



Published in final edited form as:

*Dis Esophagus*. 2016 January ; 29(1): 99–104. doi:10.1111/dote.12302.

## Birthplace and esophageal cancer incidence patterns among Asian-Americans

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### SUMMARY

The incidence of esophageal adenocarcinoma in the United States has risen rapidly over the last 30 years, whereas the incidence of esophageal squamous cell carcinoma has fallen dramatically. In contrast, parts of Asia have extremely high rates of squamous cell carcinoma, but virtually no adenocarcinoma. Within the United States, Asian-Americans as a whole, have low rates of esophageal adenocarcinoma and higher rates of squamous cell carcinoma. It is unclear what the patterns are for those Asians born in the United States. The relative influence of ethnicity and environment on the incidence of esophageal cancer in this population is unknown. We identified all cases of esophageal adenocarcinoma and squamous cell carcinoma from the California Cancer Registry 1988–2004, including 955 cases among 6 different Asian ethnicities. Time trends were examined using Joinpoint software to calculate the annual percentage changes in regression models. Rates of esophageal squamous cell carcinoma varied substantially among different Asian ethnic groups, but squamous cell carcinoma was much more common than adenocarcinoma in both foreign-born and US-born Asian-Americans. Rates of squamous cell carcinoma were slightly higher among US-born Asian men (4.0 per 100,000) compared with foreign-born Asian men (3.2 per 100,000) and White men (2.2 per 100,000),  $P = 0.03$ . Rates of adenocarcinoma were also slightly higher among US-born Asian men (1.2 per 100,000) compared with foreign-born Asian men (0.7 per 100,000),  $P = 0.01$ . Rates of squamous cell carcinoma decreased for both US-born and foreign-born Asians during this period, whereas adenocarcinoma remained low and stable. These results provide better insight into the genetic and environmental factors affecting the changing incidence of esophageal cancer histologies in the United States and Asia.

### Keywords

Asian; Asian-American; esophageal neoplasm; ethnology; residence characteristic; trend

### INTRODUCTION

An estimated 17,000 cases of esophageal cancer were diagnosed in the United States in 2013.<sup>1</sup> Adenocarcinoma and squamous cell carcinoma (SCC) histologies comprise the

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*Conflicts of interest:* None.

overwhelming majority of cases. Each histology has unique risk factors with different epidemiology. Over the past 30 years, the relative incidence of these histologies has changed dramatically in the United States. In the mid-20th century, adenocarcinoma made up less than 10% of all esophageal cancer cases in the United States. Today, adenocarcinoma comprises the majority of esophageal cancer cases in the United States. The increased rate of esophageal adenocarcinoma has been particularly striking among White men. This has coincided with a decrease in the incidence of SCC, particularly among Black men.<sup>2</sup> In contrast, the rates of esophageal adenocarcinoma have remained relatively stable among Asian-Americans during this same time period. Asian-Americans continue to have among the lowest annual rates of esophageal adenocarcinoma at 0.7 per 100,000, compared with 4.2 per 100,000 for Caucasians. However, their rates of SCC remain relatively high at 3.9 per 100,000, more than double that of Caucasians.<sup>3</sup>

The overall trends of esophageal cancer incidence in Asia have been different from those in the United States.<sup>4-7</sup> SCC continues to be the dominant form of esophageal cancer throughout Asia despite variation in incidence of esophageal SCC and adenocarcinoma from country to country. Although there are some regional differences and modest increases in parts of Asia, adenocarcinoma remains relatively rare.

The reasons for these differences in incidence are not entirely clear, but are most likely related to the different profiles of risk factors among the different Asian populations. We hypothesized that rates of SCC would be higher among foreign-born Asian-Americans compared with US-born, whereas the opposite would be true for adenocarcinoma.

To better understand the relative influence of genetics and environment on esophageal cancer incidence among Asian-Americans, we investigated the contemporary incidence patterns of esophageal adenocarcinoma and SCC among different Asian-American ethnicities using data from the California Cancer Registry (CCR) enhanced with the ability to examine trends by nativity (country of birth). The CCR is the largest population-based data set of Asian-Americans with nativity data.

