EUROPEAN JOURNAL OF CANCER 48 (2012) 655–661

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Chewing areca nut, betel quid, oral snuff, cigarette smoking and the risk of oesophageal squamous-cell carcinoma in South Asians: A multicentre case–control study

Saeed Akhtar [a,b,*], *Adnan A. Sheikh* [b,c], *Hammad U. Qureshi* [b,d]

[a] *Faculty of Medicine, Kuwait University, Jabriya, Kuwait*
[b] *Faculty of Health Sciences, Aga Khan University, Karachi, Pakistan*
[c] *Countess of Chester Hospital, Chester CH2 1UL, United Kingdom*
[d] *Queen Elizabeth Hospital, University Hospitals Birmingham NHS Trust, Birmingham B15 2TH, United Kingdom*

ARTICLE INFO

Article history:
Received 1 April 2011
Received in revised form 25 May 2011
Accepted 3 June 2011
Available online 4 July 2011

Keywords:
Areca nut
Betel quid
Smokeless tobacco
Cigarette smoking
Oesophagus
Squamous-cell carcinoma
Population attributable risk

ABSTRACT

Oesophageal cancer remains an important public health problem worldwide. This multicentre matched case–control study examined the chewing areca nut alone, betel quid with tobacco, oral snuff (snuff dipping) and cigarette smoking as the risk factors for oesophageal squamous-cell carcinoma. We enrolled 91 cases of oesophageal squamous-cell carcinoma and 364 matched controls from three tertiary-care hospitals in Karachi, Pakistan. A structured questionnaire was used to collect the data through face-to-face interview of the participants. Multivariable conditional logistic regression model showed that after adjusting for the effect of ethnicity, ever chewed areca nut alone (adjusted matched odds ratio (mOR_{adj}) = 3.7; 95% confidence interval (CI): 1.6–8.5), ever chewed betel quid with tobacco (mOR_{adj} = 12.8; 95% CI: 6.3–26.2), ever practiced snuff dipping (mOR_{adj} = 4.3; 95% CI: 1.6–11.7) and ever smoked cigarettes (mOR_{adj} = 2.9; 95% CI: 1.4–5.9) were significantly and independently associated with oesophageal squamous-cell carcinoma status. The adjusted summary population attributable risk (PAR) percent for all four substances together was 67.0. Furthermore, despite incomplete synergy, there was manifold increase in the risk of oesophageal squamous-cell carcinoma, if the respondents ever smoked cigarettes and ever chewed betel quid with tobacco (mOR_{adj} = 21.4; 95% CI: 6.3–72.4) or if they ever smoked cigarettes and ever practiced snuff dipping (mOR_{adj} = 14.4; 95% CI: 2.3–91.1). The adjusted PAR (%) was higher for the dual practice of smoking cigarettes and chewing betel quid with tobacco (64.3) than the dual practice of smoking cigarettes and snuff dipping (32.2). Public awareness to curtail the addiction to these substances may result in a substantial reduction in the incidence of oesophageal squamous-cell carcinoma and related mortality in this and similar settings.

1. Introduction

Oesophageal cancer remains an important public health problem worldwide. It is currently the 8th most common human cancer and 6th most common cause of cancer-related deaths.[1] In 2005, the worldwide estimated burden of oesophageal cancer included estimated 500,000 new cases and 416,500 related deaths. Of the new cases of oesophageal cancer and related deaths, 84% occurred in less developed countries particularly in Asia.[2] Oesophageal cancer is two to

* *Corresponding author*: Address: Department of Community Medicine and Behavioural Sciences, Faculty of Medicine, Kuwait University, P.O. Box 23924, Safat 13110, Kuwait. Fax: +965 25338948.
E-mail address: saeed.akhtar@hsc.edu.kw (S. Akhtar).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2011.06.008

four times more common among men than women.[1] By contrast, in Karachi, Pakistan, between January 1, 1995 and December 31, 2002, age-standardised rates (per 100,000 populations) of oesophageal cancer were higher in women (8.6) than in men (6.4).[3]

The most common histologic types of oesophageal cancer are squamous cell carcinoma and adenocarcinoma, which together constitute more than 90% of oesophageal malignancies. These two major histologic types of oesophageal carcinoma differ substantially in their underlying incidence patterns and key aetiologic factors thus complicating the prevention.[4] Notwithstanding a recent increase in the incidence of oesophageal adenocarcinoma in western populations,[4–6] globally oesophageal squamous cell carcinoma is the most common (90%) subtype, specifically in Eastern countries,[7] including Pakistan (86–87%).[8,9] The risk factors for oesophageal squamous cell carcinoma including low-income, cigarette smoking, high-alcohol intake, low intake of raw fruits and vegetables, ingestion of coarse and raw foods are relatively better understood in western populations and together may account for up to 98% of the oesophageal carcinoma cases.[7] However, there are limited published data on the role of these risk factors and the chewing of smokeless tobacco and areca nut in causation of oesophageal squamous-cell carcinoma in South Asia, specifically in Pakistan.

