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A prospective study of BMI and risk of esophageal and gastric adenocarcinoma

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Abstract

The incidence of esophageal adenocarcinoma (EADC) is rapidly increasing in Western countries and obesity is thought to be a major risk factor. We examined the association between BMI and EADC, gastric cardia adenocarcinoma, and gastric noncardia adenocarcinoma in a cohort of approximately 500,000 people in the US. We used Cox proportional hazards regression to estimate hazard ratios (HR) and 95% confidence intervals (CI) with control for many potential confounders. We found that compared to people with a BMI of 18.5-25 Kg/m², a BMI ≥ 35 was associated with significantly increased risk of EADC, HR (95% CI) = 2.27 (1.44-3.59), and gastric cardia adenocarcinoma 2.46 (1.60-3.80), but not gastric noncardia adenocarcinoma 0.84 (0.50-1.42). Using nonlinear models, we found that higher BMI was associated with increased risk of EADC even within the normal BMI. Increased adiposity was associated with higher risk of EADC even within the normal weight range.

Keywords

Esophageal adenocarcinoma; Gastric adenocarcinoma; Obesity; BMI; Prospective; Cohort

INTRODUCTION

In 1991 Blot *et al.* noted a precipitous increase in the incidence of esophageal adenocarcinoma (EADC) in the United States (1). Later updates from SEER (2) and from other cancer registries suggest that EADC rates have increased in many parts of the Western world (3). Unfortunately, most patients with esophageal cancer do not come to medical attention until the tumor has reached an advanced stage and therapy with curative intent is impossible (4).

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Gastric cardia adenocarcinoma incidence rates also increasing in the US (1), however the trend is not as sharp as with EADC. It is possible that some of this increase may be due to better subsite classification for gastric tumors rather than a true increase in incidence rates (5). Furthermore, most EADC and all gastric cardia adenocarcinomas occur near the gastro-esophageal junction and may overgrow the junction, so pinpointing the site of tumor origin may not be possible. No current pathological, immunohistochemical, or molecular techniques can accurately separate these two tumors, so misclassification does occur (6) and some authors have suggested that the clinical, epidemiological, pathological and molecular features are similar enough that they may represent a single disease (7).

Previous research on the association between BMI and EADC and gastric cardia adenocarcinoma has relied almost exclusively on case-control studies (8-13), because the low incidence rates have precluded accruing sufficient case numbers in most cohorts. To our knowledge, only three prospective studies have examined the association (14-16). Two of these studies could not control for important potential confounders (14), such as cigarette smoking, and the other two had incomplete information on confounders (15;16). All these studies have also relied primarily on categorical analyses of BMI and estimated the risks associated with being overweight or obese (12).

Here, we prospectively examine the association between BMI and EADC, gastric cardia adenocarcinoma, and gastric noncardia adenocarcinoma using the NIH-AARP Diet and Health Study cohort that has extensive information on potential confounders.

PATIENTS AND METHODS

Study population

The establishment and recruitment procedures of the NIH-AARP Diet and Health study have been described (17). Briefly, between 1995 and 1996, a questionnaire eliciting information on demographic characteristics, dietary intake, and health-related behaviors was mailed to 3.5 million AARP members. These members resided in six U.S. states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta, Georgia, and Detroit, Michigan) and were between 50 and 71 years of age. Of the 617,119 persons who returned the questionnaire (17.6 percent), 566,407 respondents (308,692 men and 211,702 women) filled out the survey in satisfactory detail and consented to be in the study. We excluded subjects with cancer at baseline (n=51,219), proxy respondents (15,760), those with calorie intake more than two interquartile ranges from the mean (n=4419), those whose weight (n=7267), height (n=7046), or BMI (n=211) were greater than 3 interquartile ranges from the mean, and those who died or were diagnosed with cancer on the first day of follow-up (n=10). The resulting cohort included 480,475 participants: 287,960 men and 192,515 women.

