Population Attributable Risks of Esophageal and Gastric Cancers

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Background: Several risk factors have been identified for esophageal adenocarcinoma, gastric cardia adenocarcinoma, esophageal squamous cell carcinoma, and noncardia gastric adenocarcinoma, but no study has comprehensively examined their contributions to the cancer burden in the general population. Herein, we estimate the population attributable risks (PARs) for various risk factors observed in a multicenter population-based case–control study. *Methods:* We calculated PARs by using 293 patients with esophageal adenocarcinoma, 261 with gastric cardia adenocarcinoma, 221 with esophageal squamous cell carcinoma, 368 with noncardia gastric adenocarcinoma, and 695 control subjects. We included smoking for all four tumor types and *Helicobacter pylori* infection for noncardia gastric adenocarcinoma as established causal risk factors as well as several other factors for which causality is under evaluation. *Results:* Ever smoking, body mass index above the lowest quartile, history of gastroesophageal reflux, and low fruit and vegetable consumption accounted for 39.7% (95% confidence interval [CI] = 25.6% to 55.8%), 41.1% (95% CI = 23.8% to 60.9%), 29.7% (95% CI = 19.5% to 42.3%), and 15.3% (95% CI = 5.8% to 34.6%) of esophageal adenocarcinomas, respectively, with a combined PAR of 78.7% (95% CI = 66.5% to 87.3%). Ever smoking and body mass index above the lowest quartile were responsible for 45.2% (95% CI = 31.3% to 59.9%) and 19.2% (95% CI = 4.9% to 52.0%) of gastric cardia adenocarcinomas, respectively, with a combined PAR of 56.2% (95% CI = 38.1% to 72.8%). Ever smoking, alcohol consumption, and low fruit and vegetable consumption accounted for 56.9% (95% CI = 36.6% to 75.1%), 72.4% (95% CI = 53.3% to 85.8%), and 28.7% (95% CI = 11.1% to 56.5%) of esophageal squamous cell carcinomas, respectively, with a combined PAR of 89.4% (95% CI = 79.1% to 95.0%). Ever smoking, history of gastric ulcers, nitrite intake above the lowest quartile, and *H. pylori* infection were responsible for 18.3% (95% CI = 6.5% to 41.8%), 9.7% (95% CI = 5.4% to 16.8%), 40.7% (95% CI = 23.4% to 60.7%), and 10.4% (95% CI = 0.3% to 79.6%) of noncardia gastric adenocarcinomas, respectively, with a combined PAR of 59.0% (95% CI = 16.2% to 91.4%). *Conclusion:* In this population, a few known risk factors account for a majority of esophageal and gastric cancers. These results suggest that the incidence of these cancers may be decreased by reducing the prevalence of smoking, gastroesophageal reflux, and being overweight and by increasing the consumption of fruits and vegetables. [J Natl Cancer Inst 2003;95: 1404–13]

The incidence of esophageal adenocarcinoma has increased rapidly in the United States and Western Europe over the last three decades. In the United States, the most dramatic increase has occurred in white males, among whom the rate has more than tripled since the mid-1970s *(1)*. Pronounced increases have also been observed among white females and African American males, although the rates in these groups remain much lower *(1)*. Similar but less striking trends have occurred for gastric cardia adenocarcinoma. In contrast, the rates for esophageal squamous cell carcinoma and noncardia gastric adenocarcinoma, which are highest among African American males, have remained stable or decreased during this period *(1)*.

Esophageal cancer, although relatively uncommon, is an important cause of cancer death, with about 13 900 new cases and 13 000 deaths from this disease estimated to occur in the United States in 2003 *(2)*. Gastric cancer is more common than esophageal cancer but accounts for a similar number of deaths, with 22 400 new cases and 12 100 deaths estimated in 2003.

From a multicenter population-based case–control study in the United States *(3–10)*, we previously reported relative risk estimates for a number of factors that were associated with esophageal adenocarcinoma, gastric cardia adenocarcinoma, esophageal squamous cell carcinoma, and noncardia gastric adenocarcinoma. This article presents estimates of the population attributable risk (PAR) for various risk factors observed in this study population. The PAR, which is defined as the proportion of disease in the population that is attributable to a given risk factor (or set of risk factors), is useful in estimating the public health impact of that factor. This measure is sometimes referred

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See "Notes" following "References."

to as PAR percent or population attributable fraction. Because PARs depend in part on the prevalence of risk factors in the population, these estimates may not apply to other populations with different distributions of risk factors. This is one of the first studies to comprehensively examine PARs separately for adenocarcinoma and squamous cell carcinoma of the esophagus, as well as for cardia and noncardia subsites of gastric adenocarcinoma.

MATERIALS AND METHODS

A detailed description of the methods used in this study has been published elsewhere (3). In brief, a population-based case–control study was conducted from 1993 through 1995 in New Jersey, Connecticut, and western Washington State. Persons 30–79 years of age who were newly diagnosed with esophageal adenocarcinoma, gastric cardia adenocarcinoma, esophageal squamous cell carcinoma, or noncardia gastric adenocarcinoma were identified through rapid reporting systems. Control subjects were selected via random-digit dialing (for ages 30–64 years) or via Health Care Financing Administration records (for ages 65–79 years). Control subjects and case patients with esophageal squamous cell carcinoma or noncardia gastric adenocarcinoma (comparison cases) were frequency-matched to case patients with esophageal adenocarcinoma or gastric cardia adenocarcinoma (target cases) by geographic area, 5-year age group, sex (in New Jersey and Washington State), and race (white or other, in New Jersey). Study pathologists reviewed histologic materials and reports from surgery, radiology, and endoscopy (H. Rotterdam for New Jersey and A. B. West for Washington State and Connecticut) using standardized criteria to classify tumors by anatomic site of origin and histology. If a case patient was diagnosed with an indeterminate site of tumor origin by one study pathologist, his/her records were re-reviewed by the other study pathologist, with disagreements being resolved by consensus. Study participants consisted of 293 case patients with esophageal adenocarcinoma, 261 case patients with gastric cardia adenocarcinoma, 221 case patients with esophageal squamous cell carcinoma, 368 case patients with noncardia gastric adenocarcinoma, and 695 control subjects. The study protocol was approved by the Institutional Review Boards of participating institutions, and all subjects provided signed informed consent.

