

Acetaldehyde production and microbial colonization in oral squamous cell carcinoma and oral lichenoid disease

Emilia Marttila, DDS, PhD,^{a,b} Johanna Uittamo, DDS, PhD,^{a,c} Peter Rusanen, DDS,^{a,b} Christian Lindqvist, MD, DDS, PhD,^a Mikko Salaspuro, MD, PhD,^c and Riina Rautemaa, DDS, PhD, FRCPath^{a,b,d,e}
Helsinki University Central Hospital, Helsinki, Finland; University of Helsinki, Helsinki, Finland; University of Manchester, Manchester, UK; Wythenshawe Hospital, Manchester, UK

Objective. The main aim of this prospective study was to explore the ability of the oral microbiome to produce acetaldehyde in ethanol incubation.

Study Design. A total of 90 patients [30 oral squamous cell carcinoma (OSCC); 30 oral lichenoid disease (OLD); 30 healthy controls (CO)] were enrolled in the study. Microbial samples were taken from the mucosa using a filter paper method. The density of microbial colonization was calculated and the spectrum analyzed. Microbial acetaldehyde production was measured by gas chromatography.

Results. The majority (68%) of cultures produced carcinogenic levels of acetaldehyde (>100 µM) when incubated with ethanol (22 mM). The mean acetaldehyde production by microbes cultured from smoker samples was significantly higher (213 µM) than from non-smoker samples (141 µM) ($P = .0326$).

Conclusions. The oral microbiota from OSCC, OLD patients and healthy individuals are able to produce carcinogenic levels of acetaldehyde. The present provisional study suggests smoking may increase the production of acetaldehyde. (Oral Surg Oral Med Oral Pathol Oral Radiol 2013;116:61-68)

The prominent risk factors for oral squamous cell carcinoma (OSCC) are tobacco and chronic alcohol consumption.¹⁻⁵ In addition, some oral mucosal diseases and conditions such as oral lichen planus and oral lichenoid lesions are potentially malignant.⁶⁻⁸ Malignant transformation into OSCC is seen in approximately 0.5%-2% of the oral lichen planus and oral lichenoid reactions.^{7,9}

There is a strong link between chronic inflammation and many types of cancers.¹⁰ In line with this, atrophic and erosive types of oral lichenoid lesions in particular have been linked with malignant transformation.^{11,12} Oral lichen planus is a chronic systemic inflammatory disorder and results from T-cell immune dysregulation, whereas oral lichenoid reaction is typically compatible with a type IV hypersensitivity reaction.^{13,14} Despite these distinct etiopathological features, oral lichen planus and lichenoid lesions are clinically very similar as

well as histopathologically reliably indistinguishable, whereby the final diagnosis is made based on the clinical findings.⁷

Acetaldehyde has been linked in many studies to digestive tract cancers, in both *ALDH2*-deficient (aldehyde dehydrogenase-2) patients and those with a normal *ALDH2* genotype,¹⁵⁻¹⁷ and there is increasing evidence that acetaldehyde rather than alcohol itself is responsible for the carcinogenic effect of high alcohol consumption.¹⁸⁻²⁰ Acetaldehyde is the first metabolite of ethanol and has been shown to be carcinogenic both in animal models and *in vitro* in concentrations as low as 100 µM, a concentration that can be found in the saliva after moderate alcohol consumption.¹⁹⁻²² It has been reclassified by the International Agency for Research on Cancer (IARC) as a group 1 carcinogen in association with alcohol consumption.²³ Acetaldehyde can also be found in cigarette smoke. It binds to DNA and forms DNA adducts, causes point mutations, DNA crosslinking and interferes with the synthesis and repair

This work was supported by the Yrjö Jahnsson Foundation; the Finnish Dental Society Apollonia; the Paulo Foundation; the Helsinki University Foundation; and the Helsinki University Central Hospital (Grants TLE82M0033, T1020V0015 EVO).

^aDepartment of Oral and Maxillofacial Diseases, Helsinki University Central Hospital.

^bDepartment of Bacteriology and Immunology, Haartman Institute, University of Helsinki.

^cResearch Unit on Acetaldehyde and Cancer, University of Helsinki.

^dManchester Academic Health Science Centre, Institute of Inflammation & Repair, Respiratory & Allergy Centre, University of Manchester.

^eUniversity Hospital of South Manchester, Wythenshawe Hospital.

Received for publication Jul 25, 2012; returned for revision Feb 12, 2013; accepted for publication Feb 15, 2013.

© 2013 Elsevier Inc. All rights reserved.

