Epidemiology of cancers of the upper aero-digestive tract in the French West Indies : behavioral, viral and environmental risk factors

Aviane Auguste

UNIVERSITE BIOLOGIE BRETAGNE SANTE LOIRE

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THESE DE DOCTORAT DE

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ECOLE DOCTORALE N° 605
Biologie Santé
Spécialité : Epidémiologie, analyse des risques, recherche clinique

Par

Aviane AUGUSTE

Epidémiologie des cancers des voies aéro-digestives supérieures aux Antilles Françaises

Facteurs de risque comportementaux, viraux et environnementaux

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Behavioural, viral and environmental risk factors

Thèse présentée et soutenue à Pointe-à-Pitre, le 2 décembre 2019
Unité de recherche : Irset (Institut de recherche en santé, environnement et travail) – Inserm UMR 1085
Thèse N° :

Rapporteurs avant soutenance :

Mathieu NACHER Professeur, Praticien Hospitalier, Université de Guyane
Marie-Claude ROUSSEAU Professeure, Institut National de la Recherche Scientifique, Laval, Canada

Composition du Jury :

Président :	Eustase JANKY	Professeur, Praticien Hospitalier, Université des Antilles
Examinateurs :	Moana GELU-SIMEON	Maître de conférences, Praticien Hospitalier, Université des Antilles
Rapporteurs :	Mathieu NACHER	Professeur, Praticien Hospitalier, Université de Guyane
	Marie-Claude ROUSSEAU	Professeure, Institut National de la Recherche Scientifique, Canada
Dir. de thèse :	Danièle LUCE	Directrice de recherche Inserm, Université de Rennes

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Titre : Epidémiologie des cancers des voies aéro-digestives supérieures aux Antilles Françaises : Facteurs de risque comportementaux, viraux et environnementaux

Mots clés : Cancers des voies aéro-digestives supérieures ; étude cas-témoins; tabagisme; consommation d'alcool; papillomavirus humain; Antilles françaises

Résumé :
L'objectif était d'évaluer le rôle de différents facteurs de risque dans la survenue des cancers des voies aéro-digestives supérieures (VADS) aux Antilles françaises. Dans un premier temps, nous avons utilisé les données d'une enquête transversale sur la santé pour décrire la prévalence du tabagisme, de la consommation d'alcool et de l'obésité, et mis en évidence des disparités sociales. Nous avons ensuite analysé les données d'une étude cas-témoins menée en Martinique et en Guadeloupe entre 2013 et 2016, comprenant 145 cas de cancers des VADS et 405 témoins. Une prévalence élevée d'infection orale par le papillomavirus (HPV) a été mise en évidence, avec une distribution par génotype spécifique, en particulier une faible fréquence d'HPV16. L'infection orale aux HPV à haut risque (Hr-HPV) était associée à une augmentation significative du risque de cancer des VADS. Les consommations de tabac et d'alcool augmentaient fortement le risque de cancer des VADS, avec un effet combiné synergique.
Un faible indice de masse corporelle (IMC), des antécédents familiaux de cancer des VADS, et plusieurs activités professionnelles étaient également associés à un risque accru. L'utilisation du préservatif diminuait le risque, indépendamment de l'infection à Hr-HPV. Chez les femmes, un âge précoce aux premières règles était associé à une diminution du risque. Les consommations de thé, de café, de fruits et de légumes n'étaient pas associées au cancer des VADS.
Dans la population, la majorité des cas de cancers des VADS étaient attribuables au tabagisme (62,5 %) et à l'alcool (55,4 %). Environ 14 % des cas étaient attribuables à l'infection orale à Hr-HPV, 11 % à un faible IMC, 27 % à la profession et 7 % aux antécédents familiaux. Étant donné l'impact prépondérant des facteurs modifiables, de nombreuses opportunités de prévention des cancers des VADS se présentent dans cette population.

Title : Epidemiology of cancers of the upper aero-digestive tract in the French West Indies: Behavioral, viral and environmental risk factors

Keywords : Head and neck cancer ; case-control study ; tobacco smoking ; alcohol drinking ; human papillomavirus ; French West Indies

Abstract: The objective was to assess the potential influence of a large spectrum of risk factors on head and neck cancer (HNC) development in the French West Indies (FWI). As a first step, we used data from a cross-sectional
health survey to describe the prevalence of tobacco smoking, alcohol drinking and obesity. This work highlighted significant social disparities in these risk factors in the population.
We then analysed data from a population-based case-control study conducted in Martinique and Guadeloupe between 2013 and 2016, including 145 cases of HNC and 405 controls.
The study revealed a high prevalence of oral infection with human papillomavirus (HPV) in the population, and a specific distribution of HPV genotypes. HPV52 was the most prevalent type and HPV16 was found in only 4% of cases. Tobacco smoking and alcohol drinking increased the risk of HNC, with a synergetic combined effect.
High risk HPV (Hr-HPV) was associated with a significant increase in HNC risk, particularly in non-smokers and non-drinkers. Elevated risks of HNC were found in several occupations. A low body mass index (BMI) and family history of HNC were also associated with an increased risk of HNC. Condom use was found to decrease the risk of HNC, independently of oral HPV. In women, exposure to hormones, notably having menarche before 13, was associated with a decrease in HNC risk. Consumptions of tea, coffee, fruits and vegetables were not associated with HNC.
In the population, the majority of HNC cases were attributable to tobacco smoking (62.5%) and alcohol (55.4%). About 14% of the cases were attributable to Hr-HPV, 11% to low BMI, 27% to occupation and 7% to family history of HNC. Given the predominant role of modifiable factors in HNC aetiology, there are many opportunities for prevention in this population.

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My deepest heartfelt appreciation goes to my PhD advisor, Dr Danièle Luce. Words cannot express my gratitude towards you. I count myself extremely lucky to do my PhD under your supervision. Never have I met someone who makes exceptional things seem so normal. I am truly greatful for your many teachings and your mentorship. Thank you for your availability, your immense humility, your patience, your encouragement (especially towards the end). Thank you for the general knowledge and geography lessons. An enormous thank you for the many opportunities you granted me to go outside of Guadeloupe to attend training seminars to better my research skills. Thanks so much for allowing me to monopolise your time and for not abandoning me at the most crucial times. Working on this PhD thesis with you has been a real pleasure for me and I am elated to have reached this point.

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Scientific work and training

Scientific communications relative to the doctoral thesis

Articles

Aviane Auguste, Stanie Gaete, Cécile Herrmann-Storck, Leah Michineau, Clarisse Joachim, Jacqueline Deloumeaux, Suzy Duflo, Danièle Luce.
Prevalence of oral HPV infection among healthy individuals and head and neck cancer cases in the French West Indies. Cancer Causes Control (2017) 28: 1333

Aviane Auguste, Julien Dugas, Gwenn Menvielle, Christine Barul, Jean-Baptiste Richard, Danièle Luce. Social distribution of tobacco smoking, alcohol drinking and obesity in the French West Indies. *BMC Public Health* 19, 1424 (2019)

Aviane Auguste, Jacqueline Deloumeaux, Clarisse Joachim, Stanie Gaete, Léah Michineau, Cécile Herrmann-Storck, Suzy Duflo, Danièle Luce.
Joint effect of Tobacco, Alcohol and Oral HPV infection on Head and Neck Cancer risk in the French West Indies (submitted for publication)

Aviane Auguste, Clarisse Joachim, Jacqueline Deloumeaux, Stanie Gaete, Léah Michineau, Cécile Herrmann-Storck, Suzy Duflo, Danièle Luce.
Population attributable fractions of head and neck cancer risk factors in the French West Indies (submitted for publication)

Aviane Auguste, et al.

Association between Sexual Behaviour and Head and neck cancer in the French West Indies (ongoing preparation for submission)

Oral presentations

Aviane Auguste, Stanie Gaete, Cécile Herrmann-Storck, Leah Michineau, Clarisse Joachim, Jacqueline Deloumeaux, Suzy Duflo, Danièle Luce.

Epidemiology of Head and Neck Cancer in the French West Indies: The Role of Tobacco, Alcohol and Viral Factors. Inaugural annual scientific symposium, Ecole doctorale Biologie-Santé, Université de Bretagne-Loire, Rennes, France, 12-13th December 2018.

Aviane Auguste, Stanie Gaete, Cécile Herrmann-Storck, Leah Michineau, Clarisse Joachim, Jacqueline Deloumeaux, Suzy Duflo, Danièle Luce.
Prevalence of oral HPV infection among healthy individuals and head and neck cancer cases in the French West Indies.

- Clinical research symposium of the Guadeloupe University Hospital, Abymes, Guadeloupe, 22nd -23rd November 2018
- Caribbean Biomedical Research Days, International Stress and Behaviour Society, Gros-Islet, Saint Lucia, 16-18th January 2018
- Young researchers of Irset symposium, Irset, Rennes, France, 11th January 2018

Aviane Auguste, Stanie Gaete, Cécile Herrmann-Storck, Leah Michineau, Clarisse Joachim, Jacqueline Deloumeaux, Suzy Duflo, Danièle Luce.
Epidemiology of HNC in the French West Indies. 15th Annual INHANCE Meeting, Milan, Italy, 29th June 2018

Posters

Aviane Auguste, Jacqueline Deloumeaux, Clarisse Joachim, Stanie Gaete, Léah Michineau, Cécile Herrmann-Storck, Suzy Duflo, Danièle Luce.
Exposition professionnelles et cancer des voies aérodigestives supérieures aux Antilles Françaises. 20th Aderest symposium on occupation health, Toulouse, France, 14-16th November 2019.

Aviane Auguste, Jacqueline Deloumeaux, Clarisse Joachim, Stanie Gaete, Léah Michineau, Cécile Herrmann-Storck, Suzy Duflo, Danièle Luce.
Joint effect of Tobacco, Alcohol and Oral HPV infection on Head and Neck Cancer risk in the French West Indies. 7th biannual meeting of the African Caribbean Cancer Consortium, Kingston, Jamaica, 11-14th October 2019.

Aviane Auguste, Julien Dugas, Gwenn Menvielle, Christine Barul, Jean-Baptiste Richard, Danièle Luce.
Social Distribution of Tobacco Smoking, Alcohol Drinking and Obesity in the French West Indies.

- Inaugural international BIOSPHERES symposium, Fort-de-France, Martinique, June 2019
- 6th biannual meeting of the African Caribbean Cancer Consortium, Miami, USA, October 2017

Aviane Auguste, Stanie Gaete, Cécile Herrmann-Storck, Leah Michineau, Clarisse Joachim, Jacqueline Deloumeaux, Suzy Duflo, Danièle Luce.

Prevalence of oral HPV infection among healthy individuals and head and neck cancer cases in the French West Indies. 6th biannual meeting of the African Caribbean Cancer Consortium, Miami, USA, October 2017

Other scientific communications

Articles

Christine Barul, Mireille Matrat, **Aviane Auguste** Julien Dugas, Loredana Radoï, Gwenn Menvielle, Joelle Févotte, Emilie Marrer, Isabelle Stücker, and Danièle Luce

Welding and the risk of head and neck cancer: the ICARE Study (manuscript under review in Occupational and Environmental Medicine)

Oral presentations

Aviane Auguste.

CME lecture: Population science to the service of cancer control in the OECS and presentation of study concept. Monthly CME lecture for medical practitioners in Saint Lucia (breaking the paradigm in disease prevention), Saint Lucia Medical and Dental Association, Castries, Saint Lucia, 4th July 2019.

Aviane Auguste.

Project concept presentation for AC3 Mentor-Mentee program: Description of the Cancer Health Services in Saint Lucia: Diagnosis and Treatment and Pathways (DCAP) study. Young investigators retreat, Caribbean Institute for Health Research (CAIHR), Kingston, Jamaica, 4th April 2019.

Aviane Auguste.

Regional Workshop on HIV Drug Resistance Study Results: Report on Data Management and Analysis. HIV-TB elimination programme, Organisation of Eastern Caribbean States (OECS), Port-of-Spain, Trinidad, 21st-22nd March 2019.

Posters

Loïc Delannay, Carlene Radix, Dorothy Phillip, James St. Catherine, Elizabeth Dos Santos, Owen Gabriel, **Aviane Auguste**.

Description of the Cancer Health Services in Saint Lucia: Diagnosis and Treatment and Pathways (DCAP). 7th biannual meeting of the African Caribbean Cancer Consortium, Kingston, Jamaica, 11-14th October 2019.

Leïla Cabréra, **Aviane Auguste**, Jacqueline Deloumeaux, Clarisse Joachim, Leah Michineau, Suzy Duflo, Danièle Luce.

Expositions professionnnelles et cancer du poumon aux Antilles Française. Inaugural international BIOSPHERES symposium, Fort-de-France, Martinique, June 2019

Grants and awards

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- Attribution of a small grant to conduct pilot survey on cancer care pathways in Saint Lucia from January 2019

National Institute of Health/National Cancer Institute (NCI) of the USA

- Junior investigator travel award for the15th Annual INHANCE Meeting in Milan on the 29th June 2018
- Travel grant from the Centre for Global Health to attend the National Cancer Institute's (NCI) 2018 Summer Curriculum course titled "Principles and Practice of Cancer Prevention and Control" on July 9th–August 3rd, 2018.

International training programs

- **Principles and Practice of Cancer Prevention and Control**
  National Cancer Institute (NCI) of the USA, 9th July–3rd August 2018 (4 weeks), Washington D.C, MD, USA

- **Genetic epidemiology and Aetiological epidemiology**
  European Educational Program in Epidemiology (EEPE), 3rd-7th July 2017 (5 days), Florence, Italy

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List of Abbreviations

AC3- African Caribbean Cancer Consortium

BMI- Body Mass Index

CI- Confidence interval

FWI- French West Indies

HNC- Head and neck Cancer

HNSCC- Head and neck squamous cell carcinoma

HPV-Human papillomavirus

Hr-HPV- High-risk Human papillomavirus

IARC – International Agency for Research on Cancer

INHANCE- International Head and Neck Cancer Epidemiology Consortium

MICE- Multiple imputation by chained equations

OR- Odds ratio

PAF- Population attributable fraction

PR- Prevalence ratio

SES- Socioeconomic status

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1 Introduction

My doctoral research consisted of examining the role and impact of various known and suspected risk factors on the development of head and neck cancer (HNC) in the French West Indies (FWI) in an attempt to better understand the etiology of this disease and consequently inform public health policies that are adapted to the local context. The main tool for my research was data from a case-control study conducted in the FWI between 2013 and 2016. I also used data from a cross-sectional survey, the Baromètre Santé DOM (2014)

The first part of this doctoral thesis gives an overview of the research topic and a brief literature review on HNC in particular the behavioural, viral and environmental risk factors. The second part lists my objectives; the third part provides details of the methodology and tools used during my PhD. The fourth section displays the results of this doctoral work in the form of scientific articles, followed by a general discussion on the work in its entirety and finally a summary in French.

1.1 Anatomy and pathology of head and neck cancer

Head and neck cancer affects the upper aerodigestive tract (UADT), which comprises the sino-nasal cavities, pharynx, oral cavity and the larynx (Figure 1). The oesophagus is also sometimes counted in the subsites of HNC but generally dissociated because of its histological and aetiological particularities compared to the other HNC sites. The nasal cavity is subdivided into a right and a left nasal fossa by the median nasal septum, consisting of bony and cartilaginous components. The pharynx is a muscular tube lined with mucous membrane. It extends downward from the base of the cranium to the level of the sixth cervical vertebra, where it becomes continuous with the oesophagus. The pharynx is composed of three main portions, the nasopharynx, the oropharynx and the hypopharynx. The oropharynx is positioned in the buccal portion of the pharynx positioned at the first three cervical vertebrae. The hypopharynx is positioned further down at the fourth and fifth cervical vertebrae just before the larynx at the sixth cervical vertebrae. The larynx comprises three sections, the supraglottis, glottis and subglottis [1]. The UADT support functions in respiration, phonation, deglutination, and sense apparatus for olfaction and taste.

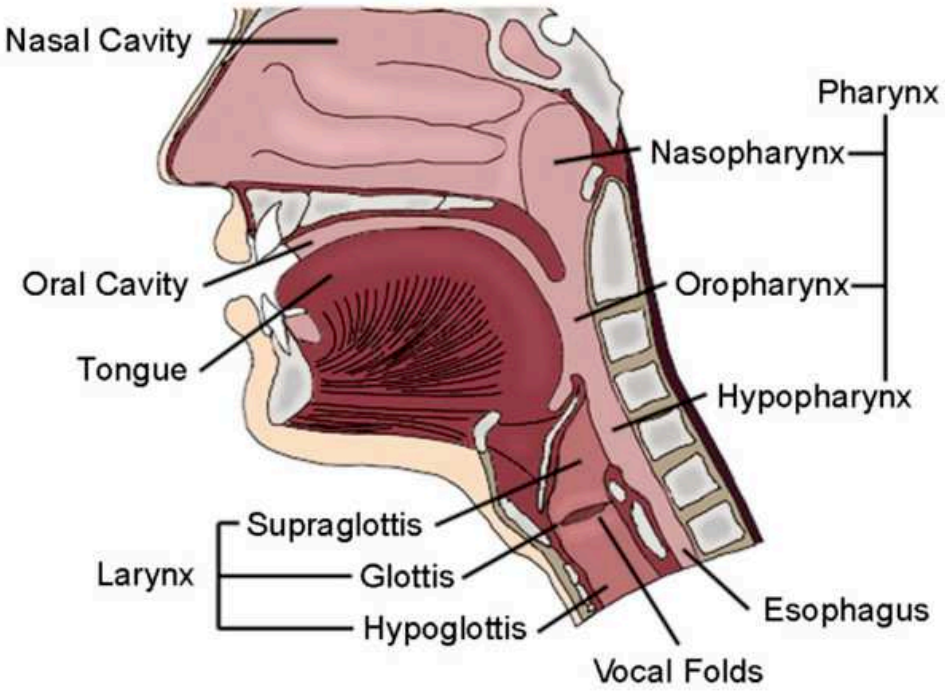

Figure 1:Main anatomical zones of human upper aerodigestive tract (source: Liebertz D et al., 2010) [2]

The majority of head and neck cancers occur in the squamous cells that line the moist, mucosal surfaces of the upper aerodigestive tract. Squamous cells are thin, flat cells that form the lining of various internal organs, including the hollow organs and ducts of some glands, the skin and eyes. These squamous cell cancers are referred to as head and neck squamous cell carcinomas (HNSCC). Other histological manifestations include adenocarcinomas and undifferenciated carcinomas. The latter histological types are found mainly in nasopharyngeal cancer, sinonasal cancer and salivary gland cancer. For the purpose of this doctoral thesis we focused primarily on cancers of the oral cavity, oropharynx, hypopharynx and the larynx.

1.2 Descriptive epidemiology of head and neck cancer

1.2.1 Incidence and mortality data in the world

Head and neck cancer accounts for more than 650,000 cases worldwide. The most common malignancy is squamous cell carcinoma (SCC) of the lip and oral cavity followed by the

pharynx and the larynx. Cancer of the salivary gland is the least frequent when compared to the other head and neck subsites [3]. Men and older persons are consistently more affected by head and neck cancer worldwide. Regions which have elevated incidence rates around the world (≥ 9.6 new cases annually per 100 000 inhabitants in 2018) are The United states of America, India, Australia, Cuba, Papua New Guinea and Most of Western Europe. Countries in Africa and South America have fewer cases annually (Figure 2).

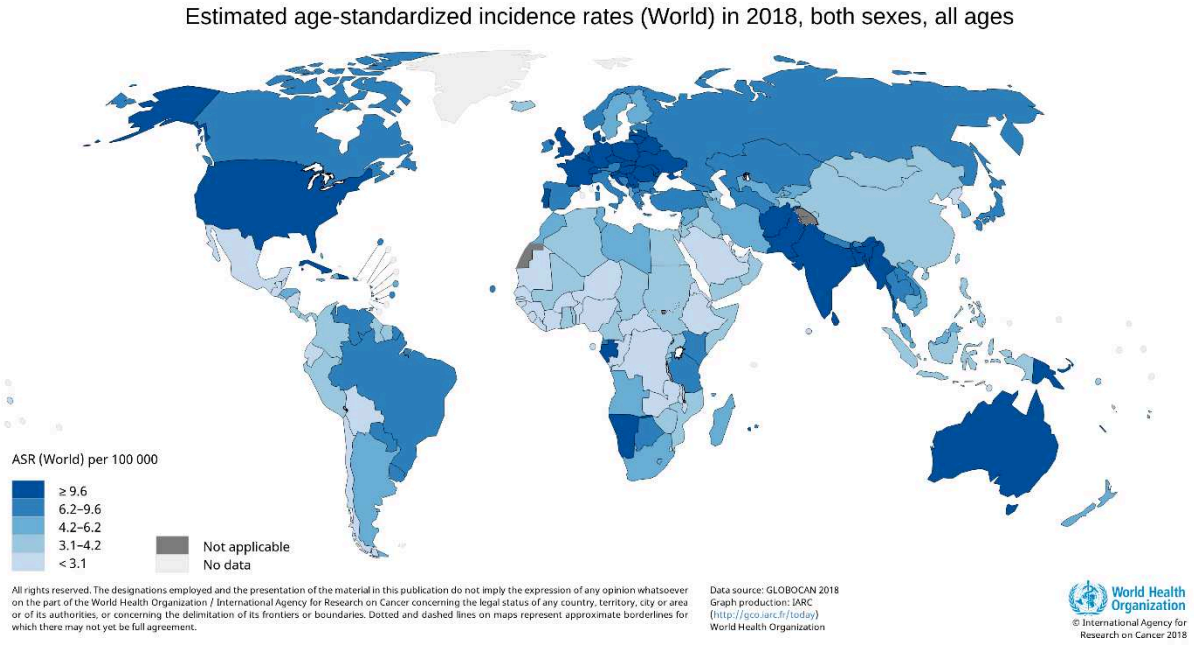

Figure 2: Heat map of age standardised incidence and mortality rate for cancers of the lip, oral cavity, oropharynx, hypopharynx and larynx in both men and women among worldwide (Source: Global Cancer Observatory: Cancer Today 2018. IARC, 2018) [4]

France is ranked overall 8th in the world for head and neck cancer (lip, oral cavity, larynx, oropharynx and hypopharynx). In 2018, age-standardized (world) incidence rates of head and neck cancer per 100,000 in France were estimated to be 25.9 in men and 7.2 in women. In terms of mortality, head and neck cancer is responsible for more than 330,000 deaths worldwide annually. Among all continents, age-standardized (world) mortality rates of head and neck cancer per 100,000 were the highest in Europe. In France, the mortality rates were 6.6 in men and 1.3 in women [4] (Figure 3-4).

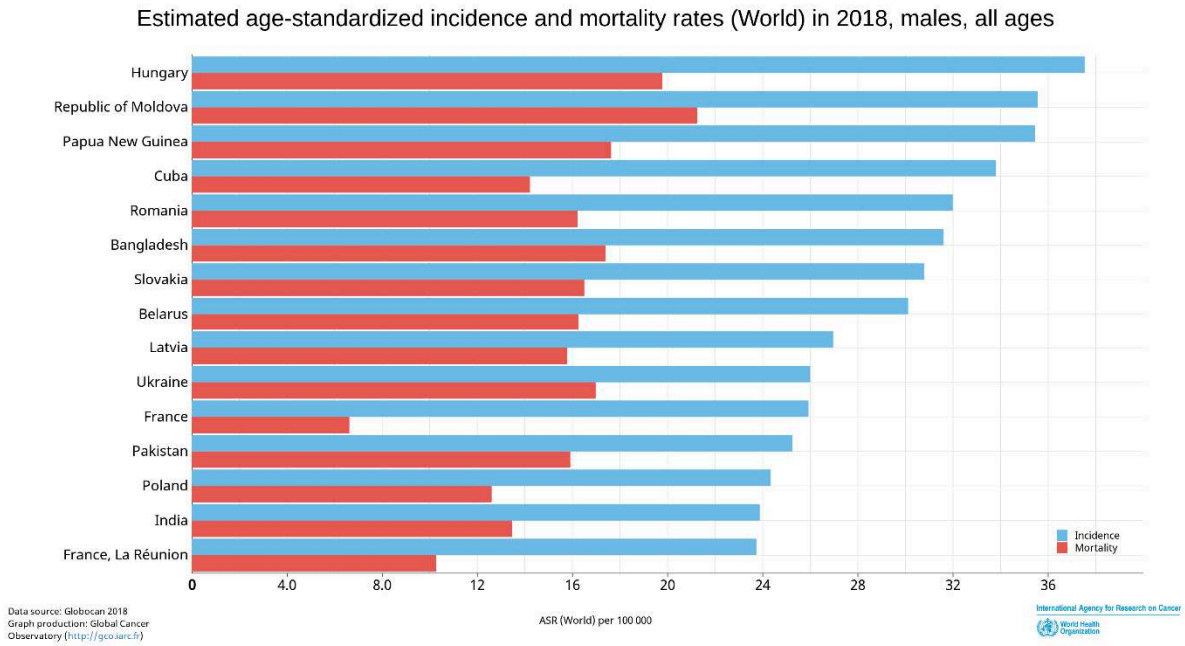

Figure 3: Age standardised incidence and mortality rate for cancers of the lip, oral cavity, oropharynx, hypopharynx and larynx in men among the first 15 countries worldwide (Source: Global Cancer Observatory: Cancer Today 2018. IARC, 2018) [4]

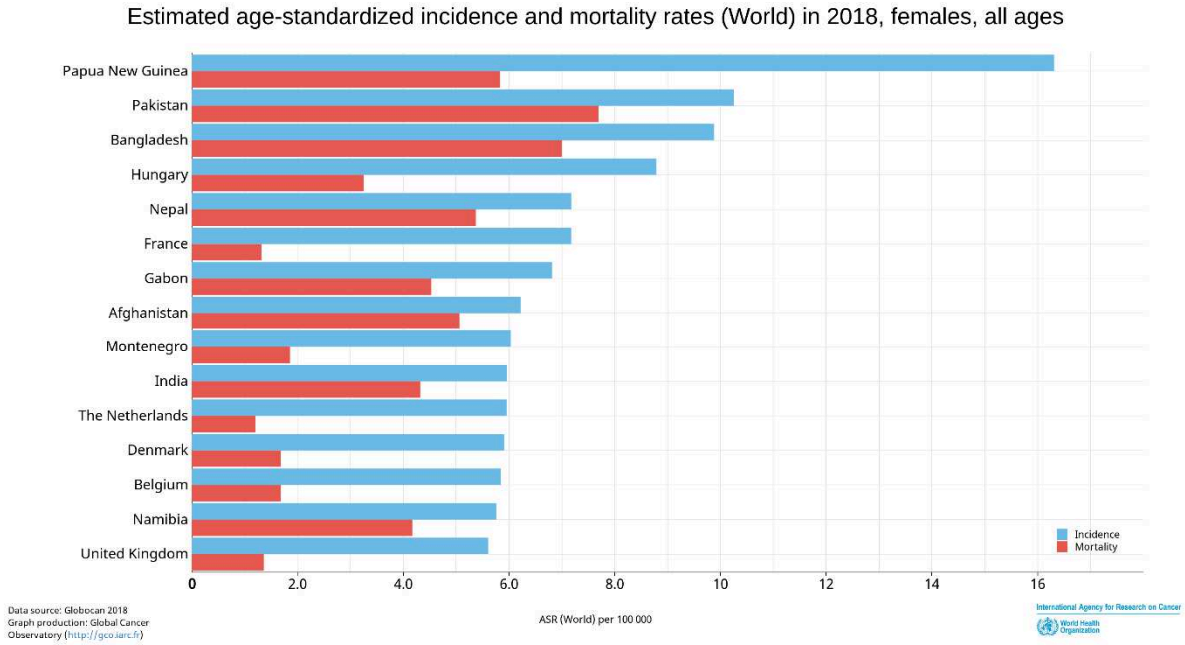

Figure 4: Age standardised incidence and mortality rate for cancers of the lip, oral cavity, oropharynx, hypopharynx and larynx in women among the first 15 countries worldwide (Source: Global Cancer Observatory: Cancer Today 2018. IARC, 2018) [4]

1.2.2 Incidence and mortality data in the French West Indies

Guadeloupe and Martinique are two French overseas territories in the French West Indies (FWI). The population of the French West Indies which is predominantly Afro-Caribbean is

covered by two regional cancer registries, the cancer registry of Guadeloupe which was established in 2008, and the Martinique cancer registry which was established in 1983. In 2018, age-standardized (world) incidence rates of head and neck cancer per 100,000 were estimated to be 8.1 in Guadeloupe (men: 15.5; women: 2.1) and 5.7 in Martinique (men: 12.1; women: 0.6). These incidence rates, especially in men, are among the highest in Latin America and the Caribbean. In terms of mortality, in 2018, age-standardized (world) rates per 100,000 were estimated to be 3.0 in Guadeloupe (men: 6.5; women: 0.2) and 2.5 in Martinique (men: 5.7; women: 0) [4] (Figure 5).

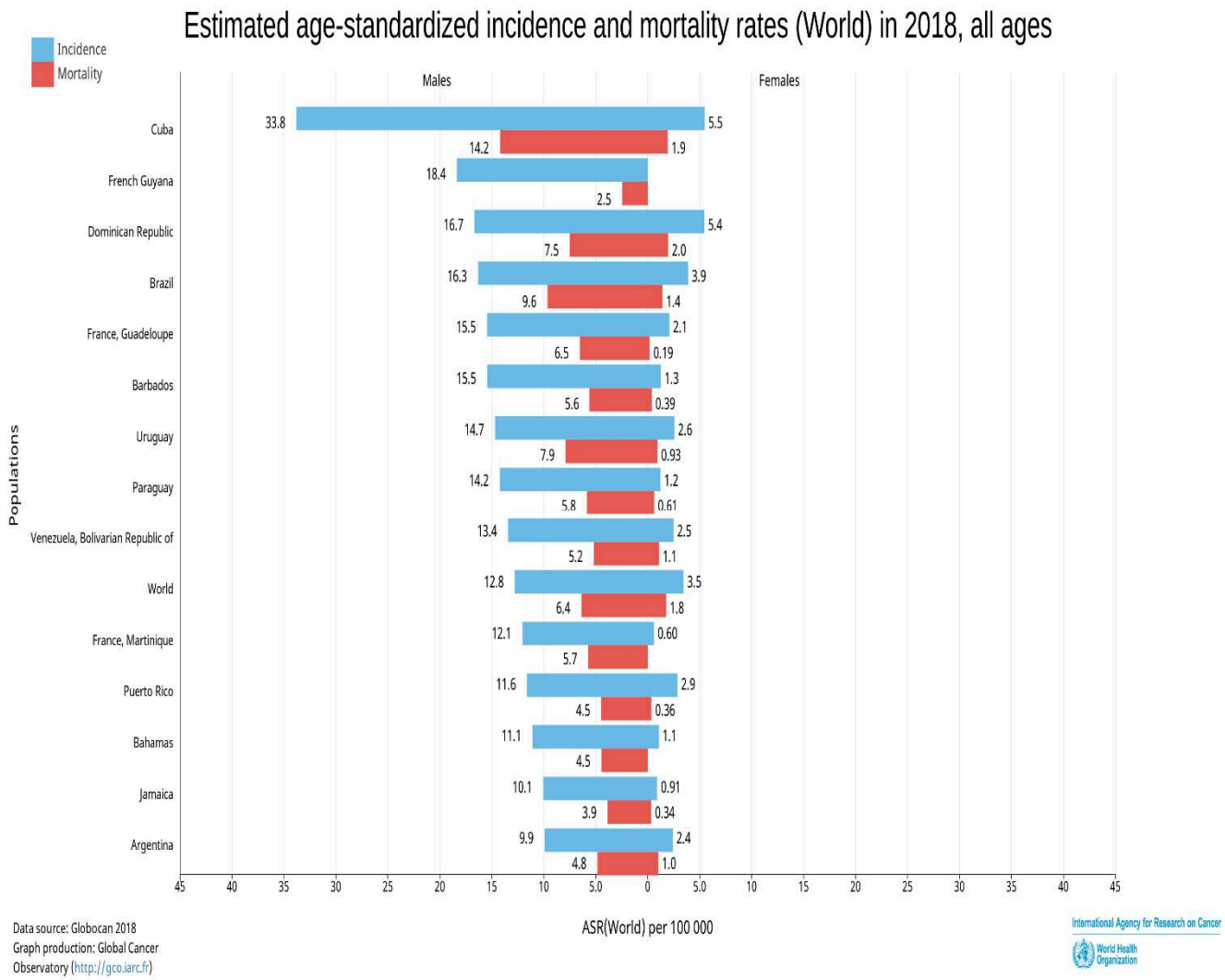

Figure 5: Age standardised incidence and mortality rate for cancers of the lip, oral cavity, oropharynx, hypopharynx and larynx in both men and women among the first 15 countries in Latin America and the Caribbean (Source: Global Cancer Observatory: Cancer Today 2018. IARC, 2018) [4]

1.3 Risk factors

1.3.1 Tobacco consumption

Tobacco smoking is an established risk factor for head and neck cancer. Tobacco smoking have been shown to induce a 4-5-fold increase in risk for oral cavity, oropharyngeal and hypopharyngeal cancer, whereas the increase was 10-fold for cancer of the larynx [5]. All forms of tobacco smoking are causally associated with head and neck cancer, including cigarettes, cigars, pipes and bidi smoking, a common form of tobacco smoking in India [6, 7].

It is however unclear whether one of these products confer a greater risk than the others [6]. On the other hand, head and neck cancer risk has been shown to differ according to the type of cigarette smoked. Rolled cigarettes and black tobacco confers a higher risk of head and neck cancer compared to manufactured cigarettes and blond tobacco [6]. There is also limited evidence that second-hand smoke, whether at home or at work, is associated with the risk of cancer of the larynx and the pharynx [6–8]. Other tobacco related practices, including tobacco chewing and using snuff tobacco, are also causally associated with cancer of the oral cavity. People in certain regions in Asia chew betel quids, containing areca nut, betel and often tobacco, which are known to increase the risk of oral and pharyngeal cancer [6, 7].

In epidemiological studies, dose-response relations have been consistently reported between head and neck cancer and intensity (cigarette/day), duration, and cumulative consumption of cigarettes (pack-years of lifetime consumption) [6]. In addition, a study from the INHANCE consortium demonstrated that the duration of cigarette smoking is the strongest determinant of the risk of head and neck cancer. Indeed the risk was more elevated in persons smoking fewer cigarettes/day for a longer duration than in person smoking greater cigarettes/day for a shorter duration [9]. The association between age at initiation of tobacco has been studied in previous reports that tended to show an inverse relationship with age and HNSCC risk [10–13]. However, a large pooled analysis by the INHANCE consortium did not show any significant increase in HNSCC risk and age at initiation of tobacco smoking [14].

1.3.2 Alcohol drinking

Alcohol drinking is associated with head and neck cancer. High intensity of alcohol drinking (50g per day) has been shown to increase the risk of cancers of the oral cavity and pharynx by three-fold, and two-fold for laryngeal cancer [15]. Alcohol drinking duration was also associated with head and neck cancer risk but had a less important role than the intensity [9]. On the other hand, age at initiation of alcohol drinking have not been demonstrated to be

associated with head and cancer risk [14, 16]. Regarding the types of beverages consumed, no clear differences have been demonstrated in head and neck cancer risk from one beverage to the next [17]. However the overall consensus is that the most frequently consumed beverage in a particular area is associated to the greatest increase in risk [15, 18].

1.3.3 Joint effect of tobacco and alcohol

It is well established in the literature that tobacco and alcohol act synergistically on head and neck cancer risk. Previous studies have shown strong evidence of more than additive and at least multiplicative joint effects [19]. The population attributable risk fraction for ever tobacco and alcohol drinking was estimated at 72% by a pooled study from the INHANCE consortium; whereas the attributable fractions for tobacco and alcohol individually were only 33% and 4% respectively. There was as well some heterogeneity in the attributable fractions between subsites. The majority of the laryngeal cancer cases were explained by the joint effect of tobacco and alcohol, whereas the attributable fraction was lower for cancers of the oral cavity and the pharynx (64% and 72% respectively).

1.3.4 Oral hygiene

Proper oral hygiene has been shown to be inversely associated to head and neck risk. A pooled analysis by the INHANCE consortium found that brushing of teeth daily, annual visits to the dentist and having not more than 5 teeth missing decreased the risk of head and neck cancer [20]. In contrast, mouthwash containing alcohol increased the risk of oral and oropharyngeal cancer [21, 22].

