The Journal
OF THE SOUTH CAROLINA MEDICAL ASSOCIATION

Head and Neck Cancer Disparities in South Carolina: Descriptive Epidemiology, Early Detection, and Special Programs

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Head and neck cancer includes mainly squamous cell carcinomas of the upper aerodigestive tract. These are usually sub-classified into multiple site groupings including the two most prevalent, oral and pharyngeal cancer (OPCA) and laryngeal cancer (LCA). OPCA comprises the majority of head and neck cancers, while LCA comprise approximately one-third of cases. In the United States (U.S.), these cancers account for three percent of all cancers diagnosed annually.[1]

OPCA is a generic term that applies to cancers diagnosed on lip, mouth (including tongue, buccal, upper and lower gums, hard palate, and floor of mouth), and pharynx (including oropharynx and hypopharynx; generally including nasopharynx, although nasopharyngeal cancer is not tobacco-related); while LCA is further divided into cancers of the supraglottis, glottis, and subglottis. In South Carolina, the most common of the OPCA sites in 2002 was the tongue (27.1%), although cancers occurring on the gums (15.9%) and the tonsils (12.4%) are also quite common.[2]

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Descriptive Epidemiology

Oral cancer is the fifth common cancer in the world,[3] culminating in over 600,000 new patients annually. Its incidence is particularly high in many countries in Asia, such as India, Papua New Guinea and Taiwan, and certain places in the Western hemisphere, including parts of France and Brazil. Like lung cancer, head and neck cancers are traceable primarily to tobacco use. However, for these sites, smokeless tobacco (e.g., chewing) are also important, as studies in Asian populations clearly indicate.[4-9] Chewing of tobacco products, in addition to smoking in various forms, is primarily responsible for the high incidence in India.[10,11] By contrast, in the Western hemisphere, tobacco smoking and alcohol drinking are major risk factors. In the U.S., the way the tobacco is chewed predisposes to cancer of the floor of mouth, or “snuff dipper’s cancer.” Relative to the other regions in the nation, cancer of this site is particularly prevalent in the Southern states.[12] Also in contrast to lung cancer, the combined carcinogenic effect of alcohol drinking with tobacco smoking has been well established from a variety of epidemiologic studies and reviews.[13-17] Therefore, in addition to chewing betel quid with tobacco and tobacco smoking, the International Agency for Research on Cancer (IARC) identifies alcoholic beverages as human carcinogens that target the oral cavity and pharynx.[13-15] In the US, about three-quarters of the risk for OPCA can be attributed to alcohol and tobacco use.[16]

Nutritional risk factors also have been implicated in cancers of the oral cavity. A number of studies have indicated that the consumption of vegetables and fruits reduces risk. These relationships may be independent of other risk factors and often evince a dose-response pattern.[17-20] Studies have reported that low intake of fruits and vegetables are associated with increased risk of OPCA.[21-23] The positive association of low serum levels of B-vitamins, including folate, with oral lesions has also been studied.[24] However, there is considerable potential for confounding, and this may be difficult or impossible to control in most epidemiologic studies on the subject.[25] Work previously conducted in India was able to overcome some of these methodological difficulties and has shown that dietary factors can modify risk – often by antagonizing the effect of tobacco.[26-28]

Taken together, tobacco use, alcohol consumption, and poor diet probably account for over 90% of cases of OPCA cases worldwide.[29] Diet clearly has an impact on oral health. It is believed that dietary intervention strategies may be effective in the prevention of OPCA. The role of diet needs to be further explored in the context of OPCA incidence in South Carolina.

In addition, viruses may also play an etiological role. For example, human papillomavirus (HPV) is considered an independent risk factor associated with some of the incidence of OPCA, especially those of tonsillar origin.[30-32] Work is needed to define the basic epidemiology and etiology of this category of disease in order to develop optimally effective prevention strategies, such as HPV vaccines.

Age is a non-modifiable risk factor for OPCA and LCA. There is an increased incidence rate in people over 40 years of age. Genetics is another non-modifiable risk factor. However, there is less research available about the genetics of OPCA than there is for many other cancer sites. On-going research may help to shed light on this.[33] Additionally, there is interest in a possible molecular link to P53 isoforms.[34] Clearly, we need to understand much more about the etiology of these cancers, while at the same time intervening on factors that we know can affect disease outcome.

