Research Article

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A Prospective Cohort Study on Overweight, Smoking, Alcohol Consumption, and Risk of Barrett's Esophagus

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Abstract

Background: Barrett's esophagus (BE) is a precursor lesion of esophageal adenocarcinoma. Besides gastroesophageal reflux, possible risk factors for BE include overweight, cigarette smoking, and alcohol consumption. Our objective was to study these associations by using prospective data.

Methods: The prospective Netherlands Cohort Study, initiated in 1986, consists of 120,852 men and women, aged 55 to 69 years at baseline. At baseline, all subjects completed a questionnaire on dietary habits and lifestyle. After 16.3 years of follow-up, 370 BE cases with specialized intestinal metaplasia and 3,866 subcohort members were available for case–cohort analysis. Cox proportional hazards models were used to calculate incidence rate ratios (RR) and 95% CIs.

Results: Body mass index (BMI) at baseline was associated with risk of BE in women [multivariable adjusted RR per 1 kg/m^2, 1.07 (1.03–1.11)] but not in men [RR per 1 kg/m^2, 0.99 (0.93–1.05)]. The association in women was not specifically due to abdominal overweight. Former cigarette smokers were at increased risk of BE (RR = 1.33, 95% CI: 1.00–1.77), but current smokers were not. Smoking duration showed a positive association with BE risk ($P_{trend} = 0.03$). For alcohol consumption, the RR per 10 g ethanol/d was 0.95 (0.87–1.03).

Conclusions: Increased BMI was a risk factor for BE in women but not in men. Several aspects of cigarette smoking were positively associated with BE risk. Alcohol consumption was not associated with an increased risk of BE.

Impact: Future research should focus on risk factors both for development and for progression of BE to esophageal adenocarcinoma. *Cancer Epidemiol Biomarkers Prev; 20(2); 345–58. ©2010 AACR.*

Introduction

Barrett's esophagus (BE) is a condition of the distal esophagus characterized by the replacement of the normal stratified squamous epithelium with a single layer of columnar epithelium. Histologic confirmation based on biopsies is required for diagnosis. According to the U.S. definition of BE, the presence of goblet cells, indicating specialized intestinal metaplasia (SIM), is required (1). The U.K. definition is less stringent: the presence of any type of metaplasia is sufficient for a diagnosis of BE (2). Both the U.S. and U.K. definitions have been used in the Netherlands, where the incidence of diagnosed BE (according to the U.S. definition) increased from 12.7 to 18.4 per 100,000 men and from 6.5 to 8.6 per 100,000 women between 1992 and 2003 (world standardized rates). The male-to-female ratio is approximately 2 (3).

BE is primarily of interest because it is associated with an increased risk of esophageal adenocarcinoma, a cancer with high mortality. The estimates of this risk of esophageal adenocarcinoma in BE patients vary between 4.1 and 6.1 per 1,000 person-years (4). In Western countries, the incidence of esophageal adenocarcinoma has strongly increased in the past decades (5–7).

The most recognized and strong risk factor for BE is chronic gastroesophageal reflux (8). In addition, overweight, cigarette smoking, and alcohol consumption might be associated with risk of BE. These factors are interesting, as they are potentially modifiable. However, the body of evidence on the role of these factors in the etiology of BE is sparse, particularly data from prospective cohort studies are lacking.

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The possible role of overweight in the etiology of BE has been investigated in several epidemiologic studies. Null associations (9, 10) and positive associations (11–13) have been found in case–control studies. The only prospective cohort study, which was conducted among women, reported a positive association (14). The relationship between cigarette smoking and risk of BE has been studied in some case–control studies (10, 12, 15, 16), whereas no cohort studies have reported on this relationship. Some observed a positive association (10, 12), whereas other studies did not observe an association (9, 16). Alcohol consumption, and its possible relationship with BE, has been studied in a few case–control studies. Null associations with alcohol have been observed (15, 17), and one study (18) found alcohol to be a risk factor. Inverse associations have been reported for wine consumption (15, 17).

The aim of this study was to investigate the associations between overweight, smoking, and alcohol consumption and risk of BE within the prospective Netherlands Cohort Study (NLCS) on diet and cancer.

Methods

Study design and subjects

The NLCS was started in September 1986. Cohort members were selected at random from 204 Dutch municipal registries, and 58,279 men and 63,573 women aged 55 to 69 were enrolled in the study. All members of the cohort completed a self-administered questionnaire. A detailed study design has previously been published (19).

For efficiency, we used a case–cohort approach (20) for data processing and analysis. Cases were derived from the entire cohort, whereas the number of person-years at risk in the entire cohort was estimated from a subcohort of 5,000 subjects. This subcohort was selected at random from the full cohort at baseline.

The subcohort was followed up for vital status, first actively, by biennially contacting the subcohort members and, later, by linkage to the Dutch municipal population registries. After 16.3 years (September 1986 to December 2002), only 1 male subcohort member was lost to follow-up. We excluded subcohort members who reported having prevalent BE or cancer (other than skin cancer; $n = 230$) at baseline (Fig. 1).

The Medical Ethics Committee of Maastricht University, the Netherlands, has approved the study.