Consumption of various forms of smokeless tobacco is an integral cultural tradition in South Asia with its' prevalence up to 21% in general population.[10–12] Smokeless tobacco is chewed as betel quid, gutka, oral snuff (snuff dipping) and/or administered through nose (nasal snuff).[13] Betel quid is a mixture of areca nut, slaked lime (aqueous calcium hydroxide paste), with or without tobacco, condiments and with and without sweeteners wrapped in a betel leaf. It is chewed and held in the mouth like a quid. Gutka is powered mixture of areca nut, tobacco, slacked lime, sandalwood and fragrance. Oral snuff is a moist mixture of tobacco and lime. Chewing of areca nut alone is also a widely practiced addiction in South and South-East Asian populations.[13,14]

In general, these orally consumed products are highly addictive, and typically contain several carcinogens that cause head, neck and throat cancers with high proportional premature mortality.[15] Smokeless tobacco-specific nitrosamines are believed to be the most strong carcinogens and play a significant role in the aetiology of oral cancer.[16] However, the role of smokeless tobacco in oesophageal squamous-cell carcinoma is not well documented. Furthermore, poor prognosis of oesophageal cancer patients (with only 5–10%, 5-year survival rates) calls for primary prevention as the desired goal. Therefore, this multicentre matched case–control study examined the use of chewable substances (areca nut alone, betel quid with tobacco, and oral snuff) and cigarette smoking as the risk factors for oesophageal squamous-cell carcinoma in urban Pakistan.

2. Participants and methods

2.1. Study design and settings

Between January 1998 and December 2002, we conducted a matched case–control study at three tertiary care teaching hospitals in Karachi. Karachi is the largest and a cosmopolitan city with a multi-ethnic 18 million population. It is a major economic hub of the country and has an influx of workers from all over the country. Therefore, people of different ethnicities identified based on their mother tongue live and work together in various neighbourhoods in the city. These different ethnic groups tend to vary in their traditions, cultural values, dietary patterns and perhaps in the use of various substances considered in this study. The study hospitals included Aga Khan University Hospital (AKUH), Civil Hospital Karachi (CHK) and Liaquat National Postgraduate Medical Center (LNPMC) and provide care to over 3500 inpatients belonging to various socioeconomic strata of the city. Patients attend these hospitals from all over the Sindh – the second largest province of Pakistan with a population of 30 million. This study was restricted to permanently domiciled residents of Karachi.

2.2. Selection of cases and controls

Cases were patients of any age and sex with biopsy proven oesophageal squamous-cell carcinoma diagnosed at any of the three study hospitals. Patients with adenocarcinoma or any other tumour of the oesophagus were excluded. Controls were inpatients admitted for a wide spectrum of acute conditions but free from oesophageal squamous-cell carcinoma. Four controls matched for age (±2 years) and sex with each case were selected from the same hospital as the case. Controls were excluded, if they had any other malignant lesion or past history of any malignancy. We also excluded controls from respiratory, cardiology and gynaecological wards or people with complaints of dysphagia. A biopsy report confirming the absence of oesophageal squamous-cell carcinoma was not required. Performing a biopsy on all controls was not logistically feasible or acceptable.

2.3. Exposure assessment

A structured questionnaire was used to collect information from each selected case and control through face-to-face interview in Urdu. Data on socio-demographic variables and various substance uses were assessed following the definitions used previously.[17] Questions were asked about the lifetime chewing areca nut alone, chewing betel quid with or without tobacco, gutka, snuff dipping, cigarette smoking or other methods of tobacco smoking (i.e. cigars, hookah, pipe, bidi) and alcohol drinking. Chewable substance users were defined as the individuals who chewed areca nut alone, chewed betel quid with or without tobacco, gutka, or practiced snuff dipping at least once a day for minimum 1 year. Smokers were persons who had ever smoked cigarettes, bidi, hookah, cigar, or a pipe daily for at least 1 year. Those who smoked at that time were referred to as current smokers, while ex-smokers were those who had stopped smoking 2 or more years before the date of diagnosis or interview. The participants who had drunk an alcohol beverage (beer and wine) more than four times a week for at least 1 year were defined as ever alcohol drinkers. The quantity and the duration of the use of these substances were also assessed. Informed consent was taken from each participant before the interview,