1.3.5 Oral HPV infections

The human papillomavirus (HPV) has long been associated to ano-genital cancers and since 1990, there has been growing evidence towards an association with head and neck cancer. Unlike cervical cancer, HPV has not been demonstrated as an indispensable driver of head and neck carcinogenesis. However, in 2007, the IARC stated for the first time that there was

adequate epidemiological and molecular knowledge to deduce an etiological role of HPV in non-ano-genital cancers [23]. Studies are providing growing evidence on a role of HPV to the oropharynx and more specifically cancers of the tonsils and the base of the tongue. Sexual transmission is thought to be involved in oral HPV infection, in particular oral sex and a high number of oral sex partners [24]. There are many different genotypes of HPV which are classified mainly according the oncogenic risk associated with them [25]. The low-risk types e.g HPV 6 and 11, are have been associated with laryngeal cancer [26] and are known to cause benign warts [27]. HPV16 and 18 are well known high-risk types and are well known to be involved in head and neck carcinogenesis [27]. Numerous studies have demonstrated significant associations with HPV16, HPV18 and other high-risk HPV types and head and neck cancer [25, 28–31].

1.3.6 Body mass index

Previous studies have shown that a low body mass index (<18.5 kg) was significantly associated with an increase in head and neck risk [32, 33]. A large pooled analysis from the INHANCE consortium showed that persons with low BMI were two times more likely to develop head and neck cancer than those with a normal BMI, Furthermore, inverse associations for obesity have been observed. These findings oppose the conventional positive association between BMI and most other cancers.

1.3.7 Socioeconomic status

Regardless of the indicator used (education, occupation or income), lower socioeconomic status has been associated with an increase in head and neck cancer when compared to persons of higher socioeconomic status [34, 35]. Health behaviour of persons across socioeconomic is thought of as a driver for these social disparities in head and neck cancer risk. However, after adjustment for tobacco smoking and alcohol drinking the association with socioeconomic status remains suggesting that these social disparities are not entirely

explained by behavioural factors [34]. Occupational exposure on the hand, could explain partially the association between socioeconomic status and head and neck cancer [36].

1.3.8 Occupational exposures

Laryngeal cancer is more consistently associated to occupational exposure than the other head and neck subsites. The International Agency for Research on Cancer (IARC) has indicated that the occupational exposures for which sufficient evidence exist for laryngeal cancer are asbestos and strong inorganic acid mists [37]. Although the evidence is limited, other occupational factors such as manufacturing of rubber have been associated with and elevated risk of laryngeal cancer. Similarly, exposure to asbestos and work in the printing industry was associated to cancer of the pharynx [38–40]. No evidence has been shown to support any causal link between occupational exposures and cancer of the oral cavity [40]. On the other hand, an augmented risk of head and neck cancer has been associated with numerous occupations such as textile and leather workers, butchers, carpet workers, machinists, female electronics workers, welders, painters, and construction workers [41, 42]. Laryngeal cancer in particular has been \associated with formaldehyde, man-made mineral fibres, mustard gas, organic solvents and dusts from cement, metal, coal, leather and wood [43–46].

1.3.9 Diet and non-alcoholic beverages

Diet and nutrition have been suggested to play an important role in the etiology of head and neck cancer. Particularly, a high consumption of fruits and vegetables has been consistently associated to a decreased risk of oral and oropharyngeal cancer and to a lesser extent laryngeal cancer [47–49]. Previous studies from Italy showed that approximately 20–25% of cancers of the head and neck low were attributable to a low vegetable and fruit consumption [50].Vegetables and fruits are rich in vitamins C and E, carotenoids as well as flavonoids, with antioxidant and antitumor effects which may help prevent head and neck cancer [51–53]. In terms of coffee and tea, no consistent evidence in the association with cancer of the oral

cavity and pharynx arose from epidemiological studies [54–56]. However, there is some evidence of an elevated risk for maté drinkers, popular herbal infusion traditionally consumed in Argentina and some areas of Brazil [57].

1.3.10 Hereditary and genetic factors

A family history of head and neck cancer among first-degree relatives is associated with an increased risk of head and neck cancer [58, 59]. Single nucleotide polymorphisms related to alcohol metabolism (ex. Alcohol dehydrogenase and aldehyde dehydrogenase) were shown to be associated with an increase of head and neck cancer [60]. Other studies investigating polymorphisms and genes involved in alcohol or tobacco metabolism, notably the genes glutathione-S-transferase M1 (GSTM1) and GSTT1 show some evidence that these genes may act as markers to determine the genetic susceptibility in HNSCC patients and in their first-degree relatives [61–63]. The INHANCE consortium conducted a genome wide association study to identify common genetic variation involved in susceptibility to head and neck cancer. Their study revealed 5 variants associated with HNSCC that in combination explained approximately 4% of HNSCC familial risk [64].

1.4 Presentation of the French West Indies

The French West Indies is a region in the Caribbean Sea and comprises overseas territories of France (*départements et collectivités d'outre-mer*), which include Guadeloupe, Martinique, Saint-Martin and Saint Barthelemy. Saint-Martin and Saint-Barthélemy were initially a part of the Guadeloupe region but became separate *collectivités d'outre mer* after a referendum in 2007. For the purpose of this thesis, we focused on Guadeloupe and Martinique, the two *départements d'outre-mer*. Guadeloupe is an archipelago of 1628 km^2 and is composed of two main islands, Basse-Terre and Grande-Terre which are joint together side-by-side by two bridges. The archipelago comprises as well several other islands like Marie-Galante, les Saintes and Désirade. Martinique is an island of 1128 km^2 south of Guadeloupe. In 2016, the population of Guadeloupe and Martinique were each approximately 400 000 inhabitants and are primary of Afro-Caribbean ethnicity [65]. Compared to mainland France, the French West Indies possess a younger population and a higher unemployment rate, in particular among persons under 20 years old. In addition, the population suffers from high levels of precarity measured by the great proportion of persons benefiting from universal health care coverage (Couverture maladie universelle) and from support for low income (Revenu de solidarité active). Further disparities exist in terms of health care. The French West Indies have a lower medical density, notably for specialist doctors. Cardio-metabolic diseases and cancer are the leading causes of death in the French West Indies. In addition, sickle cell is regarded as the leading genetic disorder in this population [66]. The cancer incidence in the FWI is generally in-between mainland France and other Caribbean territories [4, 67]. The two most frequent cancer sites in the French West Indies are prostate and breast cancer. The cancer incidence for the French West Indies is lower than that of metropolitan France for lung cancer, but higher for stomach cancer, cervical cancer and especially for prostate cancer (table 1 and table 2). These differences in cancer epidemiology could partly attributable to the African ancestry of

the French West Indian population which is notably strongly associated with high prostate cancer incidence [67] or to differences in the prevalence of risk factors [68]. . The prevalence of tobacco smoking is low in the FWI [69]. It should be noted that the difference between mainland France and the French West Indies in head and neck cancer incidence is less marked than for lung cancer despite their association with tobacco. Alcohol consumption is also moderate in the FWI population and lower than in mainland France, although the types of alcoholic beverages differ [69]. A high prevalence of high-risk HPV cervical infection has been reported in Guadeloupe, but the prevalence of oral HPV infection in the FWI is not known [70]. The FWI also have some distinctive features in terms of occupational hazards, with special activities such as banana and sugar cane farming and sugar cane industry that confers onto the population specific occupational and environmental exposures. Pesticides have been extensively used in the French West Indies over the years. Chlordecone in particular was widely used in banana plantations and the exposure to this organochlorine pesticide has been shown to increase the risk of prostate cancer [71].

Table 1: Estimated age-standardized incidence rates (World) in 2018, all ages, both sexes (per 100,000). (Source: Global Cancer Observatory: Cancer Today 2018. IARC, 2018) [4]

	Guadeloupe	Martinique	France	Latin America and Caribbean
Prostate	189.1	158.4	99.0	56.4
Breast	68.9	78.3	99.1	51.9
Colorectum	19.8	23.9	30.4	16.8
Stomach	12.3	10.0	4.9	8.7
Lung	9.4	10.6	36.1	11.8
Cervix uteri	9.3	7.6	6.7	14.6
Head and neck	8.1	5.7	16.2	6.6
All cancers	**254.6**	**250.8**	**344.1**	**189.6**

Table 2: Estimated age-standardized incidence rates (World) in 2018, all ages. (Source: Global Cancer Observatory: Cancer Today 2018. IARC, 2018) [4]

	Men				Women			
	Guadeloupe	**Martinique**	**France**	**Latin America & Caribbean**	**Guadeloupe**	**Martinique**	**France**	**Latin America & Caribbean**
Prostate	189.1	158.4	99.0	56.4	NA	NA	NA	NA
Breast	NA	NA	NA	NA	68.9	78.3	99.1	51.9
Colorectum	21.2	29.0	36.9	18.4	18.5	19.8	24.8	15.5
Stomach	16.1	13.1	7.2	11.3	9.3	7.5	2.9	6.6
Lung	13.0	12.3	51.3	15.1	6.5	9.2	22.5	9.2
Head and neck	15.5	12.1	25.9	10.9	2.1	0.6	7.2	2.9
Cervix uteri	NA	NA	NA	NA	9.3	7.6	6.7	14.6
All cancers	**342.9**	**308.9**	**405.6**	**200.3**	**183.1**	**201.1**	**292.9**	**183.7**

2 Objectives of the thesis

Despite a low prevalence of tobacco smoking and alcohol drinking, incidence rates of head and neck cancer in Guadeloupe and Martinique are among the highest in the Americas. Consequently, the HNC burden in this region was thought to be attributable to other risk factors such as human papillomavirus (HPV), diet, family history of cancer, occupational and environmental risk factors.

The overall objective of this doctoral thesis was to assess the potential influence of various risk factors on head and neck cancer development in the FWI.

Considering the lack of published data on behavioural risk factors in the FWI, the initial work of this thesis consisted of a secondary analysis of the data from a cross-sectional survey, the Baromètre Santé, to produce a detailed description of tobacco smoking, alcohol and obesity prevalence in the general population, according to gender, age and socioeconomic status.

The main part of the work was the analysis of a population-based case-control study on head and neck cancer conducted in the FWI. This is the first epidemiological study of this kind in an Afro-Caribbean population. A large spectrum of risk factors was examined, with a focus on tobacco smoking, alcohol drinking and oral HPV infection. More precisely, the objectives were:

- to study and quantify the associations between head and neck cancer risk and behavourial risk factors (tobacco, alcohol, diet, sexual behaviour), viral risk factors (HPV infection), occupational exposures, anthropometric measures, family history of cancer,
- to evaluate possible interactions between these risk factors,
- to estimate the impact of these different risk factors in this population, by calculating population attributable risks.

3 Materials et methods

3.1 Baromètre santé DOM

3.1.1 Study Design

The Baromètre Santé DOM is a national cross-sectional health survey conducted in the FWI in 2014. The survey was based on a random two stage sampling method, in Martinique and Guadeloupe, to obtain a sample representative of the general population [72].

3.1.2 Study population

Landlines and mobile phone numbers were randomly generated and individuals were randomly selected from that list and contacted by field investigators to conduct the interview over the phone. Participants aged between 15 and 75 years of age residing in Martinique or Guadeloupe and able to speak either French or Creole were eligible for inclusion. The survey sample was separated into two subgroups, the sample of persons contacted by a landline telephone, and a sample of persons contacted through a mobile phone. For the landlines group, once the eligible household was successfully reached by telephone, one person satisfying the inclusion criteria was interviewed. Replacement by another member of the family was not allowed in the survey. The method for the selection of members of a household used for this survey was the method proposed by Leslie Kish as described elsewhere [73]. In the mobile phone sample, the regular users of the mobile phone lines were selected. Conventionally, a mobile phone is a personal item; however, the number of users of that mobile phone line was verified by asking “how many persons between 15 and 75 years use regularly use this phone to receive calls including yourself”. In the case of multiple users of the same mobile phone line, the Kish method was applied in the same manner as the landline sample but this time it was among the users of the mobile phone [73].

Out of 12236 usable numbers from the phone listing, 8057 were dialled. In the end, 4089 subjects were included in the final sample for Martinique and Guadeloupe. The overall participation rate for the French West Indies was 51%.

Table 3: Breakdown of participation in the Baromètre Santé DOM survey in Martinique and Guadeloupe.

	Martinique		Guadeloupe	
landline and mobile phone sample	n	%	n	%
Usable numbers	5866		6370	
Numbers dialled	3736		4321	
Unreachable after dialling	1177	32	1655	38
Refusal (household and individual)	404	11	488	11
Abandon	134	4	110	3
Participation rate	**2021**	**54**	**2068**	**48**

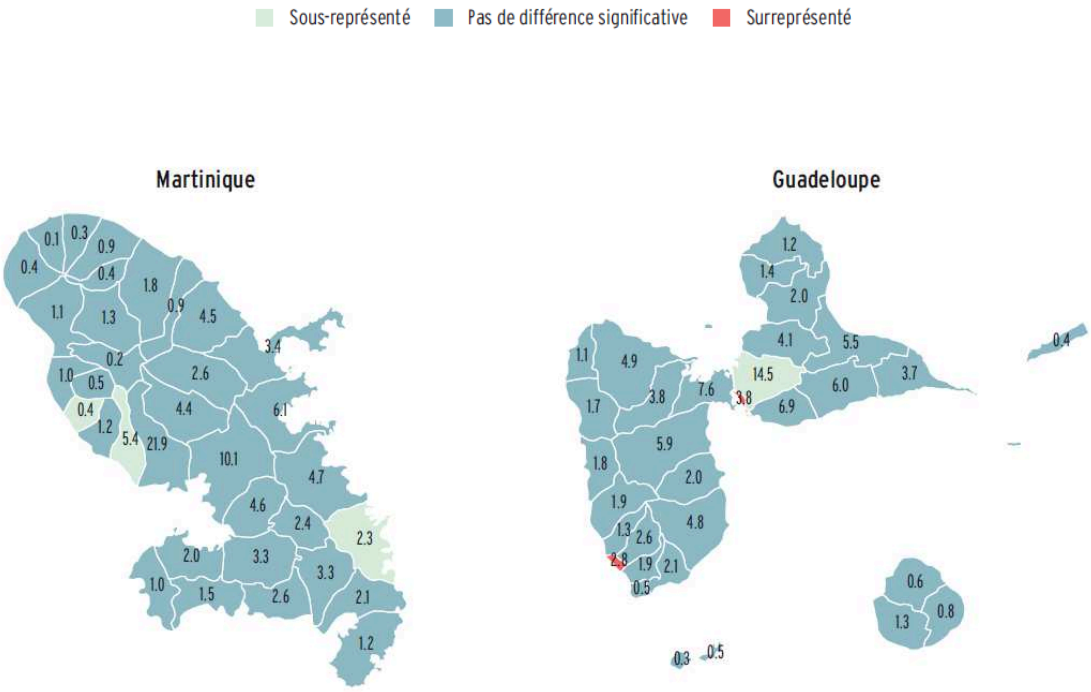

Figure 6: Difference between observed and expected frequency (Chi-square test) by municipality

3.1.3 Data collection

Field investigators were briefed on the sampling procedures and were trained to administer the questionnaire over the phone. The questionnaire covered multiple themes surrounding health including health care seeking habits, screening, health risk awareness, mental health and consumption of psychoactive substances. The field data collection was performed between April and November 2014. The study questionnaire was administered through computer-assisted telephone interviews (CATI). Every telephone number was dialled 20 times and each attempt to reach the potential participant, the field investigator allowed the phone to ring 6 times before hanging up. In the case of a busy phone line, a new attempt was made 15 minutes later. When there was no response, the number was dialled later that same day. Every number had to be dialled several days with at least two calls on Saturday before excluding the potential participant. For the purpose of this doctoral thesis, we selected a subset of variables set pertaining to cancer risk factors and socioeconomic status from the final data. We selected information on tobacco, alcohol consumption, body mass index (BMI). We used as well 4 variables related to socioeconomic status: education, occupational category, income and availability of hot water at home.

3.1.4 Statistical analysis

3.1.4.1 Univariate analysis

The details for the prevalence calculations for the cancer risk factors in the French West Indies are detailed below. Consider the contingency table below as a reference for the notations used in formulas shown in this section.

SES indicator	Risk factor+	Risk factor-	Total
SES_1	a	b	E_1
SES_2	c	d	E_0
Total	H_1	H_0	E_t

SES: socioeconomic indicator/sociodemographics (education, occupational category, income and availability of hot water at home/age and sex)

a: Person in first SES category exposed to a given risk factor

b: Person in first SES category not exposed to a given risk factor

c: Person in the 2nd SES category exposed to a given risk factor

d: Person in the 2nd SES category not exposed to a given risk factor

E: Total number of persons in a given SES stratum

H: Total number of persons exposed to a given risk factor

The overall prevalence for each risk factor in our population was calculated in the following manner:

$$P_{factor} = {}^{H_1}/_{E_t}\,(overall)$$

The prevalence for each risk factor by age and sex was calculated in the following manner, and then for each category of the four socioeconomic indicators stratified by sex:

$$P_{factor} = {}^{a}/_{E_1}\,(SES_1)$$

$$P_{factor} = {}^{c}/_{E_0}\,(SES_2)$$

3.1.4.2 Multivariate analysis

3.1.4.2.1 Poisson regression

In statistics, Poisson regression is a generalized linear model form of regression analysis used to model count data and contingency tables. This model was used to fit the data for our analyses on social inequalities in cancer risk factors because it is robust and produces prevalence ratios which are more appropriate than estimating odds ratios which would otherwise tend to overestimate the actual effect size when the event of interest is not rare [74].

The Poisson regression is based on the assumption that the outcome variable, Y and the linear combination of explanatory variables are independent and follow a Poisson distribution and assumes the logarithm of its expected value can be modelled by a linear combination of unknown parameters. The logarithm of μ is used as the link function in this model.

The basic Poisson regression model can be written as follows

$$E(Y_i|X_i) = \mu_i = e^{\beta_0+\beta_1 x_{i1}+\beta_2 x_{i2}+\ldots+\beta_n x_{in}}$$

When introducing an offset term n_i, to take into the account of the weight of the observation. The model can be written in this manner:

$$E(Y_i|X_i) = \mu_i = n_i + e^{\beta_0+\beta_1 x_{i1}+\beta_2 x_{i2}+\ldots+\beta_n x_{in}}$$

It can also be expressed as follows:

$$ln(\mu_i) = ln(n_i) + \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \ldots + \beta_n x_{in}$$

Where μ: The mathematical expectancy of the outcome variable

$\boldsymbol{\beta_0}$: intercept

$\boldsymbol{\beta_i}$: regression coefficient showing the association between each explanatory variable and the outcome variable

$\mathbf{x_i}$: explanatory variable

$\mathbf{n_i}$: The offset term accounting the weight of the observation

The regression parameters for the Poisson regression are estimated using the maximum likelihold method which consists of maximising the likelihood function. The likelihood is the probability of observing a sample and can be written as follows:

$$V(\beta) = \prod_{i=1}^{n} \left[\frac{e^{-\mu_i} - \mu_i^{y_i}}{y_i!} \right]$$

The exponential of the regression parameters from the poisson model was calculated to generate the prevalence ratios (PR) their 95% confidence intervals (CI) for our study.

3.1.4.2.2 Weighting adjustments

A sample should be representative of the source population from which it is drawn in regards to all measured variables in a survey. Usually the sample obtained deviates from this ideal situation due to several issues including non-response. The over- and under-representation of certain groups or characteristics could occur as a result of non-response. When issues such as this one arise, weighting adjustment can be used to correct for the lack of representativity. The method consists of assigning a survey weight to each participant. Persons in under-represented groups get a weight larger than 1, and those in over-represented groups get a weight smaller than 1. The individual weights are determined based on the auxiliary variables used. Auxiliary variables (e.g. age and sex) are characteristics that are measured in the study sample and for which data are available on the population distribution. This adjustment weight is used for the calculation of means, totals and percentages as well as the raw values of the variables.

In the Baromètre Santé DOM, data were weighted in two steps [72]. To account for the sampling design, sample weights were computed according to the probability of selection of the telephone number, the number of eligible individuals for each telephone number, the number of landline and cell phones of the individual. To correct for non-response, a post-stratification was then performed to match the distribution of the population, according to sex, age, education level and household structure, using data from the 2011 census in Martinique and Guadeloupe. This method works under the assumption that in each defined category by the adjustment variables, the respondents and non-respondents are on average similar in regards to the variables of interest for the survey.

3.2 Case-control study

3.2.1 Study design

The majority of data from this thesis were drawn from a population-based case-control study which was conducted in the two overseas French departments in the FWI, Martinique and Guadeloupe, and was performed with the collaboration of the cancer registries from these departments. The study is an extension of a large nationwide case-control study, the ICARE study, which has already been conducted in ten French regions covered by a cancer registry [75].

3.2.2 Study population

3.2.2.1 Recruitment of cases

Cases were all patients suffering from a primary, malignant tumor of the oral cavity, pharynx, larynx, (International Classification of Diseases, 10th Revision, codes C00-C14; C32), newly diagnosed during the study period in the two "départements" of the FWI (Martinique and Guadeloupe), of any histological type. Only histologically confirmed cases aged over 18 and less than 75 years old at the time of diagnosis were included

Poor survival for some of the cancers included in this study did not allow relying on routine inclusion of cases in the registries for their identification. A procedure was set up to expedite case identification, in order to reduce the delay between diagnosis and interview of cases. Cases were identified through active search, by regular contacts and visits to the pathology laboratories and hospital departments that usually diagnose and treat head and neck cancers. A1 list of these laboratories and hospital departments was established by each registry, based on data of the previous years. In each region, more than 95% of recorded cases have been treated in only 3 hospitals departments, and 80% of the recorded cases have been treated in the ENT departments of the two University hospitals, Pointe-à-Pitre in Guadeloupe and Fort-

de-France in Martinique. The local pathology laboratories (3 in Guadeloupe and 2 in Martinique) have notified more than 98% of the cases.

Eligible cases were invited to participate by the ENT surgeons as far as possible, at the time they find most appropriate, otherwise by another physician. A letter of information was handed to them or sent to their home. If the patient agreed, written consent was collected, notably for the donation of biological specimens, and an appointment was made for the interview. If the diagnosis was not histologically confirmed at the time of interview, cases with a strong clinical suspicion were interviewed, pending subsequent confirmation.

3.2.2.2 Recruitment of controls

The control group was a random sample of the general population of the study area. Controls were frequency matched to the cases by age, sex and study centre (Martinique or Guadeloupe). Additional stratification was used to obtain a distribution by socioeconomic category comparable to that of the population (obtained from census data), in order to control for possible selection bias arising from differential participation rates across socioeconomic status categories.

Recruitment of controls was done by telephone (landlines and cell phones) in collaboration with a polling institute experienced in this type of procedure and possessing the necessary tools and personnel. First, a random sample of numbers was generated. Each number was called 10 times before being abandoned as not answered. Calls were made in the evening on weekdays and during the day on Saturdays. Recruitment was done by trained interviewers from the polling institute. These interviewers received a half-day specific training to better understand the objectives of the study, so that they can better answer eventual queries from the contacted subjects. When an eligible subject was identified by telephone call, the objectives of the study and terms of participation were explained and agreement to participate was sought. If contacted persons agreed to participate, they were informed that an interviewer

from INSERM would contact them soon, and a letter of information was sent. A list of persons agreeing to participate was given to the study interviewer who contacted them in turn, to confirm their agreement and to make an appointment for the interview.

Control recruitment waves were conducted every two months, by groups of 40 subjects (20 by department). The number of recruits was based on the estimated total number of cases and the expected participation rate among controls. Their distribution by sex and age were initially based on the characteristics of cases notified to the registries in the two previous years, and was later adjusted as necessary depending on the age and sex distributions of cases and controls recruited at that time. Their distribution by socioeconomic status was based on census data, taking age and sex into account.

3.2.3 Data collection

Cases and controls were interviewed face-to-face. The following information was collected during the interview:

- Socio-demographic characteristics (sex, age, marital status, educational level, occupation of parents and spouse, place of birth and parents' place of birth);
- Residential history;
- Anthropometric characteristics (height, weight at interview, weight 2 years before interview, weight at 30 years of age);
- History of cancer and various diseases;
- History of cancer among first-degree relatives;
- Hormonal and reproductive factors (for women only): age at menarche, age at menopause, oral contraceptives, menopausal hormonal therapy, number and outcomes of pregnancies number of children, age at first birth

- Smoking of cigarettes, cigars, cigarillos and pipe, with beginning and end dates, quantity per day, type of cigarette (blond or brown tobacco, filtered or not, brand), for each smoking episode; questions on snuff or chewing tobacco;
- Passive smoking during childhood, at workplace and at home during adulthood;
- Alcohol consumption, with beginning and end dates, quantities, types of alcohol for each period of regular consumption (wine, beer, rum, other spirits);
- Usual diet, with a food frequency questionnaire
- Occupational history, with a detailed description of each job held, and specific occupational questionnaires for tasks or occupations frequently encountered or of special interest for the study.
    - Agriculture
    - Sugarcane industry
    - Construction
    - Hair dressing
    - Motor vehicle maintenance
    - Wood worker
    - Tool maker and machinist
    - Painting
    - Plumbing
    - Welding
    - Textile
    - Leather worker
- Sexual history and behavior (number of lifetime sexual partners, age at first intercourse, use of condoms, frequency of oral sex, and history of sexually transmitted infections…)

3.2.4 Biological specimen collection

3.2.4.1 Saliva samples

During face-to-face interviews, participants were asked to provide a saliva sample, using the Oragene® OG-500 kit (DNA Genotek). Samples were sent to the Biological Resource Centre of Guadeloupe for storage at 24°C. Oragene® saliva specimen may be stored for at least 5 years at room temperature without DNA degradation [76].

Each subject included in the study gave a written and informed consent. In order to protect the confidentiality of personal data, the questionnaire included only an identification number, without any nominative information.

3.2.4.2 Buccal swabs

Exfoliated oral cells in cases and controls were also be collected by performing superficial scrapes of the oral mucosa with cytobrushes (2 per subject). Cytobrushes were sent to the Biological Resource Center of Guadeloupe, where they were stored at -80°C.

3.2.4.3 Fresh frozen tumour samples

Fresh tumor samples were collected from biopsy or surgery at the University hospital of Guadeloupe. Samples were put in a labeled cryotube and directly immersed in a liquid nitrogen non-pressurized container, placed permanently in the operating room. Samples were then stored at -80°C in a controlled freezer (Forma 900, Thermo Fischer Scientific /Massachusetts, USA) at the Center for Biological Resources Karubiotec. Fresh frozen samples were obtained for 86 cases. This procedure could not be set-up in Martinique, for practical reasons.

3.2.5 DNA extraction and biological assays

3.2.5.1 DNA extraction from saliva

The extraction of DNA was manually performed on saliva samples. Genomic DNA extraction was carried out using prepIT®•L2P reagent. The samples were mixed and incubated overnight (16 hours) at 50°C to ensure that DNA was released and that nucleases were permanently inactivated. Addition of the prepIT®•L2P reagent revealed all impurities and the DNA in the supernatant was precipitated by adding EtOH 100%. The DNA was washed and the pellet re-suspended in a solution of DNA Hydration (Qiagen®) and then stored at – 20°C.

3.2.5.2 HPV detection and genotyping

The detection of Human Papilloma Virus was performed with InnoLipa® kit, which allows the detection of the following genotypes: HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, HPV56, HPV58, HPV59, HPV68 (High-risk), HPV26, HPV53, HPV66, HPV70, HPV73, HPV82 (Probable high risk), HPV06, HPV11, HPV40, HPV42, HPV43, HPV44, HPV54, HPV61, HPV81 (Low risk), HPV62, HPV67, HPV83, HPV89 (Other). The InnoLipa HPV genotyping assay is based on the detection of a specific region (SFP10) that is the most conserved in the L1 ORF of many HPV (6,7).

The amplification was performed using SFP10 based primers that amplify a 65-bp region, and with adding primers to amplify human HLA-DPB1 region for having a control of the DNA quality at the same time. The amplification was performed in a reagent mixture containing biotinylated primers in buffer with dNTP/dUTP mix, MgCl2 and 0.05% NaN3 as preservative and ampliTaq Gold and uracil-N-glycosylase (UNG) to prevent RNA from contaminating the sample. Before amplification, DNA was added.

All of PCR reactions were performed with a positive and a negative control. The biotinylated PCR products were genotyped by denaturation and hybridization on nitrocellulose strips

followed by a stringent wash. After the addition of the conjugate and the substrate, a colorimetric analysis revealed all the genotypes present in the sample. The hybridization process was automatically performed on the Autoblot 3000H, at the end, the strip was fixed on a support to read the HPV genotypes lines correspondence.

Due to the presence of primers that amplify all genotypes simultaneously, if there was more competition between particular genotypes, only the presence of a broad range of HPV was detected with the line control HPV1 and/or the line control HPV2. This kind of sample was notified HPV-positive without specifying the genotype. These samples were classified as "undetermined" and were included in the calculation for the prevalence of oral HPV infection regardless of the genotype. However, these samples were excluded from the individual genotype analysis.

3.2.6 Study Sample

3.2.6.1 Controls

Among the 497 eligible controls, 405 (81.5%) answered the questionnaire and among them 311 (76.2%) provided a saliva sample.

3.2.6.2 Cases

Among 257 cases identified as potentially eligible, 192 (74.7%) agreed to participate and were interviewed. Among them, after diagnosis review, 22 did not meet the inclusion criteria. Among the remaining 170 cases, 114 (72.3%) provided a saliva sample. The analyses were restricted to squamous cell carcinomas of the oral cavity, oropharynx, hypopharynx and larynx (145 cases); among them 92 had provided a saliva sample.

3.2.7 Data-entry and management

The questionnaire data from the case-control study were entered on an encrypted Excel spreadsheet. Biological data from the genotyping assays were entered on an excel spreadsheet provided by our partners at the Centre for Biological Resources Karubiotec. The international

Standard Classification of Occupations (ISCO) and the French Nomenclature of Activities (NAF) were used by a trained coder to blindly code occupations and branches of the industry, independently of the case-control status of the participants [77, 78]. This information relative to occupational history was then entered on a Microsoft Excel spreadsheet.

All the separate data set were merge together on the unique study identifier that served as a key variable. The final database was verified for incoherences and the data were coded. Variables for statistical analysis were created or derived from existing variables in the dataset. The data-management procedures were performed using SAS 9.4 software (SAS Institute, Carry, NC USA).

3.2.7.1 Creation of variables

Age

The age was calculated as the difference between the interview date and the date of birth for the controls. For the cases, the difference between diagnosis date and date of birth was used.

Smoking quantity

A smoker was defined as someone who smoked at least 100 cigarettes in their lifetime. Smoking quantity assessed as the average number of cigarettes per day over the lifetime. For smokers who responded in number of cigarettes per week, the number of daily cigarettes were calculated by dividing the weekly amount by 7. Questionnaire responses were used as is for smokers who responded in cigarettes per day.

$$\frac{\sum_i^n Q_i * D_i}{\sum_i^n D_i}$$

i: Period of identical smoking habits

n: The maximum number of distinct periods of identical smoking habits noted for a participant

Q_i: The number of cigarettes smoked during a given period

D_i: Length of time in years of a given period in participant's lifetime

The smoking quantity was then categorised into 3 groups (1 to 10, 11 to 20 and >20 cigarettes/day).

Smoking duration

Smoking duration was calculated by calculating the difference between the age at last cigarette and the age at which the participant began smoking. The total duration of smoking cessation was subtracted from the lifetime smoking duration. For participants who never stopped smoking, age at last cigarette was the same as the age at the moment of the interview/diagnosis. For participants who quit smoking prior to interview (at least 2 years before): age at end was noted as the response to the question "at what age did you stop smoking"

$$(Age_{end} - Age_{start}) - Y_{stop}$$

Age_{start}: Age when first started to smoke

Age_{end}: Age at last cigarette

Y_{stop}: Total duration of cigarette cessation during participant's lifetime

Smoking duration was then expressed in years and was divided into 4 categories (1 to 20, 21 to 30, 31 to 40, > 40 years).

Cigarette smoking was also expressed in pack-years by calculating the product of the average daily cigarettes and the smoking duration divided by 20. Smoking in pack-years was then categorised into 3 groups (< 10, 11 -20 and > 20 pack-years).

There were very few persons having smoked pipes of cigars/cigarillos and thus, we accounted for this behaviour as a binary variable for ever smoking of pipes or cigars.

Ever daily alcohol drinking

For each type of beverage, ever daily alcohol drinking was defined as at least one glass per day during at least one year.

Alcohol quantity

The average number of glasses per day was calculated over the lifetime, for each type of beverage. The individual average daily amount for each alcoholic beverage was summed to give the average number of glasses of alcohol daily.

$$\frac{\sum_i^n Q_i * D_i}{\sum_i^n D_i}$$

Where **i:** Period of identical drinking habits

n: The maximum number of distinct periods of identical drinking habits noted for a participant

Q_i: The number of drink daily during a given period

D_i: Length of time in years of a given period in participant's lifetime

The average number of glasses per day was then categorised into 3 groups (<1 glass/day, 1 to 5 glasses/day and >5 glasses per day). The same calculation was used to produce the variables for quantity of tea, coffee and juice/soda

Body mass index (BMI)

BMI was calculated at different time points (at interview, 2 years before the interview and at age 30). BMI was computed as weight (kg) divided by height squared (m^2). In relation to BMI, the study population was divided into four categories according to the World Health Organization (WHO) international classification [79]: underweight subjects (BMI < 18.5 kg/m^2), subjects with normal weight (18.5 kg/m^2 ≥ BMI < 24.9 kg/m^2), overweight subjects (25.0 kg/m^2 ≥ BMI < 29.9 kg/m^2), and obese subjects (BMI ≥ 30 kg/m^2).

3.2.8 Statistical analysis

3.2.8.1 Univariate analysis

3.2.8.1.1 HPV prevalence

The details for the prevalence calculations of oral HPV in the French West Indies are detailed below. Consider the contingency table below as a reference for the notations used in formulas shown in this section.

HPV Status	HNSCC	Control	Total
HPV+	a	b	E_1
HPV-	c	d	E_0
Total	H_1	H_0	E_t

HPV+/-: Oral HPV infection regardless of the type

a: Head and neck cancer cases tested positive for oral HPV

b: Control tested positive for oral HPV

c: Head and neck cancer cases tested negative for oral HPV

d: Control tested negative for oral HPV

E: Total number of persons in the exposure group

H: Total number of persons in one of the outcome groups.

The prevalence of oral HPV infections was estimated separately among the HNC cases and the controls. The prevalence calculation was performed by determining the absolute number of HPV-positive cases/controls and then dividing by the total number of cases/controls included in this study and 95% CI were calculated.

$$P_{Hpv+} = {}^{a}/_{H_1}\,(cases)$$

$$P_{Hpv+} = {}^{b}/_{H_0}\,(controls)$$

This was then repeated for the different category of carcinogenic risk (high risk, probable high risk, low risk and other) and the various HPV genotypes. The prevalence was also calculated for different categories of the subject characteristics: age, sex recruitment site, tobacco smoking (ever vs never), alcohol drinking (ever daily drinker, i.e. at least one glass per day during at least one year; never daily drinker).

3.2.8.1.2 Exact confidence intervals

In the case of our analyses on HPV prevalence, there were certain calculation which had too few events and did not produce accurate confidence intervals using the Wald method. The Wald methods for calculating confidence intervals for proportions is simple to compute, and is well known and used conventionally in epidemiological studies. Unfortunately, it produces intervals that are too narrow and inaccurate values when samples are small. To overcome this limitation of Wald method, we employed the Clopper-Pearson or "Exact" method, a more complicated computational method. The Clopper–Pearson interval is an exact interval since it is based directly on the binomial distribution rather than any approximation to the binomial distribution. The exact method provides more reliable confidence intervals with small samples which was appropriate for our study on HPV prevalence [80].

3.2.8.1.3 Statistical tests

A Chi-squared test was used to test the association between characteristics and HNC. The same test was performed to determine any associations between these same characteristics and oral HPV infection. An exact Fisher test was performed to assess this association for each HPV genotype individually. Tests giving a p-value lower than 5% were considered to be statistically significant.