Trained interviewers administered structured, in-person interviews to each subject or the next-of-kin of deceased subjects. The interview elicited information on demographic characteristics, tobacco and alcohol use, diet, medical and medication use history, height and weight history, and occupational history up to 1 year before diagnosis for case patients and date of interview for control subjects. Blood samples were collected in a subset of counties by two of the three study centers (New Jersey and Washington State) for logistical reasons; a 30-mL sample was obtained from subjects alive at the time of interview, including 129 case patients with esophageal or gastric cardia adenocarcinoma, 67 case patients with noncardia gastric adenocarcinoma, and 224 control subjects (63% of case patients and 67% of control subjects who were asked to provide a specimen).

Never smokers were defined as having smoked fewer than 100 cigarettes in their lifetime or fewer than one cigarette per day for 6 months or more. Former smokers were defined as having stopped smoking at least 2 years before the interview. To assess alcohol consumption, subjects were asked about their usual intake of beer, wine, and liquor from the age at which they started drinking at least one alcoholic beverage per month until 1 year before the interview. A drink was defined as 12 ounces of beer, 4 ounces of wine, or 1 ounce of liquor. A never drinker was defined as having consumed fewer than one drink per month. Total alcohol consumption was estimated by adding the number of drinks of beer, wine, and liquor.

Body mass index was computed as usual adult weight in kilograms divided by adult height in meters squared (i.e., kg/m^2). Body mass index was grouped into quartiles defined by sex-specific distributions among control subjects. The frequency and duration of gastroesophageal reflux disease was ascertained by asking the subjects about symptoms including severe heartburn (defined as heartburn sufficiently painful to awaken them or prevent them from sleeping) and acid regurgitation (defined as a sour taste from stomach contents backing up into the throat or mouth). A food-frequency questionnaire was used to assess usual diet, including nitrite intake and the frequency of consumption of fruits and vegetables in the period 3–5 years before diagnosis or interview. Nitrite intake was estimated via a nitrite database used in other epidemiologic studies of gastric cancer in North America (11); quartiles were determined by the sex-specific distributions among control subjects. Frequency of consumption (number of times per day, week, month, or year) of fruits and vegetables was calculated by summing the responses to two questions, one regarding the frequency of consumption of fruits (excluding juices) and the other regarding the frequency of consumption of vegetables (excluding salads and potatoes).

An antigen-specific enzyme-linked immunosorbent assay was used to measure serum levels of immunoglobulin G antibodies to *Helicobacter pylori,* with the antigens generated from a preparation of sonicated whole bacteria containing five different clinical *H. pylori* isolates (12). An absorbance index was calculated from the mean absorbance values at 405 nm of two assays per sample relative to that of reference sera. An *H. pylori*–positive test was defined as having an absorbance index of 1.0 or more, which was previously validated (13).

Odds ratios and 95% confidence intervals for each of the four tumor types were calculated by unconditional logistic regression analysis (14). The risk factors that we examined included the established causal risk factors cigarette smoking (never, former, current) for all four tumor types and *H. pylori* infection (antibody positive or negative) for noncardia gastric adenocarcinoma. We also examined risk factors for which causality is under evaluation, including usual body mass index (sex-specific quartiles) for esophageal and gastric cardia adenocarcinomas; frequency of gastroesophageal reflux disease symptoms (never, 1 or 2 times per year, 3–12 times per year, 13–104 times per year, 105–364 times per year, or daily) for esophageal adenocarcinoma; alcohol consumption (never or <5, 5–11, 12–30, or >30 drinks per week) for esophageal squamous cell carcinoma; and history of gastric ulcers (ever or never) and usual dietary nitrite intake (sex-specific quartiles) for noncardia gastric adenocarcinoma. In this category, we also evaluated low consumption of fruits and vegetables (less than two times per day, which was the median consumption among the control subjects) as a risk factor for all four tumor types but included it only in models of esophageal adenocarcinoma and squamous cell carcinoma, with which it was associated. The intake of fruits and vegetables was examined rather than certain plant-based nutrients that we previously associated with decreased risks of these tumors (9) in

an effort to provide information that could be most readily understood and used by the general public.

We also examined certain factors for which a causal relation to any of these cancers is less well evaluated. These speculative risk factors included usual consumption of cholesterol, animal protein, and fat (sex-specific quartiles). Despite evidence that the use of asthma medications containing theophylline or β-agonists may increase the risk of esophageal adenocarcinoma *(5,15),* it was not possible to disentangle the effects of asthma on cancer risk from the effects of its treatment. Because of this uncertainty and the low PARs observed for these medications in our study, they are not reported in this analysis. All models were adjusted for geographic center (Connecticut, New Jersey, and Washington State), age (<40, 40–49, 50–59, 60–69, and ⩾70 years), sex, race (white or other), income (grouped linearly, in dollars per year: <$15 000, $15 000–$29 999, $30 000–$49 999, $50 000–$74 999, and ⩾$75 000), and respondent type (self or proxy). Models including the nutrient risk factors were also adjusted for energy intake (continuous). All primary risk factors for a given tumor type were included in the model simultaneously to control for reciprocal confounding. However, fruit and vegetable consumption was excluded from models that included the speculative nutrient risk factors (i.e., cholesterol, animal protein, or fat). For noncardia gastric adenocarcinoma, models that were identical except for the inclusion of *H. pylori* status produced comparable risk estimates for non–*H. pylori* factors. Therefore, to increase precision, estimates for all risk factors other than *H. pylori* were calculated in models excluding *H. pylori;* however, estimates for *H. pylori* status were based on models including the other factors. Some of the relative risk estimates in this analysis differ slightly from previously published estimates from this study *(3,4,7–9)* because of the inclusion of additional covariates in the models.