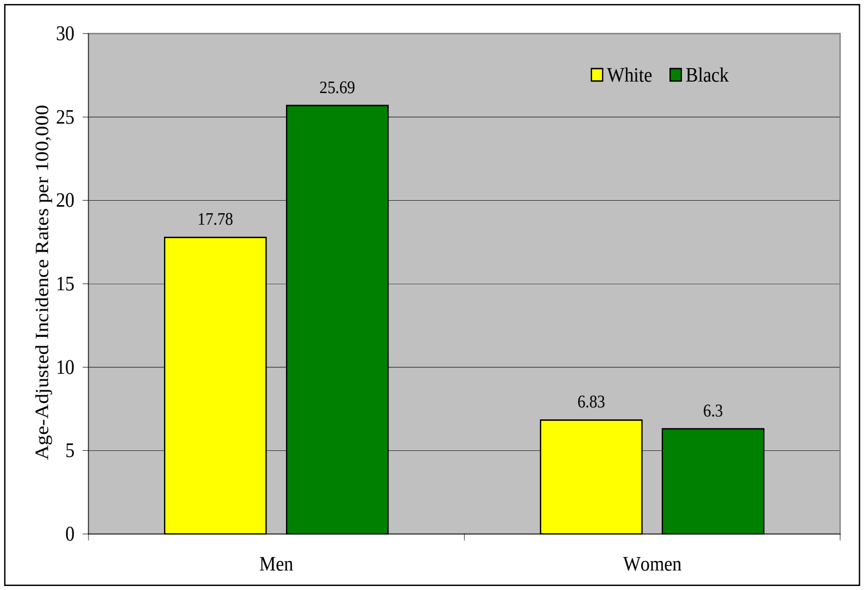

Figure 1. OPCA Age-Adjusted Incidence (1997-2002) Rates per 100,000 in SC by Race and Gender

Over 30 years ago, men were five times as likely as women to be diagnosed with OPCA. However, as with lung cancer, with the rise in the consumption of tobacco by women in this country, this gap has diminished to the point where OPCA is now only twice as common in men as in women.[35]

OPCA is the eleventh most commonly diagnosed cancer among South Carolinians. During the period 1997 – 2002, the overall age-adjusted incidence rate for men was 19.6 per 100,000 persons/year, while in women it was 6.8 per 100,000. Similarly, age-adjusted rates for LCA in men are far higher than those in women (men = 10.4 per 100,000, women = 1.8 per 100,000).

There also is a large disparity between races in the incidence of OPCA. In 1997-2002 the age-adjusted incidence rate in Black or African American (AA) men was 44.5% higher than the rate in White or European American (EA) men.[2] Nationally, this disparity is around 18%. Although smaller in absolute terms than the esophageal cancer disparity (80% in South Carolina vs. 55% nationally),[36] it is larger in proportional terms (i.e., 44.5% is about 2.5 greater than 18%). As seen in Figure 1, from 1997-2002, OPCA incidence rates were far greater in AA men than any other group. This large differential exists in South Carolina despite the relatively low rate of tobacco use in AA men in this state.[37-41] The age-adjusted incidence rates in women are similar and considerably lower for women of both races, standing at 6.8/100,000 for EA women and 6.3/100,000 for AA women.

Laryngeal cancer incidence follows the same trend, with AA men having the highest age-adjusted incidence (14.6/100,000) followed by EA men (9.2/100,000) and women, who have much lower incidence rates (AA women 1.8/100,000, EA women 1.8/100,000).

Additionally, by stage at diagnosis, a larger proportion of newly diagnosed EA cases present at early local stages compared to AA (Figures 2-5). Similarly, EA men (37%) are more likely to be diagnosed at early local stages of OPCA than AA men (20%), and EA women (48%) are more often diagnosed at early stages than AA women (29%).

The OPCA incidence rates by county seem to be evenly distributed geographically for both AA and EA men when county rates were compared to their respective national average rates (Figures 6-7). However, mortality rates differed widely by county. The highest are in Kershaw (6.7 per 100,000), Sumter (6.5 per 100,000) and Orangeburg counties (5.9 per 100,000). As can be seen in Figure 8, for EA men, the mortality rates are quite comparable to the national average for EA men; while the mortality burden carried by AA men in several South Carolina counties far exceeds that of AA men in the rest of the nation (Figure 9).

