The incidence of esophageal adenocarcinoma continues to rise: analysis of period and birth cohort effects on recent trends

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Background: During the past four decades, the incidence of esophageal adenocarcinoma (EAC) has increased markedly in Western populations. Recent reports have suggested that the rate of increase has slowed or plateaued.

Patients and methods: Using data from cancer registries in Australia, the United States and Sweden, we examined incidence trends for esophageal and gastric cardia tumors between 1984 and 2008 using joinpoint analyses and age–period–cohort models.

Results: EAC incidence continues to undergo statistically significant annual increases in Australia and the United States, although the rate of increase has slowed. Among men, incidence increased annually by 2.2% [95% confidence interval (CI) 1.5% to 2.9%] between 1994 and 2008 in Australia and 1.5% (95% CI 0.2% to 2.8%) between 1998 and 2008 in the United States. EAC incidence among men remained unchanged in Sweden between 2001 and 2008 (P = 0.52). EAC incidence among women showed significant linear increases between 1984 and 2008. Age–period–cohort models suggested strong effects for both period and birth cohort on EAC incidence in Australia and the United States, and a strong period effect for Sweden.

Conclusions: EAC incidence continues to increase in Australia and the United States. The continued increases, even among more recent birth cohorts, suggest that EAC incidence will continue to rise during coming decades.

Key words: age–period–cohort models, annual percentage change, epidemiology, esophageal adenocarcinoma, incidence, secular trends

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introduction

The epidemiology of esophageal cancer has changed over the past four decades, reflecting changes in the incidence of the main histologic subtypes. Previously, esophageal squamous cell carcinoma (ESCC) was the most common subtype in Western populations, attributed to high prevalence of smoking and heavy alcohol use [1–3]. More recently, esophageal adenocarcinoma (EAC) incidence has increased rapidly in industrialized countries and EAC is now the most common histologic subtype in these countries. In the United States, Australia and Northern Europe, countries with established population-based cancer registries, the increasing incidence trends for EAC can be traced back to the early 1970s [4–6]. The underlying causes of these trends, and the marked male predominance, remain unclear [7]. It was speculated that at least some of the increase may have been due to misclassification of cancers at adjacent sites or to changes in the delivery of health care that may have led to greater detection of these cancers, but detailed investigation of population-based data has essentially discounted these types of period effects as plausible explanations for the observed trends [4, 8].

Recent analyses of data from the United States National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) program and the Swedish Cancer Registry have suggested that the rate of increase in EAC incidence has slowed or even plateaued. The US study reported that the annual rate of increase has slowed from 8.2% between 1973 and 1996 down to 1.3% since 1996 [9]. The Swedish study reported that EAC incidence rates have been stable since 2001 [8]. No nationwide EAC incidence studies have been reported for Australia, but analyses of data from several Australian states showed an increase in EAC incidence among men between 1982 and 1993 [10]. In the most populous Australian state of New South Wales, EAC incidence increased by over 4% annually between 1988 and 2005 [11]. It is not known however whether the reported flattening of the incidence curves observed in other high-incidence populations is occurring in Australia.

To investigate the various contributions of age, period and birth cohort effects on EAC incidence, we report here the results of analyses carried out simultaneously for Australia, the United States and Sweden, countries with population cancer registries and where large epidemiological studies for EAC have been undertaken [12–16]. We have used joinpoint regression analyses to identify periods of uniform incidence trends and age–period–cohort models to distinguish the effects of birth cohort from calendar period on these trends. To determine whether misclassification or detection biases may explain some of the observed trends for EAC, we also conducted analyses of ESCC and adenocarcinoma of the gastric cardia (GGA) for the same time periods.

methods

For Australia, the United States and Sweden, we obtained aggregate data on primary tumor site and histology, sex, age at diagnosis (5-year age groups), race (SEER only) and year of diagnosis for all persons diagnosed with esophageal or gastric cardia cancers for the 25-year period from 1984 to 2008. We identified incident cases for Australia from the Australian Institute of Health and Welfare Australian Cancer Database [17]; notification of invasive cancer is a statutory requirement for all hospitals and pathology services in Australia and the data represent the entire Australian population. Incidence data for the United States were ascertained from the nine population-based cancer registries in the SEER program [18]. These nine registries cover ∼10% of the United States’ population and the SEER data are broadly representative of cancer incidence in the United States as a whole. Incident cases for Sweden were identified from the Swedish Cancer Registry [19], which covers the entire Swedish population; it is compulsory for health-care providers in Sweden to report incident cancers. Population denominators for each year between 1984 and 2008 were obtained from the Australian Bureau of Statistics, the United States Census Bureau and Statistics Sweden.

