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International variation in the incidence of oral and pharyngeal cancer

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Objective: An accurate epidemiological profile is a crucial component of any cancer strategy. The ongoing development of population-based cancer registries provides an invaluable information resource in this regard. Examination of international incidence levels indicates substantial geographical variation. This study assesses the precise extent of such variation. ***Basic Research Design:*** The age-standardised rates (ASRs) for oral and pharyngeal cancer (OPC) were analysed for 183 registries in the IARC/WHO publication CIFC - Volume VII. ***Results:*** The median annual age-standardised incidence rates were mouth (2.3 per 100,000), tongue (2.0), lip (1.2), and salivary gland (0.6); the corresponding female rates were mouth (0.8), tongue (0.7), salivary gland (0.4) and lip (0.2). A substantial level of heterogeneity existed between registries in most instances. In the case of males, the highest ASR and the inter-quartile range of ASRs were as follows – mouth (highest rate of 12.4 per 100,000; IQR 1.4 to 3.6), tongue (max. 8.0; IQR 1.1 to 2.9), lip (max. 13.5; IQR 0.3 to 2.4) and salivary gland (max. 4.2; IQR 0.4 to 0.8). Corresponding statistics for females were also recorded. Comb graphs are used to highlight the significance of specific geographical-based trends and putative aetiological factors explored. ***Conclusions:*** This study reveals substantial international variation in the incidence rates of OPC, with up to 20-fold variation between countries in annual incidence rates for individual sites. The novel presentational technique makes this information readily accessible to non-specialists and highlights the need for disaggregation in future OPC studies.

Key Words: Age-standardised rates, CIFC, epidemiology, geographical based trends, international incidence rates, oral and pharyngeal cancer, variation.

Introduction

Cancer inflicts a formidable physical, psychological and socio-economic burden on patients, their families and on health care providers. This is particularly true for oral and pharyngeal cancer (OPC), which accounts for over 575,000 new cases each year and is directly responsible for c.200,000 deaths annually (Robinson & Macfarlane, 2003). The establishment of an accurate epidemiological profile of oral and pharyngeal cancer is increasingly recognised as being fundamental to the overall planning of the appropriate response of medical systems to (i) optimise patient outcome, and (ii) to successfully implement preventive strategies. The ongoing development of a worldwide network of population-based cancer registries provides an invaluable information resource in this regard. Examination of incidence levels reported from geographically and ethnically diverse regions indicates substantial variation in the susceptibility of different populations to oral cancer. This paper explores the extent of such variation utilising incidence statistics collated by the WHO from a series of 183 internationally recognised cancer registries. A novel presentation technique is used to highlight these variations while the potential implications of this diversity are also explored.

Material And Methods

Overall, age and gender specific incidence rates of oral and pharyngeal cancer for 183 population-based registries were extracted from Volume VII, Cancer in Five Continents (CIFC). Primary site was coded according to the WHO - International Classification of Diseases for Oncology (ICD-10). Patient age was categorised into 5-year intervals, and rates were presented separately for males and females. While the time period investigated was not completely uniform across registries, the years 1988-1992 inclusive were most commonly reported.

Overall incidence rates were standardised using a theoretical world population. The statistical methods used were mainly descriptive. The median was the most frequently used measure of centrality, while quartiles were used to estimate the level of inter-registry variation. 'Comb graphs' were used to visually investigate possible systematic geographical-based trends. For any given cancer site, this method has three basic elements namely (a) the standardised rates for all registries are arranged in ascending order, (b) each registry is colour-coded to its relevant continent/sub-continent (dark blue for Europe, red for North America etc), and (c) the ascending rates are then displayed contiguously with equal horizontal space allocated to each registry.