In the United States, the overall five-year survival rate during the years 1995 to 2001 is 59.4%. For localized disease, the five-year survival is 82.1% (83.9% for EA men, 59.8% for AA men), and 51.3% (53.1% for EA men, 31.3% for AA men) in regional disease; the five-year survival rates drops dramatically for distant disease to 27.6% (25.2% for EA men, 22.5% for AA men).[35] In South Carolina, the incidence rate of patients diagnosed in late stages is 7.1 per 100,000 for OPCA and 2.0 per 100,000 for LCA. These numbers are more dramatic when comparing AA men who have an incidence rate of 18.0 per 100,000 for OPCA and 6.6 per 100,000 for LCA presenting in late stages.

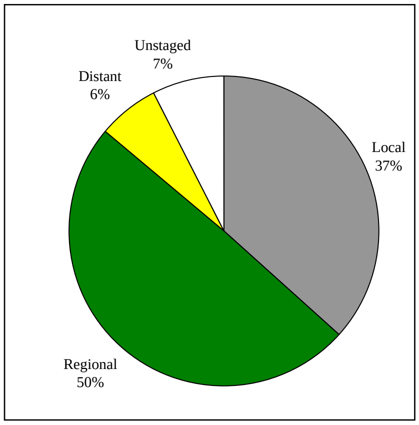

Figure 2. OPCA Stage at Diagnosis in SC among White Men, 1997-2002

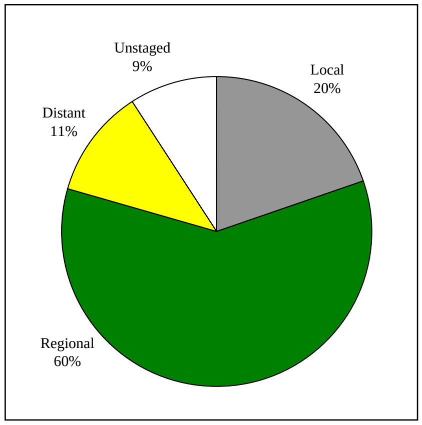

Figure 3. OPCA Stage at Diagnosis in SC among Black Men, 1997-2002

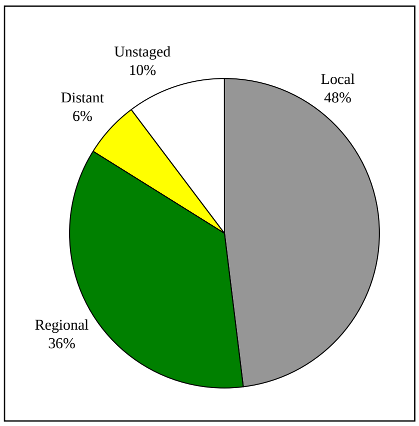

Figure 4. OPCA Stage at Diagnosis in SC among White Women, 1997-2002

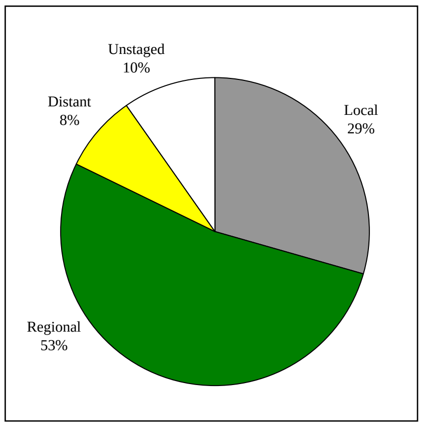

Figure 5. OPCA Stage at Diagnosis in SC among Black Women, 1997-2002

The South Carolina OPCA mortality rates have been on a steady decline for EA men, EA women, and AA women since 1978. However, the mortality rate for AA men in the same period remained relatively constant. Over this period, men were more than twice as likely to die from one of these cancers as women. Mortality rates from OPCA and LCA show similar racial disparities.

Overall, South Carolina ranks third in the nation in oral and pharyngeal cancer mortality;[2] the 1999-2004 age-adjusted rate of 3.6 per 100,000/year is 29% higher than the national average. There were a reported 517 incident cases that occurred in 2002 and 158 deaths in 2004. In 2002 there were 223 incident cases and 64 deaths in 2004 from LCA in South Carolina. AA men have the highest oral and pharyngeal cancer mortality rate with 11.8 deaths per 100,000/year, nearly three times greater than the rate in EA men (4.2 per 100,000/year). No doubt, the observed mortality disparities are partly explained by the stage distribution at the time of resection. However, it is not clear how much of the mortality difference would remain after taking this into account.