Follow-up

In the Netherlands, individuals are eligible for an esophagogastroduodenoscopy if they have symptoms that may indicate gastrointestinal problems. If the endoscopist suspects BE during the endoscopy, biopsy samples will be taken and sent to a pathology laboratory(21). There are 64 pathology laboratories in the Netherlands that are connected through the nationwide network and registry of histopathology and cytopathology in the Netherlands (PALGA; ref. 22). At each laboratory, summaries

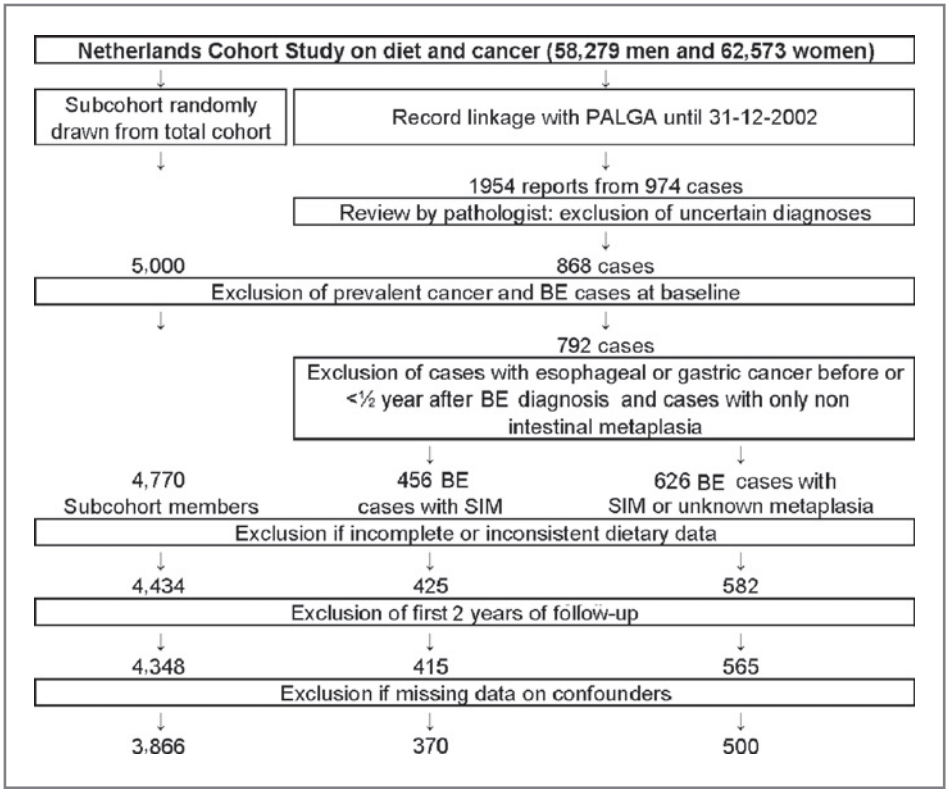

Figure 1. Flow diagram of subcohort members and BE cases on whom the analyses were based.

of all pathology reports are generated automatically. Each summary contains information on topography, morphology, function, procedure, and disease. These summaries are transferred to a central databank (22). Quality and completeness of the summaries are checked in both the local and central databanks. The existence of this nationwide pathology database is globally unique.

We carried out a computerized record linkage with PALGA to identify incident BE cases in the total cohort. We searched PALGA using the keywords "Barrett" and "metaplasia + esophagus." The linkage with PALGA was carried out for 16.3 years of follow-up. PALGA was founded in 1971, and an increasing number of laboratories joined PALGA such that it covered all 204 municipalities from which the cohort members were sampled since 1991. Because of this incomplete coverage, we may have missed BE cases diagnosed between baseline (1986) and 1991. We calculated how many cases we may have missed by multiplying the mean number of cases per year during the period a laboratory was connected by the number of years the laboratory was not connected to PALGA. This was done for each laboratory. This way we calculated that we may have missed approximately 3% of BE cases.

After the record linkage, one pathologist (A.L.C.D.) and one pathologist in training (C.J.R.H.), who were blinded to the exposure status of the cases, reviewed the summaries of all pathology records. Excluded were cases with an uncertain diagnosis of BE ($n = 106$) and cases that had prevalent cancer or BE at baseline ($n = 76$). In addition, we excluded cases ($n = 58$) with a diagnosis of esophageal or gastric cancer before or less than a half year after the diagnosis of BE and cases ($n = 108$) with a diagnosis specifying the presence of only nonintestinal type metaplasia (Fig. 1).

Two definitions of BE were used: our primary case definition included only subjects with esophageal SIM ($n = 456$). The secondary case definition included subjects (a) fulfilling the primary case definition or (b) with a pathology report stating "Barrett's," without a description of the type of metaplasia (total $n = 626$).

Exposure data

All cohort members completed a self-administered questionnaire at baseline. This questionnaire contained a 150-item food frequency questionnaire (FFQ), including detailed questions on alcohol consumption, and questions on various other cancer risk factors.

Overweight was measured by several variables: body mass index (BMI) at baseline, BMI at age 20 years, BMI change, and pant/skirt size (as a proxy for waist circumference; ref. 23). BMI at baseline and BMI at age 20 years were calculated using weight at baseline and weight at age 20 years, respectively, divided by height at baseline squared (kg/m^2). Subjects with missing values for BMI at baseline were excluded from all analyses. Subjects with a BMI under 18.5 were excluded, as there were no cases in this category. BMI change since age 20 years was calculated as BMI at baseline minus BMI at age 20 years. Recently, the use of self-reported pant/skirt size as a proxy measure for waist circumference was validated in the NLCS (23).

Questions were asked about the following aspects of cigarette smoking: whether the subject was a smoker at baseline, age at smoking initiation, age at smoking cessation, the number of cigarettes smoked daily, and the number of smoking years (excluding stopping periods). On the basis of these questions, the following variables were constructed: smoking status (never/former/current), current smoking (yes/no), frequency (*n* cigarettes/d), duration (*n* years), pack-years of cigarette smoking (*n*), and time since cessation (years).

The habitual consumption of alcohol during the year preceding the start of the study was measured by 6 items in the questionnaire: (a) beer, (b) red wine, (c) white wine, (d) sherry and other fortified wines, (e) liquor types containing, on average, 16% alcohol, and (f) (Dutch) gin, brandy, and whiskey. Questions were asked about the frequency of consumption and the number of glasses consumed on each drinking occasion. For analysis, we combined (b), (c), and (d) into "wine" and (e) and (f) into "liquor." Mean daily alcohol consumption was calculated using the Dutch food composition table (24). For "'beer" and "other alcoholic beverages," participants could indicate whether 5 years ago, they drunk (a) more than, (b) equal amounts of, or (c) less than today. The fourth answering option was (d) "I never use this." Using these questions, we selected participants with stable alcohol consumption to conduct a sensitivity analysis.