Cohort follow-up

As described previously (18), addresses for members of the NIH-AARP cohort were updated annually by matching the cohort database to that of the National Change of Address (NCOA) maintained by the U.S. Postal Service (USPS). Vital status was ascertained by annual linkage of the cohort to the Social Security Administration Death Master File (SSA DMF) on deaths in the U.S., follow-up searches of the National Death Index (NDI) for subjects that match to the SSA DMF, cancer registry linkage, questionnaire responses, and responses to other mailings. Follow-up time extended from the date that surveys were received (between 1995 and 1996) until December 31, 2003.

Identification of cancer cases

Incident cases of cancer were identified by probabilistic linkage between the NIH-AARP cohort membership and eight state cancer registry databases. We estimate that 90% of cancer cases will be detected in the cohort by this approach (18). Cancer sites were identified by anatomic site and histologic code of the International Classification of Disease for Oncology (ICD-O, second and third edition) (19). We classified tumors with site codes C150 – C159 as esophageal adenocarcinoma when the histologic code unambiguously indicated an adenocarcinoma. We classified tumors with site code C160 and adenocarcinoma histology as gastric cardia adenocarcinoma. We classified tumors with site codes C161 - C169 and adenocarcinoma histology as gastric noncardia adenocarcinoma. We conducted sensitivity analyses for gastric noncardia adenocarcinomas that excluded subjects with ICD-O codes C168 and C169, which code for ‘overlapping lesion of stomach’ and ‘gastric cancer not otherwise specified’, respectively. We excluded all lymphomas, neuroendocrine tumors, and other non-adenocarcinoma diagnoses. For analysis, cases were identified as their first head and neck, esophageal, or stomach cancer. The NIH-AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the U.S. National Cancer Institute (NCI).

Variable definitions

We derived all exposure variables from information provided in the baseline questionnaire. We categorized BMI into 5 quantiles based on the WHO standard definitions; $<18.5 \text{ kg/m}^2$, $18.5\text{--}<25$, $25\text{--}<30$, $30\text{--}<35$, and ≥ 35 . We categorized tobacco smoking as never smokers, former smokers who smoked ≤ 20 cigarettes/day, former smokers who smoked >20 cigarettes/day, current smokers who smoke ≤ 20 cigarettes/day, and current smokers who smoke >20 cigarettes/day. We measured alcohol consumption as pyramid servings per day. We categorized education into four ordinal categories; high school graduate or less, post high-school training or some college, college graduate, post-graduate education. We measured fruit and vegetable intake separately as pyramid servings per day. We used two physical activity variables: vigorous physical activity and usual routine throughout the day at baseline. Vigorous physical activity contained six categories: never, rarely, 1-3 times/month, 1-2 times/week, 3-4 times/week, 5 or more times per week. The activity throughout the day variable contained five categories: sit all day, sit much of the day/walk some, stand/walk often/no lifting, lift/carry light loads, and carry heavy loads. Follow-up time was calculated from the day of study entry until diagnosis of an upper gastrointestinal cancer, death, or the current end of follow-up (31 December 2000).

Statistical analysis

All analyses were carried out using SAS (SAS Institute, Cary, NC). We interpreted $p < 0.05$ and/or 95% confidence intervals that excluded 1 as statistically significant. We used two-sided tests exclusively.

We tabulated data by BMI category to examine potential confounding variables. We used multivariate Cox Proportional Hazards Models to estimate hazard ratios and 95% confidence intervals. We built parsimonious regression models by adding potentially confounding variables and retaining those that changed the beta coefficients for BMI by $\geq 10\%$, were independently associated with disease, or were considered important potential confounders *a priori*. We explored whether fitting the variables as continuous or categorical variables made a difference in the BMI estimates and choose the more conservative models. We sought to make a single model for a three diseases to ease interpretation, but relaxed this constraint for ethnicity. Because most of the cohort is non-Hispanic Caucasian (91%) we had too few cases of this disease to model the effect of ethnicity for esophageal adenocarcinoma and gastric cardia adenocarcinoma. But, we did have sufficient cases of gastric noncardia cancer to model ethnicity, so these variables were retained for this disease alone.