For Australia and the United States, we used anatomic site and histologic codes of the International Classification of Diseases for Oncology, Third Edition (ICD-O-3), to define invasive cancers: esophageal (site codes, C15.0–C15.9) and gastric cardia (C16.0). We included incident data on all patients with histologically confirmed adenocarcinoma (histologic codes, M8140–8573) and squamous cell carcinoma (M8050–8082). For Sweden, we used the seventh revision of the International Classification of Diseases (ICD-7) and histology codes (pathological anatomic diagnosis, PAD) to define EAC (ICD-7 150; PAD 096), ESCC (ICD-7 150; PAD 146) and GCA (ICD-7 151.1; PAD 096).

statistical analysis

Age-standardized (2000 United States standard population) incidence rates were calculated according to country, sex, race, age group and year of diagnosis. We estimated annual percentage change in incidence rates by fitting a least-squares regression line to the natural logarithm of the rate, using calendar year as a regressor variable. This method uses a statistical algorithm to determine whether there are any significant changes in the magnitude or direction of trends over time. A maximum of three joinpoints were allowed, and a minimum of four observations were required between two joinpoints [20]. Monte Carlo permutation tests were used to examine trends for each combination of joinpoints and we selected the trend line that provided the best fit to the data [21]. We used Joinpoint Software version 3.5.2 (http://surveillance.cancer.gov/joinpoint/) and a significance level of α = 0.05.

Age, period and birth cohort effects were estimated by fitting a log-linear Poisson regression model, assuming that the number of cases followed a Poisson distribution. We sequentially fitted five models (age, age–drift, age–period, age–cohort and age–period–cohort) [22] and estimated the parameters of the model using the maximum-likelihood method. To attempt to address the nonidentifiability problem (i.e. parameters for age, period and cohort are not uniquely identifiable due to their linear dependence), we constrained the regression parameters for the first and last periods (when estimating cohort effects) and the first and last cohorts (when estimating period effects) to zero [22].

Age–period–cohort analyses were carried out using 5-year calendar periods (1984–1988 to 2004–2008), 5-year age intervals (40–44 to 80–84 years) and a total of 13 overlapping 10-year birth cohorts (1900–1909 to 1960–1969, identified by the central year of birth from 1905 to 1965). Period and birth cohort effects were estimated as relative risks, using the 1984–1988 period and 1905 birth cohort as the respective reference categories. The goodness-of-fit was evaluated by the Pearson statistics and likelihood ratio tests, and age–period–cohort analyses were carried out using R software version 2.12.2 (http://www.r-project.org/).
results

Between 1984 and 2008, there were 7714 men and 1658 women diagnosed with EAC in Australia, 10,330 men and 1783 women diagnosed with EAC in the SEER 9 registries (hereafter 'United States'), and 2393 men and 577 women diagnosed with EAC in Sweden (supplementary Table S1, available at Annals of Oncology online). The proportion of all esophageal cancers that were EAC increased from 20% to 52% in Australia, from 18% to 63% in the United States and from 19% to 50% in Sweden.

The age-standardized incidences of EAC increased in all three countries during the study period and are plotted in Figure 1. Rates were typically twofold higher in Australia and the United States than in Sweden. The best fitting models for incidence trends and the inflection points identified by joinpoint regression are shown in Table 1. EAC incidence was approximately sixfold higher in men than in women in Australia and Sweden and eightfold higher in men than in women in the United States, and this marked male predominance remained throughout the study period (Figure 1). Among men in Australia and the United States, joinpoint regression identified one significant inflection point (1994 and 1998, respectively) and thus two linear segments (trends). Age-standardized incidence rates for EAC rose by 7.7% (CI 5.8% to 9.6%) annually between 1984 and 1994 in Australia and by 7.1% (CI 5.8% to 8.4%) annually between 1984 and 1998 in the United States. The rates of increase slowed in subsequent years; however, we found statistically significant annual increases in EAC incidence in Australia between 1994 and 2008 (2.2%; CI 1.5% to 2.9%) and the United States between 1998 and 2008 (1.5%; CI 0.2% to 2.8%). The patterns were similar in the United States when we restricted our analyses to Hispanic and non-Hispanic whites (Table 1). In Sweden, the incidence pattern was different. EAC incidence in men was stable between 1984 and 1993 (nonsignificant trend, \( P = 0.47 \)), then increased by 12.2% (CI 7.1% to 17.4%) annually between 1993 and 2001, and thereafter remained unchanged (\( P = 0.52 \)).