The FFQ has been validated against a 9-day diet record, and the Spearman correlation coefficient between the alcohol intake assessed by the questionnaire and that estimated by the diet record was 0.89 for all subjects and 0.85 for users of alcoholic beverages (25). The reproducibility of the FFQ was established and the test–retest correlation was 0.90 for alcohol intake, and this correlation declined only 0.01 to 0.02 per year (26). This indicates that the single FFQ measurement could rank subjects according to alcohol intake and this ability dropped only slightly over time. The single FFQ measurement that is used in our cohort study can characterize dietary habits for a period of at least 5 years (26).

Questionnaire data were key-entered and processed in a standardized manner, blinded with respect to case/subcohort status in order to minimize observer bias in coding and data interpretation.

Statistical analysis

To evaluate the potential influence of prediagnostic BE at baseline on smoking and alcohol consumption habits and BMI, BE cases were categorized according to the year of follow-up in which they were diagnosed. A *t* test was used to compare the differences in mean levels of these exposures between early (0–2 years) and late (2–16.3 years) follow-up. For the *t* test, the exposures were ln (natural logarithm) transformed to normalize the

distributions. The average daily alcohol consumption among early cases (2.8 g ethanol) was statistically significantly lower than among late cases (10.2 g ethanol; figures for cases with SIM). Therefore, we decided to exclude these early cases from all analyses in order to prevent bias. In addition, subcohort members and cases with inconsistent or incomplete dietary questionnaire data (25) and those with missing data on the confounders were excluded. Complete data were available for 3,866 subcohort members, 370 BE cases fulfilling the primary case definition, and 500 BE cases fulfilling the secondary case definition (Fig. 1).

The multivariable regression models included the following variables: age, sex, BMI (kg/m^2), cigarette smoking (current, frequency, and duration), and alcohol consumption (g/d). Exact model specifications can be found in the table footnotes. The following variables were potential confounders but were not included in the models because they did not change the incidence rate ratio (RR) by more than 5%: highest level of education, family history of esophageal or gastric cancer, reported long-term (>0.5 years) use of nonsteroidal anti-inflammatory drugs (NSAID) or aspirin, lower esophageal sphincter (LES) relaxing medication (27, 28), nonoccupational physical activity, and daily intakes of vegetables and fruit.

Multivariable adjusted RRs and corresponding 95% CIs were estimated using Cox proportional hazards models (29). The Stata 9.2 statistical software package (StataCorp) was used for analysis. Standard errors were estimated using the robust Huber–White sandwich estimator to account for additional variance introduced by sampling from the cohort. This method is equivalent to the variance–covariance estimator by Barlow and colleagues (30). We tested the proportional hazards assumption by using the scaled Schoenfeld residuals (31). Tests for dose–response trends were assessed by fitting ordinal exposure variables as continuous terms. Two-sided P values are reported throughout the article. Interaction with sex was assessed by including a cross-product term in the model. If the interaction was statistically significant, we presented only results stratified by sex.

Results

Incidence of BE in the cohort

The age-specific incidence rates of BE with SIM in the NLCS increased with age and were higher among men than among women. For men 55 to <65, 65 to <75, and 75 to <85 years of age, these rates were 14, 37, and 50 per 100,000 person-years, respectively, whereas the rates for women in the same age categories were 10, 24, and 37 per 100,000 person-years. The male-to-female ratio of the incidence between ages 55 and 85 was 1.40.

Characteristics

With respect to the characteristics mentioned in Table 1, there were no important differences between the BE cases fulfilling the primary and secondary case definitions. The most marked differences between subcohort members and cases are the following. Cases were more likely to be men and former smokers than subcohort members, whereas cases had a slightly lower ethanol intake. The BMI at baseline and the change in BMI from age 20 were somewhat higher among cases than among the subcohort. Furthermore, cases were somewhat less physically active and consumed somewhat less fruit and vegetables than the subcohort. NSAIDs and aspirin, and LES relaxing medication, were more likely used by cases than by subcohort members.

Cox regression results

All results from Cox regression analyses were very similar for BE cases defined by primary and secondary case definitions. We therefore showed only the results based on the BE cases that met the primary case definition. Likewise, only multivariable adjusted results are shown, as these were very similar to the age-adjusted results (see Supplementary Tables 1–3).

Overweight

Women who were overweight (BMI = 25 to <30) or obese (BMI: ≥30) at baseline were at increased risk of BE. Compared with normal weight (BMI = 18.5 to <25) women, the RRs were 1.73 (95% CI: 1.22–2.44) for overweight and 1.67 (95% CI: 0.96–2.90) for obese women. The results for men were significantly different from those for women ($P_{interaction} = 0.01$). Men who were overweight or obese at baseline were not at increased risk of BE: RRs were 0.85 (95% CI: 0.63–1.14) and 1.21 (95% CI: 0.60–2.47), respectively (Table 2).

An interaction with sex was also found for BMI at age 20 ($P_{interaction} = 0.01$). A positive association was found for women (RR for BMI ≥25 at age 20 years = 1.56, 95% CI: 0.79–3.10), $P_{trend} = 0.05$], whereas an inverse association was found for men (RR for BMI ≥25 at age 20 years = 0.37, 95% CI: 0.15–0.87, $P_{trend} = 0.02$). A change in BMI during adulthood was not associated with risk of BE in men, but a positive trend was observed in women ($P_{trend} = 0.01$), mainly because women who lost weight during adulthood were at decreased risk (RR = 0.33, 95% CI: 0.15–0.75) when compared with those who gained 0 to less than 4 BMI points. The multivariable adjusted results differed from the age-adjusted results, and this difference was caused by the adjustment for BMI at age 20.

When RRs for BMI at baseline were additionally adjusted for pant/skirt size, the associations for women were somewhat attenuated; for men, the associations were similar when compared with analyses without adjustment for pant/skirt size. Analyses with pant/skirt size as independent variable showed a positive association in women ($P_{trend} = 0.01$), which disappeared after adjustment for BMI at baseline. For men, no association was observed for pant/skirt size ($P_{trend} = 0.73$), and adjustment for BMI at baseline did not change this observation (Table 2).