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Results

Extent of cancer registration world-wide

Based on Volume VII, CIFC, approx. 6.1% of the world's population is covered by cancer registration (Parkin *et al*, 1997). On a global basis, registration is seen to roughly reflect the state of economic development of the various regions. The rate of coverage varies substantially from 60.1% for Oceania to just 2.1% for Asia and 0.7% for Africa (Figure 1). A sharp contrast also exists between the proportion of the world's population resident in each region compared with the contribution made by that area to world-wide cancer registration. While the two most affluent regions in the world, North America and Western Europe, account for only one tenth of the world's population they contribute over half of world-wide cancer registrations. Conversely, while Africa, South America and Asia collectively account for over 80% of the world's population, these regions contribute just over 25% of all cancer registration. The WHO/IARC has invested considerable effort into fostering the development of population-based caner registration in these regions. However, it must currently be accepted that certain data-sets from developing countries may be less than complete due to problems arising from local medical and economic issues such as under-diagnosis and inaccurate population enumeration (Parkin *et al*, 2003). Nonetheless, these data-sets are a valuable source of information on previously unrecorded populations which may retain unique cultural habits providing potential clues to cancer aetiology (Parkin *et al*, 2002)

Median age-standardised rates

On the basis of the age-standardised rates from 183 registries worldwide, the median annual male incidences ranged from 2.3 per 100,000 per annum for mouth and 2.0 for tongue down to 0.3 for pharynx NOS (Not Otherwise Specified) as shown in Figure 2. Substantially lower rates are seen for females in each instance, ranging from 0.8 per 100,000 per annum for mouth, 0.7 for tongue down to 0.1 for pharynx NOS.

