



Oral cancer in Papua New Guinea: looking back and looking forward

Rose Andrew Kelwaip, BDS, MPH,^a Seth Fose, MBBS,^{a,b} Mahmood S. Siddiqui, BDS,^c Charles P. Molumi, MBBS, MSc,^b Laurence M. Apaio, BDS, MDS,^c David I. Conway, FDS, DPH, RCS, PhD,^d Newell W. Johnson, CMG, FMedSci,^e Steve J. Thomas, PhD, FRCS,^f Daniel W. Lambert, BSc, PhD,^g and Keith D. Hunter, PhD, FRCPath^g

Oral diseases, including cancers, affect 3.5 billion people globally and remain largely untreated in low- to middle-income countries because of lack of resources. In Papua New Guinea (PNG), oral cancer has, for many decades, been identified as the most common cancer in men, but as the GLOBOCAN 2018 data are estimates extrapolated from surrounding countries, the real prevalence of this disease is not known. The PNG National Health Plan (2011–2020) highlights the need to improve health care, but oral health is not identified as a priority. Alcohol, tobacco, and areca nut/betel quid, which are the social and commercial determinants of oral cancer, are common risk factors, and there are robust data linking these risk factors to oral cancer in PNG. Our recent Global Challenges Research Fund Workshop on Oral Cancer, held in Port Moresby, PNG, brought together a number of researchers in oral cancer epidemiology and translational science with clinicians from PNG to assess the current situation and plan ways to move forward. In this article, we will review the literature on oral cancer in PNG, and make suggestions as to how, collaboratively, we can address the issues identified, ultimately, for the benefit of the people of PNG. (*Oral Surg Oral Med Oral Pathol Oral Radiol* 2020;130:292–297)

Oral cancer (OC; International Classification of Diseases-10, C00-06, thus including the posterior third of the tongue¹) is an important cause of morbidity and mortality with an estimated 354,000 new cases occurring annually worldwide, over two-thirds of them in men (GLOBOCAN 2018²). The importance of this as a component of the global health challenge that oral diseases present has been highlighted in a series of articles in *The Lancet*.³ There are marked international variations in the reported incidence rates for OC, and in many iterations of global cancer incidence data, Melanesia, a grouping of independent states in the South Pacific, has been indicated as the area of the world with the highest incidence rates of oral cancer. This region encompasses Vanuatu, Solomon Islands, Fiji, and Papua New Guinea (PNG), in addition to New Caledonia, and the Indonesian region of Western New Guinea (Figure 1). PNG is the largest of these states/regions and is an exceptionally culturally diverse nation, with a population of around 8 million. It is primarily a nonurban society, with many hundreds of languages. Access to many parts of the country is

very limited because of lack of infrastructure and dissemination of public health information is challenging because of low levels of adult literacy. Life expectancy at birth is around 64 years (2017), and infant mortality rates are high, largely as a result of the prevalence of preventable diseases, such as malaria, tuberculosis, and infant sepsis.^{4–8} These problems are likely to escalate in the coming years because of the increasing prevalence of communicable diseases in an expanding population, together with decreased spending on health care provision, which was less than 2% of the country's gross domestic product in 2016.⁹ Oral health is particularly poor, with high levels of dental caries, periodontal disease, facial trauma, and problems associated with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), and oral cancer.⁸ Oral health has not been identified as a priority in PNG's health care policy, as reflected by only a passing mention in the current PNG National Health Plan (2011–2020).¹⁰ There is a profound shortage of dentists, dental therapists, and specialists, such as oral surgeons and pathologists—a situation compounded by the lack of a national dental plan. In this article, we will review the literature on oral cancer in PNG in view of a Global Challenges Research Fund (GCRF)—funded workshop held in Port Moresby, PNG, in June 2019, and make suggestions as to how, collaboratively, we can start to address the issues identified, ultimately, for the benefit of the people of PNG.

^aNational Department of Health, Port Moresby, Papua New Guinea.

^bPort Moresby General Hospital, Port Moresby, Papua New Guinea.

^cUniversity of Papua New Guinea, Port Moresby, Papua New Guinea.

^dGlasgow Dental School, University of Glasgow, Glasgow, UK.

^eMenzies Health Institute Queensland & School of Dentistry and Oral Health, Griffith University, Australia and Faculty of Dentistry, Oral and Craniofacial Sciences, King's College London, London, UK.

^fBristol Dental School, University of Bristol, Bristol, UK.