We examined the association between BMI and cancer using different metrics and models. First we used the five categories described above. Because the relatively small number of cases limited the precision of the categorical estimates, we also modeled the BMI cancer association using nonlinear models using PROC GAM in SAS. To facilitate computation, we reduced the cohort to a matched case: control data set. For each cancer site we randomly incidence density matched 10 controls to each case on age (within 1 year at baseline) and sex. First, to test the suitability of the reduced data set we used conditional logistic regression and tested and found that the BMI categorizations produced similar estimates in the reduced data set compared to the full cohort (data not shown). After fitting the GAM model we plotted the associations as the logit of the effect and the 95% confidence intervals versus BMI at study baseline. We excluded subjects with BMI less than 18.5 or greater than 42, the 99th percentile for the full cohort, because of the limited precision for estimates in these areas.

RESULTS

Table 1 presents the cohort characteristics by BMI category. Less than 1% of the cohort had a BMI <18.5 and 35% of the cohort had a normal BMI between 18.5 and 25 at the time of the baseline interview. 43% of the cohort was overweight, 16% was obese, and 6% were extremely obese, with a BMI over 35. Subjects with higher BMI were younger and had fewer years of education, smoked less, drank less alcohol, and had less physical activity.

Table 2 presents both age and sex, and multivariate adjusted hazard ratios (HR) and 95% confidence intervals (CI) for the associations between BMI categories and risk of EADC, gastric cardia adenocarcinoma, and gastric noncardia adenocarcinoma. First, the age and sex adjusted estimates were similar to the multivariate adjusted HRs. For each of the cancer sites underweight subjects with BMI <18.5 had nonsignificantly elevated risk of cancer, but these estimates are based on small numbers of cases. For EADC, each of the three BMI categories greater than normal had significantly and progressively increased risk of cancer. The HR (95% CI) for a BMI ≥ 35 compared to the referent was 2.27 (1.44-3.59). For gastric cardia adenocarcinoma, subjects in with a baseline BMI ≥ 30 had a significantly elevated risk. For gastric noncardia adenocarcinoma there was clear pattern of association using these categorizations, but subjects with BMI <18.5 at baseline were at significantly elevated risk, HR (95% CI) = 2.97 (1.38-6.39).

Because tobacco smoking is a potentially strong confounder or effect-modifier of the BMI-cancer associations, we stratified the cohort into non-smokers (i.e. never and former smokers who quit at least one year prior to study baseline) and current smokers (including those who quit in the past year) and recalculated the associations. The data were limited for current smokers, but in general the pattern of risks was similar to that for non-smokers and the overall study population. Stratifying the cohort as ever versus never smokers produced similar results (data not shown).

To better model the associations between BMI and these three cancers we used continuous BMI in nonlinear models. We found significant positive associations between BMI and risk of EADC ($p < 0.0001$) and gastric cardia cancer ($p < 0.0001$). A borderline insignificant inverse association was found for risk of gastric noncardia cancer ($p = 0.057$). The associations are plotted in Figure 1 as the logit of the effect versus the baseline BMI. For EADC, the association with BMI appeared monotonic with an inflection point between at a BMI of 27, such that the increased risk of EADC per BMI unit was greater across the normal BMI range than in the overweight and obese range. For gastric cardia adenocarcinoma, there was a monotonic increase in risk above a BMI of 25. For gastric noncardia adenocarcinoma there was no clear pattern.

There were no statistically significant deviations from the proportional hazards assumption. But, to further examine the robustness of the associations, we deleted one, two, three, four, or five years of follow-up and fit the models using the 5 BMI categories (Table 3). Overall, the point estimates for associations between BMI category and disease were unaffected.

DISCUSSION

We found a strong monotonically increasing association between BMI and the risk of esophageal adenocarcinoma; compared to subjects with a normal BMI of 18.5-25, we saw significantly and progressively increased risk for subjects in BMI categories of 25-<30, 30-<35, and ≥ 35 . For gastric cardia adenocarcinoma, compared to our referent group, there was no increased risk for subjects with a BMI of 25-<30, but risk was significantly increased in subjects with BMIs of 30-<35 and for those with a BMI ≥ 35 . We found no clear pattern of association between increasing BMI and risk of gastric noncardia adenocarcinoma using either categorical or nonlinear continuous models.