PARs and 95% confidence intervals were estimated by a method that is based on unconditional logistic regression *(16,17).* This method provides adjusted PAR estimates by combining adjusted odds ratio estimates and the observed prevalence of the risk factors among case patients. Because the same logistic models are used to estimate both the odds ratio and the PAR, these measures are adjusted for the same risk factors in the same manner. A PAR adjusted for confounding and stratified by one or more factors is estimated by

$$PAR = 1 - \sum_{k=1}^{K} \sum_{i=1}^{I} \sum_{j=1}^{J} \rho_{ijk} R_{i|j,k}^{-1},$$

where

$$R_{i|j,k} = \frac{\Pr(D=1|X=x_i,\ C=c_j,\ S=s_k)}{\Pr(D=1|X=x_I,\ C=c_j,\ S=s_k)}$$

and

$$\rho_{ijk} = \Pr(X=x_i,\ C=c_j,\ S=s_k|D=1),$$

given disease status D ($D = 1$ denoting presence of disease), a discrete exposure factor X with I levels ($X = x_1, x_2, \ldots, x_I$), a confounder C with J levels ($C = c_1, c_2, \ldots, c_J$), and a stratifying factor S with K levels ($S = s_1, s_2, \ldots s_K$); by convention, x_1 corresponds to the lowest risk category of exposure (i.e., baseline level). The relative risk $R_{i|j,k}$ is estimated by the corresponding odds ratio from the logistic model.

PARs were estimated for individual risk factors and for combinations of factors. The PAR for a combination of risk factors is usually less than the sum of the PARs for each individual factor because, in the logistic models, the relative risk for a combined exposure is approximately multiplicative in the individual exposure relative risks and, therefore, exceeds the relative risk for the additive excess relative risk model; it is possible for the sum of the individual PARs to exceed 100%, although an individual PAR will never exceed that value. A logit transformation *(18)* was used to produce 95% confidence intervals confined to (0,1), except when the estimated PAR was negative, in which case the confidence limits were computed by adding and subtracting 1.96 times the estimated standard error of the PAR. Odds ratios and PARs were estimated separately by sex, although the number of case patients who were women was small and yielded imprecise estimates for most tumor types. PARs were compared between men and women with a chi-square test for two independent samples. All statistical tests were two-sided.

This method of estimating PARs assumes a random sample of case patients from the population; however, the comparison case patients in our study (i.e., with esophageal squamous cell carcinoma or noncardia gastric adenocarcinoma) were frequency-matched to the case patients with esophageal or gastric cardia adenocarcinoma. Therefore, we also estimated the PARs for the comparison cancers by use of the observed prevalence of the risk factors among control subjects *(19),* reweighted to the age, sex, and race distribution of the appropriate states from the 1990 census; these estimates were similar to those obtained with the observed prevalence of the risk factors among case patients, indicating that the comparison case patients in this study were representative of case patients with those cancers in the population. All analyses were performed with the Interactive Risk Assessment Program (IRAP) (available from Dr. Mitchell Gail at gailm@mail.nih.gov).

A PAR represents the proportion of cancer cases that were caused by a risk factor and were thus preventable by eliminating that factor from the population. For each speculative risk factor analyzed in this study, the PAR represents the potential reduction in disease that could be achieved by eliminating that factor if causality were subsequently proven. PARs for well-established and speculative risk factors are clearly distinguished in this article.

RESULTS

As previously reported *(3,8),* the majority of case patients were male for all four tumor types, ranging from 69.0% for noncardia gastric adenocarcinoma to 85.4% for gastric cardia adenocarcinoma (Table 1). Case patients were also predominantly Caucasian, accounting for more than 96% of case patients with esophageal or gastric cardia adenocarcinoma and more than 75% with esophageal squamous cell carcinoma or noncardia gastric adenocarcinoma. The median ages were 64 years for control subjects and 66, 65, 67, and 70 years for case patients with esophageal adenocarcinoma, gastric cardia adenocarcinoma, esophageal squamous cell carcinoma, and noncardia gastric adenocarcinoma, respectively. Almost half of the study subjects were from New Jersey (46.5%), with 30.9% from Connecticut and 22.6% from Washington State. The mean body mass index was 25.1 ± 4.6 kg/m^2 (± standard deviation) for females and 25.4 ± 3.2 kg/m^2 for males. Most control subjects were self-respondents (96.5%), while the proportion of self-

Table 1. Sociodemographic characteristics of case patients and control subjects in a study of esophageal and gastric cancers in Connecticut, New Jersey, and Washington State (1993–1995)