^gSchool of Clinical Dentistry, University of Sheffield, Sheffield, UK.

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EPIDEMIOLOGY

According to GLOBOCAN 2018 estimates, Melanesia has the highest incidence of oral cancer in the world

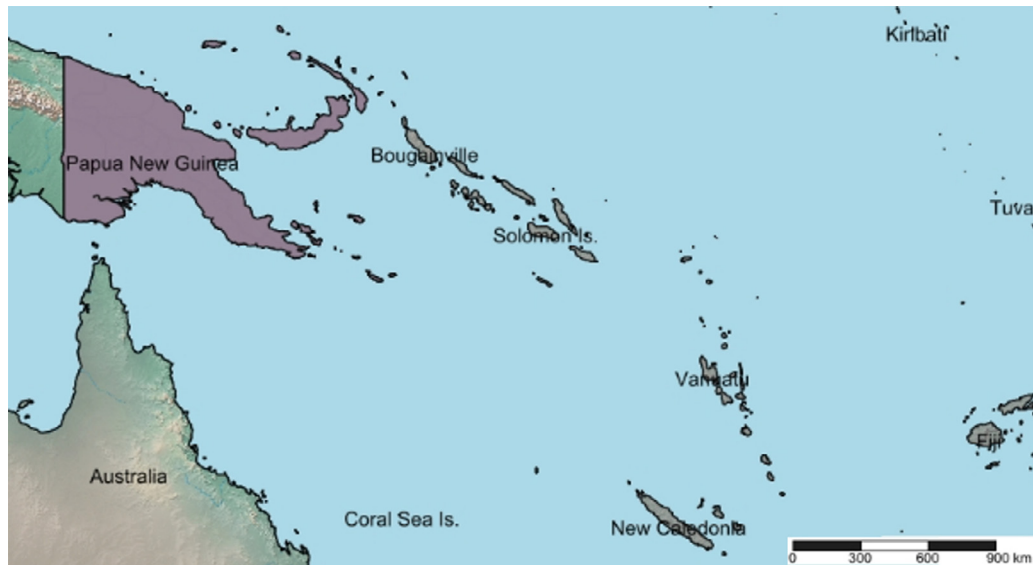


Fig. 1. Schematic map of Melanesia, with Papua New Guinea highlighted.

(36.3 per 10^5 men per annum and 23.6 per 10^5 women), and oral carcinoma is the most common cancer in PNG.² The incidence rates are also high across South Asia.^{11,12} The main issue with the GLOBOCAN data for PNG is that all data are estimates because they were extrapolated from data on the neighboring countries and the cancer registries in the same region. Analyses based on data collected until 1988 confirmed that oral cancer was the most common cancer in men, and the second most common in women.¹³ These data also indicated that the geographic spread of oral cancer cases was changing, with a relative 5-fold increase in the highland region, which had previously reported rates lower than those in lowland areas. The possible explanations for this are numerous but include better physical access into the highland regions (with migration resulting in changes in the risk factor profile) and better cancer registration processes. Nevertheless, even these historical data are based on tissue diagnoses, not on true population data, and this raises questions as to how representative they are of the whole population.¹⁴ No cancer registry data have been collected at all since 2011.

RISK FACTORS

Tobacco, both smoked and smokeless (usually chewed or used as snuff), has been consistently associated with increased risk of oral cancer, but smoking patterns do not adequately explain geographic variations in its incidence in PNG.¹⁵ A further risk factor that may explain these variations in disease incidence is the chewing of betel quid (referred to as “buai” in PNG). Betel quid constituents vary across cultures in South East Asia and the Pacific but generally consist of Areca nut (the endosperm

of the *Areca catechu* palm tree), parts of the *Piper betle* vine (inflorescence, leaf, or stem), and slaked lime (either as a powder or a paste). The addition of tobacco and spices that are common in other regions of South Asia, has not been reported in PNG.^{16,17} Lime is largely derived from river shells in inland areas and from coral in coastal regions, and its composition may be another determinant of oral cancer risk.^{16,17}