Case-control studies have consistently shown an association between higher BMI and increased risk of EADC (12). This association has also been reported in three prospective studies (14-16), which lacked or had limited information on potentially important confounders. The consistency between the results of the current study and previous reports suggest that the theoretical limitations of those studies did not preclude them from obtaining the same general results as this prospective study. When reported, the association between BMI and gastric cardia adenocarcinoma has been weaker than that for EADC (8;10).

The association between BMI and gastric noncardia adenocarcinoma has not been consistently seen in previous studies, with several studies showing no association (10;15;20;21) and one showing significantly increased risk with increasing BMI among women (22). Reduced risk of gastric noncardia adenocarcinoma with increasing BMI has been seen in at least one prospective study of a lean population in China (23). In the Nutrition Intervention Trial cohort from Linxian, China the 25th and 75th percentiles of BMI were 20 and 23 kg/m². A BMI greater than 23 was associated with a 32% decreased risk of gastric noncardia adenocarcinoma compared to subjects with a BMI <20 (23). Another study showed significantly decreasing risk of gastric noncardia adenocarcinoma with increasing BMI among lean subjects at the time of diagnosis, but the risk increased among subjects with a BMI >26 (24).

EADC and gastric cardia adenocarcinoma are adjacent tumors that are difficult to separate clinically and are thought to have similar risk factors. Misclassification of the site of the tumor origin is almost certain to occur (6). Several groups have proposed novel classification systems that seek to more consistently group tumors at or near the gastro-esophageal junction (7;25). The SEER classification system based on current ICD-O codes for upper gastrointestinal adenocarcinomas has been used to demonstrate the changing incidence trends (1;2) and we used the same classification system in our study. We found similar associations between BMI and risk of EADC compared to gastric cardia adenocarcinoma in the highest BMI category, but our nonlinear models produced different curves at the low end of the BMI range. Our results coupled with the differences in the time trends for cancer incidence for EADC and gastric cardia adenocarcinoma suggest that is useful to maintain the current distinction between the tumor sites for etiologic studies, especially given that the necessary clinical information is not routinely available from cancer registries (25).

The use of nonlinear models revealed an important aspect of the association between higher BMI and esophageal adenocarcinoma. Most previous studies have relied solely on categorical analyses using either the WHO classifications of BMI or population quantiles. In these studies, and in our categorical analysis, the entire range of normal BMI is used as the reference group.

This method of modeling eliminates the possibility of understanding the association between BMI and EADC within the normal range. A recent study of BMI and gastro-esophageal reflux disease demonstrated an essentially linear association between increasing BMI and gastro-esophageal reflux disease, even across the normal BMI range (26). Likewise, our nonlinear models suggest that higher BMI is associated with increased risk of EADC even in subjects that are not classified as overweight or obese.

To our knowledge, our study is the largest prospective study of the association between BMI and EADC to date with complete information on important confounders such as smoking and had nearly complete follow-up. On the other hand, we relied on self-reported rather than measured weight and height.

In summary, in this prospective cohort study, we found a clear, monotonic association showing an increased risk of EADC with increasing BMI, which conforms well to previous case-control study results. The associations between increasing BMI and risk of EADC and gastric cardia adenocarcinoma were distinct from each other.

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Abbreviations

EADC

Esophageal adenocarcinoma

Figure 1. Non-linear associations between current BMI and odds of upper gastrointestinal adenocarcinomas in the NIH-AARP Diet and Health study

The associations between current BMI and odds of upper gastrointestinal adenocarcinomas are plotted on the logit scale. The point estimates are plotted using black circles and the 95% confidence intervals are plotted using grey triangles. The vertical dotted lines demarcate the bounds used in the categorical analysis.