## METHODS

### Cancer cases

We obtained information on all California residents diagnosed with primary invasive esophageal cancer, including gastroesophageal junction cancers (International Classification of Diseases for Oncology, 3rd Edition site codes C150–159) from January 1, 1988 through December 31, 2004, from the CCR, comprising three of the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program registries.<sup>8</sup> Since 1988, all new cancer cases diagnosed in California residents have been required to be reported to the CCR. Data were restricted to this time period for which population estimate data defined by nativity were available. Primary invasive esophageal cancers were classified according to histologic type as SCC (histology codes 8050–8078, 8083–8084) or adenocarcinoma (histology codes 8140–8141, 8143–8145, 8190–8231, 8260–8263, 8310, 8401, 8480–8490, 8550–8551, 8570–8574, 8576). Other histologies were excluded (histology codes 000–8049,

8079–8082, 8085–8139, 8142, 8146–8189, 8232–8259, 8264–8309, 8311–8400, 8402–8479, 8491–8549, 8552–8569, 8575, 8577–9989).

There were a total of 955 cases from 6 Asian ethnic populations. Of these, 334 (35%) cases were Chinese, 222 (23%) Japanese, 162 (18%) Filipino, 60 (8%) Korean, 69 (7%) South Asian (including Asian Indians, Pakistanis, Sri Lankans, and Bangladeshis), and 77 (8%) Vietnamese.

Because patients in the cancer registry with unknown birthplace data are more likely to be US-born than those with available data,<sup>9–12</sup> we developed a method using patients' social security numbers (SSN) to more accurately classify patient immigrant status, as described previously.<sup>13</sup> Among Asian-American subgroups, registry data on nativity were available for 81% of eligible cases (88% from hospital medical records and 12% from death certificates). For the 19% of cases with unknown birthplace, statistical imputation using the patient's SSN was used to determine immigrant status. By comparing the age of SSN issue with self-reported birthplace in previously interviewed cancer patients ( $n = 1836$ ) and based on maximization of the area under the receiver operating characteristic curve and confirmation with logistic regression modeling, we considered cases who received an SSN before age 25 years as US-born, and those who had received a SSN at or after age 25 years as foreign-born. This age cut point resulted in 84% sensitivity and 80% specificity for assigning foreign-born status across the Asian-American populations. The 0.8% of cases with missing or invalid SSNs were assigned an immigrant status on the basis of the ethnicity–sex–age birthplace distribution of the overall sample. We did not compute incidence rates for US-born Korean, South Asian, and Vietnamese patients due to small case ( $N = 13$  for all three groups) and population numbers.

### Population data

From the 1990 through 2000 US Census Summary File 3, we obtained population counts to estimate incidence rates by sex, race/ethnicity, immigrant status, and 5-year age group for California. For intercensal years, we estimated the foreign-born Hispanic and Asian population sizes by using cohort component interpolation and extrapolation methods,<sup>14</sup> adjusting estimates to the populations by age and year provided by the US Census for years 1988–2004. We also used data from the 5% integrated public use microdata sample of the census to estimate age- and birthplace-specific population counts for the six Asian groups<sup>15,16</sup> by smoothing with a spline-based function.<sup>17</sup>

### Statistical analyses

We used SEER\*Stat software 8.0<sup>18</sup> to compute age-adjusted incidence rates (directly standardized to the 2000 US standard million population) with 95% confidence intervals (CIs). To comply with CCR regulations, we do not present case counts or rates based on fewer than five cases. Time trends between 1988 and 2004 were examined using Joinpoint Regression software<sup>19</sup> to calculate the annual percentage changes (APCs) in log-linear regression models that allowed up to one joinpoint. Joinpoint regression analysis is a widely accepted method to describe changing trends over successive segments of time. Due to small population denominators, we grouped years into 3-year periods (1988–1990, 1991–1993,

1994–1996, 1997–1999, 2000–2002, and 2003–2004). Joinpoint also produces graphic trends where the slope of the line describes the APC.

## RESULTS

From 1988 to 2004, 1064 total cases of esophageal cancer (SCC, adenocarcinoma, and others) were recorded among Asian-Americans in the registry. SCC continued to be the dominant histology among Asian-Americans, comprising 73% (782) of these cases. In contrast, during the same period, SCC accounted for only 39% of cases among non-Hispanic Whites. The rate of SCC among Asian men was significantly higher than non-Hispanic White men (Table 1). Asian women, however, had low rates of SCC, similar to non-Hispanic White women.