3.2.8.2 Multivariate analysis

3.2.8.2.1 Unconditional logistic regression

The logistic regression is used to model the probability of a binary event such as alive/dead or healthy/sick. In the logistic model, the log-odds (the logarithm of the odds) for the dependant variable (outcome of interest noted as "1" and the opposite condition "0") is a linear combination of one or more independent variables ("predictors"). In the logistic model, the increase of one of the independent variables multiplicatively scales the odds of the given outcome at a constant rate, with each independent variable having its own parameter (denoted as β). The estimates for the value of parameters of the independent variables are determined using the maximum likelihood estimator by maximising the likelihood function. The exponential of these regression parameters was calculated to determine the odds-ratios (OR) and 95% CI in our case-control study.

$$Logit(p) = \ln\left(\frac{p}{1-p}\right) = \alpha + \sum_i (\beta_i X_i)$$

Where **p:** probability of begin diagnosed with head and neck cancer (outcome variable)
α : intercept
β_i : regression coefficient showing the association between each explanatory variable and the outcome variable
x_i : explanatory variable

3.2.8.2.2 Selection of adjustment variables

Firstly, the variables that were used to frequency match the controls to the cases (age, sex and region) were systematically added to all the multivariate models that we constructed. Given the strong evidence on tobacco smoking and alcohol drinking as risk factors of head and neck

cancer in the literature we adjusted for them systematically in all multivariate model where we attempted to look at the link between head and neck cancer and other known or suspected risk factors. We also considered variables which followed the strict definition of a confounding factor. That is to say, a third variable which is associated simultaneously to the outcome and the exposure variable without being the consequence of that exposure.

Tobacco smoking was considered under several forms for the adjustment, ever smoking, smoking status, smoking quantity, smoking duration, the combination of quantity and duration and pack-years. Alcohol drinking was considered as either daily drinking or quantity of alcohol per day. Given the small sample size of the study, we were unable to fit our regression models with many variables, thus we tested several models for adjustment to determine the one that was the most parsimonious. We used the Akaike information criterion (AIC) to assist us the selection of the model that best fit our data without losing too much precision. The AIC is a criterion that is based on the balance between goodness-of-fit and simplicity. The AIC assess the quality of adjustment of the model whilst penalising for the number of parameters computed in the model.

Akaike information criterion is calculated as follows:

$$AIC = 2k - 2\ln(L)$$

Where **k:** the number of parameters to be estimated in the model

L: the maximum of likelihood function for that model.

3.2.8.3 Mesures of impact

The measures of impact are used to assess the pertinence of a risk factor from a public health point of view. Contrarily to the measures of association, the measures of impact take into consideration not only the strength of the association but also the frequency of the exposure to the risk factor and thus, the importance of that factor for prevention. The measures of

impact are known under a variety of names such as attributable risk, attributable fraction and etiological fraction. The attributable fraction indicates the proportion of cases would be prevented if it were possible to eliminate one or more exposures from a particular target population [81]. This proportion could be calculated in the exposure group exclusively or for the population. For the purpose of this doctoral thesis, the emphasis will be placed on population attributable fractions (PAF). To compute the PAF, the relative risks need to be estimated for the risk factor(s) of interest as well as those for additional risk factors which may be potential confounders for the disease outcome in a multivariate model. The formula used to calculate the PAF in case-control studies is detailed below:

$$\frac{PE_{case}(OR-1)}{OR}$$

PE_{case}: proportion of exposed subjects among the cases

To calculate the PAFs for the analyses in our study, the aflogit procedure was used in the STATA software package [82].

3.2.8.4 Mesures of interaction

An effect modifier is characterised by a change in the effect of one risk factor on an outcome according to whether it is present of not. If the effect of the studied variable is the same within strata of the suspected effect modifier, then there is no interaction. When the effect of one risk factor is different within strata defined by the other, then there is an interaction. Assessing interactions between variables is useful and may provide insight into the mechanisms for the outcome. In epidemiology, interactions are most often measured on either an additive scale (biological interaction) or a multiplicative scale (statistical interaction) [83].

Table 4: Explanation of the concept of interaction - Notations

	Factor A	
Factor B	Unexposed	Exposed
Unexposed	1 (ref)	OR_{01}
Exposed	OR_{10}	OR_{11}

3.2.8.4.1 Additive scale

Additive interactions are assessed by measuring the extent to which the effect of two factors together exceeds the sum of each effect considered individually. The relative excess risk due to interaction (RERI) is a common measure used for interactions on an additive scale and it is calculated in the following manner.

$$RERI = OR_{11} - OR_{10} - OR_{01} + 1$$

If RERI = 0, there is no additive interaction

If RERI > 0, the interaction is said to be positive or "super-additive"

If RERI < 0, the interaction is said to be negative or "sub-additive"

3.2.8.4.2 Multiplicative scale

Multiplicative interactions are assessed by measuring the extent to which the effect of two factors together exceeds the product of each effect considered individually. The Ψ (Phi) is a common measure used for interactions on a multiplicative scale and it is calculated in the following manner:

$$\Psi = \frac{OR_{11}}{OR_{10} \times OR_{01}}$$

If Ψ = 1, there is no multiplicative interaction

If Ψ > 1, the interaction is said to be positive or "super-multiplicative"

If $\Psi < 1$, the interaction is said to be negative or "sub-multiplicative"

The Ψ as well as it confidence interval is also equivalent to the regression coefficient of the cross-product term of two variables in a logistic regression model.

3.2.8.5 *Management of missing data and multiple imputations*

HPV status was missing for 151 (27%) subjects (53 cases and 98 controls) that refused to provide a saliva sample. In addition, missing data were observed for smoking status (one case) smoking quantity (19 cases, 3 controls), smoking duration (6 cases, 1 control) and alcohol quantity (4 controls).

Missing data are a common problem in epidemiological research. Multiple imputation by chained equations (MICE) (also known as "fully conditional specification") has emerged in the statistical literature as a popular method to deal with missing data. MICE operates under the assumption that given the variables to be imputed are Missing At Random (MAR), meaning that the probability that a value is missing depends only on observed values and not on unobserved values [84]. In the MICE procedure a series of regression models are run whereby each variable with missing data is modelled conditional upon the other variables in the data. This is conditionally according to the distribution of the variable to be imputed rather than assuming a joint normal distribution for all the variables. The MICE method consists of regressing on the variable with missing data on the other variables in an imputation model containing other variables in the data set without missing data. The missing data are then replaced by predictions from the regression models and these variables are then used an explanatory variable the values for other variables in a subsequent regressions [84]. For the analyses in this doctoral thesis, we used MICE to deal with missing data. The imputation model contained all the basic characteristics of the study subjects (age, sex recruitment site and education level), variables related to alcohol and smoking (ever daily alcohol drinking, quantity of alcohol, smoking status, smoking duration, and smoking

quantity), HPV status (low-risk, probable high-risk, high-risk, and other HPV types) and the case-control status, Missing values for continuous variables (smoking quantity and duration, quantity of alcohol) were imputed by fitting a linear regression model. Categorical variables were imputed by fitting a logistic regression model with maximum likelihood estimate based on augmented data. The logistic regression with augmented data is a method employed to deal with issues associated with perfect prediction during the computation of the maximum likelihood estimate [16]. All variables in the imputation model which had missing values were imputed for our analyses. We generated 20 datasets. The MICE method was performed using the PROC MI procedure from SAS 9.4 software (SAS Institute, Carry, NC USA). The MIANALYZE procedure on SAS was invoked to combine the estimates and their variances/covariances into one data set using the pooling algorithm suggested by Rubin et al. to perform statistical inferences [85].

4 Results

The results of this PhD thesis are presented in the form of five research manuscripts in the following order:

Barometre Santé DOM:

1. Social Distribution of Tobacco Smoking, Alcohol Drinking and Obesity in the French West Indies

Case-control study:

2. Prevalence of oral HPV infection among healthy individuals and head and neck cancer cases in the French West Indies
3. Joint effect of tobacco, alcohol and oral hpv infection on head and neck cancer risk in the French West Indies
4. Population attributable fractions of head and neck cancer risk factors in the French West Indies
5. Association between sexual behaviour and head and neck cancer in the French West Indies

Other analyses were performed on certain risk factors but were not sufficiently advanced to produce a manuscript draft. There results are presented in a chapter called “Supplementary results”. The risk factors in this section are:

- Fruits and vegetables
- Non-alcoholic beverages
- Occupational risk factors

4.1 Social Distribution of Tobacco Smoking, Alcohol Drinking and Obesity in the French West Indies

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Social distribution of tobacco smoking, alcohol drinking and obesity in the French West Indies

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Abstract

Background: Tobacco smoking, alcohol and obesity are important risk factors for a number of non-communicable diseases. The prevalence of these risk factors differ by socioeconomic group in most populations, but this socially stratified distribution may depend on the social and cultural context. Little information on this topic is currently available in the Caribbean. The aim of this study was to describe the distribution of tobacco smoking, alcohol drinking and obesity by several socioeconomic determinants in the French West Indies (FWI).

Methods: We used data from a cross-sectional health survey conducted in Guadeloupe and Martinique in 2014 in a representative sample of the population aged 15–75 years ($n = 4054$). All analyses were stratified by gender, and encompassed sample weights, calculated to account for the sampling design and correct for non-response. For each risk factor, we calculated weighted prevalence by income, educational level, occupational class and having hot water at home. Poisson regression models were used to estimate age-adjusted prevalence ratios (PR) and 95% confidence intervals (CI).

Results: Current smoking and harmful chronic alcohol use were more common in men than in women (PR = 1.80, 95% CI = 1.55–2.09; PR = 4.53, 95% CI = 3.38–6.09 respectively). On the other hand, the prevalence of obesity was higher in women than in men (PR = 0.67, 95% CI = 0.57–0.79). Higher education, higher occupational class and higher income were associated with lower prevalence of harmful alcohol drinking in men (PR = 0.43, 95% CI = 0.25–0.72; PR = 0.73, 95% CI = 0.53–1.01; PR = 0.72, 95% CI = 0.51–1.03 respectively), but not in women. For tobacco smoking, no variation by socioeconomic status was observed in men whereas the prevalence of current smoking was higher among women with higher occupational class (PR = 1.47, 95% CI = 1.13–1.91) and higher income (PR = 1.50, 95% CI = 1.11–2.03). In women, a lower prevalence of obesity was associated with a higher income (PR = 0.43, 95% CI = 0.33–0.56), a higher occupational class (PR = 0.63, 95% CI = 0.50–0.80), a higher educational level (PR = 0.36, 95% CI = 0.26–0.50) and having hot water at home (PR = 0.65, 95% CI = 0.54–0.80).

Conclusion: Women of high socio-economic status were significantly more likely to be smokers, whereas alcohol drinking in men and obesity in women were inversely associated with socioeconomic status.

Keywords: Social disparities, Tobacco smoking, Alcohol drinking, Obesity, Non-communicable diseases, Caribbean, France

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Background

The French West Indies (FWI) is a part of the Caribbean region which is made up of the two overseas French regions, Martinique and Guadeloupe. The French West Indies have a particular situation in the Caribbean. As French territories, Martinique and Guadeloupe are classified as high-income countries, whereas most of other Caribbean states are low or middle-income countries. The FWI population benefits from the same health insurance and financial redistribution systems as the mainland French population. While the French West Indies appear to be a privileged region within the Caribbean, the comparison with the mainland is much less favourable. Although the gross domestic product per capita is one of the highest in the Caribbean, it is only about 65% of the French national average. When compared to the national average, the population of the FWI is characterized by a lower median income, a lower educational level and a higher rate of unemployment. On the other hand, the FWI are close to their Caribbean neighbours with regards to the cultural, historical and climatic context. This unique situation reflects in health conditions, with for most of them an intermediate position between mainland France and other countries in the Caribbean. Cancer and cardiovascular diseases were in 2016 the leading causes of death in the FWI, accounting each for about 25% of all deaths [1]. Cancer incidence rates are overall lower than in mainland France, with the exception of prostate, stomach and cervical cancer, but higher than in other Caribbean countries for most cancer sites. Mortality rates from cardiovascular diseases, although higher than in mainland France, are among the lowest in the Caribbean [1–5]. The prevalence of diabetes is also high in the FWI [6]. Tobacco smoking, alcohol drinking and obesity are important risk factors for a number of non-communicable diseases (NCD), including cancer, diabetes and cardiovascular disease. These risk factors were described in previous studies to be inequitably distributed across the different socio-economic strata. Worldwide, the prevalence of these risk factors tends to be higher in persons of lower socioeconomic status (SES) than in the more affluent groups [7, 8]. This trend however varies with country-level development and the indicators used [7–10]; in mainland France, and other developed countries, lower SES is usually associated to a greater prevalence of these risk factors; whereas, in low and middle-income countries, the reverse association is usually observed [7, 11–13]. However, data in regards to social disparities and NCD risk factors are very scarce in the Caribbean. A study in Barbados addressed the social distribution of NCD risk factors [14]. A systematic review reported data on social determinants of obesity and alcohol consumption in the Caribbean; however, they provide unclear conclusions on the social disparities in this population, due to few data [15]. Knowing the social distribution of risk factors is crucial for the designing of prevention programs and policy in these regions [15]. The specific features of the FWI further warrant a sound understanding of the social distribution of the known NCD risk factors to take appropriate measures for prevention.

In this study, we performed a secondary data analysis from a national survey in order to describe the social distribution of tobacco smoking, alcohol drinking and obesity in the French West Indies.

Methods

Study population, data collection

The data for this study were drawn from a national cross-sectional health survey conducted in the FWI in 2014 ("Baromètre Santé DOM", Health Barometer) [16]. The survey was based on a random two stage sampling method: telephone numbers (landlines and cell phones) were randomly generated, then one person was randomly selected among eligible household members or among cell phone users, using the Kish method [17]. Persons aged between 15 and 75 years of age living in Martinique or Guadeloupe who spoke French or Creole were eligible for inclusion. Field investigators conducted the interview over the phone.

Participation was anonymous and voluntary. Anonymity and respect of confidentiality were guaranteed using a procedure erasing the phone number. All included subjects gave informed consent before the telephone interview. Parental consent was obtained for participants under 18. As the participants were contacted exclusively over the phone, the consents were verbal. The overall procedure was approved by the French regulatory authority, the Commission Nationale de l'Informatique et des Libertés (CNIL).

Overall, 8057 numbers were dialled (3687 landlines and 4407 cell phones). Among them, 35% could not be reached, 11% refused to participate and 3% abandoned the survey before the end of the interview. In the end, 4054 subjects were included in the final sample for Martinique and Guadeloupe. The overall participation rate for the French West Indies was 51% (56% for landlines, 46% for cell phones).

Data were weighted in two steps. To account for the sampling design, sample weights were computed according to the probability of selection of the telephone number, the number of eligible individuals for each telephone number, the number of landline and cell phones of the individual. To correct for non-response, a post-stratification was then performed to match the distribution of the population, according to sex, age, education level and household structure, using data from the 2011 census in Martinique and Guadeloupe.

Variables

All risk factors analysed in our current study were dichotomised. Current smokers were persons who smoked any

tobacco product. Lifetime tobacco smokers were those who had smoked tobacco in their lifetime regardless of the duration or frequency. Daily alcohol drinkers were persons who drank at least one glass of alcohol per day. Harmful chronic alcohol use was defined as drinking more than 21 drinks a week for a man and 14 for a woman or drinking six drinks or more on a single occasion weekly [18]. Self-reported height and weight were collected during the phone call and body mass index (BMI) was calculated (weight in kg/height in m^2). An obese person was regarded as someone with a BMI of at least 30 kg/m^2. We used four variables related to socioeconomic status: education, occupational category, income and having hot water at home. Education was defined as the highest educational attainment achieved by an individual participant and categorised into four groups: without diploma or primary education (up to approximately 6 years of schooling), less than high school diploma (up to approximately 9 years of schooling), high school diploma (up to approximately 12 years), and tertiary education (associate's degree or higher) [19]. Occupation was defined as the current occupation for active workers and as the last occupation for retired or unemployed persons, and was classified into three groups based on the French classification of occupations and socio-professional categories [20, 21]: qualified workers (self-employed and entrepreneurs, professionals and managers), unqualified workers (farmers, clerical, sales and service workers, manual workers) and inactive, who were persons who never worked.. Individual income was split into three groups according to the tertiles of the overall distribution of income in our sample. Having hot water at home described someone living in a household where a water heating system was available to heat the running water in the house. Hot water at home is strongly linked to the household income in the FWI and can therefore be viewed as a surrogate for self-reported income, which may be more subject to misclassification or misreporting [22].

Statistical analysis

The prevalence for each risk factor was calculated by gender, age and according to the four socio-economic indicators. Age-adjusted prevalence ratios (PR) and their 95% confidence intervals (CI) estimating the associations of the different socio-economic indicators with the risk factors were calculated using a Poisson-regression model. Chi-squared tests were performed to assess the statistical trend between the socio-demographics and gender. All analyses encompassed sample weights.

Results

Characteristics and risk factor prevalence

In total 4054 persons were included for the purpose of our analysis. Table 1 shows the distribution of socio-demographic characteristics of participants in our sample. The participants were equally distributed between Martinique and Guadeloupe and there were slightly more women than men (ratio of women to men 1.2). Men were more frequently under 25 years of age and had higher income when compared to women. On the other hand, women had more frequently tertiary education and hot water at home when compared to men. Very few data were missing for most variables (≤1%) with the exception of individual income and body mass index (14 and 6% respectively). Table 2 shows the prevalence of risk factors. Overall, ever tobacco smoking was the most prevalent risk factor among participants. Men were significantly more likely to be smokers and alcohol drinkers. The prevalence of ever and current smokers was two-fold grater in men than in women (PR = 1.98, 95% CI = 1.75–2.24 and PR = 1.80, 95% CI = 1.55–2.09 respectively). Similarly, the prevalence of daily alcohol drinking and harmful chronic drinking was 4 times greater in men than in women (PR = 4.15, 95% CI = 3.11–5.55 and PR = 4.53, 95% CI = 3.38–6.09 respectively). Inversely men were significantly less likely to be obese than women (PR = 0.67, 95% CI = 0.57–0.79).

Table 3 shows the prevalence of risk factors by gender and age. In both men and women, for all tobacco and alcohol-related variables, the highest prevalence was consistently observed in the 25 to 34 age group when compared to the other age groups. We observed a regular decrease of the prevalence of current tobacco smoking from 24 to 75 years of age, A similar trend, although less apparent, was found for ever smoking. On the other hand, in both men and women, daily alcohol drinking increased with age whereas harmful chronic alcohol drinking decreased with age. In terms of obesity, women between 55 and 64 years were the most frequently obese (28.9%), followed by the 25 to 34 age group with 23.8%. The obesity prevalence in men was quite homogenous across age groups with the exception of men under 24 years for whom the prevalence was notably lower (4.9%).

Social distribution of risk factors

Tables 4 and 5 show in women and men respectively, the prevalence of risk factors by socio-economic category, as well as age-adjusted prevalence ratios, and 95% CI of the Poisson regression model, estimating the associations between the socio-economic indicators and those risk factors. In women, ever smoking prevalence was seen to increase with higher socio-economic status. The prevalence was significantly greater in women who had tertiary education (PR = 1.45, 95% CI = 1.07–1.96), and who occupied qualified jobs (PR = 1.60, 95% CI = 1.30–1.98) and who had the highest incomes (PR = 1.63, 95% CI = 1.28–2.08). Similarly, compared to persons in lower SES class, current smoking prevalence was significantly greater in women of in qualified jobs, and those

Table 1 Distribution of socio-demographic characteristics of participants by gender

Characteristic	Category	Men		Women		Overall		$p^{\dagger}$
		$n = 1849$	%[a]	$n = 2205$	%[a]	$n = 4054$	% [a]	
Age (years)								0.0721
	15–24	351	(19.0)	348	(15.8)	699	(17.2)	
	25–34	232	(12.5)	311	(14.1)	543	(13.4)	
	35–44	348	(18.8)	459	(20.8)	807	(19.9)	
	45–54	396	(21.4)	466	(21.1)	862	(21.3)	
	55–64	303	(16.4)	359	(16.3)	662	(16.3)	
	65–75	219	(11.8)	263	(11.9)	481	(11.9)	
Recruitement site								0.9135
	Martinique	922	(49.9)	1104	(50.1)	2026	(50.0)	
	Guadeloupe	927	(50.1)	1101	(49.9)	2028	(50.0)	
Education level								< 0.0001
	Up to primary education	462	(25.2)	511	(23.3)	973	(24.2)	
	Less than high school diploma	811	(44.3)	818	(37.4)	1629	(40.5)	
	High school diploma	279	(15.2)	421	(19.2)	700	(17.4)	
	Tertiary education	280	(15.3)	439	(20.1)	719	(17.9)	
	Missing	17		16		33		
Occupational Class								0.0567
	Inactive	245	(13.2)	339	(15.4)	584	(14.4)	
	Non-qualified	1032	(55.9)	1241	(56.4)	2273	(56.1)	
	Qualified	571	(30.9)	621	(28.2)	1191	(29.4)	
	Missing	1		4		5		
Individual income								< 0.0001
	Low-income	471	(30.3)	724	(37.7)	1195	(34.4)	
	Middle-income	523	(33.7)	630	(32.8)	1153	(33.2)	
	High-income	561	(36.1)	566	(29.5)	1127	(32.4)	
	Missing	294		285		579		
Hot water at home								0.0153
	Yes	1283	(69.5)	1609	(73.0)	2892	(71.4)	
	No	563	(30.5)	596	(27.0)	1159	(28.6)	
	Missing	3		0		3		

Baromètre Santé DOM survey, 2014

[a]Column percentage calculated by dividing the total number of men,women or overall sample

†: *p*-value of Chi-squared test, assessing the association between participant's socio-demographic characteristics and gender

had higher income. In contrast, daily alcohol and harmful chronic alcohol drinking were not associated with SES in women. However, though the prevalence difference for occupational class was not significant, women with qualified jobs, and hot water at home tended to engage less in harmful chronic drinking. Having hot water at home was not significantly associated with tobacco and daily alcohol consumption. In men, no distinct trend or significant association was found in regards to tobacco and socio-economic status. However, in men, a harmful chronic drinking and daily alcohol drinking were inversely and significantly associated with educational level With the exception of daily alcohol in women, we found that occupationally inactive persons had significantly lower alcohol drinking prevalence for both genders when compared to unqualified workers. Obesity prevalence was inversely associated with socio-economic status, in particular in women, where we observed significant decreases of at least 35% in obesity prevalence in those of the highest stratum for each socio-economic indicator (education PR = 0.36, 95% CI = 0.26–0.50; occupational class PR = 0.63, 95% CI = 0.50–0.80; income PR = 0.43, 95% CI = 0.33–0.56; hot water at home PR = 0.65, 95% CI = 0.54–0.80).

Table 2 Prevalence of risk factors and prevalence ratios comparing men to women

Risk factor	Men		Women	
	n = 1849		*n* = 2205	
Ever tobacco smoking				
Prevalence (%)	682	(38)	421	(19)
Adjusted PR (95% CI)	1.98	(1.75–2.24)	1	ref
Missing (n)	36		8	
Current tobacco smoking				
Prevalence (%)	422	(23)	286	(13)
Adjusted PR (95% CI)	1.80	(1.55–2.09)	1	ref
Missing (n)	43		0	
Daily alcohol drinking				
Prevalence (%)	201	(11)	59	(3)
Adjusted PR (95% CI)	4.15	(3.11–5.55)	1	ref
Missing (n)	1		0	
Harmful chronic alcohol use				
Prevalence (%)	213	(12)	57	(3)
Adjusted PR (95% CI)	4.53	(3.38–6.09)	1	ref
Missing (n)	1		0	
Obesity				
Prevalence (%)	209	(12)	443	(22)
Adjusted PR (95% CI)	0.67	(0.57–0.79)	1	ref
Missing (n)	100		146	

PR Prevalence ratio, *95%CI* 95% confidence interval
Baromètre Santé DOM survey, 2014

Discussion

Social disparities in NCD risk factors distribution were reported in previous studies in many countries [7, 14, 15, 23] but data on this topic are scarce in the Caribbean. We attempted to shed some light on disparities in chronic diseases by describing the social distribution of these risk factors in the French West Indies. We were able to highlight gender-specific social disparities in regards to these risk factors, in this population.

While tobacco smoking was predominantly found in women of high SES, in men, the prevalence did not differ in regards to SES. The social pattern for tobacco smoking did not correspond to what has been described in developed countries, and in particular in mainland France, where persons of lower SES were more frequently smokers [24–26]. Furthermore, the social distribution of tobacco smoking in Barbados and Cuba was discordant with what we found. In men, a negative association between smoking and SES was found in both countries. In women, the social distribution for tobacco smoking in Barbados did not have any distinct pattern and in Cuba it went in the opposite direction to ours [14, 27]. Previous reports have shown that economic development and urbanicity affect socio-economic behaviour and would explain the variation of our results from other studies [7, 8]. Data from the World Health Surveys in 53 countries showed that in the most urban countries, which were mainly middle-income countries in this study, smoking in women was concentrated in the higher education groups, whereas in men smoking was inversely associated with education, regardless of urbanicity [7]. The FWI have a high level of urbanicity, with more than 80% of the population living in urban areas, and our results are consistent with these findings for women, but not for men. The global tobacco epidemic, as described elsewhere, explains well these differences [26]. It is a process which begins first in the most affluent men in society; then, it spreads through the other socioeconomic classes. The same habit then initiates in women of high SES; before finally transitioning to the lower socioeconomic class, since those in higher SES tend to become conscious of their unhealthy lifestyle and possess greater means to alter their behaviour or environment. Our findings suggest that the FWI have not reached the last stage of tobacco epidemic, and that tobacco consumption could increase in the lower SES categories in the future.

The association between alcohol use and SES is complex, vary across genders, country development level and cultures, and depends on the measures used for alcohol drinking [12, 28]. Alcohol drinking measures differ in the previous studies, which made comparisons difficult. We found that in men the prevalence of daily alcohol drinking and harmful alcohol use was lower in the highest socioeconomic strata, a pattern consistent with the inverse association with SES reported in Barbados for heavy episodic alcohol consumption [14] and in a multinational study (including France) for heavy drinking [12]. In women, no clear trend was found, similarly to Barbados [14] but inconsistent with mainland France where the prevalence of heavy drinking was higher in the highest educational level [12].

In terms of obesity, there was an inverse association with the socio-economic status for both genders with a more marked socioeconomic gradient in women. This gradient was the most apparent for income, where the prevalence was twice as high in women of low income when compared to those of high income. A French study [29] and a study in Guadeloupe [6] reported a social pattern for obesity in men and women concordant to our sample. In contrast, the study in Barbados reported no socioeconomic gradient for obesity [14]. Previous studies showed that in developed countries, women of high socio-economic status are more sensitive to body image because small body size is viewed as attractive [30, 31]. Although in our study height and weight were self-reported, our findings were globally similar to those of studies that used anthropometric measurements [6, 29].

Our findings are also consistent with the local context. A previous study conducted in the FWI investigating

Table 3 Risk factor prevalence by age group

Risk factor	15–24 yrs		25–34 yrs		35–44 yrs		45–54 yrs		55–64 yrs		65–75 yrs	
	n = 699	%	*n* = 543	%	*n* = 807	%	*n* = 862	%	*n* = 662	%	*n* = 481	%
Ever tobacco smoking												
Total	180	(25.8)	191	(35.2)	224	(27.7)	227	(26.4)	174	(26.2)	107	(22.3)
Women	72	(20.9)	87	(28.4)	101	(22.0)	90	(19.3)	48	(13.3)	23	(8.8)
Men	108	(32.4)	104	(46.5)	123	(35.7)	137	(35.1)	126	(41.7)	84	(38.6)
Current tobacco smoking												
Total	167	(24.5)	155	(29.2)	153	(19.1)	133	(15.5)	68	(10.2)	33	(6.9)
Women	64	(18.6)	69	(22.6)	69	(15.0)	65	(14.0)	13	(3.6)	6	(2.4)
Men	102	(30.6)	86	(38.4)	84	(24.6)	68	(17.2)	55	(18.2)	27	(12.3)
Daily alcohol drinking												
Total	17	(2.4)	41	(7.6)	41	(5.1)	43	(5.0)	63	(9.5)	55	(11.4)
Women	1	(0.2)	14	(4.4)	15	(3.3)	7	(1.4)	9	(2.6)	13	(5.1)
Men	16	(4.6)	27	(11.8)	26	(7.5)	37	(9.3)	54	(17.7)	41	(18.9)
Harmful chronic alcohol use												
Total	73	(10.4)	60	(11.1)	56	(7.0)	44	(5.1)	23	(3.4)	13	(2.8)
Women	15	(4.4)	14	(4.5)	13	(2.9)	10	(2.1)	1	(0.2)	3	(1.3)
Men	58	(16.4)	46	(20.0)	43	(12.3)	34	(8.6)	22	(7.3)	10	(4.6)
Obesity												
Total	51	(7.9)	96	(19.0)	130	(17.1)	159	(19.6)	139	(21.8)	78	(17.0)
Women	35	(11.0)	70	(23.8)	83	(19.6)	103	(23.4)	101	(28.9)	52	(21.7)
Men	16	(4.9)	26	(12.3)	47	(13.9)	56	(15.1)	38	(13.3)	26	(11.9)

Baromètre Santé DOM survey, 2014

Table 4 Associations between SES and risk factors in women

SES indicator	Ever tobacco		Current tobacco		Daily alcohol		Harmful chronic alcohol use		Obesity	
	Prev	PR (95% CI)	Prev	PR (95% CI)	Prev	PR (95% CI)	Prev	PR (95% CI)	Prev	PR (95% CI)
Education level										
Up to primary education	14.8	1 (ref)	10.4	1 (ref)	2.9	1 (ref)	2.7	1 (ref)	31.3	1 (ref)
Less than high school diploma	16.2	1.00 (0.75–1.33)	11.1	0.89 (0.63–1.25)	3.2	1.29 (0.67–2.48)	1.9	0.55 (0.26–1.16)	24.5	0.79 (0.63–0.98)
High school diploma	23.2	1.30 (0.96–1.78)	16.8	1.13 (0.79–1.63)	1.9	1.71 (0.68–4.28)	4.0	0.97 (0.46–2.02)	14.9	0.53 (0.39–0.73)
Tertiary education	26.2	1.45 (1.07–1.96)	16.5	1.09 (0.76–1.58)	2.2	0.72 (0.30–1.70)	2.3	0.50 (0.21–1.19)	12.1	0.36 (0.26–0.50)
Occupational Class										
Inactive	18.9	1.04 (0.73–1.49)	16.4	1.02 (0.68–1.53)	0.7	1.19 (0.35–4.04)	1.6	0.21 (0.08–0.55)	17.2	1.27 (0.88–1.83)
Non-qualified	15.6	1 (ref)	10.3	1 (ref)	3.0	1 (ref)	3.1	1 (ref)	25.4	1 (ref)
Qualified	26.3	1.60 (1.30–1.98)	16.7	1.47 (1.13–1.91)	3.2	1.07 (0.61–1.85)	2.0	0.54 (0.27–1.05)	16.2	0.63 (0.50–0.80)
Individual income										
Low-income	16.6	1 (ref)	11.6	1 (ref)	2.5	1 (ref)	2.5	1 (ref)	31.8	1 (ref)
Middle-income	17.6	1.12 (0.86–1.45)	13.3	1.21 (0.89–1.63)	2.4	0.87 (0.43–1.76)	3.0	1.14 (0.60–2.18)	19.2	0.59 (0.47–0.74)
High-income	25.5	1.63 (1.28–2.08)	15.6	1.50 (1.11–2.03)	3.7	1.38 (0.74–2.61)	3.0	1.22 (0.63–2.38)	14.3	0.43 (0.33–0.56)
Hot water at home										
Yes	19.3	1.06 (0.85–1.32)	13.1	1.06 (0.81–1.37)	2.6	0.76 (0.40–1.30)	2.1	0.60 (0.35–1.02)	19.0	0.65 (0.54–0.80)
No	18.5	1 (ref)	13.0	1 (ref)	2.9	1 (ref)	3.8	1 (ref)	28.6	1 (ref)

Prev Risk factor prevalence, *PR* Age-adjusted prevalence ratio, *95%CI* 95% confidence interval
Baromètre Santé DOM survey, 2014

Table 5 Associations between SES and risk factors in men

SES indicator	Ever tobacco		Current tobacco		Daily alcohol		Harmful chronic alcohol use		Obesity	
	Prev	PR (95% CI)	Prev	PR (95% CI)	Prev	PR (95% CI)	Prev	PR (95% CI)	Prev	PR (95% CI)
Education level										
Up to primary education	40.3	1 (ref)	22.9	1 (ref)	15.2	1 (ref)	13.2	1 (ref)	15.2	1 (ref)
Less than high school diploma	36.2	0.91 (0.75–1.09)	22.6	0.91 (0.72–1.17)	12.0	0.87 (0.64–1.18)	12.1	0.82 (0.59–1.13)	11.4	0.79 (0.57–1.10)
High school diploma	35.9	0.89 (0.69–1.14)	26.2	0.88 (0.65–1.21)	6.0	0.46 (0.26–0.80)	12.7	0.74 (0.48–1.15)	9.7	0.77 (0.48–1.22)
Tertiary education	40.1	0.98 (0.77–1.25)	23.9	0.90 (0.66–1.23)	5.5	0.40 (0.23–0.70)	6.8	0.43 (0.25–0.72)	10.0	0.64 (0.40–1.01)
Occupational Class										
Inactive	27.1	0.67 (0.48–0.94)	24.5	0.63 (0.44–0.91)	2.4	0.31 (0.12–0.81)	9.9	0.37 (0.22–0.62)	5.2	1.11 (0.43–2.87)
Non-qualified	38.6	1 (ref)	24.1	1 (ref)	12.2	1 (ref)	13.4	1 (ref)	13.4	1 (ref)
Qualified	40.3	1.04 (0.88–1.22)	21.3	0.95 (0.76–1.19)	12.2	0.93 (0.69–1.25)	8.9	0.73 (0.53–1.01)	12.1	0.88 (0.65–1.18)
Individual income										
Low-income	36.1	1 (ref)	24.4	1 (ref)	11.8	1 (ref)	15.1	1 (ref)	13.2	1 (ref)
Middle-income	34.8	0.98 (0.79–1.21)	19.2	0.84 (0.64–1.10)	10.4	0.85 (0.59–1.24)	9.6	0.68 (0.48–0.98)	11.0	0.70 (0.48–1.02)
High-income	42.7	1.18 (0.97–1.44)	24.4	1.08 (0.84–1.40)	9.3	0.74 (0.50–1.08)	10.0	0.72 (0.51–1.03)	12.1	0.76 (0.52–1.09)
Hot water at home										
Yes	38.1	1.02 (0.87–1.21)	23.5	1.02 (0.83–1.26)	10.8	0.94 (0.69–1.26)	10.0	0.68 (0.52–0.89)	10.4	0.65 (0.49–0.87)
No	36.8	1 (ref)	22.9	1 (ref)	11.2	1 (ref)	15.0	1 (ref)	15.6	1 (ref)

Prev Risk factor prevalence, *PR* Age-adjusted prevalence ratio, *95%CI* 95% confidence interval
Baromètre Santé DOM survey, 2014

area-level socio-economic status and incidence of cancer revealed that women living in deprived areas were found to have a lower incidence of lung and head and neck cancers when compared to more affluent areas, which is consistent with the lower prevalence of tobacco smoking (a major risk factor for respiratory cancer) among women of low SES reported in our study [32]. That same study showed that breast cancer incidence was higher in women from deprived areas. Our results on obesity, a known risk factor for breast cancer, coincided well with the incidence data in that study, since our female obesity was consistently more prevalent in the lower SES strata.

In addition to the social distribution, our analysis revealed interesting estimates for the prevalence of risk factors by gender. The FWI were found to have a particular NCD risk factor profile, especially when compared to Caribbean neighbours and mainland France. Overall, the prevalence of risk factors in the FWI was in-between mainland France and other Caribbean territories. The prevalence of current smokers was 23% in men and 13% in women, lower than in mainland France (32.3 and 24.3%) [33], and similar in men to the other territories in the Caribbean [4]. However, in the FWI the prevalence of current smokers in women was higher than in other Caribbean territories (5.9% in Jamaica and 3.7% in Barbados) [14, 34]. Daily alcohol drinking prevalence was also lower in the FWI (12% in men, 3% in women) than in mainland France (15% in men, 5% in women) [35]. Harmful chronic alcohol use was however similar in men (FWI: 12%, mainland France: 11%) and in women (FWI: 3%, mainland France: 4%). The other reports in the Caribbean used different definitions for alcohol drinking to us which made it difficult to evaluate differences between countries.

In our study obesity prevalence was assessed from self-reported data and may be underestimated [36]. In a survey in mainland France using the same methodology than ours, obesity prevalence in women (12%) was lower to that in the FWI (22%), whereas in men the prevalence was similar in both territories (12%) [37]. In a survey based on measurements of height and weight conducted in 2008 in the FWI obesity prevalence was slightly higher than in our study (17% in men and 27% in women) [38]. A national survey in mainland France, also using measurements, reported an obesity prevalence of 16% in men and 17% in women [29]. It should be noted that regardless the method used (self-report or measurements): the prevalence of obesity in men is similar in mainland France and in the FWI; the prevalence of obesity in women is higher in the FWI; in mainland France, the prevalence of obesity is similar in men and women, whereas in the FWI obesity is much more frequent in women., On the contrary, obesity among men and women in the FWI was much lower compared to the prevalence reported by Caribbean neighbours and Nicaragua [14, 39–42]. These observed differences could be due to the FWI being overseas French regions, and the population may share similar behaviour patterns from their mainland counterparts; however, they are

under the Caribbean influence due to their geographic position. These conditions could explain this particular risk factor profile in the FWI.