		Case patients			
Characteristic	Control subjects, No. (%)	Esophageal adenocarcinoma, No. (%)	Gastric cardia adenocarcinoma, No. (%)	Esophageal squamous cell carcinoma, No. (%)	Noncardia gastric adenocarcinoma, No. (%)
Total No.	695	293	261	221	368
Sex					
Female	140 (20.1)	48 (16.4)	38 (14.6)	45 (20.4)	114 (31.0)
Male	555 (79.9)	245 (83.6)	223 (85.4)	176 (79.6)	254 (69.0)
Age					
≤44 y	46 (6.6)	15 (5.1)	19 (7.3)	8 (3.6)	18 (4.9)
45–54 y	103 (14.8)	43 (14.7)	38 (14.6)	22 (10.0)	35 (9.5)
55–64 y	208 (29.9)	66 (22.5)	64 (24.5)	57 (25.8)	73 (19.8)
65–74 y	246 (35.4)	119 (40.6)	108 (41.4)	99 (44.8)	168 (45.7)
≥75 y	92 (13.2)	50 (17.1)	32 (12.3)	35 (15.8)	74 (20.1)
Educational level					
Not a high school graduate	130 (18.7)	65 (22.2)	56 (21.5)	88 (39.8)	117 (31.8)
High school/technical school graduate	353 (50.8)	171 (58.4)	146 (55.9)	105 (47.5)	189 (51.4)
College/graduate school	212 (30.5)	56 (19.1)	58 (22.2)	28 (12.7)	61 (16.6)
Income (per year)					
<$15 000	93 (13.4)	60 (20.5)	41 (15.7)	71 (32.1)	87 (23.6)
$15 000–$29 999	177 (25.5)	87 (29.7)	81 (31.0)	75 (33.9)	115 (31.3)
$30 000–$49 999	175 (25.2)	69 (23.6)	65 (24.9)	56 (25.3)	100 (27.2)
$50 000–$74 999	126 (18.1)	42 (14.3)	37 (14.2)	9 (4.1)	46 (12.5)
≥$75 000	124 (17.8)	35 (12.0)	37 (14.2)	10 (4.5)	20 (5.4)
Geographic center					
Connecticut	206 (29.6)	80 (27.3)	82 (31.4)	83 (37.6)	117 (31.8)
New Jersey	333 (47.9)	138 (47.1)	113 (43.3)	99 (44.8)	172 (46.7)
Washington	156 (22.5)	75 (25.6)	66 (25.3)	39 (17.7)	79 (21.5)
Race					
Caucasian	646 (93.0)	289 (98.6)	252 (96.6)	168 (76.0)	306 (83.2)
African American	34 (4.9)	2 (0.7)	4 (1.5)	48 (21.7)	36 (9.8)
Other	15 (2.2)	2 (0.7)	5 (1.9)	5 (2.3)	26 (7.1)
Smoking status					
Never smoker	244 (35.1)	63 (21.5)	53 (20.3)	22 (10.0)	106 (28.8)
Former smoker	296 (42.6)	144 (49.2)	123 (47.1)	91 (41.2)	164 (44.6)
Current smoker	155 (22.3)	86 (29.4)	85 (32.6)	108 (48.9)	96 (26.1)
Cumulative smoking*					
1–20 pack-years	158 (35.0)	56 (24.4)	41 (19.7)	34 (17.1)	70 (26.9)
21–40 pack-years	120 (26.6)	54 (23.5)	64 (30.8)	41 (20.6)	71 (27.3)
41–60 pack-years	79 (17.5)	54 (23.5)	50 (24.0)	49 (24.6)	53 (20.4)
>60 pack-years	93 (20.6)	63 (27.4)	48 (23.1)	72 (36.2)	62 (23.9)
Body mass index at usual weight					
17.6–22.9 kg/m^2	171 (24.6)	48 (16.4)	49 (18.8)	79 (35.8)	108 (29.4)
23.0–24.9 kg/m^2	170 (24.5)	56 (19.1)	54 (20.7)	54 (24.4)	76 (20.7)
25.0–26.9 kg/m^2	163 (23.5)	77 (26.3)	63 (24.1)	46 (20.8)	79 (21.5)
27.0–43.3 kg/m^2	188 (27.1)	111 (37.9)	95 (36.4)	41 (18.6)	102 (27.7)
Interview type					
Self-respondent	671 (96.5)	198 (67.6)	192 (73.6)	144 (65.2)	254 (69.0)
Proxy	24 (3.5)	95 (32.4)	69 (26.4)	77 (34.8)	114 (31.0)

*Restricted to current and former smokers.

respondents among case patients varied between 65.2% and 73.6% for the various tumor types.

Esophageal Adenocarcinoma

Although the relative risk of esophageal adenocarcinoma was higher for current smokers than for former smokers, the PAR was lower for current smokers (16.6%, 95% CI = 10.2% to 25.8%) than for former smokers (23.1%, 95% CI = 13.5% to 36.6%) because of the large proportion of former smokers in this population (Table 2). The PAR for ever smoking was 39.7% (95% CI = 25.6% to 55.8%). The PAR rose with increasing body mass index across quartiles, with a cumulative attributable risk of 41.1% (95% CI = 23.8% to 60.9%), about half of which was from the highest quartile. The frequency of gastroesophageal reflux disease symptoms showed a positive trend in the PAR, with symptoms at least once per day accounting for almost half the PAR associated with the presence of any gastroesophageal reflux disease symptoms (29.7%, 95% CI = 19.5% to 42.3%). Consumption of fruits and vegetables less than twice a day on average had a modest PAR of 15.3% (95% CI = 5.8% to 34.6%). In this population, 78.7% (95% CI = 66.5% to 87.3%) of esophageal adenocarcinoma cases could be attributed to one or more of these well-established risk factors, with smoking and body mass index contributing the most.

Gastric Cardia Adenocarcinoma

PARs for gastric cardia adenocarcinoma were similar for current smoking (21.1%, 95% CI = 14.4% to 29.8%) and former smoking (24.0%, 95% CI = 14.7% to 36.7%), despite the higher relative risk associated with current smoking (Table 3). The

Table 2. Odds ratios (ORs)*, population attributable risks (PARs)*, and 95% confidence intervals (CIs) for the main risk factors for esophageal adenocarcinoma in a case–control study in Connecticut, New Jersey, and Washington State (1993–1995)