Although most Asian-American ethnic groups had higher rates of SCC compared with non-Hispanic Whites, rates of SCC varied substantially among the different Asian-American ethnic groups (Table 2). Foreign-born Japanese men had the highest rate (14.5 per 100,000). Rates of adenocarcinoma were lower than for non-Hispanic Whites, and there was less variation among Asian ethnicities (Tables 3 and 4).

### Patterns by nativity and gender

Overall, US-born Asians had a slightly higher rate of SCC than foreign-born Asians (2.4 per 100,000, 95% CI 2.1–2.8 vs. 1.9 per 100,000, 95% CI 1.7–2.0). However, this was not the case for each ethnicity. The highest rates of SCC were among foreign-born Japanese men who had a rate of 14.5 per 100,000 compared with 3.9 among US-born Japanese men. Other groups with high rates of SCC were US-born Chinese (5.2 per 100,000) and foreign-born Vietnamese (5.6 per 100,000). As a whole, rates of adenocarcinoma were higher for US-born than for foreign-born Asians, but were still far lower than for Whites. (Table 4).

Both SCC and adenocarcinoma were four times more common in men compared with women (Tables 1 and 3). Male predominance was seen across all ethnic groups except for foreign-born South Asians (Table 2). Among non-Hispanic Whites, there was a similar male predominance for adenocarcinoma (4.3 per 100,000 men vs. 0.7 per 100,000 women), with less of a difference in SCC (2.2 per 100,000 men vs. 1.8 per 100,000 women).

### Temporal trends

From 1988 to 2004, rates of SCC showed a 6.3% annual decrease among US-born Asians and a 3.3% annual decrease among foreign-born Asians (Fig. 1). These trends were primarily driven by decreases in incidence among men. During the same time period, the incidence rate of SCC decreased by 1.5% annually among non-Hispanic Whites.

Among non-Hispanic Whites, esophageal adenocarcinoma incidence rates increased by 7.1% annually from 1988 to 1999 and by 2.5% annually from 1999 to 2004. In contrast, for both US-born and foreign-born Asians, the rates of adenocarcinoma remained stable over time.

## Conclusions

We found that the rate of SCC was higher among both foreign-born and US-born Asian men, compared with non-Hispanic White men. In contrast, the rate of adenocarcinoma among foreign-born and US-born Asians was lower than non-Hispanic Whites. The rate of SCC varied significantly among different Asian ethnic groups, whereas the rate of adenocarcinoma was uniformly low across all Asian ethnic groups. In regard to nativity, US-born Asians had a slightly higher rate of SCC compared with foreign-born Asians as a whole. However, the groups with the highest rates of SCC were foreign-born Japanese and foreign-born Vietnamese men.

From 1988 to 2004, the rate of SCC among both US-born and foreign-born Asians decreased slightly. During the same time period, the rate of adenocarcinoma did not significantly change.

The interaction among genetic and environmental factors in the pathogenesis of esophageal cancer is not well known. Rates of esophageal SCC are higher throughout much of Asia compared with the United States, but surprisingly, the rate of SCC was slightly higher among US-born Asians compared with foreign-born Asians. Moreover, the rates between both groups decreased over the last two decades. In the United States, the majority of esophageal SCC is associated with smoking and/or alcohol use.<sup>20</sup> There is some evidence that US-born Asians are more likely to be current drinkers compared with foreign-born Asians, although the incidence of heavy drinking and total volume consumed is less.<sup>21</sup> Other factors, such as drinking hot tea and poor nutrition have also been linked to SCC in Asian nations.<sup>22</sup> Previous studies have found that foreign-born Asians are more likely to consume certain Asian foods. Although SCC has also been associated with foods containing N-nitrosamines and pickled vegetables, it has also been associated with the consumption of red meat, which is increased among US-born Asians..<sup>23</sup>