Oral cancer data from PNG are scant and not current; thus, the information in GLOBOCAN 2012 and 2018 is extrapolated from neighboring island nations. GLOBOCAN oral cancer data also include data on lesions from the oropharynx (e.g., base of the tongue) that may be associated with human papillomavirus (HPV) infection, thus adding interpretive difficulties to the data. Much of the available data on true oral cavity tumors were gathered in the 1980s and 1990s when one of the authors (S.T.) was working as an oral and maxillofacial surgeon in New Ireland, PNG. A large case-control study was undertaken in 6 lowland and island provinces of PNG (in 143 oral cancer cases with 477 controls) where the use of buai is common: This quid does not contain tobacco, and tobacco smoking and betel quid exposure were accurately recorded.¹⁸ This study was later complemented by a case-control study nested in a cross-sectional study of oral leukoplakia, which included 1670 adults.¹⁹ The results of these studies were integrated with systematic reviews of risk factors for oral cancer and precancer.^{18,19}

The use of betel quid without the addition of tobacco is associated with oral cancer development in a dose-related manner, but the highest risk in the PNG population was found in those who used betel quid *and*

smoked tobacco.¹⁸ The risk of oral cancer in those who smoked tobacco *and* chewed betel quid was 4.85 (95% confidence interval [CI] 1.10–22.25) with those who neither smoked nor chewed betel quid. The odds ratio (OR) associated with betel chewing was 2.03 for current users (95% CI 1.01–4.09), and 2.63 for current daily smokers (95% CI 1.32–5.22), with a higher OR in heavy users of either risk factor.

In similar analyses, the OR for leukoplakia in those who chewed betel quid but did not smoke was 3.9 (95% CI 1.3–11.5); in smokers who did not chew betel quid, it was 6.6 (95% CI 1.5–29.3); and in those who both smoked tobacco and chewed betel quid, it was 24.3 (95% CI 8.7–67.4), relative to those who neither smoked nor chewed betel quid currently. Oral cancer and leukoplakia in PNG are concentrated at the corner of the mouth and cheek, in striking contrast to Western populations (most commonly concentrated at the lateral and ventral tongue or floor of the mouth), and corresponded precisely with the site of application of lime in 77% of 169 cancer cases earlier described by Thomas and MacLennan.¹⁷

DISTINCTIVE BIOLOGIC FEATURES OF ORAL CANCER IN PNG

These epidemiologic studies have been linked to a series of laboratory studies exploring the possible causative mechanisms and molecular biology of oral cancer. The free calcium hydroxide content and pH of 25 PNG lime samples were highly correlated with the generation of reactive oxygen species from a range of areca nut extracts *in vitro*, and DNA damage *in vitro*, measured as 8-hydroxy-2'-deoxyguanosine.¹⁶ In a field study, powdered slaked lime applied to the chewed Areca nut with *Piper betle* inflorescence at the corner of the mouth caused the mean saliva pH to rise to almost 10,¹⁷ at which level reactive oxygen species are generated from betel quid ingredients *in vitro*. Reactive oxygen species, together with sustained lime-induced cell proliferation, suggest a possible mechanism of carcinogenesis for this tumor.

Mutations of the *p53* gene in the conserved mid-region (exons 5–9) are a common feature of oral cancers in the developed world,²⁰ but far fewer genetic lesions of this type were found in PNG.²¹ Mutations were found in 3 of 30 oral cavity tumors from PNG (10%), whereas 9 mutations were detected among the 20 tumors (45%) from the United States ($P < .01$). The presence of HPV DNA in the PNG cases was examined by using polymerase chain reaction, and viral DNA (HPV strains 11/16) was detected in 2 tumors (6.7%),²¹ a rate very similar to that reported in oral cavity cancers generally when robust criteria are applied.²² Thus, there are very important questions as to the pathobiology of oral cancer in PNG. However, given the global

changes in HPV-associated cancers of the oropharynx, the role of HPV may still be an interesting topic to explore further. These issues are compounded by the inclusion of many oropharyngeal tumors within International Classification of Diseases-10 C00-C06, which makes interpretation of much of the data rather difficult, given the recent separation of HPV-positive tumors of the oropharynx in the current World Health Organization (WHO) classification.²³

THE CURRENT SITUATION: THE 2019 WORKSHOP IN PORT MORESBY

Funded by the Global Challenges Research Fund (GCRF; <https://www.ukri.org/research/global-challenges-research-fund/>), we arranged a 2-day workshop in Port Moresby in June 2019 to create a forum for discussion of the current issues in oral cancer in PNG and to attempt to derive a way forward (Figure 2). GCRF is an initiative of the UK Government, with a £1.5 billion fund announced in late 2015, to support cutting-edge research to address the challenges faced by developing countries. Research supported under this scheme focuses on development-led projects, as defined by the United Nations Sustainable Development Goals for 2030. As implemented in the GCRF, these goals include equitable access to sustainable development (including sustainable health and well-being), issues that are indivisible from the wider context of human rights and good governance.