Clearly, there is a need for additional research to understand why incidence and mortality rates are higher in AAs than in EAs, given the difference in exposure types and overall lower exposure to known agents in AAs. The high rates in our state compared to other states along with the unexplained differences, underline the need for increased research in this area.

Recommendations for Oral/ Pharyngeal Cancer Screening

Oral and pharyngeal cancer often is preceded by asymptomatic oral precancerous lesions and conditions.[4] Moreover, the risk of oral cancer in individuals with oral precancerous lesions has been demonstrated to be very high relative to those without such lesions, even after controlling for the use of tobacco.[5] The association of oral precancerous lesions with tobacco habits follows a pattern similar to that of oral cancer.[6] Because the prevalence of oral precancerous lesions is much higher than that of oral cancer, these lesions provide useful surrogate markers for oral cancer in the clinical setting. As such, they are very useful for screening and have been used in large-scale intervention trials.[10] The oral cavity is one of few sites where screening is both an effective secondary preventive measure (i.e., where cancerous lesions detected can be treated at an early stage) and as a true primary preventive measure (i.e., where lesions can be detected in the precancerous stage and an incident cancer can be prevented altogether).

The extent of tumor involvement at diagnosis is a strong predictor of survival. The five-year relative survival rates for OPCA are three times greater when diagnosed in the early stages than late stages (81.5% for localized disease patients vs. 27.6% for patients with distant disease).[35] Unlike many cancers for which simple visual examination is impossible and palpation may be difficult, cancers of the oral and pharyngeal regions are relatively accessible. Indeed, the accessibility of the sites formed the basis for work conducted in very high-risk populations in India, which described both the epidemiology of oral cancer and the process of malignant transformation.[5-9]

Despite the accessibility of the oral cavity to visual inspection and sample collection, according to the most recent Surveillance, Epidemiology, and End Results (SEER) report for the years 1995-2001, only 34% of oral and pharyngeal cancers are diagnosed in the localized stage. Once the patient experiences symptoms from the cancer, such as pain, bleeding, ulceration, a mass or dysphagia, it usually heralds a more advanced stage of disease. These patients are then deprived of the optimal survival and minimal dysfunction that is awarded in clinical scenarios when early-stage disease is diagnosed. The discouraging fact is that the proportion of localized disease at diagnosis has not changed since 1973, indicating that efforts at early detection have not been successful or have been targeted inappropriately.[42]

Systematic review of the literature has failed to find conclusive evidence to support or refute the use of visual examination as a method of screening for oral cancer in the general population. Other adjunctive methods of screening, including toluidine blue, fluorescence imaging, or brush biopsy also failed to demonstrate either benefit or harm.[43] Review of community-based screening programs also has failed to demonstrate the effectiveness of such endeavors. Low general population prevalence of oral premalignant and malignant lesions has been cited as a possible reason.[44] However, programs that target high-risk populations and obtain good compliance from the selected individuals suggest that oral cancer screening can result in improved survival.[45,46] Opportunistic screening in high-risk groups, particularly heavy drinkers and smokers, may result in down-staging of disease. In one study on opportunistic screening, the proportion of stage I cancers increased from 22.8% to 48.2% of cases while stages II, III, IV decreased from 77.2% to 58.8% of cases.[47] Another explanation for the discrepancy in the evidence for visual screening may be due to the commitment and motivation of the examiners, physicians, and dentists. Underlining some of the difficulties in screening, it has been found that some clinicians consistently find early asymptomatic cancers while others examining the same population do not.[48]