Our study presents some limitations that should be taken into consideration when interpreting our results. The socio-economic indicators and risk factors were measured through self-reported data from our study participants and thus, are subject to misclassification bias. We cannot exclude the possibility that this misclassification was related to SES, which may have impacted our results on the social distribution of risk factors. Our study has also several strengths. Our sample size was quite large (4054 participants), and therefore could provide fairly reliable estimates and we corrected for the non-response bias by using sample weights. Our sample was representative of the FWI and included participants from both rural and urban areas; hence, our results can be considered generalisable to the FWI.

Conclusion

Our analysis revealed gender-specific social disparities in NCD risk factor distribution. Women of high socio-economic status were significantly more likely to be smokers, whereas alcohol drinking in men and obesity in women were inversely associated with socioeconomic status. Future prevention programs and policies should take into consideration our findings.

Abbreviations

BMI: Body mass index; CI: Confidence interval; FWI: French West Indies; PR: Prevalence ratio; SES: Socioeconomic status

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Authors' contributions

JBR designed the "Baromètre Santé DOM" survey and coordinated the original collection of the data; AA and DL designed the present study, conducted the analyses and draft the manuscript; JD, CB and GM contributed to the statistical analysis and interpretation of the results. All authors critically reviewed the manuscript and approved the final version.

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Availability of data and materials

Data are from the "Baromètre Santé DOM" carried out by the French National Public Health Agency (Santé Publique France). This analysis has been subject to a license for the use of data issued by Santé Publique France. Readers may contact Jean-Baptiste Richard (jean-baptiste.richard@-santepubliquefrance.fr) to request the data.

Ethics approval and consent to participate

The survey was approved by the relevant national ethics committee, the French Data Protection Authority (Commission Nationale de l'Informatique et des Libertés, CNIL). Participation was anonymous and voluntary. In accordance with the guidelines of the CNIL, all included subjects gave verbal informed consent before the telephone interview, and parental verbal consent was obtained for participants under 18.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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4.2 Prevalence of oral HPV infection among healthy individuals and head and neck cancer cases in the French West Indies

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ORIGINAL PAPER

Prevalence of oral HPV infection among healthy individuals and head and neck cancer cases in the French West Indies

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Abstract
Purpose Human papillomavirus (HPV) is known to play a role in the development of head and neck squamous cell carcinomas (HNSCC) and to date, no study has reported on the association between oral HPV infection and HNSCC in the Caribbean. The objective was to determine the prevalence of oral HPV infection in the French West Indies (FWI), overall and by HPV genotype, among HNSCC cases and healthy population controls.
Method We used data from a population-based case–control study conducted in the FWI. The prevalence of oral HPV was estimated separately among 100 HNSCC cases (mean age 59 years) and 308 population controls (mean age 57 years). Odds ratios (OR) and 95% confidence intervals (CI) were estimated using a logistic regression adjusting for age, sex, tobacco, and alcohol consumption, to assess the association between oral HPV infection and HNSCC.
Results Prevalence of oral HPV infections was 26% in controls (30% in men and 14% in women) and 36% in HNSCC cases (36% in men, 33% in women). HPV52 was the most commonly detected genotype, in cases and in controls. The prevalence of HPV16, HPV33, and HPV51 was significantly higher in cases than in controls ($p = 0.0340$, $p = 0.0472$, and 0.0144, respectively). Oral infection with high-risk HPV was associated with an increase in risk of HNSCC (OR 1.99, 95% CI 0.95–4.15). HPV16 was only associated with oropharyngeal cancer (OR 16.01, 95% CI 1.67–153.64).

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Conclusion This study revealed a high prevalence of oral HPV infection in this middle-aged Afro-Caribbean population, and a specific distribution of HPV genotypes. These findings may provide insight into HNSCC etiology specific to the FWI.

Keywords Human papillomavirus · Oral HPV · Head and neck cancer · Saliva samples · Caribbean · France

Introduction

Head and neck cancer remains a major public health problem worldwide. In the Caribbean, the estimated age-standardized (world) incidence rates for 100,000 person-years in 2012 for cancer of the lip, oral cavity, larynx, and pharynx combined are 16.8 in men and 3.7 in women, similar to incidence rates in the United States (men: 16.6; women: 5.4), but higher than in Central (men: 7.8; women: 2.6) or South America (men: 13.9; women 3.8) (1). Guadeloupe and Martinique are two French overseas territories in the French West Indies (FWI). The population consists primarily of persons of African descent (about 85%). Incidence rates of head and neck cancer in men are 25.5 per 100,000 in Guadeloupe and 15.8 per 100,000 in Martinique. Despite being lower or of the same order of magnitude than that of mainland France (22.7 per 100,000), a well-known high incidence area, these rates are among the highest in the Caribbean islands. Particularly, for pharyngeal cancer (excluding nasopharynx), Martinique (6.0 per 100,000) and Guadeloupe (6.2 per 100,000) have the top two highest incidence rates among men in the Caribbean [1]. The reasons for this relatively high incidence remain unclear. Tobacco smoking and alcohol drinking are the major risk factors for these cancers. However, a recent survey has shown that tobacco and alcohol consumption are much lower in the FWI than in mainland France [2].

Human papillomavirus (HPV) is known to play a role in the development of head and neck squamous cell carcinomas (HNSCC). There are many HPV genotypes, which all have varying levels of carcinogenic capacities, ranging from no risk to high risk. HPV16 is a recognized risk factor for oropharyngeal and base of the tongue cancer, but the evidence remains inadequate for the role of other HPV types and the association between HPV and other subsites of HNSCC [3]. In addition, significantly better clinical outcomes have been demonstrated in patients with HPV-related oropharyngeal cancer, whereas no consistent results were found for non-oropharynx subsites [4–6]. Knowing the distribution of HPV in the population is therefore a great concern for the prevention and control of HNSCC in the region. The prevalence of HPV infection, the distribution of HPV genotypes, and the proportion of head and neck cancers caused by HPV may vary substantially between different geographical regions [7–9]. To this date, no study has been conducted to address the prevalence of oral HPV infection in the FWI; furthermore, little data are available in the Caribbean. The objective of this report was primarily to determine the prevalence of oral HPV infection in the FWI population and describe the distribution of the different genotypes among HNSCC cases and healthy individuals. In addition, we evaluated the association between HPV-integrated-DNA detected in saliva and the risk of developing HNSCC.

Methods

Study population, data and specimen collection

The present report is based on data obtained from a population-based case–control study, which was conducted in the two overseas French regions in the FWI: Martinique and Guadeloupe. The study is an extension of a large nationwide case–control study, the ICARE study, which has already been conducted in ten French regions covered by a cancer registry [10]. The study in the FWI used the same protocol and questionnaire, described in details elsewhere [10], with some adaptations to the local context. Eligible cases were patients residing in the FWI, suffering from a primary, malignant tumor of the oral cavity, pharynx, sinonasal cavities, and larynx (International Classification of Diseases, 10th Revision, codes C00–C14; C30–C32) of any histological type, aged between 18 and 75 years at diagnosis, newly diagnosed, and histologically confirmed between 1 April 2013 and 30 June 2016. The inclusion of cases was performed with the collaboration of the cancer registries of Martinique and Guadeloupe. A procedure was set up to expedite case identification, in order to reduce the delay between diagnosis and interview of cases. Cases were identified through active search, by regular contacts and visits to the pathology laboratories and hospital departments that usually diagnose and treat head and neck cancers. A list of these laboratories and hospital departments was established by each registry, based on data of the previous years. The control group was selected from the general population of the FWI by random digit dialing, using incidence density sampling method. In each region (Guadeloupe or Martinique), controls were frequency-matched to the cases by sex and age. Additional stratification was used to achieve a distribution by socioeconomic status among the controls comparable to that of the general population.

Cases and controls were interviewed face-to-face with a standardized questionnaire including in particular sociodemographic characteristics and lifetime tobacco and alcohol consumption. Participants were asked to provide a saliva sample, using the Oragene® OG-500 kit (DNA Genotek).

Samples were sent to the Biological Resource Centre of Guadeloupe for storage at 24 °C. Oragene® saliva specimen may be stored for at least 5 years at room temperature without DNA degradation [11].

Among 257 cases identified as potentially eligible, 192 (74.7%) agreed to participate and were interviewed. Among them, after diagnosis review, 22 did not meet the inclusion criteria. Among the remaining 170 cases, 114 (72.3%) provided a saliva sample. Among the 497 eligible controls, 405 (81.5%) answered the questionnaire and among them 311 (76.2%) provided a saliva sample. Each subject included in the study gave a written and informed consent. In order to protect the confidentiality of personal data, the questionnaire included only an identification number, without any nominative information. The same identification number was used for biological specimen. The link between the name and the identification number (to the exclusion of any other data) was kept by the cancer registry of the area where the subject was interviewed.

The study was approved by the Institutional Review Board of the French National Institute of Health and Medical Research and by the French Data Protection Authority.

DNA extraction

The extraction of DNA was manually performed on saliva samples. Genomic DNA extraction was carried out using prepIT®·L2P reagent. The samples were mixed and incubated overnight (16 h) at 50 °C to ensure that DNA was released and that nucleases were permanently inactivated. Addition of the prepIT®·L2P reagent revealed all impurities and the DNA in the supernatant was precipitated by adding EtOH 100%. The DNA was washed and the pellet re-suspended in a solution of DNA Hydration (Qiagen®) and then stored at − 20 °C.

HPV detection and genotyping

The detection of HPV was performed with the INNO-LiPA® kit, which allows the detection of the following genotypes: HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, HPV56, HPV58, HPV59, HPV68 (high-risk), HPV26, HPV53, HPV66, HPV70, HPV73, HPV82 (probable high-risk), HPV06, HPV11, HPV40, HPV42, HPV43, HPV44, HPV54, HPV61, HPV81 (low-risk), HPV62, HPV67, HPV83, HPV89 (other). The INNO-LiPA HPV genotyping assay is based on the SPF10 consensus primer system to amplify a 65 bp fragment of the L1 region of the HPV genome [12]. The assay was carried out according to the manufacturer's instructions (INNO-LiPA HPV Genotyping *Extra*; Innogenetics, Ghent, Belgium).

The amplification was performed using SPF10 primers, with adding primers to amplify the human HLA-DPB1 region for having a control of the DNA quality at the same time. The amplification was performed in a reagent mixture containing biotinylated primers in buffer with dNTP/dUTP mix, $MgCl_2$, NaN_3 as preservative, AmpliTaq Gold® polymerase, and uracil-*N*-glycosylase. Before amplification, DNA was added. All PCR reactions were performed with a positive and a negative control. The biotinylated PCR products were genotyped by denaturation and hybridization on nitrocellulose strips followed by a stringent wash. After the addition of the conjugate and the substrate, a colorimetric analysis revealed all the genotypes present in the sample. The hybridization process was automatically performed on the AutoBlot 3000H; at the end, the strip was fixed on a support to read the HPV genotypes lines correspondence.

Due to the presence of primers which amplify all genotypes simultaneously, if there was more competition between particular genotypes, only the presence of a broad range of HPV was detected with the line control HPV1 and/or the line control HPV2. This kind of sample was notified HPV-positive without specifying the genotype. These samples were classified as "undetermined" and were included in the calculation for the prevalence of oral HPV infection regardless of the genotype. However, these samples were excluded from the individual genotype analyses.

Statistical analysis

The analysis was restricted to squamous cell carcinomas (100 cases). For three controls, the quality of the specimen collected was considered inadequate for HPV detection. Our analysis finally included 408 subjects among which 100 were cases and 308 were controls. A univariate analysis was performed to describe the characteristics of the subjects included in the study. A Chi-squared test was used to test the association between these characteristics and HNSCC. The prevalence of oral HPV infections was estimated separately among the HNSCC cases and the controls. Subjects with DNA-HPV detected in saliva sample were referred to as HPV-positive. This was then repeated for the different categories of carcinogenic risk (high-risk, probable high-risk, low-risk, and other) and the various HPV genotypes. The prevalence was also calculated for different categories of the subject characteristics: age, sex recruitment site, tobacco smoking (ever vs never), alcohol drinking (ever daily drinker, i.e., at least one glass per day during at least 1 year; never daily drinker). The prevalence calculation was performed by determining the absolute number of HPV-positive cases/controls and then dividing by the total number of cases/controls included in the study and 95% CI were calculated. The association between the oral HPV infection and the occurrence of HNSCC was assessed by estimating odds ratios (OR) adjusted for age, sex, tobacco smoking, and alcohol drinking and 95% confidence intervals

(CI), using a logistic regression model. An exact Fisher test was performed to assess this association for each HPV genotype individually. Tests giving a p value lower than 5% were considered statistically significant. Statistical analysis was performed using SAS 9.4 software (SAS Institute, Carry, NC USA).

Results

Characteristics of study population

Table 1 provides a description of selected characteristics of the cases and controls included in the study. The mean age was similar in both cases and controls (59 and 57 years, respectively), but the age distribution differed ($p = 0.0163$). The proportion of women was significantly greater in the control group ($p = 0.0026$). The proportion of subjects by region did not differ between cases and controls ($p = 0.9311$). As expected, tobacco smoking ($p < 0.0001$) and alcohol drinking ($p < 0.0001$) were more frequent among cases than among controls.

Oral HPV prevalence

Table 2 provides the oral HPV prevalence by age group, sex, recruitment site, tobacco smoking, and alcohol drinking for HNSCC cases and controls separately. Overall, oral HPV was found in 36.0% (95% CI 27.6–47.2) of the cases and 26.0% (95% CI 21.2–31.3) of the controls. The subjects aged between 55 and 64 years had the highest prevalence of HPV in both cases and controls (48.8%; 95% CI 33.35–65.5 and 35.8%; 95% CI 26.2–46.3, respectively), when compared to the other age groups. Among the controls, oral HPV was found to be twice as prevalent in men as in women, whereas the prevalence was similar in men and women among the cases. A significantly greater HPV prevalence was observed in Guadeloupe than in Martinique regardless of the cancer status. Among the controls, the prevalence of oral HPV was higher in smokers (34.0%; 95% CI 25.0–43.8) than in never smokers (22.0%; 95% CI 16.5–28.4), and in daily drinkers (38.4%; 95% CI 28.1–49.5) compared to never daily drinkers (21.2%; 95% CI 16.0–27.1). An opposite trend was observed among the cases, with a slightly lower prevalence in smokers (35.0%; 95% CI 25.5–45.9) and drinkers (32.9%; 95% CI 22.3–44.9) than in never smokers (40.0%; 95% CI 19.1–63.9) and never drinkers (44.4%; 95% CI 25.5–64.7).

Table 3 shows the prevalence of high-risk, probable high-risk, low-risk, and other HPV types, and of the individual HPV genotypes. The prevalence of high-risk HPV types was found to be 23.3% in the cases and 10.7% in the controls ($p = 0.005$). Concerning the other risk categories (probable high-risk, low-risk, and other), the prevalence did not differ significantly between cases and controls. The most frequent HPV genotypes detected among the controls were HPV66 (5.0%) and HPV52 (4.3%); whereas the genotypes HPV52, HPV56, and HPV16 were the most frequent among the cases (8.9, 5.6, and 4.4% respectively). The prevalences of HPV16, HPV33, and HPV51 were significantly higher

Table 1 Main characteristics of HNSCC cases and controls

Variable	Category	Cases ($n = 100$) n (%)	Controls ($n = 308$) n (%)	p value
Age				0.0163
	< 45	4 (4.0)	44 (14.3)	
	45–54	27 (27.0)	81 (26.3)	
	55–64	43 (43.0)	95 (30.8)	
	≥ 65	26 (26.0)	88 (28.6)	
Sex				0.0026
	Male	88 (88.0)	226 (73.4)	
	Female	12 (12.0)	82 (26.6)	
Recruitment site				0.9311
	Martinique	44 (44.0)	134 (43.5)	
	Guadeloupe	56 (56.0)	174 (56.5)	
Tobacco smoking				
	Ever	80 (80.0)	106 (34.4)	< 0.0001
	Never	20 (20.0)	202 (65.6)	
Daily alcohol drinking				< 0.0001
	Ever	73 (73.0)	86 (27.9)	
	Never	27 (27.0)	222 (72.1)	

French West Indies, 2013–2016

Table 2 Prevalence of oral HPV infection by age, sex, recruitment site, tobacco, and alcohol consumption among HNSCC cases and controls

Variable	Category	Cases ($n=100$)			Controls ($n=308$)		
		HPV+	Prevalence[a]	95% CI	HPV+	Prevalence[a]	95% CI
Age	<45	0			6	13.6	5.1–27.1
	45–54	10	37.0	21.4–57.6	21	25.9	16.8–36.9
	55–64	21	48.8	33.3–65.5	34	35.8	26.2–46.3
	≥65	5	19.2	6.5–39.3	19	21.6	13.5–31.7
Sex	Male	32	36.3	263–47.3	68	30.1	24.2–36.5
	Female	4	33.3	9.9–65.11	12	14.6	7.8–24.1
Recruitment site	Martinique	9	20.1	9.8–35.3	23	17.2	11.28–24.6
	Guadeloupe	27	48.2	34.7–62.0	57	32.8	25.8–40.3
Tobacco smoking	Ever	28	35.0	25.5–45.9	36	34.0	25.0–43.8
	Never	8	40.0	19.1–63.9	44	22.0	16.5–28.4
Daily alcohol drinking	Ever	24	32.9	22.3–44.9	33	38.4	28.1–49.5
	Never	12	44.4	25.5–64.7	47	21.2	16.0–27.1
Total		36	36.0	27.6–47.2	80	26.0	21.1–30.9

French West Indies, 2013–2016

[a]Prevalence calculated by dividing the number of HPV+ by the total number of subjects for a given category

in cases than in controls ($p=0.0340$, 0.0472, and 0.0144, respectively).

We also looked at the HPV prevalence and genotype distribution by cancer site. The following sites were distinguished: oral cavity (oral tongue, gum, mouth, floor of mouth, lips; 22 cases), oropharynx (base of tongue, tonsil, other parts of the oropharynx; 41 cases), larynx/hypopharynx (23 cases), and other sites (sinonasal cavities four cases). The prevalence rates of oral HPV infection were 34.1, 32.0, and 34.6% in cancers of the oropharynx, oral cavity, and larynx/hypopharynx, respectively. The prevalence of high-risk HPV was similar in oropharyngeal (22.0%) and non-oropharyngeal (23.0%) cancer cases. HPV-16 was detected exclusively in oropharyngeal cancer cases (four cases). The three cases positive for HPV33 were two oropharyngeal cancers cases and one oral cavity cancer. HPV51 was detected in one oropharyngeal cancer, in one oral cavity cancer, and in one laryngeal cancer. Other HPV types were not found to be associated with specific cancer sites.

Association between oral HPV and HNSCC

Table 4 gives the results of the logistic regression adjusted for age, sex, tobacco smoking, and alcohol drinking, modeling the risk of developing a HNSCC. The overall HPV infection regardless of the level of carcinogenicity was not found significantly associated to HNSCC. Oral infection with high-risk HPV was associated with a two-fold increase in risk of HNSCC (OR 1.99, 95% CI 0.95–4.15). The association between HPV16 and HNSCC risk (OR 6.24 95% CI 0.76–51.35) was limited to oropharyngeal cancer (OR 16.01 95% CI 1.67–153.64).

Discussion

This is the first study in the Caribbean reporting on oral HPV infection in both HNSCC cases and healthy individuals of African descent. We found an overall HPV prevalence of 36% among HNSCC cases, with little variation by cancer site. Our results are globally compatible with those of a recent meta-analysis that estimated for tumors from patients of Central and South America an overall HPV DNA prevalence of 33.1% (95% CI 15.4–53.6) for cancer of the oral cavity, 14.9% (95% CI 5.6–27.0) for oropharyngeal cancer, and 32.2% (95% CI 15.5–51.4) for laryngeal/hypopharyngeal cancer [7]. Another meta-analysis of HPV prevalence in tumors from HNSCC patients of African descent reported a prevalence of 17% (95% CI 8.8–27.0%), higher among oropharyngeal cancers (31.5%) than in non-oropharyngeal cancers (14.5%) [13]. The prevalence of oral HPV infection in our study was similar for oropharyngeal cancer (29.3%), but was higher for other cancer sites (28.6%). In recent case–control studies on HNSCC [14–18], the prevalence of HPV infection in the oral cavity varied from 19 to 49% for all HNSCC, and from 37 to 61% for oropharyngeal cancers. Contrary to most other studies, HPV16 was not the most frequently detected HPV type in our study, resulting in a low prevalence of HPV16 among cases. However, the prevalence of HPV16 was similar for oropharyngeal cancer (10%) to that observed in Central and South America (14.5%) [7].

We took advantage of the controls recruited in this study to estimate the prevalence of oral HPV infections in the general population of the FWI. The overall prevalence for the two regions was 26%. The prevalence that we estimated in our study was on average greater than in previous studies

Table 3 Prevalence of oral HPV infection by genotype among HNSCC cases and controls

Genotype[a]	Cases ($n=90$) n (%)[b]	Controls ($n=281$) n (%)[b]	p value[c]
High-risk	21 (23.3)	30 (10.7)	0.0050
HPV16	4 (4.4)	2 (0.7)	0.0340
HPV18	2 (2.2)	1 (0.4)	0.1501
HPV31	2 (2.2)	6 (2.1)	1
HPV33	3 (3.3)	1 (0.4)	0.0472
HPV39	0 (0.0)	1 (0.4)	1
HPV45	1 (1.1)	2 (0.7)	0.5708
HPV51	3 (3.3)	0 (0.0)	0.0144
HPV52	8 (8.9)	12 (4.3)	0.1116
HPV56	5 (5.6)	6 (2.1)	0.1473
HPV58	0 (0.0)	4 (1.4)	0.5761
HPV59	1 (1.1)	1 (0.4)	0.4306
HPV68	2 (2.2)	8 (2.8)	1
Probable high-risk	6 (6.7)	24 (8.5)	0.6628
HPV26	1 (1.1)	0 (0.0)	0.2451
HPV53	0 (0.0)	4 (1.4)	0.5761
HPV66	4 (4.4)	14 (5.0)	1
HPV70	1 (1.1)	3 (1.1)	1
HPV73	0 (0.0)	2 (0.7)	1
HPV82	1 (1.1)	2 (0.7)	0.5708
Low-risk	6 (6.7)	13 (4.6)	0.4258
HPV06	3 (3.3)	3 (1.1)	0.1603
HPV42	1 (1.1)	0 (0.0)	0.2451
HPV44	1 (1.1)	5 (1.8)	1
HPV54	0 (0.0)	1 (0.4)	1
HPV61	2 (2.2)	2 (0.7)	0.2529
HPV81	0 (0.0)	3 (1.1)	1
Other	5 (5.6)	7 (2.5)	0.1769
HPV62	2 (2.2)	2 (0.7)	0.2529
HPV67	2 (2.2)	3 (1.1)	0.6000
HPV83	0 (0.0)	2 (0.7)	1

French West Indies, 2013–2016

[a]The following HPV genotypes were not detected in our sample and were omitted from the table: HPV35, HPV26, HPV11, HPV40, and HPV89

[b]Percentage calculated by dividing by the number of cases/controls. Note that because of multiple infections the individual genotype percentages do not add up to give the total amount of the risk group that they belong to

[c]p value from exact Fisher test

Table 4 Association between oral HPV infection and HNSCC risk

HPV category	Cases n	Controls n	OR[a]	95%CI)
HPV-negative	69	228	1	Ref
Any HPV	37	80	1.13	0.63–1.99
High-risk	21	30	1.99	0.95–4.15
HPV16	4	2	6.24	0.76–51.35
Probable high-risk	6	24	0.42	0.15–1.21
Low-risk	6	13	1.85	0.56–6.11
Other	5	7	1.35	0.33–5.63

French West Indies, 2013–2016

[a]Logistic regression modeling the occurrence of HNSCC, odds ratios adjusted for age, sex, tobacco smoking, and daily alcohol drinking

reporting on oral HPV prevalence in healthy individuals from different geographic regions. In a literature review, oral HPV infection prevalence was estimated to be 4.5% (95% CI 3.9–5.1%) overall, 3.5% (95% CI 3.0–4.1%) for high-risk HPV types, and 1.3% (95% CI 1.0–1.7%) for HPV16 [9]. Our control group was, however, frequency-matched to the cases by age and sex, which skewed the results towards older ages and male gender. Furthermore, the small number of subjects below 45 years made it difficult to estimate precisely the HPV prevalence for this category. Consequently, the overall prevalence in our sample is likely to overestimate the prevalence in the general population of the FWI, but provides a fairly reliable estimate of the prevalence in the population of the FWI over 45 years of age. The prevalence of oral HPV infection in our controls is higher than that recently estimated in the US, in men (10.1%) and in women (3.6%), even in the older age categories (55–59: 11.2%, 60–64: 11.4%). The peak prevalence among individuals aged 55–64 years and the higher prevalence in men observed in this study are consistent with our results [19]. Our estimate is also higher than in a multinational sample of healthy men (6.1% in men aged 55–74 years) [20]. This distinct difference in prevalence was observed even in a study conducted in another Caribbean population. The prevalence in women in our control group (14.6%) was more than that of another study reporting on the oral HPV in Tobagonian women (6.6%) who were, however, younger (median age 42 years) than the women in our study [21]. In controls of case–control studies on HNSCC [14–18], who had an age and sex distribution similar to our controls, the prevalence of oral HPV infection varied from 5 to 17.3%. As noted above for the cases, in our controls also HPV16 was not the predominant genotype, and the high HPV prevalence observed in our control group was mainly due to genotypes other than HPV16. It is worth noting that a high prevalence of cervical infection with HPV genotypes other than 16 or 18 was also found among healthy women in Guadeloupe [22].

In our study, overall oral HPV was not found to be significantly associated with HNSCC. This absence of association was consistent with another study which found that the proportion of HPV-positive was almost identical between cases and controls [23]. Other studies reported significant associations between overall oral HPV infections and HNSCC, in particular for oral cancer and oropharyngeal cancer [14, 15,

18]. The lack of association with overall HPV infection in our study may be due to the specific distribution of HPV genotypes in our population. Indeed, we found a borderline significant association between high-risk HPV and HNSCC, and a strong and significant association between HPV16 and oropharyngeal cancer. The latter result is consistent with previous studies [3, 18, 24]. Our study revealed also a larger proportion of HPV33 and HPV51 among the HNSCC cases than the controls. The associations with HPV33, HPV51, and HNSCC were not observed in previous studies [15, 20, 21]. In addition, HPV51 was found exclusively in cases and this could provide a good lead for subsequent studies. These findings could be useful to assess the potential efficiency of current HPV vaccination strategies for the prevention of HNSCC in these regions.

We are aware that our study has some limitations that need to be accounted for when interpreting the data. Firstly, the HPV was detected using saliva samples. This means that the HPV infections were prevalent and we had no means of determining whether or not the HPV infection preceded the HNSCC diagnosis. In addition, we had no information of HPV tumor status. However, several studies have reported a good correlation between HPV DNA detection in tumor tissue and saliva rinse [17, 25, 26], and the use of saliva samples was also shown to be sensitive and specific for p16-positive oropharyngeal tumors [27]. Secondly, the relatively small number of HNSCC cases hampered detailed analyses by cancer site and HPV genotype. Selection bias may not be excluded but is thought to be minimal in the present study. The distribution by sex, age, and cancer sites of the cases included in our study was similar to that of the cases in the local cancer registries. Our study population can thus be considered representative of the HNSCC cases. The method used to select the control group was previously demonstrated to yield unbiased samples and the controls could be considered representative of the general population of similar age and sex [10]. Furthermore, this is one of the very few case–control studies which has investigated the role of oral HPV infection in men and women of African descent and will allow comparison with French HPV data to investigate potential racial disparities between these populations [28]. This study may add valuable data supporting the prevention and control of HNSCC in the people of this ethnic group.

Conclusion

To conclude, the prevalence of oral HPV infection in the French West Indies is 26.0% among healthy individuals and 36.0% in HNSCC patients. The detection of overall oral HPV was not found to influence significantly the occurrence of HNSCC. However, high-risk HPV and the individual genotypes HPV16, HPV33, and HPV51 increased the risk of HNSCC. These findings are particularly interesting because they give valuable leads on the etiology of these cancers in the FWI. Subsequent analyses will examine the potential interactions with traditional risk factors.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest.

Ethical approval French Data Protection Authority (CNIL, Commission Nationale de l'Informatique et des Libertés) n° DR-2015-2027; IRB INSERM n° 01-036.

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4.3 Joint effect of Tobacco, Alcohol and Oral HPV infection on Head and Neck Cancer risk in the French West Indies

Submitted for publication

Joint effect of Tobacco, Alcohol and Oral HPV infection on Head and Neck Cancer risk in the French West Indies

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Abstract

Objectives: To investigate the role of tobacco and alcohol consumption on the occurrence of head and neck squamous cell carcinomas (HNSCC), and the joint effects of these factors with oral HPV infection in the French West Indies, in the Caribbean.

Materials and Methods: We conducted a population-based case-control study (145 cases and 405 controls). We used logistic regression models to estimate adjusted odds-ratios (OR) and their 95% confidence intervals (CI). Two-way interactions were assessed on both multiplicative and additive scales.

Results: Current smoking (OR=11.6, 95%CI=6.7-20.1), drinking more than 5 glasses of alcohol per day (OR=2.7, 95% CI= 1.2-4.7), and oral infection with High-risk HPV (OR=2.4, 95% CI=1.1-5.0) were significantly associated with HNSCC. The combined exposure to tobacco and alcohol produced a significant synergistic effect on the incidence of HNSCC. Oral infection with High-risk HPV increased the risk of HNSCC in never smokers and non-drinkers. The effects of tobacco, alcohol and of the combined exposure of tobacco and alcohol were substantially lower in HPV-positive than in HPV-negative HNSCC.

Conclusion: This is the first case-control study to investigate the role of tobacco smoking, alcohol drinking and oral HPV infection in an Afro-Caribbean population. Although each of these risk factors has a significant effect, our findings indicate that tobacco and alcohol play a less important role in Hr-HPV-positive HNSCC. Further investigations are warranted notably on the interaction of these three risk factors by cancer site.

Keywords: Head and neck cancer; tobacco smoking; alcohol drinking; high-risk oral HPV; joint effect; interaction; French West Indies, Caribbean;

Introduction

Worldwide, more than 700,000 cases of head and neck cancer (including cancers of the oral cavity, pharynx and larynx) are diagnosed each year [1]. Tobacco smoking and alcohol drinking are the major risk factors for these cancers, their joint effect being at least multiplicative [2,3]. Human papillomavirus (HPV) is also a recognized cause of a subset of head and neck squamous cell carcinomas (HNSCC) [4,5]. While the causal role of HPV16 in oropharyngeal cancer is well established, the role of other HPV genotypes or the association between HPV and other subsites of HNSCC is still debated [6]. The manner in which tobacco, alcohol and HPV interact on HNSCC risk remains unclear, with conflicting results. Some studies demonstrated a lack of association with tobacco and alcohol in HPV16-positive HNSCC [5,7,8]. Other more recent studies have shown that tobacco smoking and alcohol drinking have rather an independent role in the etiology of HPV16-positive oropharyngeal cancer [9–11].

Guadeloupe and Martinique are two French overseas territories in the French West Indies (FWI). The population is predominantly Afro-Caribbean. Their incidence rates of head and neck cancer, especially in men, are among the highest in Latin America and the Caribbean [1], despite a relatively low prevalence of tobacco smoking and alcohol drinking [12]. The prevalence of HPV in HNC and the distribution of HPV genotypes may vary substantially according to geographical regions [13–16] and ethnicity [17]. Racial/ethnic differences in the effects of tobacco and alcohol on HNSCC have also been suggested [18].

In order to elucidate the etiology of HNSCC in the FWI, we conducted a population-based case-control study. We previously showed that oral infection with high-risk HPV was associated with an increase in risk of HNSCC. Although oral infection with HPV16 was associated with oropharyngeal cancer, HPV16 was not the predominant genotype and we also found a higher prevalence of other high-risk HPV genotypes in cases than in controls [19].

In the present study, we aimed to investigate the role of tobacco and alcohol consumption on the occurrence of HNSCC, and the joint effects of these factors with oral HPV infection. To our knowledge, this is the first study on this topic in an Afro-Caribbean population.

Methods

Study population, data and specimen collection

We conducted a population-based case-control study in Martinique and Guadeloupe. The study is an extension of a large nationwide case-control study, the ICARE study, which has already been conducted in ten French regions covered by a cancer registry [20]. The study in the FWI used the same protocol and questionnaire, described in details elsewhere [20], with some adaptations to the local context. Eligible cases were patients residing in the FWI, suffering from a primary, malignant tumour of the oral cavity, pharynx, sinonasal cavities and larynx of any histological type, aged between 18 and 75 years old at diagnosis, newly diagnosed and histologically confirmed between April 1, 2013 and June 30, 2016. The control group was selected from the general population by random digit dialling, using incidence density sampling method. Controls were frequency matched to the cases by sex, age and region. Additional stratification was used to achieve a distribution by socioeconomic status among the controls comparable to that of the general population.

Cases and controls were interviewed face-to-face with a standardized questionnaire including in particular sociodemographic characteristics and lifetime tobacco and alcohol consumption. Participants were also asked to provide a saliva sample, using the Oragene® OG-500 kit (DNA Genotek).

Among 257 cases identified as potentially eligible, 192 (74.7%) agreed to participate and were interviewed. Among them, after diagnosis review, 22 did not meet the inclusion criteria. Among the remaining 170 cases, 114 (72.3%) provided a saliva sample. Among the 497 eligible controls, 405 (81.5%) answered the questionnaire and among them 311 (76.2%)

provided a saliva sample. Each subject included in the study gave a written and informed consent. The study was approved by the Institutional Review Board of the French National Institute of Health and Medical Research (IRB INSERM n°01-036) and by the French Data Protection Authority (n° DR-2015-2027).

HPV detection and genotyping

The detection of HPV-integrated DNA from saliva samples was performed with the INNO-LiPA ® kit, according to the manufacturer's instructions (INNO-LiPA HPV Genotyping Extra; Innogenetics, Ghent, Belgium). The INNO-LiPA HPV genotyping assay allows the detection of the following genotypes: HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, HPV56, HPV58, HPV59, HPV68 (High-risk), HPV26, HPV53, HPV66, HPV70, HPV73, HPV82 (Probable high-risk), HPV06, HPV11, HPV40, HPV42, HPV43, HPV44, HPV54, HPV61, HPV81 (Low-risk), HPV62, HPV67, HPV83, HPV89 (Other). The full details on the method for HPV detection has been described elsewhere [19].

Exposure variables

Detailed information on lifetime cigarette smoking history was recorded, for each period of identical smoking habits. The questionnaire included information on age at start and end of the period, number of cigarettes per day or per week, type of tobacco (blond vs. black), filtered or not, inhalation pattern, and whether or not the product was manufactured or hand-rolled. Ever cigarette smokers were defined as persons who smoked at least 100 cigarettes in their lifetime. Ex- smokers were defined as persons who stopped smoking for at least two years. Smoking quantity was defined as the average number of cigarettes per day over the lifetime, and categorised into 3 groups (1 to 10, 11 to 20 and >20 cigarettes/day). Smoking duration was expressed in years and was divided into 4 categories (1 to 20, 21 to 30, 31 to 40, > 40 years). Never smoker was the reference category used for all smoking-related variables

in our analyses. Information on smoking pipes, cigars, chewing and snuffing tobacco was also recorded.

Lifetime alcohol drinking information was recorded as well, with for each period of regular consumption, the age at beginning and end, and the number of standard glasses per day, week or month for each type of alcoholic beverage (wine, beer, rum and other strong spirits). For each type of beverage, ever daily alcohol drinking was defined as at least one glass per day during at least one year. The average number of glasses per day was calculated over the lifetime, regardless of the type of beverage, and categorised into 3 groups (<1 glass/day, 1 to 5 glasses/day and >5 glasses per day). The reference category comprised subjects who never drank alcohol or who had drunk less than one glass per week.

Exposure to HPV was assessed in several manners. Subjects with at least one HPV infection of any type were classified as HPV-positive, others were referred as HPV-negative. The group of HPV-positive was further divided in two categories: high-risk-HPV-positive (at least one HPV type in the high-risk group) and non-high-risk-HPV-positive. A final binary variable was used for the exposure to high-risk-HPV: high-risk-HPV-Positive versus high-risk-HPV-Negative, the latter category grouping HPV-negative and non-high-risk-HPV-positive.