After an opening address from the Deputy Health Secretary (Dr. Dakulala), the first day sessions included a number of plenary presentations, focusing on the following: the main health care challenges in PNG; challenges in cancer in PNG (Dr. Goa Tau, Chief Medical Officer; and George Otto, National Cancer Manager); diagnostics and laboratory facilities (Dr. Seth Fose, Chief Pathologist); presentations on the surgical management of head and neck cancer from an ENT perspective (Dr. James Naipao, Chief ENT Surgeon); and Oral and Maxillofacial Surgery (OMFS)/dental perspective (Dr. Matupi Apiao and Dr. Rose Andrew Kelwaip). A summary of the proposed National Dental Plan was presented by Dr. Elenise Falealuga (Chief Dental Officer). These presentations formed the basis for the identification of topics and issues for further discussion on the second day.

From these presentations, despite the enthusiasm of the delegates, it became evident that oral health, including oral cancer, is not high on the national health priorities of PNG and that oral health is not mentioned in the current National Health Plan (2011–2020).¹⁰ Furthermore, the lack of a national dental plan has been problematic, and a number of the work-streams required to develop this have stalled. The challenges to provide diagnostic, surgical, and oncologic services for



Fig. 2. Group photograph of delegates at the Global Challenges Research Fund (GCRF)–funded workshop “Oral Cancer in Papua New Guinea,” held in the Stanley Hotel Port Moresby, Port Moresby, Papua New Guinea, June 2019.

patients with oral cancer in this context are great: These services are reaching only a fraction of the patients with oral cancer. Histopathology services are particularly under pressure because there is one central histopathology laboratory for the country situated at Port Moresby General Hospital (PMGH; Port Moresby, PNG), which reports receiving around 5000 cytology specimens and 5000 surgical specimens per year. The logistics of this are staggering: Specimens need to be sent by air to Port Moresby, but most often the samples are sent in batches because of financial constraints; thus, timely provision of a pathology report is almost impossible. The ENT and OMF surgical services in Port Moresby provide a surgical oncology service for head and neck cancers but are unable to meet the clinical demand because of the large number of cases. Radiotherapy is only available at the Angau Memorial Hospital (Lae, PNG), where it is based on Cobalt-60 technology, and the service has been hampered in recent years by the lack of consistent support from a radiation oncologist. However, it is not all bad news: A new comprehensive cancer center is currently under construction at Port Moresby General Hospital (Port Moresby, PNG) and is expected to open within the next year.

The key issues that were identified for discussion and planning are discussed below.

Public Health and Primary Prevention

Dental officers from the National Department of Health have undertaken a number of public health programs/interventions in recent years. One of those programs is the “No Betel-Nut Chewing Day” as part of the

Awareness Against Oral Cancer and Promoting Healthy Mouth initiative. It is not clear how effective such programs have been, and indeed, resistance to the “no betel nut” message has been encountered frequently. We discussed upstream (legislative), mid-stream (society), and downstream (clinical/community) approaches to control of the sale of areca/buai and tobacco in the country.

A Tobacco Control Act is in place in PNG, but there is no primary taxation on tobacco. Also, there is a ban on the sale of buai in the National Capital District, but it has not been fully implemented or enforced, and there is no consistent government position on control of the sale of betel nut/buai. This is very difficult, given the societal and economic considerations (including the roles of these products in the local agricultural economy and their cultural roles). The interaction of areca/buai with tobacco (and alcohol) is also important to consider in terms of prevention, but the associated public health interventions are very complex, and this necessitates learning and adoption of successful programs elsewhere in South East Asia.²⁴ Education, in schools and in other community facilities, has a key role to play in addressing the risk factors for oral cancer.²⁵ Community workers need guidelines to apply in school and community settings to fill gaps in information with regard to betel nut use. There is also a role for individual health interventions in a clinical setting and m-health/e-health, given the widespread use of smartphones. There are opportunities for informal screening in primary medical care contexts. The implementation of a national dental plan will be key to making progress in this area. Raising the overall awareness of oral

health within the National Department of Health, will allow for lobbying with the Health Minister to seek support for further action and funding. There is a need for enforcement of penalties, but whether this is realistic is open to debate, as is the need for evaluating the effectiveness of current and past interventions.

