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Comparing Trends in Esophageal Adenocarcinoma Incidence and Lifestyle Factors Between the United States, Spain, and The Netherlands

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Abstract

OBJECTIVES—The incidence of esophageal adenocarcinoma (EAC) in the western world has been rapidly increasing. The trends in obesity and other lifestyle-associated factors have been hypothesized to be important drivers of this increase. We tested this hypothesis by comparing changes in these factors with changes in EAC incidence over time between three western countries.

METHODS—Data on EAC incidence trends were abstracted from the SEER-9 registry (1975–2009) for the United States, from multiple cancer registries (1980–2004) in Spain, and from Eindhoven Cancer Registry in the Netherlands (1974–2010). In addition, we collected trend data on obesity, smoking, and alcohol consumption. The trend data were analyzed using log-linear regression.

RESULTS—In 1980, the EAC incidence was similar among the three countries ((0.46–0.63) per 100,000). EAC incidence increased in all, with the largest increase observed in the Netherlands,

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CONFLICT OF INTEREST

Guarantor of the article: S. Kroep, MSc.

Specific author contributions: S. Kroep, I. Lansdorp-Vogelaar, M. van Ballegooijen, and J.M. Inadomi were responsible for the study design, analysis and interpretation of data, and drafting of the manuscript. I. Lansdorp-Vogelaar, M. van Ballegooijen, and J.M. Inadomi were responsible for the study supervision. S. Kroep and I. Lansdorp-Vogelaar have performed the statistical analysis. S. Kroep, V.E.P.P. Lemmens, and N. Aragonés were responsible for acquisition of the data. All authors have contributed to the study concept, critical revision of the manuscript for important intellectual content, and providing administrative support. All authors have read and approved the final manuscript.

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followed by the United States and Spain (estimated annual percentage of change = 9.7 %, 7.4 %, 4.3 %, respectively). However, this pattern was not observed in lifestyle factors associated with EAC. With regards to obesity, the United States clearly has had the highest prevalence rates both in the past and in the present. For alcohol, the highest consumption rates are seen in Spain. Smoking showed a reverse trend compared with EAC among all three countries in the last 20 years.

CONCLUSIONS—International trends in EAC incidence do not match corresponding trends in lifestyle-associated factors including obesity. Our findings suggest that factors other than obesity must be the important drivers for the increase in EAC incidence.

INTRODUCTION

Esophageal cancer is the eight most common cancer in the world and because of its high fatality rate, ranks sixth among all cancers with respect to mortality (1). The cases can be divided into two major histological types, squamous cell carcinoma and esophageal adenocarcinoma (EAC). In countries where incidence rates of EAC have been examined, there has been a sharp increase in cancer incidence over the last few decades (2–10), whereas rates of squamous cell carcinoma have remained relatively stable. In many western countries (3,5,6,10–13), incidence of EAC has increased more rapidly than any other malignancy, with an average annual increases up to 8.2 % for males during the past two or three decades.

EAC is assumed to develop from Barrett ' s esophagus (BE) (14–16). BE is presumed to be a complication of gastro-esophageal-reflux disease and symptoms of gastro-esophageal-reflux disease such as heartburn and/or acid regurgitation are associated with EAC (17,18). Two lifestyle-associated factors believed to be associated with the development of EAC are obesity and smoking (19,20). Alcohol consumption has no clear association with the development of EAC (21,22). The most well-established factor is obesity, and the obesity epidemic is believed to be an important driver of the rise in EAC. If this were true, however, it would be expected that trends in obesity and other lifestyle-associated risk factors would match trends in EAC incidence. In this study, we tested this hypothesis by comparing changes in lifestyle-associated factors with changes in EAC incidence over time between the United States, Spain, and the Netherlands.