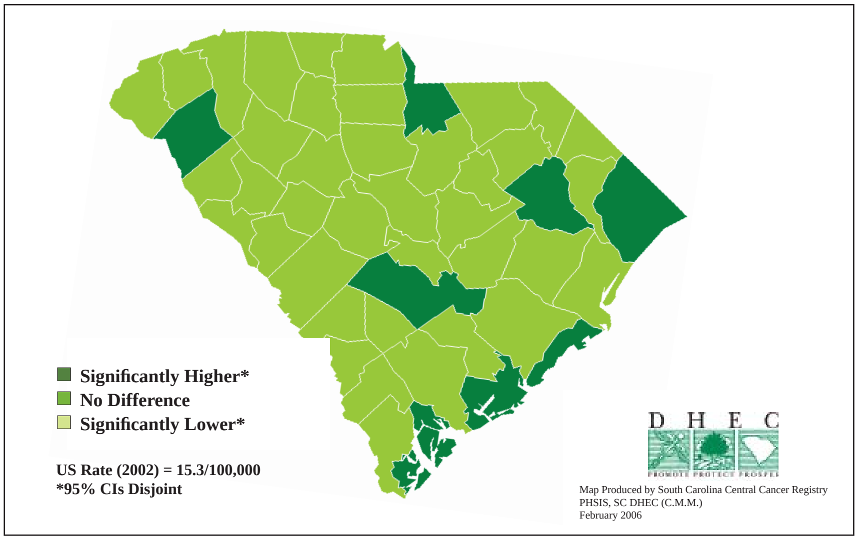

Figure 6. South Carolina Oral and Pharyngeal Cancer: Comparison of Age-Adjusted Rates, County-Specific Incidence Rates per 100,000 (1998-2002) in White Males, Compared to the US Rate Among White Males (2002)

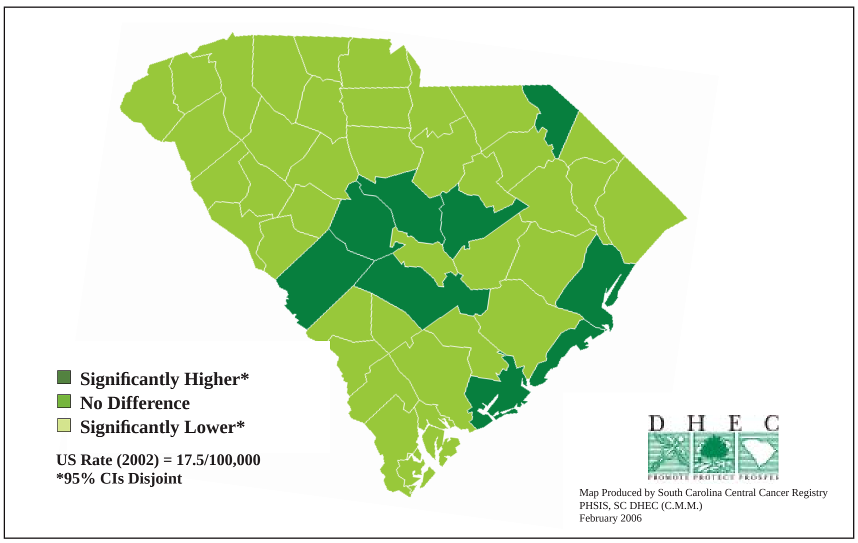

Figure 7. South Carolina Oral and Pharyngeal Cancer: Comparison of Age-Adjusted Rates, County Specific Incidence Rates per 100,000 (1998-2002) in White Males, Compared to the US Rate Among White Males (2002)

Precancerous lesions have been found to outnumber frank oral cancers up to several hundred-fold in screened populations.[26-28] Individuals diagnosed with precancerous oral lesions would have a special incentive for quitting, although they may require more intensive, specialized help for successful cessation. The effectiveness of community-based screenings may be enhanced if early detection of premalignant lesions could be coupled with treatment to prevent malignant transformation.[44] Chemoprevention is the use of pharmacologic or natural agents that inhibit the development of invasive cancer. These agents function by preventing the transformation of premalignant leukoplakia into malignant lesions. There is growing interest in chemoprevention because of the severe morbidity and mortality associated with invasive head and neck cancer. Presently, no effective chemo-protective treatments have been established from randomized clinical trials.[49] Non-steroidal anti-inflammatory drugs (NSAID) are