2212-4403/\$ - see front matter

<http://dx.doi.org/10.1016/j.oooo.2013.02.009>

Statement of Clinical Relevance

This study demonstrates that the oral microbiome is potentially capable of producing carcinogenic amounts of acetaldehyde. This highlights the importance of good oral hygiene and is especially important for patients with potentially malignant lesions in their oral cavity. The present provisional study suggests smoking may increase the production but this needs to be validated in a larger prospective study.

of DNA.^{18,19,21,24} Acetaldehyde may also induce inflammation and metaplasia of the tracheal epithelium and enhance cell injury.²²

Normal human saliva does not contain measurable levels of acetaldehyde.²² However, mutagenic concentrations of acetaldehyde are found in saliva during and after ingestion of alcohol as well as smoking.^{22,25} Chronic smoking has been shown to modify the oral microbiome to produce more acetaldehyde from ethanol both *in vitro* and *in vivo*.^{25,26} Furthermore, poor oral hygiene increases *in vitro* acetaldehyde production into saliva.²⁷ Microbes of the gastrointestinal tract and oral cavity produce acetaldehyde mainly by the oxidation of ethanol.²⁸ A spectrum of microbes, including oral streptococci, *Candida* and *Neisseria* spp., has been shown to be capable of producing significant levels of acetaldehyde.²⁹⁻³² Chronic oral candidiasis has been associated with oral carcinoma in a number of studies.³³⁻³⁶ Also, the neglect of oral hygiene and dental care has been associated with a higher incidence of OSCC.³⁷

The oral microbiome is diverse, and it is continuously being modified by the host immune responses, such as chronic inflammation in the underlying mucosa. Acetaldehyde production by oral microbes colonizing healthy, chronically inflamed or malignant oral mucosal surfaces has not been studied. All previous studies on acetaldehyde production by microbes from the oral cavity have been performed using saliva samples or mouthwashes.^{18,25,29,30} This prospective study was designed to analyze the lesion-specific oral microbial colonization of patients with OSCC and oral lichenoid disease (OLD) and compare these to that of the healthy mucosa of healthy individuals. The primary aim was to explore the ability of the oral microbiome in the different patient groups to produce acetaldehyde when exposed to clinically relevant levels of ethanol using a site-specific sampling method. Our secondary aim was to evaluate the effect of alcohol consumption and smoking on the microbial colonization and acetaldehyde production.

MATERIALS AND METHODS

Study design

A total of 90 voluntary patients (30 with newly diagnosed primary OSCC, 30 with oral lichen planus or lichenoid lesion, 30 healthy controls) being treated at the Department of Oral and Maxillofacial Surgery, Helsinki University Central Hospital or at the Helsinki University Dental Hospital during 2007-2011 were enrolled (Table I). Patients potentially suitable for enrollment were identified from the weekly theater lists by the research team members. Patients who had received antimicrobial therapy (i.e., antibiotics, antifungals, or antiviral agents) within the past 7 days, and those diagnosed with human immunodeficiency virus or hepatitis virus infection were excluded.

Table I. Patient demographics and smoking and drinking habits. The proportion of heavy drinkers (*) of alcohol consumers is given separately. One OSCC patient, three OLD patients and one control patient declined to fill the questionnaires

	OSCC	OLD	CO
Total number	30	24	30
Female:male	12:18	16:8	19:11
Age	65.6 (39-85)	54 (24-74)	30.4 (19-56)
Smokers	9 (32%)	4 (19%)	9 (31%)
Female:male	2:7	2:2	5:4
Non-drinkers	6 (21%)	2 (10%)	3 (10%)
Alcohol consumers	23 (79%)	19 (91%)	26 (90%)
Female:male	8:15	15:7	16:11
Heavy drinkers*	5 (17%)	1 (5%)	2 (7%)
Female:male	0:5	0:1	2:0
Non-responders	1 (3%)	3 (13%)	1 (3%)

Percentages of smokers and drinkers given of all responders in each group.

OSCC, oral squamous cell carcinoma patients; OLD, oral lichenoid disease patients, CO, control patients.

*Exceeds WHO levels for harmful alcohol consumption (288 g alcohol per week in men and 192 g per week in women).

All participating subjects signed an informed consent before inclusion. The study has been approved by the Ethics Committees of the Helsinki University Central Hospital and the Helsinki Municipal Health Centre.

Subjects

Patients with OSCC. Thirty patients with clinically and histopathologically diagnosed OSCC were enrolled as the OSCC group. The anatomical sites of the cancerous lesions were the gingiva ($n = 10$), the tongue ($n = 9$), the floor of the mouth ($n = 5$), the palate ($n = 3$), the sulcus ($n = 2$), and the tonsil ($n = 1$).

Patients with oral lichen planus or lichenoid lesion. Thirty patients were enrolled into the study with the clinical diagnosis of OLD (oral lichen planus or oral lichenoid lesion). Histopathology supported the clinical diagnosis in 24 cases: oral lichen planus ($n = 10$) or lichenoid reaction ($n = 14$), and these patients were included in the study as the OLD group. The anatomical sites of the OLD lesions were the cheek ($n = 17$) and the tongue ($n = 7$).

Control patients. Thirty generally healthy individuals were included as the control group (CO). These were patients referred to the Department of Oral and Maxillofacial Surgery for operative wisdom tooth extraction and had no clinically evident mucosal lesions in the oral cavity.

Patient questionnaire

Subjects filled in a modification of the World Health Organization Alcohol Use Disorders Identification Test (WHO AUDIT) questionnaire including open and

Download English Version:

<https://daneshyari.com/en/article/6057591>

Download Persian Version:

<https://daneshyari.com/article/6057591>

[Daneshyari.com](https://daneshyari.com)