Table 1. Characteristics of cases and subcohort members in the NLCS (1986–2002)

Characteristic	Mean (SD)[a]		
	Subcohort ($n = 3,866$)[b]	BE cases	
		SIM ($n = 370$)[b]	SIM or unknown metaplasia ($n = 500$)[b]
Age at baseline, y	61.3 (4.2)	61.1 (4.3)	61.3 (4.2)
Men, %	49.0	57.3	56.2
Cigarette smoking status, %			
Never smoker	37	33	33
Former smoker	36	46	44
Current smoker	27	21	23
Ever cigarette smokers			
Frequency of cigarette smoking, *n*/d	15.3 (10.3)	16.0 (10.8)	16.1 (10.4)
Duration of cigarette smoking, y	31.5 (12.2)	30.8 (11.8)	30.9 (12.0)
Pack-years of cigarette smoking, *n*	22.6 (17.8)	22.6 (16.7)	22.9 (16.8)
Abstainer from alcohol, %	23	20	21
Alcohol consumers			
Ethanol intake, g/d	13.5 (15.0)	12.9 (15.0)	13.1 (14.9)
Beer intake, glasses/d	0.3 (0.8)	0.3 (0.7)	0.3 (0.7)
Wine intake, glasses/d	0.5 (0.8)	0.5 (0.7)	0.5 (0.8)
Liquor intake, glasses/d	0.5 (0.8)	0.5 (0.8)	0.5 (0.8)
BMI at baseline, kg/m^2	25.1 (3.0)	25.4 (2.8)	25.5 (2.8)
BMI at age 20 y, kg/m^2	21.5 (2.6)	21.6 (2.5)	21.6 (2.6)
BMI change from age 20 to baseline, kg/m^2	3.6 (3.3)	3.8 (3.0)	3.8 (3.1)
Nonoccupational physical activity, min/d	74 (61)	69 (53)	70 (55)
Fruit consumption, g/d	178 (120)	171 (118)	172 (116)
Vegetable consumption, g/d	195 (82)	189 (77)	184 (76)
Highest level of education, %			
Primary	28	28	31
Lower vocational	22	20	20
Secondary and medium vocational	36	36	34
University and higher vocational	14	16	15
Family history of esophageal or gastric cancer, %	7	7	7
Use of NSAIDs and aspirin,[c] %	7	10	10
Use of LES relaxing medication,[c] %	14	17	18

[a]For categorical variables, a percentage is presented.
[b]Presented are the number of subcohort members or cases with complete data on age, sex, cigarette smoking (current yes/no, number of cigarettes smoked daily, number of smoking years), alcohol consumption and BMI. Subcohort members and cases with incomplete or inconsistent questionnaire data are excluded, as well as the first 2 years of follow-up.
[c]Self-reported use during more than 0.5 year.

Cigarette smoking

In the multivariable regression analyses on cigarette smoking (Table 3), we did not observe any statistically significant differences between associations for men and women, which permitted us to report the results for both sexes combined. Nearly all RRs associated with aspects of cigarette smoking were above unity, although these were mostly not statistically significant. Former smokers were at highest risk of BE (RR = 1.33, 95% CI: 1.00–1.77) when compared with never smokers, but current smokers were not at higher risk. Smoking frequency was found to be related to a nonsignificantly higher risk of BE ($P_{trend} = 0.46$). A longer duration of cigarette smoking was associated with an increasing risk of BE ($P_{trend} = 0.03$). Results on the association between pack-years of smoking and BE showed increased RRs, but only for subjects who had smoked 20 to less than 40 pack-years, the RR was statistically significant (1.50, 95% CI: 1.04–2.17, $P_{trend} = 0.08$). The results of analyses on smoking cessation did not indicate a lower risk of BE with increasing duration of smoking cessation ($P_{trend} = 0.82$).

Table 2. Association (multivariable-adjusted[a]) between overweight and risk of BE with SIM; NLCS (1986–2002)

	Categorical median	Men			P_{trend}	Women			$P_{interaction}$[b]
		Person time at risk in subcohort, y	No. of cases	RR (95% CI)		Person time at risk in subcohort, y	No. of cases	RR (95% CI)	
BMI at baseline, kg/m^2									
18.5 to <25	23.3	12,267	119	1 (reference)		14,327	65	1 (reference)	
25 to <30	26.6	9,801	83	0.85 (0.63–1.14)		9,151	75	1.72 (1.22–2.44)	
≥30	31.5	808	10	1.21 (0.60–2.47)		2,288	18	1.67 (0.96–2.90)	0.01
					0.73[c]				$P_{trend} = 0.01$
Continuous, 1 kg/m^2 increments		22,876	212	0.99 (0.93–1.05)		25,766	158	1.07 (1.03–1.11)	0.03
BMI at age 20 y, kg/m^2									
<20	18.7	3,603	32	0.72 (0.45–1.13)		7,057	36	1.06 (0.62–1.80)	
20 to <21.5	20.8	5,027	64	1 (reference)		5,190	25	1 (reference)	
21.5 to <23	22.2	4,885	37	0.61 (0.40–0.94)		5,386	38	1.45 (0.86–2.46)	
23 to <25	23.8	3,578	25	0.56 (0.34–0.91)		4,076	31	1.59 (0.92–2.76)	
≥25	26.0	1,323	6	0.37 (0.15–0.87)		1,775	14	1.56 (0.79–3.10)	0.01
					0.02				$P_{trend} = 0.05$
Continuous, 1 kg/m^2 increments		18,417	164	0.93 (0.87–0.99)		23,485	144	1.07 (1.01–1.13)	0.001
Change in BMI after 20 y of age,[d] kg/m^2									
<0	−1.3	1,763	8	0.56 (0.26–1.20)		2,662	8	0.33 (0.15–0.75)	
0 to <4	2.2	9,908	95	1 (reference)		10,499	67	1 (reference)	
4 to <8	5.5	5,799	51	0.77 (0.52–1.15)		7,675	51	1.12 (0.76–1.64)	
≥8	9.4	947	10	0.83 (0.39–1.78)		2,648	18	1.21 (0.69–2.10)	0.95
					0.79				$P_{trend} = 0.01$
Continuous, 1 kg/m^2 increments		18,417	164	0.99 (0.92–1.06)		23,485	144	1.06 (1.02–1.10)	0.92
BMI at baseline, additionally adjusted for pant/skirt size,[e] kg/m^2									
18.5 to <25	23.3	11,349	113	1 (reference)		14,228	65	1 (reference)	
25 to <30	26.6	8,925	77	0.81 (0.57–1.15)		9,037	75	1.56 (1.02–2.39)	
≥30	31.5	661	10	1.35 (0.59–3.06)		2,205	18	1.38 (0.65–2.89)	0.01
					0.78				$P_{trend} = 0.23$
Continuous, 1 kg/m^2 increments		20,935	200	1.00 (0.92–1.08)		25,469	158	1.06 (0.99–1.13)	0.07