Among women, the models had one segment, with EAC incidence increasing annually by 3.0% (CI 2.4% to 3.7%), 4.4%
Table 1. Annual percentage change in incidence of esophageal adenocarcinoma, esophageal squamous cell carcinoma and gastric cardia adenocarcinoma, 1984–2008

<table>
<thead>
<tr>
<th>Cancer subtype and country</th>
<th>Persons</th>
<th>APCa (95% CI)</th>
<th>Men</th>
<th>APCa (95% CI)</th>
<th>Women</th>
<th>APCa (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Esophageal adenocarcinoma</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>United States</td>
<td>1984–1998</td>
<td>2.4 (1.8–3.0)</td>
<td>1994–2008</td>
<td>2.2 (1.5–2.9)</td>
<td>1984–2008</td>
<td>4.4 (3.5–5.3)</td>
</tr>
<tr>
<td>United States (Whites)b</td>
<td>1984–1999</td>
<td>7.1 (5.9–8.2)</td>
<td>1998–2008</td>
<td>1.7 (0.5–2.9)</td>
<td>1984–2008</td>
<td>4.8 (3.8–5.7)</td>
</tr>
<tr>
<td>Sweden</td>
<td>1999–2008</td>
<td>1.5 (0.2–2.8)</td>
<td>1998–2008</td>
<td>1.6 (0.4–2.9)</td>
<td>1984–2008</td>
<td>5.3 (4.3–6.4)</td>
</tr>
<tr>
<td><strong>Esophageal squamous cell carcinoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>1984–1994</td>
<td>−0.1 (−1.3 to 1.1)</td>
<td>1984–1991</td>
<td>0.1 (−1.6 to 1.9)</td>
<td>1984–1995</td>
<td>0.4 (−1.1 to 1.9)</td>
</tr>
<tr>
<td>United States</td>
<td>1994–2008</td>
<td>−2.9 (−3.5 to −2.2)</td>
<td>1991–2008</td>
<td>−2.5 (−2.9 to −2.1)</td>
<td>1995–2008</td>
<td>−3.4 (−4.5 to −2.3)</td>
</tr>
<tr>
<td>United States (Whites)b</td>
<td>1984–2008</td>
<td>−3.2 (−3.5 to −2.9)</td>
<td>1984–2008</td>
<td>−3.6 (−3.9 to −3.3)</td>
<td>1984–2008</td>
<td>−2.7 (−3.1 to −2.2)</td>
</tr>
<tr>
<td>Sweden</td>
<td>1984–2008</td>
<td>−3.0 (−3.3 to −2.7)</td>
<td>1984–2008</td>
<td>−3.4 (−3.8 to −3.1)</td>
<td>1984–2008</td>
<td>−2.6 (−3.1 to −2.1)</td>
</tr>
<tr>
<td><strong>Gastric cardia adenocarcinoma</strong></td>
<td></td>
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<tr>
<td>Australia</td>
<td>1984–1998</td>
<td>2.1 (1.2–3.0)</td>
<td>1984–1998</td>
<td>1.7 (0.8–2.7)</td>
<td>1984–2003</td>
<td>2.2 (1.2–3.3)</td>
</tr>
<tr>
<td>United States</td>
<td>1998–2008</td>
<td>−1.0 (−2.2 to 0.2)</td>
<td>1998–2008</td>
<td>−1.3 (−2.6 to −0.1)</td>
<td>2003–2006</td>
<td>−1.25 (−3.51 to 18.0)</td>
</tr>
<tr>
<td>United States (Whites)b</td>
<td>1984–2008</td>
<td>−0.1 (−0.4 to 0.2)</td>
<td>1984–2008</td>
<td>−0.3 (−0.6 to 0.0)</td>
<td>1984–2008</td>
<td>0.5 (−0.1 to 1.0)</td>
</tr>
<tr>
<td>Sweden</td>
<td>1984–1994</td>
<td>1.9 (0.3–3.4)</td>
<td>1984–1997</td>
<td>1.4 (0.1–2.8)</td>
<td>1984–2008</td>
<td>−0.2 (−0.9 to 0.5)</td>
</tr>
<tr>
<td>1994–2008</td>
<td>−1.2 (−2.0 to −0.3)</td>
<td>1997–2008</td>
<td>−2.0 (−3.5 to −0.4)</td>
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</tbody>
</table>

APC, annual percentage change; CI, confidence interval.

aAPC derived from jointpoint regression. The age-standardized rates used in the jointpoint regression are standardized to the 2000 US standard population. Bold indicates that the APC is statistically significant from zero.

bWhites’ refers to the age-standardized incidence rates for total Whites (Hispanic and non-Hispanic whites) extracted from SEER 9.