Statistical analysis

The current analysis was restricted to squamous cell carcinomas of the oral cavity (International Classification of Diseases 10th revision codes C00.3-C00.9, C02.0-C02.3, C03.0, C03.1, C03.9, C04.1, C04.8, C04.9, C05.0, C06.0-C06.2, C06.8 and C06.9, n=35), the oropharynx (ICD-10 codes C01.9, C02.4, C05.1, C05.2, C09, C10, C 14.2, n=58), the hypopharynx (ICD-10 codes C12- C13, n=19) and the larynx (ICD-10 codes C32, n=32). Our analysis included 145 cases and 405 controls. The association between smoking, alcohol and oral HPV infection and the occurrence of HNSCC was assessed by estimating odds ratios

(ORs) adjusted for age, sex and recruitment site, and their 95% confidence intervals (CIs), using logistic regression models. The models for tobacco smoking were further adjusted for alcohol consumption. Models estimating the effect of alcohol were adjusted for smoking quantity and duration. ORs associated with oral HPV were adjusted for smoking quantity, duration, and alcohol consumption. Two-way interaction on a multiplicative scale was assessed by estimating Ψ, the multiplicative interaction parameter as follows, Ψ=OR11/(OR01*OR10). The 95% CI for Ψ was determined using the CI for the interaction term in the multivariate model. Two-way interaction on an additive scale was assessed using the Relative Excess Risk due to Interaction (RERI), RERI= OR11-OR10-OR01+1. Asymptotic 95% CI were calculated for the RERI as described elsewhere [21]. We also conducted analyses by cancer site (oropharynx/ non oropharynx). We grouped oral cavity, hypopharynx and larynx because of sample size constraints.

HPV status was missing for 147 (27%) subjects (53 cases and 94 controls) that refused to provide a saliva sample, and for three controls for whom the quality of the specimen was considered inadequate for HPV detection. In addition, missing data were observed for smoking status (one case) smoking quantity (19 cases, 3 controls), smoking duration (6 cases, 1 control) and alcohol quantity (4 controls). We used multiple imputations by chained equations (MICE) to deal with missing data [22]. The imputation model contained all the basic characteristics of the study subjects (age, sex recruitment site and education level), variables related to alcohol and smoking (ever daily alcohol drinking, quantity of alcohol, smoking status, smoking duration, and smoking quantity), HPV status (low-risk, probable high-risk, high-risk, and other HPV types) and the case-control status. All variables in the imputation model which had missing values were imputed for our analyses. We generated 20 datasets. We also performed a complete case analysis, on a dataset containing only observed data. Results were similar to those from the imputed datasets, despite wider confidence

intervals (See supplementary material). Statistical analysis was performed using SAS 9.4 software (SAS Institute, Carry, NC USA).

Results

Characteristics of study population

Table 1 shows socio-demographic characteristics of HNSCC cases and controls. The majority of subjects in our study were between 55 and 64 years old and were men. A little under half of the cases had only primary school education (42.8%) compared to 23.2% of the controls.

Tobacco, Alcohol, Oral HPV and HNSCC risk

Table 2 shows multivariate ORs of HNSCC and 95% CI associated with tobacco smoking, alcohol drinking and oral HPV. Current smokers were significantly 11 times more likely to develop HNSCC compared to never smokers. Ex-smokers were only twice as likely to develop a HNSCC compared to never smokers. The risk increased with the quantity and duration of tobacco smoking. Significant increases in risk by more than 10-fold were observed for more than 20 cigarettes/day, and for more than 30 years. We studied as well the combination between smoking quantity and duration. We observed that duration had a greater role in HNSCC aetiology than the quantity. Persons who smoked for shorter periods of time (less than 30 years) had a lower risk for developing HNSCC regardless of the quantity of cigarettes smoked per day.

Compared to never smokers, the risk of HNSCC was slightly greater for the persons who smoked only black tobacco than blond tobacco alone (OR=5.97, 95%CI=2.80-12.73; OR=4.67, 95%CI=2.55-8.54 respectively) (data not shown). The ORs were higher for those who inhaled deeply cigarette fumes (OR=5.20, 95%CI=2.94-9.18) than for those who never inhaled (OR=3.76, 95%CI=1.57-8.96) or inhaled a little (OR=3.53, 95%CI=1.85-6.75) (data not shown). Cigarette without filters (2.5%), hand-rolled cigarettes (2.8%), pipe (5.0%) and cigars (3.6%) were uncommon in our study population and were not associated with the risk

of HNSCC (data not shown). It should be noted that all cigar smokers and all pipe smokers but one case had also smoked cigarettes. No subject had chewed tobacco and only one case had snuffed.

We observed a significant inverse association for those persons who drank less than one glass per day in relation to HNSCC, when compared to non-drinkers. On the other hand, we found that drinking more than 5 glasses of alcohol per day increases the risk of HNSCC by two fold. We observed as well an increase, although not significant, in HNSCC risk for person who drank between 1 and 5 glasses per day.

Rum was the most frequently consumed alcoholic beverage in our study population regardless of case-control status. The daily consumption of rum and beer increased the risk significantly by two fold compared to the persons who never drank rum or beer daily. In contrast, daily consumption of wine and other strong spirits did not increase the risk significantly compared to non-daily drinkers.

In terms of oral HPV infections, no significant association with HNSCC was found for persons tested positive for HPV when compared to HPV-negative subjects. Non-high-risk HPV types as well did not show any significant difference in risk to HPV-negative subjects. On the other hand, subjects positive for Hr-HPV types were twice as likely to develop HNSCC compared to Hr-HPV-negative subjects.

We analysed tobacco, alcohol and oral HPV risk among oropharyngeal and non-oropharyngeal subsites separately; these results did not change in terms of direction of the association observed in the analyses with all HNSCC cases (data not shown).

Joint effect of risk factors and HNSCC risk

Table 3 shows the multivariate ORs, their 95% CIs, and measures of two-way interaction for combined exposures to risk factors, for HNSCC and by subsite. Compared to never smokers and non-drinkers, never smokers who drank alcohol daily had a non-significant increase in

HNSCC risk (OR=2.01, 95%CI=0.87-4.61) whereas smokers who did not drink alcohol were 3 times more likely to have HNSCC (OR=3.57, 95%CI=1.89-6.74). The joint effect of tobacco and alcohol was more than multiplicative but not significant for HNSCC (Ψ=2.01, 95%CI=0.75-5.37). However, a significant interaction was observed on the additive scale for tobacco and alcohol (RERI=9.82, 95%CI=3.06 to 16.57). Never smokers positive for Hr-HPV were significantly more likely to have HNSCC when compared with Hr-HPV-negative never smokers (OR=4.74, 95%CI=1.45-15.50). Moreover, Hr-HPV-negative ever smokers had an even greater risk of HNSCC (OR=6.30, 95%CI=3.44-11.52). Negative interactions, although not significant, between Hr-HPV and smoking were observed on both the multiplicative (Ψ=0.30, 95%CI=0.07-1.24) and the additive scale (RERI=-1.07, 95%CI=-8.28 to 6.15). Hr-HPV-positive non-drinkers and Hr-HPV-Negative drinkers were both significantly more likely to have HNSCC than Hr-HPV-negative non-drinkers. The joint effect of alcohol and Hr-HPV on HNSCC risk was less than additive (RERI=-3.30, 95%CI=-8.01 to 1.42) and significantly less than multiplicative (Ψ=0.24, 95%CI=0.06-0.99). Negative interactions involving oral Hr-HPV were consistently more marked for alcohol than tobacco. We also performed the above interaction analyses on oropharyngeal and non-oropharyngeal squamous cell carcinomas separately. Although the difference in effect size and trends did not differ significantly between subsites, the effect of all the studied risk factors appeared to be of greater magnitude for the oropharynx than the non-oropharynx cases. In particular, oral Hr-HPV in never smokers and in non-drinkers was found to be significant for only oropharyngeal cancer

Table 4 shows the associations for combined exposures to tobacco smoking and alcohol drinking, stratified by Hr-HPV status. In the Hr-HPV-negative subgroup, the trend was similar to the effect sizes and the measures of interaction for all study participants together.

The Hr-HPV-Positive subgroup on the other hand had overall lower effect sizes for the tobacco-alcohol profiles compared to their Hr-HPV-negative counterparts.

Discussion

Our findings provide new insight on the role of tobacco, alcohol and oral HPV infection and their combined effects on the occurrence of HNSCC in the FWI.

Similarly, to other studies, we found that the risk of HNSCC increased with the duration and intensity of smoking, and the duration had a greater effect than the average number of cigarettes/day [3,23]. Rum was found to be the beverage which conferred the greatest risk of HNSCC compared to other alcoholic beverages. This observed association for rum is likely to result from it being the most frequently consumed alcoholic beverage in the FWI rather than an independent effect of the alcohol concentration [24]. The inverse association we found for light alcohol drinking (<1 glass/day) was consistent with a French study [25]; however, a recent meta-analysis reported pooled estimates that suggested rather a non-significant positive association between light alcohol drinking and head and neck cancer [26]. Although not significant we observed a more than multiplicative effect of the combined of exposure to tobacco and alcohol on HNSCC risk which was of similar magnitude to a study conducted within the INHANCE Consortium [2]. The few studies assessing the additive interaction for tobacco and alcohol conducted their analysis in individual HNSCC subsites and reported super-additive interactions of varying degrees [27–29].

Oral Hr-HPV infections were significantly associated with HNSCC, regardless of Hr-HPV genotype. A study conducted in Canada did not find any significant association with HNSCC and Hr-HPV types excluding HPV16 [10]. In our study, only four cases and two controls were positive for HPV16, and the effect of Hr-HPV on HNSCC was maintained after removing HPV16-positive subjects. These results could be suggestive of a greater role of non-

HPV16 high risk types in HNSCC carcinogenesis in the FWI compared to other populations, as also suggested for cervical infections [30].

Concerning the joint effect of tobacco and HPV, and alcohol and HPV, we found some evidence of a negative interaction on both the additive and multiplicative scale. In particular, the combined effect of alcohol and HPV was significantly less than multiplicative. In other words, the effect of tobacco, alcohol and of the combined exposure of tobacco and alcohol were substantially lower in HPV-positive than in HPV-negative HNSCC, which is indicative of a more pre-dominant role of tobacco and alcohol in HPV-negative HNSCC as described in previous studies which investigated HPV16 specifically [5,7,8]. In contrast, other studies found that tobacco and alcohol increased the risk of both HPV-positive and HPV-negative HNSCC [11,31,32].

Analyses by subsite did not reveal important differences with regards to the effects of tobacco and alcohol; although point estimates were higher in oropharyngeal cancer than in non-oropharyngeal cancer, the confidence intervals were wide and the effect of traditional risk factors was similar in both subsites, as previously shown [9].

Our data on the joint effect of tobacco, alcohol and Hr-HPV on the occurrence of oropharyngeal cancer were supported by previous reports [9,10]. We found that Hr-HPV was associated with a significant increase in risk of oropharyngeal cancer in never smokers and in non-drinkers. These significant associations were not present in the non-oropharyngeal cases. In addition, the measures of interaction for the joint exposure with each of the risk factors and oral Hr-HPV-Positive infections were more marked in the oropharyngeal cases than the non-oropharyngeal cases. Furthermore, the significant sub-multiplicative interaction between alcohol and Hr-HPV was observed exclusively in the oropharynx. These observations support an aetiological role of oral Hr-HPV specific to oropharyngeal cancer, as in previous studies [7,8,31,32]. We demonstrated that alcohol alone did not play a role in Hr-HPV-positive

oropharyngeal cancer as described previously [9,10]. On the other hand, our results did not provide strong evidence for a role of tobacco in oropharyngeal carcinogenesis regardless of HPV status, contrarily to a recent study which emphasised the existence of a positive association in HPV16-related oropharyngeal cancer [9].

Our study presents some limitations. We had a relatively small sample size which limited the detail in our analyses. In particular, we were not able to assess three-way interactions by subsite as we would have liked with tobacco, alcohol and Hr-HPV. We had 27% missing data for HPV in our sample. To handle missing data, we used a multiple imputation procedure that has been shown to result in less biased and more precise estimates than the exclusion of individuals with missing data [22]. The case-control design coupled with the lack of temporal sequence in HPV data made it difficult to put forward a more precise mechanism between the risk factors and HPV in HNSCC risk. We had very few subjects infected with HPV16, which made comparisons with other studies difficult [7–10]. Furthermore, the use of oral HPV detection to assess the HPV status may have resulted in misclassification, which is however likely to be non-differential. Oral HPV detection has been shown to have good specificity but moderate sensitivity for HPV-positive HNSCC tumours [33]. Despite the limitations imposed by oral HPV detection, this method is indicative of the site of infections compared to HPV serology which is not site-specific.

Selection bias may not be excluded but is thought to be minimal in the present study. The distribution by sex, age and cancer sites of the cases included in our study was similar to that of the cases in the local cancer registries. Our study population can thus be considered representative of the HNSCC cases. The method used to select the control group was previously demonstrated to yield unbiased samples and the controls could be considered representative of the general population of similar age and sex [20]. We confirmed the

representativeness of the tobacco and alcohol distribution in our control group to FWI population after comparison with the data from a national health survey [12].

Conclusion

This is the first case-control study to investigate the role of tobacco smoking, alcohol drinking and oral HPV infection in an Afro-Caribbean population. Overall, we showed that these risk factors have significant independent effects on the occurrence of HNSCC. our findings suggest a less important role of tobacco and alcohol in Hr-HPV-positive HNSCC. The precise mechanisms driving these interactions on HNSCC risk are yet to be elucidated and further investigations are warranted notably on the interaction of these three risk factors simultaneously.

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Table 1: Socio-demographic characteristics of HNSCC cases and controls

Characteristics	Cases		Controls	
	n=145	col%	n=405	col%
Age (years)				
<45	3	(2.1)	62	(15.3)
45-54	40	(27.6)	107	(26.4)
55-64	61	(42.1)	129	(31.9)
>65	41	(28.3)	107	(26.4)
Sex				
Women	18	(12.4)	99	(24.4)
Men	127	(87.6)	306	(75.6)
Recruitment site				
Guadeloupe	95	(65.5)	245	(60.5)
Martinique	50	(34.5)	160	(39.5)
Education level				
Primary school	62	(42.8)	94	(23.2)
Secondary school	51	(35.2)	161	(39.8)
High school diploma	17	(11.7)	53	(13.0)
Tertiary education	15	(10.3)	97	(24.0)

French West Indies, 2013-2016

Table 2: Multivariate OR of HNSCC and 95% CI associated with tobacco smoking, alcohol drinking, oral HPV infection and HNSCC.

Risk factor	Cases n=145	col%	Controls n=405	col%	OR[†]	95%CI
Tobacco smoking[a]						
Never smoker	30	(21.8)	263	(64.9)	1	ref
Smoking status						
Current smoker	88	(61.1)	52	(12.8)	11.59	(6.69-20.08)
Former smoker	26	(18.1)	90	(22.2)	2.28	(1.24-4.17)
Missing	1		0			
Quantity (cigarette/day)						
1 to 10	35	(27.8)	71	(17.7)	4.17	(2.33-7.46)
11 to 20	35	(27.8)	51	(12.7)	6.11	(3.39-11.04)
>20	26	(20.6)	17	(4.2)	10.69	(4.89-23.41)
Missing	19		3			
Duration (years)						
1 to 20	9	(6.5)	57	(14.1)	1.43	(0.64-3.23)
21 to 30	17	(12.2)	37	(9.2)	3.94	(1.92-8.07)
31 to 40	42	(30.2)	23	(5.7)	12.25	(6.16-24.37)
> 40	41	(29.5)	24	(5.9)	13.28	(6.61-26.68)
Missing	6		1			
≤ 20 cigarettes/day						
during ≤ 30 years	16	(12.8)	84	(21.0)	2.00	(1.05-3.81)
during >30 years	53	(42.4)	37	(9.2)	12.19	(6.68-22.24)
> 20 cigarettes/day						
during ≤ 30 years	6	(4.8)	7	(1.8)	7.10	(2.13-23.70)
during > 30 years	20	(16.0)	10	(2.5)	15.38	(6.03-39.19)
Missing	20		4			
Alcohol quantity [b] (glasses/day)						
Never or occasionally	51	(35.2)	216	(53.9)	1	ref
<1 glass/day	8	(5.5)	73	(18.2)	0.40	(0.17-0.93)
1 to 5 glasses/day	45	(31.0)	84	(21.0)	1.24	(0.70-2.20)
>5 glasses/days	41	(28.3)	28	(7.0)	2.36	(1.18-4.73)
Missing	0		4			
Type of beverage (daily drinking)						
Wine	38	(26.2)	54	(13.3)	1.35	(0.76-2.39)
Beer	34	(23.5)	35	(8.6)	1.83	(0.98-3.42)
Rum	75	(51.7)	61	(15.1)	2.90	(1.74-4.84)
Other strong spirits	13	(9.0)	12	(3.0)	1.82	(0.68-4.89)
Oral HPV status[c]						
HPV-Negative	60	(65.2)	228	(73.9)		ref
Any HPV	32	(34.8)	80	(26.1)	1.44	(0.82-2.53)
HPV-Non-high risk	13	(14.1)	50	(16.3)	0.80	(0.35-1.83)

HPV-High risk	19	(20.7)	30	(9.8)	2.37	(1.13-4.97)
Missing	53		97			

French West Indies, 2013-2016

a: Model adjusted for age, sex, recruitment site, alcohol consumption (glasses/day)

b: Model adjusted for age, sex, recruitment site, tobacco smoking as the combination of quantity (cigarettes/day) and duration (years)

c: Model adjusted for age, sex, recruitment site, tobacco smoking status, alcohol consumption (glasses/day)

Table 3: Multivariate OR, their 95% CI, and measures of two-way interactions between risk factors for HNSCC, and by subsite.

Risk factor combinations	All cases		Oropharynx		Non-Oropharynx	
	OR	(95%CI)	OR	(95%CI)	OR	(95%CI)
Smoking and Alcohol[a]						
Never Smoker-Non Drinker	1	(ref)	1	(ref)	1	(ref)
Never Smoker-Drinker	2.01	(0.87-4.61)	2.81	(0.75-10.48)	1.79	(0.64-5.01)
Ever smoker-Non drinker	3.57	(1.89-6.74)	5.59	(2.06-15.20)	2.75	(1.24-6.11)
Ever Smoker-Drinker	14.39	(8.02-25.82)	19.37	(7.56-49.61)	13.23	(6.62-26.45)
Ψ (95%CI)	2.01	(0.75-5.37)	1.23	(0.28-5.67)	2.69	(0.80-9.11)
RERI (95% CI)	9.82	(3.06 to 16.57)	11.96	(-1.32 to 25.24)	9.69	(2.25 to 17.13)
Smoking and Hr-HPV[b]						
Never Smoker-Hr-HPV-	1	(ref)	1	(ref)	1	(ref)
Never Smoker-Hr-HPV+	4.74	(1.45-15.50)	5.23	(1.10-24.86)	3.26	(0.64-16.60)
Ever smoker-Hr-HPV-	6.30	(3.44-11.52)	8.82	(3.47-22.38)	5.11	(2.46-10.61)
Ever Smoker-Hr-HPV+	8.98	(3.85-20.94)	10.09	(2.94-34.56)	7.53	(2.77-20.43)
Ψ (95%CI)	0.30	(0.07-1.24)	0.22	(0.03-1.38)	0.45	(0.07-2.94)
RERI (95% CI)	-1.07	(-8.28 to 6.15)	-2.97	(-14.35 to 8.42)	0.16	(-6.67 to 6.99)
Alcohol and Hr-HPV[c]						
Non Drinker-Hr-HPV-	1	(ref)	1	(ref)	1	(ref)
Non Drinker-Hr-HPV+	4.43	(1.50-13.11)	4.76	(1.31-17.32)	3.39	(0.69-16.78)
Drinker-Hr-HPV-	3.20	(1.76-5.82)	3.85	(1.65-8.97)	3.06	(1.47-6.39)
Drinker-Hr-HPV+	3.33	(1.27-8.73)	2.40	(0.62-9.30)	3.70	(1.24-11.09)
Ψ (95%CI)	0.24	(0.06-0.99)	0.13	(0.02-0.80)	0.36	(0.05-2.40)
RERI (95% CI)	-3.30	(-8.01 to 1.42)	-5.21	(-11.93 to 1.52)	-1.75	(-6.93 to 3.43)

French West Indies, 2013-2016

a: Model adjusted for age, sex, recruitment site

b: Model adjusted for age, sex, recruitment site and ever daily alcohol consumption

c: Model adjusted for age, sex, recruitment site, tobacco smoking as the combination of quantity (cigarettes/day) and duration (years)

Ψ: Phi, measure of interaction on a multiplicative scale (interaction term)

RERI: Relative Excess Risk due to Interaction

Table 4: Multivariate OR, their 95% CI, and measures of two-way interaction of combined exposure to tobacco smoking and alcohol drinking on HNSCC risk stratified by Hr-HPV status.

Risk factor combinations	HPV-Hr-Negative		HPV-Hr-Positive	
	OR	95% CI	OR	95% CI
Smoking and Alcohol[a]				
Never Smoker –Non Drinker	1	(ref)	1	(ref)
Never Smoker -Drinker	3.09	(1.03-9.22)	0.56	(0.05-6.72)
Ever smoker- Non drinker	4.89	(1.99-12.03)	1.41	(0.27-7.32)
Ever Smoker- Drinker	23.43	(10.11-54.30)	3.57	(0.88-14.48)
Ψ (95%CI)	1.55	(0.43-5.58)	4.52	(0.21-97.84)
RERI (95% CI)	16.45	(1.76 to 31.16)	2.59	(-1.65 to 6.84)

French West Indies, 2013-2016

a: Model adjusted for age, sex, recruitment site

Ψ: multiplicative interaction parameter

RERI: Relative Excess Risk due to Interaction

Supplementary Materials

Multivariate logistic regression analyses performed on observed data

Supplementary table 1: Multivariate OR of HNSCC and 95%CI associated with tobacco smoking, alcohol drinking and oral (observed data).

Risk factor	Cases n=145	col%	Controls n=405	col%	OR[†]	95%CI
Tobacco smoking[a]						
Never smoker	30	(21.8)	263	(64.9)	1	ref
Smoking status						
Current smoker	88	(61.1)	52	(12.8)	9.04	(5.13-15.92)
Former smoker	26	(18.1)	90	(22.2)	1.97	(1.05-3.68)
Missing	1		0			
Quantity (cigarette/day)						
1 to 10	35	(27.8)	71	(17.7)	3.63	(2.01-6.57)
11 to 20	35	(27.8)	51	(12.7)	4.71	(2.56-11.04)
>20	26	(20.6)	17	(4.2)	7.79	(3.58-16.95)
Missing	19		3			
Duration (years)						
1 to 20	9	(6.5)	57	(14.1)	1.06	(0.43-2.59)
21 to 30	17	(12.2)	37	(9.2)	3.19	(1.51-6.76)
31 to 40	42	(30.2)	23	(5.7)	8.89	(4.39-18.04)
> 40	41	(29.5)	24	(5.9)	10.84	(5.33-22.05)
Missing	6		1			
≤ 20 cigarettes/day						
during ≤ 30 years	16	(12.8)	84	(21.0)	1.56	(0.79-3.09)
during >30 years	53	(42.4)	37	(9.2)	9.76	(5.29-18.02)
> 20 cigarettes/day						
during ≤ 30 years	6	(4.8)	7	(1.8)	6.03	(1.80-20.23)
during > 30 years	20	(16.0)	10	(2.5)	10.27	(4.10-25.71)
Missing	20		4			
Alcohol quantity (glasses/day)						
Never or occasionally	51	(35.2)	216	(53.9)	1	ref
<1 glass/day or <7 glasses/week	8	(5.5)	73	(18.2)	0.50	(0.21-1.19)
1 to 5 glasses/day	45	(31.0)	84	(21.0)	1.61	(0.88-2.96)
>5 glasses/days	41	(28.3)	28	(7.0)	2.50	(1.18-5.29)
Missing	0		4			
Type of beverage (daily drinking) [b]						
Wine	38	(26.2)	54	(13.3)	1.43	(0.78-2.64)
Beer	34	(23.5)	35	(8.6)	2.02	(1.06-3.83)
Rum	75	(51.7)	61	(15.1)	3.01	(1.76-5.17)
Other strong spirits	13	(9.0)	12	(3.0)	1.73	(0.64-4.70)
Oral HPV Status[c]						
HPV-Negative	60	(65.2)	228	(73.9)		ref

Any HPV	32	(34.8)	80	(26.1)	1.23	(0.66-2.30)
HPV-Non-high risk	13	(14.1)	50	(16.3)	0.74	(0.33-1.70)
HPV-High risk	19	(20.7)	30	(9.8)	2.10	(0.95-4.88)
Missing	53		97			

French West Indies, 2013-2016

a: Model adjusted for age, sex, recruitment site, alcohol consumption (glasses/day)

b: Model adjusted for age, sex, recruitment site, Tobacco smoking as the combination of quantity (cigarettes/day) and duration (years)

c: Model adjusted for age, sex, recruitment site, Tobacco smoking status, alcohol consumption (glasses/day)

Supplementary table 2: Multivariate ORs, their 95% CI, and measures of two-way interactions between risk factors for HNSCC, and by subsite (observed data).

Risk factor combinations	All cases		Oropharynx		Non-Oropharynx	
	OR	(95%CI)	OR	(95%CI)	OR	(95%CI)
Smoking and Alcohol[a]						
Never Smoker-Non Drinker	1	(ref)	1	(ref)	1	(ref)
Never Smoker-Drinker	1.97	(0.86-4.52)	2.69	(0.72-10.05)	1.79	(0.64-5.01)
Ever smoker-Non drinker	3.57	(1.89-6.74)	5.59	(2.06-15.21)	2.75	(1.24-6.11)
Ever Smoker-Drinker	14.31	(7.97-25.68)	19.13	(7.46-49.08)	13.23	(6.62-26.45)
Ψ (95%CI)	2.04	(0.76-5.45)	1.27	(0.29-5.66)	2.69	(0.80-9.11)
RERI (95% CI)	9.77	(3.06 to 16.49)	11.85	(-1.29 to 25.00)	9.69	(2.25 to 17.13)
Smoking and Hr-HPV[b]						
Never Smoker-Hr-HPV-	1	(ref)	1	(ref)	1	(ref)
Never Smoker-Hr-HPV+	7.81	(2.35-25.88)	9.86	(1.86-52.36)	3.30	(0.60-18.03)
Ever smoker-Hr-HPV-	6.67	(3.29-13.49)	9.66	(3.19-29.23)	5.22	(2.22-12.26)
Ever Smoker-Hr-HPV+	6.70	(2.39-18.76)	7.91	(1.76-35.64)	5.53	(1.66-18.46)
Ψ (95%CI)	0.13	(0.03-0.57)	0.08	(0.01-0.64)	0.32	(0.05-2.52)
RERI (95% CI)	-6.78	(-17.86 to 4.30)	-10.61	(-30.61 to 9.40)	-1.99	(-9.88 to 5.91)
Alcohol and Hr-HPV[c]						
Non Drinker-Hr-HPV-	1	(ref)	1	(ref)	1	(ref)
Non Drinker-Hr-HPV+	6.54	(2.12-20.15)	7.83	(1.73-35.38)	3.03	(0.55-16.68)
Drinker-Hr-HPV-	5.32	(2.60-10.91)	7.92	(2.79-22.52)	4.30	(1.78-10.41)
Drinker-Hr-HPV+	4.18	(1.38-12.61)	4.95	(1.01-24.40)	3.40	(0.96-12.10)
Ψ (95%CI)	0.12	(0.03-0.56)	0.08	(0.01-0.60)	0.26	(0.05-2.62)
RERI (95% CI)	-6.68	(-15.65 to 2.28)	-9.80	(-25.66 to 4.94)	-2.93	(-9.89 to 4.04)

French West Indies, 2013-2016

a: Model adjusted for age, sex, recruitment site

b: Model adjusted for age, sex, recruitment site and ever daily alcohol consumption

c: Model adjusted for age, sex, recruitment site, Tobacco smoking as the combination of quantity (cigarettes/day) and duration (years)

Ψ: Phi, measure of interaction on a multiplicative scale (interaction term)

RERI: Relative Excess Risk due to Interaction

Supplementary table 3: Multivariate ORs, their 95% CI, and measures of two-way interaction of combined exposures to tobacco smoking and alcohol drinking for HNSCC stratified by Hr-HPV status (observed data).

Risk factor combinations	HPV-Hr-Negative		HPV-Hr-Positive	
	OR	95% CI	OR	95% CI
Smoking and Alcohol[a]				
Never Smoker –Non Drinker	1	(ref)	1	(ref)
Never Smoker -Drinker	6.71	(1.95-23.09)	0.40	(0.03-4.83)
Ever smoker- Non drinker	6.49	(2.14-19.75)	0.40	(0.05-3.22)
Ever Smoker- Drinker	43.66	(15.43-123.54)	1.94	(0.44-8.57)
Ψ (95%CI)	1.00	(0.23-4.28)	12.25	(0.47-319.23)
RERI (95% CI)	31.46	(10.09-52.83)	2.14	(1.23-3.06)

French West Indies, 2013-2016

a: Model adjusted for age, sex, recruitment site

Ψ: multiplicative interaction parameter

RERI: Relative Excess Risk due to Interaction

4.4 Population attributable fractions of head and neck cancer risk factors in the French West Indies

Submitted for publication

Population attributable fractions of head and neck cancer risk factors in the French West Indies.

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Abstract

Objectives: To assess population attributable fractions (PAF) of a selection of head and neck squamous cell carcinoma (HNSCC) risk factors in the French West Indian population, in the Caribbean. In addition, we compared these PAFs among different subgroups.

Materials and Methods: We conducted a population-based case-control study (145 cases and 405 controls). We used logistic regression models to estimate adjusted odds-ratios (OR), PAFs and their 95% confidence intervals (CI).

Results: The overall PAF to all risk factors combined was 90.1% (95% CI=81.1-94.8). The majority of HNSCC cases (62.5% and 55.4%) were attributable to tobacco smoking and alcohol. These PAFs were considerably larger in men (72.7% and 60.4%) than in women (21.4% and 23.6%). The PAFs for the remaining risk factors were 7% for family history of HNSCC, 13.7% for High-risk HPV, 11.4% for low BMI and 27% for occupations. The combined PAFs by sex were significantly greater in men (93.9% 95% CI=85.8-97.4) than in women (64.6% 95% CI=13.1-85.6). After taking into account late age at menarche, we were able to further explain up to 91.1% of female cases (95% CI= 41.5-98.7).

Conclusion: Tobacco and alcohol appeared to have the greatest impact on HNSCC incidence among the studied risk factors, especially among men. Female cases, on the other hand, were rather affected by late age at menarche and other hormonal factors. Prevention programs for HNSCC in the FWI should target tobacco and alcohol cessation, particularly in men and younger persons. Future research on HNSCC should emphasise on the role of hormonal factors to better understand this disease in women.

Keywords: Head and neck cancer; Population attributable fraction; tobacco smoking; alcohol drinking; oral HPV; Family history; Body mass index; Occupational health; French West Indies;

Introduction

Head and neck cancer is a public health concern across the world, counting 700,000 new cases every year [1]. Tobacco smoking and alcohol drinking are the major risk factors. However, in Guadeloupe and Martinique, two French overseas territories in the French West Indies (FWI), the prevalence of these risk factors is relatively low whereas incidence rates of HNC among men are among the highest in Latin America and the Caribbean [2]. Thus, other risk factors known or suspected to be associated with an increased risk of HNC may be contributing actively to the cancer burden in these regions. Risk factors that have been previously found to be associated with an increased risk of head and neck cancer are infection with human papillomavirus (HPV), low vegetable and fruit consumption, low body mass index, occupational exposures and family history of HNC [3–14]. We previously demonstrated that in this population high-risk oral human papillomavirus (Hr-HPV) infections were associated with an increase in head and neck squamous cell carcinoma risk (HNSCC) [15].

Estimating population attributable fractions (PAF) of the different risk factors of HNSCC could be used to attain a better understanding of the public health impact of the various HNSCC risk factors in a given population. This knowledge could have substantial implications for the prevention of head and neck cancers in the FWI. In particular, identify specific situations for which primary prevention or screening programs could be subsequently implemented, and will provide useful data to assess the potential impact of HPV vaccination on HNC. in the FWI.

Previous studies have looked at the population attributable risks for various risk factors [16–20]. In particular, tobacco and alcohol were found to be responsible for 72% of these cancers in an international pooled analysis [18]. The results from PAF are dependent on socio-cultural

context and thus, subject to geographic variation. The studies having reported data on HNSCC risk factors have been performed in populations of European and/or of Asian descent. Although the effects of tobacco and alcohol on HNSCC risk have been reported in black populations [21, 22], data on their public health impact and that of other HNC risk factors are still scarce in populations of African descent [23]. This is the first study to investigate the impact of known or suspected risk factors of HNSCC in an Afro-Caribbean population. We aimed to assess the role and impact of a selection of HNSCC risk factors (tobacco, alcohol, family history of HNC, diet, low BMI, Hr-HPV and at-risk occupations) in the French West Indian population. We estimated population attributable fractions and we compared these PAFs in different subgroups of the study population.

Methods

Study population, data and specimen collection

We conducted a population-based case-control study in Martinique and Guadeloupe. The study is an extension of a large nationwide case-control study, the ICARE study, which has already been conducted in ten French regions covered by a cancer registry [24]. The study in the FWI used the same protocol and questionnaire, described in details elsewhere [24], with some adaptations to the local context. Eligible cases were patients residing in the FWI, suffering from a primary, malignant tumour of the oral cavity, pharynx, sinonasal cavities and larynx of any histological type, aged between 18 and 75 years old at diagnosis, newly diagnosed and histologically confirmed between April 1, 2013 and June 30, 2016. The control group was selected from the general population by random digit dialling, using incidence density sampling method. Controls were frequency matched to the cases by sex, age and region. Additional stratification was used to achieve a distribution by socioeconomic status among the controls comparable to that of the general population.

Cases and controls were interviewed face-to-face with a standardized questionnaire. The questionnaire consisted of the following items: sociodemographic characteristics (age, gender, birth country, education level, marital status), residential history, personal medical history, familial history of cancer, detailed tobacco and alcohol consumption (quantity, duration, type of product, age at starting, time since cessation), non-alcoholic beverage consumption (coffee, tea), diet (food frequency questionnaire), anthropometric variables (height, weight at interview, 2 years before the interview and at age 30), hormonal factors, detailed lifelong occupational history, and sexual behaviour .

Participants were also asked to provide a saliva sample, using the Oragene® OG-500 kit (DNA Genotek).

Among 257 cases identified as potentially eligible, 192 (74.7%) agreed to participate and were interviewed. Among them, after diagnosis review, 22 did not meet the inclusion criteria. Among the remaining 170 cases, 114 (72.3%) provided a saliva sample. Among the 497 eligible controls, 405 (81.5%) answered the questionnaire and among them 311 (76.2%) provided a saliva sample.

HPV detection and genotyping

The detection of HPV-integrated DNA from saliva samples was performed with the INNO-LiPA ® kit, according to the manufacturer's instructions (INNO-LiPA HPV Genotyping *Extra*; Innogenetics, Ghent, Belgium). The INNO-LiPA HPV genotyping assay allows the detection of the following genotypes: HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, HPV56, HPV58, HPV59, HPV68 (High-risk), HPV26, HPV53, HPV66, HPV70, HPV73, HPV82 (Probable high-risk), HPV06, HPV11, HPV40, HPV42, HPV43, HPV44, HPV54, HPV61, HPV81 (Low-risk), HPV62, HPV67, HPV83, HPV89 (Other). The full details on the method for HPV detection has been described elsewhere [15].

Exposure variables

Ever cigarette smokers were defined as persons who smoked at least 100 cigarettes in their lifetime. Ever daily alcohol drinking was defined as at least one glass per day during at least one year.

To ascertain the family history of HNC cancer, subjects were first asked to indicate whether any of their first-degree relatives (biological mother and father, and full brothers or sisters) were diagnosed with head and neck cancer. No verification of the cancer diagnosis in the relatives was performed.

We examined the relationship between BMI at different time points (at interview, 2 years before the interview and at age 30). BMI was computed as weight (kg) divided by height squared (m^2). In relation to BMI, the study population was divided into four categories according to the World Health Organization (WHO) international classification [25]: underweight subjects (BMI < 18.5 kg/m^2), subjects with normal weight (18.5 kg/m^2 ≥ BMI < 24.9 kg/m^2), overweight subjects (25.0 kg/m^2 ≥ BMI < 29.9 kg/m^2), and obese subjects (BMI ≥ 30 kg/m^2).