(Continued on the following page)

Table 2. Association (multivariable-adjusted[a]) between overweight and risk of BE with SIM; NLCS (1986–2002) (Cont'd)

Categorical median	Men			P_{trend}	Women			$P_{interaction}$[b]
	Person time at risk in subcohort, y	No. of cases	RR (95% CI)		Person time at risk in subcohort, y	No. of cases	RR (95% CI)	
Pant/skirt size as a proxy for waist circumference (men/women)[e]								
≤48/≤40	3,085	30	1.20 (0.73–1.98)		4,636	12	0.44 (0.22–0.85)	
50–51/42	4,834	40	1 (reference)		6,487	39	1 (reference)	
52–53/44	7,188	73	1.22 (0.81–1.84)		7,049	55	1.25 (0.82–1.92)	
54–55/46–48	3,961	37	1.11 (0.69–1.78)		6,487	46	1.10 (0.70–1.71)	
≥56/≥50	1,867	20	1.28 (0.72–2.27)		810	6	1.23 (0.50–3.04)	
				0.73				$P_{trend} = 0.01$
Continuous	20,935	200	1.02 (0.91–1.15)		25,469	158	1.16 (1.05–1.28)	
Pant/skirt size as a proxy for waist circumference (men/women), additionally adjusted for BMI at baseline[e]								
≤48/≤40	3,085	30	1.19 (0.72–1.98)		4,636	12	0.51 (0.26–1.01)	
50–51/42	4,834	40	1 (reference)		6,487	39	1 (reference)	
52–53/44	7,188	73	1.23 (0.81–1.87)		7,049	55	1.08 (0.70–1.69)	
54–55/46–48	3,961	37	1.12 (0.68–1.85)		6,487	46	0.76 (0.44–1.33)	
≥56/≥50	1,867	20	1.26 (0.67–2.38)		810	6	0.52 (0.15–1.83)	
				0.76				$P_{trend} = 0.66$
Continuous	20,935	200	1.03 (0.89–1.18)		25,469	158	1.03 (0.87–1.23)	

[a]Adjusted for age (years), cigarette smoking (current smoking status (yes/no), frequency (number of cigarettes/day), and duration (years)), alcohol consumption (g/d).

[b]*P* value for interaction between sex and measure of overweight (BMI, BMI at age 20, BMI change or pant/skirt size), based on cross-product term in the Cox proportional hazard model.

[c]Tests for dose–response trends were assessed by fitting ordinal variables as continuous terms in the Cox proportional hazard model.

[d]Additionally adjusted for BMI at age 20 years.

[e]Pant size (men) corresponds to the following standard waist circumferences: ≤50 = ≤88 cm; 50–51 = 88 cm; 52–53 = 93 cm; 54–55 = 98 cm; ≥56 = ≥103 cm, skirt size (women) corresponds to the following standard waist circumferences: ≤40 = ≤74 cm; 40 = 74 cm; 42 = 78 cm; 44 = 82 cm; 46 = 86 cm; 48 = 91 cm; ≥50 = ≥96 cm.

Table 3. Association (multivariable-adjusted[a]) between cigarette smoking and risk of Barrett's esophagus with SIM; NLCS (1986–2002)

	Categorical median	Total			P_{trend}[b]	Men			P_{trend}	Women			$P_{interaction}$[c]
		Person time at risk in subcohort, y	No. of cases	RR (95% CI)		Person time at risk in subcohort, y	No. of cases	RR (95% CI)		Person time at risk in subcohort, y	No. of cases	RR (95% CI)	
Smoking status[a]													
Never smokers		18,888	121	1 (reference)		3,380	27	1 (reference)		15,508	94	1 (reference)	
Former smokers		17,390	170	1.33 (1.00–1.77)		12,120	127	1.35 (0.87–2.10)		5,270	43	1.55 (1.03–2.33)	
Current smokers		12,365	79	0.93 (0.68–1.28)		7,376	58	1.04 (0.64–1.69)		4,989	21	0.81 (0.49–1.36)	0.45
					0.61				0.71				P_{trend} = 0.93
Frequency of cigarette smoking (no./d)[d]													
No cigarette smoker	0	18,888	121	1 (reference)		3,380	27	1 (reference)		15,508	94	1 (reference)	
>0 to <20	10	18,819	149	1.16 (0.75–1.81)		10,965	101	(0.50–1.86)		7,853	48	1.69 (0.91–3.13)	
≥20	20	10,936	100	1.24 (0.74–2.08)		8,531	84	1.02 (0.50–2.10)		2,405	16	1.89 (0.78–4.59)	0.99
					0.46				0.79				P_{trend} = 0.17
Continuous, 10 cigarettes/d increments		48,642	370	1.05 (0.93–1.19)		22,876	212	1.05 (0.92–1.20)		25,766	158	1.09 (0.80–1.50)	0.83
Duration of cigarette smoking,[e] y													
No cigarette smoker	0	18,888	121	1 (reference)		3,380	27	1 (reference)		15,508	94	1 (reference)	
>0 to <20	12	5,724	41	1.05 (0.68–1.60)		2,987	20	0.79 (0.41–1.52)		2,737	21	1.55 (0.88–2.73)	
20 to <40	30	14,353	129	1.37 (0.96–1.94)		9,095	95	1.35 (0.81–2.25)		5,258	34	1.56 (0.81–3.03)	
≥40	43	9,677	79	1.51 (0.97–2.34)		7,413	70	1.63 (0.90–2.95)		2,263	9	1.13 (0.42–3.04)	0.20
					0.03				0.03				P_{trend} = 0.41
Continuous, 10 y increments		48,642	370	1.07 (0.97–1.19)		22,876	212	1.10 (0.96–1.25)		25,766	158	1.08 (0.87–1.33)	0.43