(CI 3.5% to 5.3%) and 5.3% (CI 4.3% to 6.4%) in Australia, the United States and Sweden, respectively, between 1984 and 2008.

ESCC incidence showed significant linear declines in age-standardized incidence in all three populations over the study period (Table 1 and Figure 2). In contrast, the incidence of GCA increased significantly in Australia and Sweden until the mid-1990s and then appeared to decline slightly. In the United States, GCA incidence has remained largely unchanged.

The results of the age–period–cohort analyses for EAC incidence are shown in supplementary Table S1 (available at Annals of Oncology online). In Australia and the United States, the full age–period–cohort models provided a significant improvement over the age–period and age–cohort models. In contrast, there was no statistically significant cohort effect in Sweden after adjusting for age and period (P = 0.68). The results of age–period–cohort analyses when carried out separately for men and women were similar to the overall results reported here (data not shown).

Figure 3 shows the effects of age, period and cohort for each country. We calculated relative risks for EAC by period and birth cohort, with constraints on birth cohort and period in the age–period–cohort models where necessary (Table 2). These analyses suggested that the period effects in Sweden, where we observed a 228% excess risk of EAC in 2004–2008 compared with 1984–1988, were stronger than in Australia (151%) and the United States (145%). The risks of EAC increased with successive birth cohorts and, although we found no significant cohort effect for Sweden, the relative risks were similar in all three countries. We found similar relative risks and EAC incidence trends by age group, calendar period and birth cohort when we examined men and women separately (data not shown).

**Discussion**

Using data from cancer registries in Australia, the United States and Sweden, we confirmed that EAC incidence has increased over the past 25 years. While the rates of increase in incidence have slowed in each country in the past decade, these have continued to be significant increases in Australia and the United States. Further, age–period–cohort modeling showed that period and birth cohort effects were responsible for the secular trends in EAC rates in Australia and the United States. In contrast, we found no significant increase in the incidence of EAC in Sweden between 2002 and 2008, and although the birth cohort curves showed increased risks with successive generations, the effect of birth cohort on EAC incidence was not statistically significant after adjusting for age and calendar period.
In the United States, previous studies analyzing SEER registry data have reported that the rate of increase in EAC incidence between 1975 and 2001 was greater than any other solid tumor [4]. In a more recent paper, the same authors used joinpoint regression and SEER data to examine patterns of EAC incidence over time and reported that the rate of increase had slowed to 1.3% annually from 1996 to 2006 [9]. Adding two more years of incidence data involving 1601 cases of EAC, we have shown that EAC incidence had not plateaued in the United States and was still increasing by 1.7% annually. In contrast, we and others have found that the incidence of EAC in Sweden has been stable since 2002 [8].

Changes in the pattern of disease incidence over time can be due to a number of influences operating dynamically on the population. We used age–period–cohort models to estimate the effects of age, period and birth cohort on EAC incidence trends. In general, analyses reporting statistically significant effects for calendar period are typically interpreted as being due to changes in the environment (e.g. population exposures such as contagion and radiation) that affect all age groups equally, as well as to changes in diagnostic methods and disease classification. On the other hand, analyses identifying birth cohort effects are interpreted as being due to changes in the prevalence of exposure to causal factors which differ across successive generations [23].

We found a strong and statistically significant effect of birth cohort on EAC incidence in the United States population, as have others [24]. Age-cohort models also significantly explained EAC incidence in Australia, but not in Sweden (although cohort curves for EAC diagnosed after 1990 show a strong birth cohort effect). These birth cohort effects are likely to reflect changes in exposure to lifestyle and environmental factors that commence early in life.