Oral Hr-HPV status was assessed as high-risk-HPV-positive versus high-risk-HPV-negative, the latter category grouping HPV-negative and non-high-risk-HPV genotypes. Participants were as defined Hr-HPV-positive when at least one high-risk HPV type was detected in the saliva sample that they provided.

Occupational exposures were ascertained by collecting detailed lifetime job history during the interview. The international Standard Classification of Occupations (ISCO) and the French Nomenclature of Activities (NAF) were used by a trained coder to blindly code occupations and branches of the industry, independently of the case-control status of the participants [26, 27].

Information on diet was collected using a food frequency questionnaire [28]. We developed beforehand a list of food items pertinent to our research question and/or consumed regularly in the French West Indies. Participants were asked whether or not they consumed one of the foods in the list, then they were asking to specify the usual frequency at which they consumed those foods.

Information on menstruation, menopause, reproductive characteristics (pregnancies, live births, miscarriages and abortions), lifelong use of oral contraceptives, and hormone replacement therapy (HRT) were recorded exclusively for female participants. HRT was defined as hormone therapy intended to treat menopausal symptoms.

Statistical analysis

The current analysis was restricted to squamous cell carcinomas of the oral cavity (International Classification of Diseases 10th revision codes C00.3-C00.9, C02.0-C02.3, C03.0, C03.1, C03.9, C04.1, C04.8, C04.9, C05.0, C06.0-C06.2, C06.8 and C06.9, n=35), the oropharynx (ICD-10 codes C01.9, C02.4, C05.1, C05.2, C09, C10, C 14.2, n=58), the hypopharynx (ICD-10 codes C12- C13, n=19) and the larynx (ICD-10 codes C32, n=32). Our analysis included 145 cases and 405 controls. The associations between the various risk factors and the occurrence of HNSCC were assessed by estimating odds ratios (ORs) and their 95% confidence intervals (CIs), using logistic regression models. An analysis on the job history of subjects were conducted beforehand to assess the association between the occurrence of HNSCC and having held a certain occupation at least once in the participant's lifetime regardless of the duration. We then created a single variable to take into account the overall risk associated with occupation. Someone who had an at-risk occupational activity was defined as someone who held a job at least once during his/her lifetime in one or more of the occupations which were significantly associated with HNSCC risk based on our analyses,

and evidence in the literature. The occupations and sectors selected to construct this variable were: cook (ISCO 53130), banana plantation worker (ISCO 62210 and NAF 01.1F), mason, carpenter, and other construction workers (ISCO 95), labourers (ISCO 99) and workers in the manufacture of metal products (NAF 28). The ORs for the associations between HNSCC and the occupations and sector used to construct the at-risk occupational activity variable are available in the supplementary table 1.

The association between HNSCC and known risk factors were assessed prior to the final logistic regression model to calculate the PAFs. Each risk factor was regressed individually adjusting for age, sex, region, tobacco and alcohol. Another logistic regression model was then fit with all the significant risk factors as binary variables simultaneously, and the PAFs as well as their 95 % CI were calculated using the aflogit procedure available in STATA software version 13.0 (StataCorp, Texas, USA). This procedure is based on a method described by Greenland and Drescher elsewhere [29].

The PAFs were also calculated in different subgroups: in men and in women, in oropharyngeal and non-oropharyngeal cancer, and in persons <59 years and ≥59 years.

HPV status was missing for 27% of the subjects, who were excluded from the main analysis. We conducted a supplementary analysis to determine the extent to which the removal of these subjects affected estimates for other risk factors. We excluded Hr-HPV status from our final model, and ran this model in the restricted sample used in our primary analysis (excluding subjects with missing values for Hr-HPV) and in the complete dataset (including subjects with missing values for Hr-HPV). We then compared ORs and PAFs for the other risk factors estimated in the two datasets.

Results

Characteristics of study population

The majority of subjects in our study were between 55 and 64 years old and were men. A little under half of the cases have had only primary school education (42.8%) whereas the population controls had mostly secondary school education. Great disparities were observed in tertiary education; cases had less frequently tertiary education compared to controls (10% vs. 24% respectively).

Population attributable fractions of HNSCC

We found no significant association between HNSCC risk and the consumption of fruits and/or vegetables. The highest OR was found among those who consumed fruits and vegetables less than once a week (OR=1.46 95%CI=0.61-3.51), compared to a consumption of at least once a week. This variable did not reach statistical significance and was not included in the final model.

Table 1 shows ORs and PAFs for HNSCC associated with the other risk factors, overall and by subgroups. Overall, more than half of the HNSCC cases (62.5% and 55.4% respectively) were attributable to ever tobacco smoking and daily alcohol drinking. The estimates for the PAF produced large confidence intervals and it was difficult to evaluate significant differences between strata. Nevertheless, notable sex differences in PAFs to individual factors were observed. In comparison to women, a significant larger proportion of cases in men were due to ever cigarette smoking (72.7% vs. 21.4%). Similarly, 60.4% of male cases were due to alcohol drinking versus only 23% of cases in women. Compared to older participants (≥59) the proportion of cases attributable to ever smoking was notably greater among persons under 59 years (78.7% vs. 47.6%).

Family history of HNC was associated with a four-fold increase in HNSCC risk and 7.4% of the cases overall were attributable to this risk factor. Although no significant differences were

observed between subgroups, greater PAFs were found for non-oropharyngeal cancers, women and older persons.

Overall, 11.4% of cases were attributable to low BMI. Greater PAFs were noted for non-oropharyngeal cases, men and persons of younger age.

Overall, 14% of cases were attributable to Hr-HPV. Although non-significant, a greater proportion of cases in younger age group (17.9%) was attributable to Hr-HPV compared to the others (8.3%). The PAF was slightly higher for oropharyngeal cases (12.7%) than for non-oropharyngeal cases (9.8%).

Overall, 27.0% of cases were attributable to at-risk occupational activity. The PAF was 20.3% for oropharyngeal cancer and 30.4% in non-oropharyngeal cancers, 27.9% in men compared to only 10.3% of women.

The PAF for all risk factors combined (Table 2) was 90.1% (95% CI=81.1-94.8). The PAF by sex was significantly greater in men (93.9% 95% CI=85.8-97.4) than in women (64.6% 95% CI=13.1-85.6). PAF were slighted more elevated in younger person (93.6%). On the other hand, no difference was found by subsite.

ORs estimates and PAFs for tobacco, alcohol, family history, BMI and occupation remained virtually unchanged when Hr-HPV status was not included in the model. PAFs estimates from the full dataset were slightly lower for tobacco, alcohol and BMI, slightly higher for family history and similar for occupation, but overall were on the same order of magnitude (Supplementary Table 2).

Role of hormonal factors in female HNSCC

We performed an analysis on the hormonal factors on the occurrence of HNSCC on a subgroup of 117 women (18 cases and 99 controls). Although the measures of association

were not systematically significant, exogenous and endogenous exposure hormonal factors were found to be consistently associated with a decreased risk of HNSCC in women. Compared to women who used oral contraceptives for more than two years, never users and users for two years and less were found to be at a greater risk for HNSCC. Shorter lifetime menstruation (begin after 13 and end ≤ 50) was observed to be significantly associated with an increase in HNSCC risk compared to longer periods of lifetime menstruation (OR=26.49, 95% CI= 3.69-189.93). In terms of reproductive factors, giving birth to no children or only one child was significantly associated with an increase in risk of HNSCC compared to those who had 2 or more (OR=8.34 95%CI= 1.74-40.06). Women who never miscarried a child were also at a greater risk for HNSCC (Supplementary table 3). The PAFs for all risk factors combined were recalculated for women after introducing the binary variable "menarche after 13 years old" into the regression model and it was accountable for 63.8% (95% CI= 4.3-86.3) of the female cases. After taking into account age at menarche, we were able to explain 91.1% (95% CI= 41.5-98.7) of the female cases (Supplementary table 4).

Discussion

This is the first study to investigate the impact of known or suspected risk factors of HNSCC in an Afro-Caribbean population. We were able to attribute 90% of the HNSCC cases to the studied risk factors in this paper, and highlight the predominant impact of tobacco smoking and alcohol on HNSCC incidence across all subgroups studied, except in women.

Overall 62.5% and 55.4% of cases were attributable to ever tobacco smoking and alcohol drinking respectively. These two risk factors accounted for the largest proportion of cases regardless of the stratification on different characteristics. The multiplicative interaction for the joint effect between ever tobacco smokers and daily drinkers on HNSCC was non-significant, and thus, we did not assess the PAF for the joint effect or the cross-product term

in our analysis. Nevertheless, despite a low prevalence of tobacco and alcohol in the FWI [2] our results for individual impacts of tobacco and alcohol were consistent with other studies which showed that the majority of cases were attributable to tobacco smoking, alcohol and their joint effect [16–18, 30, 31].

In terms of the other HNSCC risk factors, the overall PAFs ranged from 7% to 27%. Previous studies investigated mainly PAF for tobacco and alcohol; however, those who looked at other risk factors reported PAFs which were of similar order of magnitude to ours [16, 19]. Occupational exposure accounted for 27% of the cases in our sample, and this PAF was greater than what was estimated previously in an international study [32]. The proportion of cases attributable to family history of HNC in the FWI was higher than what was reported by a pooled analysis from the INHANCE consortium and two European studies [16, 19, 33].

The PAF for oral Hr-HPV was overall 13%. Other studies reported global attributable fractions for Hr-HPV which were consistently greater for the oropharynx (between 21.3 and 30.8%) than the other the other subsites separately [20, 34, 35]. Our results, on the hand, showed no major differences by subsites (12% for oropharynx and 9% for non-oropharyngeal subsites together) and the PAFs for Hr-HPV in the oropharynx was lower than in other studies. Although the etiological fraction of Hr-HPV in the FWI was not as substantial as that of tobacco and alcohol, a noteworthy proportion of cases could be attributed to Hr-HPV infections and therefore, this population could still draw considerable benefits from primary cancer prevention through HPV vaccination [36].

Similarly, to previous studies, great sex disparities were observed in the proportion of cases explained by all the factors studied initially (93.6% in men and 64.0% in women) [16, 17]. This difference is due to the low prevalence of tobacco and alcohol in women, as well as weaker associations. We were able to further explain female HNSCC in our population by up

to 91% by adding menarche after 13 years old to our regression model. Our results on hormonal factors in women coincide with previous studies which show that exposure to estrogen reduces the risk of HNSCC [37–39].

PAFs are conventionally calculated for risk factors with an established causal link with the disease. In addition, we acknowledge that some of the factors studied are indeed non-modifiable and may not provide many avenues for prevention and control, especially in regards to BMI, and the underlying health concerns which may arise from recommending weight gain in the population. However, looking at known or suspected risk factors could contribute towards a better understanding of the etiology of HNSCC in the FWI population and assist in decision-making for public health interventions.

Our study presents several limitations. We had a small sample size and we were not able to perform analyses by all anatomical subsites individually. The risk factors were ascertained mostly by using self-reported measures and may have induced misclassification bias. We cannot disregard the possibility of a recall bias due to the retrospective study design. However, it was shown that participants in case-control studies tend to report accurately information on cancer in first-degree relatives [40, 41]. Furthermore, BMI from two years prior to the interview was used to avoid underestimating the BMI due to weight loss associated with head and neck cancer diagnosis. In our study we were able to investigate a large number of known or suspected risk factors of HNSCC that were studied in previous reports [16–18, 30, 31]. Consequently, we were able to explore various areas such as hormonal factors to explain a greater proportion of female HNSCC. Occupational exposures were assessed collectively as one variable based on occupation and thus, we are unable to produce any information for etiological fractions for specific occupational exposures.

We had 27% missing data for HPV in our sample which imposed the removal of a large proportion of subjects from our regression analysis and thus, contributed to a loss of statistical power. However, sensitivity analysis showed that the removal of these subjects did not change markedly the point estimates for our analyses (supplementary table 2). Furthermore, the use of oral HPV detection to assess the HPV status may have resulted in misclassification, which is however likely to be non-differential. Oral HPV detection has been shown to have good specificity but moderate sensitivity for HPV-positive HNSCC tumours [42].

Selection bias may not be excluded but is thought to be kept to minimum in the current study. The distribution by sex, age and cancer sites of the cases included in our study was similar to that of the cases in the local cancer registries. Our study population can thus be considered representative of the HNSCC cases. The method used to select the control group was previously demonstrated to yield unbiased samples and the controls could be considered representative of the general population of similar age and sex [24]. We confirmed the representativeness of the tobacco and alcohol distribution in our control group to FWI population after comparison with the data from a national health survey [43]. We were able to explain close to 90% of HNSCC and missing 10% could be attributable to residual risk factors that were not taken into account for our study. Factors like gene-environment interactions and medical history were not studied and could bring further clarification to HNSCC aetiology in the FWI.

Conclusion

Overall, we were able to explain 90.1% of HNSCC in the FWI based on the risk factors studied in this report. Tobacco and alcohol appeared to have the greatest impact on HNSCC incidence among the other risk factors (62.5% and 55.4% respectively). Female cases, on the other hand, were rather concerned by menarche after 13 years (63.4% of cases). Given the

large attributable fraction for occupational risk factors (27.0%) the public health impact could be considerable if we reduced these exposures. Special attention should be given to tobacco and alcohol cessation in particular in men and younger persons, when considering prevention programs for HNSCC in the FWI. More in-depth analyses are warranted on occupational exposures in the FWI, and future research on HNSCC should emphasise on the role of hormonal factors to better understand this disease in women.

Conflict of interest statement

The authors have no conflict of interest

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Ethical approval

French Data Protection Authority (CNIL, Commission Nationale de l'Informatique et des Libertés) n° DR-2015-2027; IRB INSERM n°01-036

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Table 1: Adjusted odds ratios (OR), population attributable fractions (PAF) and 95% confidence intervals (CI) for HNSCC associated with tobacco, alcohol, family history of HNC, low BMI, Hr-HPV and at-risk occupations, overall and by subgroups.

Risk factor	Cases	Controls	OR[†]	95% CI	PAF	95% CI
Tobacco smoking (ever vs never smoker)						
HNSCC	114	142	4.94	(2.52-9.66)	62.5%	(41.3-76.0)
By subsite						
Oropharynx	47	142	5.82	(2.29-14.80)	67.2%	(34.1-83.6)
Non-oropharynx	67	142	4.30	(1.82-10.12)	59.7%	(26.9-77.8)
By Sex						
Men	106	121	7.02	(3.20-15.43)	72.7%	(51.2-84.7)
Women	8	21	2.50	(0.36-17.13)	21.4%	(-39.1-55.6)
By age						
<59	60	68	9.99	(3.30-30.22)	78.7%	(50.2-90.9)
≥59	54	74	3.14	(1.26-7.86)	47.6%	(10.5-69.3)
Daily alcohol (ever vs non-daily drinkers)						
HNSCC	96	112	4.29	(2.28-8.07)	55.4%	(34.7-69.6)
By subsite						
Oropharynx	38	112	4.74	(2.00-11.20)	57.6%	(25.7-75.8)
Non-oropharynx	58	112	4.76	(2.08-10.86)	57.9%	(29.1-75.0)
By Sex						
Men	90	97	4.79	(2.34-9.79)	60.4%	(37.6-74.9)
Women	6	15	2.09	(0.35-12.44)	23.6%	(-54.4-62.2)
By age						
<59	42	35	4.72	(1.86-11.97)	53.2%	(23.3-71.4)
≥59	54	77	4.39	(1.75-11.04)	59.3%	(25.8-77.7)
Family history of HNC cancer (yes vs no)						
HNSCC	13	14	4.29	(1.30-14.17)	7.4%	(-3.2-16.9)
By subsite						
Oropharynx	4	14	2.11	(0.36-12.49)	2.9%	(-12.5-16.1)
Non-oropharynx	9	14	6.67	(1.81-24.60)	11.3%	(-3.7-24.2)
By Sex						
Men	11	10	3.94	(0.94-16.49)	6.2%	(-5.2-16.4)
Women	2	4	8.50	(0.78-92.78)	15.9%	(-18.5-40.4)
By age						
<59	6	7	3.17	(0.47-21.17)	5.1%	(-11.4-19.2)
≥59	7	7	4.72	(0.94-23.70)	9.2%	(-5.3-21.7)
Low BMI (BMI< 18.5 vs BMI≥ 18.5)						
HNSCC	12	10	6.96	(1.98-24.52)	11.4%	(0.7-20.8)
By subsite						
Oropharynx	4	10	5.83	(1.13-30.10)	9.0%	(-6.6-22.3)
Non-oropharynx	8	10	8.15	(1.87-35.50)	13.7%	(-1.4-26.5)
By Sex						
Men	11	9	7.32	(1.67-32.12)	12.0%	(0.5-22.1)
Women	1	1	51.99	(1.42-1902.37)	8.9%	(-21.2-31.6)
By age						
<59	8	5	11.36	(1.85-69.81)	16.0%	(-0.2-29.5)
≥59	4	5	4.70	(0.65-34.11)	7.3%	(-6.7-19.5)
Oral HPV Status (Hr-HPV+ vs Hr-HPV-)						
HNSCC	19	30	2.49	(1.16-5.35)	13.7%	(-0.5-26.0)
By subsite						

Oropharynx	8	30	2.41	(0.88-6.63)	12.7%	(-8.2-29.5)
Non-oropharynx	11	30	1.79	(0.69-4.61)	9.8%	(-11.7-27.1)
By Sex						
Men	17	28	2.10	(0.91-4.83)	12.4%	(-4.4-26.4)
Women	2	2	6.11	(0.51-73.23)	14.1%	(-23.6-40.4)
By age						
<59	12	13	2.49	(0.75-8.28)	17.9%	(-8.2-37.8)
≥59	7	17	2.04	(0.70-5.99)	8.3%	(-9.6-23.3)
At-risk occupational activity (yes vs no)						
HNSCC	56	87	2.94	(1.52-5.68)	27.0%	(9.7-41.0)
By subsite						
Oropharynx	19	87	2.37	(0.96-5.81)	20.3%	(-5.8-40.0)
Non-oropharynx	37	87	3.17	(1.41-7.13)	30.4%	(6.2-48.4)
By Sex						
Men	53	80	2.85	(1.38-5.86)	27.9%	(8.3-43.4)
Women	3	7	2.30	(0.22-23.68)	10.3%	(-30.3-48.6)
By age						
<59	27	48	2.41	(0.88-6.61)	24.9%	(-5.9-46.7)
≥59	29	39	3.26	(1.30-8.19)	27.4%	(4.2-45.0)

†: Adjusted for age, sex, region and all the risk factors in the table

Table 2: Population attributable fractions (PAF) and 95% confidence intervals (CI) of all risk factors combined for HNSCC, overall and by subgroups.

	Ca	Co	PAF	95% CI
HNSCC			90.1%	(81.1-94.8)
By subsite				
Oropharynx	58	405	90.2%	(74.7-96.2)
Non-oropharynx	86	405	90.9%	(78.2-96.2)
By Sex				
Men	127	306	93.9%	(85.8-97.4)
Women	18	99	64.6%	(13.1-85.6)
By age				
<59	67	203	93.9%	(81.3-98.0)
≥59	78	202	86.8%	(69.5-94.3)

Title: Population attributable fractions of head and neck cancer risk factors in the French West Indies.

Supplementary Materials

Supplementary table 1: Adjusted ORs for the individual occupations and sectors used to construct the occupational exposure variable.

ISCO code	NAF code	Title	Cases n=145	Controls n=405	OR†	95% CI
		At-risk occupational activity	56	87	2.74	(1.61-4.67)
ISCO		***Occupation***				
53130	Any	Cook, except private service	7	8	5.22	(1.64-16.67)
62210	01.1F	Banana plantation workers	9	6	3.89	(0.96-15.74)
95	Any	Bricklayers, Carpenters and Other Construction Workers	35	58	1.87	(1.02-3.44)
99	Any	Labourer	14	22	2.34	(0.98-5.61)
	NAF	***Sector***				
Any	***28***	Manufacture of fabricated metal products, except machinery and equipment	7	6	6.52	(1.69-25.14)

†: Adjusted for age, sex, region, the combination of cigarette smoking duration and intensity (cigarette/day), and daily alcohol drinking

Supplementary table 2: Comparison of the results with and without exclusion of subjects with missing values for HPV

Covariates in model	Restricted sample (exclusion of subjects with missing values for HPV						Full dataset (including subjects with missing values for HPV)			
	Model 1		Model 2				Model 2			
	OR (95%CI)	**PAF (95%CI)**	**OR**	**95%CI**		**PAF (95%CI)**	**OR**	**95%CI**		**PAF (95%CI)**
Ever smoker	4.94 (2.53-9.65)	62.5% (41.3-76.0)	4.94	2.56	9.57	62.5 (41.5-75.9)	4.36	2.56	7.54	58.1 (40.8-0.3)
Daily drinking	4.29 (2.28-8.07)	55.4% (34.7-69.6)	4.42	2.37	8.28	56.0 (35.6-69.9)	3.64	2.18	6.07	49.6 (32.2-62.5)
Family history	4.29 (1.29-14.17)	7.4% (-3.2-16.9)	4.76	1.43	15.80	7.6 (-2.8-17.0)	5.10	1.96	13.26	8.9 (0.4-16.7)
BMI < 18.5 kg/m^2	6.96 (1.98-24.52)	11.4% (0.7-0.8)	6.56	1.86	23.17	11.2 (0.06-20.6)	4.48	1.46	13.71	7.3 (1.2-15.1)
High-risk HPV	2.49 (1.16-5.35)	13.7% (-0.5-6.0)	NA	NA	NA	NA	NA	NA	NA	NA
At-risk occupation	2.94 (1.52-5.67)	27.0% (9.7-1.0)	2.77	1.45	5.29	26.2 (8.6-40.4)	2.91	1.70	4.96	26.3 (12.5-38.0)

All the models in this table have been adjusted for age, sex and region
NA: covariate not introduced in to the regression model

Supplementary table 3: Adjusted odds ratios (OR) and 95% confidence intervals (CI) for HNSCC associated with hormonal factors

Hormonal factor	Case		Control			
	n	col%	n	col%	OR†	95% CI
Exogeneous factors						
Oral contraceptive use						
Ever	9	(64.3)	83	(84.7)	1	ref
Never	5	(35.7)	15	(15.3)	2.27	(0.60-8.64)
Missing	4		1			
Duration of oral contraception (years)						
Never used oral contraception	5	(35.7)	15	(15.3)	2.75	(0.55-13.62)
≤ 2	5	(35.7)	42	(42.9)	1.41	(0.31-6.40)
2	4	(28.6)	41	(41.8)	1	ref
Missing	4		1			
Hormone replacement therapy (HRT)						
Ever	1	(7.7)	23	(35.9)	1	ref
Never	12	(92.3)	41	(64.1)	5.39	(0.61-47.54)
Missing	5		35			
Endogeneous factors						
Age at Menarche						
≤ 13	5	(35.7)	67	(68.4)	1	ref
over 13	9	(64.3)	31	(31.6)	4.95	(1.30-18.92)
Missing	4		1			
Menopause						
Yes	13	(92.9)	61	(67.8)	9.25	(0.71-120.49)
No	1	(7.1)	29	(32.2)	1	ref
Missing	4		9			
Menopause age (years)						
≤ 50	12	(92.3)	39	(66.1)	18.51	(1.37-249.83)
Over 50	1	(7.7)	20	(33.9)	1	ref
Missing	5		40			
Menopause age (years)						
Never menopause	1	(7.1)	29	(33.0)	1	ref
≤ 50	12	(85.7)	39	(44.3)	14.84	(1.04-211.34)
over 50	1	(7.1)	20	(22.7)	1.11	(0.04-29.00)
Missing	4		11			
Lifetime menstruation						
Begin after 13 – end ≤ 50	8	(61.5)	12	(20.3)	1	ref
Begin ≤ 13 – end ≤ 50	4	(30.8)	27	(45.8)	0.07	(0.01-0.53)
Begin after 13 – end after 50	1	(7.7)	8	(13.6)	0.04	(0.00-1.26)
Begin ≤ 13 – end after 50	0	(0.0)	12	(20.3)	NA	NA
Missing	5		40			

Lifetime menstruation (binary)						
Begin after 13 – end ≤ 50	8	(61.5)	12	(20.3)	26.49	(3.69-189.93)
Other scenarios	5	(37.8)	47	(79.7)	1	ref
Missing	5		40			
Ever Pregnant						
Yes	9	(75.0)	91	(93.8)	1	ref
No	3	(25.0)	6	(6.2)	5.92	(0.88-39.88)
Missing	6		2			
Number of pregnancies						
Never pregnant	3	(21.4)	6	(6.1)	5.25	(0.73-37.50)
Once	1	(7.1)	11	(11.2)	0.95	(0.07-13.83)
Twice	3	(21.4)	15	(15.3)	4.24	(0.77-23.24)
> 2	7	(50.0)	66	(67.4)	1	ref
Missing	4		1			
Parity						
Never pregnant	3	(23.1)	6	(6.4)	8.23	(0.96-70.50)
1 child	3	(23.1)	15	(16.0)	8.75	(1.13-67.71)
2 children	3	(23.1)	28	(29.8)	1.53	(0.26-8.99)
> 2 children	4	(30.8)	45	(47.9)	1	ref
Missing	5		5			
Miscarriage						
Ever	2	(16.7)	38	(41.3)	1	ref
Never	10	(83.3)	54	(58.7)	3.94	(0.68-22.84)
Missing	6		7			
Number of miscarriages						
Never miscarried	10	(83.3)	54	(59.3)	2.17	(0.35-13.37)
Once	2	(16.7)	22	(24.2)	1	ref
> 1	0	(0.0)	15	(16.5)	NA	NA
Missing	6		8			

†: Adjusted for age, sex, region, smoking status (current/former), daily alcohol drinking

Supplementary table 4: Population attributable fractions (PAF) and 95% confidence intervals (CI) of all risk factors individually and combined for female HNSCC only

Risk factor	Cases n=18	Controls n=99	OR†	95% CI	PAF	95% CI
Female HNSCC					91.1%	(41.5-98.7)
Ever Smoker	8	21	3.74	(0.36-38.56)	29.3%	(-31.4-62.0)
Ever daily drinker	6	15	3.23	(0.33-31.82)	34.5%	(-46.1-70.7)
Family history of HNC cancer	2	4	24.76	(1.20-511.45)	19.2%	(-17.3-44.3)
Leanness	1	1	24.98	(0.62-1010.6)	9.6%	(-25.2-34.7)
Hr-HPV-positive	2	2	3.98	(0.09-182.27)	15.0%	(-33.3-45.8)
At-risk occupational activity	3	7	2.85	(0.09-91.10)	19.5%	(-52.5-57.5)
Menarche after 13 years	9	31	11.36	(1.22-105.73)	63.8%	(4.3-86.3)

†: Adjusted for age, sex, region and all the risk factors in the table

4.5 Association between Sexual Behaviour and Head and neck cancer in the French West Indies

The following is a presentation of preliminary results on sexual behaviour and Head and neck cancer. Although the results are presented using the structure of a research article, complementary work is necessary before submitting this manuscript.

Association between sexual behaviour and head and neck cancer in the French West Indies

Words count for the main-text: 3397

Keywords: Head and neck cancer; Sexual behaviour; Condom use; HPV; Sexually transmitted infection; Caribbean; French West Indies;

Introduction

Head and neck cancer is a public health concern across the world, counting 700,000 new cases every year [1]. Guadeloupe and Martinique are two French overseas territories in the French West Indies (FWI). In 2018, age-standardized (world) incidence rates of head and neck cancer per 100,000 were estimated to be 8.1 in Guadeloupe (men: 15.5; women: 2.1) and 5.7 in Martinique (men: 12.1; women: 0.6). Though tobacco smoking and alcohol drinking prevalence of these risk factors are relatively low in Guadeloupe and Martinique, incidence rate of these two French overseas territories are one of the highest of HNC among men in Latin America and the Caribbean [2]. Oral HPV infections are emerging as a prominent risk factor especially in oropharyngeal cancer [1, 2]. The incidence of HPV-positive HNSCC has increased as of recent and was observed during that same period decline of 50% in HPV-negative HNSCC cancer which driven by chronic tobacco and alcohol consumption [3]. We have previously demonstrated a significant association between oral Hr-HPV and HNSCC in the French West Indies (FWI) [4]. Knowing the involvement of Hr-HPV in HNSCC, it is imperative that we acquire a solid understanding of the natural history in this virus in HNSCC development. In spite of the biological similarities to cervical cancer, the etiological pathway in regards to sexual behaviour and oral HPV infection is less clear in HNSCC [6, 7]. Sexual behaviour, including oral sex and other at risk and promiscuous behaviour have been consistently regarded as plausible drivers of oral HPV infection which in turn provoke HNSCC [8–11]. However, results from previous studies are sometimes

conflicting and few data exist on this topic in populations of African descent [12]. In the current paper we proposed an analysis investigating the association between sexual behaviour and the occurrence of head and neck in the FWI and the role of oral Hr-HPV in this association. To our knowledge, this is first study addressing this topic in an Afro-Caribbean population.

Method

Study population, data and specimen collection

We conducted a population-based case-control study in Martinique and Guadeloupe. The study is an extension of a large nationwide case-control study, the ICARE study, which has already been conducted in ten French regions covered by a cancer registry [13]. The study in the FWI used the same protocol and questionnaire, described in details elsewhere [13], with some adaptations to the local context. Eligible cases were patients residing in the FWI, suffering from a primary, malignant tumour of the oral cavity, pharynx, sinonasal cavities and larynx of any histological type, aged between 18 and 75 years old at diagnosis, newly diagnosed and histologically confirmed between April 1, 2013 and June 30, 2016. The control group was selected from the general population by random digit dialling, using incidence density sampling method. Controls were frequency matched to the cases by sex, age and region. Additional stratification was used to achieve a distribution by socioeconomic status among the controls comparable to that of the general population.

Cases and controls were interviewed face-to-face with a standardized questionnaire including in particular sociodemographic characteristics, lifetime tobacco and alcohol consumption and sexual behavior Participants were also asked to provide a saliva sample, using the Oragene® OG-500 kit (DNA Genotek).

Among 257 cases identified as potentially eligible, 192 (74.7%) agreed to participate and were interviewed. Among them, after diagnosis review, 22 did not meet the inclusion criteria.

Among the remaining 170 cases, 114 (72.3%) provided a saliva sample. Among the 497 eligible controls, 405 (81.5%) answered the questionnaire and among them 311 (76.2%) provided a saliva sample. Each subject included in the study gave a written and informed consent. The study was approved by the Institutional Review Board of the French National Institute of Health and Medical Research (IRB INSERM n°01-036) and by the French Data Protection Authority (n° DR-2015-2027).

HPV detection and genotyping

The detection of HPV-integrated DNA from saliva samples was performed with the INNO-LiPA ® kit, according to the manufacturer's instructions (INNO-LiPA HPV Genotyping *Extra*; Innogenetics, Ghent, Belgium). The INNO-LiPA HPV genotyping assay allows the detection of the following genotypes: HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, HPV56, HPV58, HPV59, HPV68 (High-risk), HPV26, HPV53, HPV66, HPV70, HPV73, HPV82 (Probable high-risk), HPV06, HPV11, HPV40, HPV42, HPV43, HPV44, HPV54, HPV61, HPV81 (Low-risk), HPV62, HPV67, HPV83, HPV89 (Other). The full details on the method for HPV detection has been described elsewhere [4].

Collection of data on sexual behaviour

Lifetime sexual behavior was ascertained during the face-to-face interviews. The questionnaire included questions pertaining to the number of lifetime sex partners, sexual orientation and whether or not the last sexual intercourse took place in the last 6 months prior to the interview. Participants were asked if they ever performed certain sexual practices and the frequency at which they did them. These variables were condom use, oral sex practice, whether or not the participants had ever received sperm in their mouth, and the age at which these acts were last practiced was also noted. Information on having multiple partners, sexual intercourse in exchange for money and sexually transmitted infections (STI) also collected. Oral sex was defined as the contact between the participant’s mouth and their partner’s

genitalia. Having multiple partners was defined as having several sexual partners during the same period. When the frequency of an activity was requested, 4 responses were possible: just once, sometimes, often, always or almost always.

Statistical analysis

We restricted the current analysis to squamous cell carcinomas of the oral cavity (International Classification of Diseases 10th revision codes C00.3-C00.9, C02.0-C02.3, C03.0, C03.1, C03.9, C04.1, C04.8, C04.9, C05.0, C06.0-C06.2, C06.8 and C06.9, n=35), the oropharynx (ICD-10 codes C01.9, C02.4, C05.1, C05.2, C09, C10, C 14.2, n=58), the hypopharynx (ICD-10 codes C12- C13, n=19) and the larynx (ICD-10 codes C32, n=32). Our analysis included 145 cases and 405 controls. The effect of sexual behaviour variables on the occurrence of HNSCC, and oral Hr-HPV infection was assessed by estimating odds ratios (ORs) and their 95% confidence intervals (CIs), using logistic regression models. Regression analyses were adjusted for age, sex and recruitment site, tobacco, alcohol and education level. Tobacco was accounted as one variable combining the quantity (the average number of cigarettes per day over one's lifetime,) and the duration of lifetime smoking. This smoking variable was divided into 4 categories (≤20 cigarettes/day during ≤ 30 years, ≤20 cigarettes/day during >30 years, >20 cigarettes/day during ≤ 30 years and >20 cigarettes/day during > 30 years). Alcohol drinking was accounted for as the average number of glasses per day was over a lifetime, regardless of the type of beverage, and was categorised into 3 groups (<1 glass/day, 1 to 5 glasses/day and >5 glasses per day). Level of education was evaluated as the highest level of formal education obtained and was divided into four categories (primary school, secondary school, high school diploma, tertiary education).

In order to assess the role of HPV as a mediator in the relationship between sexual behaviour and HNSCC we performed logistic regressions with Hr-HPV as a covariate as well as reproducing the initial analyses by Hr-HPV subgroups (Hr-HPV-negative and Hr-HPV-

positive). Oral Hr-HPV status was assessed as high-risk-HPV-positive versus high-risk-HPV-negative, the latter category grouping HPV-negative and non-high-risk-HPV genotypes. Assuming that Hr-HPV is on the causal pathway to head and neck cancer, we considered HPV as a mediator when the association between sexual behaviour and HNSCC dissipated in the Hr-HPV-positive subgroup. Hr-HPV was also regarded as a mediator when the adjustment for Hr-HPV resulted in the loss of the initial significant association.

We also studied the associations between sexual behaviour and oral Hr-HPV infection separately among population controls and HNSCC cases.

Results

Sexual behaviour and Head and neck cancer

Table 1 shows the association between sexual behaviour and HNSCC. Last intercourse beyond 6 months preceding the interview was positively associated with the occurrence of HNSCC. Having sexual intercourse after the age of 18 year was associated with 60% reduction of HNSCC risk, compared to those who began before 15 years. Similarly, HNSCC risk was significantly reduced by 50% among persons who used condoms at least occasionally (once, sometimes). In addition, after adjustment for main confounding variables, condom users were twice as likely to have engaged in sexual intercourse in the 6 month prior to their interview (OR=2.52, 95% CI=1.51-4.18) (Data not shown). Although non-significant compared to persons who never practiced oral sex, those who had practiced at least occasionally were less likely to have HNSCC. Receiving money for performing sexual intercourse was uncommon in our study, there were only 6 controls who responded “yes”, and represented 1% of the general population. Lifetime sex partners, sexual orientation, paying for sex, and having multiple partners were not associated with HNSCC.

We were interested in the role of Hr-HPV in the mediation of the associations between sexual behaviour and HNSCC from our analyses. Table 2 shows association between age at first intercourse, time since last intercourse, condom use, oral sex and HNSCC after stratification and adjustment for Hr-HPV. The associations observed for age at intercourse were unchanged after adjusting for Oral Hr-HPV and stratification. However, the associations for time since last intercourse, ever condom use and oral sex were accentuated following the adjustment for Hr-HPV. In addition, the significant effects of condom use and time since last intercourse on HNSCC appeared only in Hr-HPV-negative HNSCC whereas the association with oral sex remained non-significant regardless of HPV status.

We were then interested in the link between significantly associated sexual behaviour variables in regards to HNSCC risk. Table 3 shows the effect of age at sexual debut on HNSCC adjusted for ever condom use and stratified by condom use frequency. Age at first intercourse remained significantly associated with an increase in HNSCC risk but only among persons who used condoms inconsistently (once or sometimes) or not all. Similarly, the significant association disappeared following the adjustment on ever condom use. When compared to having few lifetime sexual partners (1 to 5), higher numbers of partners were neither associated with HNSCC in the subgroup of regular oral sex (6 to 20, OR=0.34 95%CI=0.06-1.88; >20, OR=0.62 95%CI=0.12-3.22) nor in the subgroup practicing oral sex sparingly (once or sometimes) or never (6 to 20, OR=0.52 95%CI=0.25-1.09; >20, OR=0.68 95%CI=0.26-1.78) (Table 4).

