.00 (ref)	1.3 (0.8-2.0)
	Ever	1,512,341	184	12.0 (10.3-13.8)	1.7 (1.2-2.3)	749,028	51	7.1 (5.2-9.1)	1.2 (0.8-1.8)	1.7 (1.2-2.3)
All	Never	500,801	114	23.1 (18.8-27.3)	1.00 (ref)	602,930	47	7.6 (5.4-9.8)	1.00 (ref)	3.0 (2.2-4.3)
	Ever	1,512,341	707	46.2 (42.8-49.6)	2.0 (1.7-2.4)	749,028	100	13.8 (11.1-16.5)	1.8 (1.3-2.5)	3.4 (2.7-4.1)

[*] Age standardised incidence rate per 100,000 person years.

[†] Risk estimate for ever-smoking is from an age-adjusted Cox proportional hazards model.

[‡] Risk estimate for sex from an age-adjusted Cox proportional hazards model.

Table 3

Effect of smoking on the male predominance of upper gastrointestinal adenocarcinomas by location of cancer.

Tumour site	Incidence Rate[*] (95% CI) Standardized for age			Incidence Rate[†] (95% CI) Standardized for age and smoking use		
	Males	Females	M/F ratio[‡] (95%CI)	Males	Females	M/F ratio[**] (95%CI)
Oesophagus	16.7 (14.9-18.5)	1.7 (1.0-2.4)	9.9 (6.5-15.1)	16.1 (14.4-17.9)	2.0 (1.1-2.9)	8.7 (5.7-13.4)
Cardia	12.9 (11.3-14.5)	2.7 (1.8-3.6)	4.9 (3.4-6.9)	12.3 (10.8-13.9)	3.3 (2.1-4.6)	4.2 (2.9-5.9)
Non-cardia	11.0 (9.5-12.4)	6.6 (5.2-8.0)	1.7 (1.3-2.2)	11.1 (9.6-12.6)	6.8 (5.2-8.4)	1.7 (1.3-2.2)
All sites	40.5 (37.8-43.3)	11.0 (9.2-12.8)	3.8 (3.1-4.5)	39.6 (36.8-42.4)	12.1 (9.9-14.3)	3.4 (2.9-4.1)

[*] Age-standardised incidence rate per 100,000 person-years.

[†] Age- and cigarette use- standardized incidence rate per 100,000 person-years.

[‡] Risk estimate for sex from a Cox proportional hazards model adjusted for age.

[**] Risk estimate for sex from a Cox proportional hazards model adjusted for age, cigarettes per day and for former smokers, years since cessation.