Obesity, gastroesophageal reflux and, to a lesser extent, tobacco smoking are the principal factors associated with increased risks for EAC [25], and there are data to suggest that they may act synergistically when present together [13, 26]. The decline in smoking in Australia, the United States and Sweden is thought to be the primary explanation for the declining rates of ESCC. Given that smoking confers an

![Figure 2](image-url) Time trends of age-standardized incidence rates for esophageal squamous cell carcinoma (A) and gastric cardia adenocarcinoma (B) in Australia (solid triangles), the United States (open squares) and Sweden (crosses), 1984–2008. Fitted dashed lines were derived from joinpoint regression.
approximate twofold increased risk of EAC [3, 27], it is anticipated that the decline in smoking may also have removed one of the drivers of EAC in the population. Since the late 1970s, prevalence of obesity has increased in Australia [28, 29], the United States [30–32] and Sweden [33–35], with successive generations in the United States becoming heavier at younger ages [36]. Given the presumed long latency between exposure to causal factors and onset of EAC, it is reasonable to speculate that one mechanism through which the effects of birth cohort might be mediated is the increasing population prevalence of obesity. Trends in obesity have increased at a similar rate in both sexes. While data are limited, it appears that obesity is a more potent risk factor for EAC in men than women [13, 37] and that this is thought to be related to visceral (abdominal) adiposity rather than subcutaneous adiposity. These two distributions are quite different in men and women, and this may explain the lower incidence trends seen among women. A recent study has argued against a dominant explanatory role for obesity, citing a lack of temporality [38]. However, epidemiological data suggest that the risks of EAC rise continuously, and perhaps nonlinearly, with increasing body mass, even among people with body mass close to ‘healthy’ [39]. If so, then at the population level, it is not the change in the proportion of people classified as ‘obese’ that should be considered as the driver of EAC incidence, but rather the incremental increases in body fat across the population with

![Figure 3](image-url)  
Figure 3  Age, period and cohort effects (and corresponding 95% confidence intervals) of esophageal adenocarcinoma incidence in Australia (A), the United States (B) and Sweden (C).

Table 2. Relative risks for esophageal adenocarcinoma incidence by calendar period and birth cohort

<table>
<thead>
<tr>
<th></th>
<th>Australia RR (95% CI)</th>
<th>United States RR (95% CI)</th>
<th>Sweden RR (95% CI)</th>
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<tbody>
<tr>
<td>Calendar period*</td>
<td></td>
<td></td>
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<tr>
<td>1984–1988</td>
<td>1.00 (Ref.)</td>
<td>1.00 (Ref.)</td>
<td>1.00 (Ref.)</td>
</tr>
<tr>
<td>1989–1993</td>
<td>1.42 (1.29–1.56)</td>
<td>1.48 (1.36–1.61)</td>
<td>1.13 (0.95–1.36)</td>
</tr>
<tr>
<td>1994–1998</td>
<td>1.91 (1.72–2.12)</td>
<td>1.83 (1.67–2.02)</td>
<td>1.81 (1.48–2.22)</td>
</tr>
<tr>
<td>1999–2003</td>
<td>2.17 (1.92–2.46)</td>
<td>2.20 (1.96–2.47)</td>
<td>2.81 (2.21–3.57)</td>
</tr>
<tr>
<td>2004–2008</td>
<td>2.51 (2.18–2.89)</td>
<td>2.45 (2.14–2.80)</td>
<td>3.28 (2.48–4.35)</td>
</tr>
<tr>
<td>Birth cohortb</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1905</td>
<td>1.00 (Ref.)</td>
<td>1.00 (Ref.)</td>
<td>1.00 (Ref.)</td>
</tr>
<tr>
<td>1910</td>
<td>1.21 (0.94–1.57)</td>
<td>1.08 (0.83–1.40)</td>
<td>1.00 (0.68–1.48)</td>
</tr>
<tr>
<td>1915</td>
<td>1.41 (1.11–1.80)</td>
<td>1.74 (1.37–2.22)</td>
<td>1.31 (0.92–1.87)</td>
</tr>
<tr>
<td>1920</td>
<td>1.64 (1.30–2.08)</td>
<td>2.25 (1.78–2.84)</td>
<td>1.71 (1.21–2.41)</td>
</tr>
<tr>
<td>1925</td>
<td>2.22 (1.76–2.79)</td>
<td>3.01 (2.39–3.80)</td>
<td>2.36 (1.69–3.31)</td>
</tr>
<tr>
<td>1930</td>
<td>2.70 (2.13–3.42)</td>
<td>3.76 (2.96–4.76)</td>
<td>2.99 (2.11–4.26)</td>
</tr>
<tr>
<td>1935</td>
<td>3.06 (2.41–3.90)</td>
<td>4.80 (3.77–6.10)</td>
<td>3.96 (2.76–5.68)</td>
</tr>
<tr>
<td>1940</td>
<td>3.66 (2.85–4.69)</td>
<td>5.89 (4.61–7.52)</td>
<td>5.42 (3.73–7.87)</td>
</tr>
<tr>
<td>1945</td>
<td>4.78 (3.70–6.18)</td>
<td>7.79 (6.07–10.0)</td>
<td>7.76 (5.26–11.4)</td>
</tr>
<tr>
<td>1950</td>
<td>7.06 (5.40–9.24)</td>
<td>9.63 (7.43–12.5)</td>
<td>10.8 (7.11–16.5)</td>
</tr>
<tr>
<td>1955</td>
<td>8.78 (6.57–11.7)</td>
<td>11.8 (9.01–15.6)</td>
<td>17.6 (11.0–28.3)</td>
</tr>
<tr>
<td>1960</td>
<td>11.2 (8.03–15.6)</td>
<td>13.2 (9.77–17.9)</td>
<td>21.2 (11.6–38.7)</td>
</tr>
<tr>
<td>1965</td>
<td>15.9 (10.4–24.2)</td>
<td>14.7 (9.84–22.0)</td>
<td>35.4 (15.2–82.2)</td>
</tr>
</tbody>
</table>