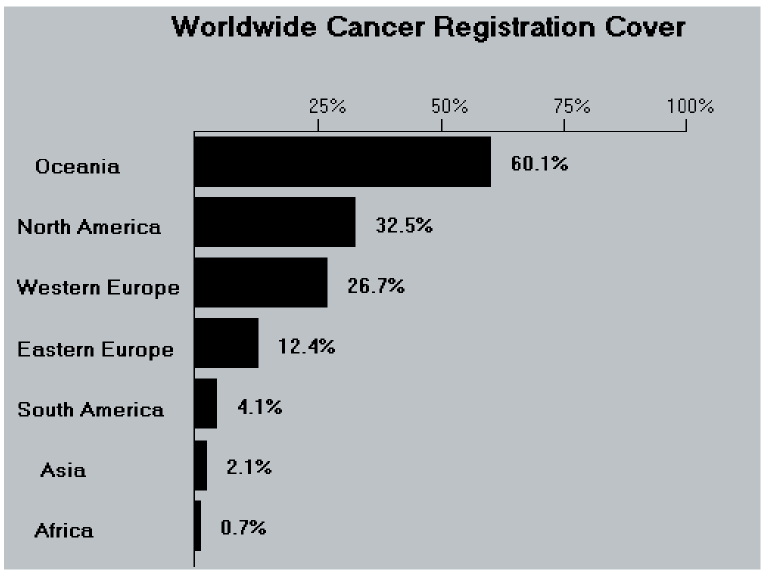

Figure 1. *Worldwide cancer registration cover.*

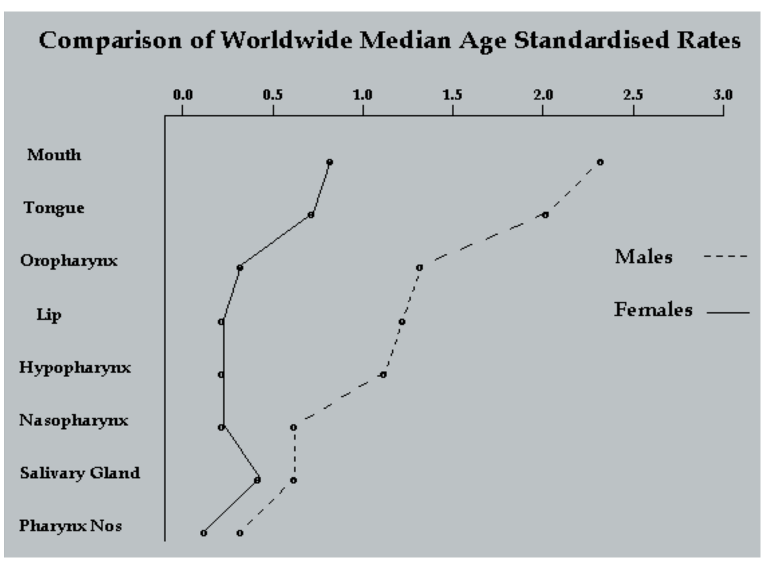

Figure 2. *Comparison of Worldwide Median Age Standardised Rates*

Evidence of geographical-based trends in incidence rates

The age-standardised rates were examined for evidence of geographical-based trends. A series of comb graphs were used to illustrate the extreme variability in international site-specific rates. Each of the 183 registries is represented by a bar colour-coded to the relevant continent. Examination of the 'comb graph' in Figure 3 provides a global insight into the pattern of 'intra-oral cancer' (ICD-10 C01-C06, C09, C10, C12-C14) highlighting the gender based differences in susceptibility to the disease, with male ASRs ranging from 0.6 to 49.5 per 100,000 (median 7.2) while the corresponding rates for females range from 0.4 to 13.4 (median 2.1). This comb graph clearly demonstrates the high European rate of intra-oral cancer in males whereas female rates are considerably lower, follow quite a different pattern and show greater uniformity. European rates for females are generally well below the median with the higher rates being recorded almost entirely by Asian registries. Figures 4, 5 & 6 illustrate the extreme variability in international site-specific rates

Lip

The wide spectrum of international experience is clearly visible in Figure 4 ranging from 0.0 to 13.5 per 100,000 males and 0.0 to 3.2 for females. Cancer of the lip has traditionally been associated with outdoor occupations such as farming, forestry and fishing (Andersen *et al*., 1999). Allegedly, this is mainly due to accumulated actinic radiation damage, particularly in fair-skinned males (Pukkala *et al*., 1994). While the incidence of lip cancer has decreased significantly over the past 50 years (Neville & Day, 2002), lip cancer rates are increasing in both genders in Australia contrary to global trends. In fact, the highest rates of lip cancer worldwide occur in S. Australia (13.5 and 3.2) with above average rates also recorded in Newfoundland, N. America (12.7).

Tongue

By comparison, tongue is the most common intra-oral site in many countries. The incidence rates range from 0.0 to 8.0 per 100,000 for males and from 0.0 to 5.7 for females. High male rates occur in many parts of Europe with the highest rate (8.0) occurring in Bas-Rhin, France. In fact, four of the five highest rates occur in France and geographical variations in the mortality of head and neck cancer are closely linked to those for alcohol mortality (Menegoz, 2002). Both the incidence and mortality of tongue cancer is increasing in many parts of Europe, and these trends reflect the pattern of tobacco and alcohol usage in these regions (La Vecchia *et al*., 2004; Levi *et al*. 2003). Female rates present a different picture as the highest rates occur among females in Zimbawbe (5.7) and India, while European rates remain at the lower end of the scale. However, the high rate recorded in Zimbabwe (5.7) must be interpreted with caution as the resources of this newly developed African registry are currently rather limited (Parkin *et al*., 2003).

Salivary gland

While salivary gland cancer is a relatively rare entity, the incidence rates (Figure 5) provide an interesting contrast to the other oral malignancies as they show relatively little international variation and are similar for males and females. Male rates range from 0.0 to 4.2, while rates for females range from 0.0 to 2.0. Median incidence rates are 0.6 for males and 0.4 for females. There is little evidence of any specific geographical pattern as is expected given the ill-defined nature of the aetiology of this disease. To date, the only established risk factors are atomic/iatrogenic radiation exposure, a history of prior cancer, and environmental factors such as EBV and diet (Chung Sun *et al*., 1999). However, above average rates have been recorded among the Inuit in Greenland, Canada and Alaska where environmental (EBV, diet) or genetic factors may play a role (Lanier *et al*., 1996). The highest female rates were recorded in N.W. Canada and San Francisco among the Philippino, Japanese and Chinese populations.