Risk factor	OR (95% CI)	% control subjects with risk factor	PAR (95% CI) All subjects	Men	Women
Smoking					
Never	1 (referent)	35.0			
Former	1.9 (1.3 to 2.8)	42.6	23.1 (13.5 to 36.6)	25.9 (14.4 to 42.1)	10.7 (1.1 to 57.2)
Current	2.3 (1.5 to 3.6)	22.4	16.6 (10.2 to 25.8)	19.4 (12.3 to 29.2)	−0.5 (−28.5 to 27.5)
Ever smoker	2.0 (1.4 to 2.9)	65.0	39.7 (25.6 to 55.8)	45.2 (28.1 to 63.5)	10.2 (0.2 to 89.2)
Body mass index at usual weight, by quartile†					
1	1 (referent)	24.9			
2	1.3 (0.8 to 2.2)	25.0	5.4 (1.0 to 23.7)	7.7 (2.3 to 23.0)	−16.1 (−60.3 to 28.1)
3	2.0 (1.2 to 3.2)	25.1	14.3 (7.6 to 25.3)	14.5 (7.2 to 27.0)	14.8 (3.7 to 43.9)
4	2.7 (1.7 to 4.4)	25.0	21.3 (14.2 to 30.8)	22.1 (14.7 to 31.9)	7.4 (0.0 to 94.6)
2–4	2.0 (1.3 to 3.0)	75.1	41.1 (23.8 to 60.9)	44.3 (25.7 to 64.6)	6.1 (0.0 to 100.0)
Frequency of gastroesophageal reflux disease symptoms					
Never	1 (referent)	53.5			
1–2 times/y	0.5 (0.2 to 1.0)	12.1	−3.0 (−5.8 to −0.3)	−3.2 (−6.5 to 0.2)	
3–12 times/y	1.2 (0.7 to 2.0)	11.1	1.1 (0.0 to 35.6)	1.2 (0.0 to 37.0)	−5.5 (−19.9 to 9.0)
13–104 times/y	2.0 (1.2 to 3.1)	11.9	8.3 (4.1 to 16.0)	9.5 (4.7 to 18.1)	5.0 (0.6 to 32.7)
105–364 times/y	3.2 (1.9 to 5.7)	5.5	9.5 (5.9 to 15.0)	8.4 (4.7 to 14.5)	16.7 (8.1 to 31.4)
≥365 times/y	4.9 (2.9 to 8.1)	5.9	13.9 (9.8 to 19.4)	12.3 (8.0 to 18.4)	23.2 (12.9 to 38.1)
Any gastroesophageal reflux disease symptoms	2.0 (1.4 to 2.7)	46.5	29.7 (19.5 to 42.3)	28.3 (17.5 to 42.4)	39.5 (17.2 to 67.3)
Low consumption of fruits and vegetables (<2 times/day)‡	1.4 (1.0 to 1.9)	46.1	15.3 (5.8 to 34.6)	16.3 (5.7 to 38.7)	1.5 (0.0 to 100.0)
PAR for all factors combined			78.7 (66.5 to 87.3)	81.6 (68.9 to 89.9)	50.6 (6.4 to 93.2)

*Adjusted for geographic center (Connecticut, New Jersey, and Washington State), age (<40, 40–49, 50–59, 60–69, and ≥70 years), sex, race (Caucasian and other), income (grouped linearly, in dollars per year: <$15 000, $15 000–$29 999, $30 000–$49 999, $50 000–$74 999, and ≥$75 000), respondent type (self and proxy), and the other factors included in the table.

†Body mass index quartiles are 17.6–23.1, 23.2–25.1, 25.2–27.2, and 27.3–40.2 kg/m^2 for males and 18.0–21.8, 21.9–24.0, 24.1–27.2, and 27.3–43.3 kg/m^2 for females.

‡Based on a food-frequency questionnaire that elicited from subjects their frequency of consumption (i.e., number of times per day, week, month, or year) of fruits and vegetables separately in the period 3–5 years before diagnosis or interview.

Table 3. Odds ratios (ORs)*, population attributable risks (PARs)*, and 95% confidence intervals (CIs) for the main risk factors for gastric cardia adenocarcinoma in a case–control study in Connecticut, New Jersey, and Washington State (1993–1995)

Risk factor	OR (95% CI)	% control subjects with risk factor	PAR (95% CI) All subjects	Men	Women
Smoking					
Never	1 (referent)	35.0			
Former	2.0 (1.4 to 3.0)	42.6	24.0 (14.7 to 36.7)	26.8 (16.4 to 40.7)	8.2 (0.2 to 78.1)
Current	2.8 (1.8 to 4.4)	22.4	21.1 (14.4 to 29.8)	24.0 (16.6 to 33.4)	6.5 (0.3 to 61.3)
Ever smoker	2.3 (1.6 to 3.3)	65.0	45.2 (31.3 to 59.9)	50.8 (34.9 to 66.5)	14.7 (0.9 to 76.7)
Body mass index at usual weight, by quartile†					
1	1 (referent)	24.9			
2	0.9 (0.6 to 1.5)	25.0	−1.6 (−11.5 to 8.2)	−0.6 (−11.1 to 10.0)	−8.3 (−39.6 to 22.9)
3	1.4 (0.9 to 2.2)	25.1	7.9 (2.3 to 24.0)	8.2 (2.2 to 26.1)	12.9 (2.2 to 49.4)
4	1.6 (1.1 to 2.5)	25.0	12.9 (5.6 to 26.9)	15.0 (7.0 to 29.2)	4.1 (0.0 to 97.8)
2–4	1.3 (0.9 to 1.9)	75.1	19.2 (4.9 to 52.0)	22.6 (6.4 to 55.3)	8.7 (0.0 to 99.5)
PAR for all factors combined			56.2 (38.1 to 72.8)	62.4 (43.0 to 78.5)	22.2 (1.0 to 88.6)

*Adjusted for geographic center (Connecticut, New Jersey, and Washington State), age (<40, 40–49, 50–59, 60–69, and ≥70 years), sex, race (Caucasian and other), income (grouped linearly, in dollars per year: <$15 000, $15 000–$29 999, $30 000–$49 999, $50 000–$74 999, and ≥$75 000), respondent type (self and proxy), and the other factors included in the table.

†Body mass index quartiles are 17.6–23.1, 23.2–25.1, 25.2–27.2, and 27.3–40.2 kg/m^2 for males and 18.0–21.8, 21.9–24.0, 24.1–27.2, and 27.3–43.3 kg/m^2 for females.

PAR for ever smoking was 45.2% (95% CI = 31.3% to 59.9%). The PARs appeared to increase with increasing body mass index, although the trend was less pronounced than it was for esophageal adenocarcinoma; the three quartiles above baseline had a combined PAR of 19.2% (95% CI = 4.9% to 52.0%). Neither gastroesophageal reflux disease symptoms nor low fruit and vegetable consumption were associated with gastric cardia adenocarcinoma in this population (data not shown). The PAR for smoking and body mass index combined was 56.2% (95% CI = 38.1% to 72.8%).