METHODS

Incidence

We used the Surveillance, Epidemiology, and End Results database (SEER)-9 to abstract the US EAC incidence data from 1975 to 2009 for white males and females (C15, ICD-O: 8,140–8,149, 8,160–8,231, 8,250–8,499, 8,501–8,574, 8,576). SEER-9 has information on all diagnosed malignancies among residents of the nine original SEER geographic areas, representing approximately 10 % of the population of the United States. From 1975 to 2009, a total of 13,225 EAC cases were registered for white race, both sexes. Spanish data were obtained from 13 population-based cancer registries in Spain from 1980 to 2004 for the incidence of adenocarcinoma in the esophagus (C15, ICD-O: 8,140–8,570) (3). The 13

registries cover approximately 26% of the total Spanish population and have collected data for at least 10 consecutive years of the study period. From 1980 to 2004, a total of 1,503 cases of EAC were registered for both sexes. Incidence data for the Netherlands were obtained from the Eindhoven Cancer Registry, which collects data on all newly diagnosed malignancies in the South of the Netherlands, covering 13 % of the Dutch population. From 1974 to 2010, 1,680 EAC cases were registered for both sexes (C15, ICD-O codes similar to the United States).

Obesity

Obesity was defined as a body mass index of 30 kg/m² or more. Available data on obesity may be measured (the weight and height of a person are directly measured by trained observers) or self-reported (gathered through questionnaire surveys). Although self-reported obesity data can be biased, leading to lower obesity prevalence than measured obesity data (23–28), we chose to use self-reported data because these were abstracted from larger national surveys instead of measured obesity data gathered by smaller local studies in Spain and the Netherlands. Self-reported obesity data obtained by national surveys are available for the United States (NHIS, 1997–2009 all races) (29), Spain (NHS, 1987–2009) (15,30), and the Netherlands (CBS, 1981–2009) (31). We abstracted these data from the Organization for Economic Co-operation and Development database (32). To obtain estimates for self-reported obesity data in the United States before 1997, we developed a linear regression model using data abstracted from the NHANES (33) national survey, which has obtained measured obesity data in the United States since 1961. A linear regression model was fitted to data from the overlapping time horizon (1997–2009) and the model was used to estimate self-reported obesity before 1997 (self-reported obesity prevalence = 0.75 × measured obesity prevalence).

Smoking

Smoking prevalence was defined as the prevalence of adult smokers (daily and occasional) in the population. The United States data were abstracted from NHANES (1965–2010, all races) (34). Before 1992, only daily smokers were registered, but since 1992 these data also include occasional smokers. Spanish smoking prevalence was derived from the various national and European health surveys (1978–2009) (15,30,32,34) where current smoking was defined as daily and occasional, over age 16. As there were no data available before 1978, we used the estimated prevalence for daily smokers from 1945 to 1975 (35). For the Netherlands, the smoking prevalence was abstracted from STIVORO (1958–2010), reporting daily and occasional smokers over age 15 (36).

Alcohol

We defined alcohol use as the recorded adult (15 +) annual alcohol consumption per capita by country. The data for the three countries were obtained from the World Health Organization (WHO) data repository (37) (1962–2009).

Statistical analysis

Annual EAC incidence rates were calculated per 100,000 person-years, and were age standardized to the European standard population (38). Temporal trends were assessed using joinpoint regression, for which the Joinpoint regression program (version 3.5.2; Statistical Research and Applications Branch, National Cancer Institute, Bethesda, MD) from the Surveillance Research Program of the US National Cancer Institute was used.

Joinpoint regression analysis finds the best-fit line through trend data, and tests whether a set of multi-segmented lines is a significantly better fit than a single line. The intersections of lines are called joinpoints with each joinpoint denoting a statistically significant ($P = 0.05$) change in trend. Each line segment between two joinpoints can be characterized with the estimated annual percentage of change (EAPC), reflecting a change in trend data at a constant percentage of the rate of the previous year within the time horizon of the line segment. The joinpoint regression analysis fits a series of joined straight lines on a log scale to the trends using $y = ax + b$, where $y = \ln(\text{rate of trend data})$, $x = \text{calendar year}$ and $a = \text{slope coefficient}$. The EAPC is calculated from the equation: $(\text{EAPC} = 100 \times (e^a - 1))$ (39,40).

The average annual percentage of change (AAPC) was used to analyze differences in the slopes of the time trends of time horizons we compared, which was the longest available time horizon for which trend data were available in all three countries. The AAPC was computed as a weighted average of the slope coefficients of the joinpoint regression line with the weights equal to the length of each line segment on the time interval

($\text{AAPC} = \left(e^{\frac{\sum w_i a_i}{w_i}} \right)$, $a_i = \text{slope coefficient for each line segment } i$, $w_i = \text{number of years in time horizon of line segment } i$).