Table 1
NIH-AARP Study of Diet and Health cohort subject characteristics overall and by BMI categories*

Variable	Whole Cohort	BMI Category 1	BMI Category 2	BMI Category 3	BMI Category 4	BMI Category 5
Quantile Boundaries (kg/m ²)						
Number (%)	480 475	<18.5	18.5 - <25	25 - <30	30 - <35	≥35
Age, Mean (SD)	62.0 (5.4)	37.00 (0.8%)	165 238 (34.4)	205 613 (42.8)	76 044 (15.8)	29 880 (6.2)
Sex, % Male	59.9	62.7 (5.4)	62.2 (5.4)	62.1 (5.3)	61.6 (5.3)	60.9 (5.3)
BMI, Mean (SD)	27.1 (4.8)	31.1	50.1	69.4	62.8	45.2
Education		17.4 (1.3)	22.8 (1.5)	27.2 (1.4)	32.0 (1.4)	39.1 (4.0)
High school or less, %	25.2	25.1	22.7	25.0	28.7	31.4
Post high school training or some college, %	33.1	33.0	32.0	33.0	34.8	36.1
College graduate, %	18.9	19.4	20.2	19.3	16.8	14.6
Post-graduate education, %	19.9	18.8	22.5	19.9	16.6	14.4
Smoking						
Never, %	36.4	35.7	39.3	34.6	34.6	37.9
Former ≤20 cigarettes/day, %	27.7	20.5	28.7	28.7	26.2	25.1
Former >20 cigarettes/day, %	21.7	11.1	15.3	24.0	27.9	26.9
Current ≤20 cigarettes/day, %	9.2	22.9	11.9	8.0	6.8	5.9
Current >20 cigarettes/day, %	5.0	9.8	5.7	4.8	4.5	4.3
Alcohol, drinks/day, Mean (SD)	0.9 (2.4)	0.8 (2.5)	0.9 (2.3)	1.0 (2.5)	0.8 (2.4)	0.6 (2.1)
Total fruit intake, servings/day, Mean (SD)	3.0 (2.4)	2.8 (2.4)	3.0 (2.4)	2.9 (2.4)	2.9 (2.4)	3.0 (2.6)
Total vegetable intake, servings/day, Mean (SD)	3.9 (2.5)	3.8 (2.6)	3.9 (2.5)	3.9 (2.4)	3.9 (2.5)	4.1 (2.6)
Vigorous physical activity						
Never, %	4.4	8.4	3.8	3.6	5.5	9.7
Rarely, %	13.6	17.2	11.0	12.4	17.5	26.1
1-3 times/month, %	13.7	12.3	11.5	13.6	16.9	18.4
1-2 times/week, %	21.8	17.9	20.2	22.7	23.3	20.5
3-4 times/week, %	27.1	22.6	29.6	28.2	23.0	16.7
≥5 times/week, %	19.4	21.6	23.9	19.4	13.8	8.7
Activity throughout the day						
Sit during day, not much walking, %	8.0	7.3	6.0	7.0	10.6	20.5
Sit much of the day, walk a fair amount, %	33.0	30.8	30.4	32.5	37.2	40.3
Stand/walk a lot, no lifting, %	38.5	39.4	41.0	39.4	35.0	27.1
Lift carry light loads, %	17.5	20.0	19.9	17.9	14.3	9.9
Heavy work, %	2.9	2.5	2.7	3.3	2.9	2.1
Cancer Sites						
Esophageal adenocarcinoma, N (%)	371 (100)	2 (1)	71 (19)	194 (52)	77 (21)	27 (7)
Gastric cardia adenocarcinoma, N (%)	307 (100)	1 (1)	76 (25)	128 (42)	71 (23)	31 (10)
Gastric noncardia adenocarcinoma, N (%)	315 (100)	7 (2)	107 (34)	123 (39)	61 (19)	17 (5)

* Some rows or columns may not total 100% due to rounding

Table 2
Age and sex and multivariate adjusted hazard ratios (HR) and 95 % confidence intervals (CI) between BMI quantiles and risk of upper gastrointestinal adenocarcinomas in the NIH-AARP Diet and Health Study Cohort