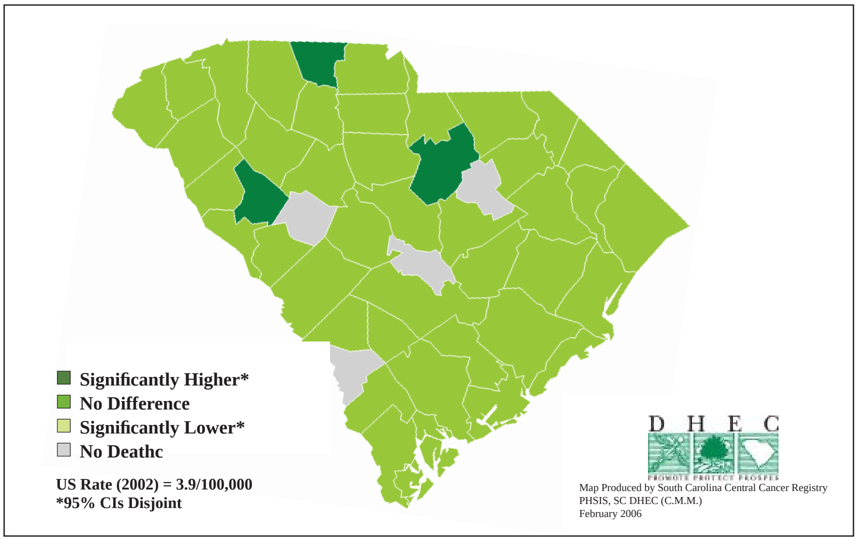

Figure 8. South Carolina Oral and Pharyngeal Cancer: Comparison of Age-Adjusted Rates, County-Specific Mortality Rates per 100,000 (1998-2002) in White Males, Compared to the US Rate Among White Males (2002)

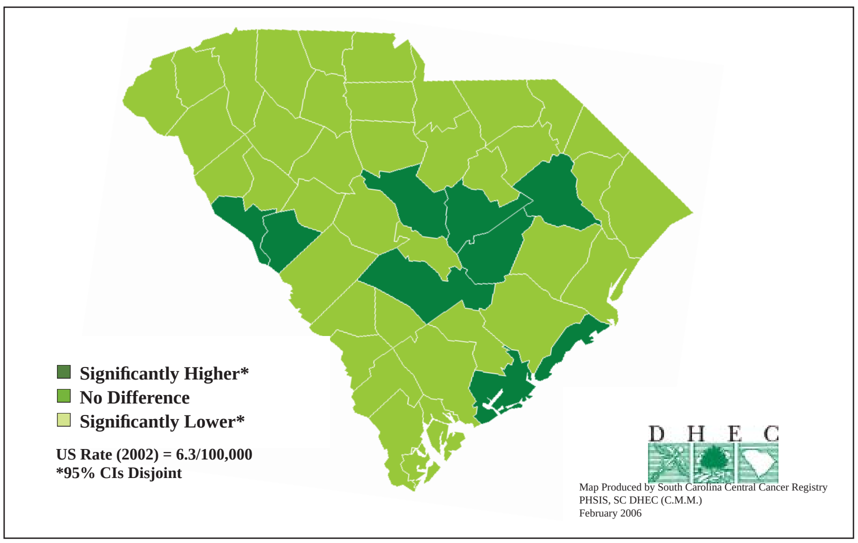

Figure 9. South Carolina Oral and Pharyngeal Cancer: Comparison of Age-Adjusted Rates, County-Specific Mortality Rates per 100,000 (1998-2002) in Black Males, Compared to the US Rate Among Black Males (2002)

a promising class of chemopreventive agents that act on the COX-2 pathway in several cancers, but further research is needed to understand the molecular mechanisms of action in oral premalignant lesions.[50]

Clearly, because the main risk factors for cancer are well known, there is good scope for prevention simply by encouraging cessation of tobacco use and reducing or eliminating the consumption of alcoholic beverages. The U.S. Preventive Services Task Force (USPSTF) states that there is insufficient evidence to recommend for or against routine screening for OPCA for low-risk individuals but advocate educational programs directed towards reducing the use of tobacco and alcohol.[51] For individuals at high risk of oral cancer, the USPSTF recommends regular dental examinations. The American Cancer Society (ACS) has no official guidelines for oral cancer detection; however, it encourages primary care physicians to perform an examination of the whole mouth as part of a routine cancer-related checkup.[1]

The American Dental Association (ADA) conducted a public service campaign in late 2001 to raise the awareness of oral cancer in U.S. adults and the role of the dentist in early detection.[52] In 2003, the ADA launched a campaign urging dentists to examine patients for signs of early cancer. In tandem, a five-year, $1.2 million grant from the National Cancer Institute was awarded to train dentists in oral cancer screening.[53] The NIH National Institute of Dental and Craniofacial Research currently supports research on salivary biomarkers for early detection of OPCA.[54]

Special Projects Addressing Screening in South Carolina

Through efforts supported by the Centers for Disease Control, South Carolina Department of Health and Environmental Control-South Carolina Central Cancer Registry (DHEC-SCCCR), South Carolina Cancer Alliance (SCCA), and the Head and Neck Tumor Program at the Medical University of South Carolina (MUSC) Hollings Cancer Center, a statewide collaborative was initiated in 2001 to improve the prevention and early detection of oral cancers in South Carolina.