The difference between two AAPCs was obtained by using the approximate 95 % confidence interval (CI) with the estimated difference of $\text{AAPC}^{(1)} - \text{AAPC}^{(2)}$.

RESULTS

Incidence

In 1980, the first year of commonly available data, EAC incidence was comparable in the three countries (United States 0.63/100,000, the Netherlands 0.55/100,000, and Spain 0.46/100,000; Figure 1). In subsequent years, however, both the United States and the Netherlands reported a greater increase in incidence than Spain. The incidence in the Netherlands was comparable to the United States incidence until 1998; thereafter, EAC incidence in the Netherlands exceeded the United States incidence. For the complete period 1975–2009, the rate at which EAC incidence increased was significantly greater in Netherlands (AAPC = 9.6, 95 % CI 8.1–11.2) than in the United States (AAPC = 6.1, 95 % CI 5.4–6.8). When comparing the somewhat shorter overlapping period between data from Spain and the United States of 1980–2004, the increase in EAC is significantly greater in the United States (AAPC = 7.4, 95 % CI 6.5–8.2) than in Spain (AAPC = 4.3, 95 % CI 3.1–5.5) (Table 1).

Obesity

The obesity trends for the three countries demonstrate a different sequence than the EAC incidence trends (Figure 2a). From 1987 onward, the United States has had the highest obesity prevalence (15.0 %), followed by Spain (6.8 %), and the Netherlands (5.3 %); this order is preserved throughout the entire observation period. In the last year of observation (2009), the obesity prevalence had increased to 27.7 %, 16.0 %, and 11.8 %, respectively, for the United States, Spain, and the Netherlands.

Smoking

In 1965, the first year of commonly available data, smoking prevalence was highest in the Netherlands (58.7 %), followed by the United States (41.9 %), and Spain (21.6 %). This sequencing was altered when the Spanish smoking prevalence increased from 1965 to a peak in 1985, exceeding that of the Netherlands and the United States (Figure 2b). Both the United States and the Netherlands had decreasing smoking prevalence (Table 2) through the whole observation period. In the final year of commonly available data (2009), the smoking prevalence was highest in Spain (29.9 %), followed by the Netherlands (28.0 %), and the United States (20.6 %).

Alcohol

In 1962, the highest annual alcohol consumption per capita was in Spain (14.6 l), followed by the United States (8.0 l), and the Netherlands (4.3 l) (Table 1). Spain continued to have the highest alcohol consumption per capita during the observation time frame, although after a peak in 1976 consumption decreased to a consumption level comparable to the Netherlands in 2005 (Figure 2c). The Netherlands has exceeded the United States trend since 1973. In 2009, the alcohol consumption was highest in Spain (11.4 l), followed by the Netherlands (9.2 l), and the United States (8.7 l).

Trends by sex

There is a large difference in the EAC incidence rates between males and females. Female EAC incidence in the Netherlands is greater than the United States through the entire observation period, while the male EAC incidence in the Netherlands exceeds the United States after 2003. In both males and females, the lowest rates are seen in Spain.

Identical country sequencing is found in the obesity trends for males and females. The differences between male and female obesity prevalence are similar among the Netherlands and the United States, with the uniform feature of higher female obesity prevalence. In Spain, male obesity has exceeded female obesity since 2006.

For smoking prevalence, the United States and the Netherlands show similar trends for males and females, both having decreased since 1967, with males having a higher smoking prevalence than females. In Spain, male smoking prevalence peaked in the 1970s, when the female prevalence was still negligible, whereas female prevalence peaked after the 1990s.

For the alcohol consumption per capita, no sex-specific data are available, although we assume that alcohol consumption is higher in men than in women (41). In the

Supplementary Files online, sex-specific tables and figures for EAC incidence, obesity, and smoking prevalence are shown.

DISCUSSION

EAC incidence in the United States, Spain, and the Netherlands show large differences in both absolute rates and time trends; however, all trends have increased over time. Time trends for obesity, smoking, and alcohol in these countries, however, do not correlate with EAC incidence trends. These findings suggest that even if obesity were to provide a mechanism supporting the development of EAC, alternative factors must be the underlying drivers for the increasing incidence of EAC.