CI, confidence interval; RR, relative risk.

*aBased on the full age–period–cohort model with cohort constraints (parameters for the first and last cohorts set to zero).

*bBased on the full age–period–cohort model with period constraints (parameters for the first and last periods set to zero).
successive generations. The increasing prevalence of reflux [40], independent of the rise in obesity rates, may explain part of the continued rise in EAC incidence.

Another factor associated with risk of EAC, and for which marked cohort effects have been observed [41], is infection with *Helicobacter pylori*. There are consistent data to show that infection with this organism confers markedly reduced risks of EAC and its precursor [42, 43]. The rates of *H. pylori* infection appear to be declining with successive birth cohorts in Western populations [44]; thus, more recent birth cohorts have experienced lower infection rates and would be expected to have higher rates of EAC assuming a causal association.

In addition to birth cohort effects, we found strong and statistically significant period effects in all three countries; indeed, this was the dominant feature in the Swedish data. Like others [4], we found no evidence to suggest that the period effects were due to anatomic reclassification of gastric cardia cancers as EAC. While rates of GCA decreased in Sweden at the same time that EAC rates increased, the extra 1023 EAC diagnoses over 10 years were 10-fold higher than the concurrent decrease in GCA diagnoses; thus, reclassification does not explain the period effect. No discussion of period effects for EAC can overlook the profound changes in the availability of pharmacological agents to suppress gastric acid production, starting with H2-receptor antagonists in the 1980s, and the proton-pump inhibitors in the 1990s and 2000s [45–47]. Some have speculated that long-term use of these drugs may alter the stomach chemistry and promote EAC by allowing bile reflux, which produces fewer symptoms than acid reflux, into the lower esophagus [48]. If such causal pathways exist, then it remains possible that the widespread uptake of these drugs in recent decades may at least partly explain the observed period effect. While proton-pump inhibitor use was negligible in the mid-1990s and cannot explain the marked increase in EAC incidence since the 1970s, we cannot exclude its potential role in more recent increases.

Strengths of our study include the complete enumeration of all persons diagnosed with invasive esophageal and gastric cardia cancers between 1984 and 2008 in Australia, the United States SEER 9 registries and Sweden. We used common diagnoses and histology codes, adjacent tumor sites to explore misdiagnoses and uniform analytical methods to examine secular trends. Furthermore, as the registries collected data prospectively and independently of our study hypotheses, our results cannot be influenced by systematic recall or information bias. The main limitation of our study is that it was based on cancer registration data and that no information on individual risk factors was available. As such, we can only speculate as to the drivers of the period and cohort effects we observed for the EAC incidence trends. Although we suggest that generational changes in body fat and *H. pylori* infection are the most likely explanations for the observed effects of birth cohort, it is clearly possible that other factors were responsible. Finally, as the trends for the most recent birth cohorts were based on few cases, the relative risk estimates for these birth cohorts should be interpreted cautiously.

In summary, EAC incidence continues to rise among men and women, and while the rate of increase appears to have slowed recently, our observation that age-specific rates continue to increase in successive birth cohorts would suggest that the ‘epidemic’ may be expected to continue for some time yet.

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**disclosure**

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