Esophageal Squamous Cell Carcinoma

Smoking was a major contributor to esophageal squamous cell carcinoma burden in this population, with ever smoking having a PAR of 56.9% (95% CI = 36.6% to 75.1%) (Table 4). Alcohol consumption showed a trend of increasing PAR with

Table 4. Odds ratios (ORs)*, population attributable risks (PARs)*, and 95% confidence intervals (CIs) for the main risk factors for esophageal squamous cell carcinoma in a case–control study in Connecticut, New Jersey, and Washington State (1993–1995)

Risk factor	OR (95% CI)	% control subjects with risk factor	PAR (95% CI)		
			All subjects	Men	Women
Smoking					
Never	1 (referent)	35.0			
Former	2.1 (1.2 to 3.8)	42.6	22.0 (11.3 to 38.5)	24.1 (11.5 to 43.8)	21.5 (6.3 to 52.7)
Current	3.5 (1.9 to 6.5)	22.4	34.9 (25.0 to 46.4)	33.6 (21.5 to 48.3)	38.6 (21.4 to 59.2)
Ever smoker	2.6 (1.5 to 4.6)	65.0	56.9 (36.6 to 75.1)	57.6 (32.3 to 79.5)	60.1 (27.5 to 85.7)
Frequency of alcohol consumption					
Never	1 (referent)				
<5 drinks/wk	1.3 (0.6 to 3.0)	24.5	2.0 (0.1 to 26.7)	2.4 (0.2 to 20.8)	4.3 (0.1 to 61.2)
5–11 drinks/wk	2.5 (1.1 to 5.6)	18.5	6.9 (3.1 to 14.6)	6.7 (2.8 to 15.2)	12.0 (4.4 to 28.7)
12–30 drinks/wk	4.7 (2.2 to 9.7)	20.4	18.6 (12.5 to 26.7)	18.8 (12.2 to 27.8)	23.9 (12.7 to 40.4)
>30 drinks/wk	9.4 (4.6 to 19.2)	12.8	44.9 (36.7 to 53.4)	52.4 (43.1 to 61.6)	24.4† (13.8 to 39.5)
Any alcohol consumption	4.2 (2.2 to 8.1)	76.1	72.4 (53.3 to 85.8)	80.2 (57.6 to 92.4)	64.6 (37.9 to 84.5)
Low consumption of fruits and vegetables (<2 times/day)‡	1.6 (1.0 to 2.3)	67.7	28.7 (11.1 to 56.5)	21.3 (7.8 to 46.6)	30.6 (10.5 to 62.3)
PAR for all factors combined			89.4 (79.1 to 95.0)	92.8 (82.0 to 97.3)	87.7 (67.1 to 96.1)

*Adjusted for geographic center (Connecticut, New Jersey, and Washington State), age (<40, 40–49, 50–59, 60–69, and ≥70 years), sex, race (Caucasian and other), income (grouped linearly, in dollars per year: <$15 000, $15 000–$29 999, $30 000–$49 999, $50 000–$74 999, and ≥$75 000), respondent type (self and proxy), and the other factors included in the table.

†$P = .0007$ using a chi-square test comparing PARs between men and women.

‡Based on a food-frequency questionnaire that elicited from subjects their frequency of consumption (i.e., number of times per day, week, month, or year) of fruits and vegetables separately in the period 3–5 years before diagnosis or interview.

increasing frequency of consumption, with a PAR of 44.9% (95% CI = 36.7% to 53.4%) for persons consuming more than 30 alcoholic drinks per week compared with never drinkers. Overall, any alcohol consumption had a PAR of 72.4% (95% CI = 53.3% to 85.8%). Low consumption of fruits and vegetables showed a smaller PAR (28.7%, 95% CI = 11.1% to 56.5%) than either smoking or alcohol consumption. The PAR for these risk factors combined was 89.4% (95% CI = 79.1% to 95.0%).

Noncardia Gastric Adenocarcinoma

Ever smoking had a PAR of 18.3% (95% CI = 6.5% to 41.8%) for noncardia gastric adenocarcinoma (Table 5), which

was substantially lower than the corresponding values for the other tumors examined. History of gastric ulcers also had a relatively low PAR of 9.7% (95% CI = 5.4% to 16.8%). Dietary nitrite intake showed a dose–response trend, with the PAR for all quartiles above baseline combined being an appreciable 40.7% (95% CI = 23.4% to 60.7%). Although there was only a small, statistically nonsignificant increased risk associated with *H. pylori* seropositivity, the high prevalence of infection in this population resulted in a PAR of 10.4% (95% CI = 0.3% to 79.6%). Low fruit and vegetable consumption was not associated with a substantial PAR among these subjects (data not shown). Smoking, history of gastric ulcers, nitrite intake, and *H. pylori* sero-

Table 5. Odds ratios (ORs)*, population attributable risks (PARs)*, and 95% confidence intervals (CIs) for the main risk factors for noncardia gastric adenocarcinoma in a case–control study in Connecticut, New Jersey, and Washington State (1993–1995)

Risk factor	OR (95% CI)	% control subjects with risk factor	PAR (95% CI)		
			All subjects	Men	Women
Smoking					
Never	1 (referent)	35.3			
Former	1.3 (0.9 to 1.9)	42.7	11.2 (3.5 to 30.2)	19.7 (9.0 to 37.9)	1.4 (0.0 to 100.0)
Current	1.4 (0.9 to 2.0)	22.0	7.1 (2.1 to 21.1)	8.9 (2.8 to 24.9)	9.6 (2.4 to 31.6)
Ever smoker	1.3 (1.0 to 1.8)	64.7	18.3 (6.5 to 41.8)	28.6 (12.7 to 52.5)	11.0 (0.7 to 69.2)
Gastric ulcer (ever)	2.0 (1.3 to 3.0)	9.3	9.7 (5.4 to 16.8)	10.5 (5.4 to 19.4)	8.5 (2.7 to 23.6)
Nitrite intake (quartiles)†					
1	1 (referent)	25.2			
2	1.5 (1.0 to 2.4)	24.6	8.4 (3.1 to 21.0)	9.3 (3.3 to 23.4)	6.6 (0.4 to 55.3)
3	1.8 (1.1 to 3.0)	25.1	11.4 (5.6 to 21.8)	13.3 (6.6 to 24.8)	7.0 (0.6 to 49.1)
4	2.5 (1.4 to 4.3)	25.1	20.9 (13.2 to 31.4)	22.3 (13.2 to 35.1)	18.6 (7.3 to 40.0)
2–4	1.7 (1.1 to 2.6)	74.8	40.7 (23.4 to 60.7)	44.8 (24.9 to 66.6)	32.2 (7.0 to 74.9)
PAR for all factors combined			55.8 (38.8 to 71.6)	64.4 (45.9 to 79.4)	44.9 (16.1 to 77.6)
Helicobacter pylori antibody positive‡	1.2 (0.6 to 2.5)	38.4	10.4 (0.3 to 79.6)	12.9 (0.6 to 77.2)	—§
PAR for all factors combined (including *H. pylori*)			59.0 (16.2 to 91.4)	65.9 (20.3 to 93.6)	