We analyzed time trends for different lifestyle-associated factors. Although obesity is increasing in all three countries, the differences in absolute prevalence and prevalence changes over time between countries do not match the EAC incidence trend, as would be expected if obesity were the most significant risk factor. Moreover, a comparison between Spain and the United States reveals a reverse relationship; whereas the increase in EAC incidence is greater in the United States than Spain, the obesity increase in Spain is greater than in the United States. Moreover, the Netherlands has a greater increase in EAC incidence than the United States, but there was no difference in the AAPCs of obesity between the Netherlands and the United States (1981–2009). Regarding smoking, a prior pooled analysis revealed an odds ratio of 1.96 for ever smokers vs. never smokers (20). However, the expected lag between exposure and cancer would be no > 50 years; therefore, the absence of an observed decrease in EAC incidence suggests smoking is not an important risk factor. Finally, the trends do not support alcohol to be a risk factor for EAC (Table 3).

When interpreting the time trends several alternative explanations for the increasing EAC incidence may be postulated. First, the time trends might reflect changes in diagnostics. With the refinement of various diagnostic modalities and the increased use of endoscopy among patients with gastro-esophageal-reflux disease symptoms or BE, increased diagnosis might be a reason for the observed increased incidence of EAC. As there has been a concomitant increase in EAC mortality, it is unlikely that changes in diagnostics are a major influence on EAC incidence. Second, a reclassification of tumors could result in an observed increase in EAC incidence. However, changes in reclassification of tumors would be expected to show corresponding reductions in tumors adjacent to the esophagus, which have not been observed. Gastric cardia incidence has remained stable in all of the examined countries for the last two decades. In addition, we observed a steady rise of EAC incidence, instead of a discrete change that would represent reclassification influences. Finally, although the trends imply that obesity, smoking, and alcohol are not the primary cause for the rise in EAC incidence, it is possible that the effect of these risk factors could be masked by an unknown protective factor with differential prevalence across the countries. Specifically, the potential protective effects of medication such as aspirin, proton pump inhibitors, or stat-ins could counter the aggravating factors of obesity, tobacco, or alcohol.

If the incidence of EAC is increasing, yet not caused by obesity or smoking alternative explanations must be sought. Chronic *Helicobacter pylori* (*H. pylori*) infection has been

hypothesized to protect against gastro-esophageal-reflux disease and BE due to induction of atrophic gastritis and hypochlorhydria (42). Advances in sanitation and the widespread use of antibiotics have been postulated to contribute to the decline in *H. pylori* infection, especially in western countries. Therefore, it is conceivable that the increase in EAC incidence in western countries may be in part caused by the decline in *H. pylori* colonization rates (43,44). As a result of the paucity on *H. pylori* infection trend data across the countries, we were not able to include this factor in our study.

We chose to include the United States, Spain, and the Netherlands in our study because while the incidence rates of EAC are increasing in all countries, the rate of change differs, and the trends in lifestyle-associated factors vary greatly. Although several prior studies have compared EAC incidence between multiple countries (2,5,10,45,46), only one examined trends in risk factors (10). Our study is unique because we have simultaneously compared EAC incidence rates between three countries and the trends in lifestyle-associated factors hypothesized to cause EAC, which is also the strength of this study. If we would have analyzed the trends for each country individually, our conclusions might have been different. Looking only at the United States, we may have supported the hypothesis that obesity and smoking are drivers for the EAC trend as obesity has the steepest slope in the lifestyle factor trend data. For the Netherlands, we would have concluded that smoking might be the driving lifestyle factor because the obesity increase starts increasing relatively late in time. For Spain, the conclusion would be that smoking and alcohol consumption would have no influence on EAC increase at all, and obesity is the only supporting lifestyle factor. However, by examining all countries simultaneously, it appears that smoking and obesity cannot be the main drivers because their trends are inconsistent among the three countries.