(Continued on the following page)

Table 3. Association (multivariable-adjusted[a]) between cigarette smoking and risk of Barrett's esophagus with SIM; NLCS (1986–2002) (Cont'd)

	Categorical median	Total			P_{trend}[b]	Men			P_{trend}	Women			$P_{interaction}$[c]
		Person time at risk in subcohort, y	No. of cases	RR (95% CI)		Person time at risk in subcohort, y	No. of cases	RR (95% CI)		Person time at risk in subcohort, y	No. of cases	RR (95% CI)	
Pack-years of cigarette smoking[f]													
No cigarette smoker	0	18,888	121	1 (reference)		3,380	27	1 (reference)		15,508	94	1 (reference)	
>0 to <20	9	15,872	125	1.27 (0.94–1.72)		8,787	79	1.24 (0.78–1.97)		7,085	46	1.55 (1.01–2.38)	
20 to <40	28	9,612	87	1.50 (1.04–2.17)		7,220	71	1.51 (0.92–2.47)		2,393	16	1.80 (0.94–3.45)	
≥40	48	4,270	37	1.44 (0.91–2.28)		3,490	35	1.59 (0.89–2.84)		781	2	0.65 (0.15–2.90)	0.55
					0.08				0.09				P_{trend} = 0.37
Continuous, 10 pack-years increments		48,642	370	1.05 (0.98–1.12)		22,876	212	1.05 (0.98–1.13)		25,766	158	1.08 (0.91–1.28)	0.15
Smoking cessation[a]													
Never smokers		18,888	121	1 (reference)		3,380	27	1 (reference)		15,508	94	1 (reference)	
Stopped ≥ 20 y ago	25	5,413	47	1.16 (0.79–1.71)		3,972	37	1.18 (0.70–1.99)		1,441	10	1.38 (0.68–2.82)	
Stopped 10 to <20 y ago	14	5,960	64	1.46 (1.03–2.07)		4,205	53	1.63 (0.99–2.67)		1,755	11	1.21 (0.61–2.38)	
Stopped >0 to <10 y ago	5	5,985	58	1.32 (0.91–1.91)		3,943	37	1.23 (0.72–2.10)		2,042	21	1.88 (1.12–3.17)	
Current smokers	0	12,365	79	0.93 (0.68–1.28)		7,376	58	1.04 (0.64–1.69)		4,989	21	0.82 (0.49–1.37)	0.34
					0.82				0.78				P_{trend} = 0.79

[a]All analyses were adjusted for age (years), alcohol consumption (g/d), and BMI (kg/m^2).
[b]Tests for dose–response trends were assessed by fitting ordinal variables as continuous terms in the Cox proportional hazard model.
[c]*P* value for interaction between sex and cigarette smoking, based on cross-product term in the Cox proportional hazard model.
[d]Additionally adjusted for current smoking status (yes/no) and smoking duration (years).
[e]Additionally adjusted for current smoking status (yes/no) and smoking frequency (number of cigarettes/d).
[f]Additionally adjusted for current smoking status (yes/no).

Alcohol consumption

As can be seen in Table 4, there was no interaction between sex and alcohol consumption in the analyses of BE risk. Analyses of the association between alcohol intake and risk of BE indicated no increased risk. Subjects in the highest category of intake (≥30 g ethanol/d) had an RR of 0.82 (95% CI: 0.51–1.29) when compared with abstainers. A sensitivity analysis was carried out on the basis of subjects who had stable alcohol consumption in the period starting 5 years before baseline until baseline. This analysis included approximately 65% of the study population. Broadly speaking, the results were comparable with those based on the total study population.

Also shown in Table 4 are RRs associated with consumption of alcoholic beverages. These RRs are adjusted for ethanol intake, thus represent associations with other substances in the alcoholic beverages. The RRs for beer and wine consumption do not shown clear inverse or positive associations. Increasing liquor consumption was associated with a nonsignificantly increased risk of BE (RR for >2 glasses/d = 1.60, 95% CI: 0.79–3.24, $P_{trend} = 0.17$).

Discussion

In this large prospective cohort study, overweight was found to be a risk factor for BE in women but not in men. Several aspects of cigarette smoking were associated with an increase in risk of BE, whereas alcohol consumption was not associated with risk of BE.

Overweight

Our observation of a positive association between increased BMI and risk of BE in women is comparable with a recent observation in another prospective cohort study among women. They found obese women to be at increased risk of BE (OR: 1.52, 95% CI: 1.02–2.28; ref. 14) However, no association with overweight was found in that study (OR: 0.92, 95% CI: 0.66–1.27), whereas we did find a positive association with overweight. There are no studies that present results specifically for men. Three case–control studies showed an increased risk of BE for overweight and obesity for both sexes combined (11–13). These studies were based on predominantly male populations (60%–100% male cases); thus, it is likely that overweight and obese men were at increased risk, although no separate results by sex were presented. We did not observe an increased risk in men. Before we speculate on the reasons for this null observation, this observation should be confirmed in other studies. Previously, a positive association between overweight and risk of esophageal adenocarcinoma has also been described in the NLCS (32) and a meta-analysis (33).