South Carolina was one of two states awarded funds for the Cancer Surveillance Research Oral/Pharynx Cancer Project (U58/CCU420312 – Part IV of PA 01102). The purpose of this three-year study was to assess the completeness, timeliness, and quality of the registry's oral and pharyngeal cancer surveillance data. It is suspected that oral and pharyngeal cancer diagnoses may be routinely underreported. Preliminary analyses of South Carolina data using standardized incidence/mortality ratios points to under-ascertainment of cases in South Carolina border counties. Special focus was given to these counties as well as those categorized as medically underserved in the state. The SCCCR selected and applied methods to assess and improve data collection, reliability, and validity that will accommodate any distinct attributes of oral/pharyngeal cancer data. Methods included audits for coding reliability and validity across all hospital cancer registries in the state, re-abstracting and case-finding audits.

Results thus far reveal that problems with missed cases arise from diagnoses and treatments provided in physician offices and not reported to the cancer registry, miscoding of cases by physicians and registrars resulting in inaccurate case counts, and possible missed diagnoses in rural populations. In response, the SCCCR established an Oral Cancer Advisory Team (OCAT) to guide the study efforts and provide support for the applied improvements in the clinical community. Dr. Terry Day at MUSC chairs this group of clinicians and epidemiologists. Pathology laboratories specializing in oral /maxillofacial pathology that were not routinely reporting their cases to the cancer registry have been identified both in and out of South Carolina. The study was completed in September 2004. Additional results are expected when the case-finding audits are completed and final analyses are done. However, the OCAT is seeking alternate funding in order to further improve on the data quality of the registry.

In 2002, with the support of MUSC Hollings Cancer Center and assistance of the South Carolina DHEC, a study to assess the self-reported baseline rates of oral cancer examinations of the adults of South Carolina was conducted using the cross-sectional South Carolina Behavioral Risk Factor Surveillance System (SC BRFSS) mechanism.[55] The oral cancer examination questions were those used in previous national surveys. The prevalence for having had an oral cancer screening in the past twelve months for those 40 years and older, was 14.5% for South Carolina compared to 13% in the U.S.[56] The U.S. Healthy People 2010 Objective 21-7 is to have an annual oral cancer examination for at least 20% of adults aged 40 years and older.[57] South Carolina's results also showed that increasing income was directly related to having had an oral cancer examination and to having had the oral cancer examination within the past year. When asked what type of medical care personnel performed the examination, 70% reported "dentist," followed by 20% reporting "doctor/physician", and 5% reporting "dental hygienist." One of the conclusions was that intervention is necessary to increase the proportion of South Carolina adults who, in the past 12 months, receive an examination to detect oral cancers. We also note that special measures may be needed to reach the population at highest risk of oral cancer.

To assess the quality of training of future health care professionals in this state receive, studies were performed on South Carolina dental[58] and medical[59] students, focusing on students' knowledge of signs and symptoms of oral cancer, tobacco cessation techniques, and the ability to perform oral cancer examinations. These studies have suggested a need for further improvements on the curriculum pertaining to oral cancer early detection and prevention. South Carolina medical and dental students need additional training to increase knowledge of risk factors, knowledge of signs and symptoms and to improve examination skills to improve oral cancer detection and prevention. It has also been suggested that dental students be required to conduct oral examination as part of their certification.

Special Projects on Epidemiology Research in South Carolina

In 2004, the Centers for Disease Control awarded the MUSC Hollings Cancer Center a grant to reduce the impact of tobacco-related malignancies in South Carolina, including oral and oropharyngeal cancer. This grant includes statewide collaboration, combining groups at the Medical University of South Carolina, the University of South Carolina, and DHEC-SCCCR to further expand existing efforts. Epidemiology and health services delivery research addressing health disparities are currently in progress. A statewide rapid case ascertainment (RCA) system to identify new patients quickly is being implemented at the SCCCR in order to facilitate patient recruitment for future statewide population-based research. The long-term goal is to conduct a cross-site case-control study that examines sections of tumors and looks at biological differences in the case series. This may provide some explanation for the differences in incidence rates between EAs and AAs, and the factors that negatively influence incidence. A better understanding of the biologic and genetic contributions to the racial disparity in incidence and mortality would allow for more precise adjustments in future disparity research in the social context.

As noted for prostate cancer,[60] South Carolina provides an ideal context to examine heretofore neglected factors that may have an impact on oral cancer incidence. The possible interaction of geological factors with underlying biological factors, such as metal transporter gene expression by race, needs to be explored in South Carolina.[61,62] Much of South Carolina's AA population resides in rural areas that contain unique water and mineral concentrations. A population-based study that examines these regions in South Carolina will allow testing of novel hypotheses connecting high concentrations of zinc, iron and copper with oral cancer incidence. This will allow us to bring together considerable expertise ranging from geography information system (GIS) surveillance mapping and spatial statistics to basic biology and genetics.