Although the inclusion of multiple countries is a strength of this study, analyzing time trends between countries also has limitations. First, definitions of predictors and outcomes can be dissimilar between various data sources. For example, morphology codes for EAC incidence differed slightly between Spain and the other countries. Using the Spanish morphology codes in the United States would result in an increase of 0.33 % in total EAC cases from 1975 to 2009. In addition, EAC incidence trends in the United States were based on whites only for comparability with rates in Spain and the Netherlands. However, long-term data for obesity were available for the total population only. Given the comparability of trends between blacks and whites and the fact that whites constitute a large majority of the population, we do not expect this to substantially influence our results. Second, there were variations in ages, collection methods, and inclusion criteria between the three countries. However, we do not believe this variation influenced our results significantly because we examined trend data that were highly correlated over ages, collection methods, and inclusion criteria. Third, the available time horizons of the data were dissimilar between countries for lifestyle-associated factors and EAC incidence trends. However, the overlapping periods were sufficient for testing our hypothesis whether these factors could be main drivers for the increasing EAC incidence. Furthermore, the level of detail available for the risk factors we studied was limited. We were unable to identify the quantity of smoking by country and sex, and the composition of cigarettes for each country. The distribution of alcohol consumption in the population, and the type of alcohol consumption would reflect more specific trends. The consumption of wine has been significantly larger in Spain than the two other countries,

while the consumption of beer was modestly largest in the Netherlands up to 2006. These differences, as well as differences in quantity of smoking may influence the risk for EAC incidence. Fourth, results of ecological analysis at the population level may not reflect associations at the individual level. Furthermore, interactions between the lifestyle factors and development of EAC cannot be analyzed in this study design. Fifth, differences in health-care practices and adoption of new practices between the three countries could not be specified and implemented in our analysis. Finally, it is possible that the time period was insufficient to observe the impact of lifestyle factors on EAC incidence. If smoking and obesity are associated with the development of BE, the impact of these factors on EAC may require a long lag time.

In conclusion, international trends in lifestyle-associated factors most commonly implicated in EAC development, including obesity, are discordant with the trends in EAC incidence. This analysis suggests that other important drivers for the increase in EAC incidence in the three observed countries must be present.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ The increase in esophageal adenocarcinoma (EAC) incidence is approximately sevenfold in the last four decades.
- ✓ Factors associated with EAC include gastro-esophageal reflux symptoms, Barrett ' s esophagus, obesity, and smoking.
- ✓ The reason for the large increase in EAC incidence remains unclear.

WHAT IS NEW HERE

- ✓ Although the EAC incidence has risen in the compared western countries the United States, Spain, and the Netherlands, the EAC increase in the United States and the Netherlands is significantly greater than the EAC increase in Spain.
- ✓ Trends in lifestyle factors including obesity, smoking, and alcohol consumption do not support their role in driving the trends in EAC incidence.
- ✓ Other important drivers for the increase in EAC incidence in the observed countries must be present.
- ✓ Reversing the obesity trend is important for overall health of the population; however, reduction in EAC must rely on identification of additional causative factors.

Figure 1. Esophageal adenocarcinoma (EAC) incidence rate trends over time for the United States, Spain, and the Netherlands.

Figure 2. Lifestyle factor trends over time for the United States, Spain, and the Netherlands. **(a)** Obesity prevalence. **(b)** Smoking prevalence. **(c)** Annual alcohol consumption.

EAPC of EAC incidence rate, obesity, and smoking prevalence, and alcohol consumption with joinpoint log-regression analysis for the United States, Spain and the Netherlands

Table 1

Joinpoint analysis: total available period									
Joinpoint analysis: overlapping periods					Trend 1				
EAC incidence	Years	IR start year	IR end year	AAPC	CI	Trend 2		Trend 3	
						Years	EAPC	Years	EAPC
United States	1980–2004	0.63	3.32	7.4 ^a	6.5	8.2	1975–1997	8.5 ^a	1997–2009
Spain	1980–2004	0.46	0.86	4.3 ^a	3.1	5.5	1980–2004	4.3 ^a	1.8 ^a
The Netherlands	1980–2004	0.55	4.45	9.7 ^a	6.8	12.7	1974–2010	8.8 ^a	
Obesity prevalence	Years	PR start year	PR end year	AAPC	CI	Trend 2		Trend 3	
						Years	EAPC	Years	EAPC
United States	1987–2009	15.01	27.70	2.8 ^a	2.6	3	1961–1978	0.9 ^a	1978–2009
Spain	1987–2009	6.80	16.00	4.0 ^a	3.3	4.7	1987–1997	5.4 ^a	2.9 ^a
The Netherlands	1987–2009	5.30	11.80	4.1 ^a	3.7	4.5	1981–1986	0.2	1986–2009
Smoking prevalence	Years	PR start year	PR end year	AAPC	CI	Trend 2		Trend 3	
						Years	EAPC	Years	EAPC
United States	1965–2009	41.90	20.60	-1.6 ^a	-2.0	-1.2	1961–2010	-1.7 ^a	4.1 ^a
Spain	1965–2009	29.65	29.87	-0.0	-0.5	0.4	1945–1985	1.5 ^a	-1.3 ^a
The Netherlands	1965–2009	58.70	28.00	-2.0 ^a	-2.3	-1.6	1958–1970	-0.0	1970–1989
Alcohol consumption	Years	ANC start year	ANC end year	AAPC	CI	Trend 2		Trend 3	
						Years	EAPC	Years	EAPC
United States	1962–2009	7.99	8.67	0.2 ^a	0.1	0.3	1962–1971	2.3 ^a	1971–1982
Spain	1962–2009	14.64	11.37	-0.4	-0.8	0.1	1962–1972	1.8 ^a	1972–1993
The Netherlands	1962–2009	4.29	9.20	1.7 ^a	1.3	2	1962–1975	7.9 ^a	1975–1979
								0.5	1979–1988
								-1.7 ^a	1988–2009
								-0.4 ^a	