We observed an inverse association between BMI at age 20 and risk of BE in men, which was an unexpected finding. Previous studies found no association, although no sex-specific analyses were carried out in these studies (12). The inverse association was also seen in never smokers (17 cases) and thus is not likely to be explained by residual confounding by smoking.

Several possible biological mechanisms may be involved in the association between overweight and development of BE. Some studies observed that adjustment for gastroesophageal reflux disease caused attenuation or disappearance of the effect of increased BMI on BE risk (10, 34), whereas this adjustment did not affect the RRs in other studies (9, 14). Therefore, it is probable that the BMI acts through other mechanisms besides gastroesophageal reflux disease, as was also suggested recently in a comprehensive review (35). Another possible mechanism relates to the distribution of body fat. Abdominal fat is more metabolically active than subcutaneous fat and secretes several factors that may be involved in systemic inflammation and cancer development (35, 36). Two case–control studies observed positive associations between measures of abdominal overweight and BE risk (12, 37). In our study, we did not observe an increased risk of BE for women with abdominal overweight when total overweight was accounted for. However, the use of clothing size measures as a proxy for waist circumference may not have been optimal. Results from the Nurses' Health Study did not show an association for abdominal overweight either (14). Thus, there are some inconsistencies between observations on the role of abdominal overweight in the development BE.

Cigarette smoking

Our observation that several aspects of cigarette smoking were associated with an increased risk of BE are in agreement with results from some previous case–control studies (10, 12).

It is remarkable that we observed an increased risk of BE in former but not in current smokers. Two case–control studies have found comparable results (12, 16). One possible explanation is that former smokers have more health-seeking behavior and may therefore be more likely to be diagnosed with BE. But the increasing risk with duration of smoking is not in agreement with this explanation. Another explanation may be that current smokers might be more susceptible to acquisition or persistence of infection with *Helicobacter pylori* (38, 39), which has been associated with decreased risk of BE (40). However, the literature on this subject is limited. We therefore suggest further investigation of this topic.

In an earlier analysis within the NLCS, we investigated the association of cigarette smoking with risk of esophageal adenocarcinoma (41). The association of cigarette smoking with esophageal adenocarcinoma was stronger [RR for ≥40 pack-years = 2.93 (95% CI: 1.59–5.40)] than the association with its precursor BE. This difference in strength of the associations with BE and esophageal adenocarcinoma is consistent with the literature (e.g., refs. 9, 12, 16, 42, 43). This observation may indicate that smoking plays a role in the later stages of esophageal carcinogenesis: in the progression of BE to esophageal

Table 4. Association (multivariable-adjusted[a]) between alcohol consumption and risk of Barrett's esophagus with SIM; NLCS (1986–2002)

	Categorical median	Total			P_{trend}[b]	Men			P_{trend}	Women			$P_{interaction}$[c]
		Person time at risk in subcohort, y	No. of cases	RR (95% CI)		Person time at risk in subcohort, y	No. of cases	RR (95% CI)		Person time at risk in subcohort (y)	No. of cases	RR (95% CI)	
Alcohol consumption, g ethanol/d													
Abstainer	0	11,282	75	1 (reference)		3,243	24	1 (reference)		8,039	51	1 (reference)	
>0 to <5	2	14,416	122	1.22 (0.90–1.65)		4,860	50	1.37 (0.81–2.31)		9,556	72	1.19 (0.82–1.73)	
5 to <15	9	10,925	78	0.94 (0.67–1.31)		6,026	58	1.28 (0.77–2.13)		4,899	20	0.66 (0.38–1.16)	
15 to <30	22	7,692	64	1.00 (0.69–1.45)		5,335	52	1.26 (0.75–2.13)		3,273	15	0.75 (0.40–1.41)[d]	0.35
≥30	40	4,327	31	0.82 (0.51–1.29)		3,411	28	1.02 (0.57–1.84)					
					0.16				0.54				P_{trend} = 0.12
Continuous, 10 g ethanol/d increments		48,642	370	0.95 (0.87–1.03)		22,876	212	0.97 (0.89–1.07)		25,766	158	0.84 (0.65–1.08)	0.20
Alcohol consumption (g ethanol/d) stable users[e]													
Abstainer	0	9,099	58	1 (reference)		2,513	17	1 (reference)		6,586	41	1 (reference)	
>0 to <5	2	8,447	80	1.43 (1.00–2.06)		3,133	34	1.60 (0.85–3.00)		5,313	46	1.43 (0.92–2.23)	
5 to <15	9	6,694	46	0.96 (0.64–1.45)		3,904	35	1.36 (0.73–2.53)		2,790	11	0.62 (0.30–1.27)	
15 to <30	22	4,239	38	1.19 (0.76–1.88)		3,022	33	1.71 (0.90–3.26)		1,734	6	0.53 (0.21–1.35)[d]	0.27
≥30	40	2,346	17	0.90 (0.50–1.62)		1,829	16	1.29 (0.62–2.67)					
					0.42				0.73				P_{trend} = 0.05
Continuous, 10 g ethanol/d increments		30,825	239	0.97 (0.87–1.09)		14,402	135	1.03 (0.91–1.15)		16,423	104	0.73 (0.51–1.05)	0.09
Alcoholic beverages, glasses/d[f]													
Beer													
No beer	0	32,777	221	1 (reference)		9,591	72	1 (reference)			[g]		
>0 to 1	0.2	12,552	130	1.31 (1.01–1.69)		10,162	121	1.60 (1.16–2.21)					
>1 to 2	1.4	2,167	14	0.81 (0.45–1.48)		2,043	14	0.95 (0.51–1.77)					
>2	3.7	1,146	5	0.59 (0.23–1.51)		1,080	5	0.67 (0.26–1.75)					
					0.10				0.10				

(Continued on the following page)

Table 4. Association (multivariable-adjusted[a]) between alcohol consumption and risk of Barrett's esophagus with SIM; NLCS (1986–2002) (Cont'd)