Mouth

The international incidence rates for mouth cancer (Figure 5) are much more variable, ranging from 0.3 to 12.4 in males and from 0.0 to 8.9 in females. High male rates are seen in many parts of Europe with three of the top five rates recorded in France; this is again linked to the

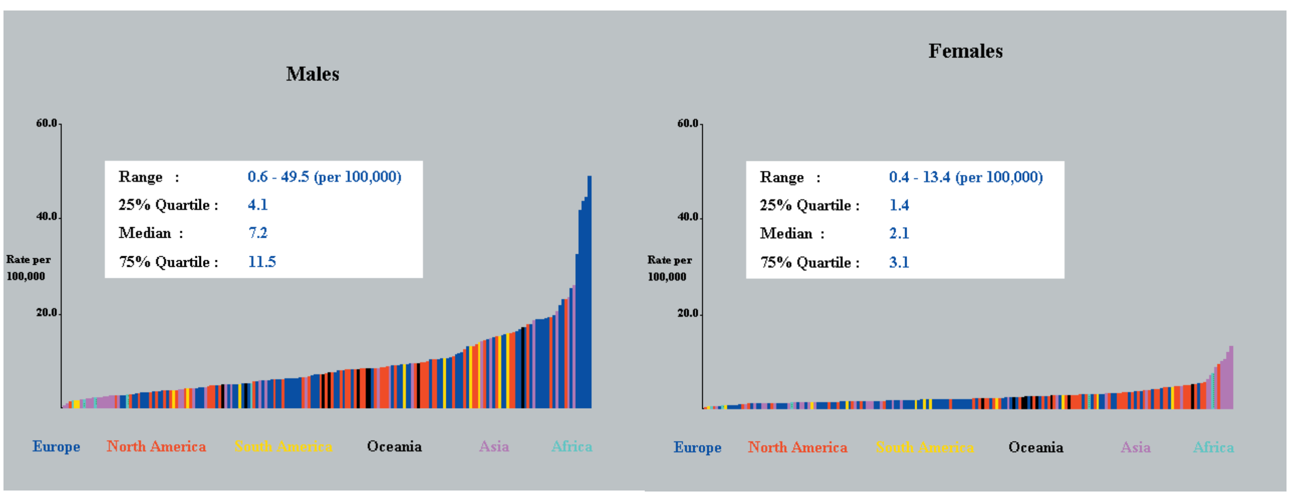

Figure 3. *Comparison of Age Standardised Rates for Intra-Oral Cancer i.e. (ICD-10 C01-C06, C09, C10, C12-C14)*