We also examined the effect of Hr-HPV on HNSCC risk taking into account significant sexual behaviour variables individually and in different combinations as covariates in the multivariate model (Table 5). Adjustment for ever condom use, and/or oral sex tended to increase slightly the effect of Hr-HPV on HNSCC risk (relative variation=15-26%) contrarily to age at first sexual intercourse which caused a slight decrease. Overall, the association

between Hr-HPV and HNSCC was not markedly changed after adjustment for sexual behaviour variables.

Oral HPV and sexual behaviour in population controls and in HNSCC cases

Table 6 shows the association between sexual behaviour and oral Hr-HPV infection in population controls and among HNSCC cases. After adjusting for confounding factors, none of the sexual behaviour variables studied in the current paper were significantly associated with oral HPV infections in controls, who may be considered as representative of the general FWI population. However, oral Hr-HPV was non-significantly associated with an increase in the frequency of oral sex. Although not significant, first intercourse before 15 years appeared to occur more frequently in Hr-HPV-positive controls compared to persons who began intercourse after 18 years. Likewise, Hr-HPV-positive controls were non-significantly more likely to use condoms at least once, and have repeated sexually transmitted infections when compared to control who never had an STI.

In contrast, the associations between sexual behaviour and oral Hr-HPV infections were consistently more apparent in HNSCC cases. Cases who had a sexual debut between the ages of 15-18 years were significantly less likely to be positive for Hr-HPV. A fewer number lifetime sex partners was more frequent among Hr-HPV-negative cases compared to their Hr-HPV-positive counterparts (51% vs. 35%). Non-heterosexual cases were significantly more likely to have an oral Hr-HPV infection when compared to heterosexuals. Practicing oral sex regularly (often or always) was associated with Hr-HPV positivity when compared to cases who never practiced. In addition, recent oral sex encounters (<1 year) preceding the interview were more frequent among the Hr-HPV-positive cases than their Hr-HPV-negative counterparts. The use of condoms was associated with a non-significant increase in the likelihood of a case having an oral Hr-HPV infection. Cases were significantly more likely to

be positive for Hr-HPV when they had multiple sexual partners simultaneously from more than 5 years preceding the interview

Discussion

The data from our study revealed significant associations between age at first intercourse condom use, time since last sexual intercourse, and HNSCC risk. We found no clear association in the population controls with any of the indicators studied. Case-to-case comparisons however, yielded evidence that is in favour of an association between risky sexual behaviour and oral Hr-HPV infection.

Ever oral sex did not reach statistical significance but it was inversely associated with HNSCC, similarly to results from other studies, including a large pooled analysis from the INHANCE consortium [8, 14]. On the contrary, these results opposed findings which highlight rather a positive association with ever oral sex and head and neck cancer [15–17].

Our study did not provide any evidence of an association between the number of lifetime intercourse partners and HNSCC which was concordant with previous findings [9, 17, 18]. We stratified the number of lifetime sex partner by oral sex frequency in an attempt to produce a proxy for oral sex partners. Even in persons who perform oral sex often or always, the number of lifetime oral sex partners did not yield any significant association with HNSCC risk which corresponded to previous reports on number of oral sex partners [17, 18].

In regards to oral Hr-HPV infections in the control group, we unable to highlight any clear association with sexual behaviour based on the variables we studied. Although non-significant, oral sex appeared to increase the risk of Hr-HPV infections in population controls which coincided with a previous study [16]. Given the absence of significant association with sexual behaviour and Hr-HPV in population controls, other factors such as fomites or self-inoculation could be considered as means of contamination in the general population [19].

Despite the lack of the putative effects of oral sex, and number of sexual partners [8, 15, 16, 20, 21] on HPV transmission and HNSCC in our study, we were able to highlight associations with other sexual behaviour indicators. We found that persons who had their first sexual intercourse at a younger age were at a greater risk of HNSCC compared to a sexual debut after the age of 18. These findings coincided with other studies [9, 18]; however, summary estimates from a meta-analysis suggest that overall, age at first intercourse did not affect HNSCC risk significantly [15]. In terms of this association between sexual behaviour and oral Hr-HPV infection, our positive association for sexual intercourse debut between 15-18 years among HNSCC cases was consistent with another study [22] but discordant with the non-significant association described in previous reports [20, 23, 24]. The positive associations we observed for oral sex and oral HPV infections among cases were consistent with previous reports [8, 20, 23] whereas same-sex contact was discordant in a study having done a similar analysis [23]. Data on multiple partners and HPV positivity in HNSCC cases was less frequent but our results were consistent with reports which mentioned that women with multiple partners were at higher risk for cervical cancer [6].

Regarding the use of condoms, we observed a significant protective effect for ever condom use on HNSCC, similarly to another case-control study on oropharyngeal cancer [9]. The observed association with age at first intercourse disappeared after adjusting for ever condom use, and in subgroup analysis among persons who used condoms regularly (often or always). On the other hand, this significant association was maintained in the subgroup of person who used condoms very inconsistently or not at all; thus, reinforcing the evidence that association between age at sexual debut and HNSCC is mediated by risky sexual habits [25].

Despite the associations observed between sexual behaviour and HNSCC, we did not find any evidence of an association mediated by oral Hr-HPV infections. Indeed, ever condom use was significantly associated with a reduction in HNSCC risk; however, this effect was neither

attenuated after adjusting for Hr-HPV nor in HPV-negative subject alone. Furthermore, the association between condom use and oral Hr-HPV in both control and cases was non-significantly negative. Contrarily to a Canadian study [16], our results allude to a risk reduction by condom use which is independent of oral Hr-HPV infections.

Subjects who had their last sexual intercourse from more than 6 months from their interview were significantly more likely to have HNSCC. There were not any studies which looked at this particular indicator [26] but this difference could have arisen from bodily changes linked to their illness which could have reduced their desire to initiate in sexual intercourse [27].

Information on HIV seropositivity, which has been shown to influence sexual behaviour [28, 29] was not available. Moreover, HIV-seropositivity is known to be associated with greater HPV prevalence and can potentiate the carcinogenic activity of an HPV infection and thus, would clarify the differences in HPV transmission through sexual behaviour between cases and controls [30–35].

Our study presents several limitations. Our findings are exposed to the possibility of a recall bias due to the retrospective nature of the case-control Furthermore, we had a small sample size and we were not able to perform analyses by anatomical subsite. In addition, sexual behaviour in the Caribbean is regarded as a taboo [36] and could induce misclassification bias, in particular in regards to number of sexual partners. Our sample comprising mainly of men, the average number of sexual partners may be more likely to be overestimated [37]. In terms of sexual orientation, homosexuality is thought to be underestimated in our sample because of discrimination faced by this group in the FWI [38]. Furthermore, the use of oral HPV detection to assess the HPV status may have caused misclassification. Oral HPV detection has been shown to have good specificity but moderate sensitivity for HPV-positive HNSCC tumours [39].

Selection bias may not be ruled out but is thought to be kept to minimum in the present analysis. There were more missing data in cases than in controls; however, we do not believe that omission of this part of the question was linked to sexual behaviour. In addition, the questions pertaining to sexual behaviour were at the end of the questionnaire and cases tended to stop the interview prior to those questions more often than controls due to fatigue. 27% of the data for HPV was missing in our sample which imposed the removal of a large proportion of subjects from our regression analysis and thus, resulted in a reduction in statistical power in our analyses involving HPV. Nevertheless, the distribution by sex, age and cancer sites of the cases included in our study was similar to that of the cases in the local cancer registries. Our study population can thus be considered representative of the HNSCC cases. The method used to select the control group was previously demonstrated to yield unbiased samples and the controls could be considered representative of the general population of similar age and sex [24]. We confirmed the representativeness of sexual behaviour distribution in our control group to FWI population after comparison with the data from a regional KABP survey [40]. During our study, we did not collect any information on HIV status which is a factor suspected to modify the natural history of HPV in head and neck cancer [34] and could provide clues to link between sexual behaviour and head and neck cancer considering that the prevalence of HIV is high in the FWI [41, 42]. Future studies on sexual behaviour should take into account HIV and other viral agents to better understand the biological mechanism between sexual behaviour and neck cancer.

Conclusion

This is the first study to investigate the role of sexual behaviour in the occurrence of head and neck in an Afro-Caribbean population while taking into account oral HPV infections. In light of our analyses, first intercourse before 15, time interval since last intercourse and never

condom use were positively associated with HNSCC independently of oral Hr-HPV infection. Oral Hr-HPV infections were associated with riskier sexual behaviour in HNSCC cases but not in population controls. These results do not provide any strong evidence of Hr-HPV as a mediator of these observed associations, in particular with condom use. However, other sources of contamination such as fomites, as well as HIV infections could play a role in the causal pathway to HNSCC. Further investigation on this topic in the FWI is warranted and special attention should be given to the interaction between viral factors to better substantiate the natural history of HPV in HNSCC thus, providing additional prospects for prevention.

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Table 1: Association between sexual behaviour and HNSCC

	Case n (col%)	Control n (col%)	OR	95% CI
Age at first sexual intercourse (years)				
< 15	39 (33.9)	71 (17.9)	1	ref
15 - 18	61 (53.0)	217 (54.8)	0.58	(0.31-1.06)
> 18	15 (13.0)	108 (27.3)	0.41	(0.19-0.91)
Missing	30	9		
Time since last intercourse (months)				
≤ 6	61 (56.5)	309(79.2)	1	ref
> 6	47 (43.5)	81 (20.8)	2.35	(1.32-4.18)
Missing	37	15		
Number of lifetime partners				
1	10 (9.3)	36 (9.2)	1	ref
2 to 5	37 (34.3)	141 (36.1)	1,59	(0.55-4.59)
6 to 9	16 (14.8)	58 (14.8)	1,34	(0.39-4.58)
10 to 20	17 (15.7)	96 (24.6)	0,58	(0.18-1.89)
20 to 50	17 (15.7)	34 (8.7)	1,41	(0.40-4.97)
50 to 100	6 (5.6)	15 (3.8)	0,69	(0.15-3.16)
> 100	5 (4.6)	9 (2.3)	2,02	(0.39-10.51)
Missing	37	16		
Number of lifetime partners				
1 to 5	47 (43.5)	177 (45.5)	1	ref
6 to 20	33 (30.6)	154 (39.6)	0.56	(0.29-1.07)
> 20	28 (25.9)	58 (14.9)	0.87	(0.41-1.85)
Missing	37	16		
Sexual orientation				
Heterosexual	89 (80.9)	345 (88.7)	1	ref
Non-Heterosexual	21 (19.1)	44 (11.3)	1.77	(0.86-3.67)
Missing	35	16		
Condom use				
Ever	61 (57.0)	303 (77.3)	0.51	(0.28-0.93)
Never	46 (43.0)	89 (22.7)	1	ref
Missing	38	13		
Condom use, frequency				
Never	46 (43.0)	89 (22.6)	1	ref
Once, sometimes	40 (37.4)	183 (46.5)	0.51	(0.27-0.97)
Often, always or almost always	21 (19.6)	122 (31.0)	0.51	(0.24-1.08)
Missing	38	11		
Oral sex				
Ever	69 (63.3)	288 (72.4)	0.76	(0.42-1.38)
Never	40 (36.7)	106 (26.6)	1	ref
Missing	36	11		
Oral sex, frequency				
Never	40 (37.0)	106 (27.4)	1	ref
Once, sometimes	39 (36.1)	201 (51.9)	0.67	(0.35-1.27)
Often, always or almost always	29 (26.9)	80 (20.7)	0.88	(0.41-1.89)
Missing	37	18		
Received sperm in mouth				

Never oral sex ,never sperm, just once	66 (90.4)	233 (91.4)	1	ref
Sometimes, often, always or almost always	7 (9.6)	22 (8.6)	1.81	(0.56-5.92)
Missing	72	150		
Paid for sex				
Ever	27 (24.1)	95 (23.9)	1	ref
Never	85 (75.9)	302 (76.1)	1.54	(0.82-2.86)
Missing	33	8		
STI, Frequency				
Never	75 (68.8)	248 (63.1)	1	ref
Once	11 (10.1)	60 (15.3)	0.51	(0.19-1.18)
More than once	23 (21.1)	85 (21.6)	0.88	(0.44-1.74)
Missing	36	12		
Recent multiple partners				
Never multiple partners	68 (61.3)	244 (61.8)	1	ref-
≤ 5 years	12 (10.8)	42 (10.3)	0.93	(0.39-2.22)
> 5 years	31 (27.9)	109 (27.6)	0.81	(0.40-1.48)
Missing	34	10		

a: OR adjusted for age, sex, recruitment site, cigarette quantity and duration combined, alcohol quantity and level of education

Table 2: Association between age at first intercourse, condom use, oral sex and HNSCC after adjusting for Hr-HPV and stratification on Hr-HPV status

	Ca	Co	Univariate OR[a] (95% CI)	Conf OR[b] (95% CI)	Conf+Hr-HPV OR[c] (95% CI)	Hr-HPV- OR[b] (95% CI)	Hr-HPV+ OR[b] (95% CI)
Age at first sexual intercourse							
< 15	39	71	3.44 (1.73-6.85)	2.42 (1.09-5.33)	2.32 (0.92-5.28)	2.60 (0.90-7.49)	NA
15 - 18	61	217	1.87 (1.01-3.49)	1.38 (0.68-2.78)	1.34 (0.59-3.05)	1.20 (0.47-3.05)	NA
> 18	15	108	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Time since last intercourse							
≤ 6	69	288	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
> 6	40	106	3.34 (2.07-5.39)	2.37 (1.33-4.22)	3.09 (1.53-6.25)	2.39 (1.11-513)	10.90 (0.72-165.34)
Condom use							
Ever	61	303	0.32 (0.20-0.52)	0.51 (0.28-0.93)	0.33 (0.16-70)	0.30 (0.13-70)	0.56 (0.08-4.01)
Never	46	89	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Oral sex							
Ever	69	288	0.56 (0.35-0.90)	0.76 (0.42-1.38)	0.49 (0.24-0.99)	0.56 (0.25-1.23)	0.22 (0.02-2.58)
Never	40	106	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)

Conf: confounders

a: OR adjusted for age, sex, recruitment site

b: OR adjusted for age, sex, recruitment site, cigarette quantity and duration combined, alcohol quantity and level of education

c: OR adjusted for age, sex, recruitment site, cigarette quantity and duration combined, alcohol quantity and level of education and high-risk HPV status

NA: Estimates were not computed because of convergence issues in the regression model due too few subjects.

Table 3: Association between Age at first intercourse and head and neck cancer stratified by Frequency of condom use

Age at first sexual intercourse	**All subjects**		Condom use							
			Ca	Co	**Often, Always**		Ca	Co	**Never, Once, Sometimes**	
	OR[b]	(95% CI)	n=29	n=80	OR[a]	(95% CI)	n=77	n=305	OR[a]	(95% CI)
<15	2.01	(0.87-4.65)	9	18	0.78	(0.07-9.23)	23	50	4.00	(0.97-16.48)
15-18	1.53	(0.73-3.20)	17	50	0.46	(0.05-4.22)	42	161	2.92	(0.80-10.70)
>18	1	ref	3	12	1	ref	12	94	1	ref

a: OR adjusted for age, sexe, recruitment site, cigarette quantity and duration combined, alcohol quantity and level of education
b: Model from "a" further adjusted for ever condom use

Table 4: Number of lifetime sexual partners stratified by oral sex frequency

Number of lifetime partners	Oral sex frequency			
	Often or always		Never, Once, Sometimes	
	OR	95% CI	OR	95% CI
1 to 5	1.00	ref		ref
6 to 20	0.34	(0.06-1.88)	0.52	(0.25-1.09)
> 20	0.62	(0.12-3.22)	0.68	(0.26-1.78)

Table 5: Association between Hr-HPV and HNSCC risk after adjusting for age at first intercourse, condom use and oral sex

		OR	(95% CI)
	Hr-HPV-	1	ref
Covariate(s)			
Univariate[a]	Hr-HPV+	2.23	(1.17-4.25)
Univariate+Confounders[b]	Hr-HPV+	2.23	(0.98-5.11)
Univariate+Confounders[b]+:	Hr-HPV+		
Age at first sexual intercourse	Hr-HPV+	2.00	(0.86-4.70)
Condom use	Hr-HPV+	2.69	(1.13-6.39)
Oral sex	Hr-HPV+	2.57	(1.11-5.96)
Condom use+ Oral sex	Hr-HPV+	2.80	(1.18-6.64)
Age at first sexual intercourse+Condom use	Hr-HPV+	2.46	(1.02-5.93)
Age at first sexual intercourse+Oral sex	Hr-HPV+	2.41	(1.02-5.67)
Age at first sexual intercourse+Condom use+ Oral sex	Hr-HPV+	2.59	(1.08-6.23)

a: OR adjusted for age, sexe, recruitment site
b: OR adjusted for age, sex, recruitment site, cigarette quantity and duration combined, alcohol quantity and level of education

Table 6: Association between sexual behaviour and Oral HPV infection in population controls and HNSCC cases

	Controls				Cases			
	Hr-HPV- n (col%)	Hr-HPV+ n (col%)	OR[a]	95% CI	Hr-HPV- n (col%)	Hr-HPV+ n (col%)	OR[a]	95% CI
Age at first sexual intercourse (years)								
< 15	45 (16.6)	7 (23.3)	1	ref	21 (31.3)	9 (50.0)	1	ref
15 - 18	149 (55.0)	18 (60.0)	1.05	(0.38-2.91)	36 (53.7)	7 (38.9)	0.15	(0.03-0.85)
> 18	77 (28.4)	5 (16.7)	0.65	(0.18-2.36)	10 (14.9)	2 (11.1)	0.10	(0.01-1.44)
Missing	6	0			6	1		
Time since last intercourse (months)								
≤ 6	213 (79.5)	27 (93.1)	1	ref	34 (54.0)	11 (64.7)	1	ref
> 6	55 (20.5)	2 (6.9)	0.26	(0.05-1.27)	29 (46.0)	6 (35.3)	0.93	(0.20-4.31)
Missing	8	2			10	2		
Number of lifetime partners								
1 to 5	124 (46.8)	8 (27.6)	1	ref	33 (51.6)	6 (35.3)	1	ref
6 to 20	106 (40.0)	15 (51.7)	1.89	(0.69-5.16)	17 (26.6)	6 (35.3)	3.88*	(0.32-46.74)
> 20	35 (13.2)	6 (20.7)	1.27	(0.34-4.70)	14 (21.9)	5 (29.4)	8.59*	(0.86-85.66)
Missing	12	1			9	2		
Sexual orientation								
Heterosexual	237 (89.1)	26 (86.7)	1	ref	51 (86.7)	9 (50.0)	1	ref
Non-Heterosexual	29 (10.9)	4 (13.3)	0.78	(0.23-2.67)	12 (13.3)	9 (50.0)	6.37	(1.23-33.04)
Missing	11	0			10	1		
Condom use								
Ever	208 (78.3)	26 (86.7)	1.54	(0.45-5.27)	33 (54.1)	12 (66.7)	2.82	(0.56-14.41)
Never	61 (21.7)	4 (13.3)	1	ref	28 (45.9)	6 (33.3)	1	ref
Missing	8	0			12	1		
Condom use, frequency								
Never	61 (22.7)	4 (13.3)	1	ref	28 (45.9)	6 (33.3)	1	ref

Once, sometimes	120 (44.6)	19 (63.3)	1.98	(0.57-6.83)	22 (36.1)	8 (44.4)	3.41	(0.57-20.22)
Often, always or almost always	88 (32.7)	7 (23.3)	0.79	(0.19-3.35)	11 (18.0)	4 (22.2)	2.10	(0.29-15.20)
Missing	8	0			12	1		
Oral sex								
Ever	196 (72.9)	26 (86.7)	1.73	(0.52-5.79)	37 (57.8)	13 (72.2)	0.09	(0.01-1.75)
Never	73 (27.1)	4 (13.3)	1	ref	27 (42.2)	5 (27.8)	1	ref
Missing	8	0			9	1		
Oral sex, frequency								
Never	73 (27.9)	4 (13.3)	1	ref	27 (42.2)	5 (27.8)	1	ref
Once, sometimes	140 (53.4)	15 (50.0)	1.52	(0.44-5.28)	25 (39.1)	5 (27.8)	0.46	(0.05-3.85)
Often, always or almost always	49 (18.7)	11 (36.7)	2.72	(0.69-10.76)	12 (18.8)	8 (44.4)	11.06	(1.12-109.06)
Missing	14	1			9	1		
Years since last oral sex								
Never oral sex	73 (28.2)	4 (13.8)	1	ref	27 (44.3)	5 (31.3)	1	ref
<1	105 (40.5)	19 (65.5)	2.67	(0.74-9.60)	10 (16.4)	9 (56.3)	6.69	(0.79-56.63)
1-10	57 (22.0)	5 (17.2)	1.13	(0.26-4.93)	15 (24.6)	2 (12.5)	0.29	(0.02-5.12)
> 10	24 (9.3)	1 (3.5)	0.57	(0.06-5.85)	9 (14.8)	0 (0.0)	NA	NA
Missing	18	1			12	3		
Received sperm in mouth								
Never oral sex ,never sperm, just once	164 (91.6)	12 (85.7)	1	ref	45 (90.0)	5 (71.4)	1	ref
Sometimes, often, always or almost always	15 (8.4)	2 (14.3)	9.84	(0.47-207.68)	5 (10.0)	2 (28.6)	4.91†	(0.10-239.62)
Missing	98	16			23	12		
Paid for sex								
Ever	62 (22.8)	10 (33.3)	1	ref	14 (21.5)	6 (33.3)	1	ref
Never	210 (77.2)	20 (66.7)	1.20	(0.49-2.95)	51 (78.5)	12 (66.7)	0.58	(0.13-2.62)
Missing	5	0			8	1		
STI, Frequency								
Never	176 (65.4)	15 (51.7)	1	ref	45 (71.4)	14 (82.4)	1	ref

Once	43 (16.0)	7 (24.1)	0.63	(0.12-3.23)	6 (9.5)	0 (0.0)	NA	NA
More than once	50 (18.6)	7 (24.1)	1.82	(0.70-4.72)	12 (19.1)	3 (17.7)	0.41	(0.05-3.17)
Missing	8	1			10	2		
Recent multiple partners								
Never multiple partners	172 (63.5)	16 (53.3)	1	ref	43 (67.2)	10 (55.6)	1	ref
≤ 5 years	27 (10.0)	3 (10.0)	0.73	(0.18-3.07)	4 (6.3)	1 (5.6)	2.18	(0.07-70.68)
> 5 years	72 (26.6)	11 (36.7)	1.15	(0.47-2.84)	17 (26.6)	7 (38.9)	6.07	(1.05-35.28)
Missing	6	0			9	1		

a: OR adjusted for age, sex, recruitment site, cigarette quantity and duration combined, alcohol quantity and level of education
*: Level of education accounted for as three categories instead of four.
†: OR adjusted for age, sex, recruitment site, cigarette quantity and duration, alcohol quantity and level of education in three categories

4.6 Supplementary results

4.6.1 Fruits and vegetable consumption and head and neck cancer

Analyses for this risk factor are still ongoing and complementary studies are necessary before beginning a draft for an original research manuscript. The following is a presentation of main results on fruit and vegetable consumption and head and neck cancer in the French West Indies.

Table 5: Association between fruits and vegetable consumption and HNSCC

	HNSCC		Control					
	n	**col%**	**n**	**col%**	**OR[a]**	**95%CI**	**OR[b]**	**95%CI**
Fruits and Vegetables								
Never or exceptionally, occasionally	16	(13.1)	22	(5.5)	2.62	(1.33-5.17)	1.46	(0.61-3.51)
At least once per week or per day	106	(86.9)	382	(94.6)	1	ref	1	ref
Fruits and Vegetables								
Never or exceptionally, occasionally, at least once per week	49	(40.2)	137	(33.9)	1.31	(0.86-1.98)	0.86	(0.52-1.42)
At least once per day	73	(59.8)	267	(66.1)	1	ref	1	ref
Fruits and Vegetables								
Never or exceptionally	1	(0.8)	1	(0.3)	3.66	(0.23-59.18)	0.86	(0.02-41.72)
Occasionally	15	(12.3)	21	(5.2)	2.61	(1.28-5.32)	1.52	(0.63-3.63)
At least once per week	33	(27.1)	115	(28.5)	1.05	(0.66-1.67)	0.73	(0.42-1.27)
At least once per day	73	(59.8)	267	(66.1)	1	ref	1	ref

a : Crude odds ratio, no adjustment on matching variable or confounding factors

b: Model adjusted for age, sex, recruitment site, combination of cigarette quantity and duration, quantity of alcohol

Table 6: Association between fruits and vegetable consumption and ever tobacco smoking

	Tobacco smoking					
	Never		Ever			
	n	col%	n	col%	OR[a]	95%CI
Fruits and Vegetables						
Never or exceptionally, occasionally	14	(4.8)	24	(10.2)	1.58	(0.75-3.31)
At least once per week or per day	277	(95.2)	211	(89.8)	1	ref
Fruits and Vegetables						
Never or exceptionally	1	(0.3)	1	(0.4)	0.80	(0.04-16.75)
Occasionally	13	(4.5)	23	(9.8)	2.00	(0.92-4.33)
At least once per week	69	(23.7)	79	(33.6)	1.80	(1.17-2.76)
At least once per day	208	(71.5)	132	(56.2)	1	ref

a: Model adjusted for age, sex, recruitment site, and case-control status

Table 7: Association between fruits and vegetable consumption and daily alcohol drinking

	Daily alcohol drinking					
	Never		Ever			
	n	col%	n	col%	OR[a]	95%CI
Fruits and Vegetables						
Never or exceptionally, occasionally.	13	(4.0)	25	(12.5)	2.83	(1.31-6.14)
At least once per week or per day	313	(96.0)	175	(87.5)	1	ref
Fruits and Vegetables						
Never or exceptionally	0	(0.0)	2	(1.0)	NA	NA
Occasionally	13	(4.0)	23	(11.5)	2.95	(1.32-6.59)
At least once per week	89	(27.3)	59	(29.5)	1.39	(0.88-2.18)
At least once per day	224	(68.7)	116	(58.0)	1	ref

a: Model adjusted for age, sex, recruitment site, and case-control status

Table 8: Association between fruits and vegetable consumption and HNSCC stratified by daily alcohol drinking

Fruits and Vegetables	HNSCC	Control	Never daily alcohol drinking		HNSCC	Control	Ever daily alcohol drinking		P_{inter}
	n	n	OR[a]	95%CI	n	n	OR[a]	95%CI	
									0.061
Never or exceptionally, occasionally	4	9	4.81	(1.32-17.51)	12	13	0.83	(0.32-2.14)	
At least once per week or At least once per week	30	283	1	ref	76	99	1	ref	

a: Model adjusted for age, sex, recruitment site, combination of cigarette quantity and duration,

P_{inter} : Statistical test assessing the multiplicative interaction between frequency of fruit and vegetable consumption and daily alcohol drinking

4.6.2 Tea, coffee and juice/soda consumption and head and neck cancer

Table 9: Association between tea,coffee and juice/soda consumption and HNSCC

Beverage quantity	Crude OR	95%CI	OR[a]	95%CI
Coffee				
Never or occasionnally	1	ref	1	ref
<1 cup/day	0.34	(0.15-0.74)	1.17	(0.41-3.34)
1-5 cups/day	0.33	(0.20-0.54))	0.53	(0.25-1.12)
> 5 cups/day	1.01	(0.34-3.04)	0.64	(0.14-2.97)
Tea				
Never or occasionnally	1	ref	1	ref
<1 cup/day	0.18	(0.07-0.47)	0.53	(0.18-1.59)
1-5 cups/day	0.35	(0.18-0.71)	0.84	(0.34-2.05)
> 5 cups/day	0.66	(0.07-6.39)	0.86	(0.03-23.32)
Juice or soda				
Never or occasionnally	1	ref	1	ref
<1 glass/day	0.12	(0.05-0.28)	0.42	(0.15-1.18)
1-5 glasses/day	0.31	(0.18-0.53)	0.52	(0.25-1.12)
> 5 glasses /day	0.44	(0.15-1.26)	0.77	(0.20-3.04)

a: Adjusted for age, sex, recruitment site, tobacco smoking status, cigarette quantity, smoking duration and quantity of alcohol

4.6.3 Occupational exposures and head and neck cancer in the French West Indies

Preliminary results for occupational risk factors were accepted for a poster presentation at the Aderest symposium in Toulouse, France in November 2019. Analyses are still ongoing and complementary studies are necessary before beginning a draft for an original research manuscript. The following is a presentation of main results occupational risk factors and head and neck cancer in the French West Indies.

Table 10: Association between occupations and HNSCC using major occupational groups

Major occupation groups	ISCO code	Case		Control				
		n	%col	n	%col	OR[a]	IC95%	
Professional, technical and related workers	0/1	24	16.6	122	30.1	0.47	0.26	0.86
Administrative and managerial workers	2	8	5.5	21	5.2	0.72	0.26	1.96
Clerical and related workers	3	21	14.5	119	29.4	0.36	0.19	0.66
Sales workers	4	26	17.9	72	17.8	0.82	0.43	1.55
Service workers	5	32	22.1	106	26.2	1.17	0.63	2.17
Agricultural, animal husbandry and forestry workers, fishermen and hunters	6	45	31.0	78	19.3	1.35	0.78	2.34
Production and related workers, transport equipment operators and labourers	7/8/9	90	62.1	192	47.4	1.50	0.89	2.54

a: Age, sex, recruitment site, smoking quantity and duration combined and daily alcohol drinking

Table 11: Association between occupations and HNSCC using two-digit ISCO codes

Occupation title	ISCO code	Case	Control	OR[a]	95%CI	
Architects, Engineers and Related Technicians	03	7	18	0.94	0.32	2.79
Aircraft and Ships' Officers	04	1	1	2.88	0.07	115.31
Medical, Dental, Veterinary and Related Workers	06	1	6	0.70	0.06	8.75
Medical, Dental, Veterinary and Related Workers	07	3	16	**0.24**	**0.06**	**0.98**
Statisticians, Mathematicians, Systems Analysts and Related Technicians	08	1	6	0.31	0.03	3.27
Teachers	13	10	53	0.67	0.29	1.55
Professional, Technical and Related Workers Not Elsewhere Classified	19	5	14	1.98	0.54	7.23
Managers	21	6	21	0.57	0.19	1.68
Government Executive Officials	31	5	25	0.63	0.2	2.00
Stenographers, Typists and Card- and Tape-Punching Machine Operators	32	3	21	0.28	0.05	1.43
Bookkeepers, Cashiers and Related Workers	33	5	32	**0.33**	**0.11**	**0.99**
Mail Distribution Clerks	37	1	15	0.16	0.02	1.42
Clerical and Related Workers Not Elsewhere Classified	39	8	43	0.55	0.22	1.36
Managers (Wholesale and Retail Trade)	40	2	2	1.81	0.17	19.25
Sales Supervisors and Buyers	42	12	2	0.58	0.1	3.31
Technical Salesman, Commercial Travellers and Manufacturers' Agents	43	3	8	0.65	0.14	3.02
Insurance Real Estate, Securities and Business Services Salesmen and Auctioneers	44	2	11	0.30	0.05	1.77
Salesmen, Shop Assistants and Related Workers	45	17	47	0.84	0.39	1.80
Working Proprietors (Catering and Lodging Services)	51	3	3	0.90	0.12	6.7
Cooks, Waiters, Bartenders and Related Workers	53	12	28	1.40	0.55	3.57
Maids and Related Housekeeping Service Workers Not Elsewhere Classified	54	5	36	1.16	0.34	3.94
Building Caretakers, Charworkers, Cleaners and Related Workers	55	4	27	1.00	0.31	3.25
Launderers, Dry-Cleaners and Pressers	56	1	1	12.11	0.73	201.34
Hairdressers, Barbers, Beauticians and Related Workers	57	1	3	0.39	0.03	5.71
Protective Service Workers	58	6	14	1.55	0.48	5.06
Service Workers Not Elsewhere Classified	59	6	13	1.40	0.41	4.78
Farmers	61	5	23	0.58	0.17	1.96
Agricultural and Animal Husbandry Workers	62	33	54	1.31	0.71	2.41
Fishermen, Hunters and Related Workers	64	8	8	2.53	0.65	9.75
Production Supervisors and General Foremen	70	2	18	0.19	0.02	1.74
Miners, Quarrymen, Well Drillers and Related Workers	71	1	2	1.19	0.09	16.3
Chemical Processers and Related Workers	74	1	2	0.93	0.05	16.32
Food and Beverage Processers	77	6	11	0.89	0.25	3.24

Tailors, Dressmakers, Sewers, Upholsterers and Related Workers	79	1	7	1.24	0.14	10.72
Cabinetmakers and Related Woodworkers	81	3	6	1.23	0.23	6.55
Blacksmiths, Toolmakers and Machine Tool Operators	83	3	9	1.49	0.31	7.29
Machinery Fitters, Machine Assemblers and Precision-Instrument Makers (except Electri	84	11	24	1.31	0.52	3.36
Electrical Fitters and Related Electrical and Electronics Workers	85	6	22	0.73	0.23	2.29
Broadcasting Station and Sound-Equipment Operators and Cinema Projectionists	86	1	3	2.01	0.16	24.67
Plumbers, Welders, Sheet-Metal and Structural Metal Preparers and Erectors	87	12	22	0.98	0.38	2.51
Painters	93	10	13	0.99	0.35	2.85
Production and Related Workers Not Elsewhere Classified	94	1	3	1.34	0.08	22.62
Bricklayers, Carpenters and Other Construction Workers	95	35	58	**1.87**	**1.02**	**3.44**
Material Handling and Related Equipment Operators, Dockers and Freight Handlers	97	16	30	1.51	0.69	3.29
Transport Equipment Operators	98	18	47	0.94	0.46	1.91
Labourers Not Elsewhere Classified	99	14	22	**2.34**	**0.98**	**5.61**

a: Age, sex, recruitment site, smoking quantity and duration combined and daily alcohol drinking

Table 12. Association between occupations and HNSCC using five-digit ISCO codes

Occupation title	ISCO code	Case	Control	OR[a]	95%CI	
Telecommunications technician	03430	2	5	0.69	0.10	4.65
Mechanical engineering technician (motors and engines)	03520	1	1	2.54	0.05	119.45
Other engineering technicians	03990	1	1	12.11	0.73	201.34
General physician	06105	1	1	2.56	0.06	116.99
Professional nurse (general)	07110	1	4	0.30	0.03	3.44
Medical X-ray technician	07710	1	3	0.41	0.03	4.79
Computer programmer	08420	1	4	0.37	0.03	4.22
Other university and higher education teachers	13190	1	2	1.09	0.08	15.61
Languages and literature teacher (second level)	13215	2	5	1.11	0.17	7.45
Mathematics teacher (second level)	13220	1	6	0.70	0.06	8.00
Technical education teacher (second level)	13280	2	5	0.82	0.06	10.46
First-level education teacher	13320	3	9	2.08	0.45	9.58
Head teacher	13940	1	5	0.76	0.06	9.81
Other teachers	13990	1	9	0.48	0.05	5.07
Social welfare worker	19320	1	2	2.67	0.16	45.2
Culture centre worker	19330	1	2	5.43	0.46	63.55
Interpreter	19540	1	1	2.54	0.05	119.45
General manager	21110	3	8	0.61	0.12	3.06
Industrial relations and personnel manager	21980	1	1	1.15	0.04	30.57
Other managers	21990	3	9	0.69	0.15	3.07
Government executive official	31010	5	25	0.63	0.20	2.00
Bookkeeper (general)	33110	2	10	0.48	0.08	2.96
Bank teller	33140	1	3	0.60	0.05	7.39
Other bookkeepers, cashiers and related workers	33990	1	3	1.10	0.05	23.60
Postman	37030	1	3	1.05	0.07	15.62
Storeroom clerk	39140	4	18	0.72	0.20	2.64
Office clerk (general)	39310	2	10	0.35	0.06	1.96
Other receptionists and travel agency clerks	39490	1	1	5.23	0.27	102.48
Manager, wholesale trade	40020	1	1	2.44	0.07	82.27
Manager, retail trade	40030	1	1	1.42	0.06	34.26
Sales supervisor (retail trade)	42130	2	8	1.29	0.21	8.09
Technical salesman	43120	2	3	1.27	0.17	9.29
Commercial traveller	43220	1	4	0.33	0.03	3.72
Insurance salesman	44120	1	1	1.26	0.06	27.00
Advertising salesman	44230	1	2	0.44	0.03	6.31
Retail trade salesman	45130	9	33	0.59	0.24	1.49
Other salesmen, shop assistants demonstrators	45190	5	8	3.19	0.78	13.00
Street vendor	45220	3	4	0.75	0.08	6.73
Working proprietor (restaurant)	51030	2	2	1.93	0.22	17.41
Cook, except private service	53130	7	8	**5.22**	**1.64**	**16.67**
Waiter, general	53210	3	11	0.48	0.08	2.93