	Categorical median	Total			P_{trend}[b]	Men			P_{trend}	Women			$P_{interaction}$[c]
		Person time at risk in subcohort, y	No. of cases	RR (95% CI)		Person time at risk in subcohort, y	No. of cases	RR (95% CI)		Person time at risk in subcohort (y)	No. of cases	RR (95% CI)	
Continuous, 1 glass/d increments		48,642	370	0.86 (0.69–1.08)		22,876	212	0.86 (0.69–1.07)					
Wine													
No wine	0	22,196	161	1 (reference)		11,012	89	1 (reference)		11,184	72	1 (reference)	
>0 to 1	0.2	20,214	166	1.19 (0.94–1.50)		9,050	97	1.34 (0.98–1.82)		11,163	69	1.11 (0.77–1.62)	
>1 to 2	1.4	4,097	30	1.15 (0.73–1.79)		1,800	17	1.23 (0.68–2.24)		3,418	17	1.48 (0.72–3.01)[d]	0.50
>2	2.7	2,135	13	1.03 (0.53–2.01)		1,014	9	1.20 (0.54–2.69)					
					0.91				0.72				P_{trend} = 0.29
Continuous, 1 glass/d increments		48,642	370	1.04 (0.86–1.28)		22,876	212	1.06 (0.84–1.33)		25,766	158	1.71 (0.83–3.55)	0.42
Liquor													
No liquor	0	24,989	169	1 (reference)		8,300	70	1 (reference)		16,689	99	1 (reference)	
>0 to 1	0.2	17,954	149	1.16 (0.91–1.48)		9,790	92	1.15 (0.82–1.62)		8,164	57	1.20 (0.84–1.71)	
>1 to 2	1.9	4,068	37	1.35 (0.86–2.11)		3,316	36	1.48 (0.89–2.47)		913	2	0.53 (0.13–2.14)[d]	0.44
>2	2.8	1,631	15	1.60 (0.79–3.24)		1,470	14	1.50 (0.68–3.28)					
					0.17				0.17				P_{trend} = 0.51
Continuous, 1 glass/d increments		48,642	370	1.10 (0.89–1.36)		22,876	212	1.13 (0.89–1.42)		25,766	158	0.70 (0.35–1.41)	0.14

[a]Adjusted for age (years), cigarette smoking [current smoking status (yes/no), frequency (number of cigarettes/day), and duration (years)], BMI (kg/m^2).

[b]Tests for dose–response trends were assessed by fitting ordinal variables as continuous terms in the Cox proportional hazard model.

[c]*P* value for interaction between sex and alcohol consumption, based on cross-product term in the Cox proportional hazard model.

[d]For analyses on women, the highest two categories of consumption were combined because of low case numbers.

[e]Subjects who had not changed their alcohol consumption habits in the 5 years before baseline.

[f]Additionally adjusted for ethanol intake.

[g]It was not possible to carry out analyses on beer consumption in women because too few women consumed beer.

adenocarcinoma. In a population of BE patients, risk of progression was indeed found to be increased for patients who had smoked, although this was not statistically significant [RR = 1.53 (95% CI: 0.68–6.44); ref. 44]. Further investigation on this topic may yield interesting insights.

Alcohol consumption

Our finding that there was no association between alcohol intake and risk of BE is consistent with results from most studies (12, 15, 17). Also, the findings are analogous to the null association between alcohol and risk of esophageal adenocarcinoma (41, 42, 45).

Wine consumption has been reported to be inversely associated with BE risk (15, 17). In the NLCS, we conducted slightly different analyses: we investigated whether substances in wine, other than ethanol, were associated with risk of BE and found no association.

Strengths and limitations

An important strength of this study is its prospective character. The advantage of the prospective design is the relative insensitivity for selection and information bias compared with a case–control design. Second, this study is one of the largest with respect to the number of BE cases, specifically the number of female cases. This large number of cases allowed the investigation of interaction and separate analyses for men and women. A third strength is the availability of extensive information about the exposure variables investigated, which allowed a detailed look at these exposures.

There are also some limitations to our study. The first is the lack of information on the presence of gastroesophageal reflux disease and the use of medications for this disease. Consequently, we were not able to investigate possible confounding effects of these factors or their possible intermediate role in the associations investigated. Second, the use of clothing size as a proxy measure for waist circumference is suboptimal compared with measurement of waist circumference. Third, subcohort members who were not diagnosed with BE were assumed to be disease free, but we were unable to verify this assumption. Therefore, there may be some BE cases missing in our data set, which may have reduced the power. BE is usually diagnosed in patients with gastroesophageal reflux disease, but it has also been described in asymptomatic individuals, who are therefore not diagnosed with the disease (46–48). It is possible that undiagnosed BE patients differ from diagnosed BE patients, and this may have influenced our findings. Finally, the power of the study also may have been reduced because of the incomplete coverage of the NLCS population by PALGA before 1991. Because of this incompleteness, we may have missed some BE cases or the registered incidence date may be later than the true incidence date. We estimated that we may have missed 3% of the BE cases in our cohort at most.

Recommendations for further research

Most studies that investigated overweight, smoking, and alcohol consumption in relation to the risk of BE had a case–control design. Reversed causation can be a problem in studies investigating etiology, specifically in studies with a case–control design. This is illustrated by our finding that cases with a diagnosis during the first 2 years of follow-up reported different alcohol consumption habits at baseline than later cases. Only one prospective cohort study previously reported on overweight and risk of BE, whereas we are the first prospective cohort study to report on alcohol and smoking. We therefore suggest that additional cohort studies investigate these factors in association with BE risk. Future studies should, whenever possible, investigate whether associations differ by sex. Differences in associations between sexes may help to explain the higher male-to-female ratio in esophageal adenocarcinoma than in BE. As mentioned before, studying risk factors for progression of BE to esophageal adenocarcinoma also deserves further attention.

Disclosure of Potential Conflicts of Interest

The Dutch Cancer Society had no involvement in study design, in collection, analysis, and interpretation of data, in the writing of the report, or in the decision to submit the report for publication. No conflicts of interest exist.

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