Cancer Epidemiology 37 (2013) 579–584

Contents lists available at SciVerse ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.cancerepidemiology.net

Sex differences in the proportion of esophageal squamous cell carcinoma cases attributable to tobacco smoking and alcohol consumption

Nirmala Pandeya [a,1,*], Catherine M. Olsen [b,1], David C. Whiteman [b,1]

[a] School of Population Health, University of Queensland, Brisbane, Australia
[b] Cancer Control Group, Queensland Institute of Medical Research, Brisbane, Australia

ARTICLE INFO

Article history:
Received 1 November 2012
Received in revised form 31 May 2013
Accepted 31 May 2013
Available online 2 July 2013

Keywords:
Tobacco
Alcohol
Population attributable fraction
Esophageal cancer

ABSTRACT

Objective: Alcohol and tobacco are the two major established environmental factors associated with squamous cell carcinoma of the esophagus (ESCC). However, the prevalence of these exposures differs substantially between men and women. Moreover, the prevalence of smoking has declined in recent years, whereas per capita consumption of alcohol has remained steady in both sexes. Quantifying the burden of ESCC attributable to these causal factors is necessary to inform potential preventive strategies. *Methods*: We estimated the population attributable fraction (PAF) of ESCC due to smoking and alcohol, using data from an Australian population based case–control study (305 ESCC cases, 1554 controls). *Results*: Estimated PAF for ESCC were 49% (95% CI: 38–60) and 32% (95% CI: 25–40) due to smoking and heavy alcohol consumption respectively. More than 75% of the ESCC burden in men could be attributed to smokers with heavy alcohol consumption. The highest burden was among ≥30 pack years smokers who also consumed alcohol heavily (>17 drinks/week); this differed significantly between men (PAF 36%, 95% CI 29–44) and women (PAF 5%, 95% CI 2–10). Among women only, low intakes of fruit and vegetables accounted for about 9% of the ESCC burden. *Conclusion*: The burden of ESCC attributable to smoking combined with heavy alcohol consumption is remarkably high in men. In women, the burden of ESCC due to these factors is lower, and poor nutrition may also play a role.

1. Introduction

Esophageal squamous cell carcinoma (ESCC) is 2–4 fold more common in males than females in Western countries such as the US and Australia [1]. In these countries ESCC has been largely attributed to smoking and alcohol, the two strongest risk factors for ESCC [2–4]. Women typically have lower prevalence of exposure to these agents, yet little is known about the sex-specific associations of smoking and alcohol with ESCC. To quantify the potential scope for preventing this disease, we have computed population attributable fractions of ESCC associated with the key causal factors. We extend previous analyses [5–7] by calculating the burden of ESCC attributable to alcohol and tobacco, independently as well as in combination, while adjusting for other potential confounders. Moreover, we have calculated these measures for both sexes separately.

2. Methods

2.1. Study participants

The study methods of the Australia-wide population-based case–control study have been described previously [8]. Eligible cases were people aged 18–79 years, living in Australia, with a histologically confirmed primary invasive cancer of the esophagus or gastro-esophageal junction diagnosed between July 1, 2002 (July 1, 2001 in Queensland) and June 30, 2005. Cases were recruited through either major treatment centers or state cancer registries. Of the 1577 patients with esophageal cancer invited to participate in the study (1191 through clinics and 386 through cancer registries), 1102 patients (70%) returned a completed questionnaire; 8 case patients were deemed ineligible on later review and excluded. Of the 364 EAC, 425 GEJAC and 305 ESCC eligible patients, these analyses include 305 ESCC patients.

Controls were randomly selected from the national electoral roll and were frequency matched by age (in 5-year age bands) and state of residence to the case group. Of 3258 potentially eligible control participants who were contacted and invited to participate (646 were un-contactable and deemed ineligible), 175 were excluded because they were deceased (16), too ill (61), or unable to communicate in English (98), and 41 were lost to follow-up

* Corresponding author at: School of Population Health, The University of Queensland, Level 2, Public Health Building, Herston Road, Herston, QLD 4006, Australia. Tel.: +61 07 3346 4696.
E-mail address: n.pandeya1@uq.edu.au (N. Pandeya).
[1] See Appendix A.

1877-7821/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.canep.2013.05.011

between initial contact and participation. Of the 3042 remaining controls, 1680 (55%) accepted. Completed questionnaires were returned by 1580 controls (49% of all potentially eligible controls).

The study was approved by the ethics committees of the Queensland Institute of Medical Research and all participating hospitals and cancer registries.

2.2. Exposure measurement

Information was collected using a self-administered questionnaire, which included questions about demographic, medical, hormonal, reproductive, diet, family history, and other potential risk factors. Exposures were assessed before a reference date, defined as 1 year before the date of diagnosis (or date of first approach for controls), because more recent exposures in cases could have been influenced by the presence of subclinical disease. Detailed questions about past and current smoking habits asked participants whether, over their whole life, they had ever smoked more than 100 cigarettes, cigars, or pipes; positive responses elicited further questions about the ages at which they started and stopped smoking and about typical daily consumption, overall and for each decade of their life. Current smokers and ex-smokers were defined by their smoking status at their reference age (1 year prior to age at diagnosis for cases, age at study participation for controls). For each participant a decade-specific smoking dose was calculated in pack-years as the product of the average number of cigarettes smoked per day/20, the number of days per week smoked and the total number of years smoked within that decade. Lifetime cumulative quantity of tobacco smoked (or total pack years) was then calculated by summing up the decade specific pack-years.