The decline in SCC has not been accompanied by a rise in the rates of esophageal adenocarcinoma among Asian-Americans. Adenocarcinoma remains a relatively rare form of cancer in this population, across ethnic groups for both men and women regardless of nativity. This may reflect a protective genetic effect found in the Asian population or it may reflect other factors, such as the lack of obesity among Asian-Americans.<sup>24</sup> Non-Hispanic Whites are about three times more likely to be obese compared with Asian-American adults. Likewise, US-born Asians are more likely to be obese than foreign-born Asians, which may explain the increased rate of adenocarcinoma among US-born Asians compared with foreign-born.<sup>25</sup> A previous case-control study examined the association of smoking, alcohol use, and body mass index (BMI) with adenocarcinoma of the stomach and esophagus among different ethnic groups in Los Angeles County and found that smoking and increased BMI were independent risk factors for esophageal adenocarcinoma among Whites and non-Whites.<sup>26</sup> US-born Asians appear to have diets that are lower in fiber and antioxidants, which have been found to be associated with esophageal adenocarcinoma. Foreign-born Asian-Americans are more likely to be *Helicobacter pylori* seropositive than US-born Asians, and there is evidence that the absence of *H. pylori* may be a risk factor for esophageal adenocarcinoma.

Our analysis, based on 16 years of high-quality population-based cancer registry data from California, which includes more than half of the SEER Asian population, enhanced with the capability to examine rates by nativity, is, to our knowledge, the largest and most representative data set on Asian-Americans.<sup>8</sup> Asian ethnic group classification is coded directly from registry records (usually medical records) or by applying a validated algorithm.<sup>27</sup> Cancer registry classification of specific Asian ethnicity shows good-to-excellent agreement with self-report.<sup>28</sup> For Asian esophageal cancer cases with available registry birthplace information (the vast majority), agreement with self-report is excellent; for the remaining cases, we applied a validated imputation algorithm based on cases' SSNs with good sensitivity and specificity.<sup>11</sup> It should also be noted that we did not have information regarding the length of residence in the United States. Although in general, those born in the United States have higher degrees of acculturation, the level of acculturation is related to duration of residence.<sup>25</sup> Thus, some of the foreign-born Asians may have had diet and other environmental factors more similar to US-born Asians.

Despite it being the largest database of its kind, we are nonetheless limited by small sample sizes. Small case and denominator counts may have resulted in unstable rates and limited our ability to detect significant trends, as evidenced by wide CIs for some APCs. The low numbers of adenocarcinoma cases does however underscore the rarity of the disease among various Asian ethnicities. Cancer registry data lack details regarding potentially important clinical information, such as tumor markers, parental race/ethnicity, and risk factor information. Finally, there may be errors associated with the inter- and postcensal annual population estimates, which is a concern for the extrapolated estimates after the year 2000.<sup>29</sup> Therefore, we restricted our trend assessment to extend only through 2004.

The low rate of esophageal adenocarcinoma among both US-born and foreign-born Asian-Americans contrasts strongly with the rising rate among White Americans. As obesity rates increase among Asian-Americans, esophageal adenocarcinoma may become a more significant problem. A better understanding of the specific genetic and environmental factors that are driving these trends could help identify better ways to prevent and perhaps screen higher risk groups. The very high rates of SCC among foreign-born Japanese men also deserve further investigation.

## Acknowledgments

*Financial disclosure:* The collection of cancer incidence data used in this study was supported by the California Department of Health Services as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute's Surveillance, Epidemiology, and End Results Program under contract HHSN261201000140C (awarded to the Cancer Prevention Institute of California), contract HHSN261201000035C (awarded to the University of Southern California), and contract HHSN261201000034C (awarded to the Public Health Institute); and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement #1U58 DP000807-01 (awarded to the Public Health Institute).

The ideas and opinions expressed herein are those of the authors, and endorsement by the State of California, the California Department of Health Services, the National Cancer Institute, or the Centers for Disease Control and Prevention or their contractors and subcontractors is not intended nor should be inferred.