There are many transnational initiatives in this area, including HEADSpAcE (<https://headspace.iarc.fr/>), focusing on the poor prognosis for patients with oral cancer; strategies for diagnosis, including assessment of lifestyle; and the effect of infectious and genetic factors on poor clinical outcome. The engagement of PNG with such a project has a number of advantages both for PNG and for the global oral cancer community, given the challenges outlined above.

Cancer Registration and Data

There was a discussion on the background to the current lack of country-specific cancer incidence data for PNG, the reasons for which are complex and multifactorial. There are some data for 2007–2011 but not for the subsequent period, and this issue applies to all cancers, not just oral cancer. It is very difficult to plan clinical services for a country with no accurate data, as is currently the case with PNG. Trends which were noted in the data in the 1990s (and earlier) require to be followed up. In particular, confirming the data relating to the changes in the geographic spread of oral cancer would be very interesting, as the most recent data (and subsequent reporting from the field) have suggested an increasing incidence in the highland area of PNG.¹³

A key element of progress in this subject will be engagement with the International Agency for Research on Cancer/WHO Regional Hub (<http://gicr.iarc.fr/hub/pacific-islands/>) to be activated later in 2020. However, it would be prudent to start with a demonstration project in registry to get this restarted, and this will be taken forward into the planning of further projects.

International Collaborative Projects in Epidemiology and Potential for Tissue-Based Research

The workshop participants discussed the need to follow up on the many interesting observations from earlier research on tumor biology and to explore emerging areas of interest, such as the role of the tumor microenvironment (including stromal cells, such as fibroblasts and immune cells). The topics included the relative absence of *p53* mutations, as shown in the earlier work by Thomas²¹. There are also interesting questions regarding the role of HPV and comorbidities associated with HIV infection. Data on oral cancer in PNG have been collected and are stored in Australia, and interaction with current international initiatives, such as the

Voyager sequencing initiative, may allow these specimens to be used to provide preliminary data which could be used to leverage funding for subsequent work. We also discussed, at length, the possibility of new collections of oral cancer cases from the PMGH pathology archive. Such new collections will need to be based within a truly collaborative project space with due involvement and acknowledgment of PNG clinicians and researchers in the design of projects, intellectual property, use of clinical samples, and resulting publications.

Skills, Resources, and Training

A key element of making sustainable progress is to enhance the skills and resources of health care providers in PNG because long-term solutions to these issues must be generated locally by those who understand the culture and health problems in PNG. In addition to the Medical School at the University of Papua New Guinea (UPNG), much of the specialist medical training (in the widest sense) is provided outside of PNG, most notably in Australia, which is much more convenient than training in the United Kingdom or the United States. There are, however, significant possibilities for provision of training, largely in research (but also in clinical practice), and discussions are needed for the creation of doctoral and/or visiting scholarships. This will need to involve the School of Medicine and its Division of Dentistry at the UPNG, and this was discussed with the Executive Dean of Medicine, UPNG, during a visit to PNG.

Such initial informal links must be followed by a meaningful Memorandum of Understanding (MOU) between overseas universities and the UPNG, and we have started discussions at the faculty level on a doctoral study network between the United Kingdom (Sheffield) and the UPNG faculties, in addition to Griffith University in Australia, to increase the capacity and skills of PNG clinicians. However, it is also very important to maintain existing relationships, for example, those between the Royal College of Pathologists of Australasia and the UPNG/PMGH. These links are being explored further to allow training in pathology (specifically oral pathology) and to create opportunities for scholarships.

CONCLUSIONS

In summary, to make progress in tackling oral cancer in PNG, particular attention must be paid in the short to medium term, to gathering of accurate data on the incidence of oral cancer in PNG. This should be facilitated by the work of the WHO Pacific Hub, but more work on the ground with historical (pathology-based) data is required. Completion and adoption of an overall national dental plan will give the impetus to making

improvements in public health interventions and diagnostics (both clinical and laboratory).

The current situation regarding oral cancer in PNG is critical, and progress has been hampered by the lack of robust data on the incidence of oral cancer. Engagement of the global community with the health care system in PNG, with vital input from nongovernmental organizations, such as the WHO and the International Agency for Research on Cancer, will be required to effectively address the issues we have discussed here. However, the solutions are not likely to be quick: Infrastructural and resource limitations mean that those willing to help may have to commit significant time and effort to see any progress, which is so desperately required.

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Reprint requests:

Professor Keith Hunter
Academic Unit of Oral Medicine and Pathology
School of Clinical Dentistry
University of Sheffield
Claremont Crescent
Sheffield S10 2 TA
UK
k.hunter@sheffield.ac.uk