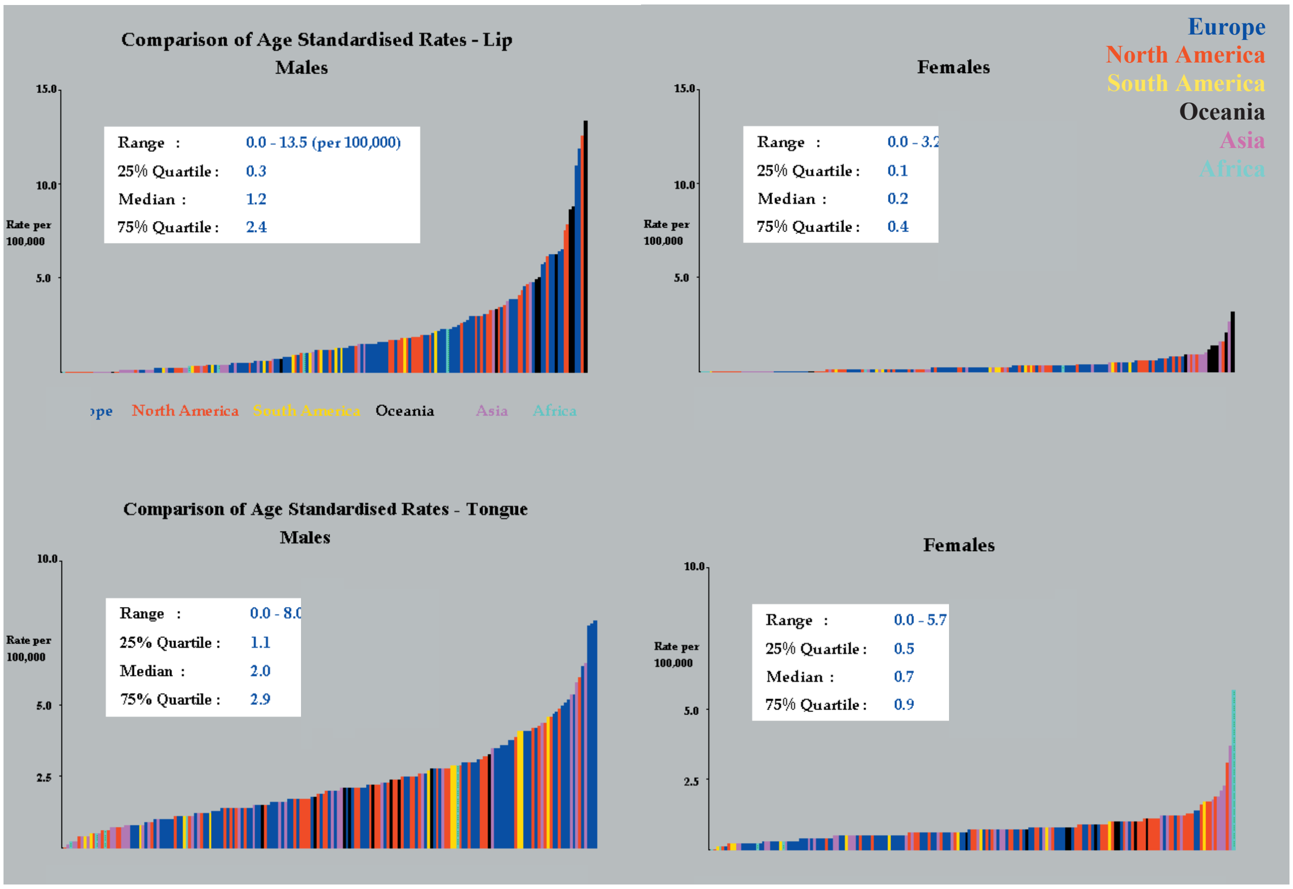

Figure 4. *Comparison of Age Standardised Rates (ASR) for Lip and Tongue Cancer*

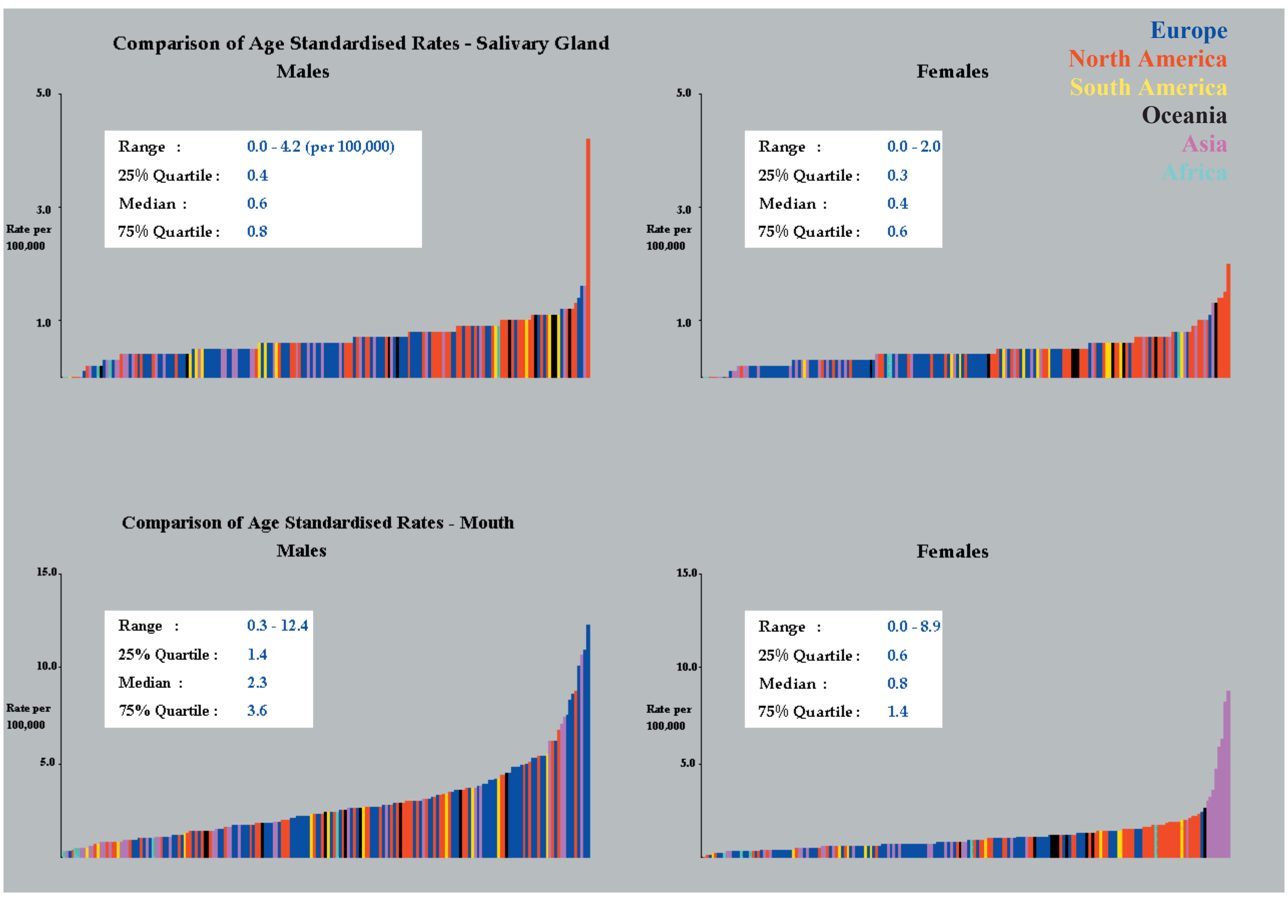

Figure 5. *Comparison of Age Standardised Rates - Salivary Gland and Mouth*

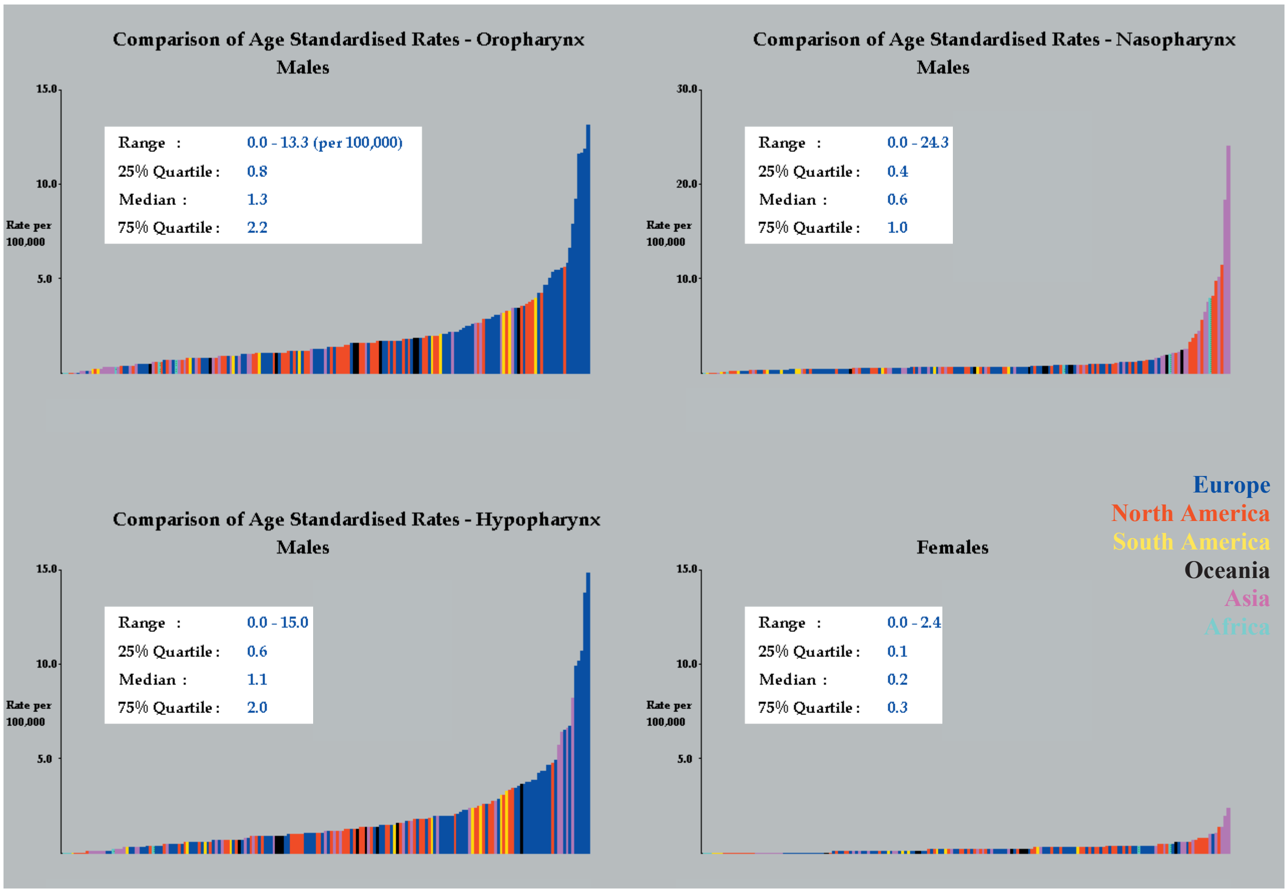

Figure 6. *Comparison of ASRs for Male Oropharyngeal & Nasopharyngeal Cancer and Hypopharyngeal Cancer in Males and Females*

high tobacco and alcohol intake of that region. Female rates present a completely different picture, the dominance of the Asian continent in the pattern of female mouth cancer being clearly seen where it is associated with local habits of pan chewing and smoking. A worrying upward trend has been noted among European females and younger males especially in Scotland, Germany, and Denmark which may be related to changes in behavioural patterns, particularly to increased alcohol consumption (Partridge, 2000; Johnson, 1999).

Oropharynx

Figure 6 highlights the significance of the European experience in the pattern of oropharyngeal cancer in males. While the range extends from 0.0 to 13.3, the inter-quartile range (IQR) is narrow (0.0 - 2.2); indeed, few registries record a rate in excess of 5.0 per 100,000 apart from the European registries. The highest male incidence is recorded in Somme, Northern France. In fact, the five highest recorded rates are all from French registries and the majority of the top fifteen incidence rates are reported by European registries. These trends have been linked with very high levels of alcohol and tobacco consumption in those regions, and particularly to the combined usage of these substances. High male rates were also reported in areas of Central and Eastern Europe, and Latin America (Francheschi *et al*., 2000).