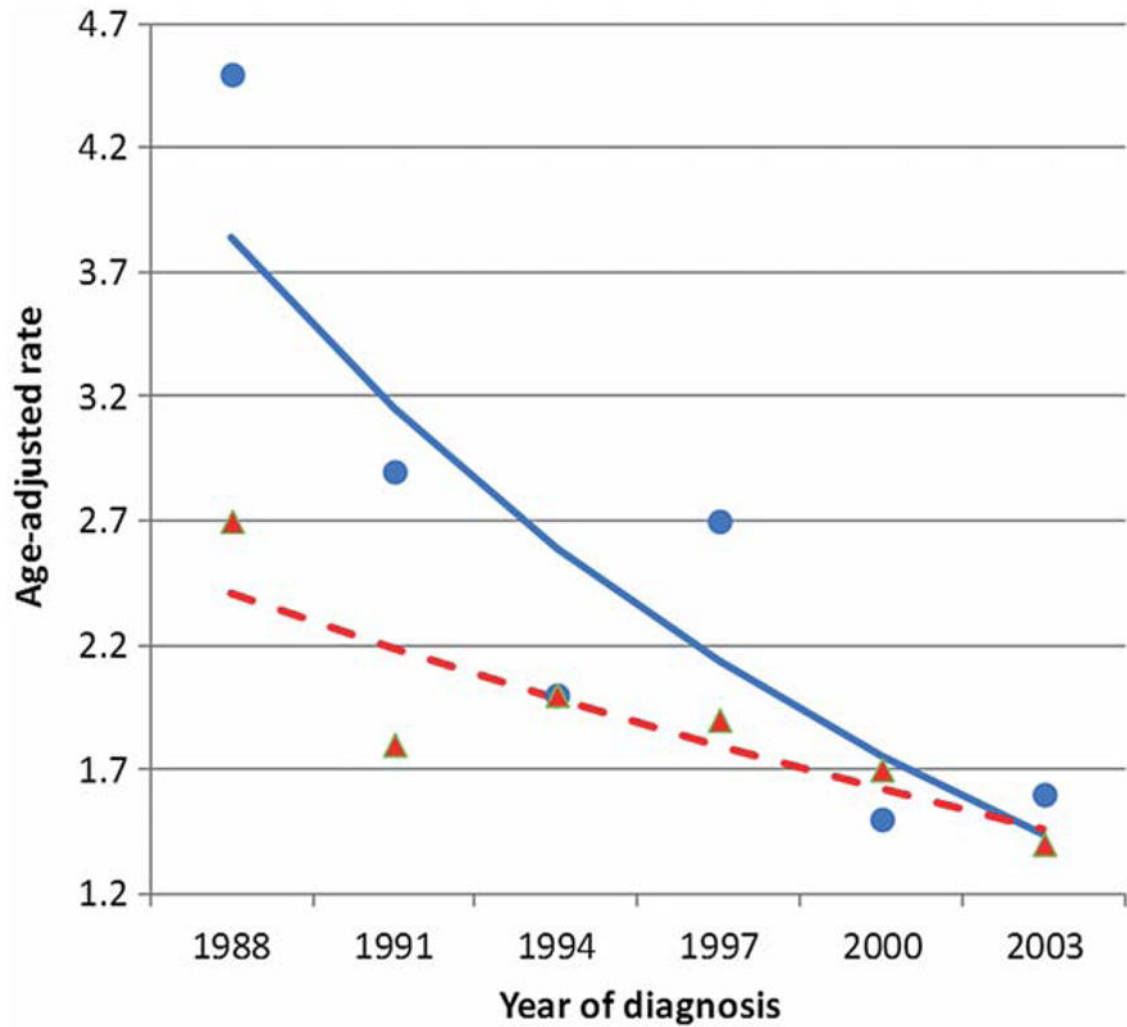


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**Fig. 1.** Trend in age-adjusted rate of esophageal squamous cell carcinoma per 100,000 among Asian-Americans 1988–2004. ●, US Asian observed; —, US Asian APC =  $-6.3^*$ ; ▲, FB Asian observed; - - -, FB Asian APC =  $-3.3^*$ . APC, annual percent change; US, US-born; FB, foreign-born.

Age-adjusted esophageal squamous cell cancer rates (per 100,000) by race in California 1988–2004

Table 1

| Ethnicity            | Sex    | Cases | Population  | Rate | 95% Confidence interval |
|----------------------|--------|-------|-------------|------|-------------------------|
| White (non-Hispanic) | Male   | 3069  | 139,386,726 | 2.2  | 2.1–2.3                 |
|                      | Female | 2533  | 142,615,254 | 1.8  | 1.7–1.8                 |
| Black (non-Hispanic) | Male   | 984   | 18,738,199  | 5.3  | 4.9–5.6                 |
|                      | Female | 459   | 19,386,300  | 2.4  | 2.2–2.6                 |
| Hispanic             | Male   | 678   | 84,981,776  | 0.8  | 0.7–0.9                 |
|                      | Female | 229   | 80,023,043  | 0.3  | 0.3–0.3                 |
| US-born Asian        | Male   | 142   | 8,733,094   | 4.0  | 3.4–4.7                 |
|                      | Female | 36    | 8,371,924   | 1.0  | 0.7–1.4                 |
| Foreign-born Asian   | Male   | 455   | 16,676,051  | 3.2  | 2.9–3.5                 |
|                      | Female | 149   | 18,865,657  | 0.8  | 0.7–1.0                 |
| All races            | Male   | 5390  | 273,871,809 | 2.0  | 1.9–2.0                 |
|                      | Female | 3435  | 274,830,507 | 1.2  | 1.2–1.3                 |