Bartender	53250	2	2	0.43	0.03	7.03
Nursemaid	54035	3	12	2.41	0.51	11.47
Other maids and related housekeeping ,service workers	54090	2	9	2.51	0.46	13.64
Concierge (apartment house)	55120	1	2	3.38	0.28	41.34
Charworker	55220	2	20	1.00	0.22	4.64
Other charworkers, cleaners and related workers	55290	1	1	4.29	0.16	115.99
Policeman	58220	1	5	0.39	0.03	4.50
Private police guard	58240	2	1	11.17	0.76	165.05
Watchman	58940	1	2	6.17	0.53	72.23
Other protective service workers	58990	1	1	1.77	0.06	53.96
Sightseeing guide	59130	2	2	3.37	0.27	41.67
Nursing aid	59940	2	9	0.71	0.12	4.19
Other service workers not elsewhere classified	59990	1	1	2.90	0.16	53.45
General farmer	61110	1	4	0.88	0.08	9.87
Field crop farmer	61220	4	14	0.71	0.16	3.1
Farm helper (general)	62110	4	12	0.43	0.12	1.59
Field crop farm worker (general)	62210	10	8	**3.90**	**1.13**	**13.4**
Sugar-cane farm worker	62260	10	18	1.48	0.53	4.09
Other field crop and vegetable farm workers	62290	1	1	11.66	0.69	196.76
Other livestock workers	62490	1	1	1.50	0.06	35.44
Gardener	62740	11	14	1.60	0.57	4.49
Motorised farm equipment operator	62820	2	4	0.38	0.06	2.39
Groundsman	62960	1	4	0.43	0.04	5.00
Inland and coastal waters fisherman	64130	8	7	2.96	0.74	11.9
Supervisor and general foreman, construction work	70075	1	13	0.23	0.02	2.28
Charcoal burner	74930	1	1	1.18	0.05	27.59
Butcher, general	77310	1	1	2.56	0.07	89.4
Baker, general	77610	1	1	1.94	0.06	65.07
Bread baker	77620	2	6	0.39	0.03	4.52
Pastry maker	77630	2	2	1.59	0.16	16.29
Cabinetmaker	81120	3	3	1.61	0.25	10.23
Blacksmith (general)	83110	1	2	0.98	0.05	18.55
Machine-tool operator (general)	83410	1	2	1.48	0.07	32.79
Automobile mechanic	84320	6	14	1.40	0.42	4.66
Other motor-vehicle mechanics	84390	1	1	3.10	0.08	116.32
Machinery mechanic (general)	84910	1	1	1.37	0.06	29.33
Agricultural machinery mechanic	84955	1	2	6.67	0.57	78.14
Maintenance electrician	85560	1	1	0.79	0.04	14.13
Plumber (general)	87105	5	9	0.84	0.22	3.18
Pipe fitter (general)	87110	4	5	0.93	0.18	4.98
Gas and electric welder (general)	87210	2	5	1.06	0.14	8.07
Vehicle sheet-metal worker	87370	2	1	2.33	0.06	94.98
Building painter	93120	6	13	0.45	0.13	1.52
Quality inspector	94980	1	1	2.56	0.07	89.4

Tile setter	95150	1	5	0.69	0.05	8.70
Reinforced concreter (general)	95210	22	36	1.70	0.82	3.53
Concrete shutterer	95220	1	5	1.15	0.12	10.78
Reinforcing iron worker	95230	2	2	1.81	0.16	21.15
Carpenter, general	95410	2	1	3.83	0.15	100.36
Construction carpenter	95415	1	2	0.91	0.05	17.08
Construction joiner	95420	1	5	1.64	0.18	15.00
Bench carpenter	95470	1	2	1.65	0.07	36.94
Housebuilder (general)	95910	3	5	0.68	0.10	4.62
Other construction workers	95990	2	1	**15.56**	**0.99**	**244.54**
Dockers	97120	1	4	0.28	0.03	2.77
Warehouse porter	97145	8	11	**2.50**	**0.8**	**7.81**
Hand packer	97150	1	4	1.08	0.08	15.59
Machine packer	97155	1	3	1.65	0.14	19.15
Other Dockers and freight handlers	97190	2	3	1.53	0.20	11.49
Lifting-truck operator	97920	3	4	**5.13**	**0.99**	**26.52**
Taxi driver	98530	2	3	0.75	0.09	6.18
Motor bus driver	98540	2	10	0.76	0.13	4.32
Lorry and van driver (local transport)	98550	12	29	1.10	0.46	2.62
Lorry and van driver (long-distance transport)	98560	1	3	0.88	0.06	14.12
Labourer	99910	14	22	**2.34**	**0.98**	**5.61**

a: Age, sex, recruitment site, smoking quantity and duration combined and daily alcohol drinking

Table 13: Association between industries and HNSCC using two-digit NAF codes

Industry title	Code NAF	Case	Control	OR[a]	95%CI	
Agriculture, hunting and related service activities	01	28	54	1.34	0.70	2.56
Fishing, fish farming and related service activities	05	8	8	2.62	0.68	10.09
	14	1	5	0.40	0.03	4.75
Manufacture of food products, beverages and tobacco	15	20	44	1.05	0.51	2.19
Manufacture of wearing apparel; dressing and dyeing of fur	18	1	3	3.02	0.28	32.58
Manufacture of wood and of products of wood and cork, except furniture; manufacture of articles of straw and plaiting materials	20	3	6	1.87	0.35	10.10
Publishing, printing and reproduction of recorded media	22	2	6	0.57	0.09	3.60
Chemical industry	24	3	8	0.79	0.16	3.86
Manufacture of rubber products	25	2	1	2.10	0.17	25.42
Manufacture of fabricated metal products, except machinery and equipment	28	7	6	**6.52**	**1.69**	**25.14**
Manufacture of machinery and equipment n.e.c.	29	2	5	0.93	0.11	7.68
Manufacture of medical, precision and optical instruments, watches and clocks	33	1	5	1.62	0.18	14.91
Manufacture of motor vehicles, trailers and semi-trailers	34	2	2	1.40	0.14	14.38
Manufacture of other transport equipment	35	2	4	2.28	0.30	17.48
Manufacture of furniture; manufacturing n.e.c.	36	4	7	1.94	0.38	9.79
Electricity, gas, steam and hot water supply	40	1	9	0.54	0.05	5.39
Construction	45	42	100	0.95	0.55	1.63
Sale, maintenance and repair of motor vehicles and motorcycles; retail sale of automotive fuel	50	14	33	1.26	0.54	2.90
Wholesale trade and commission trade, except of motor vehicles and motocycles	51	5	20	0.57	0.16	2.07
Retail trade, except of motor vehicles and motocycles and personal and household goods	52	20	67	0.67	0.33	1.33
Hotels and restaurants	55	13	32	1.03	0.43	2.47
Land transport; transport via pipelines	60	9	33	0.47	0.19	1.15
Water transport	61	2	1	3.51	0.18	67.63
Air transport	62	2	3	1.28	0.14	11.39
Supporting and auxiliar transport activities; activities of travel agencies	63	9	17	1.25	0.47	3.36
Post and telecommunications	64	4	30	0.34	0.10	1.10
"Financial intermadiationFinancial intermediation, except insurance and pension funding	65	1	14	0.13	0.02	1.16
Insurance and pension funding, except compulsory social security	66	1	6	0.28	0.03	3.23
Real estate activities	70	2	15	0.30	0.06	1.57
Rental without operator	71	1	5	0.52	0.05	5.86
Computer and related activities	72	3	3	0.72	0.09	5.90
Research and development	73	1	3	0.39	0.03	4.95

Other business activities	74	9	37	0.50	0.19	1.30
Public administration and defence; compulsory social security	75	48	147	0.76	0.46	1.27
Education	80	18	109	0.54	0.29	1.03
Health and social work	85	7	53	**0.29**	**0.11**	**0.76**
Activities of membership organizations n.e.c.	91	1	19	0.22	0.03	1.92
Recreational, cultural and sporting activities	92	4	25	**0.25**	**0.06**	**0.96**
Other service activities	93	4	7	2.38	0.49	11.66
Domestic services	95	17	37	2.12	0.96	4.68

a: age, sex, recruitment site, smoking quantity and duration combined and daily alcohol drinking

5 General discussion

5.1 Background

This doctoral thesis investigated at a wide panel of suspected and known HNC risk factors in an attempt to better understand the aetiology of these cancers in the French West Indies. This current work revealed new information on HNC epidemiology and clues for further investigations and prevention. This thesis was based on the first case-control study looking at these cancers in the French West Indies and therefore, we focused our analyses on the classical risk factors, tobacco and alcohol, and we had a particular interest in the role of HPV.

The population of the French West Indies presents an interesting framework for study for HNC in terms of risk factor distribution and ethno-geographic origins. HNC incidence is elevated in this region considering the smoking and alcohol drinking prevalence which is lower when compared to countries with similar incidence rates. In addition, the population comprises mostly persons of African descent and very few studies have investigated HNC epidemiology in this ethnic group, and to our knowledge this is the first study conducted in an Afro-Caribbean population. Furthermore, the participation of the local cancer registries further added to the methodological robustness of our study and ensured a representative capture of the cases.

5.2 Main findings

Regarding the secondary analysis on the data from the Baromètre Santé DOM survey, we were able to describe finely the distribution of tobacco, alcohol and obesity in the population and highlight significant social disparities. The intention of this investigation was to explain the particularities of HNSCC epidemiology in the FWI through the distribution of common cancer risk factors and produce data on a topic which was rarely studied in the Caribbean region. We found that the prevalence of tobacco smoking was significantly greater in women

of higher SES. Futhermore, harmful chronic alcohol use in men was significantly greater in the lower SES strata. Likewise, the prevalence of obesity was greater in both men and women of lower SES. Overall, the social distributions of risk factors observed for both sexes in the FWI coincided partially with previous studies from the Caribbean and mainland France [86–89]. Indeed, the previously described descriptive statistics on cancer incidence showed distinct trends between the French West Indies and mainland France despite having similar health care system [67]. In light of this current work, we have seen that this specific cancer epidemiology in the French West Indies is also reflected in the risk factor distribution and could be attributed to their economic development and the culture being midway between the Caribbean and mainland France [90].

Considering that this is first time that any aetiological research on HNC of this magnitude has been conducted in the FWI, a thourough investigation on the tobacco and alcohol was conducted initially to confirm their role in this population. Then the other risk factors were examined, notably oral HPV infection which was a key focus of my research in addition to traditional risk factors.

Concerning the results from the case-control study in the FWI, tobacco and alcohol indeed play a considerable role in HNSCC etiology and the majority of the cases in the FWI were attributable these factors. These findings were concordant with other studies which attributed more than 60% of cases to these two risk factors [19, 91, 92]. Analysis by HNSCC subsites did not reveal any significant difference in the effects of tobacco, alcohol contrarily to other reports which attribute greater role of tobacco and alcohol to the larynx [5].

The overall HPV prevalence in the general population was 26% and was higher than what was reported previously in other countries (4.7 to 17.3%) [30, 93–99]. Likewise, the prevalence by sex was also higher than reports from other countries. However, the HPV

distribution by sociodemographics coincided with other studies; HPV was more prevalent among men, persons between 45 and 65 years [96, 99]. Among HNSCC cases, the HPV prevalence was 36% and was similar to regions of Central and Latin America (33%) according to a recent meta-analysis [100] but notably higher than pooled estimates for populations of African descent (17%) [101]. We found that oral HPV infections were more frequent among cases who were never smoker or non-drinkers. The reverse trend was observed in the control group; the prevalence was greater in smokers and daily drinkers. These data on HPV prevalence were further supported by the detailed analysis we performed on the interactions with tobacco and alcohol. The analyses on oral HPV genotype are indicative of an ethno-geographic particularity of the HPV distribution. Unlike most studies which showed an elevated risk for HPV16 solely [102], we found that the other high-risk types were also very involved in HNC in the FWI [103]. The findings are consistent with a study on in Guadeloupe which highlighted a higher prevalence of Hr-HPV types other than HPV16 and HPV18 in the cervix of healthy women [70]. The viral factors linked to HNSCC presents opportunities for cancer prevention, notably because of the availability of the HPV vaccine [27].

HNSCC was associated high-risk oral HPV infections and 13% of the cases were attributable to these infections. Furthermore, the data on interaction between tobacco, alcohol and HPV from previous studies are inconclusive [30, 102, 104–107]. Our results are in favour of a less important role of tobacco and alcohol in Hr-HPV-positive HNSCC. In addition, we were able show evidence of significant negative interactions with alcohol on both the additive and multiplicative scale. These negative interactions were consistent with previous studies including a large study from IARC [106, 108]. However, despite non-significant negative interaction we found between tobacco and Hr-HPV, we cannot exclude tobacco as an independent risk factor in Hr-HPV-positive HNSCC as was suggested in another study [106].

Likewise, the effect of Hr-HPV was similar across the subsites; in contrast to previously described associations which were exclusively for the oropharynx [102, 106]. Indeed, despite inconsistency in the association related to HPV, we cannot completely complete rule out the involvement of Hr-HPV in the other subsites in this population.

Sexual behavior is thought to be involved in the causal pathway between oral HPV infection and the development of HNSCC; however previous work studying the association between sexual behavior and HNSCC have shown conflicting results [13, 30, 94, 108–113]. Therefore, we were interested in exploring sexual behavior as a risk factor of HNSCC. Our preliminary analyses revealed that condom use was significantly associated with a reduction in HNSCC risk. Contrarily to another study [114] our results did not allude to a mediating role of oral HPV infection in the effect of sexual behavior on HNSCC but rather an independent relationship. Given the risky behavior associated to HPV-positivity in cases and the lack of association among controls, we suspect there are other factors driving the causal pathway to HNSCC, such as HIV infections. In light of our findings, we believe that the underlying mechanism between sexual behavior and HNSCC in the French West Indies are yet to be elucidated and require further studies.

Family history, BMI and occupational exposures were also significantly associated to HNSCC and accounted for a smaller proportion of cases compared to tobacco and alcohol. Other studies which investigated these risk factors produced similar results in regards to their effect and their impact on HNC [32, 33, 58, 59, 115]. We found associations between HNSCC and some occupations and industries which were previously described in the literature. Cooks, construction workers, labourer and workers in the metal industry were significantly more likely to have HNSCC than persons who never worked in those occupations or industries [116–118]. The increased HNSCC risk among banana plantations workers is a new finding, as this occupation can only be investigated in a limited number of

populations, and requires further analysis, given the extensive use of chlordecone and other pesticides in banana farming in the French West Indies [119–121].

The current work on fruits and vegetables showed a confounding effect of tobacco and alcohol on the association between fruits and vegetable consumption and HNSCC risk. The inverse association we found for regular fruit and vegetable consumption coincided with past findings [122, 123]. The effect disappeared upon adjusting for these risk factors. We were able to highlight as well daily alcohol use as an effect modifier in this relationship between fruit and vegetable consumption and HNSCC. This result seems to be in line with a previous study where alcohol use dissipated the protective effect of serum retinol on HNSCC [124].

The previous studies on tea and coffee consumption are inconsistent. Although non-significant, the point estimates for tea and coffee were consistently below 1 in our study and suggestive of an inverse association with HNSCC. While there were quite a few studies which studied these factors [55–57, 91, 125], some of them reported positive associations which opposed what we found [56, 57, 91].

Table 14 provides a summary of the statistical associations that were found during the work for this thesis.

Table 14:Summary of statistical associations from the thesis

Risk factors	Statistical association			Interactions		
	Negative	None	Positive	Tobacco	Alcohol	Hr-HPV
Tobacco smoking			x		>+	<*
Alcohol drinking			x	>+		<*
HPV, Any		x				
HPV, High-risk			x	<*	<*	
At-risk occupations			x			
BMI, Low (<18.5)			x			
BMI, High (≥30)	x					
Diet rich in fruits and vegetables		x				
Coffee		x				
Tea		x				
Family history, any cancer		x				
Family history, HNC			x			
Hormone exposure	x					

> + : Joint effect significantly more than additive
< * : Joint effect significantly less than multiplicative

5.3 Strengths and limitations

Several limitations in this doctoral thesis should be considered. Firstly, the fact that we performed a secondary analysis on the Baromètre Santé DOM survey meant that we utilised that data for a purpose other than the one it was initially designed for. Consequently, we were limited in the manner in which we went about answering our research question on the social distribution of cancer risk factor in the French West Indies which would have benefitted from greater detail on tobacco and alcohol consumption and a longitudinal study design. Nevertheless, the survey provided a large sample that was representative of the general population [69, 72].

Concerning our case-control study, the small sample restricted the possibility of the types of analyses that we could perform and affected considerably the precision in our estimates. We had missing data for HPV in our sample which forced us to further reduce the sample size for some analyses. When we believed it was necessary, we used an imputation procedure to deal with missing data to avoid the loss of subjects.

Selection bias is thought to be kept to minimum in this study. The distribution by sex, age and cancer sites of the cases included in our sample was similar to that of the cases in the Martinique and Guadeloupe cancer registries. Our study population can thus be considered representative of the HNSCC cases in the French West Indies. In terms of the controls, the method used to select the control group was previously demonstrated to yield unbiased samples and controls could be considered representative of the general population of similar age and sex [75]. We confirmed the representativeness of the distribution for tobacco, alcohol, BMI and level of education in our control group to FWI population after comparison with the data from a Baromètre Santé DOM [69]. Sexual behaviour distribution in the control group

was conform to that of the general population after verification with data from a regional KABP survey [126].

The retrospective character of the case-control design could expose our analyses to several biases, notably recall bias. Furthermore, the use of oral HPV detection to assess the HPV status may have resulted in misclassification. Oral HPV detection has been shown to have good specificity but moderate sensitivity for HPV-positive HNSCC tumours [39]. In spite of the possible errors in classification, they are likely to be non-differential in regards to the case-control status.

6 Conclusion and perspectives

Despite a lower prevalence of tobacco smoking and alcohol drinking, it is clear that they are primary drivers for HNSCC in the French West Indies. High risk-HPV as well played a substantial role in the aetiology of HNSCC noted particularly by the significant modification of the effects of tobacco and alcohol. In addition, the particular HPV genotype distribution further raises clues to substantiate the high incidence of HNSCC in this population where the prevalence of the main risk factors is low. Associations with HNSCC were found also for family history, BMI and certain occupations, and together with tobacco and alcohol contributed to close to 90% of the HNSCC burden in the FWI.

Viral factors constitute an important lever for prevention and control of HNSCC and future studies should continue to focus on oral HPV especially in tumours and consider other viral biomarkers. Tumour samples from Guadeloupe are currently in our possession and we have the intention of pursuing these analyses in a subsequent phase of the study. In addition, sexual behaviour and the mode of transmission of HPV were unclear and should be examined more closely in this population.

The role of other risk factors such as occupational risks were associated with HNSCC but were not fully analysed and require further investigation. We possess detailed information from occupation-specific questionnaires covering a panel of occupations which are classically linked to HNSCC. These data were not used during the analyses for this thesis; however, they could be used subsequently to elucidate the exposures involved in HNSCC carcinogenesiss. Similarly, our results on hormonal factors alluded to a significant role in HNSCC however this analyses warrant further studies on a bigger sample to further substantiate the associations that we found.

About 10% HNSCC cases were not explained during this doctoral thesis and could be attributable to residual risk factors that were not taken into account for our study. In

particular, genetic factors and their interaction with environment are yet to be studied in our sample and could bring further clarification to HNSCC aetiology in the FWI. These types of analyses require a substantial amount of subjects in order to have sufficient power to detect significant differences, and are increasingly performed within consortia. Our small sample size is an inherent characteristic of studies in small populations. In the near future we would like to pursue analyses on HPV in tumour biopsies, as well as on genetic susceptibility and gene-environnement interactions. These genetic and biological factors will be mainly examined through pooled analyses within the INHANCE [127] and African Caribbean Cancer Consortium (AC3) consortia [128] that we are already members of.

Given the involvement of modifiable risk factors in HNSCC, there is great opportunity in the French West Indies to reduce the disease burden through tobacco cessation programmes and possibly HPV vaccination. Decision-makers and public health administrators should be aware of the specific cancer epidemiology of the French West Indies and thus, should be attentive to these particularites and advocate for further research and policies appropriate to this population and the Franco-caribbean context.

7 Résumé en Français

7.1 Introduction

Les voies aérodigestives supérieures (VADS) correspondent à la partie supérieure de l'appareil digestif et respiratoire et comprennent les cavités naso-sinusiennes, le pharynx, la cavité buccale et le larynx. La plupart des cancers des VADS sont des cancers de la cavité buccale, de l'oropharynx, et l'hypopharynx et du larynx et sont majoritairement des carcinomes épidermoïdes. Plus de 650 000 cas de cancer des VADS surviennent dans le monde chaque année. En Guadeloupe et en Martinique, les deux départements d'outre-mer des Antilles françaises, les taux d'incidence standardisés sur l'âge (monde) des cancers des lèvres, de la cavité buccale, du pharynx (hors nasopharynx) et du larynx pour 100 000 étaient de 8.1 en Guadeloupe (15.5 chez les hommes et 2.1 chez les femmes) et 5.7 en Martinique (12.1 chez les hommes et 0.6 chez les femmes). Ces taux d'incidence sont inférieurs à ceux de la France hexagonale, une zone bien connue d'incidence élevée. Ils sont en revanche parmi les plus élevés d'Amérique latine et des Caraïbes.

Les consommations de tabac et d'alcool sont les facteurs de risque majeurs de ces cancers, et leur effet conjoint est au moins multiplicatif. Le papillomavirus humain (HPV), en particulier de type 16 est une cause reconnue de cancers de l'oropharynx et de la cavité buccale, et suspectée de cancer du larynx. Les expositions professionnelles peuvent également jouer un rôle dans ces cancers. Des associations entre cancers des VADS et exposition professionnelle à l'amiante, aux HAP et aux solvants ont été mises en évidence dans plusieurs études, et des risques élevés de cancer des VADS ont été rapportés dans plusieurs professions ou industries. Les autres facteurs de risque connus ou suspectés d'être associés à un risque accru de cancer des VADS sont notamment un faible statut socioéconomique, une faible consommation de

légumes et de fruits, un faible indice de masse corporelle, et une mauvaise santé bucco-dentaire.

Dans la population antillaise, la prévalence du tabagisme est faible et la consommation d'alcool modérée. La prévalence de l'infection orale à HPV n'est pas connue. Les raisons de l'incidence relativement élevée des cancers des VADS aux Antilles restent à élucider.

7.2 Objectifs

L'objectif général de cette thèse était d'évaluer le rôle et l'impact de différents facteurs de risque sur la survenue des cancers des VADS aux Antilles françaises.

Dans un premier temps, en raison du manque de données publiées sur la prévalence des facteurs de risque comportementaux, une analyse secondaire des données d'une enquête transversale, le Baromètre Santé DOM, a été réalisée, afin de produire une description détaillée de la prévalence du tabagisme, de l'alcool et de l'obésité dans la population générale antillaise, en fonction du sexe, de l'âge et du statut socio-économique.

L'essentiel du travail de thèse s'est ensuite appuyé sur les données d'une étude cas-témoins en population sur les cancers des VADS menée aux Antilles françaises. Il s'agit de la première étude épidémiologique sur ces cancers dans une population afro-caribéenne. Un large éventail de facteurs de risque a été examiné, avec un intérêt particulier pour le tabagisme, la consommation d'alcool et l'infection orale à HPV. Plus précisément, les objectifs étaient :

- d'étudier et de quantifier les associations entre risque de cancer des VADS et facteurs comportementaux, viraux (infection à HPV) et environnementaux ;
- d'évaluer les éventuelles interactions entre ces facteurs,
- d'estimer l'impact des différents facteurs de risque dans cette population, en calculant des fractions de risque attribuables.

7.3 Matériel et Méthodes

Le Baromètre Santé DOM est une enquête transversale conduite en 2014 sur un échantillon représentatif de la population de Guadeloupe et de Martinique âgée de 15 à 75 ans (n=4054). Les données ont été pondérées pour tenir compte du plan de sondage à deux degrés et obtenir des estimations corrigées du biais des non-réponses par un calage sur les données du recensement. Les pondérations ont été prises en compte dans les calculs de prévalence, ainsi que dans les régressions de Poisson utilisées pour estimer des rapports de prévalence ajustés sur l'âge.

L'étude cas-témoins est une étude en population générale, conduite en Guadeloupe et en Martinique entre 2013 et 2016. Les cas incidents ont été identifiés avec la collaboration des registres des cancers. Les témoins ont été sélectionnés par une procédure d'appels téléphoniques au hasard. Le recrutement a été stratifié de façon à obtenir une répartition des témoins par âge, sexe et département comparable à celle des cas, et une répartition par catégorie socio-professionnelle comparable à celle de la population. Les cas et les témoins ont été interrogés par des enquêteurs spécialement formés, avec un questionnaire comprenant notamment les caractéristiques sociodémographiques, les consommations détaillées d'alcool et de tabac, la taille et le poids à différents âges, les antécédents médicaux personnels et familiaux, le comportement sexuel, et un historique professionnel complet. Du matériel biologique (salive à l'aide de kits Oragene et tumeurs) a également été recueilli. Une banque d'ADN des sujets de l'étude a été constituée à partir des prélèvements de salive. La recherche et le génotypage des HPV ont été réalisés à l'aide du test INNO-LiPA, qui permet la détection spécifique de 28 types d'HPV. Au total, 170 cas et 405 témoins ont été inclus dans l'étude. Les analyses ont été restreintes aux 145 cas de carcinomes épidermoïdes de la cavité buccale, de l'oropharynx, de l'hypopharynx et du larynx.

Les données ont été analysées principalement à l'aide de modèles logistiques. Les interactions ont été évaluées sur une échelle multiplicative et sur une échelle additive. Des imputations multiples ont été réalisées pour prendre en compte les données manquantes. Les proportions de cas attribuables ont été estimées à partir de l'odds-ratio et de la proportion de cas exposés

7.4 Principaux résultats

7.4.1 Tabagisme, consommation d'alcool et obésité dans la population antillaise

La prévalence du tabagisme (actuel et vie entière), de la consommation d'alcool (consommation quotidienne et consommation à risque chronique) et de l'obésité a été étudiée en fonction du sexe, de l'âge, et de plusieurs indicateurs socio-économiques (niveau d'études, catégorie socio-professionnelle, revenu et présence d'eau chaude dans le logement). Les prévalences du tabagisme et des consommations d'alcool étaient dans l'ensemble faibles, et plus élevées chez les hommes alors que la prévalence de l'obésité était élevée chez les femmes. L'étude a permis de mettre en évidence des disparités sociales spécifiques. Les femmes de statut socioéconomique élevé étaient plus souvent fumeuses, alors que la consommation d'alcool chez les hommes et l'obésité chez les femmes étaient inversement associées au statut socioéconomique.

7.4.2 Prévalence de l'infection orale à HPV dans la population générale et les cas de cancer des VADS

La prévalence des infections orale à HPV, globale et par génotype, a été estimée à partir des données de l'étude cas-témoins. La prévalence de l'HPV tous types confondus était de 26 % chez les témoins et de 36 % chez les cas de cancer des VADS. La prévalence des infections à HPV à haut-risque oncogène (Hr-HPV) a été estimée à 10 % chez les témoins et à 23 % chez les cas. Le génotype le plus fréquemment détecté était HPV52, l'infection à HPV16 ne concernait que 4 cas et deux témoins. La prévalence d'HPV16, HPV33 et HPV51 était significativement plus élevée chez les cas que chez les témoins. L'infection orale à Hr-HPV

était associée à une augmentation du risque de cancer des VADS. HPV-16 n'était associé qu'au cancer de l'oropharynx. Cette étude a mis en évidence une prévalence élevée de l'infection orale à HPV dans la population et une distribution par génotype spécifique.

7.4.3 Effets conjoints du tabac, de l'alcool et de l'infection orale à HPV sur le risque de cancer des VADS

Le rôle des consommations de tabac et d'alcool dans la survenue des cancers des VADS a été examiné de façon détaillée, ainsi que les interactions entre ces facteurs et avec l'infection orale à HPV. Le tabac et l'alcool étaient significativement associés au risque de cancer des VADS. Le risque augmentait avec quantité journalière de tabac, la durée du tabagisme et avec le nombre de verres d'alcool par jour. Un effet synergétique du tabac et de l'alcool significatif a été mis en évidence. L'infection orale à Hr-HPV augmentait le risque de cancer des VADS, particulièrement chez les non fumeurs et les non buveurs. Les effets du tabac, de l'alcool et de l'exposition combinée au tabac et à l'alcool étaient nettement plus faibles chez les sujets HPV positifs que chez les sujets HPV négatifs.

7.4.4 Fractions de cancers des VADS attribuables aux différents facteurs de risque

Outre le tabac, l'alcool et l'infection à HPV, d'autres facteurs de risque ont été étudiés. Un faible indice de masse corporelle et l'existence d'antécédents familiaux de cancer des VADS étaient associés à une augmentation significative du risque cancer des VADS. Des risques élevés de cancer des VADS ont également été observés dans plusieurs professions ou industries : cuisiniers, travailleurs de la construction, manœuvres, ouvriers agricoles de la banane, travail des métaux. En revanche, aucune association avec l'alimentation, en particulier la consommation de fruits et légumes, n'a été mise en évidence. Les proportions de cas attribuables aux différents facteurs de risque ont été calculées. La majorité des cas étaient attribuables au tabac (63 %) et à l'alcool (55%). Les proportions de cas attribuables à l'alcool et au tabac étaient cependant bien plus faibles chez les femmes (21 % et 24 %) que

chez les hommes (73 % et 60%). Environ 14% des cas étaient attribuables à l'infection orale à Hr-HPV. Les proportions de cas attribuables aux autres facteurs étaient de 27% pour les expositions professionnelles, 12% pour l'indice de masse corporelle et 7 % pour les antécédents familiaux. Au total, 90% des cancers des VADS, 94 % chez les hommes et 65 % chez les femmes, étaient attribuables aux facteurs de risque étudiés. En outre, chez les femmes, un âge aux premières règles supérieur à 13 ans était associé à un risque augmenté de cancer des VADS ; la fraction de risque attribuable globale passait à 91% après la prise en compte de ce facteur. Dans l'ensemble, ces résultats mettent en évidence l'importance des facteurs de risque modifiables dans la survenue des cancers des VADS aux Antilles.

7.4.5 Comportement sexuel et risque de cancer des VADS

La transmission par voie sexuelle étant impliquée dans l'infection orale à HPV, les associations entre comportement sexuel et risque de cancer des VADS ont également été examinées. L'absence d'utilisation du préservatif et un délai de moins de 6 mois depuis le dernier rapport étaient associés à une augmentation significative du risque. Le risque diminuait avec l'âge au premier rapport. Cependant, ces associations n'étaient pas modifiées après ajustement sur l'infection orale à Hr-HPV. Aucune augmentation de risque associée aux rapports oro-génitaux n'a été mise en évidence. Bien que certains comportements sexuels soient associés au risque de cancer des VADS, l'infection à HPV ne semble pas jouer de rôle médiateur dans ces associations.

7.5 Conclusion et perspectives

Les travaux réalisés ont permis d'explorer un large spectre de facteurs de risque. D'autres travaux de recherches sont à prévoir. L'analyse des HPV dans les tumeurs, prévue à court terme, permettra de mieux comprendre le rôle de ces virus dans la survenue de ces cancers. Certains facteurs de risque n'ont pas été ou n'ont été que partiellement étudiés, comme les antécédents médicaux, les expositions professionnelles et l'alimentation. L'étude des facteurs

de susceptibilité génétique et de leur interaction avec les facteurs environnementaux pourrait certainement apporter des informations pertinentes dans cette population majoritairement Afro-Caribéenne. En raison de la faible taille de notre échantillon, qui est la limite principale de notre étude, ces facteurs devront être étudiés dans le cadre d'analyses groupées au sein de consortiums.

Dans l'ensemble, ces travaux de thèse ont permis de produire de nouvelles connaissances sur l'étiologie des cancers des VADS aux Antilles Françaises, avec des implications potentiellement importantes pour la santé publique. Etant donné le rôle prépondérant des facteurs de risque modifiables, de nombreuses opportunités de prévention se présentent, notamment des programmes d'arrêt de tabac et éventuellement la vaccination contre HPV.

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UNIVERSITE BIOLOGIE BRETAGNE SANTE LOIRE

UNIVERSITÉ DE RENNES 1

Titre : Epidémiologie des cancers des voies aéro-digestives supérieures aux Antilles Françaises : Facteurs de risque comportementaux, viraux et environnementaux

Mots clés : Cancers des voies aéro-digestives supérieures ; étude cas-témoins; tabagisme; consommation d'alcool; papillomavirus humain; Antilles françaises

Résumé :

L'objectif était d'évaluer le rôle de différents facteurs de risque dans la survenue des cancers des voies aéro-digestives supérieures (VADS) aux Antilles françaises. Dans un premier temps, nous avons utilisé les données d'une enquête transversale sur la santé pour décrire la prévalence du tabagisme, de la consommation d'alcool et de l'obésité, et mis en évidence des disparités sociales. Nous avons ensuite analysé les données d'une étude cas-témoins menée en Martinique et en Guadeloupe entre 2013 et 2016, comprenant 145 cas de cancers des VADS et 405 témoins. Une prévalence élevée d'infection orale par le papillomavirus (HPV) a été mise en évidence, avec une distribution par génotype spécifique, en particulier une faible fréquence d'HPV16. L'infection orale aux HPV à haut risque (Hr-HPV) était associée à une augmentation significative du risque de cancer des VADS. Les consommations de tabac et d'alcool augmentaient fortement le risque de cancer des VADS, avec un effet combiné synergique.

Un faible indice de masse corporelle (IMC), des antécédents familiaux de cancer des VADS, et plusieurs activités professionnelles étaient également associés à un risque accru. L'utilisation du préservatif diminuait le risque, indépendamment de l'infection à Hr-HPV. Chez les femmes, un âge précoce aux premières règles était associé à une diminution du risque. Les consommations de thé, de café, de fruits et de légumes n'étaient pas associées au cancer des VADS.

Dans la population, la majorité des cas de cancers des VADS étaient attribuables au tabagisme (62,5 %) et à l'alcool (55,4 %). Environ 14 % des cas étaient attribuables à l'infection orale à Hr-HPV, 11 % à un faible IMC, 27 % à la profession et 7 % aux antécédents familiaux. Étant donné l'impact prépondérant des facteurs modifiables, de nombreuses opportunités de prévention des cancers des VADS se présentent dans cette population.

Title : Epidemiology of cancers of the upper aero-digestive tract in the French West Indies: Behavioral, viral and environmental risk factors

Keywords : Head and neck cancer ; case-control study ; tobacco smoking ; alcohol drinking ; human papillomavirus ; French West Indies

Abstract: The objective was to assess the potential influence of a large spectrum of risk factors on head and neck cancer (HNC) development in the French West Indies (FWI). As a first step, we used data from a cross-sectional
health survey to describe the prevalence of tobacco smoking, alcohol drinking and obesity. This work highlighted significant social disparities in these risk factors in the population.

We then analysed data from a population-based case-control study conducted in Martinique and Guadeloupe between 2013 and 2016, including 145 cases of HNC and 405 controls.

The study revealed a high prevalence of oral infection with human papillomavirus (HPV) in the population, and a specific distribution of HPV genotypes. HPV52 was the most prevalent type and HPV16 was found in only 4% of cases. Tobacco smoking and alcohol drinking increased the risk of HNC, with a synergetic combined effect.

High risk HPV (Hr-HPV) was associated with a significant increase in HNC risk, particularly in non-smokers and non-drinkers. Elevated risks of HNC were found in several occupations. A low body mass index (BMI) and family history of HNC were also associated with an increased risk of HNC. Condom use was found to decrease the risk of HNC, independently of oral HPV. In women, exposure to hormones, notably having menarche before 13, was associated with a decrease in HNC risk. Consumptions of tea, coffee, fruits and vegetables were not associated with HNC.

In the population, the majority of HNC cases were attributable to tobacco smoking (62.5%) and alcohol (55.4%). About 14% of the cases were attributable to Hr-HPV, 11% to low BMI, 27% to occupation and 7% to family history of HNC. Given the predominant role of modifiable factors in HNC aetiology, there are many opportunities for prevention in this population.