*Adjusted for geographic center (Connecticut, New Jersey, and Washington State), age (<40, 40–49, 50–59, 60–69, and ≥70 years), sex, race (Caucasian and other), income (grouped linearly, in dollars per year: <$15 000, $15 000–$29 999, $30 000–$49 999, $50 000–$74 999, and ≥$75 000), respondent type (self and proxy), energy intake (continuous), and the other factors included in the table.

†Nitrite intake quartiles are 1.7–5.8, 5.9–7.5, 7.6–9.9, and 10.0–39.2 mg for males and 1.9–5.3, 5.4–6.9, 7.0–9.1, and 9.2–31.2 mg for females.

‡Results are based on 67 case patients and 223 control subjects.

§There were too few female case patients with known *H. pylori* infection status for analysis.

positivity combined accounted for 59.0% (95% CI = 16.2% to 91.4%) of noncardia gastric adenocarcinoma cases.

Speculative Risk Factors

The PARs for these speculative risk factors represent the potential reduction in cancer burden that could be achieved by eliminating these factors if the associations are confirmed to be causal. Dietary cholesterol was associated with all four tumor types in this study, with intake above the lowest quartile accounting for 53.1% (95% CI = 30.5% to 73.7%) of esophageal adenocarcinomas, 32.0% (95% CI = 12.1% to 62.8%) of gastric cardia adenocarcinomas, 38.2% (95% CI = 12.5% to 71.1%) of esophageal squamous cell carcinomas, and 42.9% (95% CI = 24.9% to 63.7%) of noncardia gastric adenocarcinomas. Dietary intake of animal protein contributed to 28.3% (95% CI = 7.0% to 68.4%) of esophageal adenocarcinomas, 22.7% (95% CI = 5.4% to 64.5%) of gastric cardia adenocarcinomas, and 25.9% (95% CI = 5.7% to 68.1%) of esophageal squamous cell carcinomas. Consumption of fat accounted for 30.4% (95% CI = 7.2% to 70.8%) of esophageal adenocarcinomas. These speculative risk factors combined with the well-established risk factors for the respective tumors increased the combined PARs to 89.0% (95% CI = 78.9% to 95.3%) for esophageal adenocarcinoma, 74.7% (95% CI = 56.6% to 86.9%) for gastric cardia adenocarcinoma, 94.2% (95% CI = 86.8% to 97.2%) for esophageal squamous cell carcinoma, and 75.3% (95% CI = 28.4% to 95.8%) for noncardia gastric adenocarcinoma.

Subanalyses

Although appreciable differences were observed between male and female estimates for relative risks and PARs, the female estimates were based on very small numbers and, consequently, were imprecise. The only statistically significant sex difference in PARs was for the highest alcohol consumption category for esophageal squamous cell carcinoma (Table 4). Only two (1.5%) female control subjects were in this category, so this difference should be interpreted with caution.

To address concerns about possible bias, either differential or nondifferential, resulting from the use of proxy respondents, we repeated the above analyses restricted to self-respondents. Results were very similar to those reported (data not shown), suggesting that no important bias was introduced by the use of proxies.

DISCUSSION

Results of this population-based case–control study suggest that a few clinical conditions and modifiable lifestyle factors account for the majority of esophageal and gastric cardia adenocarcinomas, offering opportunities for intervention to reverse the rapidly rising incidence of these cancers. About 79% of the cases of esophageal adenocarcinoma could be attributed to smoking, body mass index, gastroesophageal reflux disease symptoms, or low consumption of fruits and vegetables. More than half (56%) of the cases of gastric cardia adenocarcinoma could be explained by smoking or body mass index. In addition, a large majority (89%) of the cases of esophageal squamous cell carcinoma could be accounted for by smoking, alcohol consumption, or low consumption of fruits and vegetables. Most (59%) of the cases of noncardia gastric adenocarcinoma were attributable to smoking, gastric ulcers, elevated dietary nitrite intake, or *H. pylori* infection.

The established risk factors that were included in this analysis, and described in greater detail in previous reports from this study (3,4,7–9), have been confirmed by a number of other studies as follows: associations of excess weight with esophageal adenocarcinoma (20–25) and gastric cardia adenocarcinoma (20,22,24,26); gastroesophageal reflux disease symptoms with esophageal adenocarcinoma (27–29); smoking with esophageal and gastric cancers (20,24,30–48); alcohol consumption with esophageal squamous cell carcinoma (24,31–33,37,49); low consumption of fruits and vegetables with esophageal adenocarcinoma and squamous cell carcinoma (21,25,50–57); and gastric ulcers, nitrite intake, and *H. pylori* infection with noncardia gastric cancer (11,40,58–66).

Several studies have reported an inverse association of fruit and vegetable intake with risk of gastric cancer (67–71). We found no evidence of such an association in this study, although we did observe an inverse relation with estimated dietary and supplemental vitamin C intake (9). Such inconsistencies among study populations may result from differences in the types of fruits and vegetables consumed or in their methods of preparation.

The weak association observed in this study between noncardia gastric adenocarcinoma and *H. pylori* infection, a well-established major risk factor for this tumor (65,66), is probably explained in part by the loss of *H. pylori* colonization associated with atrophic gastritis of the corpus and its progression to gastric cancer (72), which can lead to *H. pylori* seroreversion among previously infected patients with gastric cancer (73). Results of a recent pooled analysis of nested case–control studies of *H. pylori* and gastric cancer (66) suggested that the association is underestimated when *H. pylori* status is assessed close to the time of cancer diagnosis. That study also observed less of an association among subjects older than 60 years; the median age of case patients with noncardia gastric cancer in our study was 70 years. In the pooled analysis, the relative risk estimates for noncardia gastric adenocarcinoma in the individual studies ranged from 1.5 to 11.1, with a pooled estimate of 5.9 (95% CI = 3.4 to 10.3). Worthy of further study is the inverse association that we observed between *H. pylori* infection and esophageal/gastric cardia adenocarcinoma (7), possibly related to a protective effect of *H. pylori* colonization of gastric mucosa, which inhibits the production and subsequent reflux of gastric acid.