Age-adjusted esophageal squamous cell cancer incidence rates (per 100,000) in Asian-Americans by ethnicity, gender, and nativity in California 1988–2004

Table 2

| Ethnicity   | Sex    | Foreign-born |            |      |           | US-born |            |      |         | 95% CI | P-value |      |
|-------------|--------|--------------|------------|------|-----------|---------|------------|------|---------|--------|---------|------|
|             |        | Cases        | Population | Rate | 95% CI    | Cases   | Population | Rate | 95% CI  |        |         |      |
| Asian       | Male   | 455          | 16,676,051 | 3.2  | 2.9–3.5   | 142     | 8,733,094  | 4.0  | 3.4–4.7 | 1.2    | 1.0–1.5 | 0.03 |
|             | Female | 149          | 18,865,657 | 0.8  | 0.7–1.0   | 36      | 8,371,924  | 1.0  | 0.7–1.4 | 1.2    | 0.8–1.7 | 0.43 |
| Chinese     | Male   | 184          | 5,012,626  | 3.5  | 3.0–4.1   | 42      | 2,490,417  | 5.2  | 3.7–7.1 | 1.5    | 1.0–2.1 | 0.03 |
|             | Female | 50           | 5,626,259  | 0.9  | 0.6–1.2   | 12      | 2,359,603  | 1.3  | 0.7–2.3 | 1.5    | 0.7–2.9 | 0.29 |
| Japanese    | Male   | 57           | 764,644    | 14.5 | 10.6–19.3 | 89      | 1,823,921  | 3.9  | 3.1–4.9 | 0.3    | 0.2–0.4 | 0    |
|             | Female | 26           | 1,236,742  | 1.6  | 1.0–2.5   | 19      | 1,829,367  | 0.9  | 0.5–1.4 | 0.5    | 0.3–1.1 | 0.08 |
| Korean      | Male   | 60           | 1,934,398  | 4.4  | 3.3–5.9   | ^       | 624,311    | ^    | ^       | ~      | ~       | ~    |
|             | Female | ^            | 2,306,719  | ^    | ^         | ^       | 607,767    | ^    | ^       | ~      | ~       | ~    |
| Vietnamese  | Male   | 66           | 2,601,506  | 5.6  | 4.1–7.4   | ^       | 792,157    | ^    | ^       | ~      | ~       | ~    |
|             | Female | 5            | 2,524,663  | 0.3  | 0.1–0.9   | ^       | 739,613    | ^    | ^       | ~      | ~       | ~    |
| Filipino    | Male   | 67           | 4,487,122  | 1.5  | 1.1–1.9   | 6       | 2,365,263  | 1.4  | 0.5–3.3 | 0.9    | 0.3–2.3 | 1    |
|             | Female | 34           | 5,577,737  | 0.6  | 0.4–0.9   | ^       | 2,231,765  | ^    | ^       | ~      | ~       | ~    |
| South Asian | Male   | 21           | 1,875,755  | 2.9  | 1.7–4.7   | 0       | 637,025    | 0    | 0–8.0   | 0      | 0–3.0   | 0.38 |
|             | Female | 30           | 1,593,537  | 3.1  | 1.9–4.7   | ^       | 603,809    | ^    | ^       | ~      | ~       | ~    |

^ Statistic not displayed due to fewer than five cases.

~ Statistic could not be calculated.

CI, confidence interval.