Nasopharynx

Nasopharyngeal cancer (NPC) is a rare event in most regions as displayed by the IQR 0.4-1.0. An examination of international rates in Figure 6 shows a very interesting trend, with high male rates being recorded only in Asia and in areas with a strong immigrant Asian population. The highest recorded figures for both sexes occur in Hong Kong (24.3 and 9.5) followed by Chinese men in Singapore, San Francisco, and Los Angeles. The geographic and ethnic distribution of NPC suggests that the disease is associated with specific genetic and environmental factors (Grulich *et al*., 1995). Unlike most other head and neck sites, the aetiology of NPC is not linked to alcohol and tobacco, but rather to infection by the Epstein-Barr virus and the consumption of unusual dietary items (such as salted fish, principally in southern China and Tunisia). It is also linked with Chinese lineage, which may confer a genetic disposition mediated through the histocompatibility leukocyte antigen system (Muir & Weiland, 1995).

Hypopharynx

High rates for males are again seen in a number of European and Asian registries while female rates are considerably lower and show greater uniformity, ranging from 0.0 to 2.4 per 100,000. The top five male rates were recorded by French registries, with elevated female rates recorded for several Asian populations. The male/female contrast is quite pronounced at this site. Figure 6 provides a graphic illustration of the duality of nature versus nurture, highlighting the immense impact of behavioural issues such as alcohol abuse in male hypopharyngeal cancer.

Discussion

Oral and pharyngeal cancer is a collective term for a range of relatively rare cancers involving fourteen major sites (ICD-10 C01-C14) and up to 30 specific sub-sites. The group is also quite diverse in terms of aetiology, manifestations, therapeutic options and eventual outcome. While none of the oral and pharyngeal sites individually account for over 1% of all cancer cases, collectively OPC is currently the sixth most common cancer in the world accounting for 5.6% of all cancer registrations; this ranges from 5% in developed countries to approx. 40% in many Asiatic countries (Parkin *et al*., 1997).

Epidemiology has an important role to play in the fight against cancer. Analysis of relevant patient details may lead to the identification of aetiological factors, highlight referral patterns, identify regional variation in incidence and mortality rates, and assist in the development of preventive strategies and improved services. This study reveals the existence of substantial international variation in the incidence rates of OPC, with up to 20-fold variation between countries in annual incidence rates for individual sites. Specific geographical trends are identified and putative aetiological factors explored, including UV radiation, tobacco, alcohol, dietary and genetic factors and viral agents. The synergistic effect of heavy drinking and smoking (Rodriguez *et al*, 2004) is clearly highlighted in relation to tongue, mouth, oropharyngeal and hypopharyngeal cancers. Issues requiring further investigation include possible occupational, dietary and genetic links, particularly in younger patients, and those with no known risk factors.

The significant inter-site variation in incidence patterns revealed in this study, highlights the need for disaggregation of the ten OPC sites in all future studies of oral and pharyngeal cancer. While the common practice of aggregating intra-oral and pharyngeal sites, as shown in Figure 3, may be justified on the basis of common causality, histopathology and disease progression, the extent of the geographical and aetiological diversity revealed in this series strongly suggests that the present trend of aggregating adjacent but quite dissimilar sites such as lip, tongue, salivary gland and nasopharynx under the term 'head & neck cancer', 'oral cancer' or OPC must be actively discouraged.

Conclusion

Cancer registration plays a pivotal role in the fight against cancer as it provides the data that enables us to monitor the patterns of disease, assess treatment outcomes, organise primary and secondary prevention strategies, and plan appropriate services. The ongoing development of cancer registries throughout the world, and the increasing adoption of standardised ascertainment, data recording, operational and analytic practices within such registries, provides a vitally important resource in optimising the response of modern societies and health care systems to the challenge posed by malignant disease. Therefore, it is imperative that optimal use is made of the information collected by cancer registries at both national and international level and that the quality of the data so painstakingly collected is not corrupted by inappropriate aggregation.

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