Site	Case Counts	BMI Category 1			BMI Category 2			BMI Category 3			BMI Category 4			BMI Category 5		
		HR	(95% CI)	REF	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)		
EADC ¹	371	1.86	(0.46-7.57)	1.0	1.71	(1.30-2.24)	2.10	(1.52-2.90)	2.64	(1.69-4.12)						
CARDIA ¹	307	0.80	(0.11-5.75)	1.0	1.10	(0.82-1.46)	1.84	(1.33-2.54)	2.69	(1.77-4.09)						
NONCARDIA ¹	315	3.29	(1.53-7.08)	1.0	0.85	(0.65-1.10)	1.24	(0.91-1.70)	1.06	(0.64-1.77)						
EADC ²	371	1.61	(0.39-6.55)	1.0	1.65	(1.26-2.18)	1.91	(1.38-2.66)	2.27	(1.44-3.59)						
CARDIA ²	307	0.70	(0.10-5.06)	1.0	1.06	(0.79-1.41)	1.70	(1.22-2.36)	2.46	(1.60-3.80)						
NONCARDIA ²	315	2.97	(1.38-6.39)	1.0	0.80	(0.61-1.04)	1.08	(0.78-1.50)	0.84	(0.50-1.42)						
Non-Smokers																
EADC ²	293	2.82	(0.69-11.60)	1.0	1.70	(1.24-2.34)	2.13	(1.47-3.09)	2.33	(1.39-3.93)						
CARDIA ²	245	1.18	(0.16-8.54)	1.0	1.03	(0.74-1.42)	1.67	(1.15-2.43)	2.54	(1.58-4.10)						
NONCARDIA ³	252	1.46	(0.36-5.97)	1.0	0.95	(0.71-1.29)	1.29	(0.90-1.86)	0.93	(0.52-1.67)						
Smokers																
EADC ²	70	ND ⁴	--	1.0	2.24	(1.23-4.10)	2.17	(0.99-4.78)	4.37	(1.65-11.57)						
CARDIA ²	58	ND	--	1.0	1.43	(0.76-2.70)	2.22	(1.04-4.76)	3.39	(1.21-9.50)						
NONCARDIA ³	54	5.31	(2.02-13.96)	1.0	0.40	(0.50-0.80)	0.72	(0.31-1.67)	1.06	(0.31-3.59)						

¹ Age and sex adjusted

² Adjusted for age, sex, cigarette smoking, alcohol consumption, education, and physical activity

³ Also adjusted for ethnicity

⁴ ND indicates that there were no cases in this stratum

Table 3

Adjusted hazard ratios (HR) and 95 % confidence intervals (CI) between BMI quantiles and risk of upper gastrointestinal adenocarcinomas in the NIH-AARP Diet and Health Study Cohort with different initial lag periods

Site	Case Counts	BMI Category 1 (95% CI)	BMI Category 2 REF	BMI Category 3 (95% CI)	BMI Category 4 (95% CI)	BMI Category 5 (95% CI)
EADC²						
No lag	371	1.61	1.0	1.65	1.91	2.27
1 year lag	335	ND ⁴	1.0	1.62	2.00	2.44
2 year lag	293	ND	1.0	1.73	2.05	2.39
3 year lag	242	ND	1.0	1.78	2.05	2.80
4 year lag	183	ND	1.0	1.69	2.17	3.38
5 year lag	143	ND	1.0	1.52	2.02	2.62
CARDIA²						
No Lag	307	0.70	1.0	1.06	1.70	2.46
1 year lag	265	ND	1.0	0.97	1.61	1.99
2 year lag	223	ND	1.0	1.18	1.81	2.42
3 year lag	191	ND	1.0	1.22	1.86	2.85
4 year lag	149	ND	1.0	1.32	2.00	2.74
5 year lag	105	ND	1.0	1.74	2.34	3.17
NONCARDIA³						
No Lag	315	2.97	1.0	0.80	1.08	0.84
1 year lag	269	3.39	1.0	0.77	1.04	0.85
2 year lag	214	3.57	1.0	0.77	1.04	0.88
3 year lag	184	3.83	1.0	0.79	1.09	0.86
4 year lag	142	5.98	1.0	0.90	1.08	0.99
5 year lag	110	2.97	1.0	0.84	1.21	1.08

² Adjusted for age, sex, cigarette smoking, alcohol consumption, education, and physical activity

³ Also adjusted for ethnicity

⁴ ND indicates that there were no cases in this stratum