**Table 3**  
Age-adjusted esophageal adenocarcinoma rates (per 100,000) by race in California 1988–2004

| Ethnicity            | Sex    | Cases | Population  | Rate | 95% Confidence interval |
|----------------------|--------|-------|-------------|------|-------------------------|
| White (non-Hispanic) | Male   | 6060  | 139,386,726 | 4.3  | 4.2–4.5                 |
|                      | Female | 1020  | 142,615,254 | 0.7  | 0.7–0.8                 |
| Black (non-Hispanic) | Male   | 108   | 18,738,199  | 0.6  | 0.5–0.7                 |
|                      | Female | 37    | 19,386,300  | 0.2  | 0.1–0.3                 |
| Hispanic             | Male   | 672   | 84,981,776  | 0.8  | 0.7–0.9                 |
|                      | Female | 112   | 80,023,043  | 0.1  | 0.1–0.2                 |
| US-born Asian        | Male   | 37    | 8,733,094   | 1.2  | 0.8–1.7                 |
|                      | Female | 8     | 8,371,924   | 0.2  | 0.1–0.4                 |
| Foreign-born Asian   | Male   | 94    | 16,676,051  | 0.7  | 0.5–0.9                 |
|                      | Female | 34    | 18,865,657  | 0.2  | 0.1–0.3                 |
| All races            | Male   | 7036  | 273,871,809 | 2.6  | 2.5–2.6                 |
|                      | Female | 1216  | 274,830,507 | 0.4  | 0.4–0.5                 |

Age-adjusted esophageal adenocarcinoma incidence rates (per 100,000) in Asian-Americans by ethnicity, gender, and nativity in California 1988–2004

Table 4

| Ethnicity   | Sex    | Foreign-born |            |      |         | US-born |            |      |         | 95% CI | P-value |      |
|-------------|--------|--------------|------------|------|---------|---------|------------|------|---------|--------|---------|------|
|             |        | Cases        | Population | Rate | 95% CI  | Cases   | Population | Rate | 95% CI  |        |         |      |
| Asian       | Male   | 94           | 16,676,051 | 0.7  | 0.5–0.9 | 37      | 8,733,094  | 1.2  | 0.8–1.7 | 1.7    | 1.1–2.6 | 0.01 |
|             | Female | 34           | 18,865,657 | 0.2  | 0.1–0.3 | 8       | 8,371,924  | 0.2  | 0.1–0.4 | 1.2    | 0.5–2.7 | 0.76 |
| Chinese     | Male   | 29           | 5,012,626  | 0.6  | 0.4–1.0 | 6       | 2,490,417  | 0.7  | 0.3–1.6 | 1.2    | 0.4–2.8 | 0.92 |
|             | Female | 11           | 5,626,259  | 0.2  | 0.1–0.4 | ^       | 2,359,603  | ^    | ^       | ~      | ~       | ~    |
| Japanese    | Male   | ^            | 764,644    | ^    | ^       | 26      | 1,823,921  | 1.3  | 0.8–2.0 | ~      | ~       | ~    |
|             | Female | ^            | 1,236,742  | ^    | ^       | 5       | 1,829,367  | 0.2  | 0.1–0.6 | ~      | ~       | ~    |
| Korean      | Male   | ^            | 1,934,398  | ^    | ^       | 0       | 624,311    | 0    | 0–5.9   | ~      | ~       | ~    |
|             | Female | ^            | 2,306,719  | ^    | ^       | 0       | 607,767    | 0    | 0–3.6   | ~      | ~       | ~    |
| Vietnamese  | Male   | 6            | 2,601,506  | 0.5  | 0.2–1.2 | 0       | 792,157    | 0    | 0–14.9  | 0      | 0–43.1  | 1    |
|             | Female | 0            | 2,524,663  | 0    | 0–0.6   | 0       | 739,613    | 0    | 0–13.5  | ~      | ~       | ~    |
| Filipino    | Male   | 44           | 4,487,122  | 1.0  | 0.7–1.4 | ^       | 2,365,263  | ^    | ^       | ~      | ~       | ~    |
|             | Female | 11           | 5,577,737  | 0.2  | 0.1–0.5 | 0       | 2,231,765  | 0    | 0–1.3   | 0      | 0–8.2   | 0.68 |
| South Asian | Male   | 11           | 1,875,755  | 0.9  | 0.4–1.8 | ^       | 637,025    | ^    | ^       | ~      | ~       | ~    |
|             | Female | 7            | 1,593,537  | 0.9  | 0.3–2.1 | ^       | 603,809    | ^    | ^       | ~      | ~       | ~    |

^ Statistic not displayed due to fewer than five cases.

~ Statistic could not be calculated.

CI, confidence interval.