Participants were asked a series of detailed questions about past and current alcohol consumption. Participants were asked whether they currently drank alcohol, were life-long non-drinkers, or used to drink alcohol in the past but had stopped; positive responses elicited further questions about the age at which they first started and stopped drinking alcohol and typical weekly consumption at different time periods (20–29 years, 30–49 years, and 50 years and older). The typical weekly intake for 6 classes of alcoholic beverages (reduced-alcohol beer, regular beer, white wine, red wine, port/sherry, and spirits/liqueurs) was recorded on an ordinal scale as none, less than 1, 1, 2–4, 5–6, 7–13, 14–20, 21–27, and 28 or more drinks per week. The total weekly alcohol consumption was calculated by summing the average weekly consumption of all beverages by the standard drink volume and alcohol content by weight (in grams of alcohol) for each age interval and then for total lifetime. Average weekly consumption over adult lifetime was calculated by dividing the total lifetime consumption by the number of weeks in life starting from age 20 to the reference age. Our previous analyses of these data have shown a threshold for alcohol consumption, whereby those drinking >17 drinks per week have significantly higher risks of ESCC than those drinking lesser amounts [2–4]. Thus, for the analyses presented here, we dichotomized participants into low to moderate drinkers (≤ 17 drinks/week) and heavy drinkers (>17 drinks per week) for both men and women. We combined non-drinkers with low to moderate drinkers as we have previously observed no significant difference in the magnitude of associations between non-drinkers and light to moderate drinkers [3].

Participants self-reported height and weight one year ago. BMI, calculated as weight in kilograms divided by height in meters squared, was classified using the World Health Organization definitions of obesity (underweight: <18.5; normal weight: 18.5–24.9; overweight: 25–29.9; class I obesity: 30–34.9; class II obesity: 35–39.9; and class III obesity: ≥ 40 kg/m^2) [9]. Due to small numbers in the underweight and class III obesity categories, we collapsed the two highest and lowest categories for these analyses. Participants were asked about frequency of heartburn ('a burning pain behind the breastbone after eating') or acid reflux ('a sour taste from acid or bile rising up into the mouth or throat') 10 years before diagnosis, and frequency of aspirin or nonsteroidal anti-inflammatory drug (NSAID) use in the past 5 years. Dietary data were obtained on a subsample of 91% participants using a food frequency questionnaire as described previously [10]. Briefly, we asked participants about their consumption in the previous year (controls) and the year before diagnosis (cases). In addition to the itemized foods, two summary questions on total number of serves of fruits and vegetables consumed per day were assessed. We categorized participants into two categories of adequate (at least 2 serves of fruits and 5 serves of vegetables daily) and inadequate (less than 2 serves of fruits or 5 serves of vegetables daily) consumption according to NHMRC dietary guidelines for all Australians [11].

2.3. Statistical methods

To calculate adjusted population attributable risks with 95% confidence intervals we used the method of Bruzzi et al. [12] which uses adjusted ORs derived from unconditional logistic regression models as well as the prevalence of the risk factors in the study cases. This method takes into account multiple levels of exposure and controls for confounding by other factors. Confidence intervals for the model-based PAFs were calculated using logit transformation as described by Benichou and Gail [13]. Firstly, PAFs were calculated for individual risk factors for all cases and separately for men and women. We estimated relative risks associated with each stratum of smoking (smoking status and pack-years smoked) and alcohol consumption (low to moderate vs. heavy) adjusting for age, sex, education (High school or less, technical college, trade certificate and university) frequency of reflux symptoms (never, less than weekly and weekly or more), frequency of aspirin or NSAID use (never, less than weekly and weekly or more) and BMI. Missing data for the confounding factors were included in the analysis as a separate category. For smoking, the 'never' category was used as the reference; for alcohol consumption, low to moderate consumption was used as the reference category. We then computed partial PAFs for combinations of smoking (never', 'ex-smoker', 'current smoker' or 4 groups of pack years smoked) and alcohol consumption (low to moderate, heavy). The partial PAF is calculated by cross-classifying the two exposures and setting the lowest level as a reference category. The partial PAF for all combinations of the cross-classified exposure variables sums to PAF. The reference group for the combined smoking and alcohol exposures was never smokers who reported low to moderate alcohol consumption. These were computed for the total sample (i.e. both sexes combined) adjusted for age, sex, education, frequency of aspirin or NSAID use, and frequency of heartburn or reflux. We then repeated the analyses separately for males and females. Finally, in a subset of participants for whom complete data including dietary data were available (172 cases and 1259 controls), we conducted combined analyses of smoking, alcohol and intake of fruits & vegetables to estimate the burden of disease that could be attributed to these factors. All analyses were conducted using the Interactive Risk Assessment Program (IRAP) Version 2.2 (available from the US National Institute of Health; http://dceg.cancer.gov/bb/tools/irap). Statistical significance was determined at $\alpha = 0.05$, and all tests for statistical significance were two-sided. We compared the PAFs between men and women for each exposure using the independent t test.

3. Results

The characteristics of study cases and controls are presented in Table 1. Of the 305 cases of ESCC, 174 (57%) were men and 131