Innovative Treatment/ Basic Science Research

Treatment for early-stage tumors typically involves surgery or radiation, whereas advanced-stage disease requires combination therapy. As with many cancers, OPCA is highly curable if the disease is treated in the early stages of development.

The addition of radiation-sensitizing chemotherapy drugs during radiotherapy, otherwise known as concomitant chemo-radiotherapy (CCRT), have shown marked improvements in survival of head and neck cancer patients when compared with radiotherapy alone.[63-65] Several new drugs have been developed that show promise utilizing this multidisciplinary approach. One such agent is cetuximab, a monoclonal antibody antagonist of the epidermal growth factor receptor (EGFR), which showed significant locoregional control and survival advantages in a recent large scale clinical trial.[66]

Unfortunately, most patients continue to be diagnosed in advance stages, resulting in poor survival rates. Extent of treatment is typically stage related and thus, treatment-related morbidity including problems with speech, swallowing, chewing and cosmetic deformities are aggravated with advanced disease stage.

Novel therapeutic approaches such as immune therapy have gained recent interest as a possible alternative treatment. OPCA patients have profound immune defects that are associated with increased recurrence. A reduced T-cell proliferative capability to mitogenic stimulation have been associated with a poorer outcome for OPCA patients.[67] While OPCA cells are able to directly inhibit anti-tumor immune defenses, they also induce the appearance of immune inhibitory cells. Studies from the laboratory of Young et al.[68] examining South Carolina patients have shown that the OPCA can skew immune responses towards less effective anti-cancer reactivity. Their studies have also shown that OPCA stimulate an increase in the number of bone marrow-derived progenitor cells having immune inhibitory activity.[69] Clinical trials using vitamin D3 analogs in patients with late-stage OPCA showed the feasibility of diminishing the levels of these immune inhibitory cells and restore immune competence by inducing differentiation of these cells into immune stimulatory cells.[70] Trials are currently open to determine if treatment with vitamin D3 analogs can stimulate immune reactivity against the OPCA within the tumor mass.

In the clinical arena, the Head and Neck Tumor Program at MUSC Hollings Cancer Center has a group of over 100 clinicians as members that provide a comprehensive multidisciplinary program aimed at improving the surgical, radiation, chemotherapy, speech, swallowing, dental, and many other important aspects of head and neck cancer care. Other centers of excellence for multidisciplinary care include the Dorn VA Medical Center in Columbia, the Cancer Center of the Carolinas in Greenville and the Gibbs Regional Cancer Center in Spartanburg. Clinical trials are also available at most of these sites.

OPCA survival rates have not improved significantly in decades, despite many advances in surgical techniques, technology, radiation therapy, and chemotherapy. In recent years, research into the causes of racial differences in treatment suggests that more equitable receipt of cancer treatment may help reduce racial disparities in cancer morbidity, and survival from OPCA.[71]

Summary

Recognizing that relatively easily detected precancerous lesions precede many cancers, there is a need to investigate the effectiveness of early interventions on the reduction of incidence rates in well-designed large randomized control trials. If early detection can reduce mortality rates of OPCA, evaluation of the capacity of dentists and physicians to screen or detect precancerous lesions related to oral cancers may have merit. Presently, there is a paucity of research regarding ecological barriers in the healthcare system, and improving access to adequate dental and medical care among the rural minority population in South Carolina certainly deserves emphasis. Additional research, specific to South Carolina, which includes comprehensive assessment of multiple social, behavioral, and biological factors, is needed. Interdisciplinary collaboration will be particularly important to dissect key factors contributing to the racial disparities observed in South Carolina. These differences should be taken into account while recommending and implementing public health strategies for the control of these cancers.

Acknowledgement

We would like to acknowledge funding of the South Carolina Cancer Disparities Community Network (SCCDCN) through grant number 1 U01 CA114601-01 from the National Cancer Institute (Community Networks Program), grant H75/CCH424532 from the CDC, and the South Carolina Central Cancer Registry for the state cancer incidence and mortality data provided. The SCCCR is funded by the CDC National Program of Cancer Registries, cooperative agreement number U55CCU421931, and SCDHEC. The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the agencies that have funded this work.

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