Associations between nutrients and the four tumors examined in this study have not been well established. Few of the studies that examined this question were population-based. Inconsistent results have been reported for the association of fat, cholesterol, and animal protein intake with these tumors (25,33,56,67,68,74, 75). Our PAR estimates for these factors should be interpreted with caution until these associations are confirmed in future studies. Other risk factors for these cancers have been suggested but were not included in these analyses because the evidence was inconclusive or because we did not find such associations in our data.

The PAR estimates in the present study resemble those reported in previous studies of North American populations with similar distributions of the pertinent risk factors. In a Washington State study (24), the estimated PARs for smoking and body mass index in relation to esophageal and gastric cardia adenocarcinomas were comparable to estimates in our study, although we did not confirm the association reported with alcohol consumption. For esophageal squamous cell carcinoma, the PAR

estimate of 73% for smoking in the Washington State study was somewhat higher than in our study, but the estimates for alcohol consumption were comparable. Several studies have reported PAR estimates for smoking or alcohol consumption in relation to esophageal cancer that resemble our estimates for esophageal squamous cell carcinoma *(76–78),* which would be expected, given that these studies were conducted at a time when squamous cell carcinomas accounted for most esophageal cancers. In addition, a Canadian case–control study of gastric cancer *(76)* reported estimates that were similar to the attributable risk that we found for smoking.

Attributable risks tended to be lower for females than for males, particularly for lifestyle factors such as smoking and alcohol consumption, due mainly to lower intake levels among women. However, the appreciably lower incidence of these tumors among females than among males resulted in few female case patients in our study, except for those with noncardia gastric adenocarcinoma. The risk estimates for females consequently had very wide confidence intervals, limiting their interpretation and comparison to the estimates for males.

Time trends in the prevalence of several lifestyle risk factors have probably contributed to the divergent incidence trends of these tumors. Previous analyses of smoking patterns among subjects in our study suggest a latency period of approximately 30 years for smoking and the risk of esophageal and gastric cardia adenocarcinomas *(3).* Therefore, the increasing prevalence of cigarette smoking among American men from the early 1900s until the 1960s may partially account for the rising incidence of these cancers in recent decades. In contrast, smoking appears to act at later stages in the development of esophageal squamous cell carcinoma *(3).* The 44% decline in the prevalence of smoking in the United States between 1965 and 1999, partially offset by an increase in smoking among teenagers since the late 1980s *(79),* is likely to decrease the PAR of this cancer from smoking in the coming years. However, dramatic increases between 1960–1962 and 1988–1994 in the prevalence of being overweight and obese among Americans (increases of 25% and 75%, respectively) *(80),* along with a parallel increase in the prevalence of gastroesophageal reflux disease *(81),* will likely continue to contribute to the upward trends of esophageal and gastric cardia adenocarcinomas. Consumption of fruits and vegetables, which reduces the risk of various cancers, has increased slightly in recent years but remains below recommended levels *(82,83).*

Use of aspirin and other nonsteroidal anti-inflammatory drugs was associated with a 50%–60% reduction in the risk of esophageal adenocarcinoma, esophageal squamous cell carcinoma, and noncardia gastric adenocarcinoma in our study *(6).* Other studies have reported similar findings *(84,85).* We did not include these medications in the present analyses because evidence for their protective effect on esophageal and gastric cancers is limited and because our main focus was on the clinical conditions and lifestyle factors that elevate risk and are potentially remediable.

Although our population-based study is one of the largest to date of esophageal and gastric cardia adenocarcinoma, it has some limitations. Most of the risk factors examined were based on self-reported data and may be subject to recall bias. We conducted structured personal interviews to minimize such concerns. In addition, several variables that were considered were not widely known to be risk factors for these cancers and thus would be less likely to be systematically overreported or underreported by subjects. Comparison of associations across the different tumor types, which have generally dissimilar risk factors, also provided no evidence of differential recall or selection bias. There was probably some random misclassification in factors such as diet that have complex patterns, which would tend to attenuate risk estimates. The central etiologic role of gastroesophageal reflux disease in esophageal and probably gastric cardia adenocarcinomas was likely to be underestimated by our study because of difficulties in detecting gastroesophageal reflux disease by interview data alone. Subanalyses excluding proxy respondents produced results comparable to those of analyses including all subjects, indicating no evidence of appreciable bias from the use of surrogates. Blood specimens, used to assess *H. pylori* status, were provided by only 58% of case patients with noncardia gastric adenocarcinoma and 67% of control subjects who were asked to provide a specimen. Among both case patients and control subjects who were asked for a specimen, donors were more likely than non-donors to be male, but the groups had similar age and ethnic distributions. In addition, risk estimates for all factors other than *H. pylori* seropositivity were similar between subjects who did and did not provide a blood sample.

In conclusion, a few well-established risk factors account for a majority of esophageal and gastric cancers in this study population. These factors include smoking, being overweight, having gastroesophageal reflux, and consuming low amounts of fruits and vegetables for esophageal adenocarcinoma; smoking and being overweight for gastric cardia adenocarcinoma; smoking, heavy alcohol use, and consuming small amounts of fruits and vegetables for esophageal squamous cell carcinoma; and smoking and having gastric ulcers, elevated nitrite intake, or *H. pylori* infection for noncardia gastric adenocarcinoma. The rapid increase in the incidence of esophageal and gastric cardia adenocarcinomas appears to result from increases in the prevalence of several modifiable and interrelated risk factors. Efforts to reduce the prevalence of being overweight, having gastroesophageal reflux, and smoking and to improve diet could reverse this troubling cancer trend.

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