AAPC, average annual percentage of change; CI, 95 % confidence interval; ANC, annual liter consumption per capita; EAC, esophageal adenocarcinoma; EAPC, estimated annual percentage of change; IR, incidence rate; PR, prevalence.

^aSignificant different from zero, 95 % CI.

Table 2

Comparisons of average annual percentages change in EAC incidence, obesity, smoking, and alcohol consumption for the United States, Spain, and the Netherlands

Trend	Years	Countries	AAPC ⁽¹⁾	AAPC ⁽²⁾	AAPC ⁽¹⁾ -AAPC ⁽²⁾	CI
EAC incidence	1975–2009	United States	6.1 ^a	9.6 ^a	-3.5 ^a	-4.9 -1.6
	1980–2004	United States	7.4 ^a	4.3 ^a	-3.1 ^a	1.4 4.5
	1980–2004	Spain	4.3 ^a	9.7 ^a	-5.4 ^a	-7.9 -2.3
Obesity prevalence	1981–2009	United States	2.8 ^a	3.4 ^a	-0.6	-1.5 0.4
	1987–2009	United States	2.8 ^a	4.0 ^a	-1.2 ^a	-2.1 -0.2
	1987–2009	Spain	4.0 ^a	4.1 ^a	-0.1	-0.4 0.3
Smoking prevalence	1965–2009	United States	-1.6 ^a	-2.0 ^a	0.4	-0.7 1.4
	1965–2009	United States	-1.6 ^a	-0.1	-1.5 ^a	-2.8 -0.8
	1965–2009	Spain	-0.1	-2.0 ^a	1.9 ^a	1.3 3.1
Alcohol consumption	1962–2009	United States	0.2 ^a	1.7 ^a	-1.5 ^a	-2.1 -0.8
	1962–2009	United States	0.2 ^a	-0.4	0.6	-0.4 1.5
	1962–2009	Spain	-0.4	1.7 ^a	-2.1 ^a	-3.1 -0.9

AAPC, average annual percentage of change; CI, confidence interval; EAC, esophageal adenocarcinoma.

^aSignificant different from zero, 95 % CI.

Table 3

Hypotheses of the relationship between lifestyle factors and EAC incidence

Hypotheses	Absolute rates	Change in rates
Obesity is a driver of the increase in EAC	Does not support: the country sequencing of EAC incidence and obesity prevalence differ.	Supports: the EAC incidence and obesity prevalence is increasing in all countries. Does not support: Spain has a lower increase than the United States in EAC incidence ^a (1980–2004), but a greater increase in obesity prevalence ^a (1987–2009). Furthermore, the Netherlands have a greater increase in EAC incidence than the United States ^a (1975–2009), but a similar increase in obesity prevalence (1981–2009).
Smoking is a driver of the increase in EAC	Supports: the country sequencing of EAC incidence and smoking prevalence may correlate, but only with a lag time > 50 years.	Does not support: prevalence of smoking is decreasing in all countries.
Alcohol is a driver of the increase in EAC	Does not support: the country sequencing of alcohol consumption does not correlate with EAC incidence.	Does not support: alcohol consumption is decreasing, while EAC incidence is increasing in all countries.

CI, confidence interval; EAC, esophageal adenocarcinoma.

^aSignificant, 95 % CI.